NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Safety of Palbociclib Among Breast Cancer Patients in the United States
Protocol number	A5481105
Protocol version identifier	Final Version 1
Date of last version of protocol	19 December 2017
EU Post Authorisation Study (PAS) register number	EUPAS21948
Active substance	Palbociclib ATC: L01XE33
Medicinal product	Palbociclib (Trade name: Ibrance®)
Research question and objectives	Research question: What are the incidence rates of safety events among new users of palbociclib in a real-world setting? Primary Objective: 1. Describe patient characteristics and incidence rates of safety events among all new users of palbociclib. Secondary Objective: 1. Describe patient characteristics and incidence rates of safety events among the following subgroups of new users of palbociclib: a) concomitant fulvestrant new users; b) concomitant letrozole new users; and c) no new use of letrozole or fulvestrant. 2. Describe patient characteristics and incidence rates of safety events

	among the following subgroups of new users of palbociclib who also meet algorithm-defined advanced stage estrogen receptor positive (ER+)/human epidermal growth factor receptor 2 negative (HER2-) breast cancer: a) concomitant fulvestrant new users; b) concomitant letrozole new users; and c) no new use of letrozole or fulvestrant. 3. Compare the incidence rates of safety events between new users of palbociclib with fulvestrant to new users of the following subgroups of fulvestrant users alone (historical controls from pre-2015): a) any new users of fulvestrant alone; and b) new users of fulvestrant alone who meet algorithm-defined ER+/HER2- breast cancer.
Author	Daniel C. Beachler, PhD, MHS Research Manager, Safety and Epidemiology HealthCore, Inc. Phone: 302-230-2089 Fax: 302-230-2020 E-mail: dbeachler@healthcore.com

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

Abbreviation or Special Term	Definition
ADIN	Action, Decision, Issue, Notification
AE	Adverse event
ALT	Alanine Transaminase
ALP	Alkaline Phosphatase
AST	Aspartate Transaminase
CCQP	Cancer Care Quality Program
CDK	Cyclin-dependent kinase
CFR	Code of Federal Register
CPT	Current Procedural Terminology
CSR	Clinical study report
DCC	Data Coordination Center
DSA	Data Sharing Agreement
DVT	Deep Vein Thrombosis
EMA	European Medicines Agency
ER	Estrogen Receptor
ER+	Estrogen Receptor positive
FDA	Food and Drug Administration
GPI	Generic Product Identifier
GPP	Good Pharmacoepidemiology Practices
HCPCS	Healthcare Common Procedure Coding System
HER2	Human Epidermal Growth Factor Receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIRD	HealthCore Integrated Research Database^{SM}
HIRE	HealthCore Integrated Research Environment
HIV	Human Immunodeficiency Virus
HR	Hormone Receptor
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
ISPE	International Society for Pharmacoepidemiology
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10	International Classification of Diseases, Tenth Revision
ILD	Interstitial Lung Disease

Abbreviation or Special Term	Definition
IRB	Institutional Review Board
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LDH	Lactic acid dehydrogenase
MACE	Major Acute Cardiovascular Events
MI	Myocardial infarction
NDC	National Drug Code
NI	Non-interventional
PAS	Post authorisation study
PASS	Post-Authorisation Safety Study
PHI	Protected Health Information
PPV	Positive Predictive Value
PR	Progesterone Receptor
ROC	Receiver Operating Characteristic
SAS	Statistical Analysis System
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamate-pyruvate transaminase
SOP	Standard Operating Procedure
QC	Quality control
US	United States

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
Cynthia de Luise, PhD	Senior Director, Epidemiology	Pfizer, Inc.	New York, NY
Daniel Beachler, PhD, MHS	Research Manager, Safety & Epidemiology	HealthCore Inc.	Wilmington, DE

3. ABSTRACT

Title	Safety of Palbociclib among Breast Cancer Patients in the United States Final Version 18 December 2017 Daniel Beachler HealthCore Inc.
Background and Rationale	Palbociclib is a selective cyclin-dependent kinase (CDK) 4/6 inhibitor that was approved in the United States (US) in February 2015 to treat advanced stage estrogen receptor positive (ER+)/human epidermal growth factor receptor 2 negative (HER2-) breast cancer in combination with letrozole. Subsequently, in February 2016 the Food and Drug Administration (FDA) approved palbociclib in combination with fulvestrant for advanced or metastatic hormone receptor positive (HR+)/HER2- breast cancer. The safety of palbociclib in patients with and without ER+/HER2- breast cancer and how it compares to the safety profile of other breast cancer treatments has not been well established in real world settings.
Research Question and Objectives	What are the incidence rates of safety events among new users of palbociclib in a real-world setting? Primary Objective: 1. Describe patient characteristics and incidence rates of safety events among all new users of palbociclib. Secondary Objective: 1. Describe patient characteristics and incidence rates of safety events among the following subgroups of new users of palbociclib: a) concomitant fulvestrant new users; b) concomitant letrozole new users; and c) no new use of letrozole or fulvestrant. 2. Describe patient characteristics and incidence rates of safety events among the following subgroups of new users of palbociclib who also meet algorithm-defined advanced stage ER+/HER2- breast cancer: a) concomitant fulvestrant new users; b) concomitant letrozole new users; and c) no new use of letrozole or fulvestrant.

	3. Compare the incidence rates of safety events between new users of palbociclib with fulvestrant to new users of the following subgroups of fulvestrant users alone (historical controls from pre-2015): a) any new users of fulvestrant alone; and b) new users of fulvestrant alone who also meet algorithm-defined ER+/HER2- breast cancer.
Study Design	Retrospective longitudinal new user study
Population	Patients must meet all of the following inclusion criteria to be eligible for the study 1. At least one dispensing for palbociclib from 01 February 2015 through 31 September 2017 (or latest available date) OR dispensing for fulvestrant from 01 January 2011 through 31 January 2015; AND 2. Aged 18 years or older at time of first dispensing of a study drug; 3. At least three months membership in the HealthCore Integrated Research Database (HIRD) with no dispensing of palbociclib (or any other CDK4/6 inhibitor such as ribociclib) before the first dispensing of palbociclib, as a minimal baseline period to define new use and characterize baseline risk: a. For Secondary Objectives 2 and 3, for some of the analyses we will restrict to individuals with algorithm defined advanced stage ER+/HER2-breast cancer further described in Section 8.2.3.[4] The date of algorithm defined advanced ER+/HER2-breast cancer must occur before or within three months of the first dispensing of palbociclib for inclusion in this subcohort (further described in Section 8.2.3.1). b. For Secondary Objective 3, at least three months membership in the HIRD with no dispensings of palbociclib OR fulvestrant OR another CDK4/6 inhibitor before the first dispensing of palbociclib OR fulvestrant, as a minimal baseline period to define new use and characterize baseline risk.
Variables – including exposures, outcomes, and key co-variates	Exposures: Exposure to palbociclib, fulvestrant, and letrozole will be assessed using the pharmacy claims and medical claims data available in the HIRD for each cohort member. Additional information will be

	available on the dates these medications were dispensed, days supplied, quantity dispensed, as well as the strength and brand of medication dispensed. Treatment episodes (ie, person-time classified as exposed to study drugs) will be constructed for each patient by concatenating consecutive dispensings. Outcomes: Outcomes will be assessed during the follow-up period of the treatment episodes using claims data in the HIRD and will include the following safety events of interest including leukopenia, pulmonary embolism, anemia, and serious infections using claims definitions (Section 8.3.2; Annex 2). Covariates: Demographics, medical history, exposure to other breast and other cancer therapies, healthcare utilization, medication use (breast cancer and non-breast cancer related), and co-morbidities will all be described for each objective and considered for utilization in propensity score matching for Secondary Objective 3 (Section 8.3.3).
Data Sources	HealthCore Integrated Research Database: The study will be conducted using the HIRD. The HIRD is a broad, clinically rich, and geographically diverse spectrum of longitudinal medical and pharmacy claims data from health plan members across the US. Member enrollment, medical care (professional and facility claims), outpatient prescription drug use, outpatient laboratory test result data, and health care utilization are tracked for health plan members in the database dating back to January 2006.
Study Size	The study will include eligible patients from 2011 through 2017. We currently estimate that approximately 2,300 patients in HIRD are new users of palbociclib and approximately 1,600 of them have algorithm-defined advanced stage ER+/HER2-breast cancer. The number of patients treated with fulvestrant (without palbociclib) exceeds the number treated with palbociclib with fulvestrant (~700 patients).
Data Analysis	The distribution of descriptive variables will be described for the total palbociclib and fulvestrant cohorts and separately for each of the subcohorts outlined in Figure 1.

	The incidence of the safety events of interest will be computed by dividing the total number of events that are identified by the total at-risk person-time accumulated for all cohort members for that specific event. Only cohort members who do not have any history of one of the events of interest will contribute to the computation of at-risk person-time for that event (unless otherwise specified). Confidence intervals for the incidence estimates will be computed using methods based on the Poisson distribution. The incidence of the safety events of interest will be presented overall as well as stratified by subgroup of interest. Hazard ratios will be computed comparing the risk of each pre-specified safety events between new users of palbociclib with fulvestrant and propensity score matched new users of fulvestrant using Cox proportional hazard regression analysis in the two study cohorts (all users; all users with algorithm-defined advanced stage ER+/HER2-breast cancer).
Milestones	The planned start date of data collection is 02 January 2018 and the planned end date of data collection is 02 March 2018. The planned final report date is 23 May 2018.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned date
Start of data collection (start of data extraction)	02 January 2018
End of data collection (end of data extraction)	02 March 2018
Final study report	23 May 2018

6. RATIONALE AND BACKGROUND

This is a non-interventional, real world, observational study to assess the safety of palbociclib in the treatment of patients with advanced stage Estrogen Receptor Positive (ER+)/Human Epidermal Growth Factor Negative (HER2-) breast cancer and without advanced ER+/HER2-breast cancer. Palbociclib (Pfizer Inc.) is a selective cyclin-dependent kinase (CDK) 4/6 inhibitor that received accelerated approval by the US Food and Drug Administration (FDA) in February 2015 and by the European Medicines Agency (EMA) in November 2016.[1] The FDA first approved palbociclib for the treatment of advanced stage ER+/HER2- breast cancer in combination with letrozole as the first hormonal based therapy in women who have gone through menopause. Subsequently, in February 2016, palbociclib was approved for use in combination with fulvestrant in women with hormone receptor positive (HR+)/HER2-breast cancer with disease progression following hormonal therapy.[1] Results from recent randomized trials (PALOMA2 and PALOMA3) demonstrated that palbociclib statistically significantly increased progression-free survival; adverse events (AEs) were more common in the palbociclib arm compared to the control arm.[2,3]

Our previous work (Pfizer-HealthCore study A5481080: "Standing Cohorts of Individuals with Early or Advanced ER+/HER2- Breast Cancer")[4] developed a validated claims algorithm for advanced stage ER+/HER2-breast cancer utilizing predictive modeling in a subset of breast cancer patients with clinically confirmed stage and biomarker data. The study also presented the incidence rates of safety events among patients with advanced stage ER+/HER2-breast cancer. The indication for palbociclib was expanded in 2016 to include those with advanced HR+/HER2-breast cancer, which includes individuals with progesterone receptor positive (PR+) or ER+ breast cancer. The vast majority of HR+ cases are also ER+; in our clinical HealthCore Integrated Research Environment (HIRE) Oncology database (further described in Section 8.4) approximately 98% of HR+/HER2-breast cancers were also ER+/HER2-breast cancers. Because the ER+ and HR+ breast cancers almost entirely overlap, the existing algorithm would identify HR+ breast cancer with similar accuracy to ER+ breast cancer.

The safety of palbociclib in patients with and without ER+/HER2-breast cancer and how it compares to the safety profile of other breast cancer treatments has not been well established in real world settings. This study will examine the event rates of pre-specified safety events in study A5481080 among all new palbociclib users, and in the subset with the algorithm-defined advanced ER+/HER2-breast cancer.[4] The event rates of prespecified safety events among individuals initiating palbociclib with fulvestrant will be compared with those who received fulvestrant alone prior to the FDA approval of palbociclib in 2015. This

non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

What are the incidence rates of safety events among new users of palbociclib in a real-world setting?

Primary Objective:

1. Describe patient characteristics and incidence rates of safety events among all new users of palbociclib.

Secondary Objective:

1. Describe patient characteristics and incidence rates of safety events among the following subgroups of new users of palbociclib:

    a. Concomitant fulvestrant new users;

    b. Concomitant letrozole new users; and

    c. No new use of letrozole or fulvestrant.

2. Describe patient characteristics and incidence rates of safety events among the following subgroups of new users of palbociclib who also meet algorithm-defined advanced stage ER+/HER2-breast cancer:

    a. Concomitant fulvestrant new users;

    b. Concomitant letrozole new users; and

    c. No new use of letrozole or fulvestrant.

3. Compare the incidence rates of safety events between new users of palbociclib with fulvestrant to new uses of the following subgroups of fulvestrant users alone (historical controls from pre-2015):

a. Any new users of fulvestrant alone; and

b. New users of fulvestrant alone who also meet algorithm-defined ER+/HER2-breast cancer.

8. RESEARCH METHODS

8.1. Study Design

This study is a retrospective longitudinal new user cohort design among breast cancer patients initiating palbociclib or fulvestrant alone utilizing health insurance claims data. Incidence rates of safety events will be calculated among all new users of palbociclib, and compared between new users taking palbociclib with fulvestrant to new users taking fulvestrant alone, after adjusting for key covariates through propensity score matching. Pre-specified safety endpoints of interest will be identified from codes recorded in claims (Annex 2).

8.2. Setting

The study will be conducted using the HealthCore Integrated Research Database (HIRD). The HIRD is a broad, clinically rich and geographically diverse spectrum of longitudinal claims data from United States (US) commercial health plan members in the Northeastern, Mid-Atlantic, Southeastern, Midwest, Central, and Western regions of the US. The HIRD dates back to 01 January 2006 and currently contains claims for services up to 31 August 2017. Most of the analyses will restrict to the study period after palbociclib was FDA approved, from February 2015 until the most currently available data (September 2017 or later). For Secondary Objective 3, we will also include data for individuals who newly received fulvestrant alone before the FDA approved palbociclib from 01 January 2011 until 31 January 2015 ("historical controls"). For this comparison group, we will not include new users of fulvestrant alone after the FDA approval of palbociclib since they may differ from patients receiving palbociclib and fulvestrant by factors not measured in the database.

Patient enrollment data, inpatient and outpatient medical care, outpatient prescription drug use, and healthcare charges are tracked for each patient in the database. In the HIRD, diagnoses and procedures will be identified by International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) and Tenth Revision (ICD-10), Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS) codes, for both outpatient visits and inpatient stays. Drug claims are captured by National Drug Codes (NDCs), which can then be translated to broader categories of coding such as Generic Product Identifier (GPI) codes. Information on physician specialty is also retained in the HIRD.

8.2.1. Inclusion Criteria

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

1. At least one dispensing for palbociclib from 01 February 2015 through 31 September 2017 (or latest available date) OR dispensing for fulvestrant from 01 January 2011 through 31 January 2015; AND

2. Aged 18 years or older at time of first dispensing of a study drug; AND

3. At least three months membership in the HIRD with no dispensings of palbociclib (or any other CDK4/6 inhibitor such as ribociclib) before the first dispensing of palbociclib, as a minimal baseline period to define new use and characterize baseline risk:

    a. For Secondary Objectives 2 and 3, for some of the analyses we will restrict to individuals with algorithm defined advanced stage ER+/HER2-breast cancer further described in Section 8.2.3.[4] The date of algorithm defined advanced ER+/HER2-breast cancer must occur before or within three months of the first dispensing of palbociclib for inclusion in this subcohort (further described in Section 8.2.3.1).

    b. For Secondary Objective 3, at least three months membership in the HIRD with no dispensings of palbociclib OR fulvestrant OR another CDK4/6 inhibitor before the first dispensing of palbociclib OR fulvestrant, as a minimal baseline period to define new use and characterize baseline risk.

8.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

8.2.3. Study Population

The study will include all new users of palbociclib of aged ≥18 years.

This group of new users of palbociclib will then be stratified into three mutually exclusive hierarchal subcohorts:

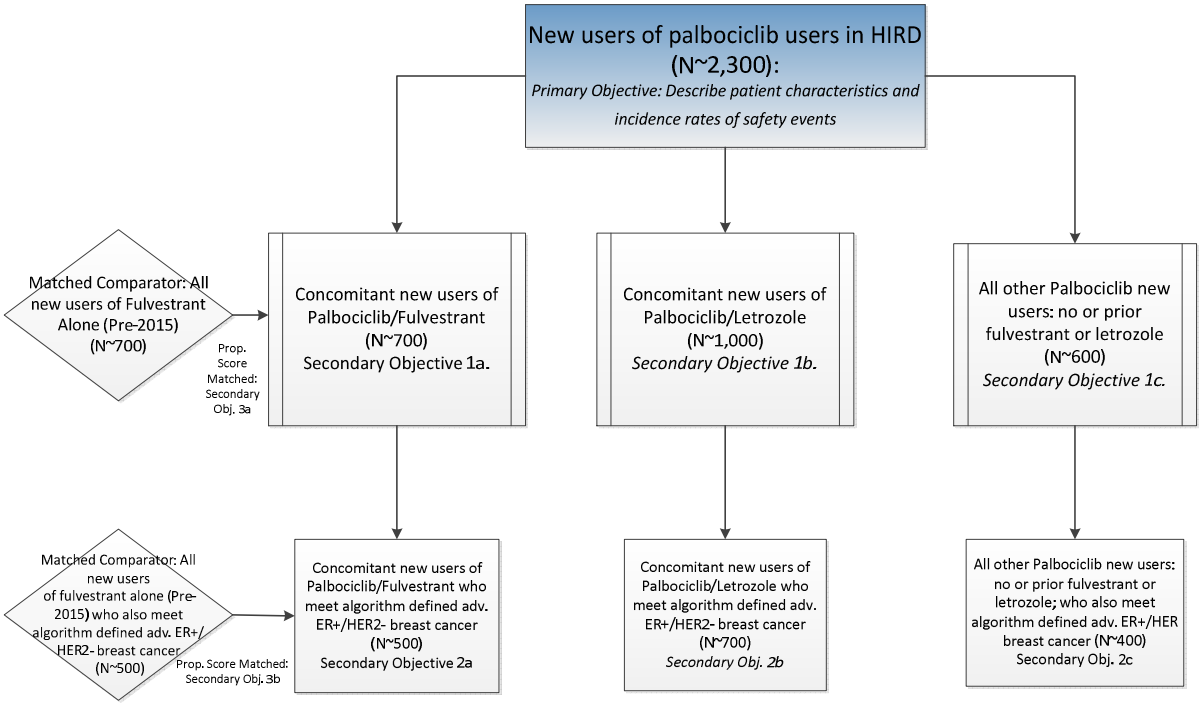
1. New users of palbociclib and fulvestrant.

2. New users of palbociclib and letrozole.

3. Other new users of palbociclib: those who did not newly initiate fulvestrant or letrozole (ie, were not included in subcohort one or two).

Creation of the study subcohorts and further subgroups are depicted in Figure 1, and described further below:

Figure 1. Description of Study Population and Their Estimated Study Sizes



Abbreviations: N, number; ER, estrogen receptor; HER2, human epidermal growth factor receptor

8.2.3.1. New Users of Palbociclib with Fulvestrant (Secondary Objectives 1a and 2a)

For Secondary Objective 1a, we will restrict individuals in this subcohort to include those who had at least three months membership in the HIRD with no dispensings of palbociclib or fulvestrant before the first dispensing of palbociclib or fulvestrant. The first dispensing of fulvestrant (administered through an injection) must occur within 30 days before or after a patient's first palbociclib dispensing (administered orally) to qualify for this subcohort.

For Secondary Objective 2a, we will further restrict to individuals who met our validated algorithm for advanced stage ER+/HER2-breast cancer that was previously defined in our recent study (A5481080) and in Table 1 below.[4] This analysis will assess incidence rates of safety events among individuals very likely to be in the subgroup for which palbociclib is indicated. The algorithm includes treatments, procedures and diagnosis codes positively or inversely associated with advanced stage ER+/HER2-breast cancer, and was found to have a positive predictive value (PPV) of 91.4% and a sensitivity of 53.9% at the chosen predictive probability cut-off point of 70%. In order to achieve a higher sensitivity, we will utilize a predictive probability cut-off point of 50% which has a PPV of 85.5% and a sensitivity of 68.2%. Using the 50% cut-off point instead of the 70% cut-off increases the sensitivity, and thus increases the number of concomitant new users of palbociclib with fulvestrant with algorithm-defined advanced ER+/HER2-breast cancer from ~400 to ~500. This will allow further power to examine more moderately sized safety endpoints.

Table 1. Patient Features and Coefficients in the Regression Model for Advanced Stage ER+/HER2-Breast Cancer

Features associated with confirmed advanced stage ER+/HER2-Breast Cancer (True Positives)		Features associated with confirmed not advanced stage ER+/HER2-Breast Cancer (False Positives; ie, other types of breast cancer)	
Patient feature	**Coefficient**	**Patient feature**	**Coefficient**
Fulvestrant	2.3029	Intercept	-2.7882
Secondary malignancy to other specified sites	1.9304	HER2 positive Therapy (Trastuzumab, Lapatinib, Ado-trastuzumab, Pertuzumab)	-6.0778
Palbociclib	1.533	Lumpectomy in last 6 months	-0.7586
Secondary malignancy to respiratory or digestive systems	1.0335	Mastectomy in last 6 months	-0.5514
Tamoxifen	0.7931	Diagnostic Imaging in last 6 months	-0.4185
Everolimus	0.7409	Tomosynthesis	-0.4046
Radical mastectomy in the last six months	0.6261	Corticosteroids	-0.3006
Letrozole	0.6211	Antifungals	-0.2937
Anastrazole	0.4478	Chemotherapy	-0.2642
Denosumab or Pamidronate	0.396		
Exemestane	0.3617		
Secondary malignancy to lymph nodes of head, face, and neck	0.3364		

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2

The date when a patient reaches a predictive probability of at least 50% for the algorithm defined advanced stage ER+/HER2-breast cancer will be defined as the date of advanced stage ER+/HER2-breast cancer. In order for a patient to be included in the "advanced ER+/HER2-breast cancer" subgroup analyses (Secondary Objective 2a), this advanced stage ER+/HER2-breast cancer date must occur before or within three months of the first dispensing of palbociclib.

8.2.3.2. New Users of Palbociclib with Letrozole (Secondary Objectives 1b and 2b)

For Secondary Objective 1b, we will restrict individuals in this subcohort to include those who had at least three months membership in the HIRD with no dispensings of palbociclib or letrozole before the first dispensing of palbociclib or letrozole (administered orally). The first dispensing of letrozole must occur within 90 days before or after a patient's first palbociclib dispensing to qualify for this subcohort, and the patient must not have qualified as a "new user of palbociclib and fulvestrant," subcohort described in Section 8.2.3.1.

For Secondary Objective 2b, we will further restrict to individuals who met our validated algorithm for advanced stage ER+/HER2-breast cancer as described in Section 8.2.3.1.

8.2.3.3. Other New Users of Palbociclib

For Secondary Objective 1c, we will include all new users of palbociclib who did not qualify for the first two subcohorts described in Sections 8.2.3.1 and 8.2.3.2. This will include new users who did not use fulvestrant or letrozole around the time they initiated palbociclib, and those individuals who had a history of using fulvestrant or letrozole prior to initiating palbociclib.

For Secondary Objective 2c, we will further restrict to individuals who met our validated algorithm for advanced stage ER+/HER2-breast cancer as described in Section 8.2.3.1.

8.2.3.4. New Users of Fulvestrant

For Secondary Objective 3a, we will include a comparison group of patients who newly initiated fulvestrant between 01 January 2011 and 31 January 2015 before the FDA approval of palbociclib. Similar to the other new user definitions, we will require at least three months membership in the HIRD with no dispensings of fulvestrant before the first dispensing of fulvestrant, as a minimal baseline period to define new use and characterize baseline risk.

These patients will then be propensity score matched to concomitant new users of palbociclib with fulvestrant described in Section 8.2.3.1. The propensity score matching is further described in Section 8.7.

For Secondary Objective 3b, we will further restrict to individuals who met our validated algorithm for advanced stage ER+/HER2-breast cancer as described in Section 8.2.3.1.

8.3. Variables

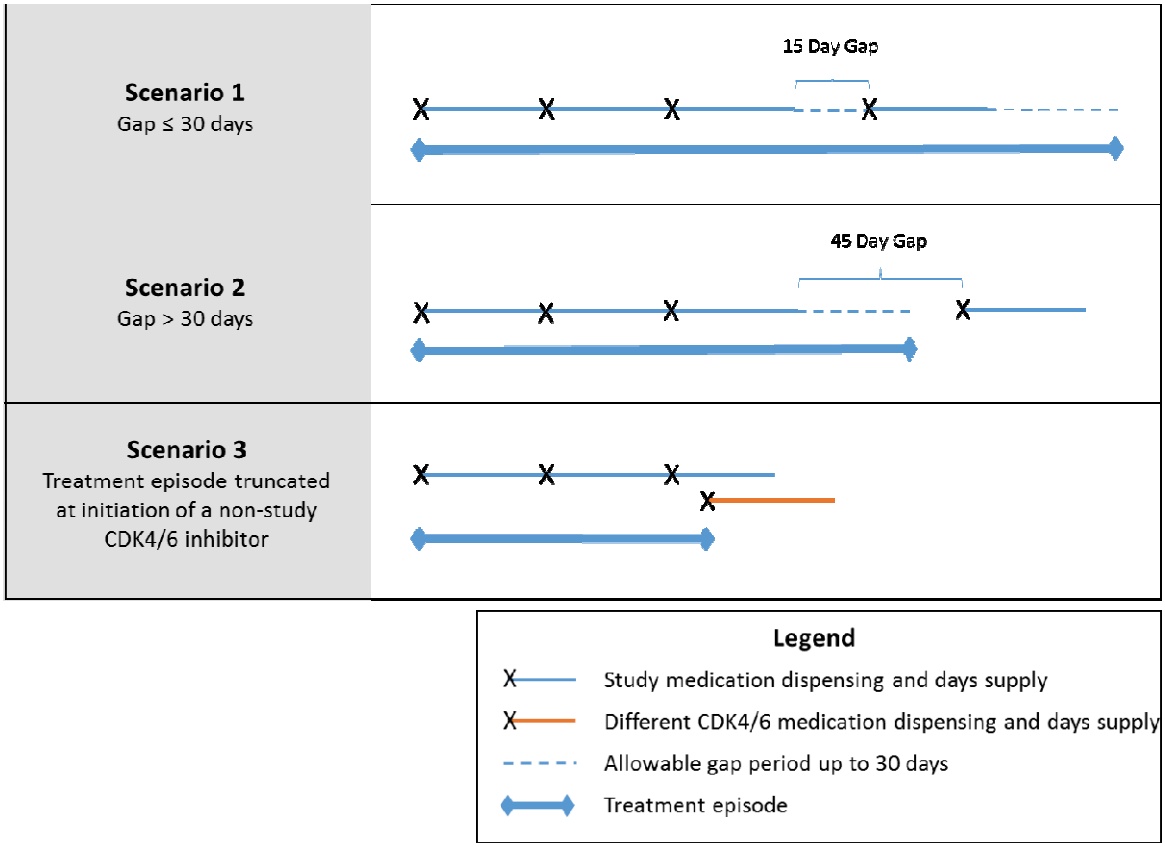
8.3.1. Exposure Definition and Assessment

Exposure to different therapies for treating breast and other cancers will be assessed using the pharmacy claims and medical claims data available in the HIRD for each cohort member, as was done in the recent standing cohorts study (A5481080).[4] Pharmacy claims exposures will be identified using NDC and GPI codes for the specific medications of interest. Additional information will be available including: dates these medications were dispensed, days supplied, quantity dispensed, as well as the strength and brand of medication dispensed. In the medical claims, CPT and HCPCS codes will be utilized to identify the administration of any of the medications of interest.

For each cohort except for the comparator as described in Secondary Objective 3, the index date is defined as the date of the first dispensing of palbociclib. For the comparator described in Secondary Objective 3, the index date is defined as the date of the first dispensing of fulvestrant. Exposure episodes for study medication will be created using dispensing date, plus the number of days supplied, plus 30 days to account for possible non-adherence and non-concordance of dispensing date and administration (eg, patients may obtain new medication before previous medication has been completed). Consecutive dispensings defined in this manner will be concatenated into a single continuous episode. Palbociclib exposure episodes will be truncated by discontinuation (>30 days from most recent exposed day without another dispensing) or switch to another CDK4/6 inhibitor.

Fulvestrant exposure episodes for Secondary Objective 3 will be similarly truncated by discontinuation (>30 days from most recent exposed day without another dispensing). Analyses will focus on the safety events of interest occurring during the exposure episodes of the study medications (Figure 2).

Figure 2. Examples of Treatment Episode Construction with 30 Day Allowable Gap



For example, for scenario 2 (Figure 2), assuming the days supply is 30 days, this individual has 75 days in between her third and fourth dispensing. She would be considered exposed for the first 60 days (30 days supply +30 day extension period), but then considered unexposed for the next 15 days. So if she had a safety event during those 15 days, it wouldn't be included. However after the full 75 days, the patient has a new dispensing – and any safety event occurring after that dispensing within a treatment episode would be counted. The two episodes would be separated with that 15 day gap and would not be concatenated in this scenario as we've currently designed it.

Treatment episodes (ie, person-time classified as exposed to study drugs) will be constructed for each patient by concatenating consecutive dispensings. Treatment episode length for individuals in the concomitant new users of palbociclib and fulvestrant subgroup (Section 8.2.3.1) and concomitant new users of palbociclib and letrozole (Section 8.2.3.2) subgroup will be based on the use of palbociclib alone. For example, if a patient discontinues fulvestrant after six months but continues on palbociclib for three additional months, the treatment episode will continue until the end of the palbociclib use

(nine months). We will separately report the amount of "palbociclib alone" person-time for each of these groups in the analyses.

8.3.2. Outcome Definitions and Assessment

Patients will be followed forward from the index date to the earliest of the following dates:

- End of the current study period (31 September 2017 or latest data available);
- End of continuous health plan enrollment (left health plan or death);
- End of palbociclib (or relevant) treatment episode (Section 8.3.1), except for secondary malignancy endpoint;
- First occurrence of one of the outcomes (safety events) of interest. Note that follow-up for that specific outcome will end but follow-up for other outcomes will continue.

The occurrence of the safety events of interest listed below will be identified in the HIRD using claims-based algorithms. Incident events are of interest, so any individuals with a history of one of the safety events of interest on or prior to the index date will be excluded from the computation of incidence for that specific event. The exceptions will be for common events such as vomiting, fatigue, nausea, and diarrhea, along with pulmonary embolism and related venous thrombotic events in which individuals will be allowed to have a history of these events on or prior to index date to evaluate the occurrence of repeat events during follow-up. Outcomes will be assessed during the follow-up period of the treatment episodes using claims data in the HIRD and will include the following safety events of interest including leukopenia, pulmonary embolism, anemia, and serious infections using claims definitions (Section 8.3.2; Annex 2).

Coding algorithms for identifying the safety events of interest in the HIRD can be found in Annex 2. All counts <10 will reported as "<10" per HealthCore/Anthem guidelines.

- Neutropenia;
- Febrile neutropenia;
- Leukopenia;
- Alopecia;
- Vomiting;
- QT prolongation;
- Fatigue;

- Serious infections:
  - Brain and spinal cord;
  - Pericardial/myocardial;
  - Pulmonary;
  - Gastrointestinal;
  - Genitourinary/renal;
  - Dental;
  - Ear, nose, and throat;
  - Skin, bones, and joints;
  - Influenza infection;
  - Other infections;
- Diarrhea;
- Interstitial lung disease (ILD)/pneumonitis;
- Anemia;
- Nausea;
- Thrombocytopenia;
- Pulmonary embolism:
  - Pulmonary embolism – analyzed as "once treated, always at risk";
- Other venous embolism and thrombosis:
  - Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT);
- Embolism and thrombosis of unspecified artery;
- Cataracts and other ocular disorders;
- Stomatitis and mucositis;

- Fever;
- Anorexia;
- Peripheral neuropathy;
- Diabetes mellitus;
- Hyperglycemia;
- Secondary malignancies (second primary) – will be analyzed once treated, always at risk:
  - Non-melanoma skin cancer;
- Liver function tests (on a subset of patients with laboratory values):
  - ALT – Alanine Transaminase (serum glutamate-pyruvate transaminase [SGPT]);
  - AST – Aspartate Transaminase (serum glutamic oxaloacetic transaminase [SGOT]);
  - ALP – Alkaline Phosphatase;
- Liver failure;
- Sudden cardiac death;
- Ischemic colitis;
- Hepatitis B.

8.3.3. Covariate Definitions and Assessment

Covariates prior to the initiation of palbociclib (or fulvestrant for Secondary Objective 3) including demographics, medical history, cancer therapy history, healthcare utilization, medication use (breast cancer and non-breast cancer related), and co-morbidities will be included in descriptive analysis and these covariates are considered potential confounders and will be considered for inclusion in the propensity score (described in Section 8.7). The presence of these variables will be assessed in the six months on or before the index date. The coding algorithms for a subset of these covariates including the co-morbidities are shown in Annex 2. Other coding algorithms are available upon request.

8.4. Data Sources

The study will be conducted in the HIRD. The HIRD is a broad, clinically rich, and geographically diverse spectrum of longitudinal medical and pharmacy claims data from health plan members across the US. Member enrollment, medical care (professional and facility claims), outpatient prescription drug use, outpatient laboratory test result data, and health care utilization may be tracked for health plan members in the database dating back to January 2006.

The algorithm to be utilized for advanced stage ER+/HER2-breast cancer was validated in study A5481080 using the HIRE Oncology resource. The HIRE Oncology data is an enhancement to the HIRD that includes clinical data pertinent to oncology in a subset of the HIRD's cancer patients. The clinical data in the HIRE Oncology program are obtained by the Cancer Care Quality Program (CCQP), which is a program initiated in the summer of 2014 by the Anthem Inc. health plans, and are shown to be comparable to medical records.[5] The developed claims based algorithm performed well with a PPV of 91% and a sensitivity of 54% at a predictive probability cut-off of 0.70. When utilizing a predictive probability cut-off of 0.50 as planned in this study, the PPV remained high (86%) with a higher sensitivity (68%).[4]

The safety event outcomes will be defined using claims definitions, and will not be validated via medical records in this study. However, they could be validated in follow-up studies.

8.5. Study Size

The study will include eligible patients utilizing palbociclib from 2015 through 2017, and eligible patients utilizing fulvestrant (without palbociclib) from 2011 through 2015. We currently estimate approximately 2,300 patients in HIRD who are new users of palbociclib and approximately 1,600 of them having algorithm-defined advanced stage ER+/HER2-breast cancer (Figure 1). The number of new users be concurrently initiating palbociclib and letrozole is estimated to be approximately 1,000 with approximately 700 having algorithm-defined ER+/HER2-breast cancer. The number of patients treated with fulvestrant (without palbociclib) exceeds the number treated with palbociclib with fulvestrant (n~700) for the Secondary Objective 3 analysis. Thus, we expect after 1:1 propensity score matching (described in Section 8.7.2), we expect ~700 matched patients treated with fulvestrant (without palbociclib).

This study will examine over 40 safety events that vary considerably in prevalence, thus the amount of power available will largely vary depending on the safety event (outcome). This study will not prioritize any pre-specified primary safety events over the other safety events, by noting them as "primary outcomes". Given the large number of outcomes, we expect that at least a few outcomes will be significantly different between new users of palbociclib vs. fulvestrant by chance alone. Multiple comparisons will not be addressed in these analyses, however interpretation of results will note this study as hypothesis generating with mention of the number outcomes and lack of multiple comparison adjustment.

8.6. Data Management

All data management and analyses will be conducted by HealthCore in accordance with their standard operating procedures (SOPs) and guidelines. The investigator records including study database, analytic files, and statistical programming will be documented, stored electronically, and archived, for a minimum of 15 years after completion (eg, completion of the clinical study report [CSR], non-interventional study report or manuscript) 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. De-identified and aggregated results will be reported to Pfizer. All analyses will be completed using Statistical Analysis System (SAS) Enterprise Guide Version 7.4 or higher.

Structurally, HealthCore's Data Coordination Center (DCC) controls access to patient data. The DCC is physically secured by a controlled access facility, with only authorized personnel having access to network servers, tape libraries, and other media that contain patient identifiers. HealthCore's computer networks all have been designed to separate patient identified data from de-identified (or masked) data. Computer files are protected both physically and electronically. Physically, computers with Protected Health Information (PHI) access are located away from regular and high-traffic areas, and protected with cubical walls. Electronically, computer files are protected by computers with password-access only via secured encrypted connections (secure socket layering pages) and automatic, password protected screen savers that will begin running after 10 minutes of inactivity. Computers are locked upon screen saver activation and when personnel leave their workstation. The HealthCore corporate computer systems are protected by company firewalls as well as being physically protected and controlled, with electronic key-activated doors preventing unauthorized personnel from entering any office door.

8.7. Data Analysis

8.7.1. Descriptive Analyses for Primary Objective 1, and Secondary Objective 1 and 2

The distribution of descriptive variables will be described for the total palbociclib and fulvestrant cohorts and separately for each of the subcohorts outlined in Figure 1, including new users of concomitant palbociclib with letrozole. Characteristics including demographics, medical history, imaging, breast cancer treatment patterns, healthcare utilization, co-morbidities and non-breast cancer related medication use identified from claims will be described using measures of central tendency (mean, standard deviation, median, and interquartile range) for continuous variables and frequencies of categorical variables.

Hazard ratios will be computed comparing the risk of each pre-specified safety events between new users of palbociclib with fulvestrant and propensity score matched new users of fulvestrant using Cox proportional hazard regression analysis in the two study cohorts (all users; all users with algorithm-defined advanced stage ER+/HER2-breast cancer). The incidence of the safety events of interest will be computed by dividing the total number of events that are identified by the total at-risk person-time accumulated for all cohort members for that specific event. Only cohort members who do not have any history of one of the

events of interest will contribute to the computation of at-risk person-time for that event (unless otherwise specified). Confidence intervals for the incidence estimates will be computed using methods based on the Poisson distribution. The incidence of the safety events of interest will be presented overall as well as stratified by subgroup of interest.

8.7.2. Propensity Score Adjusted Analyses – Secondary Objective 3

For analyses in Secondary Objective 3, results among patients newly initiating palbociclib with fulvestrant will be compared to patents newly initiating fulvestrant alone (prior to the FDA approval of palbociclib in 2015). Similar to the analyses described in Section 8.7.1, descriptive analyses will be presented for both groups using measures of central tendency for continuous variables and frequencies of categorical variables. Incidence rates of safety events in both groups will be described as in Section 8.7.1. Unadjusted hazard ratios for each safety event comparing palbociclib with fulvestrant new users to fulvestrant only new users will be conducted utilizing Cox proportional hazards regression modeling. The assumptions of the Cox proportional hazards regression models will be assessed by including interaction terms between treatment groups and follow-up time.

Propensity score matching will be utilized to adjust for measured (observed) potential confounders including demographics, medical history, imaging, breast cancer treatment patterns, healthcare utilization, co-morbidities and non-breast cancer related medication. A logistic regression model will be used to identify covariates that are predictors of any of the outcomes of interest for the propensity score. Variables will be included regardless of their measured relation to the exposures, as simulation studies suggest that inclusion of these variables can increase the precision of the estimated effect of the exposure without increasing bias.[6]

The distribution of the propensity scores will be examined graphically and compared between new users of palbociclib and fulvestrant. Patients whose propensity score lies outside the region of overlap will be excluded (trimmed). We will then stratify the propensity score strata in 10 mutually exclusive strata defined by the deciles of the propensity score using the distribution of the palbociclib (with fulvestrant) exposed population. We will consider reducing the number of strata if feasible. Each palbociclib/fulvestrant new user will then be matched to one (1:1) new user of fulvestrant alone by propensity score stratum.[7]

To assess comparability, absolute standardized differences will be computed for each covariate.[8] For continuous variables ($d_{Continuous}$), the absolute standardized difference will be calculated as the absolute value of the difference in the mean of the variable in the palbociclib and fulvestrant groups divided by the pooled standard deviation.

$$d_{Continous} = \left| \frac{\bar{x}_p - \bar{x}_c}{\sqrt{\frac{s_p^2 + s_f^2}{2}}} \right|$$

For categorical variables, the absolute standardized difference ($d_{Categorical}$) will be defined as the absolute value of the difference between the prevalence of each level of the covariate in the palbociclib and fulvestrant groups divided by the pooled standard deviation.

$$d_{Categorical} = \left| \frac{\hat{p}_p - \hat{p}_f}{\sqrt{\frac{\hat{p}_p(1-\hat{p}_p) + \hat{p}_f(1-\hat{p}_f)}{2}}} \right|$$

For any baseline covariates with a standardized difference greater than 0.1, residual differences will be further controlled in the analysis by including the specific variables in the proportional hazards model. A separate propensity score will be calculated within each cohort analysis (all new users and new users restricted to advanced stage ER+/HER2-breast cancer), as described above.

8.8. Quality Control

The study will be tracked at various levels to help ensure that all aspects including project delivery, infrastructure, quality processes, resource management, and financial issues are addressed. To help ensure the highest level of quality on every project, HealthCore has established several layers of quality assurance throughout the project lifecycle.

- Role Based Control Checks: Each member of the team is responsible to perform thorough quality control checks on their work; in addition, the Principal Investigator and Research Project Manager are also accountable for quality of all deliverables.
- Quality Check Points: Centralized "checkpoints" have been implemented during the data management cycle to help ensure accurate translation of programming requests.
- Quality Assurance Standards: Standard review procedures have been developed and are applied throughout the project lifecycle.
- Automation: HealthCore has developed standard definitions of many variables and disease states and developed programs to apply these standards as needed on projects. These standards help ensure consistency, repeatability and accuracy for each project.

HealthCore's research team documents study progress and scientific and quality review of all study activities and deliverables (eg, protocol, data management, data analysis, reports, manuscripts, etc.) in an ADIN (Action, Decision, Issue, Notification) log and in a Quality Control (QC) Log. The ADIN Log provides documentation of study progress, action items, issues/issue resolution, and notifications, and is updated weekly during internal project team meetings. In addition, the QC Log documents the quality control measures performed for each study activity during the conduct of the study.

All programming required for study database extraction and creation of the analytic datasets from the HIRD will be performed in accordance with HealthCore Programming Standards. The HealthCore Programming Standards are a set of documents describing data extraction methods that are referenced in HealthCore SOPs and provide a guideline for basic, frequently used terms and definitions and respective coding information to maintain operational consistency. Data validation will occur throughout the data management and analysis process. Data quality checks include, but are not limited to, programming checks by an individual who is not the main programmer for the study, internal dataset consistency, and checks to ensure that Protocol criteria were met. If validation checks are not satisfied then an examination of the problem will be performed on the dataset or datasets in question and the problem resolved.

8.9. Limitations of the Research Methods

8.9.1. Lack of Validated Outcomes

There are several limitations to our approach. The safety events (outcomes) of interest will be identified using diagnosis and procedure codes in the HIRD and the accuracy of this approach is unknown. It is possible that this approach will lead to the identification of safety events that are false positives. The current study does not include medical record review to validate the safety events of interest but this could be considered as part of a subsequent study. For select outcomes, we will include sensitive and specific definitions of the outcome to provide a range of potential rates for that outcome.

8.9.2. Multiple Comparisons (Outcomes)

We also examine over 40 safety event outcomes in this study, without specifying any primary outcomes. Thus, by chance alone we expect at least a few of the outcomes to be higher than expected and/or associated with palbociclib with fulvestrant exposure. Multiple comparisons will not be addressed in these analyses, however interpretation of results will note this study as hypothesis generating with mention of the number outcomes and lack of multiple comparison adjustment.

8.9.3. Unmeasured Confounding

For Secondary Objective 3, the adjustment for confounding will be addressed via propensity score matching. The propensity scores will be estimated based only on covariates measured at baseline and thus will not account for changes that may arise during the follow-up period. While propensity scores have demonstrated the ability to control for numerous measured confounders, they cannot control for confounding from unmeasured or unknown factors that are not available in claims (such as body mass index and smoking status).

8.9.4. Generalizability

Compared with the general population, coverage of the HIRD is skewed towards younger ages and the representativeness of the HIRD for individuals aged 65 years and older is unknown. Since breast cancer incidence increases with age the population of ER+/HER2-patients identified in the HIRD may not be representative of the general population of palbociclib or fulvestrant users. As with any study, this study conducted in the HIRD will be most generalizable to similar commercial data sources, and generalizability to other data sources is uncertain.

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

HealthCore maintains Data Sharing Agreements (DSAs) and Business Associate Agreements with covered entities that provide PHI incorporated into the HIRD. HealthCore's access, use, and disclosure of PHI are in compliance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule [45 Code of Federal Register (CFR) Part 160 and Subparts A and E of Part 164]. HealthCore does not access, use, or disclose PHI other than as permitted by HIPAA and its Business Associate Agreements. When using PHI for research, this typically means PHI will be used to create limited data sets for research, or when that is not feasible we may obtain a specific waiver of the HIPAA authorization requirements from an institutional review board (IRB). HealthCore also takes into consideration other federal and state laws and regulations that might limit use of certain types of data more than HIPAA, including those laws related to identifiable records related to substance abuse and human immunodeficiency virus (HIV).

The current study is designed as an analysis based on medical and pharmacy claims data from a large insured population in the US. There is no active enrollment or active follow-up of study subjects, and no data will be collected directly from individuals. The HIPAA Privacy Rule permits PHI in a limited data set to be used or disclosed for research, without individual authorization, if certain criteria are met (further described 45 CFR Part 160 and Subparts A and E of Part 164). Thus informed consent and IRB review is not required.

At no time during the conduct of this study will HealthCore provide individual or provider identifying information to the Sponsor. De-identified aggregated results will be reported to Pfizer, Inc. Pfizer will not attempt to re-identify any results provided for the study.

9.2. Patient Withdraw

Not applicable.

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

Institutional Review Board approval is not required in this study, as described in Section 9.1.

9.4. 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 Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study includes unstructured data (eg, narrative fields in the database) that will be converted to structured (ie, coded) data solely by a computer using automated/algorithmic methods and/or data that already exist as structured data in an electronic database. In these data sources, it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (ie, identifiable patient, identifiable reporter, a suspect product, and event) are not available and AEs are not reportable as individual AE reports.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The deliverables for this study include a Protocol (one draft and one final version) and a Final Report including study results in table format. The Final Report will summarize the study design, objectives, results and discussion. Two drafts and one final version of the Final Report will be provided. Additional deliverables include one manuscript for submission to a peer-reviewed journal and one abstract for submission to a national conference.

COMMUNICATION OF ISSUES

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 NI study protocol that the investigator becomes aware of.

12. REFERENCES

1. Administration, U.S.F.D. *Palbociclib (IBRANCE)*. 2017; Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm549978.htm.

2. Turner, N.C., et al., *Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer.* N Engl J Med, 2015. **373**(3): p. 209-19.

3. Finn, R.S., et al., *Palbociclib and Letrozole in Advanced Breast Cancer.* N Engl J Med, 2016. **375**(20): p. 1925-1936.

4. Beachler, D.C.Y., R.; Cochetti, P.T.; Jemison, J.; Gangemi, K.; de Luise, C.; Lanes, S.; *Identifying breast cancer stage and ER/HER2 status in claims data using predictive models*, in *33rd International Conference of Pharmacoepidemiology and Therapeutic Risk Management (ICPE)*. 2017: Montreal, CA.

5. Kern, D.M., et al., *A validation of clinical data captured from a novel Cancer Care Quality Program directly integrated with administrative claims data.* Pragmat Obs Res, 2017. **8**: p. 149-155.

6. Brookhart, M.A., et al., *Variable selection for propensity score models.* Am J Epidemiol, 2006. **163**(12): p. 1149-56.

7. Austin, P.C., *An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies.* Multivariate Behav Res, 2011. **46**(3): p. 399-424.

8. Austin, P.C., *Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples.* Stat Med, 2009. **28**(25): p. 3083-107.

13. LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Code list for medications of interest in the HIRD

Drug Name	GPI Code	HCPCS Code
Palbociclib	21531060x	NA
Hormone Therapies		
Letrozole	21402860x	NA
Anastrazole	21402810x	S0170
Exemestane	21402835x	S1056
HER2+ Therapies		
Trastuzumab	21353070x	J9355
Lapatinib	21534050x	NA
Ado-Trastuzumab	21355070x	J9354
Other Common ER+/HER2- Therapies		
Fulvestrant	21403530x	J9395
Tamoxifen	21402680x	S0187

Code list for identifying the safety events of interest in the HIRD

Note: All events were identified based on at least one inpatient hospitalization with the diagnosis code of interest OR two outpatient visits (including emergency department visits) on separate dates with one of the diagnosis codes of interest. The event date was defined as the second service date for a qualifying event for those requiring two visits.

Safety event of interest	ICD-9-CM diagnosis code	ICD-10 diagnosis code
Neutropenia (sensitive)*	288.00 (neutropenia, unspecified) 288.02 (cyclic neutropenia) 288.03 (drug-induced neutropenia) 288.09 (other neutropenia)	D701 D702 D704 D708 D709
Neutropenia (specific – drug induced only)*	288.03 (drug-induced neutropenia)	D701 D702
Febrile neutropenia (sensitive)*	Meets the definition for neutropenia (sensitive) specified above AND has a medical claim indicating fever on the same date: 780.60 (fever, unspecified) 780.61 (fever presenting with conditions classified elsewhere)	Meets the definition for neutropenia (sensitive) specified above AND has a medical claim indicating fever on the same date: R509 R502 R5081
Febrile neutropenia (specific – drug induced only)*	Meets the definition for neutropenia (specific) specified above AND has a medical claim indicating fever on the same date: 780.60 (fever, unspecified) 780.61 (fever presenting with conditions classified elsewhere)	Meets the definition for neutropenia (specific) specified above AND has a medical claim indicating fever on the same date: R509 R502 R5081
Leukopenia (sensitive)*	288.5x (decreased white blood cell count)	D72810 D72818 D72819
Leukopenia (specific)*	288.50, 288.59	D72818 D72819
Anemia (sensitive)*	280.xx (iron deficiency anemias) 281.xx (other deficiency anemias) 283.xx (acquired hemolytic anemia) 284.xx (aplastic anemia and other bone marrow	D500, D501, D508, D509, D510, D511, D513, D518, D520, D521, D528, D529, D530, D531, D532, D538, D539, D590, D591, D593, D594, D595, D596, D598, D599, D600, D601, D608, D609, D6101, D6109, D611,

Safety event of interest	ICD-9-CM diagnosis code	ICD-10 diagnosis code
	failure syndromes) 285.xx (other and unspecified anemias)	D612, D6181, D61810, D61811, D61818, D6182, D6189, D619, D62, D630, D631, D638, D640, D641, D642, D643, D644, D6481, D6489, D649, D512, D592, D613
Anemia (specific)*	281.3, 281.4, 284.89, 284.1, 284.11, 284.12, 284.19, 284.2, 284.9, 285.22, 285.3	D530, D531,, D611, D612, D6181, D61810, D61811, D61818, D6182, D6189, D619, D630, D6481,
Pulmonary embolism*	415.11, 415.13, 415.19	I2692, I2699, I2602, I2609
Alopecia	704.00 (alopecia, unspecified) 704.09 (other alopecia)	L658, L659, L660, L662, L668, L630, L631, L640, L648, L649, L651, L652, L669
Vomiting	787.01 (nausea with vomiting) 787.03 (vomiting alone)	R1110, R1111, R1112, R112
QT prolongation	426.82 (long QT syndrome) 427.1x (paroxysmal ventricular tachycardia) 427.4x (ventricular fibrillation and flutter) 427.5x (cardiac arrest) 427.9x (cardiac dysrhythmia, unspecified) 780.2x (syncope and collapse)	I4581, I469, I472, I4901, I4902, I499, R55, I462, I468, I470, I493
Fatigue	780.71 (chronic fatigue syndrome) 780.79 (other malaise and fatigue)	G933, R531, R5381, R5382, R5383, R530
Serious Infection	Assume any of the specific infections below that occur at an inpatient hospitalization or emergency department visit	
Infections		
Brain and spinal cord	320.xx (bacterial meningitis) 321.xx (meningitis due to other organisms) 323.xx (encephalitis myelitis and encephalomyelitis) 324.xx (intracranial and intraspinal abscess)	B451, G000, G001, G002, G003, G008, G009, G01, G02, G0400, G0401, G042, G0430, G0431, G0432, G0439, G0481, G0489, G090, G091, G053, G054, G060, G061, G062, G092, G92, G07, G374
Pericardial/Myocardial	420.91 (acute idiopathic pericarditis) 422.92 (septic myocarditis)	I300, I400
Pulmonary*	491.22 (obstructive chronic bronchitis with acute bronchitis) 493.21(chronic obstructive asthma with status asthmaticus) 480.xx (viral pneumonia) 481.xx (pneumococcal pneumonia) 482.xx (other bacterial pneumonia)	B250, B440, J10.0%, J12.%, J13, J14, J15.%, J16.%, J17, J18.%, J20.%, J85.%

Safety event of interest	ICD-9-CM diagnosis code	ICD-10 diagnosis code
	483.xx (pneumonia due to other specified organism) 484.xx (pneumonia in infectious diseases classified elsewhere) 485.xx (bronchopneumonia, organism unspecified) 486.xx (pneumonia, organism unspecified) 487.0x (influenza with pneumonia) 513.0x (abscess of lung) 510.xx empyema	
Gastrointestinal	566.xx (abscess of anal and rectal regions) 567.2x (other suppurative peritonitis) 567.9 (unspecified peritonitis)	K610, K611, K613, K650, K651, K652, K659, K50014, K50114, K50814, K50914, K612, K614,
Genitourinary/Renal	112.2x (candidiasis of other urogenital sites) 583.9x (nephritis and nephropathy, not specified as acute or chronic, with unspecified pathologic lesion in kidney) 590.xx (infections of kidney) 595.0x (acute cystitis) 595.3x (trigonitis) 595.4x (cystitis in diseases classified elsewhere) 595.89 (other specified types of cystitis) 595.9x (cystitis, unspecified) 597.0x (urethral abscess) 597.80 (urethritis, unspecified) 599.0x (urinary tract infection, site not specified) 614.xx (inflammatory disease of ovary fallopian tube pelvic tissue and peritoneum) 616.3x (abscess of Bartholin's gland) 996.64 (infection and inflammatory reaction to indwelling urinary catheter)	N059, N10, N110, N118, N12, N151, N159, N16, N2884, N2885, N2886, N3000, N3001, N3030, N3031, N3080, N3081, N3090, N3091, N340, N341,N342, N390, N7001, N7002, N7003, N7011, N7012, N7013, N7091, N7092, N7093, N730, N731, N732, N733, N734, N736, N738, N739, N751, T8351XA, T8351XD, A5601, A5611, B3741, N069, N079, N111, N119, N136, N735, N74
Dental	522.4x (acute apical periodontitis of pulpal origin) 522.5x (periapical abscess without sinus) 522.7x (periapical abscess with sinus)	K044, K046, K047
Ear, Nose and Throat	380.10 (infective otitis externa, unspecified) 382.xx (suppurative and unspecified otitis media)	H6000, H6010, H60319, H60329, H60399, H66009,

Safety event of interest	ICD-9-CM diagnosis code	ICD-10 diagnosis code
	383.0x (acute mastoiditis) 383.9x (unspecified mastoiditis) 460.xx (acute nasopharyngitis) 461.xx (acute sinusitis) 462.xx (acute pharyngitis) 473.0x (chronic maxillary sinusitis) 475.xx (peritonsillar abscess) 478.19 (other disease of nasal cavity and sinuses) 478.5x (other diseases of vocal cords) 478.21 (cellulitis of pharynx or nasopharynx) 478.22 (parapharyngeal abscess) 478.24 (retropharyngeal abscess) 527.3x (abscess of salivary gland) 528.00 (stomatitis and mucositis, unspecified) 528.3x (cellulitis and abscess of oral soft tissues) 529.0x (glossitis)	H66019, H6613, H6623, H663X9, H6640, H6690, H679, H70009, H70019, H70099, H7090, J00, J0100, J0110, J0120, J0130, J0140, J0190, J029, J320, J340, J341, J3489, J36, J390, J391, K113, K122, K1230, K140, H6001, H6002, H6003, H6011, H6012, H6013, H60311, H60312, H60313, H60321, H60322, H60323, H60391, H60392, H60393, H66001, H66002, H66003, H66004, H66005, H66006, H66007, H66011, H66012, H66013, H66014, H66015, H66016, H66017, H6610, H6611, H6612, H6620, H6621, H6622, H663X1, H663X2, H663X3, H6641, H6642, H6643, H6691, H6692, H6693, H671, H672, H673, H70001, H70002, H70003, H70011, H70012, H70013, H70091, H70092, H70093, H7091, H7092, H7093, J0101, J0111, J0121, J0131, J0141, J0180, J0181, J0191, J028, J349, R0981
Skin, Bones and Joints	680.xx (carbuncle and furuncle) 681.xx (cellulitis and abscess of finger and toe) 682.xx (other cellulitis and abscess) 683.xx (acute lymphadenitis) 684.xx (impetigo) 685.xx (pilonidal cyst) 686.xx (other local infections of skin and subcutaneous tissue)	A1801, A1802, B781, E832, K122, L0100, L0101, L0102, L0103, L0109, L011, L0201, L0202, L0203, L0211, L0212, L0213, L02211, L02212, L02213, L02214, L02215, L02216, L02219, L02221, L02222, L02223, L02224, L02225, L02226, L02229, L02231, L02232, L02233, L02234, L02235, L02236, L02239, L0231, L0232, L0233, L02411, L02412, L02413, L02414, L02415, L02416, L02419, L02421, L02422, L02423,

Safety event of interest	ICD-9-CM diagnosis code	ICD-10 diagnosis code
	690.8x (other erythematosquamous dermatosis) 711.xx (arthropathy associated with infections) 720.81 (inflammatory spondylopathies in diseases classified elsewhere) 728.0x (infective myositis) 727.89 (other disorders of synovium, tendon, and bursa) 728.86 (necrotizing fasciitis) 730.0x (acute osteomyelitis)	L02424, L02425, L02426, L02429, L02431, L02432, L02433, L02434, L02435, L02436, L02439, L02511, L02512, L02519, L02521, L02522, L02529, L02531, L02532, L02539, L02611, L02612, L02619, L02621, L02622, L02629, L02631, L02632, L02639, L02811, L02818, L02821, L02828, L02831, L02838, L0291, L0292, L0293, L03011, L03012, L03019, L03021, L03022, L03029, L03031, L03032, L03039, L03041, L03042, L03049, L03111, L03112, L03113, L03114, L03115, L03116, L03119, L03121, L03122, L03123, L03124, L03125, L03126, L03129, L03211, L03212, L03221, L03222, L03311, L03312, L03313, L03314, L03315, L03316, L03317, L03319, L03321, L03322, L03323, L03324, L03325, L03326, L03327, L03329, L03811, L03818, L03891, L03898, L0390, L0391, L040, L041, L042, L043, L048, L049, L0501, L0502, L0591, L0592, L080, L0881, L0882, L0889, L089, L303, L88, L928, L980, L983, M0000, M00011, M00012, M00019, M00021, M00022, M00029, M00031, M00032, M00039, M00041, M00042, M00049, M00051, M00052, M00059, M00061, M00062, M00069, M00071, M00072, M00079, M0008, M0009, M0010, M00111, M00112, M00119, M00121, M00122, M00129, M00131, M00132, M00139, M00141, M00142, M00149, M00151, M00152, M00159, M00161, M00162, M00169, M00171, M00172, M00179, M0018, M0019, M0020, M00211, M00212, M00219, M00221, M00222, M00229, M00231, M00232, M00239, M00241, M00242, M00249, M00251, M00252, M00259, M00261, M00262, M00269, M00271, M00272, M00279, M0028, M0029, M0080, M00811, M00812, M00819, M00821, M00822, M00829, M00831, M00832, M00839, M00841, M00842, M00849, M00851, M00852, M00859, M00861, M00862, M00869, M00871, M00872, M00879, M0088, M0089, M009, M01X0, M01X11, M01X12, M01X19, M01X21, M01X22, M01X29, M01X31, M01X32, M01X39, M01X41, M01X42, M01X49, M01X51, M01X52, M01X59, M01X61, M01X62, M01X69, M01X71, M01X72, M01X79, M01X8, M01X9,

Safety event of interest	ICD-9-CM diagnosis code	ICD-10 diagnosis code
		M0210, M02111, M02112, M02119, M02121, M02122, M02129, M02131, M02132, M02139, M02141, M02142, M02149, M02151, M02152, M02159, M02161, M02162, M02169, M02171, M02172, M02179, M0218, M0219, M0230, M02311, M02312, M02319, M02321, M02322, M02329, M02331, M02332, M02339, M02341, M02342, M02349, M02351, M02352, M02359, M02361, M02362, M02369, M02371, M02372, M02379, M0238, M0239, M0280, M02811, M02812, M02819, M02821, M02822, M02829, M02831, M02832, M02839, M02841, M02842, M02849, M02851, M02852, M02859, M02861, M02862, M02869, M02871, M02872, M02879, M0288, M0289, M352, M4980, M4981, M4982, M4983, M4984, M4985, M4986, M4987, M4988, M4989, M60000, M60001, M60002, M60003, M60004, M60005, M60009, M60011, M60012, M60019, M60021, M60022, M60029, M60031, M60032, M60039, M60041, M60042, M60043, M60044, M60045, M60046, M60051, M60052, M60059, M60061, M60062, M60069, M60070, M60071, M60072, M60073, M60074, M60075, M60076, M60077, M60078, M6008, M6009, M6500, M65011, M65012, M65019, M65021, M65022, M65029, M65031, M65032, M65039, M65041, M65042, M65049, M65051, M65052, M65059, M65061, M65062, M65069, M65071, M65072, M65079, M6508, M6720, M67211, M67212, M67219, M67221, M67222, M67229, M67231, M67232, M67239, M67241, M67242, M67249, M67251, M67252, M67259, M67261, M67262, M67269, M67271, M67272, M67279, M6728, M6729, M6780, M67811, M67812, M67813, M67814, M67819, M67821, M67822, M67823, M67824, M67829, M67831, M67832, M67833, M67834, M67839, M67841, M67842, M67843, M67844, M67849, M67851, M67852, M67853, M67854, M67859, M67861, M67862, M67863, M67864, M67869, M67871, M67872, M67873, M67874, M67879, M6788, M6789, M7100, M71011, M71012, M71019, M71021, M71022, M71029, M71031, M71032, M71039, M71041, M71042, M71049, M71051, M71052, M71059, M71061, M71062, M71069, M71071, M71072, M71079,

Safety event of interest	ICD-9-CM diagnosis code	ICD-10 diagnosis code
		M7108, M7109, M7180, M71811, M71812, M71819, M71821, M71822, M71829, M71831, M71832, M71839, M71841, M71842, M71849, M71851, M71852, M71859, M71861, M71862, M71869, M71871, M71872, M71879, M7188, M7189, M726, M8600, M86011, M86012, M86019, M86021, M86022, M86029, M86031, M86032, M86039, M86041, M86042, M86049, M86051, M86052, M86059, M86061, M86062, M86069, M86071, M86072, M86079, M8608, M8609, M8610, M86111, M86112, M86119, M86121, M86122, M86129, M86131, M86132, M86139, M86141, M86142, M86149, M86151, M86152, M86159, M86161, M86162, M86169, M86171, M86172, M86179, M8618, M8619, M8620, M86211, M86212, M86219, M86221, M86222, M86229, M86231, M86232, M86239, M86241, M86242, M86249, M86251, M86252, M86259, M86261, M86262, M86269, M86271, M86272, M86279, M8628, M8629
Hepatitis B	070.2x (viral hepatitis B with hepatic coma) 070.3x (viral hepatitis B without mention of hepatic coma)	B160, B161, B162, B169, B180, B181, B1910, B1911
Influenza	487.xx (influenza) 488.xx (influenza due to certain identified influenza viruses)	J09019, J0902, J0903, J09090, J09098, J09119, J0912, J0913, J09190, J09198, J09X1, J09X2, J09X3, J09X9, J1008, J101, J1100, J111, J112, J1181, J1189, J129, J09010, J09018, J09091, J09092, J09110, J09118, J09191, J09192, J1000, J1001, J102, J1081, J1082, J1083, J1089, J1108, J1182, J1183
Other infections	001.xx- to 139.xx (infectious and parasitic diseases) 245.0x (acute thyroiditis) 254.1x (abscess of thymus) 360.00 (purulent endophthalmitis) 611.0x (inflammatory disease of breast)	A000, A001, A009, A0100, A0101, A0102, A0103, A0104, A0105, A0109, A011, A012, A013, A014, A020, A021, A0220, A0221, A0222, A0223, A0224, A0225, A0229, A028, A029, A030, A031, A032, A033, A038, A039, A040, A041, A042, A043, A044, A045, A046, A047, A048, A049, A050, A051, A052, A053, A054, A055, A058, A059, A060, A061, A062, A063, A064, A065, A066, A067, A0681, A0682, A0689, A069, A070, A071, A072, A073, A074, A078, A079, A080, A0811, A0819, A082, A0831, A0832, A0839, A084, A088, A09, A150, A154, A155, A156, A157, A158, A159, A170,

Safety event of interest	ICD-9-CM diagnosis code	ICD-10 diagnosis code
		A171, A1781, A1782, A1783, A1789, A179, A1801, A1802, A1803, A1809, A1810, A1811, A1812, A1813, A1814, A1815, A1816, A1817, A1818, A182, A1831, A1832, A1839, A184, A1850, A1851, A1852, A1853, A1854, A1859, A186, A187, A1881, A1882, A1883, A1884, A1885, A1889, A190, A191, A192, A198, A199, A200, A201, A202, A203, A207, A208, A209, A210, A211, A212, A213, A217, A218, A219, A220, A221, A222, A227, A228, A229, A230, A231, A232, A233, A238, A239, A240, A241, A242, A243, A249, A250, A251, A259, A260, A267, A268, A269, A270, A2781, A2789, A279, A280, A281, A282, A288, A289, A300, A301, A302, A303, A304, A305, A308, A309, A310, A311, A312, A318, A319, A320, A3211, A3212, A327, A3281, A3282, A3289, A329, A35, A360, A361, A362, A363, A3681, A3682, A3683, A3684, A3685, A3686, A3689, A369, A3700, A3701, A3710, A3711, A3780, A3781, A3790, A3791, A380, A381, A388, A389, A390, A391, A392, A393, A394, A3950, A3951, A3952, A3953, A3981, A3982, A3983, A3984, A3989, A399, A400, A401, A403, A408, A409, A410, A4101, A4102, A411, A412, A413, A414, A4150, A4151, A4152, A4153, A4159, A4181, A4189, A419, A420, A421, A422, A427, A4281, A4282, A4289, A429, A430, A431, A438, A439, A440, A441, A448, A449, A46, A480, A482, A483, A484, A4851, A4852, A488, A490, A4901, A4902, A491, A492, A493, A498, A499, A5001, A5002, A5003, A5004, A5005, A5006, A5007, A5008, A5009, A501, A502, A5030, A5031, A5032, A5039, A5040, A5041, A5042, A5043, A5044, A5045, A5049, A5051, A5052, A5053, A5054, A5055, A5056, A5057, A5059, A506, A507, A509, A510, A511, A512, A5131, A5132, A5139, A5141, A5142, A5143, A5144, A5145, A5146, A5149, A515, A519, A5200, A5201, A5202, A5203, A5204, A5205, A5206, A5209, A5210, A5211, A5212, A5213, A5214, A5215, A5216, A5217, A5219, A522, A523, A5271, A5272, A5273, A5274, A5275, A5276, A5277, A5278, A5279, A528, A529, A530, A539, A5400, A5401, A5402,

Safety event of interest	ICD-9-CM diagnosis code	ICD-10 diagnosis code
		A5403, A5409, A541, A5421, A5422, A5423, A5424, A5429, A5430, A5431, A5432, A5433, A5439, A5440, A5441, A5442, A5443, A5449, A545, A546, A5481, A5482, A5483, A5484, A5485, A5486, A5489, A549, A55, A5600, A5601, A5602, A5609, A5611, A5619, A562, A563, A564, A568, A57, A58, A5900, A5901, A5902, A5903, A5909, A598, A599, A6000, A6001, A6002, A6003, A6004, A6009, A601, A609, A630, A638, A64, A65, A660, A661, A662, A663, A664, A665, A666, A667, A668, A669, A670, A671, A672, A673, A679, A680, A681, A689, A690, A691, A6920, A6921, A6922, A6923, A6929, A698, A699, A70, A710, A711, A719, A740, A7481, A7489, A749, A750, A751, A752, A753, A759, A770, A771, A772, A773, A7740, A7741, A7749, A778, A779, A78, A790, A791, A7981, A7989, A799, A800, A801, A802, A8030, A8039, A804, A809, A8100, A8101, A8109, A811, A812, A8181, A8182, A8183, A8189, A819, A820, A821, A829, A830, A831, A832, A833, A834, A835, A836, A838, A839, A840, A841, A848, A849, A850, A851, A852, A858, A86, A870, A871, A872, A878, A879, A880, A881, A888, A89, A90, A91, A920, A921, A922, A9230, A9231, A9232, A9239, A924, A928, A929, A930, A931, A932, A938, A94, A950, A951, A959, A960, A961, A962, A968, A969, A980, A981, A982, A983, A984, A985, A988, A99, B000, B001, B002, B003, B004, B0050, B0051, B0052, B0053, B0059, B007, B0081, B0082, B0089, B009, B010, B0111, B0112, B012, B0181, B0189, B019, B020, B021, B0221, B0222, B0223, B0224, B0229, B0230, B0231, B0232, B0233, B0234, B0239, B027, B028, B029, B03, B04, B050, B051, B052, B053, B054, B0581, B0589, B059, B0600, B0601, B0602, B0609, B0681, B0682, B0689, B069, B070, B078, B079, B08010, B08011, B0802, B0803, B0804, B0809, B081, B0820, B0821, B0822, B083, B084, B085, B0860, B0861, B0862, B0869, B0870, B0871, B0872, B0879, B088, B09, B1001, B1009, B1081, B1082, B1089, B150, B159, B160, B161, B162, B169, B170, B1710, B1711, B172, B178, B179, B180, B181, B182, B188, B189, B190, B1910,

Safety event of interest	ICD-9-CM diagnosis code	ICD-10 diagnosis code
		B1911, B1920, B1921, B199, B20, B250, B251, B252, B258, B259, B260, B261, B262, B263, B2681, B2682, B2683, B2684, B2685, B2689, B269, B2700, B2701, B2702, B2709, B2710, B2711, B2712, B2719, B2780, B2781, B2782, B2789, B2790, B2791, B2792, B2799, B300, B301, B302, B303, B308, B309, B330, B331, B3320, B3321, B3322, B3323, B3324, B333, B334, B338, B340, B341, B342, B343, B344, B348, B350, B351, B352, B353, B354, B355, B356, B358, B359, B360, B361, B362, B363, B368, B369, B370, B371, B372, B373, B3741, B3742, B3749, B375, B376, B377, B3781, B3782, B3783, B3784, B3789, B379, B380, B381, B382, B383, B384, B387, B3881, B3889, B389, B390, B391, B392, B393, B394, B395, B399, B400, B401, B402, B403, B407, B4081, B4089, B409, B410, B417, B418, B419, B420, B421, B427, B4281, B4282, B4289, B429, B430, B431, B432, B438, B439, B440, B441, B442, B447, B4489, B449, B450, B451, B452, B453, B457, B458, B459, B460, B461, B462, B463, B464, B465, B468, B469, B470, B471, B479, B480, B481, B482, B483, B484, B488, B49, B500, B508, B509, B510, B518, B519, B520, B528, B529, B530, B531, B538, B54, B550, B551, B552, B559, B560, B561, B569, B570, B571, B572, B5730, B5731, B5732, B5739, B5740, B5741, B5742, B5749, B575, B5800, B5801, B5809, B581, B582, B583, B5881, B5882, B5883, B5889, B589, B59, B600, B6010, B6011, B6012, B6013, B6019, B602, B608, B64, B650, B651, B652, B653, B658, B659, B660, B661, B662, B663, B664, B665, B668, B669, B670, B671, B672, B6731, B6732, B6739, B674, B675, B6761, B6769, B677, B678, B6790, B6799, B680, B681, B689, B690, B691, B6981, B6989, B699, B700, B701, B710, B711, B718, B719, B72, B7300, B7301, B7302, B7309, B731, B740, B741, B742, B743, B744, B748, B749, B75, B760, B761, B768, B769, B770, B7781, B7789, B779, B780, B787, B789, B79, B80, B810, B811, B812, B813, B814, B818, B820, B829, B830, B831, B832, B833, B834, B838, B839, B850, B851, B852, B853, B854, B86, B870, B871, B872, B873, B874, B8781, B8782, B8789, B879,

Safety event of interest	ICD-9-CM diagnosis code	ICD-10 diagnosis code
		B880, B881, B882, B883, B888, B889, B89, B900, B901, B902, B908, B909, B91, B92, B940, B941, B942, B948, B949, B950, B951, B952, B953, B954, B955, B956, B9561, B9562, B957, B958, B960, B961, B962, B9620, B9621, B9622, B9623, B9629, B963, B964, B965, B966, B967, B9681, B9682, B9689, B970, B9710, B9711, B9712, B9719, B9721, B9729, B9730, B9731, B9732, B9733, B9734, B9735, B9739, B974, B975, B976, B977, B9781, B9789, B998, B999, D860, D861, D862, D863, D8681, D8682, D8683, D8684, D8685, D8686, D8687, D8689, D869, E060, E321, G02, G032, G14, H32, H44001, H44002, H44003, H44009, I32, I39, I673, J020, J0300, J0301, J17, J200, J201, J202, J203, J204, J205, J206, J207, K9081, L081, L444, L946, M0010, M00111, M00112, M00119, M00121, M00122, M00129, M00131, M00132, M00139, M00141, M00142, M00149, M00151, M00152, M00159, M00161, M00162, M00169, M00171, M00172, M00179, M0018, M0019, M0230, M02311, M02312, M02319, M02321, M02322, M02329, M02331, M02332, M02339, M02341, M02342, M02349, M02351, M02352, M02359, M02361, M02362, M02369, M02371, M02372, M02379, M0238, M0239, M352, M60009, N341, N61, NO DX, R1111, Z16
Diarrhea	787.91 (Diarrhea)	K522, K5289, R197
Interstitial lung disease (ILD)/ Pneumonitis	415.11 (iatrogenic pulmonary embolism and infarction) 486.xx (pneumonia, organism unspecified) 515.xx (postinflammatory pulmonary fibrosis), 508.8x (respiratory conditions due to other specified external agents) 508.9x (respiratory conditions due to unspecified external agent) 511.0x (pleurisy without mention of effusion or current tuberculosis) 511.1x (pleurisy with effusion, with mention of bacterial cause other than tuberculosis)	I2690, I2699, J189, J708, J709, J80, J82, J840, J8409, J841, J8410, J84111, J84112, J84113, J84114, J84115, J84116, J84117, J842, J848, J8489, J849, J869, J90, J918, J941, J942, J948, J949, R091, T800XXA, T800XXD, T81718A, T81718D, T8172XA, T8172XD,

Safety event of interest	ICD-9-CM diagnosis code	ICD-10 diagnosis code
	511.89 (other specified forms of effusion, except tuberculosis) 511.9x (unspecified plural effusion) 516.3x (idiopathic interstitial pneumonia) 516.8x (other specified alveolar and parietoalveolar pneumonopathies) 516.9x (unspecified alveolar and parietoalveolar pneumonopathy) 518.3x (pulmonary eosinophilia) 518.82 (other pulmonary insufficiency, not elsewhere classified)	T82817A, T82817D, T82818A, T82818D, J188, J702, J703, J704, J8417, J920, J929, J940
Ischemic colitis	557.xx (vascular insufficiency of intestine) within three months of a colonoscopy (CPT codes 45378-45387; ICD-9-CM procedure 45.23, 45.25) or colectomy (CPT codes 44140-44160; ICD-9-CM procedure 45.7x, 45.8x) AND none of the following alternative diagnoses: 558.9x (non-infectious gastroenteritis and colitis) Crohn's disease (555.xx) Ulcerative colitis (556.xx) Clostridium dificile enteritis (008.45)	K55% (vascular insufficiency of intestine) within three months of a colonoscopy (CPT codes 45378-45387; ICD-10-CM procedure codes: 0DJD8ZZ, 0D9EZX, 0D9E4ZX, 0D9E7ZX, 0D9F%, 0D9G%, 0D9H%, 0D9K%, 0D9L%, 0D9M%, 0D9N%, 0DB%) or colectomy (CPT codes 44140-44160; ICD-10-CM procedure 0DT%, ODB%) AND none of the following alternative diagnoses: K52% (non-infectious gastroenteritis and colitis) Crohn's disease (K50%) Ulcerative colitis (K51%) Clostridium dificile enteritis (A04.7)
Nausea	787.02 (nausea alone) 787.01 (nausea with vomiting)	R110, R112
Thrombocytopenia	287.1x (qualitative platelet defects) 287.4x (secondary thrombocytopenia) 287.5x (thrombocytopenia, unspecified) 287.3x (primary thrombocytopenia)	D473, D691, D693, D6941, D6942, D6949, D6951, D696
Other venous embolism and thrombosis*	451.xx (phlebitis and thrombophlebitis) 453.xx (other venous embolism and thrombosis)	*I82.%*
Acute venous embolism and thrombosis of deep vessels of lower extremity **(DVT)**	453.4x (acute venous embolism and thrombosis of deep vessels of lower extremity)	I82409, I82401, I82402, I82403, I82419, I82429, I82439, I824Y9, I82411, I82412, I82413, I82421, I82422, I82423, I82431, I82432, I82433, I824Y1, I824Y2, I824Y3, I82449, I82499, I824Z9, I82441, I82442, I82443,

Safety event of interest	ICD-9-CM diagnosis code	ICD-10 diagnosis code
		I82491, I82492, I82493, I824Z1, I824Z2,I824Z3
Chronic venous embolism and thrombosis of deep vessels of lower extremity	453.5x (chronic venous embolism and thrombosis of deep vessels of lower extremity)	I82509, I82599, I82501, I82502, I82503, I82591, I82592, I82593, I82519, I82529, I82539, I825Y9, I82511, I82512, I82513, I82521, I82522, I82523, I82531, I82532, I82533, I825Y1, I825Y2, I825Y3, I82549, I825Z9, I82541, I82542, I82543, I825Z1, I825Z2, I825Z3
Venous embolism and thrombosis of superficial vessels of lower extremity	453.6x (venous embolism and thrombosis of superficial vessels of lower extremity)	I82811, I82812, I82813, I82819
Chronic venous embolism and thrombosis of other specified vessels	453.7x (chronic venous embolism and thrombosis of other specified vessels)	I82719, I82711, I82712, I82713, I82729, I82721, I82722, I82723, I82709, I82701, I82702, I82703, I82A29, I82A21, I82A22, I82A23, I82B29, I82B21, I82B22, I82B23, I82C29, I82C21, I82C22, I82C23, I82291, I82211, I82891
Acute venous embolism and thrombosis of other specified veins	453.8x (acute venous embolism and thrombosis of other specified veins)	I82609, I82619, I82629, I82890, I82A19, I82B19, I82C19, I82210, I82601, I82602, I82603, I82611, I82612, I82613, I82621, I82622, I82623, I8290, I82A11, I82A12, I82A13, I82B11, I82B12, I82B13, I82C11, I82C12, I82C13
Other venous embolism and thrombosis of unspecified site	453.9x (other venous embolism and thrombosis of unspecified site)	I9291
Embolism and thrombosis of unspecified artery	444.9x (embolism and thrombosis of unspecified artery)	I749
Cataracts and other ocular disorders	366.xx (cataract) 368.xx (visual disturbances) 379.3 (aphakia and other disorders of the lens)	E0836, E0936, E1036, E1136, E1336, H25011, H25012, H25013, H25019, H25031, H25032, H25033, H25039, H25041, H25042, H25043, H25049, H25091, H25092, H25093, H25099, H2510, H2511, H2512, H2513, H2520, H2521, H2522, H2523, H25811, H25812, H25813, H25819, H2589, H259, H26001, H26002, H26003,

Safety event of interest	ICD-9-CM diagnosis code	ICD-10 diagnosis code
		H26009, H26011, H26012, H26013, H26019, H26031, H26032, H26033, H26039, H26041, H26042, H26043, H26049, H26051, H26052, H26053, H26059, H26061, H26062, H26063, H26069, H2609, H26101, H26102, H26103, H26109, H26111, H26112, H26113, H26119, H26121, H26122, H26123, H26129, H26131, H26132, H26133, H26139, H2620, H26211, H26212, H26213, H26219, H26221, H26222, H26223, H26229, H26231, H26232, H26233, H26239, H2630, H2631, H2632, H2633, H2640, H26411, H26412, H26413, H26419, H26491, H26492, H26493, H26499, H268, H269, H28, H53001, H53002, H53003, H53009, H53011, H53012, H53013, H53019, H53021, H53022, H53023, H53029, H53031, H53032, H53033, H53039, H5310, H5311, H53121, H53122, H53123, H53129, H53131, H53132, H53133, H53139, H53141, H53142, H53143, H53149, H5315, H5316, H5319, H532, H5330, H5331, H5332, H5333, H5334, H5340, H53411, H53412, H53413, H53419, H53421, H53422, H53423, H53429, H53431, H53432, H53433, H53439, H53451, H53452, H53453, H53459, H53461, H53462, H53469, H5347, H53481, H53482, H53483, H53489, H5350, H5351, H5352, H5353, H5354, H5355, H5359, H5360, H5361, H5362, H5363, H5369, H5371, H5372, H538, H539, R441, R483
Stomatitis and mucositis*	528.0x (stomatitis and mucositis)	K12, K120, K121, K122, K123, K1230, K1231, K1232, K1233, K1239 (i.e. K12.%)
Fever	780.6 (fever and other physiological disturbances of temperature regulation) 780.60 (fever, unspecified) 780.61 (fever presenting with conditions classified elsewhere)	R502, R5081, R509
Anorexia (decreased appetite)	783.0x (anorexia)	R630

Safety event of interest	ICD-9-CM diagnosis code	ICD-10 diagnosis code
Peripheral neuropathy	356.8x (other specified idiopathic peripheral neuropathy) 356.4x (idiopathic progressive neuropathy) 356.9x (unspecified idiopathic peripheral neuropathy) 357.0x (acute infective polyneuritis) 357.1x (polyneuropathy in collagen vascular disease) 357.6x (polyneuropathy due to drugs) 357.7x (polyneuropathy due to other toxic agents) 357.8x (other inflammatory and toxic neuropathies) 357.9x (unspecified inflammatory and toxic neuropathies) 729.2x (neuralgia, neuritis, and radiculitis, unspecified	G603, G608, G609, G610, G6181, G6189, G619, G620, G622, G6281, G63, M5410, M792, G611, G6282, G6289, G629, G64, M0550, M05511, M05512, M05519, M05521, M05522, M05529, M05531, M05532, M05539, M05541, M05542, M05549, M05551, M05552, M05559, M05561, M05562, M05569, M05571, M05572, M05579, M0559, M5418
Sudden cardiac death	798.1x (instantaneous death) 798.2x (death occurring in less than 24 hours from onset of symptoms, not otherwise explained) 798.9x (unattended death) 799.9x (other unknown and unspecified cause of morbidity and mortality)	R69, R99
Diabetes mellitus*	250.xx (diabetes mellitus)	E10.%, E11.% (includes E1010, E1011, E1021, E1029, E10311, E10319, E1036, E1039, E1040, E1051, E10618, E10620, E10621, E10622, E10628, E10630, E10638, E10641, E10649, E1065, E1069, E108, E109, E1100, E1101, E1121, E1129, E11311, E11319, E1136, E1139, E1140, E1151, E11618, E11620, E11621, E11622, E11628, E11630, E11638, E11641, E11649, E1165, E1169, E118, E119, E1022, E10321, E10329, E10331, E10339, E10341, E10349, E10351, E10359, E1041, E1042, E1043, E1044, E1049, E1052, E1059, E10610, E1122, E11321, E11329, E11331, E11339, E11341, E11349, E11351, E11359, E1141, E1142, E1143, E1144, E1149, E1152, E1159, E11610

Safety event of interest	**ICD-9-CM diagnosis code**	**ICD-10 diagnosis code**
Type 2 Diabetes mellitus*	250.x0, 250.x2	E11.%
Hyperglycemia	790.29 (other abnormal glucose)	R7309, R739
Liver failure	570.xx (acute and subacute necrosis of the liver) 790.4x (Nonspecific elevation of levels of transaminase or lactic acid dehydrogenase [LDH])	K7200, K762, R740, K7201
(Second primary cancers)		
Melanoma	172.xx (malignant melanoma of skin)	C43%
Colon	153.xx (malignant neoplasm of colon) 154.xx (malignant neoplasm of rectum rectosigmoid junction and anus) 235.2x (neoplasm of uncertain behavior of stomach, intestines, and rectum)	C18%, C19%, C20%
Gynecologic	183.xx (malignant neoplasm of ovary and other uterine adnexa) 236.2x (neoplasm of uncertain behavior of ovary) 182.xx (malignant neoplasm of body of uterus) 179.xx (malignant neoplasm of uterus, part unspecified) 180.xx (malignant neoplasm of cervix uteri) 184.xx (malignant neoplasm of other and unspecified female genital organs) 236.1x (neoplasm of uncertain behavior of placenta)	C56%, CD391%, C54%, C55%, C53%, C57%, C58%,
Non melanomatous skin cancer	173.xx (other and unspecified malignant neoplasm of skin) 238.2x (neoplasm of uncertain behavior of skin)	C44%, D485%
Urinary Tract	188.xx (malignant neoplasm of bladder) 189.xx (malignant neoplasm of kidney and other and unspecified urinary organs) 236.7x (neoplasm of uncertain behavior of bladder) 236.91 (neoplasm of uncertain behavior of kidney and ureter) 239.4x (neoplasm of unspecified nature of bladder)	C67%, C64%, D41%, D494%, D495%

Safety event of interest	ICD-9-CM diagnosis code	ICD-10 diagnosis code
	239.5x (neoplasm of unspecified nature of other genitourinary organs)	
Head/neck	140.xx to 149.9x (malignant neoplasm of lip, oral cavity, and pharynx) 160.xx (malignant neoplasm of nasal cavities middle ear and accessory sinuses) 161.xx (malignant neoplasm of larynx) 162.xx (malignant neoplasm of trachea bronchus and lung) 195.0x (malignant neoplasm of head, face, neck)	C00% to C14%, C30% to C34%
Lung	162.xx (malignant neoplasm of trachea bronchus and lung) 235.9 (neoplasm of uncertain behavior of other and unspecified respiratory organs) 239.1x (neoplasm of unspecified nature of respiratory system)	C34%, D385%, D386%
Non colon gastrointestinal (GI)	150.xx (malignant neoplasm of esophagus) 151.xx (malignant neoplasm of stomach) 152.xx (malignant neoplasm of small intestine including duodenum) 155.xx (malignant neoplasm of liver and intrahepatic bile ducts) 156.xx (malignant neoplasm of gallbladder and extrahepatic bile ducts) 157.xx (malignant neoplasm of pancreas) 158.xx (malignant neoplasm of retroperitoneum and peritoneum) 159.xx (malignant neoplasm of other and ill-defined sites within the digestive organs and peritoneum) 235.xx (neoplasm of uncertain behavior of digestive and respiratory organs) 235.0x (neoplasm of uncertain behavior of major salivary glands) 235.1x (neoplasm of uncertain behavior of lip, oral cavity, and pharynx) 235.2x (neoplasm of uncertain behavior of	C15%, C16%, C17%, C22%, C23%, C25%, C48%, C26%, D370%, D37%, D38%, D490%

Safety event of interest	ICD-9-CM diagnosis code	ICD-10 diagnosis code
	stomach, intestines, and rectum) 235.3x (neoplasm of uncertain behavior of liver and biliary passages) 239.0x (neoplasm of unspecified nature of digestive system)	
Brain	190.xx (malignant neoplasm of eye) 191.xx (malignant neoplasm of brain) 192.xx (malignant neoplasm of other and unspecified parts of nervous system) 237.5x (neoplasm of uncertain behavior of brain and spinal cord) 237.6x (neoplasm of uncertain behavior of meninges) 239.6x (neoplasm of unspecified nature of brain)	C68%, C70%, C71%, C72%, D43%, D42%, D496%
Bone/Soft tissue	170.xx (malignant neoplasm of bone and articular cartilage) 171.xx (malignant neoplasm of connective and other soft tissue) 238.1x (neoplasm of uncertain behavior of connective and other soft tissue) 238.2x (neoplasm of uncertain behavior of skin)	C40%, C47%, C49%, D48%
Endocrine	193.xx (malignant neoplasm of thyroid gland) 194.xx (malignant neoplasm of other endocrine glands and related structures) 237.0x (neoplasm of uncertain behavior of pituitary gland and craniopharyngeal duct) 237.4x (neoplasm of uncertain behavior of other and unspecified endocrine glands) 239.7x (neoplasm of unspecified nature of endocrine glands and other parts of nervous system)	C73%, C74%, C75%, D44%, D497%
Pleura/mediastinum	163.xx (malignant neoplasm of pleura) 164.xx (malignant neoplasm of thymus heart and mediastinum)	C37, C38%

Safety event of interest	ICD-9-CM diagnosis code	ICD-10 diagnosis code
Non-specific site	195.xx (malignant neoplasm of other and ill-defined sites) 199.xx (malignant neoplasm without specification of site) 238.8x (neoplasm of uncertain behavior of other specified sites) 238.9x (neoplasm of uncertain behavior, site unspecified) 239.8x (neoplasm of unspecified nature of other specified sites) 239.9x (neoplasm of unspecified nature, site unspecified)	C76%, C80%, D487, D489, D498%, D499%

* The ICD-9 and ICD-10 codes for the noted safety events were reviewed by Dr. Joe Singer, Chief Medical Officer at HealthCore Inc. The ICD-9 codes for other safety events were developed in consultation with clinical teams at Pfizer, and an Anthem mapping program was utilized to define the ICD-10 codes.

Code lists for lab values in the HIRD

Safety (lab) event of interest	Lab (LOINC) codes	Related CPT Codes
Aspartate Transaminase (AST)	1920-8, 30239-8	80050, 80053, 84450, 80076
Alanine transaminase (ALT)	1742-6, 1743-4	80050, 80053, 84460
Alkaline Phosphatase (ALP)	6768-6	84075, 84080

Code lists for comorbidities of interest in the HIRD

Comorbidities	**ICD-9-CM diagnosis code**	**ICD-10 diagnosis code**
Pathological fracture*	733.1x (pathologic fracture)	M84.4%, M84.5%, M84.6% (includes M8440XA, M84429A, M84439A, M4850XA, M8448XA, M8468XA, M84459XA, M84459A, M84453A, M84469A, M84419A, M84479A, M8448XA)
Pathological fracture (specific – neoplastic disease only for ICD10)*	n/a	M84.5%
Osteoporosis	733.00 (osteoporosis, unspecified) 733.09 (other osteoporosis)	M810, M818, Z13820, M816
Pure hypercholesterolemia	272.0x (pure hypercholesterolemia)	E780, E781, E782, E783, E784, E785, I10, I674, Z136
Uterine malignancies	179.xx (malignant neoplasm of uterus, part unspecified)	C55
MACE events (measurable, nonfatal)		
Acute MI	410.xx (acute myocardial infarction)	I21.%, I22.% (i.e. (I2109, I2111, I2119, I2129, I213, I214, I2101, I2102, I2121, I220, I221, I222, I228, I229)
Cerebrovascular disease	430.xx (subarachnoid hemorrhage) 431.xx (intracerebral hemorrhage) 432.xx (other and unspecified intracranial hemorrhage) 433.xx (occlusion and stenosis of precerebral arteries) 434.xx (occlusion of cerebral arteries) 435.xx (transient cerebral ischemia) 436.xx (acute, but ill-defined cerebrovascular disease)	I6000, I6001, I6002, I6010, I6011, I6012, I6020, I6022, I6030, I6031, I6032, I604, I6050, I6051, I6052, I606, I607, I608, I610, I611, I612, I613, I614, I615, I616, I618, I6201, I6202, I6203, I6300, I63011, I63012, I6302, I63031, I63032, I63039, I6309, I6310, I63111, I63112, I6312, I63131, I63132, I6319, I63211, I63212, I63231, I63232, I6329, I63311, I63312, I63319, I63321, I63322, I63329, I63331, I63332, I63339, I63341, I63342, I63349, I6339, I63411, i63412, I63419, I63421, I63422, I63422, I63429, I63431, I63432, I63439, I63441, I63442, I63449, I6349, I63511, I63512, I63519, I63521, I63529, I63531,

Comorbidities	ICD-9-CM diagnosis code	ICD-10 diagnosis code
		I63532, I63539, I63521, I63522, I63529, I63531, I63532, I63539, I63541, I63542, I63549, I636, I638, I639, I6501, I6502, I6503, I6521, I6522, I6523, I6601, I6602, I6603, I6611, I6612, I6613, I6621, I6622, I6623, I663, I668, I67841, I678, I6789
Diabetes mellitus	250.xx (diabetes mellitus)	E1010, E1011, E1021, E1029, E10311, E10319, E1036, E1039, E1040, E1051, E10618, E10620, E10621, E10622, E10628, E10630, E10638, E10641, E10649, E1065, E1069, E108, E109, E1100, E1101, E1121, E1129, E11311, E11319, E1136, E1139, E1140, E1151, E11618, E11620, E11621, E11622, E11628, E11630, E11638, E11641, E11649, E1165, E1169, E118, E119, E1022, E10321, E10329, E10331, E10339, E10341, E10349, E10351, E10359, E1041, E1042, E1043, E1044, E1049, E1052, E1059, E10610, E1122, E11321, E11329, E11331, E11339, E11341, E11349, E11351, E11359, E1141, E1142, E1143, E1144, E1149, E1152, E1159, E11610, E1300, E1301, E1310, E1311, E1321, E1322, E1329, E13311, E13319, E13321, E13329, E13331, E13339, E13341, E13349, E13351, E13359, E1336, E1339, E1340, E1341, E1342, E1343, E1344, E1349, E1351, E1352, E1359, E13610, E13618, E13620, E13621, E13622, E13628, E13630, E13638, E13641, E13649, E1365, E1369, E138, E139
Hyperglycemia	790.29 (other abnormal glucose)	R7309, R739

* The ICD-9 and ICD-10 codes for the noted co-morbidities were reviewed by Dr. Joe Singer, Chief Medical Officer at HealthCore Inc. The ICD-9 codes for other co-morbidities were developed in consultation with clinical teams at Pfizer, and an Anthem mapping program was utilized to define the ICD-10 codes.

ANNEX 3. TABLE SHELLS

Table 1-5 Incidence rates and unadjusted hazard ratios of the safety events in new users of palbociclib and fulvestrant and new users of fulvestrant alone

[Secondary Objective 3a]

	Before Propensity Score Matching												
	All new users of palbociclib and fulvestrant					All new users of fulvestrant alone (pre-2015)					Unadjusted Hazard Ratios		
Event	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			HR	95% LCL	95%UCL
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			
Neutropenia (sensitive)													
Neutropenia (specific)													
Febrile neutropenia (sensitive)													
Febrile neutropenia (specific)													
Leukopenia (sensitive)													
Leukopenia (specific)													
Alopecia													
Vomiting*													
QT prolongation													
Fatigue*													
Serious infection													
Brain/spinal infection													
Pericardial/myocardial infection													
Pulmonary infection													
GI infection													
Genitourinary/Renal infection													
Dental infection													
Ear, nose, and throat infection													
Skin, bones, and joint infection													
Hepatitis B infection													
Influenza infection													
Other infection													
Diarrhea*													
Interstitial lung disease/pneumonitis													
Anemia (sensitive)													
Anemia (specific)													

	Before Propensity Score Matching												
	All new users of palbociclib and fulvestrant					All new users of fulvestrant alone (pre-2015)					Unadjusted Hazard Ratios		
Event	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			HR	95% LCL	95%UCL
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			
Nausea*													
Thrombocytopenia													
Pulmonary embolism*													
No history													
Other venous embolism and thrombosis*													
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)													
No history of "Other venous embolism and thrombosis"													
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)													
Embolism and thrombosis of unspecified artery													
Cataracts and other ocular disorders													
Stomatitis and mucositis													
Fever													
Anorexia													
Peripheral neuropathy													
Sudden cardiac death													
Diabetes mellitus													
Type 2 Diabetes mellitus													
Hyperglycemia													
Liver failure													
Abnormal ALT (incident)^													
Abnormal ALT (incident or prevalent)^													
Abnormal AST (incident)^													
Abnormal AST (incident or prevalent)^													
Abnormal ALP (incident)^													
Abnormal ALP (incident or prevalent)^													

	Before Propensity Score Matching												
	All new users of palbociclib and fulvestrant					All new users of fulvestrant alone (pre-2015)					Unadjusted Hazard Ratios		
Event	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			HR	95% LCL	95%UCL
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			
Secondary malignancies													
Non-melanoma skin cancer													

Abbreviations: PT, person time; IR; incidence rate; CI, confidence interval; HR, Hazard ratios, LCL, lower confidence limit; UCL, upper confidence limit

*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date.

^Abnormal AST >40 U/L, Abnormal ALT >40 U/L; Abnormal ALP >147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.

All counts <10 are reported as "<10" per HealthCore/Anthem guidelines; related calculations are not available (n/a) to avoid back calculation of the counts.

Table 1-6 Incidence rates and adjusted hazard ratios of the safety events of interest in propensity score matched new users of palbociclib and fulvestrant and new users of fulvestrant alone

[Secondary Objective 3a]

	After Propensity Score Matching												
	New users of palbociclib and fulvestrant					New users of fulvestrant alone (pre-2015)					Adjusted Hazard Ratios		
Event	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			aHR	95% LCL	95%UCL
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			
Neutropenia (sensitive)													
Neutropenia (specific)													
Febrile neutropenia (sensitive)													
Febrile neutropenia (specific)													
Leukopenia (sensitive)													
Leukopenia (specific)													
Alopecia													
Vomiting*													
QT prolongation													
Fatigue*													
Serious infection													
Brain/spinal infection													
Pericardial/myocardial infection													
Pulmonary infection													
GI infection													
Genitourinary/Renal infection													
Dental infection													
Ear, nose, and throat infection													
Skin, bones, and joint infection													
Hepatitis B infection													
Influenza infection													
Other infection													
Diarrhea*													
Interstitial lung disease/pneumonitis													
Anemia (sensitive)													
Anemia (specific)													
Nausea*													

	After Propensity Score Matching												
	New users of palbociclib and fulvestrant					New users of fulvestrant alone (pre-2015)					Adjusted Hazard Ratios		
Event	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			aHR	95% LCL	95%UCL
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			
Thrombocytopenia													
Pulmonary embolism*													
No history													
Other venous embolism and thrombosis*													
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)													
No history of "Other venous embolism and thrombosis"													
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)													
Embolism and thrombosis of unspecified artery													
Cataracts and other ocular disorders													
Stomatitis and mucositis													
Fever													
Anorexia													
Peripheral neuropathy													
Sudden cardiac death													
Diabetes mellitus													
Type 2 Diabetes mellitus													
Hyperglycemia													
Liver failure													
Abnormal ALT (incident)^													
Abnormal ALT (incident or prevalent)^													
Abnormal AST (incident)^													
Abnormal AST (incident or prevalent)^													
Abnormal ALP (incident)^													
Abnormal ALP (incident or prevalent)^													
Secondary malignancies													
Non-melanoma skin cancer													
Abbreviations: PT, person time; IR, incidence rate; CI, confidence interval; aHR, adjusted hazards ratio; LCL, lower confidence limit; UCL, upper confidence limit.													
*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date													
^Abnormal AST >40 U/L, Abnormal ALT >40 U/L; Abnormal ALP >147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.													
All counts <10 are reported as "<10" per HealthCore/Anthem guidelines; related calculations are not available (n/a) to avoid back calculation of the counts.													

Table 2.1. Characteristics of patients utilizing palbociclib with algorithm-defined advanced stage ER+/HER2- breast cancer patients identified in the HIRD

[Secondary Objective 2]

Characteristics	All new users of Palbociclib		New users of palbociclib with fulvestrant		New users of palbociclib with letrozole		All other new users of palbociclib (no new use of fulvestrant or letrozole)	
	N/Mean	%/STD	N/Mean	%/STD	N/Mean	%/STD	N/Mean	%/STD
Overall								
Demographics								
Age at index date (in years)								
Age (years)								
<45								
45-64								
65+								
Calendar year of index date								
2015								
2016								
2017								
Geographic region of residence								
Midwest								
South								
Northeast								
West								
Duration of health plan enrollment prior to index date (days)								
Medical History								
Other primary cancer prior to first breast cancer diagnosis code								
Secondary malignancy								
Lymph nodes of head, face, and neck								
Respiratory and digestive systems								
Other specified sites								
Deyo-Charlson comorbidity index (DCI) without cancer codes								
Secondary malignant neoplasm of breast								
Breast Cancer (Female) diagnosis code								
InSitu Breast Cancer								
History of Breast Cancer								

Characteristics	All new users of Palbociclib		New users of palbociclib with fulvestrant		New users of palbociclib with letrozole		All other new users of palbociclib (no new use of fulvestrant or letrozole)	
	N/Mean	%/STD	N/Mean	%/STD	N/Mean	%/STD	N/Mean	%/STD
Cancer Therapy History								
Radiation therapy								
Implantation (Brachytherapy)								
External Beam								
Surgery								
Mastectomy in the last six months								
Lumpectomy in the last six months								
Radical Mastectomy in the last six months								
Chemotherapy								
Infusion based chemo (procedure)								
Imaging								
CT related imaging in the last six months								
MR related imaging for needle placement								
Diagnostic imaging in the last six months								
Mammography								
MRI related imaging								
Tomosynthesis (3D Mammography)								
Healthcare Utilization (6 months prior to index date)								
Number of outpatient visits								
Number of outpatient visits to an oncologist								
Number of inpatient hospitalizations								
Number of inpatient hospitalizations for breast cancer								
Number of inpatient hospitalizations for any cancer								
Number of emergency department visits								
Medication Use (breast cancer related)								
Palbociclib								
Hormone Therapy								
Letrozole								
Anastrazole								
Exemestane								
HER2 positive Therapy								
Trastuzumab								
Lapatinib								
Ado-trastuzumab								
Pertuzumab								
Tamoxifen								
Fulvestrant								
Denosumab or Pamidronate								

Characteristics	All new users of Palbociclib		New users of palbociclib with fulvestrant		New users of palbociclib with letrozole		All other new users of palbociclib (no new use of fulvestrant or letrozole)	
	N/Mean	%/STD	N/Mean	%/STD	N/Mean	%/STD	N/Mean	%/STD
Everolimus								
Medication Use (not breast cancer related)								
Anticonvulsants								
Antidepressants								
Antidiabetics								
Antifungals								
Antihypertensives								
Antimycobacterials								
Antivirals								
Corticosteroids								
Oral contraceptive use (progestin)								
Oral contraceptive use (combination)								
Oral contraceptive use (unspecified)								
Lipid lowering agent								
Vaginal estrogen (local hormone treatment)								
Macrolides								
Sedatives/hypnotics								
Selective estrogen receptor modulators								
Unopposed estrogen HRT								
Co-morbidities (six months prior to index date)								
Pathologic fracture								
Osteoporosis								
Uterine malignancies								
Pure hypercholesterolemia								
Major adverse cardiac events (MACE)								
Acute myocardial infarction (MI)								
Cerebrovascular disease								
Stroke								
Diabetes								
Hyperglycemia								
Deyo-Charlson Index (DCI)								
0-3								
4-7								
8-11								
12 or more								
Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; N, number; STD, standard deviation								
All counts <10 are reported as "<10" per HealthCore/Anthem guidelines; related calculations are not available (n/a) to avoid back calculation of the counts.								

Table 2.2. Incidence of the safety events of interest in all new users of palbociclib with algorithm-defined advanced stage ER+/HER2-breast cancer

[Secondary Objective 2]

	All new users of palbociclib with advanced stage ER+/HER2-breast cancer				
Event	**# Events**	**PT at risk**	**IR (per 100 person-years)**		
			IR	**95% Lower CI**	**95% Upper CI**
Neutropenia (sensitive)					
Neutropenia (specific)					
Febrile neutropenia (sensitive)					
Febrile neutropenia (specific)					
Leukopenia (sensitive)					
Leukopenia (specific)					
Alopecia					
Vomiting*					
QT prolongation					
Fatigue*					
Serious infection					
Brain/spinal infection					
Pericardial/myocardial infection					
Pulmonary infection					
GI infection					
Genitourinary/Renal infection					
Dental infection					
Ear, nose, and throat infection					
Skin, bones, and joint infection					
Hepatitis B infection					
Influenza infection					
Other infection					
Diarrhea*					
Interstitial lung disease/pneumonitis					
Anemia (sensitive)					
Anemia (specific)					
Nausea*					
Thrombocytopenia					

	All new users of palbociclib with advanced stage ER+/HER2-breast cancer				
Event	**# Events**	**PT at risk**	**IR (per 100 person-years)**		
			IR	**95% Lower CI**	**95% Upper CI**
Pulmonary embolism*					
No history					
Other venous embolism and thrombosis*					
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)					
No history of "Other venous embolism and thrombosis"					
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)					
Embolism and thrombosis of unspecified artery					
Cataracts and other ocular disorders					
Stomatitis and mucositis					
Fever					
Anorexia					
Peripheral neuropathy					
Sudden cardiac death					
Diabetes mellitus					
Type 2 Diabetes mellitus					
Hyperglycemia					
Liver failure					
Abnormal ALT (incident)^					
Abnormal ALT (incident or prevalent)^					
Abnormal AST (incident)^					
Abnormal AST (incident or prevalent)^					
Abnormal ALP (incident)^					
Abnormal ALP (incident or prevalent)^					
Secondary malignancies					
Non-melanoma skin cancer					

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PT, person time; IR; incidence rate; CI, confidence interval

*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date.

^Abnormal AST >40 U/L, Abnormal ALT >40 U/L; Abnormal ALP >147 U/L; Abnormal Total Bilirubin >1.9 mg/dL. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.

All counts <10 are reported as "<10" per HealthCore/Anthem guidelines; related calculations are not available (n/a) to avoid back calculation of the counts.

Table 2-3. Incidence of the safety events of interest in new users of palbociclib subgroups with algorithm defined advanced stage ER+/HER2-Breast Cancer

[Secondary Objective 2]

	New users of palbociclib and fulvestrant					New users of palbociclib and letrozole					All other new users of palbociclib (no new use of fulvestrant or letrozole)				
Event	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)		
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI
Neutropenia (sensitive)															
Neutropenia (specific)															
Febrile neutropenia (sensitive)															
Febrile neutropenia (specific)															
Leukopenia (sensitive)															
Leukopenia (specific)															
Alopecia															
Vomiting*															
QT prolongation															
Fatigue*															
Serious infection															
Brain/spinal infection															
Pericardial/myocardial infection															
Pulmonary infection															
GI infection															
Genitourinary/Renal infection															
Dental infection															
Ear, nose, and throat infection															
Skin, bones, and joint infection															
Hepatitis B infection															
Influenza infection															
Other infection															
Diarrhea*															
Interstitial lung disease/pneumonitis															
Anemia (sensitive)															
Anemia (specific)															

	New users of palbociclib and fulvestrant					New users of palbociclib and letrozole					All other new users of palbociclib (no new use of fulvestrant or letrozole)				
Event	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)		
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI
Nausea*															
Thrombocytopenia															
Pulmonary embolism*															
No history															
Other venous embolism and thrombosis*															
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)															
No history of "Other venous embolism and thrombosis"															
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)															
Embolism and thrombosis of unspecified artery															
Cataracts and other ocular disorders															
Stomatitis and mucositis															
Fever															
Anorexia															
Peripheral neuropathy															
Sudden cardiac death															
Diabetes mellitus															
Type 2 Diabetes mellitus															
Hyperglycemia															
Liver failure															
Abnormal ALT (incident)^															
Abnormal ALT (incident or prevalent)^															
Abnormal AST (incident)^															
Abnormal AST (incident or prevalent)^															
Abnormal ALP (incident)^															
Abnormal ALP (incident or prevalent)^															
Secondary malignancies															
Non-melanoma skin cancer															

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PT, person time; IR; incidence rate; CI, confidence interval.
*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date.
^Abnormal AST >40 U/L, Abnormal ALT >40 U/L; Abnormal ALP >147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.
All counts <10 are reported as "<10" per HealthCore/Anthem guidelines; related calculations are not available (n/a) to avoid back calculation of the counts.

Table 2-4. Characteristics of breast cancer patients utilizing palbociclib with fulvestrant and new users of fulvestrant alone with algorithm-defined advanced stage ER+/HER2-Breast Cancer

[Secondary Objective 3b]

	Before Propensity Score Matching					After Propensity Score Matching				
Characteristics of patients with advanced stage ER+/HER2-Breast Cancer	**New users of palbociclib with fulvestrant**		**New users of fulvestrant alone (pre-2015)**		**Standardized difference**	**New users of palbociclib with fulvestrant**		**New users of fulvestrant alone (pre-2015)**		**Standardized difference**
	N/Mean	**%/STD**	**N/Mean**	**%/STD**		**N/Mean**	**%/STD**	**N/Mean**	**%/STD**	
Overall										
Demographics										
Age at index date (in years)										
Age (years)										
<45										
45-64										
65+										
Calendar year of index date										
2011										
2012										
2013										
2014										
2015										
2016										
2017										
Geographic region of residence										
Midwest										
South										
Northeast										
West										
Duration of health plan enrollment prior to index date (days)										
Medical History										
Other primary cancer prior to first breast cancer diagnosis code										
Secondary malignancy										
Lymph nodes of head, face, and										

	Before Propensity Score Matching					After Propensity Score Matching				
Characteristics of patients with advanced stage ER+/HER2-Breast Cancer	**New users of palbociclib with fulvestrant**		**New users of fulvestrant alone (pre-2015)**		**Standardized difference**	**New users of palbociclib with fulvestrant**		**New users of fulvestrant alone (pre-2015)**		**Standardized difference**
	N/Mean	**%/STD**	**N/Mean**	**%/STD**		**N/Mean**	**%/STD**	**N/Mean**	**%/STD**	
neck										
Respiratory and digestive systems										
Other specified sites										
Deyo-Charlson comorbidity index (DCI) without cancer codes										
Secondary malignant neoplasm of breast										
Breast Cancer (Female) diagnosis code										
InSitu Breast Cancer										
History of Breast Cancer										
Cancer Therapy History										
Radiation therapy										
Implantation (Brachytherapy)										
External Beam										
Surgery										
Mastectomy in the last six months										
Lumpectomy in the last six months										
Radical Mastectomy in the last six months										
Chemotherapy										
Infusion based chemo (procedure)										
Imaging										
CT related imaging in the last six months										
MR related imaging for needle placement										
Diagnostic imaging in the last six months										
Mammography										
MRI related imaging										
Tomosynthesis (3D Mammography)										
Healthcare Utilization (6 months prior to index date)										
Number of outpatient visits										
Number of outpatient visits to an oncologist										

	Before Propensity Score Matching					After Propensity Score Matching				
Characteristics of patients with advanced stage ER+/HER2-Breast Cancer	**New users of palbociclib with fulvestrant**		**New users of fulvestrant alone (pre-2015)**		**Standardized difference**	**New users of palbociclib with fulvestrant**		**New users of fulvestrant alone (pre-2015)**		**Standardized difference**
	N/Mean	**%/STD**	**N/Mean**	**%/STD**		**N/Mean**	**%/STD**	**N/Mean**	**%/STD**	
Number of inpatient hospitalizations										
Number of inpatient hospitalizations for breast cancer										
Number of inpatient hospitalizations for any cancer										
Number of emergency department visits										
Medication Use (breast cancer related)										
Palbociclib										
Hormone Therapy										
Letrozole										
Anastrazole										
Exemestane										
HER2 positive Therapy										
Trastuzumab										
Lapatinib										
Ado-trastuzumab										
Pertuzumab										
Tamoxifen										
Fulvestrant										
Denosumab or Pamidronate										
Everolimus										
Medication Use (not breast cancer related)										
Anticonvulsants										
Antidepressants										
Antidiabetics										
Antifungals										
Antihypertensives										
Antimycobacterials										
Antivirals										
Corticosteroids										
Oral contraceptive use (progestin)										
Oral contraceptive use (combination)										
Oral contraceptive use (unspecified)										

	Before Propensity Score Matching					After Propensity Score Matching				
Characteristics of patients with advanced stage ER+/HER2-Breast Cancer	**New users of palbociclib with fulvestrant**		**New users of fulvestrant alone (pre-2015)**		**Standardized difference**	**New users of palbociclib with fulvestrant**		**New users of fulvestrant alone (pre-2015)**		**Standardized difference**
	N/Mean	**%/STD**	**N/Mean**	**%/STD**		**N/Mean**	**%/STD**	**N/Mean**	**%/STD**	
Lipid lowering agent										
Vaginal estrogen (local hormone treatment)										
Macrolides										
Sedatives/hypnotics										
Selective estrogen receptor modulators										
Unopposed estrogen HRT										
Co-morbidities (six months prior to index date)										
Pathologic fracture										
Osteoporosis										
Uterine malignancies										
Pure hypercholesterolemia										
Major adverse cardiac events (MACE)										
Acute Myocardial Infarction (MI)										
Cerebrovascular disease										
Stroke										
Diabetes										
Hyperglycemia										
Deyo-Charlson Index (DCI)										
0-3										
4-7										
8-11										
12 or more										

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; N, number; STD, standard deviation.

All counts <10 are reported as "<10" per HealthCore/Anthem guidelines; related calculations are not available (n/a) to avoid back calculation of the counts.

Table 2-5. Incidence rates and unadjusted hazard ratios of the safety events in new users of palbociclib and fulvestrant and new users of fulvestrant alone with algorithm-defined advanced stage ER+/HER2-Breast cancer

[Secondary Objective 3b]

	Before Propensity Score Matching												
	New users of palbociclib and fulvestrant with advanced stage ER+/HER2- breast cancer					New users of fulvestrant alone (pre-2015) with advanced stage ER+/HER2- breast cancer					Unadjusted Hazard Ratios		
Event	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			HR	95% LCL	95%UCL
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			
Neutropenia (sensitive)													
Neutropenia (specific)													
Febrile neutropenia (sensitive)													
Febrile neutropenia (specific)													
Leukopenia (sensitive)													
Leukopenia (specific)													
Alopecia													
Vomiting*													
QT prolongation													
Fatigue*													
Serious infection													
Brain/spinal infection													
Pericardial/myocardial infection													
Pulmonary infection													
GI infection													
Genitourinary/Renal infection													
Dental infection													
Ear, nose, and throat infection													
Skin, bones, and joint infection													
Hepatitis B infection													
Influenza infection													
Other infection													
Diarrhea*													
Interstitial lung disease/pneumonitis													

	Before Propensity Score Matching												
	New users of palbociclib and fulvestrant with advanced stage ER+/HER2- breast cancer					New users of fulvestrant alone (pre-2015) with advanced stage ER+/HER2- breast cancer					Unadjusted Hazard Ratios		
Event	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			HR	95% LCL	95%UCL
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			
Anemia (sensitive)													
Anemia (specific)													
Nausea*													
Thrombocytopenia													
Pulmonary embolism*													
No history													
Other venous embolism and thrombosis*													
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)													
No history of "Other venous embolism and thrombosis"													
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)													
Embolism and thrombosis of unspecified artery													
Cataracts and other ocular disorders													
Stomatitis and mucositis													
Fever													
Anorexia													
Peripheral neuropathy													
Sudden cardiac death													
Diabetes mellitus													
Type 2 Diabetes mellitus													
Hyperglycemia													
Liver failure													
Abnormal ALT (incident)^													
Abnormal ALT (incident or prevalent)^													
Abnormal AST (incident)^													
Abnormal AST (incident or prevalent)^													
Abnormal ALP (incident)^													
Abnormal ALP (incident or prevalent)^													
Secondary malignancies													
Non-melanoma skin cancer													

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PT, person time; IR, incidence rate; CI, confidence interval; HR, hazard ratio; LCL, lower confidence limit; UCL, upper confidence limit.
*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date.
^Abnormal AST >40 U/L, Abnormal ALT >40 U/L; Abnormal ALP >147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.
All counts <10 are reported as "<10" per HealthCore/Anthem guidelines; related calculations are not available (n/a) to avoid back calculation of the counts.

Table 2-6. Incidence rates and adjusted hazard ratios of the safety events in new users of palbociclib and fulvestrant and new users of fulvestrant alone with algorithm-defined advanced stage ER+/HER2-Breast cancer

[Secondary Objective 3b]

	After Propensity Score Matching												
	New users of palbociclib and fulvestrant with advanced stage ER+/HER2-breast cancer					New users of fulvestrant alone (pre-2015) with advanced stage ER+/HER2-breast cancer					Adjusted Hazard Ratios		
Event	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			aHR	95% LCL	95%UCL
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			
Neutropenia (sensitive)													
Neutropenia (specific)													
Febrile neutropenia (sensitive)													
Febrile neutropenia (specific)													
Leukopenia (sensitive)													
Leukopenia (specific)													
Alopecia													
Vomiting*													
QT prolongation													
Fatigue*													
Serious infection													
Brain/spinal infection													
Pericardial/myocardial infection													
Pulmonary infection													
GI infection													
Genitourinary/Renal infection													
Dental infection													
Ear, nose, and throat infection													
Skin, bones, and joint infection													
Hepatitis B infection													
Influenza infection													
Other infection													
Diarrhea*													
Interstitial lung disease/pneumonitis													

	After Propensity Score Matching												
	New users of palbociclib and fulvestrant with advanced stage ER+/HER2-breast cancer					New users of fulvestrant alone (pre-2015) with advanced stage ER+/HER2-breast cancer					Adjusted Hazard Ratios		
Event	# Events	PT at risk	IR (per 100 person-years)			# Events	PT at risk	IR (per 100 person-years)			aHR	95% LCL	95%UCL
			IR	95% Lower CI	95% Upper CI			IR	95% Lower CI	95% Upper CI			
Anemia (sensitive)													
Anemia (specific)													
Nausea*													
Thrombocytopenia													
Pulmonary embolism*													
No history													
Other venous embolism and thrombosis*													
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)													
No history of "Other venous embolism and thrombosis"													
Acute venous embolism and thrombosis of deep vessels of lower extremity (DVT)													
Embolism and thrombosis of unspecified artery													
Cataracts and other ocular disorders													
Stomatitis and mucositis													
Fever													
Anorexia													
Peripheral neuropathy													
Sudden cardiac death													
Diabetes mellitus													
Type 2 Diabetes mellitus													
Hyperglycemia													
Liver failure													
Abnormal ALT (incident)^													
Abnormal ALT (incident or prevalent)^													
Abnormal AST (incident)^													
Abnormal AST (incident or prevalent)^													
Abnormal ALP (incident)^													
Abnormal ALP (incident or prevalent)^													
Secondary malignancies													
Non-melanoma skin cancer													

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PT, person time; IR, incidence rate; CI, confidence interval; aHR, adjusted hazard ratios; LCL, lower confidence limit; UCL, upper confidence limit.
*Allowed history of these events on or prior to index date. All other events excluded individuals with a history of these events prior to the index date.
^Abnormal AST >40 U/L, Abnormal ALT >40 U/L; Abnormal ALP >147 U/L. Incident analyses required a normal lab value prior to the index date, and an abnormal value after the index date. "Prevalent and Incident" analyses only required an abnormal value after the index date and included individuals who did not have a lab value prior to the index date and individuals who had abnormal values prior to the index date.
All counts <10 are repotted as "<10" per HealthCore/Anthem guidelines; related calculations are not available (n/a) to avoid back calculation of the counts.

Document Approval Record

Document Name:	A5481105_PROTOCOL_19DEC2017 V1
Document Title:	A5481105_PROTOCOL_19DEC2017 V1

Signed By:	Date(GMT)	Signing Capacity
Sobel, Rachel E	20-Dec-2017 19:13:46	Manager Approval
Reynolds, Robert F	20-Dec-2017 20:56:35	Final Approval
Dumas, Francoise Yvette	26-Dec-2017 22:26:34	Final Approval