NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS Information

Title	A multinational active safety surveillance study of crizotinib in Europe and the United States
Protocol number	A8081038
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Active substance	L01XE16/Crizotinib
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Marketing Authorisation Holder (MAH)	Pfizer Limited
Joint PASS	No
Research question and objectives	The objective of this study is to evaluate the safety and effectiveness of crizotinib among lung cancer patients in the real world setting in Europe and the United States.
Countries of study	Denmark, Finland, Sweden, the Netherlands and the United States
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090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

1. TABLE OF CONTENTS

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

LIST OF TABLES

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

LIST OF FIGURES

APPENDICES

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ATC	Anatomical therapeutic chemical
CIOMS	The Council for International Organizations of Medical Sciences
cMET	Mesenchymal epithelial growth factor
CR	Complete response
CVV	Classificatie van verrichtingen (Dutch medical procedure codes)
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
GI	Gastrointestinal
GPP	Good Pharmacoepidemiology Practices
HGFR	Hepatocyte growth factor receptor
ICPM	International Classification of Procedures in Medicine
ICD	International classification of diseases
IEA	International Epidemiological Association
ILD	Interstitial lung disease
IR	Interim report
IRR	Independent radiology review
ISPE	The International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
NSCLC	Non small cell lung cancer
PASS	Post-authorization safety study
PCR	Polymerase chain reaction
PFS	Progression-free survival
PPV	Positive predictive values
RLS	Record Linkage System
RON	Recepteur d'Origine Nantais
SAE	Serious adverse event
SEER	Surveillance, Epidemiology, and End-Results
SmPC	Summary of Product Characteristics
TKI	Tyrosine kinase inhibitors

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090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

4. ABSTRACT

Study title: A multinational active safety surveillance study of crizotinib in Europe and the United States (US).

Rationale and background: Crizotinib, an orally administered selective ATP competitive small molecule inhibitor of the anaplastic lymphoma kinase (ALK), has been approved multinationally, including in the US and Europe, for the treatment of patients with locally advanced or metastatic ALK-positive non small cell lung cancer (NSCLC). To supplement the data obtained within the clinical program, this proposed post-authorization safety study (PASS) is designed to evaluate the safety and effectiveness of crizotinib in the real-world setting in Europe and the US.

Research question and objectives: The objective of this study is to evaluate the safety and effectiveness of crizotinib among lung cancer patients in the real world setting. The primary objective is to estimate the incidence rate and incidence proportion over an approximately 3-year period of observation for hepatotoxicity, pneumonitis/interstitial lung disease (ILD), QTc prolongation related events, bradycardia, and visual disorders among lung cancer patients receiving crizotinib dispensation/prescription. Incidence rates and proportions of the same endpoints will be calculated for patients receiving dispensation/prescription of ceritinib, erlotinib, and gefitinib in order to provide context to the findings.

Study design: This is a non-interventional, active safety surveillance study using existing health care data sources.

Study population: The study population includes eligible patients that are diagnosed with primary lung cancer and receive dispensation/prescription for crizotinib, ceritinib, erlotinib, or gefitinib as recorded in national or regional health care databases in Denmark, Finland, the Netherlands, Sweden and the US from September 1st, 2011 to June 30th, 2017. In addition, all other cancer patients receiving crizotinib dispensation/prescription will be studied.

Data sources: This study links existing national or regional databases/registries within Sweden, Denmark, the Netherlands, Finland, and the US, which contain medical information for approximately 37.65 million people. Additionally, data from these national or regional databases/registries will be linked to patient medical records/charts to evaluate the validity of using diagnostic and/or procedural codes to capture primary study endpoints in national or regional databases/registries.

Variables: The variables that are evaluated in this study include lung cancer patient demographics, tumor characteristics, pertinent medical history, comorbidities, safety outcomes of interest, and overall patient survival.

Sample size: In this descriptive study, eligible patients with primary lung cancer treated with crizotinib, ceritinib, erlotinib, or gefitinib in the target existing databases/registries meeting inclusion and exclusion criteria during the study period will be included.

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Data analysis: All statistical analyses will be descriptive. Demographics and baseline characteristics will be tabulated. Incidence rates and incidence proportions for all study endpoints will be calculated for patients receiving dispensation/prescription of crizotinib, ceritinib, erlotinib or gefitinib. Subgroup analyses by age (dichotomized at ≥65 years old), presence or absence of brain metastases, and pre-existing renal or hepatic impairment at baseline will be conducted for all primary study endpoints. Kaplan-Meier survival probability will be estimated at one-year, two-year, and three-year periods of observation among lung cancer patients receiving crizotinib, ceritinib (if approved in Europe), erlotinib and gefitinib dispensation/prescription. In addition, sensitivity, specificity and positive predictive value of primary study endpoints captured using diagnostic and/or procedural codes in regional or national healthcare databases (compared to patient medical records/charts) will be calculated.

Milestones: The date when the first eligible patient in these existing health care databases could join the study was September 1st, 2011 right after local approval and reimbursement of crizotinib in at least one of these participating countries. Crizotinib was authorized in the US on August 11th, 2011, which was the first authorisation worldwide. The end date of the study is June 30th, 2017, allowing for lag time in obtaining claims data and at least a 6-month time period for data abstraction, data analysis, and preparation of the final study report in time for submission to the European Medicines Agency (EMA). The first interim report, the second interim report, and the final study report are going to be submitted to the EMA in June 2015, June 2016, and June 2018 respectively.

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5. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1.1	February 28, 2014	Substantial	Sections 3, 7, 8.1.2, 9.3, 9.5, 9.6.3, 9.8, 11, Appendix 1 and Appendix 2	This protocol was amended primarily to add malignant melanoma as one of secondary objectives. In addition, changes were also made in the management and reporting of adverse events/adverse reactions section. Furthermore, additional analyses on pneumonitis/ILD were added in the data analysis section. Finally, a few minor corrections/changes were also made throughout the protocol.	Malignant melanoma is considered a new important potential risk by Pfizer. This study may help better understand this potential risk in this active safety surveillance study. The adverse event reporting language was updated to ensure that it would be consistent with Pfizer internal SOP as well as the local law and regulations. The additional analyses on pneumonitis/ILD were to further comprehend the risk in a real world setting.
1.2	February 19, 2015	Substantial	PASS information, Abstract, Sections 7, 8, 9, Appendix 1, and Appendix 2	This protocol was amended for following reasons: 1) Norway withdrew from the study; 2) Optum database in the US was added to the study; 3) GI perforation was added as a secondary study endpoint; 4); ceritinib was added as one of comparators; 5) safety data presented in the background section were updated.	Investigators in Norway decided to withdraw from this study due to other competing obligations and lack of resources. After reaching out to other researchers in many European countries, it was concluded that no additional European countries had linkable existing databases required by the study at the moment. Therefore, Optum database in the US was added. Additionally, GI perforation is currently recognized as a new risk. This study may also help to better understand this risk in a real world setting. Furthermore, ceritinib is approved for the treatment of patients with ALK-positive, metastatic NSCLC with disease progression on or who are intolerant to crizotinib in the US in 2014 and currently is seeking approval in Europe. It will be important to collect data on patients treated with ceritinib since the drug is in the same class as crizotinib. Finally, the background section of the protocol was updated based on data from two crizotinib phase III clinical trials since data presented in the previous version of this protocol was based on phase I and II trials.

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6. MILESTONES

Milestone	Date
Study commencement (i.e. the date when the first eligible patient could join the study)	September 1st 2011
Start of data collection	December 30th 2014
End of data collection	June 30th 2017
Interim report I	June 30th 2015
Interim report II	June 30th 2016
Registration in the EU PAS register	December 2nd 2014
Final study report	June 30th 2018

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7. RATIONALE AND BACKGROUND

Crizotinib is an orally administered selective ATP competitive small molecule inhibitor of the anaplastic lymphoma kinase (ALK), mesenchymal epithelial growth factor (c MET) hepatocyte growth factor receptor (HGFR), Recepteur d'Origine Nantais (RON), and ROS receptor tyrosine kinases and their oncogenic variants (eg, c Met/HGFR mutations and ALK or ROS1 fusion proteins). It exhibited potent and selective growth inhibitory activity against tumor cells exhibiting translocation/inversion of the ALK gene locus, inversion events exhibiting translocation of the ROS1 gene locus, or amplification of the c Met/HGFR gene locus in clinical studies. Based on efficacy and safety data from single arm Phase 1 and 2 clinical trials, crizotinib has been approved multinationally, including in the United States (US) and Europe, for the treatment of patients with locally advanced or metastatic ALK-positive non small cell lung cancer (NSCLC). Two Phase 3 trials in an ALK-positive advanced NSCLC treatment setting have released its primary endpoint results. To supplement the data obtained within the clinical program, this proposed non-interventional study is designed to evaluate the safety and effectiveness of crizotinib in the real-world setting in Europe and in the United States (US).

NSCLC accounts for approximately 85% of cases of lung cancer (Sher, Dy, and Adjei 2008)[1] and is a leading cause of mortality in developed countries (Jemal et al. 2011).[2] NSCLC has low response rates to conventional chemotherapeutic regimens. United States Surveillance, Epidemiology, and End-Results (SEER) data show that the 5-year survival rate between 2002 and 2008 among all NSCLC patients was only 17.5% (Howlader et al. 2012),[3] and median survival has been estimated to be less than 1 year after diagnosis (Schiller et al. 2002).[4]

Treatment for NSCLC depends on stage at diagnosis. For early-stage, non-invasive lung cancers, surgical resection may be sufficient treatment. More commonly, however, surgical resection is followed by chemotherapy and radiation. In advanced-stage (ie, Stage IV) NSCLC, surgical resection and radiation are often replaced by chemotherapy, except in the case of palliative therapy. In such NSCLC cases treatment most likely includes combination chemotherapy with a platinum-based regimen. In addition, targeted therapy may be used as described in detail below.

An increased understanding of molecular abnormalities in lung cancer has spurred recent research efforts focused on identifying molecular targets for therapy. One abnormality that is particularly common in NSCLC is epidermal growth factor receptor (EGFR) mutation. Two EGFR tyrosine kinase inhibitors (TKIs), erlotinib (TARCEVA®) and gefitinib (IRESSA®) have been developed and approved to treat EGFR mutation in advanced-stage NSCLC patients.

ALK rearrangements are a novel target for the treatment of NSCLC (Soda et al. 2007).[5] When the ALK gene is translocated, chimeric proteins are generated, leading to the deregulation of cell proliferation, survival and cell cycling (Chen et al. 2008).[6] These rearrangements are found in approximately 2.7 (Varella-Garcia et al. 2010)[7] -7% (Soda et al. 2007)[5] of NSCLC cases, with a higher incidence in younger patients and in adenocarcinomas. Evidence with regard to the association between ALK rearrangements and smoking history is conflicting: while some reports have found ALK rearrangements in both

smokers and never smokers, others have found significant correlation with never or light smokers (Tiseo et al. 2011).[8] ALK rearrangements are detected using several methods. In the United States, break-apart fluorescence in situ hybridization (FISH) assay has been approved by the Food and Drug Administration (FDA) as the companion diagnostic test to detect ALK-rearranged NSCLC in conjunction with accelerated approval of crizotinib; likewise such a companion diagnostic has received European Conformity mark in the European Union and is being used in conjunction with conditional approval of crizotinib. ALK rearrangements can also be detected using reverse transcriptase polymerase chain reaction (PCR) and immunohistochemistry.

Crizotinib administered orally at a starting dose of 250 mg BID demonstrated robust and clinically meaningful efficacy in patients with ALK-positive advanced NSCLC regardless of treatment line. This conclusion is supported by the results of 2 randomized Phase 3 studies that both clearly demonstrated that crizotinib provided statistically significant, robust, and clinically meaningful improvement in independent radiology review (IRR)-assessed Progression-free survival (PFS): in Study A8081014 as compared with platinum-based combination chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) in the treatment of patients with previously untreated ALK-positive advanced non-squamous NSCLC (median PFS 10.9 months vs 7.0 months; HR: 0.454, p-value <0.0001), and in Study A8081007 as compared with single-agent chemotherapy (pemetrexed or docetaxel) in the treatment of patients with previously treated ALK-positive advanced NSCLC (median PFS 7.7 months vs 3.0 months; HR: 0.487, p-value <0.0001).

A number of important risks have been associated with crizotinib including hepatotoxicity, pneumonitis/ interstitial lung disease (ILD), QT interval prolongation, bradycardia, vision disorder, neuropathy, leukopenia, gastrointestinal (GI) perforation, renal cyst, and edema across the crizotinib clinical trials (including Studies A8081001, A8081005, A8081007, and A8081014); each of these risks is listed in the crizotinib label or Summary of Product Characteristics (SmPC) and the US Label. In Study A8081014, all-causality elevated transaminases were reported for 61 (35.7%) patients in the crizotinib arm and 22 (13.0%) patients in the chemotherapy arm. All-causality hepatotoxicity was reported for 2 (1.2%) patients in the crizotinib arm and 0 patients in the chemotherapy arm. All-causality adverse events suggestive of hepatotoxicity occurred with a frequency of 33.3% across the crizotinib clinical trials. Drug-induced hepatotoxicity with fatal outcome has occurred with a frequency of <1% in crizotinib-treated patients across the crizotinib clinical trials. Crizotinib has also been associated with severe, life-threatening, or fatal interstitial lung disease/pneumonitis. In Study A8081014, all-causality ILD/ pneumonitis was reported for 2 (1.2%) patients in the crizotinib arm and 1 (0.6%) patient in the chemotherapy arm. Severe, life-threatening, or fatal treatment-related ILD/ pneumonitis has occurred in <2% of patients across the clinical studies based on the assessment by an independent review committee. Additionally, all-causality Electrocardiogram QT interval corrected for heart rate (QTcF) prolonged was reported for 10 (5.8%) patients in the crizotinib arm and 3 (1.8%) patients in the chemotherapy arm in Study A8081014. Grade 3 Electrocardiogram QT prolonged AEs have occurred in <2% of patients across clinical trials. There have been no Grade 4 AEs of Electrocardiogram QT prolonged in the clinical trials.

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One of the most common adverse events of crizotinib is vision disorder. All-causality vision disorder was reported for 122 (71.3%) patients in the crizotinib arm and 16 (9.5%) patients in the chemotherapy arm in Study A8081014. Patients reported each event lasting ≤1 minute and visual effects were not at all or a little bothersome. As reported by patients who completed the Visual Symptom Assessment Questionnaire (VSAQ-ALK), visual disturbances occurred at a frequency of >1 day/week for most patients, lasted ≤1 minute, and had minimal or no impact on daily activities. Across the clinical trials, all-causality adverse events suggestive of vision disorder occurred with a frequency of 63.6 %. All-causality bradycardia in Study A8081014 was reported for 23 (13.5%) patients in the crizotinib arm and 1 (0.6%) patients in the chemotherapy arm. Across the clinical trials, all-causality adverse events suggestive of bradycardia occurred with a frequency of 12.3%. In Study A8081014, all-causality neuropathy was reported for 35 (20.5%) patients in the crizotinib arm and 38 (22.5%) patients in the chemotherapy arm. All-causality adverse events suggestive of neuropathy occurred with a frequency of 24.9% (95% CI 22.87, 27.07) across the clinical trials. In Study A8081014, all-causality neutropenia was reported for 36 (21.1%) patients in the crizotinib arm and 51 (30.2%) patients in the chemotherapy arm. All-causality leukopenia was reported for 12 (7.0%) patients in the crizotinib arm and 26 (15.4%) patients in the chemotherapy arm. Across clinical trials with crizotinib, all-causality adverse events suggestive of leukopenia occurred with a frequency of 27.4%. Evaluation of leukopenia by laboratory values shows that approximately 75% were Grade ≤1. Evaluation of neutropenia by laboratory values shows that the proportion of patients with Grade ≤1 was lower (69%). There is no case of GI perforation reported in Study A8081014. Across the clinical trials, all-causality adverse events suggestive of gastrointestinal perforation occurred with a frequency of 0.2%. In addition, a number of other adverse events have been considered potential risk related to crizotinib, including malignant melanoma and photosensitivity.

While all of the above risks have been observed in a clinical trial setting, it is important to characterize risks associated with crizotinib in routine practice and in subpopulations of patients that may be vulnerable to these risks. Therefore, ongoing monitoring of these risks is important to further evaluate crizotinib's role in their etiology.

Moreover, a number of populations were either not studied, or insufficiently studied, in the pre-authorization phase. For instance, crizotinib has not been well-studied in populations with hepatic impairment. Given that the product is metabolized extensively in the liver, hepatic impairment may augment plasma crizotinib concentrations. Similarly, in the majority of clinical trials, patients were excluded if they had severe forms of renal impairment. Further, the experience in elderly patients (65 years of age or older) is limited, Additional research in this population is therefore warranted.

This multinational post-authorization active safety surveillance study using existing health care data sources in Europe and the US is designed to monitor the safety of crizotinib in a real-world setting. Its primary objective is to estimate the incidence of hepatotoxicity, pneumonitis/ILD, QTc prolongation related events, bradycardia, and vision disorder among lung cancer patients receiving crizotinib dispensation/prescription in the routine clinical setting. It also aims to evaluate the effectiveness of crizotinib and further characterize the safety of crizotinib in subgroups, including lung cancer patients with brain metastases, renal

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

and hepatic impairment, and the elderly. In the case of rare exposures, such as crizotinib treatment, as well as rare safety outcomes, an active surveillance study using existing health care data sources permits collection of safety data in an efficient and timely manner, compared to a study involving primary data collection.

In April, 2014, the US FDA granted accelerated approval to ceritinib (ZKADIA®) for the treatment of patients with ALK-positive, metastatic NSCLC with disease progression on or who are intolerant to crizotinib. In order to contextualize the findings, data will be obtained on the same risks among lung cancer patients receiving dispensation/prescription of ceritinib, erlotinib or gefitinib. Each of the 3 drugs is a TKI that is formulated for oral administration. Moreover, all 3 products are indicated to treat advanced NSCLC and thus are likely to be administered to a similar patient population regardless of ALK tumor status.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to European Medicines Agency (EMA).

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Objectives

This active safety surveillance study using existing health care data sources in Denmark, Finland, the Netherlands, Sweden and the US evaluates safety outcomes and effectiveness among lung cancer patients receiving crizotinib dispensation/prescription over an approximately 3-year period under real-world conditions. To contextualize the findings, this study obtains data among lung cancer patients receiving dispensation/prescription of ceritinib, erlotinib or gefitinib in the same data sources during the study period. In addition, the study also collects data on other cancer patients receiving crizotinib dispensation/prescription.

8.1.1. Primary Objective

- To estimate the incidence rate and incidence proportion over an approximately 3-year period of observation for hepatotoxicity, pneumonitis/ILD, QTc prolongation related events, bradycardia, and visual disorders among lung cancer patients receiving crizotinib dispensation/prescription.

8.1.2. Secondary Objectives

- To estimate the incidence rate and incidence proportion over an approximately 3-year period of observation for renal cysts, edema, leukopenia, neuropathy, malignant melanoma, GI perforation, and photosensitivity among lung cancer patients receiving crizotinib dispensation/prescription.
- To estimate Kaplan-Meier survival probability over one-year, two-year, and three-year periods of observation among lung cancer patients receiving crizotinib dispensation/prescription.
- To estimate the incidence rate and incidence proportion over an approximately 3-year period of observation for hepatotoxicity, pneumonitis/ILD, QTc prolongation related events, bradycardia, visual disorders, and other safety outcomes among lung cancer patients receiving dispensation/prescription of ceritinib, erlotinib or gefitinib.

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- To estimate Kaplan-Meier survival probability over one-year, two-year, and three-year periods of observation among lung cancer patients receiving dispensation/prescription of ceritinib, erlotinib or gefitinib.

- To describe clinical characteristics, comorbidities, and concomitant medications of patients receiving dispensation/prescription of crizotinib, ceritinib, erlotinib or gefitinib.

- To describe demographics, clinical characteristics and comorbidities of patients receiving dispensation/prescription of crizotinib for other cancer.

9. RESEARCH METHODS

9.1. Study Design

This is a non-interventional, active safety surveillance study using existing health care data sources in Europe and the US to evaluate safety outcomes among lung cancer patients receiving dispensation/prescription of crizotinib, ceritinib, erlotinib, or gefitinib during an approximately 3-year period of observation.

9.2. Setting

The study population includes eligible patients who are diagnosed with primary lung cancer and receive dispensation/prescription for crizotinib, ceritinib, erlotinib, or gefitinib as recorded in national or regional health care databases in Denmark, Finland, the Netherlands, Sweden, and the US from September 1st, 2011 to June 30th, 2017. In addition, the study population will also include all other cancer patients receiving crizotinib dispensation/prescription.

9.2.1. Inclusion Criteria

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

1. At least 1 dispensation/prescription of crizotinib, ceritinib, erlotinib, or gefitinib no less than 6 months prior to the end of the study.

2. A record of primary lung cancer diagnosis for patients receiving dispensation/prescription of erlotinib, gefitinib, or ceritinib prior to or at the time of the first dispensation/prescription.

3. For patients receiving dispensation/prescription of erlotinib or gefitinib, there is no prior record of dispensation/prescription of erlotinib or gefitinib for at least 6 months before the first dispensation/prescription during the study period.

4. Have a record of at least a 6 month length prior to the first dispensation/prescription of crizotinib, ceritinib, erlotinib, or gefitinib.

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9.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

9.3. Variables

Variables and their roles are shown below. Data sources are described in Appendix 1.

Table 1. Variables, Roles, Data Sources and Operational Definitions

Variable	Role	Data source(s)	Operational definition
Patient demographic and clinical characteristics			
Age	Baseline characteristic, Sub-group identifier	See Appendix 1	N/A
Sex	Baseline characteristic	See Appendix 1	N/A
Lung cancer (primary)	Baseline characteristic	See Appendix 1	Appendix 2
Histology	Baseline characteristic	See Appendix 1	N/A
Cancer stage	Baseline characteristic	See Appendix 1	N/A
Brain metastases	Sub-group identifier	See Appendix 1	See Appendix 2
Cancer tumor genotyping	Baseline characteristic	See Appendix 1	N/A
Other cancers╪	Baseline characteristic	See Appendix 1	See Appendix 2
Drugs dispensed			
Crizotinib	Exposure	See Appendix 1	See Appendix 2
Ceritinib	Exposure	See Appendix 1	See Appendix 2
Gefitinib	Exposure	See Appendix 1	See Appendix 2
Erlotinib	Exposure	See Appendix 1	See Appendix 2
Other drugs prescribed	Risk factor/confounder (proxy indicators), sub-group identifiers	See Appendix 1	See Appendix 2
Primary study endpoints			
Hepatotoxicity	Outcome¥	See Appendix 1	See Appendix 2
Pneumonitis/ILD	Outcome¥	See Appendix 1	See Appendix 2
QTc prolongation related events	Outcome¥	See Appendix 1	See Appendix 2
Bradycardia	Outcome¥	See Appendix 1	See Appendix 2
Vision disorders	Outcome¥	See Appendix 1	See Appendix 2
Secondary study endpoints			
Renal cysts	Outcome¥	See Appendix 1	See Appendix 2
Edema	Outcome	See Appendix 1	See Appendix 2
Leukopenia	Outcome	See Appendix 1	See Appendix 2
Neuropathy	Outcome¥	See Appendix 1	See Appendix 2
GI perforation	Outcome¥	See Appendix 1	See Appendix 2
Malignant melanoma	Outcome¥	See Appendix 1	See Appendix 2
Photosensitivity	Outcome	See Appendix 1	See Appendix 2
Mortality	Outcome	See Appendix 1	See Appendix 2
Comorbidities[1]			
Pre-existing renal impairment	Sub-group identifier	See Appendix 1	See Appendix 2
Pre-existing hepatic impairment	Sub-group identifier	See Appendix 1	See Appendix 2

╪ For patients receiving crizotinib dispensation/prescription only

[1] This list represents illustrative comorbidities only; additional comorbidities will be considered and added as appropriate

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¥Sub-group analyses will also be conducted for those with and without pre-existing diagnoses or treatment for these conditions. The conditions will be captured using the similar codes for the specific outcomes of interests.

9.4. Data Sources

9.4.1. Sources of Population-Based Data

A number of European countries and the US have health care databases which provide a unique opportunity for the post-approval surveillance of anti-cancer drugs. This study links existing national or regional health care databases within Sweden, Denmark, the Netherlands, Finland, and the US, which contain medical information for approximately 37.65 million people; the size of these databases will facilitate evaluation of exposures and rare outcomes in a cohort setting. Each participating country's health care databases are described below, followed by a discussion of sources to be used for key study variables. As access to these databases requires permission from various governing bodies, if permission in one of the above-specified countries is not granted then the country will not participate in this study.

Sweden: The Swedish register system is a large, complete source of population-based data, including data on the entire Swedish population of 9.5 million individuals. These databases include the following: Total Population Register, Cause-of-Death Register, Patient Register, Swedish Cancer Register, and the Swedish Prescribed Drug Register; these registers are linked via each individual's unique personal identification number (termed the national registration number), used by each resident throughout life.

Denmark: Denmark's health information systems are similarly comprehensive and population-based, including data for the country's entire population of 5.6 million individuals and a dynamic cohort of about 8 million individuals. Databases, linked by a unique identifier (central person registration number), include the Central Person Registry, Danish National Registry of Patients, Cause of Death Registry, the Danish Cancer Registry, the Pathology Database, and the Danish National Database of Reimbursed Prescriptions.

Netherlands: The Dutch PHARMO Record Linkage System (RLS) includes information on 3 million residents in the Netherlands, and includes data from the General Practitioner database, Dutch Hospital Database, Clinical Laboratory File, Community Pharmacy Database, Hospital Pharmacy Database, Mortality Database, among others. In addition, the PHARMO RLS can be linked with the Eindhoven Cancer Registry, in the Southeastern Netherlands, covering a population of roughly 1 million residents. Databases are linked probabilistically, based on gender, date of birth, first initial, first letter, and soundex code of last name, and the first four characters of the zip code.

Finland: Finnish national health-care databases include information on the country's entire population of 5.38 million residents. Databases are linked via a unique personal identification number held by each Finnish citizen, and include a Hospital Care Registry, Primary Care Registry, Vital Statistics Registry, Prescription Registry, and Cancer Registry.

Each of these European databases routinely record key data elements critical to the research objective of this study, namely: 1) Patient characteristics; 2) Inpatient and outpatient hospital diagnoses (safety outcomes of interest and comorbidities); 3) Drug dispensations, and 4)

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Medical procedures. In prescription databases, drugs dispensed in community outpatient pharmacies are classified according to the global Anatomical Therapeutic Chemical (ATC) classification system. Data on strength and package size, number of packages, and dispensing date are included in the prescription database, and duration of a prescription can be estimated based on the package size, the number of packages, and the daily defined dose (DDD). Methods of recording medical procedures vary across countries. In the Netherlands, procedures are recorded using Classificatie van verrichtingen (CVV) codes, which are based on the ICPM (International Classification of Procedures in Medicine). In Denmark and Finland, procedures are recorded using NOMESCO codes, and in Sweden, procedures are recorded using Klassifikation av kirurgiska åtgärder codes (Swedish version of NOMESCO codes).

US: The Optum database consists of patients' longitudinal records of enrollment, inpatient and outpatient medical claims, pharmaceutical claims, and laboratory results for over 65 million unique managed care members across the United States. This database consists of de-identified Health Insurance Portability and Accountability Act compliant patient records of enrollees of a large health insurance plan in the United States. For 2013, data relating to approximately 12.6 million individuals with both medical and pharmacy benefit coverage are available. Underlying information is geographically diverse across the US and fairly representative of the US population. Of the 12.6 million individuals, race/ethnicity, and financial resource information was available for approximately 75-85% of the individuals. Pharmacy claims data using National Drug codes (NDC) also include drug name, dosage form, drug strength, fill date, days of supply, and de-identified patient and prescriber codes, allowing for longitudinal tracking of medication refill patterns and changes in medications. Medical claims or encounter data are collected from all available health care sites (inpatient hospital, outpatient hospital, ER, physician's office, surgery center, etc.) for virtually all types of provided services, including specialty, preventive and office-based treatments. Medical claims and coding conform to insurance industry standards. Medical claims include: multiple diagnosis codes recorded with the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM or ICD-10-CM) diagnosis codes; procedures recorded with ICD-9-CM or ICD-10-CM procedure codes, Current Procedural Terminology (CPT), or Healthcare Common Procedure Coding System (HCPCS) codes; site of service codes; provider specialty codes; revenue codes (for facilities); paid amounts; and other information. Typically, facility claims do not include medications dispensed in hospital. Pharmacy claims are typically added to the research database within six weeks of dispensing; approximately six months following the delivery of services are required for complete medical data in the research database.

The source of data for each key element, for each participating country, is illustrated in Appendix 1.

9.4.2. Adjudication and Validation of Primary Endpoints from Population-Based Health Care Data Sources

To evaluate the accuracy of international classification of diseases (ICD) diagnostic codes and procedural codes used to capture primary safety endpoints in this study, inpatient and outpatient medical records/charts at a hospital of all patients treated with crizotinib and a

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same number of patients treated with ceritinib, erlotinib or gefitinib, would be abstracted matched by the same hospital/center and age at time of lung cancer diagnosis (±5 years) in Sweden, the Central region of Denmark, in the Helsinki region of Finland, PHARMO databases in the Netherlands and Optum database in the US provided that approval would be granted by ethics committees, and other local and/or national governing bodies.

The process of linking administrative data to medical records/charts will vary by country. In Denmark and the US, hospital administrative data will be linked directly to medical records / charts via the unique personal identifier. In Sweden and Finland, the unique National Identification Number will be obtained in order to link the two data sources. In the Netherlands, patient administrative data will be matched to patient medical records/charts on hospital, ward, age and gender.

Case definition information (Appendix 2) from patient medical records/charts will be abstracted by local medical professionals in these countries using a standardized data abstraction form. Data abstraction forms will collect detailed information on events of interest, for example, date of onset, clinical and diagnostic evidence, and relevant laboratory testing. Next, data elements on the data abstraction forms will be entered into study databases in each of participating countries. The electronic data abstraction results for each endpoint will be reviewed by two clinical adjudicators at Aarhus University in Demark who are blinded to drug exposure status: each case will be classified as either 'definite' or 'possible' outcome or "no event" based on pre-specified event definition criteria. Cases labeled 'definite' will be those where event definition criteria are applicable and no doubt exists about the diagnosis. In the case of adjudicator disagreement, a third adjudicator will be brought in to serve as a tie breaker. If insufficient information is available to apply definition criteria but the diagnosis is not ruled out, the event will be labeled 'possible'. Given that medical professionals from the hospitals/clinics in which patients are receiving care would perform data abstraction, none of the participating countries require patient consent in order to access patient medical records/ charts. Figure 1 describes the validation process.

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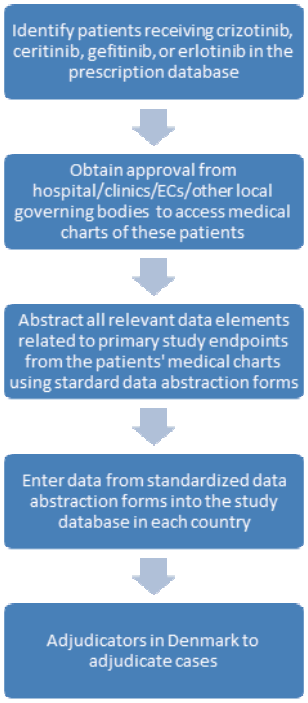
Figure 1. Process of Validating Primary Endpoints



In patients receiving dispensation/prescription of crizotinib, positive predictive values (PPV), sensitivity and specificity of the claims coding algorithms will be calculated for each primary endpoint of interest, using the medical record as the gold standard. For patients receiving dispensation/prescription of ceritinib, erlotinib or gefitinib, PPV will be estimated for each primary endpoint. Results of the validated data will be presented in the final study report.

9.5. Study Procedures

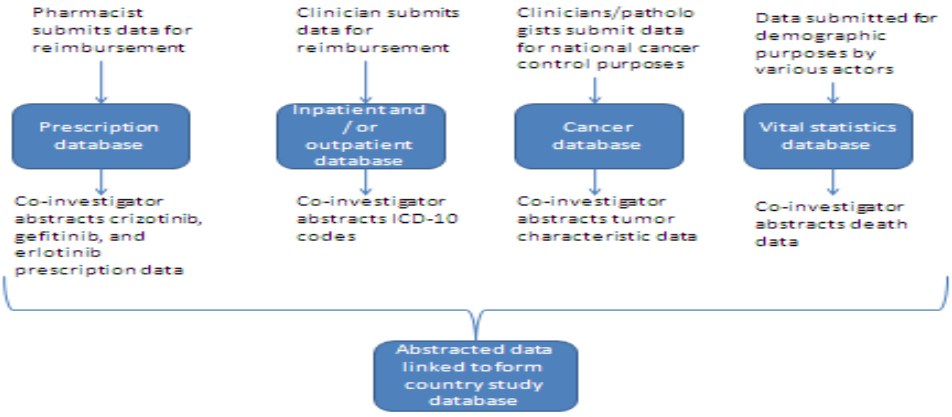
This is a non-interventional active surveillance study; therefore, patients will be prescribed treatment with crizotinib, ceritinib, erlotinib, or gefitinib as per usual clinical practice.

All data for this study will be obtained through routine data collection practices of participating countries' registers/databases as described in Figure 2. The data in the participating registers/databases are updated on a regular basis. Each investigator will obtain and manage data for this study from his/her country. Specifically, at regular intervals during the study period as described below, the pharmacy register/database within each country's data system will be queried to identify patients who have received at least 1 dispensation/prescription for crizotinib, ceritinib, erlotinib, or gefitinib and met the inclusion and exclusion criteria during the study period. For those patients receiving dispensation/prescription of at least one of these medications (and in the case of erlotinib, ceritinib, or gefitinib, a record of primary lung cancer as identified in either hospital discharge, outpatient databases, or cancer registry databases), routinely collected data will be abstracted from relevant databases for the following covariates: demographics; clinical

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

characteristics; medical history, other dispensation/prescription received in the 6-month period prior to the study start date in each country, concurrent with or subsequent to the first dispensation/prescription for crizotinib, ceritinib, erlotinib, or gefitinib during the study; comorbidities in the 6-month period prior to the study start date in each country, concurrent with or subsequent to the first dispensation/prescription for crizotinib, ceritinib erlotinib, or gefitinib during the study, and the safety endpoints of interest during the study.

Figure 2. Study Data Abstraction



The overall study period is from September 1st, 2011 to June 30th, 2017. Depending on local approval and reimbursement of crizotinib in participating countries, study commencement dates (i.e the date when the first eligible patient in these existing health care databases could join the study) have been September 1st, 2011 in the US, June 1st, 2013 in Denmark, September 1st, 2013 in Sweden, and on April 1st, 2014 in Finland and the Netherlands. The final date of data collection will vary by country, in order to account for differences between countries in lag times in recording and obtaining claims data in participating countries. The final date of data collection will be June 30th, 2017 for Demark, December 30th, 2016 for Sweden, Finland, and the Netherlands, and September 31st, 2016 for the US. Thus, countries with either delayed reimbursement/availability of crizotinib or with longer lag times , such as the Netherlands, will contribute approximately 2.75 years of data, while others with earlier approval and reimbursement of crizotinib and shorter lag times, such as the US and Denmark, will likely contribute up to 5 and 4 years of data to the study respectively. The earliest end date for following up patients in databases will be September 31st, 2016 and the latest end date of the study will be June 30th, 2017. Both dates take into consideration at least a 6-month time period for data abstraction, data analysis, and preparation for study report prior to submission of the final study report to EMA in June 2018. Data collection timelines by country are shown in Figure 3.

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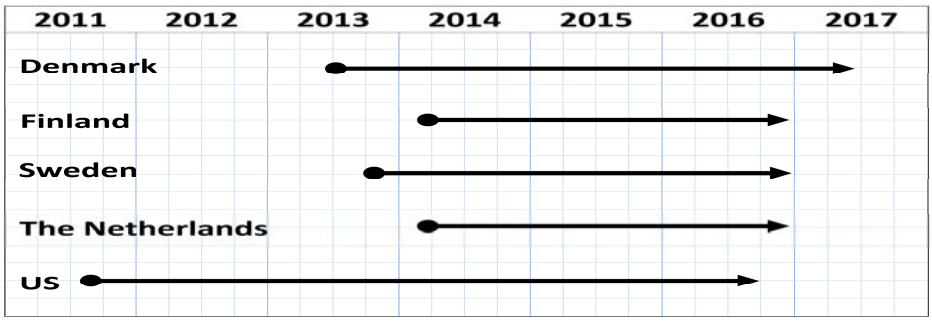
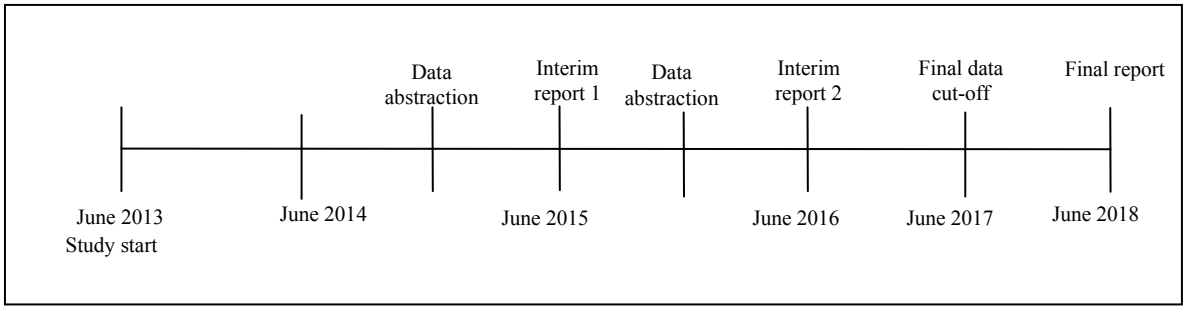
Figure 3. Study Duration by Country



Eligible patients are followed from the date of the first crizotinib, ceritinib, erlotinib, or gefitinib dispensation/prescription during the study period until the end of the study in each country, death, or loss to follow-up (whichever occurs first) for the occurrence of the endpoints of interest. To allow sufficient time to observe safety outcomes of interest, patients must receive the first dispensation/prescription of crizotinib, ceritinib, erlotinib, or gefitinib at least 6 months before the end of data collection in participating countries. For the first interim report (IR), investigators in Demark and Sweden are obtain and analyze data from their countries, with the first (IR) submission from the countries occurring in June 2015. The Netherlands will not submit the first IR, because the PHARMO database is updated by calendar year, and 2014 data will not be available until August 2015. Finland won't be able to submit the first IR as originally planned because a very limited number of patients are expected to receive crizotinib dispensation/prescription by that time due to delays in reimbursement of crizotinib. Since the US will join the study after the first IR, the US will not contribute to the first IR. For the second IR, each investigator in Demark, Sweden, Finland, the Netherlands, and the US will obtain and analyze data from his/her country in December 2015, with the second IR submission in June 2016. At the end of the study period, anonymous datasets from all participating countries will be combined for the final analysis, and a final report combining data from the five countries will be submitted in June 2018. The timing of IRs and final study report submission is shown in Figure 4.

Figure 4. Study Timeline



9.6. Study Size

All eligible lung cancer patients receiving dispensation/prescription for ceritinib, erlotinib and gefitinib, and all eligible cancer patients receiving crizotinib dispensation/prescription during the study period will be included. The estimated number of lung cancer patients likely to be included in the study is described below.

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9.6.1. Estimated Number of ALK-Positive NSCLC Patients Receiving Crizotinib Treatment

While this study will not require ascertainment of ALK-positive status, it is estimated (based on several assumptions) that 677 incident ALK-positive advanced NSCLC patients are likely treated with crizotinib over the approximately 3-year period in these countries based on its approved indication (see Table 2). Additionally, prevalent previously treated ALK-positive advanced NSCLC patients who were diagnosed prior to the start of this study in these countries could also receive crizotinib treatment after failure with 1 or more prior treatment regimens. Thus, it is possible that the total number of patients eligible for crizotinib treatment based on its approved indication and included in this study can be more than 667. However, it should be noted that physicians' perception about molecular targeted therapy, as well as both the timing and amount of reimbursement for crizotinib, may affect the number of patients likely to be treated with crizotinib within participating countries. Crizotinib may also be prescribed for other, non-NSCLC, tumors, potentially increasing the total number of patients receiving crizotinib dispensation/prescription.

Table 2. Estimated Numbers of ALK-Positive NSCLC Patients Likely Treated with Crizotinib in an approximately 3-year Database Study in Sweden, Denmark, the Netherlands, Finland, and the US

Country	Sweden	Denmark	Southeastern Netherlands	Finland	US
Population covered (millions)†	9.45	5.57	2	5.39	12.6
Incidence of lung cancer (per 100,000) (Ferlay, Parkin and Seliarova-Foucher 2010) [9]	37.2	75.9	62	40.6	60.1 [10]
Estimated number of incident ALK-positive NSCLC patients treated with crizotinib per year††	32	37	11	20	68
Estimated duration (years) of data collection in each country†††	3.25	4	2.75	2.75	5
Total in each country ††††	102	151	31	54	339
Overall total	677				

† population covered in database is based on total population figures (http://data.worldbank.org/indicator/SP.POP.TOTL) with the exception of Southeastern Netherlands and the US where population covered is based on total population for whom linkable data are available in the databases.

†† population covered in the database*incidence of lung cancer in the country*60% (newly diagnosed lung cancer in advanced stages (Howlader et al. 2012))[3] *85% (lung cancers that are NSCLC (Jemal et al. 2011))[11] *2.7% (NSCLCs that are ALK-positive (Varella-Garcia et al. 2010))[7] *65% (ALK-positive NSCLCs with advanced stages that have failed 1 or more previous treatment regimens each year).

††† takes into consideration timing of reimbursement and lag time in obtaining full complement of claims data in each country

†††† estimated number of ALK-positive NSCLC patients treated with crizotinib per year*estimated duration of data collection in each country

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9.6.2. Estimated Number of NSCLC Patients Likely Treated with Ceritinib, Erlotinib or Gefitinib

It is difficult to estimated number of NSCLC patients likely treated with ceritinib. As of February 19th, 2015, ceritinib has not been approved in the European Union. Based on several assumptions, it is estimated that approximately 2,006 incident advanced NSCLC patients with an EGFR mutation would likely be treated with either erlotinib or gefitinib over the approximately 3-year period in these countries based on their approved indication (see Table 3). Based on an estimated EGFR mutation prevalence of 30% in NSCLC patients of East Asian ethnicity and 8% in NSCLC patients of other ethnicities (Shigematsu et al. 2005)[10], the estimate of 2,006, conservatively assumes a prevalence of EGFR mutation in 8% among NSCLC patients in Sweden, Denmark, the Netherlands, Finland, and the US. Additionally, prevalent advanced NSCLC patients with an EGFR mutation that were diagnosed prior to the start of this study in these countries could also receive erlotinib or gefitinib treatment if their disease has failed 1 or more prior treatment regimens. Thus, the total number of patients who are eligible for erlotinib or gefitinib treatment based on their approved indications in this database study would likely be more than 2,006.

Table 3. Estimated Numbers of NSCLC Patients Likely Treated with Erlotinib or Gefitinib in an approximately 3-Year Study using Existing Data Sources in Sweden, Denmark, the Netherlands, Finland, and the US

Country	Sweden	Denmark	Southeastern Netherlands	Finland	US
Population covered (millions)†	9.45	5.57	2	5.39	12.6
Incidence of lung cancer (per 100,000) (Ferlay, Parkin and Seliarova-Foucher 2010)[9]	37.2	75.9	62	40.6	60.1[10]
Estimated number of incident NSCLC patients with EGFR mutation treated with either erlotinib or gefitinib per year††	94	111	33	58	201
Estimated duration (years) of data collection in each country†††	3.25	45	2.75	2.75	5
Total new users in each country ††††	303	449	91	160	1005
Overall total	2006				

† population covered in database is based on total population figures (http://data.worldbank.org/indicator/SP.POP.TOTL) with the exception of Southeastern Netherlands and the US where population covered is based on total population for whom linkable data are available in the databases.

†† population covered in the database*incidence of lung cancer in the country*60% (newly diagnosed lung cancer in advanced stages (Howlader et al. 2012))[3] *85% (lung cancers that are NSCLC (Jemal et al. 2011))[11] *8% (estimate of the proportion of NSCLCs with EGFR mutation (Shigematsu et al.2005)[11] *65% (NSCLCs with advanced stages that have failed 1 or more previous treatment regimens each year).

††† takes into consideration timing of reimbursement and lag time in obtaining full complement of claims data in each country

†††† estimated number of EGFR mutation -positive NSCLC patients treated with erlotinib or gefitinib per year*estimated duration of data collection in each country.

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9.6.3. Precision Calculations

This active safety surveillance study aims to estimate the incidence of safety endpoints among patients receiving crizotinib dispensations/prescriptions, rather than conduct a hypothesis testing. Therefore, calculations for the precision of incidence estimates are most appropriate. According to data from crizotinib clinical trials, all incidence proportions of safety endpoints of interest in ALK positive NSCLC patients treated with crizotinib range from 0.2% to 63.6% (Xalkori RMP 2014 version 6).[13] The estimated precision for the proportions of safety endpoints was presented on Table 4 with the following assumptions:

- Estimated 677 ALK positive NSCLC patients likely receiving crizotinib dispensations/prescriptions in the study;
- Two-sided 95% confidence limits.

Based on these calculations, given 677 ALK positive NSCLC patients likely treated with crizotinib, this study would have achieved the precision of observed incidence proportions of a safety outcome between ±0.34% and ±3.69% where the incidence proportion of the safety outcome ranges from 0.2% to 63.6% respectively. The Confidence Interval (CI) for One Proportion with simple asymptotic formula from PASS software (version 2008.0.5) was used for the calculations.

Table 4. Precision Calculations for Different Incidence Proportions

Incidence proportion of a safety outcome in ALK positive NSCLC patients treated with crizotinib	Precision of observed incidence proportion of a safety outcome in ALK positive NSCLC patients treated with crizotinib in the study	95% CIs of observed incidence proportion of a safety outcome in ALK positive NSCLC patients treated with crizotinib in the study
0.2%	±0.34%	-0.14%-0.54%
1.6%	±0.95%	0.66%-2.55%
2%	±1.06%	0.95%-3.06%
3%	±1.29%	1.72%-4.29%
4%	±1.48%	2.52%-5.48%
5%	±1.64%	3.36%-6.64%
10%	±2.26%	7.74%-12.26%
20%	±3.01%	16.99%-23.01%
30%	±3.45%	26.55%-33.45%
40%	±3.69%	36.31%-43.69%
50%	±3.77%	46.23%-53.77%
60%	±3.69%	56.31%-63.69%

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9.7. Data Management

9.7.1. Data Management

All data for this study is collected through the routine data collection practices of databases in the participating countries as described in Section 9.5. The data to be used in the study include the study outcomes, pre-existing renal and hepatic conditions, comorbidities, use of crizotinib, ceritinib, erlotinib, or gefitinib, and tumor characteristics as described in Appendix 2. The data in the databases are updated continually. Investigators of each country is either independently generate the study data by linking the regional or national databases or receive study specific data generated by the owner of national or regional databases.

Data will be stored in the form of SAS or STATA datasets at secure servers, and will be maintained by a trained cadre of statisticians and data managers ensuring compliance with national regulations. SAS or STATA software will be used for statistical analyses.

9.7.1.1. Data Linkage

Investigators of each country will either independently generate the study data by linking the regional or national databases or receive study specific data generated by the owner of national or regional databases. In Sweden, Denmark, and Finland, data from all registries are linked on the individual level using a unique personal identifier that is assigned to all residents at birth or immigration. In Sweden, the National Board of Health and Welfare will link the data using the unique National Identification Number, and will deliver the data after providing a unique individual serial number which allows linkage of the data. In Denmark, study investigators will link individual databases based on the unique personal number. In Finland, collaborators at EPID Research would receive de-identified patient data. In the Netherlands, the PHARMO RLS links data from different sources via validated algorithms that do not include patient identifiers, and generate patient numbers that are unique to the PHARMO RLS. The Optum database in the US links different claims through unique patient identification numbers.

9.7.1.2. Data Cleaning

Data will be recorded by health authorities using their standard quality procedures. Frequency tables of variables of interest will be generated to check for plausibility and consistency. Logic checks comparing similar data points between registers or databases will be conducted on a regular basis.

9.8. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan, which will be dated, filed and maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

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The study population will include all patients who are eligible for this study. All statistical analyses will be descriptive. Comparisons between patients receiving crizotinib dispensation/prescription and patients receiving ceritinib, erlotinib or gefitinib dispensation/prescription will not be formally evaluated using statistical tests due to the anticipated limited number of patients receiving crizotinib dispensation/prescription and the rarity of safety outcomes of interest.

Demographics and baseline characteristics will be tabulated. Frequencies and percentages will be presented for categorical variables. For continuous variables, means, standard deviations, and ranges, or medians and inter-quartile ranges, will be reported as appropriate.

Incidence rates and incidence proportions for all study endpoints will be calculated separately for patients receiving dispensation/prescription of crizotinib, ceritinib, erlotinib or gefitinib for primary lung cancer. The incidence rate is the number of patients with each new safety endpoint during a specified time period at risk divided by person-time at risk in the timeframe of interest. Person-time at risk will be calculated in the following two ways: 1) follow-up time and 2) time on treatment for each treatment.

In terms of incidence rates using follow-up time as person-time at risk, the numerator will be the total number of patients with an incident safety endpoint diagnosis during the patient follow-up period, and the denominator will be total patient-years of follow-up. For patients experiencing a safety endpoint, patient-years at risk will be derived by calculating [(the date of safety endpoint diagnosis minus the date of the first dispensation/prescription for crizotinib, ceritinib, erlotinib or gefitinib) divided by 365.25]. For patients not experiencing the endpoint, patient-years at risk will be derived by calculating [(the date of last patient follow-up minus the date of the first dispensation/prescription for crizotinib, ceritinib, erlotinib or gefitinib) divided by 365.25].

$$\text{Incidence rate} = \frac{\text{Number of new cases during follow-up}}{\text{Sum of person-time contributed during follow-up}}$$

For incidence rates using time on treatment as the measure of person-time at risk, all patients would be given a 28-day at risk period after the end of each treatment (ie, the last day of dispensation/prescription coverage) for each product to allow for residual treatment effects. The numerator will be the total number of patients with an incident safety endpoint diagnosis up to 28 days after the end of the treatment period with each individual product, and the denominator will be total person-years treated with that product, plus up to a 28 day at-risk period at the end of each treatment period. Thus, incidence rates using time on treatment will allow patients on more than one of the study drugs (eg, both erlotinib and gefitinib) to contribute data toward each exposure, if applicable.

For patients experiencing the endpoint, total person-years treated for the patients will be derived in two ways depending on pattern of dispensation. If a patient receives dispensation/prescription for treatment continuously during the study, person-years treated for the patient will be derived by calculating [(the difference between the date of a safety endpoint diagnosis and the date of the first dispensation/prescription) divided by 365.25]. In

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

the case of intermittent treatment with the same product and if a gap between treatment is 28 days or less, then the treatment would be considered continuous. If a patient receives intermittent dispensation/prescription with a gap between treatment greater than 28 days, person-years treated for the patient will be derived by calculating [(the difference between the date of a safety endpoint diagnosis and the date of the first dispensation/prescription for the product preceding the endpoint) minus (days without the dispensation/prescription for that product between the date of the first dispensation/prescription and the date of the safety endpoint diagnosis) divided by 365.25.

For patients not experiencing a safety endpoint, total person-time treated for the patients will be similarly derived in two ways depending on pattern of dispensation/prescription. If a patient receives a dispensation/prescription continuously during the study, person-years treated for the patient will be derived by calculating [(the difference between the last coverage date of last dispensation/prescription and the date of the first dispensation/prescription plus a 28-day at risk period) divided by 365.25]. If a patient receives intermittent dispensation/prescription of a product, person-years treated for the patient for the product will be derived by calculating [(the difference between the last coverage date of the last dispensation/prescription of the product and the date of the first dispensation/prescription of the product plus up to a 28-day at risk period after the end of each treatment of the product) minus (days without the dispensation/prescription for that product between the date of the first dispensation/prescription and the last coverage date of the last dispensation/prescription of the product) divided by 365.25].

$$\text{Incidence rate} = \frac{\text{Number of new cases during treatment}}{\text{Sum of person-time on treatment contributed}}$$

The incidence proportion is defined as the number of patients with each incident safety endpoint diagnosis divided by the number of people observed in the treatment group during the study.

For crizotinib treated cancer patients, incidence rates and incidence proportions for primary study endpoints will be calculated for 1) all cases identified in administrative data (ie, ICD- and/or procedure-coded cases), 2) definite cases, and 3) definite and possible cases, as described under Section 9.4.2. Additional sensitivity analyses on primary endpoints will be conducted in Denmark, Finland, and the US given that validation of the codes is done among a proportion of the entire population. For patients treated with ceritinib, erlotinib or gefitinib in these countries, incidence rates and incidence proportions will be calculated for all cases identified in administrative data or claims data only; however, a sensitivity analysis will be conducted on primary endpoints based on the sensitivity, specificity, and PPV calculated for each endpoint using the validation sample.

Estimates of overall survival probability at one-year, two-year, and three-year periods for patients receiving crizotinib, ceritinib, gefitinib, or erlotinib dispensation/prescription will be calculated with the use of the Kaplan-Meier method. Additionally, subgroup analyses on overall survival probability will be conducted. Subgroup analyses by age (dichotomized at ≥65 years old), presence or absence of brain metastases, and pre-existing renal or hepatic

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impairments at baseline will be conducted for all primary study endpoints. Moreover, time to occurrence of pneumonitis/ILD among NSCLC patients receiving crizotinib, ceritinib, erlotinib, or geftinib dispensation/prescription will be estimated and features and risk factors of pneumonitis/ILD will be described.

Sensitivity, specificity, and PPV of ICD codes used for each safety endpoint against data on pre-specified diagnostic criteria of the endpoint abstracted from medical charts/ records will be calculated for the validation of the codes in Sweden, Demark, the Netherlands, and in the US.

- Sensitivity is the proportion of patients with the endpoint identified by medical chart (ie, true cases) that is correctly identified as having the endpoint by ICD codes.

$$\text{Sensitivity} = \frac{\text{Number of true cases identified as having the endpoint via ICD codes}}{\text{Total number of true cases with the endpoint identified by medical chart}}$$

- Specificity is the proportion of patients without the endpoint based on medical chart (ie, non-cases) that is correctly identified as not having the endpoint by ICD codes.

$$\text{Specificity} = \frac{\text{Number of true non-cases identified via ICD codes}}{\text{Total number of non-cases based on medical chart}}$$

Positive Predictive Value is the proportion of patients identified by ICD codes as having the endpoint in question who actually have the endpoint identified by medical chart.

$$\text{PPV} = \frac{\text{Number of true cases confirmed by medical chart}}{\text{Total number of cases identified via ICD codes}}$$

Additional exploratory analyses and sensitivity analyses may be conducted.

9.8.1. Interim Report

The incidence of each primary study endpoint will be assessed on an interim basis during the study as described under the study procedures (Section 9.5). These analyses will be conducted for each participating country separately and will be descriptive in nature. Frequencies and percentages of subjects will be presented for categorical variables. For continuous variables, means, standard deviations and ranges, or medians and inter-quartile ranges, will be reported as appropriate. Calculations for interim reports will be based on all cases identified in administrative data (ie, will include non-validated cases). Given the limited data available, the interim reports are likely to be reduced compared with the final study report.

9.9. Quality Control

Investigators are responsible for following their standard institutional procedures to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, description of available data, and extent of validation of endpoints.

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9.10. Limitations of the Research Methods

This study has several limitations. One limitation is the dependency on drug dispensing from pharmacy/hospital data as a measure for actual use of the drug. It is possible that a patient may not actually take the drug. However, since crizotinib, ceritinib, erlotinib, and gefitinib are molecular targeted agents, it is reasonable to assume that the majority of patients who receive a dispensation/prescription for these drugs would actually take it until the patient experiences disease progression or experiences an adverse reaction that is not tolerable or determined by the physician to warrant discontinuation. Drug treatments received during hospitalization are not recorded in the pharmacy databases/prescription register and inpatient databases, with exception of a drug which has a hospital drug code. Therefore, it is possible that patients who only receive crizotinib, ceritinib, erlotinib, or gefitinib treatment during hospitalization will not be included in this study unless there is a hospital drug code for these drugs. Given that the vast majority of patients would receive these drugs in the outpatient setting, it is reasonable to assume that a negligible number of patients exposed to these products would be missed. Another limitation is that this study relies on administrative claims data. Conditions not requiring any treatment tend to be systematically undercoded (eg, vision disorders, renal cyst, and mild edema) in administrative databases. However, a validation of some of these ICD codes used to capture safety endpoints will be conducted among patients receiving crizotinib dispensation/prescription and the same number of patients receiving dispensation/prescription of ceritinib, erlotinib or gefitinib. This will allow evaluation of the magnitude of undercoding as well as provide more accurate estimation of the incidence of primary safety endpoints in databases in these countries.

Worsening existing conditions can only be identified through inference based on clinical treatment of the conditions. For example, no code differentiates mild bradycardia from serious bradycardia unless patients with serious bradycardia receive a drug or a procedure to treat or correct the condition. Likewise, use of administrative data makes it difficult to stratify patients by severity of illness for a specific condition, though it is possible to stratify patients based on the number and type of comorbid conditions. Furthermore, laboratory tests and ECG results are either not recorded or not reliably recorded in these existing databases. Thus, this study is unable to adequately evaluate safety outcomes such as abnormal liver function tests and ECG changes. Additionally, in Finland, the US, and Sweden it cannot be determined from data sources whether a genetic test for ALK positive tumor or EGFR mutation is done. It is therefore possible that not all patients receiving dispensation/prescription for these products would be screened in these countries. However, since this is an observational study, lung cancer patients in this study will receive dispensation/prescription of these products as per usual practice, and therefore, it is reasonable to assume that the large majority of patients receive dispensation/prescription for these products as per their indications. Moreover, genetic status of patients' tumors is not expected to significantly affect the incidence of the primary safety endpoints.

One of the key strengths of this study is that the use of large existing health care data sources allows for the possibility of studying the safety of crizotinib (a rare exposure), as well as rare safety outcomes, in a reasonable period of time and in the context of routine clinical care. In addition, observational data sources like administrative claims data and cancer registry data

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

may provide insight regarding safety outcomes in patients who are underrepresented in crizotinib clinical trials, including patients with brain metastases, pre-existing renal or hepatic impairment, and elderly patients. Furthermore, results based on this population-based study would be more generalizable than those obtained from clinical trials.

9.11. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information and Consent

Not applicable.

10.2. Patient Withdrawal

Not applicable.

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

Protocol review and approval by Independent Ethics Committees, Data Privacy, and/or Data Protection boards will be sought as required by local law. All correspondence with the IEC will be retained in the Investigator File, and copies of IEC approvals will be forwarded to Pfizer.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), EMA, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Draft Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study uses existing health care databases, in which it is generally not possible to link (ie, identify a potential association between) a particular product and medical event for any individual.

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

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

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

- All serious and non-serious AEs with explicit attribution to any Pfizer drug that appear in the reviewed information must be recorded on the chart abstraction form and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these safety events with an explicit attribution to (AEs) or associated with use of (other scenarios listed above), a Pfizer product, the data captured in the medical record will constitute all clinical information known regarding these adverse events. No follow-up on related adverse events will be conducted; Exposure during pregnancy cases will be followed up, where possible, for pregnancy outcomes.

All research staff members will complete the Pfizer requirements regarding training on the following: *"Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* and any relevant Your Reporting Responsibilities supplemental training. This training will be provided to all research staff members prior to study start. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Interim reports and the final study report will be submitted to EMA. The manuscript of the study will be submitted to a peer reviewed journal for publication.

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

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090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

Appendix 1. DATA SOURCES BY COUNTRY

	Sweden	Denmark	Netherlands	Finland	US
Patient demographic and clinical characteristics					
Age	Patient register	Danish Civil Registration System	PHARMO central patient register	All registers	Medical claims
Sex	Patient register	Danish Civil Registration System	PHARMO central patient register	All registers	Medical claims
Lung cancer	ICD-10 codes in Patient Register or ICD-O codes in the Cancer Register	ICD-10 or ICD-O codes in the Danish Cancer Registry or Danish National Registry of Patients	ICD-O codes in the Eindhoven Cancer Registry or SNOMED CT in Pathology Database	Hospital care register and / or Cancer Register	Medical claims
Histology	ICD-O codes in the Cancer Register	Danish Cancer Register and SNOMED CT in Pathology Register	Eindhoven Cancer Registry or SNOMED CT in Pathology Database	Hospital care register and / or Cancer Register	May be available in Medical claims or laboratory database
Stage	Cancer Register	Danish Cancer Register through 2004 and SNOMED CT in Pathology Register	Eindhoven Cancer Registry or SNOMED CT in Pathology Database	Hospital care register and / or Cancer Register	Not available
Brain metastases	ICD-O code in Cancer Register (primary diagnosis only), Quality Register for Lung Cancer and/or National Patient Register	ICD-10 code in Danish Cancer Register and Danish National Registry of Patients	ICD-O code in Eindhoven Cancer Registry or SNOMED CT in Pathology Database	Not available	May be available in Medical claims
Genotyping	Not available	SNOMED CT in Pathology Register	SNOMED CT in Pathology Database	Not available	May be available using medical claims or laboratory database
Other tumors	ICD-10 codes in Patient Register or ICD-O codes in the Cancer Register	ICD-10 or ICD-O codes in the Danish Cancer Registry or Danish National Registry of Patients	ICD-O codes in the Eindhoven Cancer Registry or SNOMED CT in Pathology Database	Hospital care register and / or Cancer Register	Medical claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Drugs prescribed					
Crizotinib	ATC code and drug name in Prescribed Drug Register	ATC code in National Prescription Database, hospital drug code in National Registry of Patients	ATC code in Hospital Pharmacy Database	ATC code in Prescription Register	Pharmacy claims
Ceritinib	ATC code and drug name in Prescribed Drug Register	TC code in National Database of Reimbursed Prescriptions, hospital treatment code in National Registry of Patients	ATC code in Hospital Pharmacy Database	ATC code in Prescription Register	Pharmacy claims
Gefitinib	ATC code and drug name in Prescribed Drug Register	ATC code in National Database of Reimbursed Prescriptions, hospital treatment code in National Registry of Patients	ATC code in Hospital Pharmacy Database	ATC code in Prescription Register	Pharmacy claims
Erlotinib	ATC code and drug name in Prescribed Drug Register	ATC code in National Database of Reimbursed Prescriptions, hospital treatment code in National Registry of Patients	ATC code in Hospital Pharmacy Database	ATC code in Prescription Register	Pharmacy claims
Other drugs prescribed	ATC code and drug name in Prescribed Drug Register	ATC code in National Database of Reimbursed Prescriptions, hospital treatment code in National Registry of Patients	ATC code in Community or Hospital Pharmacy Database	ATC code in Prescription Register	Pharmacy claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Primary study endpoints					
Hepatotoxicity					
Hepatic failure (acute, sub acute, chronic, unspecified, with and without coma)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, and / or ATC codes in Community or Hospital Pharmacy Database	ICD-10 or NOMESCO codes in Hospital Care Register, and/or ATC code in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Toxic encephalopathy	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, and / or ATC codes in Community or Hospital Pharmacy Database	ICD-10 or NOMESCO codes in Hospital Care Register, and/or ATC code in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Toxic liver disease (with hepatic necrosis, hepatitis, acute hepatitis, unspecified, with and without coma)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, and / or ATC codes in Community or Hospital Pharmacy Database	ICD-10 or NOMESCO codes in Hospital Care Register, and/or ATC code in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Central hemorrhagic necrosis of liver	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, and / or ATC codes in Community or Hospital Pharmacy Database	ICD-10 or NOMESCO codes in Hospital Care Register, and/or ATC code in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Pneumonitis/ILD					
Interstitial pulmonary diseases (specified and unspecified)	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database or ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
Drug-induced interstitial lung disorders (acute, chronic and unspecified)	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database or ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
Interstitial pneumonitis (acute and idiopathic non-specific, idiopathic not otherwise specified)	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database or ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
Pulmonary eosinophilia, not elsewhere classified	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database or ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
Acute respiratory distress syndrome / pulmonary insufficiency not elsewhere classified	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database or ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Pulmonary fibrosis, unspecified	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database or ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
Other alveolar and parieto-alveolar conditions	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database or ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
Idiopathic interstitial pneumonia, not otherwise specified	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database or ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
Pleural effusion (not elsewhere classified, in other conditions classified elsewhere, unspecified)	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database or ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
Pleurisy	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database or ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
QTc prolongation related events[1]					
Ventricular fibrillation	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, and / or ATC codes in Community or Hospital Pharmacy Database	ICD-10 or NOMESCO codes in Hospital Care Register, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Ventricular flutter	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, and / or ATC codes in Community or Hospital Pharmacy Database	ICD-10 or NOMESCO codes in Hospital Care Register, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Ventricular tachycardia	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, and / or ATC codes in Community or Hospital Pharmacy Database	ICD-10 or NOMESCO codes in Hospital Care Register, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims

[1] Danish Heart Register covers 3 of 5 Danish regions.

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Tachycardia, unspecified	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, and / or ATC codes in Community or Hospital Pharmacy Database	ICD-10 or NOMESCO codes in Hospital Care Register, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Long QT Syndrome	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients Database (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, and / or ATC codes in Community or Hospital Pharmacy Database	ICD-10 or NOMESCO codes in Hospital Care Register, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Cardiac dysrhythmia, unspecified	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, and / or ATC codes in Community or Hospital Pharmacy Database	ICD-10 or NOMESCO codes in Hospital Care Register, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Cardiac arrest , unspecified	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, and / or ATC codes in Community or Hospital Pharmacy Database	ICD-10 or NOMESCO codes in Hospital Care Register, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Bradycardia[2]					
Bradycardia, unspecified	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, and / or ATC codes in Community or Hospital Pharmacy Database	ICD-10 or NOMESCO codes in Hospital Care Register, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Other specified cardiac arrhythmias	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, and / or ATC codes in Community or Hospital Pharmacy Database	ICD-10 or NOMESCO codes in Hospital Care Register, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims

[2] Danish Heart Register covers 3 of 5 Danish regions.

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Atrioventricular block (complete, unspecified, second degree, other specified)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, and / or ATC codes in Community or Hospital Pharmacy Database	ICD-10 or NOMESCO codes in Hospital Care Register, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Conduction disorder (unspecified, other unspecified)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, and / or ATC codes in Community or Hospital Pharmacy Database	ICD-10 or NOMESCO codes in Hospital Care Register, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Visual disturbances					
Diplopia	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register , ICD-10 or SPAT code in GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Visual disturbances (other, other subjective, unspecified, unspecified subjective)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register , ICD-10 or SPAT code in GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Unspecified visual field defects	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register , ICD-10 or SPAT code in GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Other localized visual field defect (right eye, left eye, bilateral, unspecified)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register , ICD-10 or SPAT code in GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims

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	Sweden	Denmark	Netherlands	Finland	US
Vitreous membranes and strands (right eye, left eye, bilateral, unspecified)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register , ICD-10 or SPAT code in GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Other vitreous opacities (right eye, left eye, bilateral, unspecified)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register , ICD-10 or SPAT code in GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Vitreous degeneration (right eye, left eye, bilateral, unspecified)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register , ICD-10 or SPAT code in GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims

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	Sweden	Denmark	Netherlands	Finland	US
Transient vision loss (right eye, left eye, bilateral, unspecified)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register , ICD-10 or SPAT code in GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Unspecified disorder of binocular vision	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register , ICD-10 or SPAT code in GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Unspecified disorder of vitreous body	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register , ICD-10 or SPAT code in GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Unspecified retinal disorder	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register , ICD-10 or SPAT code in GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Toxic maculopathy(right eye, left eye, bilateral, unspecified)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register , ICD-10 or SPAT code in GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Retinal hemorrhage (right eye, left eye, bilateral, unspecified)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register , ICD-10 or SPAT code in GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Retinal edema	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register , ICD-10 or SPAT code in GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Visual distortions of shape and size	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register , ICD-10 or SPAT code in GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Glare sensitivity	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register , ICD-10 or SPAT code in GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Secondary study endpoints					
Renal cysts	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database	ICD-10 codes in Hospital Care Register	ICD-9 or 10 codes in Medical claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Edema					
Localized	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
Generalized	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
Unspecified	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
Angioneurotic (initial encounter, subsequent encounter, sequellae)	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
Unspecified eye, unspecified eyelid	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
left eye, unspecified eyelid	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
left lower eyelid	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
left upper eyelid	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
right eye, unspecified eyelid	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
right lower eyelid	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
Right upper eyelid	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
Urticaria (allergic, idiopathic, cholinergic, other, unspecified)	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
Edema of larynx	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
Edema of nasopharnyx	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims
Wheezing	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICPC codes in the GP Database	ICD-10 codes in Hospital Care Register or GP Database	ICD-9 or 10 codes in Medical claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Leukopenia					
Decreased white blood cell count, (other, unspecified)	ICD-10 codes in the Patient register and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, ICPC codes in the GP Database, laboratory database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 codes in Hospital Care Register or GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Lymphocytopenia	ICD-10 codes in the Patient register and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, ICPC codes in the GP Database, laboratory database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 codes in Hospital Care Register or GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Agranulocytosis (secondary to cancer chemotherapy, other drug-induced)	ICD-10 codes in the Patient register and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, ICPC codes in the GP Database, laboratory database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 codes in Hospital Care Register or GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Neutropenia (unspecified, cyclic, due to infection, other)	ICD-10 codes in the Patient register and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, ICPC codes in the GP Database, laboratory database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 codes in Hospital Care Register or GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Disorders of white blood cells (Other specified , unspecified)	ICD-10 codes in the Patient register and/or ATC codes in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients	ICD-10 codes in the Dutch Hospital Database, ICPC codes in the GP Database, laboratory database and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 codes in Hospital Care Register or GP Database and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Neuropathy					
Disturbance of skin sensation (Anesthesia of skin, hypoesthesia of skin, paresthesia of skin, hyperesthesia, other disturbances of skin sensation, unspecified disturbances of skin sensation)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes or SPAT codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Toxic optic neuropathy	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes or SPAT codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Lumbosacral plexus disorders	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes or SPAT codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Lumbosacral root disorders, not elsewhere classified	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Mononeuritis multiplex	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Neuralgia neuritis and radiculitis unspecified	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Polyneuropathy (critical illness, Idiopathic progressive, in other diseases classified elsewhere, unspecified, drug-induced)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Inflammatory polyneuropathy (other, unspecified)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Unspecified idiopathic peripheral neuropathy	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Other idiopathic peripheral autonomic neuropathy	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Disturbance of skin sensation (paresthesia, hypoesthesia, hyperesthesia, unspecified, other)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Muscle weakness	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Pain in limb (right, left, unspecified, arm and leg, unspecified limb)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Pain in upper arm (right, left, unspecified)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Pain in forearm (right, left, unspecified)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Pain in hands and fingers (right, left, unspecified hand, right and right, left and unspecified fingers)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Pain in thigh (right, left, unspecified)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Pain in lower leg (right, left, unspecified)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Pain in foot and toes (right, left, unspecified foot, right and right, left and unspecified toes)	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Malignant melanoma	ICD-10 codes in Patient Register or ICD-O codes in the Cancer Register	ICD-10 or ICD-O codes in the Danish Cancer Registry or Danish National Registry of Patients	ICD-O codes in the Eindhoven Cancer Registry or SNOMED CT in Pathology Database	Hospital care register and / or Cancer Register	ICD-9 or 10 codes in Medical claims
Photosensitivity					
Photosensitivity, photosensitization (sun) skin	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICPC codes in the GP Database	ICD-10 codes in GP Database	ICD-9 or 10 codes in Medical claims
Acute skin change due to ultraviolet radiation, unspecified	ICD-10 codes in the Patient register	ICD-10 codes in Danish National Registry of Patients	ICPC codes in the GP Database	ICD-10 codes in GP Database	ICD-9 or 10 codes in Medical claims
Mortality	Death Register	Central Person Registry	Mortality database	Cause of death register	Vital Statistics, ICD-9 or 10 codes in Medical claims

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Comorbidities[3]					
Pre-existing renal impairment					
Chronic renal disease	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Pre-existing hepatic impairment					
Hepatitis	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims

[3] This list represents illustrative comorbidities only; additional comorbidities will be considered and added as appropriate

090177e18627024f\Approved\Approved On: 25-Feb-2015 14:49

	Sweden	Denmark	Netherlands	Finland	US
Liver fibrosis	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims
Liver cirrhosis	ICD-10 codes in the Patient register, Klassifikation av kirurgiska åtgärder code in Patient Register, and / or ATC code and drug name in Prescribed Drug Register	ICD-10 codes in Danish National Registry of Patients, NOMESCO codes in Danish National Registry of Patients (if applicable)	ICD-10 codes in the Dutch Hospital Database, CVV codes in the Dutch Hospital Database, ICPC codes in the GP Database, and / or ATC codes in Hospital or Community Pharmacy Databases	ICD-10 or NOMESCO codes in Hospital Care Register, ICD-10 codes in GP Database, and/or ATC codes in National Prescription Database	ICD-9 or 10 codes in Medical claims and/or NDC code in pharmacy claims

Appendix 2. CASE DEFINITION FOR PRIMARY STUDY ENDPOINTS OF VALIDATION STUDY

Hepatotoxicity

Include:

- Clinical diagnosis of unspecified hepatitis (excluding viral hepatitis, and hepatitis A, B, C and E) and ALAT>3 times ULN;
- Clinical diagnosis of severe hepatic injury;
- ALAT>3 times ULN and jaundice, or ALAT >3x ULN AND Total bilirubin >2x ULN (Hy's Law) or prothrombin time >50% prolonged (INR 1.5x ULN) or hepatic coma/encephalopathy;
- Clinical diagnosis of fulminant hepatic failure;
- Clinical diagnosis of subacute liver failure;
- Clinical diagnosis of acute liver failure;
- Hepatic coma/encephalopathy and severe coagulopathy or thrombocytopenia or hypothrombinemia.

QTc prolongation (ECG records reviewed by Adjudication Committee on request)

Include:

- Clinical diagnosis of polymorphic ventricular tachycardia (≥3 consecutive beats at rate >100 min^{-1}) or ventricular flutter / fibrillation, documented by an ECG recording;
- Syncope or seizures (convulsions) recorded in case notes;
- Clinical diagnosis of torsade de pointes or TdP documented by an ECG recording;
- Clinical diagnosis of sudden death or sudden cardiac death;
- ECG showing Fridericia rate-corrected QT interval ($QT/RR^{1/3}$) >450 ms in men or >470 ms in women;
- QTcF (Fridericia correction) change ≥ 60 msec from baseline;
- Absolute QT or QTc of >500 msec.

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Exclude:

- Known coronary syndromes or known congenital long QT syndromes.

Bradycardia

Include:

- Clinical diagnosis of symptomatic bradycardia or symptomatic sinus bradycardia (HR <40 bpm);
- Clinical diagnosis of symptomatic bradyarrhythmias (eg sinus arrhythmia, bradycardia);
- Clinical diagnosis of sinus arrest or sinus pauses >3 sec.

Pneumonitis/ILD

Include:

- Clinical diagnosis of pneumonitis;
- Clinical diagnosis of interstitial lung disease;
- Clinical diagnosis of eosiniphilic pneumonia;
- Clinical diagnosis of pulmonary fibrosis;
- Clinical diagnosis of idiopathic interstitial pneumonia;
- Clinical diagnosis of ARDS: Adult Respiratory Distress Syndrome.

Vision disorders

Include:

- Clinical diagnosis of vision disturbances including blurred vision, photophobia, photopsia, palinopsia, visual illusion, reduced visual acuity, diplopia, visual impairment, visual field defect, and vitreous floaters, maculopathy, retinal edema, retinal hemorrhage.

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Exclude:

- Refractive error, amblyopia, corneal disorder (abnormal sensation in eye, anterior chamber collapse, anterior chamber opacity, aqueous humour leakage, asthenopia, chemical burns of eye, chemical eye injury, contact lens intolerance, corneal suture, corneal sutures removal, deposit eye, dry eye, eye burns, eye inflammation, eye injury, eye irritation, eye laser surgery, eye operation complication, eye penetration, flat anterior chamber of eye, foreign body in eye, foreign body sensation in eyes, hypoaesthesia eye, ocular toxicity, slit-lamp tests abnormal, superficial injury of eye, thermal burns of eye, vitamin A deficiency eye disorder, xerophthalmia, acquired corneal dystrophy, allergic keratitis, arcus lipoides, atopic keratoconjunctivitis, benign neoplasm of cornea, biopsy cornea, biopsy cornea abnormal, bowman's membrane disorder, corneal abrasion, corneal bleeding,corneal cyst, corneal decompensation, corneal defect, corneal degeneration, corneal deposits, corneal diameter decreased, corneal diameter increased, corneal disorder, corneal endothelial cell loss, corneal endotheliitis, corneal epithelial microcysts, corneal epithelium defect, corneal erosion, corneal exfoliation, corneal flap complication, corneal graft rejection, corneal hypertrophy, corneal implant, corneal infiltrates, corneal lesion, corneal lesion removal, corneal light reflex test abnormal, corneal oedema, corneal opacity, corneal operation, corneal perforation, corneal pigmentation, corneal reflex decreased, corneal scar, corneal staining, corneal striae, corneal thickening, corneal thinning, corneal touch, corneal transplant, corneoconjunctival intraepithelial neoplasia, dellen, detached Descemet's membrane, diffuse lamellar keratitis, injury corneal, iridocorneal endothelial syndrome, Kayser-Fleischer ring, keratectomy, keratitis, keratitis interstitial, keratitis sclerosing, keratoconus, keratomalacia, keratometry, keratomileusis, keratopathy, keratorhexis, keratotomy, limbal hyperaemia, limbal swelling, macrocornea, malignant neoplasm of cornea, microcornea, neoplasm of cornea unspecified malignancy, neurotrophic keratopathy, photokeratitis, photorefractive keratectomy, punctate keratitis, Terrien's marginal degeneration, topography corneal abnormal, ulcerative keratitis, vital dye staining cornea present, vitamin A deficiency related corneal disorder), visual impairing cataracts, uncontrolled diabetes, brain tumor, age-related macular degeneration, toxic maculopathy (eg, Chloroquine or Tamoxifen), epiretinal membrane, vitreomacular adhesions, ocular or retinal metastases.

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