NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS Information

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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.
Countries of study	Denmark, Finland, Norway, Sweden, and the Netherlands
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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
e-HRD	Electronic health related databases
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
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
ISPE	The International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
NSCLC	Non small cell lung cancer
ORR	Objective response rate
PASS	Post-authorization safety study
PCR	Polymerase chain reaction
PPV	Positive predictive values
PR	Partial response
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

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Study title: A mutinational active safety surveillance study of crizotinib in Europe

Rationale and background: Crizotinib (XALKORI®), an orally administered selective ATP competitive small molecule inhibitor of the anaplastic lymphoma kinase (ALK), has been approved multinationally, including in Europe, for the treatment of patients with previously treated 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.

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. The primary objective is to estimate the incidence rate and incidence proportion over a 3-year period of observation for hepatotoxicity, pneumonitis/ILD, QTc prolongation related events, bradycardia, and visual disorders among lung cancer patients receiving crizotinib dispensation. Incidence rates and proportions of the same endpoints will be calculated for patients treated with 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 in Europe.

Study population: The study population will include all patients that are diagnosed with primary lung cancer and receive dispensation for crizotinib, erlotinib, or gefitinib as recorded in national or regional health care databases in Denmark, Norway, Finland, the Netherlands, and Sweden during the study period.

Data sources: This study will link existing national or regional databases/registries within Sweden, Denmark, the Netherlands, Finland, and Norway, which contain medical information for approximately 30 million people. Data from 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 will be evaluated in this study include demographics, tumor characteristics, pertinent medical history, comorbidities, safety outcomes of interest, and overall patient survival.

Sample size: In this descriptive study, all patients with primary lung cancer treated with crizotinib, erlotinib, or gefitinib in the target databases during the study period will be included.

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 of crizotinib, erlotinib or gefitinib. Subgroup analyses by age (dichotomized at ≥65 years old), presence or absence of

brain metastases, and pre-existing renal or hepatic impairments 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, erlotinib and gefitinib dispensation. In addition, sensitivity, specificity and positive predictive value (PPV) of primary study endpoints captured using diagnostic and/or procedural codes in claims databases (compared to patient medical records / charts) will be calculated.

Milestones: This study is projected to begin (ie, eligible patients will be entering in databases) in June 2013 after local approval and reimbursement of crizotinib in at least one of these countries. The end date of the study is June 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.

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned date
Study commencement	June 1st 2013
Start of data collection	December 1st 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	Prior to December 1st 2014
Final study report	June 30th 2018

7. RATIONALE AND BACKGROUND

Crizotinib (XALKORI®) 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 Europe, for the treatment of patients with previously treated locally advanced or metastatic ALK-positive non small cell lung cancer (NSCLC). One Phase 3 trial in a second-line ALK-positive advanced NSCLC treatment setting is complete, and others are in various stages of progress. 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.

NSCLC accounts for approximately 85% of cases of lung cancer (Sher, Dy, and Adjei 2008)[9] and is a leading cause of mortality in developed countries (Jemal et al. 2011).[5] 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), [4] and median survival has been estimated to be less than 1 year after diagnosis (Schiller et al. 2002).[8]

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).[11] 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).[1] These rearrangements are found in approximately 2.7 (Varella-Garcia et al. 2010)[13] -7% (Soda et al. 2007) [11] 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).[12] 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 conjuction with conditional approval of crizotinib. ALK rearrangements can also be detected using reverse transcriptase polymerase chain reaction (PCR) and immunohistochemistry. Crizotinib has a favorable benefit/risk profile for the treatment of patients with previously treated locally advanced or metastatic ALK-positive NSCLC, based on data available as of 30 March 2012. In the dose-escalation part of an open-label, single-arm, two-part, Phase 1 trial (Study A8081001), 2 ALK-positive NSCLC were enrolled, one at 200 mg BID and one at 300 mg BID. Both experienced disease improvement. In the second part of this trial, an expanded cohort of locally advanced or metastatic ALK-positive NSCLC patients received 250 mg twice daily, with a median duration of treatment of 32 weeks. As assessed by investigators, the objective response rate (ORR) for 143 evaluable patients was 60%, including a complete response (CR) in 3 patients (2%), and a partial response (PR) in 85 patients (59%). Stable disease at ≥6 weeks was observed in 29% of patients, and preliminary median progression-free survival was estimated to be 10 months. An ongoing non-comparative open-label multicenter Phase 2 trial (Study A8081005) has enrolled 340 patients with locally advanced or metastatic ALK-positive NSCLC, with a median duration of treatment of 19 weeks at the time of analysis. The investigator-assessed ORR in the trial at the time of analysis was 46%, including 4 patients (1%) who had a CR and 152 patients (45%) who had a PR. The results of a Phase 3, randomized open-label trial (Study A8081007) comparing crizotinib to standard of care second-line chemotherapy (pemetrexed or docetaxel) among patients with previously treated ALK-positive advanced NSCLC showed that median progression-free survival was 7.7 months for patients randomized to crizotinib, statistically significantly greater than the 3.0 months for patients randomized to chemotherapy: the hazard ratio of crizotinib compared to chemotherapy was 0.487 (95% CI: 0.371, 0.638; p <0.0001), The ORR for 173 crizotinib-treated patients was 65% ,which was statistically significantly greater than the ORR of 20% for 174 patients treated with chemotherapy, p-value <0.0001.

A number of risks have been associated with crizotinib in Studies A8081001 and A8081005 including hepatotoxicity, pneumonitis/ interstitial lung disease (ILD), QT interval prolongation, bradycardia, and vision disorder; each of these risks is listed in the crizotinib label or Summary of Product Characteristics (SmPC). Out of 588 ALK-positive NSCLC patients treated with crizotinib in studies A8081001 and A8081005 before 01 June 2011, 95 (61.2%) experienced treatment-related adverse events (AEs) compatible with possible hepatotoxicity; 5 cases of potentially drug-related severe hepatotoxicity were noted, four of which (including 2 cases associated with a fatal outcome) were noted between 01 June 2011 and 31 December 2011. These cases occurred during crizotinib treatment in less than 1% of patients. Concurrent elevations in ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN without elevated alkaline phosphatase >2 x ULN were similarly observed in less than 1% patients. Increases to Grade 3 (5 - ≤20X ULN) or Grade 4 (>20 x ULN) ALT elevations were observed in 6% of patients in Study A8081001 and 8% of patients in Study A8081005. Nine patients (1.5%) experienced treatment-related pneumonitis, ranging from Grade 1 to Grade 5 severity. In addition, 1.9% of 588 patients experienced a treatment-

related AE potentially compatible with QTc prolongation (1.4% QT prolongation as determined by electrocardiogram (ECG), 0.5% syncope). Population pharmacokinetics and pharmacodynamic assessment of crizotinib plasma concentration and QTc (corrected by study specific method, and calculated using Bazett's and Fridericia's correction factors, where appropriate) predicted a small (<10 msec) increase in the QT interval when C_{max} is reached under steady state conditions for the clinical dose of 250 mg BID. Treatment-related AEs compatible with bradycardia were experienced by 3.4% of patients (2.2% bradycardia and 1.2% sinus bradycardia). Finally, low grade visual effects were reported frequently (55.4% of patients) during crizotinib treatment. The most common treatment-related visual effects were visual impairment (39.3%), photopsia (8.5%), blurred vision (3.9%) and vitreous floaters (2.7%); the mean duration of vision disorder events was 98 days (SD=108) and median duration was 68 days (range: 1-615 days). The majority (58%) of these events were Grade 1 in severity, with 10 cases (1.7%) of Grade 2 and 1 case (0.2%) of Grade 3 visual impairment. Patient responses to a Visual Symptom Assessment Questionnaire demonstrated that most events were transient (duration <60 seconds), with no or minimal impact on activities of daily living.

In addition, a number of other risks have been recognized in studies A8081001 and A8081005. Out of 588 patients, 3 patients (0.5%) experienced a treatment-related AE compatible with renal cysts (either renal cyst or renal abscess). Edema has also been noted to be a risk, with a large proportion of patients (26%) experiencing treatment-related AEs compatible with edema. All but two of these events were Grade 1 or 2 in severity. Given the multifactorial causes of edema, the relative contribution of crizotinib towards these events is uncertain. Treatment-related AEs compatible with leukopenia occurred in 71 (12.1%) of patients. Since the majority of patients had previously received prior cytotoxic treatment, the role of crizotinib in these events is unclear and these events did not have any impact on patient management. Finally, fifty eight patients (9.9%) experienced treatment-related AEs compatible with neuropathy. These were primarily Grade 1 or Grade 2 in severity, tended to be sensory in nature, and the extent to which platinum or taxane agents contributed to these events is unclear.

Study A8081007 found that vision disorder, elevated transaminases, edema,[1] diarrhea, nausea, vomiting, and constipation, were reported with higher incidence in patients randomized to crizotinib; however, incidences of Grade 3 and 4 AEs were similar between arms, with the exception of elevated transaminases. Serious AEs (SAEs) included pulmonary embolism, neutropenia,[2] disease progression, and pneumonia,; all but neutropenia were reported with higher incidences in the crizotinib arm. 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.

[1] Clustered AE terms

[2] Clustered AE term

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 is limited, with only 14.1% of 588 patients exposed to the drug in Phase 1 and 2 studies, and 14.4% of participants in study A8081007, 65 years of age or older. Additional research in this population is therefore warranted.

This multinational post-authorization active safety surveillance study using existing European health care data sources 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 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 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 order to contextualize the findings, data will be obtained on the same risks among lung cancer patients receiving dispensation of 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 study will complement 6 ongoing clinical studies covering FDA Post-Marketing Requirements that are futher evaluating vision disorder, QTc prologation, and renal and hepatic impairment in patients treated with crizotinib. The combination of this study in a real-world setting and these 6 ongoing clinical studies should provide sufficient additional post-approval safety data for crizotinib in ALK-positive NSCLC patients.

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

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Objectives

This prospective active safety surveillance study using existing health care data sources in Denmark, Norway, Finland, the Netherlands, and Sweden will evaluate safety outcomes and effectiveness among lung cancer patients receiving crizotinib dispensation over a 3-year period under real-world conditions. To contextualize the findings, the study will also obtain data among lung cancer patients receiving dispensation of erlotinib or gefitinib in the same data sources during the study period.

8.1.1. Primary Objective

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

8.1.2. Secondary Objectives

- To estimate the incidence rate and incidence proportion over a 3-year period of observation for renal cysts, edema, leukopenia, neuropathy, and photosensitivity among lung cancer patients receiving crizotinib dispensation.

- To estimate Kaplan-Meier survival probability over one-year, two-year, and three-year periodsof observation among lung cancer patients receiving crizotinib dispensation.

- To estimate the incidence rate and incidence proportion over a 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 of erlotinib or gefitinib.

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

- To describe clinical characteristics and comorbidities of patients receiving dispensation of crizotinib, erlotinib or gefitinib.

9. RESEARCH METHODS

9.1. Study Design

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

9.2. Setting

The study population will include all patients who are diagnosed with primary lung cancer and receive dispensation for crizotinib, erlotinib, or gefitinib as recorded in national or regional health care databases in Denmark, Finland, Norway, the Netherlands, and Sweden during the study period. In addition, this study will also include all other cancer patients receiving crizotinib dispensation.

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 of crizotinib, 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 of erlotinib or gefitinib prior to or at the time of the first prescription.

3. At least one recorded encounter in inpatient or outpatient database within a 6 month period prior to the first dispensation of crizotinib, erlotinib, or gefitinib

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, and operational definitions of comorbidities and safety endpoints (based on ICD diagnosis codes, medications, and/or available procedure codes), are shown in Appendix 3.

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
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
Photosensitivity	Outcome	See Appendix 1	See Appendix 2
Mortality	Outcome	See Appendix 1	See Appendix 2
Comorbidities[3]			
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 only
¥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 have population-based health care databases which provide a unique opportunity for the post-approval surveillance of anti-cancer drugs. This study will link existing national or regional health care databases within Sweden, Denmark, the Netherlands, Finland, and Norway, which contain medical information for approximately 30 million people; the size of these databases will facilitate evaluation of a rare exposure and

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

rare outcomes among those exposed. 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. In this case, Pfizer would reach out to additional countries with required health care data sources to take part in the 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 5.5 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, Laboratory File (North and Central regions only) and the National Prescription Database.

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.

Norway: Norwegian health-care databases include information on the country's entire population of 4.95 million inhabitants. These registries include the Norwegian Patient Registry, the Norwegian Prescription Database, the Cancer Registry, and the Cause of Death Register. Registry data can be linked using a unique 11-digit personal identity number, assigned to all individuals living in Norway after 1960.

Each of these 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 prescription, and 4) Medical procedures. In drug prescription databases, dispensed drugs 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. 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, Finland and Norway, procedures are recorded using NOMESCO codes, and in Sweden, procedures are recorded using Klassifikation av kirurgiska åtgärder codes (Swedish version of NOMESCO codes). The source of data for each key element, for each participating country, is illustrated in Appendix 1.

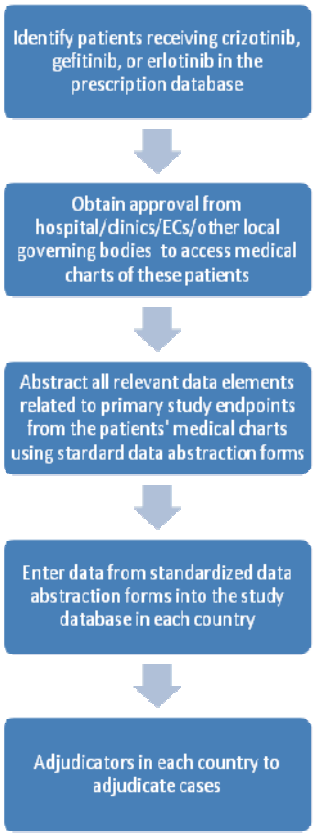
9.4.2. Adjudication and Validation of Primary Endpoints from Population-Based Health Care Data Sources

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 sample of 20% of patients treated with erlotinib or gefitinib, would be abstracted in Sweden, Norway, Northern and Central regions of Denmark, in the Helsinki region of Finland and PHARMO databases in the Netherlands 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, hospital administrative data will be linked directly to medical records / charts via the unique personal identifier. In Sweden, Norway, 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 local clinical adjudicators 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.

Figure 1. Process of Validating Primary Endpoints



In patients receiving dispensation 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 of erlotinib or gefitinib, PPV will be estimated for each primary endpoint. Results of the validated data will be presented in interim reports as well as in the final study report.

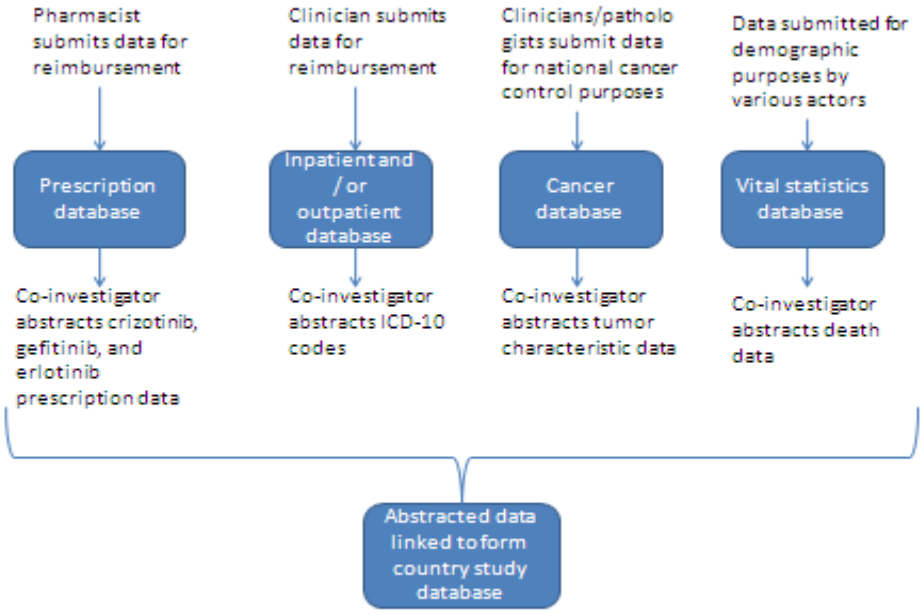
9.5. Study Procedures

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

All data for this study will be obtained through routine data collection practices of participating country registers/databases as described in Figure 2. The data in 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 prescription for crizotinib, erlotinib, or gefitinib. For those patients exposed to at least one of these medications (and in the case of erlotinib or gefitinib, a record of primary lung cancer as identified in either hospital discharge and / or cancer registry databases), routinely collected data will be

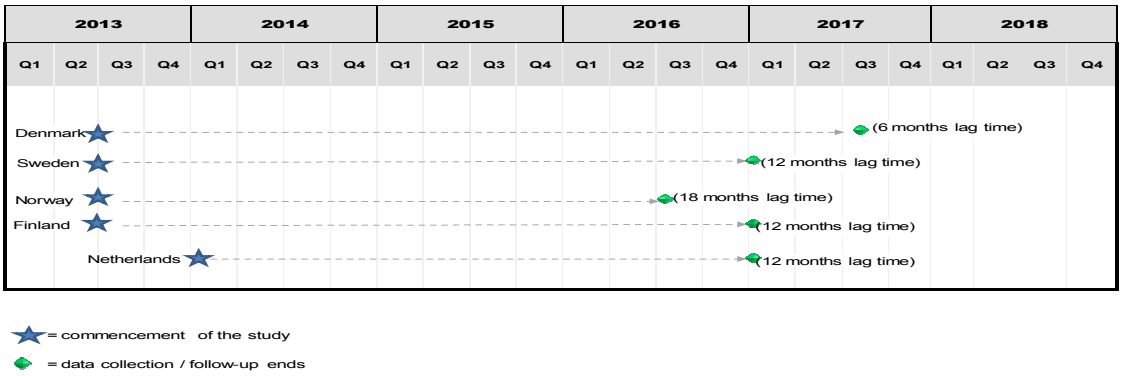
abstracted from relevant databases for the following covariates: demographics; clinical characteristics; medical history, other dispensation received in the 6-month period prior to the study start date in each country, concurrent with or subsequent to the first prescription for crizotinib, erlotinib, 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 prescription for crizotinib, erlotinib, or gefitinib during the study, and the safety endpoints of interest during the study.

Figure 2. Study Data Abstraction



This study is projected to begin (ie, eligible patients in databases will be entering in databases) in June 2013 after local approval and reimbursement of crizotinib in at least one of these countries. Final date of collection of data from databases will vary by country, in order to account for differences between countries in the timing of crizotinib reimbursement / availability, as well as lag times in recording and obtaining claims data in participating countries. 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 reimbursement of crizotinib and shorter lag times, such as Denmark, will likely contribute up to 3.75 years of data to the study. The earliest end date for following up patients in databases will be June 2016 (allowing for 18 months lag time in obtaining claims data) and the latest end date of the study will be June 2017 (allowing for 6 months lag time in obtaining claims data); 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.

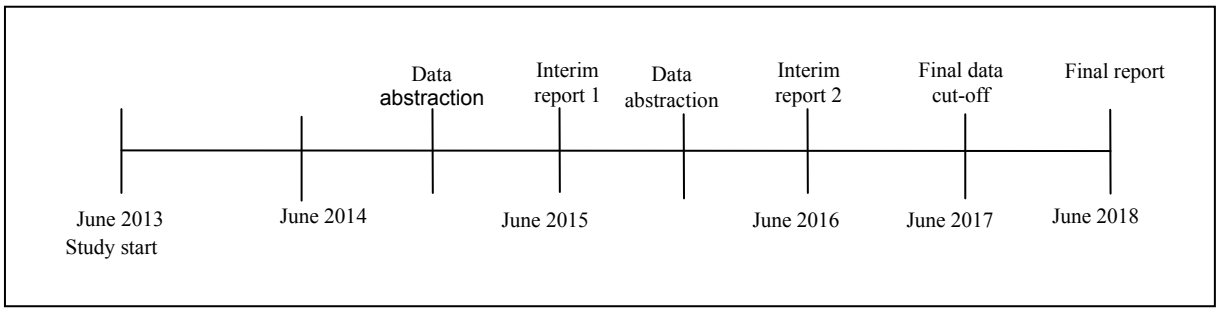
Figure 3. Study Duration (Data Collection Timelines) by Country



Eligible patients will be followed from the date of the first crizotinib, erlotinib, or gefitinib dispensation 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 of crizotinib, erlotinib, or gefitinib at least 6 months before the end of data collection in participating countries.

For the first interim report, each investigator will obtain and analyze data from his/her country in December 2014, with the first interim report (IR) submission from each participating country 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. For the second IR, each investigator 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 containing aggregate data from the five countries will be submitted in June 2018. The timing of interim reports and final study report submission is shown in Figure 4.

Figure 4 Study Timeline



9.6. Study Size

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

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 422 incident previously treated ALK-positive advanced NSCLC patients will be treated with crizotinib over the 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, the total number of patients eligible for crizotinib treatment based on its approved indication and included in this study would likely be more than 422. 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.

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

Country	Sweden	Denmark	Southeastern Netherlands	Finland	Norway
Population covered (millions)†	9.45	5.57	2	5.39	4.95
Incidence of lung cancer (per 100,000) (Ferlay, Parkin and Seliarova-Foucher 2010)[2]	37.2	75.9	62	40.6	53.1
Estimated number of incident ALK-positive NSCLC patients treated with crizotinib per year††	32	37	11	20	24
Estimated duration (years) of data collection in each country†††	3.5	3.75	2.75	3.25	3.25
Total in each country ††††	111	140	31	64	76
Overall total	422				

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

†† population covered in the database*incidence of lung cancer in the country*60% (newly diagnosed lung cancer in advanced stages (Howlader et al. 2012))[4] *85% (lung cancers that are NSCLC(Jemal et al. 2011))[5] *2.7% (NSCLCs that are ALK-positive (Varella-Garcia et al. 2010))[13] *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

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

Similarly, based on several assumptions, it is estimated that approximately 1,248 incident advanced NSCLC patients with an EGFR mutation would likely be treated with either erlotinib or gefitinib over the 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 1,248 conservatively assumes a prevalence of EGFR mutation in 8% among NSCLC patients in Sweden, Denmark, the Netherlands, Finland, and Norway. 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 1,248.

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

Country	Sweden	Denmark	Southeastern Netherlands	Finland	Norway
Population covered (millions)†	9.45	5.57	2	5.39	4.95
Incidence of lung cancer (per 100,000) (Ferlay, Parkin and Seliarova-Foucher 2010)[2]	37.2	75.9	62	40.6	53.1
Estimated number of incident NSCLC patients with EGFR mutation treated with either erlotinib or gefitinib per year††	94	111	33	58	70
Estimated duration (years) of data collection in each country†††	3.5	3.75	2.75	3.25	3.25
Total in each country ††††	328	415	90	189	227
Overall total	1248				

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

†† population covered in the database*incidence of lung cancer in the country*60% (newly diagnosed lung cancer in advanced stages (Howlader et al. 2012))[4] *85% (lung cancers that are NSCLC (Jemal et al. 2011))[5] *8% (estimate of the proportion of NSCLCs with EGFR mutation (Shigematsu et al.2005)[10] *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 ALK-positive NSCLC patients treated with crizotinib per year*estimated duration of data collection in each country.

9.6.3. Precision Calculations

This active safety surveillance study aims to estimate the incidence of safety endpoints among patients receiving crizotinib dispensations, rather than conduct a hypothersis 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 except photosensitivity in ALK positive NSCLC patients treated with crizotinib range from 1.6% to 55.2% (Xalkori RMP 2013).[15] The incidence proportion for photosensitivity is 0.3%. The estimated precision for the proportions of safety endpoints was presented on Table 4 with the following assumptions:

- Estimated 422 ALK positive NSCLC patients likely receiving crizotinib dispensations in the study;

- Two-sided 95% confidence limits.

Based on these calculations, given 422 ALK positive NSCLC patients likely treated with crizotinib, this study would have achieved the precision of observed incidence proportions of a safety outcome between ± 1.2% and ± 4.7% where the incidence proportion of the safety outcome ranges from 1.6% to 60% 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
0.3%	±0.5%	-0.2%-0.8%
1.6%	±1.2%	0.4%-2.8%
2%	±1.3%	0.7%-3.3%
3%	±1.65%	1.4%-4.6%
4%	±1.85%	2.1%-5.9%
5%	±2.1%	2.9%-7.1%
10%	±2.85%	7.1%-12.9%
20%	±3.8%	1.6%-23.8%
30%	±4.35%	25.6%-34.4%
40%	±4.65%	35.3%-44.7%
50%	±4.75%	45.2%-54.8%
60%	±4.65%	55.3%-64.7%

9.7. Data Management

9.7.1. Data Management

All data for this study will be 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, erlotinib, or gefitinib, and tumor characteristics as described in Appendix 2. The data in the databases are updated continually. 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.

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, Finland and Norway, 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 patient id. In Finland, collaborators at EPID Research would receive de-identified patient data, and in Norway, Kreftregisteret would receive separate data files identified by unique patient ID, with the exception of Prescription Register which is de-identified. 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. .

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.

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 and patients receiving erlotinib or gefitinib dispensation will not be formally evaluated using statistical tests due to the anticipated limited number of patients receiving crizotinib dispensation 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 of crizotinib, erlotinib or gefitinb. 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 prescription for crizotinib, 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 prescription for crizotinib, 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 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 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) divided by 365.25]. In 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 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 for the product preceding the endpoint) minus (days without the dispensation for that product between the date of the first dispensation and the date of the safety endpoint diagnosis) divided by 365.25.

For patients <u>not experiencing a safety endpoint</u>, total person-time treated for the patients will be similarly derived in two ways depending on pattern of dispensation. If a patient receives a dispensation 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 and the date of the first dispensation plus a 28-day at risk period) divided by 365.25]. If a patient receives intermittent dispensation 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 of the product and the date of the first dispensation 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 for that product between the date of the first dispensation and the last coverage date of the last dispensation 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 patients, incidence rates and incidence proportions for primary study endpoints will be calculated for 1) all cases identified in administrative data (i.e., 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 and Finland given that validation of the codes is done among a proportion of the entire population. For patients treated with erlotinib or gefitinib in these countries, incidence rates and incidence proportions will be calculated for all cases identified in administrative 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, gefitinib, or erlotinib dispensation 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 impairments at baseline will be conducted for all primary study endpoints.

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, and the Netherlands.

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

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

- 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.

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

- 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.

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

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).

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.

9.10. Limitations of the Research Methods

9.11. Strengths of the Research Methods

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 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.

9.12. 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, erlotinib, and gefitinib are chemotherapy agents, it is reasonable to assume that the majority of patients who receive a 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, 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

prescription and 20% of patients receiving dispensation of 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 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 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 of these products as per usual practice, and therefore, it is reasonable to assume that the large majority of patients receive dispensation 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.

9.13. Other Aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

1.1. Patient Information and Consent

Not applicable.

10.1. Patient Withdrawal

Not applicable.

1.2. 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.

1.3. 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 will use de-identified patient-level electronic health related databases (e-HRD), in which it is generally not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Furthermore, while the identifiable patient criterion may be met, the identifiable reporter criterion (a particular individual with firsthand knowledge of the identifiable patient) will not. Thus, the minimum criteria for reporting an adverse event (ie, identifiable patient, identifiable reporter, a suspect product, and event) will not be available, and hence adverse events will not be reportable as individual adverse event reports.

This study will abstract information from patient medical records/charts as part of data validation, in which it is generally not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. However, in these countries, the medical professionals who abstract the information from the medical charts /records are obligated to report adverse events (AE) with explicit attribution to any Pfizer drug that appear in the defined dataset.

While the primary purpose of this study does not encompass assessment of drug-related effects in individuals, the reviewer may identify a SAE or non-serious AE with explicit attribution to any Pfizer drug via narrative/verbatim field review (and with an identifiable reporter). Such SAEs or non-serious AEs must be reported to Pfizer or its representative for submission to regulatory authorities. Explicit attribution is not inferred by a temporal relationship between drug administration and an SAE or non-serious AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the SAE or non-serious AE.

DEFINITION OF AN ADVERSE EVENT

An AE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including infant and toddler formulas [hereinafter “pediatric formulas”]) or medical device. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;

- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

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

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

SERIOUS ADVERSE EVENTS

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

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

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

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

If there is a written notation in the medical chart/narrative field indicating that a physician attributed a serious adverse event or non-serious AE to a Pfizer drug, Pfizer or it's representative/the reviewer will complete a Non-Interventional Study Adverse Event Report Form within 24 hours of identification of the event and submit it to Pfizer Safety.

COMMUNICATION OF ISSUES

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

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.

13. REFERENCES

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Appendix 1. DATA SOURCES BY COUNTRY

	Sweden	Denmark	Netherlands	Finland	Norway
Patient demographic and clinical characteristics					
Age	Patient register	Danish Civil Registration System	PHARMO central patient register	All registers	Patient register and / or Cancer Register
Sex	Patient register	Danish Civil Registration System	PHARMO central patient register	All registers	Patient register and / or Cancer Register
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	Patient register and / or Cancer Register
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	Cancer Register and / or Pathology 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	Cancer Register (simplified staging scheme, may be manually approximated to standard stage classifications)
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 Registryor SNOMED CT in Pathology Database	Not available	May be available in patient register and / or Cancer Register (provided manual review of cases with distal spread)
Genotyping	Not available	SNOMED CT in Pathology Register	SNOMED CT in Pathology Database	Not available	May be available using pathology 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	Patient register and / or Cancer Register

	Sweden	Denmark	Netherlands	Finland	Norway
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	ATC code in Prescription Register
Gefitinib	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	ATC code in Prescription Register
Erlotinib	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	ATC code in Prescription Register
Other drugs prescribed	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 Community or Hospital Pharmacy Database	ATC code in Prescription Register	ATC code in Prescription Register
Primary study endpoints					
Hepatotoxicity					
Hepatic failure (acute, subacute, 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, NOMESCO codes in Danish National Registry of Patients and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database

	Sweden	Denmark	Netherlands	Finland	Norway
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, NOMESCO codes in Danish National Registry of Patients and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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, NOMESCO codes in Danish National Registry of Patients and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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, NOMESCO codes in Danish National Registry of Patients and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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-10 codes in Patient Register

	Sweden	Denmark	Netherlands	Finland	Norway
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-10 codes in Patient Register
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-10 codes in Patient Register
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-10 codes in Patient Register
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-10 codes in Patient Register
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-10 codes in Patient Register
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-10 codes in Patient Register
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-10 codes in Patient Register

	Sweden	Denmark	Netherlands	Finland	Norway
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-10 codes in Patient Register
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-10 codes in Patient Register
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database

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

	Sweden	Denmark	Netherlands	Finland	Norway
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database

	Sweden	Denmark	Netherlands	Finland	Norway
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database

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

	Sweden	Denmark	Netherlands	Finland	Norway
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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, NOMESCO codes in Danish National Registry of Patients, and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database

	Sweden	Denmark	Netherlands	Finland	Norway
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, NOMESCO codes in Danish National Registry of Patients, and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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, NOMESCO codes in Danish National Registry of Patients, and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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, NOMESCO codes in Danish National Registry of Patients, and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database

	Sweden	Denmark	Netherlands	Finland	Norway
Vitreous mebranes 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, NOMESCO codes in Danish National Registry of Patients, and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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, NOMESCO codes in Danish National Registry of Patients, and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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, NOMESCO codes in Danish National Registry of Patients, and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database

	Sweden	Denmark	Netherlands	Finland	Norway
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, NOMESCO codes in Danish National Registry of Patients, and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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, NOMESCO codes in Danish National Registry of Patients, and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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, NOMESCO codes in Danish National Registry of Patients, and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database

	Sweden	Denmark	Netherlands	Finland	Norway
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, NOMESCO codes in Danish National Registry of Patients, and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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, NOMESCO codes in Danish National Registry of Patients, and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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, NOMESCO codes in Danish National Registry of Patients, and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database

	Sweden	Denmark	Netherlands	Finland	Norway
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, NOMESCO codes in Danish National Registry of Patients, and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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, NOMESCO codes in Danish National Registry of Patients, and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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, NOMESCO codes in Danish National Registry of Patients, and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and/or ATC code in National Prescription Database
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-10 codes in Patient Register
Edema					

	Sweden	Denmark	Netherlands	Finland	Norway
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-10 codes in Patient Register
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-10 codes in Patient Register
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-10 codes in Patient Register
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-10 codes in Patient Register
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-10 codes in Patient Register
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-10 codes in Patient Register
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-10 codes in Patient Register
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-10 codes in Patient Register
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-10 codes in Patient Register

	Sweden	Denmark	Netherlands	Finland	Norway
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-10 codes in Patient Register
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-10 codes in Patient Register
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-10 codes in Patient Register
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-10 codes in Patient Register
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-10 codes in Patient Register
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-10 codes in Patient Register
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 and/or ATC code in National Prescription Database	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-10 codes in Patient Register and/or ATC codes in Prescription Register

	Sweden	Denmark	Netherlands	Finland	Norway
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 and/or ATC code in National Prescription Database	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-10 codes in Patient Register and/or ATC codes in Prescription Register
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 and/or ATC code in National Prescription Database	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-10 codes in Patient Register and/or ATC codes in Prescription Register
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 and/or ATC code in National Prescription Database	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-10 codes in Patient Register and/or ATC codes in Prescription Register
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 and/or ATC code in National Prescription Database	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-10 codes in Patient Register and/or ATC codes in Prescription Register
Neuropathy					

	Sweden	Denmark	Netherlands	Finland	Norway
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register

	Sweden	Denmark	Netherlands	Finland	Norway
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register

	Sweden	Denmark	Netherlands	Finland	Norway
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register

	Sweden	Denmark	Netherlands	Finland	Norway
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register

	Sweden	Denmark	Netherlands	Finland	Norway
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register

	Sweden	Denmark	Netherlands	Finland	Norway
Pain in hands and fingers (right, left, unspecified hand, right and right, left and uspecified 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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register

	Sweden	Denmark	Netherlands	Finland	Norway
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register
Photosensitivity					
Photosensitivit, 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-10 code in Patient Register
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-10 code in Patient Register
Mortality	Death Register	Central Person Registry	Mortality database	Cause of death register	Vital Statistics Register
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register
Pre-existing hepatic impairment					

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

	Sweden	Denmark	Netherlands	Finland	Norway
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register
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 and/or ATC code in National Prescription Database	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-10 or NOMESCO codes in Patient Register and / or ATC codes in Prescription Register

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.

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.

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.

Appendix 3. CODING ALGORITHMS USED TO IDENTIFY PATIENT BASELINE CHARACTERISTICS, EXPOSURES, SUB-GROUP IDENTIFIERS AND STUDY ENDPOINTS

BASELINE CHARACTERISTICS

Description	ICD-O codes	ICD-10 codes	ICD-9 codes
Lung cancer (primary)	Site codes 340–343, 348–349, morphology codes 8000–8576, excluding 8041–8045 [small cell carcinoma]	C33, C34.00, C34.01, C34.02, C34.10, C34.11, C34.12, C34.30, C34.31, C34.32, C34.80, C34.81, C34.82, C34.90, C34.91, C34.92	162.0, 162.2, 162.3, 162.4, 162.5, 162.8, 162.9, 231.2, 197.0
Other cancers		**C00.xx–D48.xx**	140.x-230.x

EXPOSURES

Description	ATC codes
Crizotinib	L01XE16
Erolotinib	L01XE03
Gefitinib	L01XE02

SUB-GROUP IDENTIFIERS

Brain metastases

Description	ICD-10 codes	ICD-9 codes
Brain metastases	C79.31	198.2

Pre-existing renal impairment

Description	ICD-10 codes	ICD-9 codes
Pre-existing renal impairment	I12.0, I13.11, I13.2, N18.1, N18.2, N18.3, N18.4, N18.5, N18.6, N18.9, N18, N26.9, M10.3, M10.30, I12.9, I13.10, I13.0, N04.4, N02.2, N04.3, N04.0, N098, N04.8, N04.9, N03.2, N03.3, N03.5, N03.8, N08, N03.9, N05.9, N05.2, N05.5, N17.1, N17.2, N08, N05.8, N11.0, N11.8, N28.9, Q61.3, Q61.2, Q61.19, E11.29, E10.29, E11.21, E11.65, E10.21, E10.65, I15.0, I82.3, N00.3, N01.3, N00.8, N00.9, N17.0, N17.8, N17.9, N10, N15.1, N28.84, N28.85, N28.86, N12, N16, N28.0, S37.009A, S37.019A OR S37.029A, S37.039A, S37.069A, S37.009A, S31.001A, S37.019A, S37.029A, S37.049A, S37.059A, S31.0, S37.029A, S37.069A, C90.00, C90.01, C90.02, E85.9, E85.0, E85.1, E85.3, E85.8, D69.0, M30.0, M30.1, M31.30, M31.1, M32.10, M34.0, M34.1, M34.9, C64.9, C65.9, D09.10, D09.19, D41.00, D41.20, D49.5, I77.3, N27.0, N27.1, N27.9, N13.30, N13.8, N13.4, N13.70, N13.71, N13.721, N13.722, N13.729, N13.722, N13.729, N28.81, N28.1, N13.5, N28.89, N28.82, N28.89, N32.0, Q60.2, Q60.5, Q61.00, Q61.9, Q61.01, Q61.4, Q61.5, Q61.02, Q61.8, Q62.39, Q62.11, Q62.12, Q62.31, Q62.10, Q62.11, Q63.0, Q63.1, Q63.2, Q63.3, Q63.8, N25.0, N25.81, N25.89, N25.9, Z94.0, Z99.2, Z91.15, Z49.31, Z49.32, C7A.093, Z85.528, Z85.53, T86.10, T86.11, T86.12, N40.1, N40.3, R80.3, R80.9	403.11, 403.91, 404.12, 404.92, 404.13, 404.93, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9, 586, 587, 274.1, 274.19, 403.1, 403.9, 404.1, 404.9, 404.11, 404.91, 581.0, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9, 582.0, 582.1, 582.2, 582.4, 582.89, 582.81, 582.9, 583, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9, 590.00, 590.01, 593.9, 753.12, 753.13, 753.14, 250.40, 250.41, 250.42, 250.43, 403.00, 403.01, 404.00, 404.01, 404.02, 404.03, 405.01, 453.3, 580.0, 580.4, 580.81, 580.89, 580.9, 584.5, 584.6, 584.7, 584.8, 584.9, 590.10, 590.11, 590.2, 590.3, 590.80, 590.81, 593.81, 866.00, 866.01, 866.02, 866.03, 866.10, 866.11, 866.12, 866.13, 203.00, 203.01, 203.02, 277.30, 277.31, 277.39, 287.0, 446.0, 446.20, 446.21, 446.29, 446.4, 446.6, 710.0, 710.1, 189.0, 189.1, 233.9, 236.91, 239.5, 447.3, 589.0, 589.1, 589.9, 591, 593.4, 593.5, 593.70, 593.71, 593.72, 593.73, 593.1, 593.2, 593.3, 593.82, 593.89, 596.0, 753.0, 753.10, 753.11, 753.15, 753.16, 753.17, 753.19, 753.20, 753.21, 753.22, 753.23, 753.29, 753.3, 588.0, 588.81, 588.89, 588.9, V42.0, V45.11, V45.12, V56.0, V56.8, 209.24, V10.52, V10.53, 996.81, 50320. 50323, 50325, 50327, 50328, 50329,

		50340, 50360, 50365, 50370, 50380, 50547, 600.01, 600.11, 600.21, 600.91,791.0

Pre-existing hepatic impairment

Description	ICD-10 codes	ICD-9 codes
Pre-existing hepatic impairment	K72.9, K72.91, K71.6, K75.9, K72.00, K76.2, K71.10, K71.11, K71.2, K71.9, K72.00, K72.01, D68.32, D68.4, D68.9, J80, K76.7, K70.0, K70.10, K70.11, K70.2, K70.30, K70.31, K70.40, K70.41, K70.9, K73.9, K73.0, K75.4, K73.2, K73.8, K74.0, K74.60, K74.69, K74.3, K74.4, K74.5, K76.0, K76.89, K74.1, K76.9, K75.0, K75.1, K76.6, K72.1, K72.9, Z94.4, K76.1, K77, K76.3, K76.81, K76.1, K76.89, K76.9, B15.0, B15.9, B16.2, B19.11, B16.0, B18.1, B18.0, B16.9, B19.10, B16.1, B18.1, B18.0, B17.11, B17.0, B17.2, B18.2, B17.8, B17.10, B17.0, B17.2, B18.2, B18.8, B18.9, B19.0, B19.20, B19.21, B19.9, Q44.6, E74.00, E74.01 OR E74.04 OR E75.09, R16.0, A52.74, A51.45, B58.1, C22.0, C22.2, C22.7, C22.8, C22.1, C22.9, R17, T86.40, T86.41, T86.42, Z94.4	572.2, 570, 573.3, 286.7, 286.9, 518.82, 572.4, 571.0, 571.1, 571.2, 571.3, 572.2, 571.40, 571.41, 571.42, 571.49, 571.5, 571.6, 571.8, 571.9, 572.0, 572.1, 572.3, 572.8, V42.7, 573.0, 573.1, 573.2, 573.4, 573.5, 573.8, 573.9, 070.0, 070.1, 070.20, 070.21, 070.22, 070.23, 070.30, 070.31, 070.32, 070.33, 070.41, 070.42, 070.43, 070.44, 070.49, 070.51, 070.52, 070.53, 070.54, 070.59, 070.6, 070.70, 070.71, 070.9, 751.62, 271.0, 789.1, 095.3, 091.62, 130.5, 155.0, 155.1, 155.2, 782.4, 996.82, 47125, 47130, 47135, 47140-42 , 070.32, 070.33, 070.54, 456.0, 456.1, 456.20, 456.21

Procedures / drugs	Drug or procedure code
Intravenous N-acetylcysteine	V03AB23 (ATC code)[7]
Liver dialysis[8]	
Liver transplant	47125, 47130, 47135, 47140-42 (ICD-9 CPT), 0FY00Z0, 0FY00Z1, 0FY00Z2(ICD-10 CPT), V42.7(ICD9), Z94.4 (ICD10) JJC 00, JJC 20, JJC 30, JJC 40, JJC 50, JJC 60, JJC 96 (Nomesco and Klassifikation av kirurgiska åtgärder codes[9])

ENDPOINTS

Hepatotoxicity

Description	ICD-10 codes	ICD-9 codes
Hepatic failure	K72, K72.00, K72.10, K72.11, K72.01, K72.90, K72.91	570, 572.8
Hepatic encephalopathy	G92	572.2, 323.71, 323.72, 349.82
Hepatitis / toxic liver disease	K71.10, K71.11, K71.2, K71.9, K71.6	573.3
Hepatorenal syndrome	K76.7	572.4
Jaundice	R17	782.4
Hepatic failure / liver necrosis	K72.00, K72.01	570

Procedures / drugs	Drug or procedure code
Intravenous N-acetylcysteine	V03AB23 (ATC code)[10]
Liver dialysis[11]	
Liver transplant	47125, 47130, 47135, 47140-42 (ICD-9 CPT), 0FY00Z0, 0FY00Z1, 0FY00Z2(ICD-

[7] Corresponding CVV codes will be presented once identified

[8] If feasible ; no procedure code identified

[9] Corresponding CVV codes will be presented once identified

[10] Corresponding CVV codes will be presented once identified

[11] If feasible ; no procedure code identified

	10 CPT), V42.7(ICD9), Z94.4 (ICD10) JJC 00, JJC 20, JJC 30, JJC 40, JJC 50, JJC 60, JJC 96 (Nomesco and Klassifikation av kirurgiska åtgärder codes[12])

Visual disorders

Description	ICD-10 codes	ICD-9 codes
Diplopia	H53.2	368.2
Photopsia (or visual disturbance)	H53.19, H53.121, H53.122, H53.123, H53.129, H53.30	368.15, 368.18, 368.3
Blurred vision (or visual disturbances)	H53.8, H53.9, H53.10	368.8, 368.9, 368.1
Visual field defect	H53.40; (H53.451, H53.452, H53.453, H53.459 AND NOT brain metastases[13])	368.4, (368.44 AND NOT brain metastases[14])
Vitreous floaters	H43.311, H43.312, H43.313, H43.319, H43.391, H43.392, H43.393, H43.399, H43.811, H43.812, H43.813, H43.819, H43.9	379.24, 379.24, 379.21, 379.29
Photophobia (light sensitivity)	H53.71 AND NOT (H25.x OR H26.x)	368.8 AND NOT 366.x
Maculopathy	(H35.381, H35.382, H35.383, H35.389) AND NOT (Chloroquine OR Tamoxifen[15])	362.55 AND NOT (Chloroquine OR Tamoxifen[16])
Retinal hemorrhage	(H35.60, H35.61, H35.62, H35.63) AND NOT (ocular OR retinal metastases[17])	362.81 AND NOT (ocular OR retinal metastases[18])

[12] Corresponding CVV codes will be presented once identified

[13] ICD-10 codes C71.x OR C79.31

[14] ICD-9 codes 171.x OR 198.3

[15] Can lead to toxic maculopathy

[16] Can lead to toxic maculopathy

[17] C69.x

[18] 190.x

Retinal edema	H35.81 AND NOT (ocular OR retinal metastases[19])	362.83 (ocular OR retinal metastases[20])
Misc	H53.15, H35.9	368.14, 362.9

Procedures / drugs <u>to exclude for all of the above</u>	**Drug or procedure code**
Photodynamic therapy	ZXC 15 (Nomesco and Klassifikation av kirurgiska åtgärder codes[21])
Exudative age-related macular degeneration	H35.32 (ICD-10); 362.52 (ICD-9)
Vitreomacular adhesion	H43.82-89 (ICD-10); 379.27 (ICD-9)
Avastin (bevacizumab)	L01XC07 (ATC code)
Eylea (aflibercept)	S01LA05 (ATC code)
Lucentis (ranibizumab)	S01LA04 (ATC code)
Visudyne (verteporfin)	S01LA01 (ATC code)
Macugen (pegaptanib)	S01LA03 (ATC code)

<u>QTc prolongation</u>

Description	**ICD-10 codes**	**ICD-9 codes**
Ventricular fibrillation	I49.01	427.41
Ventricular flutter	I49.02	427.42
Ventricular tachycardia / Paroxysmal entricular tachycardia, tachycardia unspecified	147.2, R00.0	427.1, 785
Long QT Syndrome	I45.81	426.82
Cardiac dysrhythmia, unspecified	I49.9	427.9
Cardiac arrest , unspecified	I46.9	427.5

[19] C69.x

[20] 190.x

[21] Corresponding CVV codes will be presented once identified

Syncope and collapse	R55	780.2
Death (Instantaneous, not otherwise explained, unattended, ill-defined and unknown cause of mortality / unknown and unspecified causes of mortality and morbidity)	R99	798.1, 798.2, 798.9, 799.9

Procedures / drugs	**Drug or procedure code**
Intravenous magnesium sulfate	B05XA05 (ATC code)
Betablockers (stratification variable; may confound diagnosis of bradycardia)	C07Aaxx (ATC code)
Implantation / presence of cardiac pacing devices	37.94, 37.95, 37.96, 37.97, 37.98, 0.51, 0.54, 996.04 (ICD-9 PCS) 02H40KZ, 02HK0KZ, 02H73KZ, 02H60KZ, 02H43KZ, 02HL0KZ, 02HN0KZ, 02HK3KZ, 02HN3KZ, 02H63KZ, 02H70KZ, 02HL3KZ, 02HN4KZ, 02H44KZ, 02HK4KZ, 02H74KZ, 02H64KZ, 02HL4KZ, 0JH838Z, 0JH638Z, 0JH808Z, 0JH608Z, 0JH839Z, 0JH639Z, 0JH809Z, 0JH609Z NOT PRECEDED BY 02PA0MZ, 02PA3MZ, 02PAXMZ, 02PA4MZ (ICD-10 PCS) FPG 10, FPG 20, FPG 30, FPG 33, FPG 36, FPG 40, FPG 43, FPG 96 (Nomesco and Klassifikation av kirurgiska åtgärder codes[22])

Bradycardia

Description	**ICD-10 codes**	**ICD-9 codes**
Bradycardia, unspecified	R00.1	427.81, 427.89
Other specified cardiac arrhythmias	I49.8	427.89

[22] Corresponding CVV codes will be presented once identified

Atrioventricular block	I44.2, I44.30, I44.1	426.0, 426.10, 426.12, 426.13
Other specified heart block	I45.5	426.6
Conduction disorder (unspecified and other specified)	I45.9, I45.89	426.9, 426.89

Procedures / drugs	**Drug or procedure code**
See QTc Prolongation, above	

Pneumonitis

Description	**ICD-10 codes**	**ICD-9 codes**
Interstitial lung disease	J84.89, J84.9, J70.2, J70.4, J70.3, J84.113, J84.114	515, 516.9, 508.8, 516.32, 516.33
Eosiniphilic pneumonia	J82	518.3
Pulmonary fibrosis	J84.10	515
Idiopathic interstitial pneumonia	J84.111, J84.09, J86.9, J94.1, J94.8, J94.9, R09.1, J90, J94.2, J91.8	516.3, 516.8, 511.0, 511.1, 511.89, 511.9
Other pulmonary insufficiency	J80	518.82

Procedures / drugs	**Drug or procedure code**
No specific procedures / drugs	

Edema

Description	ICD-10 codes	ICD-9 codes
Peripheral edema	R60.0, R60.1, R60.9	782.3
Angioneurotic edema	T78.3XXA, T78.3XXD, T78.3XXS, H02.849, H02.846, H02.845, H02.844, H02.843, H02.842, H02.841, J38.4, J39.2	995.1, V58.89, 909.9, 374.82, 478.6, 478.25, 478.26, 478.29
Urticaria	L50.0, L50.1, L50.5, L50.8, L50.9,	708.0, 708.1, 708.5, 708.8, 708.9
Wheezing	R06.2	786.07

Procedures / drugs	Drug or procedure code
No specific procedures / drugs	

Leukopenia

Description	ICD-10 codes	ICD-9 codes
Lymphocytopenia	D72.819, D72.810	288.50, 288.51
Other decreased white blood cell count	D72.818	288.59
Neutropenia	D70.1, D70.2, D70.3, D70.4, D70.8, D70.9	288.03, 288.00, 288.02, 288.04, 288.09
Other or unspecified disorders of white blood cells	D72.89	288.8, 288. 9

Procedures / drugs	Drug or procedure code
Neupogen (filgrastim)	L03AA02 (ATC code)
Neulasta (pegfilgrastim)	L03AA13 (ATC code)
Leukine (sargramostim)	L03AA09 (ATC code)
Civacir, Flebogamma, Gamunex (Intravenous immune globulin)	J06BA02, J06BA01 (ATC codes)

Granulocyte transfusions[23]	

Neuropathy

Description	ICD-10 codes	ICD-9 codes
Disturbance of skin sensation	R20.0, R20.1, R20.2, R20.3, R20.8, R20.9	782.0
Toxic optic neuropathy	H46.3	377.34
Lumbosacral plexus disorders	G54.1	353.1
Lumbosacral root disorders	G54.4	353.4
Mononeuritis multiplex	G58.7	354.5
Neuralgia neuritis and radiculitis	M54.10, M79.2	729.2
Polyneuropathy	G62.81, G61.1, G60.3, G63, G62.9, G61.89, G61.9, G62.0	357.82, 357.7, 356.4, 357.4, 357.9, 357.89, 357.9, 357.6
Idiopathic peripheral neuropathy	G60.9, G90.09	356.9, 337.00, 337.09
Disturbance of skin sensation	R20.2, R20.1, R20.3, R20.9, R20.8	782.0
Muscle weakness	M62.81	728.87
Pain in limb	M79.60x, M79.62x, M79.63x, M79.64x, M79.65x, M79.66x, M79.67x	729.5

Procedures / drugs	Drug or procedure code
Gralise, Neurontin (gabapentin)	N03AX12 (ATC code) AND NOT (fibromyalgia, migraine, OR epilepsy)[24]
Topamax (topiramate)	N03AX11 (ATC code) AND NOT (fibromyalgia, migraine, OR epilepsy)[25]

[23] If feasible ; no procedure code identified

[24] M79.7 (ICD-10) or 729.1 (ICD-9); G43.x (ICD-10) or 346.x (ICD-9); G40.x (ICD-10) or 345.x (ICD-9)

[25] M79.7 (ICD-10) or 729.1 (ICD-9); G43.x (ICD-10) or 346.x (ICD-9); G40.x (ICD-10) or 345.x (ICD-9)

Lyrica (pregabalin)	N03AX16 (ATC) AND NOT (fibromyalgia, migraine, OR epilepsy)[26]
Carbatrol, Tegretol (carbamazepine)	N03AF01 (ATC) AND NOT (fibromyalgia, migraine, OR epilepsy)[27]
Dilantin, Phenytek (phenytoin)	N03AB02 (ATC) AND NOT (fibromyalgia, migraine, OR epilepsy)[28]
Qutenza (capcaisin)	M02AB01 or N01BX04 AND NOT (post-herpetic neuralgia[29])
Lidoderm (lidocaine)	D04AB01 or N01BB02 or N01BB52 AND NOT (post-herpetic neuralgia[30])
Dorsal rhizotomy	63190[31] (CPT code)[32]
Regional nerve block[33]	
Alcohol injection[34]	

Renal cysts

Description	ICD-10 codes	ICD-9 codes
Acquired kidney cyst	N28.1	593.2

Procedures / drugs	Drug or procedure code
No specific procedures / drugs	

Photosensitivity

[26] M79.7 (ICD-10) or 729.1 (ICD-9); G43.x (ICD-10) or 346.x (ICD-9); G40.x (ICD-10) or 345.x (ICD-9)

[27] M79.7 (ICD-10) or 729.1 (ICD-9); G43.x (ICD-10) or 346.x (ICD-9); G40.x (ICD-10) or 345.x (ICD-9)

[28] M79.7 (ICD-10) or 729.1 (ICD-9); G43.x (ICD-10) or 346.x (ICD-9); G40.x (ICD-10) or 345.x (ICD-9)

[29] B02.23 (ICD-10) or 053.13 (ICD-9); B02.9 (ICD-10) or 053.9

[30] B02.23 (ICD-10) or 053.13 (ICD-9); B02.9 (ICD-10) or 053.9

[31] Laminectomy with rhizotomy; more than 2 segments

[32] Corresponding NOMESCO, Klassifikation av kirurgiska åtgärder, and CVV codes will be presented once identified

[33] If feasible ; no procedure code identified

[34] If feasible ; no procedure code identified

Description	ICD-10 codes	ICD-9 codes
Dermatitis due to solar radiation	L56.8, L56.9, L57.8	692.79, 692.70, 692.74
Dermatitis due to other radiation	L59.8	692.82
Dermatitis due to drugs	L27.0, L27.1	693.0

Procedures / drugs	Drug or procedure code
No specific procedures / drugs	

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