NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS INFORMATION

Title	An Active Safety Surveillance Program To Monitor Selected Events In Patients With Long-Term Voriconazole Use
Protocol number	A1501103
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Active substance	Voriconazole ATC code J02AC03
Medicinal product	Vfend®
Product reference	EMEA/H/C/000387
Procedure number	EMEA/H/C/000387/II/097
Marketing Authorisation Holder (MAH)	Pfizer Limited Ramsgate Road, Sandwich, Kent CT130NJ United Kingdom
Research question and objective	To estimate the incidence rate of hepatic disorders, phototoxicity, SCC of the skin, visual disorders and periostitis among adult and paediatric patients receiving voriconazole, particularly with long-term use.
Country(-ies) of study	Sweden

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse Event Monitoring
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
EC	Oesophageal Candidiasis
EMA	European Medicines Agency
EMR	Electronic Medical Records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GPP	Good Pharmacoepidemiology Practices
GvHD	Graft-versus-host disease
HIV	Human Immunodeficiency Virus
IA	Invasive Aspergillosis
ICC	Candidiasis including Candidemia
ICD	International Classification of Diseases (
IDSA	Infectious Diseases Society of America
IEA	International Epidemiological Association
IFI	Invasive Fungal Infection
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorisation Holder
NIS	Non-Interventional Study
NOMESCO	Nordic Medico-Statistical Committee
NCSP	Nordic Classification of Surgical and Medical Procedures
NPR	National Patient Register
PASS	Post-Authorization Safety Study
RMMs	Risk Minimisation Measures
SAP	Statistical Analysis Plan
SCC	Squamous Cell Carcinoma
SmPC	Summary of Product Characteristics
SOT	Solid Organ Transplant
CIOMS	Council for International Organisations of Medical Sciences
ERG	Electroretinogram
FDA	Food and Drug Administration
GEP	Good Epidemiological Practice
HSCT	Haematopoietic Stem Cell Transplantation
ICD	International Classification of Diseases
IEC	Independent Ethics Committee
IQR	Interquartile Range
LT	Lung Transplant
PAS	Post-Authorisation Studies
PSUR	Periodic Safety Update Reports
RMP	Risk Management Plan
RA	Rheumatoid Arthritis
SLE	Systemic Lupus Erythematosus
VOLD	Veno-occlusive Liver Disease

2. RESPONSIBLE PARTIES

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Country Coordinating Investigators

Not applicable

3. ABSTRACT

Protocol # A1501103: Amendment-I; version 1.1;18 June, 2015

An active safety surveillance program to monitor selected events in patients with long-term voriconazole use.

Principal Investigators:

Helle Kieler, MD, PhD; Associate Professor, Centre for Pharmacoepidemiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

Rationale and background

Voriconazole (Vfend®), a broad spectrum triazole antifungal agent, has been available for adults and paediatrics aged 2 years and above for the treatment of invasive aspergillosis (IA), candidemia in non-neutropenic patients, fluconazole-resistant serious invasive *Candida* infections (including *Candida krusei*), serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp. in the European Union (EU) since 2002. Also, on 24 June, 2014, voriconazole was approved for prophylaxis of invasive fungal infections (IFI) in high-risk haematopoietic stem cell transplantations (HSCT) recipients in the EU. In addition to the approved indications, published reports indicate that voriconazole is being used as prophylaxis to prevent IFI in patients with immunocompromised status such as patients with solid organ transplant (SOT).

Recently, concerns have been raised about potentially increased risks of hepatic disorders , squamous cell carcinoma (SCC) of the skin, visual disorders and periostitis with long-term use of voriconazole (ie, ≥180 days of treatment).

To ensure risks of hepatic disorders, SCC of the skin and phototoxicity are adequately minimised and managed, the Marketing Authorisation Holder (MAH) has in place routine and additional risk minimisation measures (RMMs) in the EU. The voriconazole Summary of Product Characteristics (SmPC) Sections 4.4 and 4.8.'Warnings and Precautions' and 'undesirable effects' warn prescribers about these risks. The additional RMM constitute a comprehensive educational program including a Healthcare Professional (HCP) Checklist, HCP Questions and Answer (Q&A) Brochure, and Patient Alert Card aimed to educate and remind prescribers and patients of the risks of hepatic disorders, phototoxicity and SCC of the skin and how to minimise them. The voriconazole SmPC Sections 4.4 and 4.8 also warn about periostitis.

The MAH monitors the safety profile of voriconazole via routine pharmacovigilance activities. To further strengthen the safety monitoring for the risks of hepatic disorders, phototoxicity, SCC of the skin, visual disorders and periostitis (hereafter referred to as 'safety events') with voriconazole exposure particularly with long-term use, the MAH has planned an 'active safety surveillance program'. In the case of rare exposures such as voriconazole use and a rare safety outcomes such as SCC of the skin and periostitis, an active surveillance program using existing healthcare data source(s) permits collection of safety

data in an efficient and timely manner and thereby allows monitoring of targeted safety events by periodically estimating the incidence of these events. A recently completed study feasibility assessment by the MAH showed that it is feasible to establish an active safety surveillance program for voriconazole using existing population-based registers in Sweden (Study Feasibility Assessment Report submitted on 30 April 2014).

This non-interventional (NI) study is designated as a post-authorisation safety study (PASS) and is a commitment to the European Medicines Agency (EMA).

Research question and objectives

The overall objective of this study is to monitor selected safety events in patients receiving voriconazole in the real world setting, particularly with long-term voriconazole use.

Specifically:

To estimate the incidence rate of hepatic disorders, phototoxicity, SCC of the skin, visual disorders and periostitis among adult and paediatric patients receiving voriconazole, particularly with long-term use.

Study design& population

In this observational cohort study, eligible patients will be identified from population-based Swedish National Registers. All patients with a filled prescription of voriconazole during a 12-year inclusion period from 1 January, 2006 through 31 December, 2017 will be included. The study will utilize retrospective data (i.e., already accumulated data since January 2006 through 2015) as well as prospective data accumulated in future years (i.e., by the data cut-off date of 30 June, 2021) from the Swedish National Registries.

Eligibility criteria

Patients with at least one filled prescription of voriconazole in the Swedish Prescribed Drug Register will be included in this study.

Note: Although the study will include patients with at least one filled prescription of voriconazole to be inclusive for safety reporting purposes, the analysis for the study objective will mainly focus on patients treated with long-term voriconazole use.

Data sources

Data will be obtained from the Swedish National Registers including the Swedish Prescribed Drug Register (SPDR), the Swedish Cancer Register (SCR), the National Patient Register (NPR), the Causes of Death Register (CDR), and the Registers of Statistics Sweden. The national health registers cover all residents of Sweden (9.6 million in 2013). A unique personal identity number is issued to all residents of Sweden upon birth or immigration and is used throughout life which is used to link patient-level data from the different registers.

Variables

Main exposure variable is voriconazole use including the duration of voriconazole treatment, and outcome variables including hepatic disorders, phototoxicity, SCC of the skin, periostitis and visual disorders. In addition, data on patients' demographic and clinical characteristics including co-morbid/underlying conditions, use of voriconazole for approved indications or non-approved (i.e., off label use) and concomitant medications will be collected.

Study size

All study eligible patients with a filled prescription of voriconazole in the Swedish Prescribed Dug Register from 1 January, 2006 through 31 December, 2017 will be included in the study. Preliminary counts of patients treated with voriconazole during a seven- year period (2006 through 2012) showed an annual average of 305 patients (including 37 paediatric patients aged ≦19 years annually). Based on the average of 305 patients per year, approximately 3,660 (305x12) patients exposed to voriconazole are expected from 1 January, 2006 through 31 December, 2017 in the database. It is to be noted that patients with long-term voriconazole use will be a subset of all patients exposed to voriconazole in the database.

Data analyses

Descriptive analyses (no formal hypothesis-testing) will be conducted to address the study objective. Counts and proportions to describe categorical variables, and mean and standard deviations (or median with inter quartile range (IQR), where appropriate) for continuous variables will be calculated. Safety events (i.e., hepatic disorders, phototoxicity, visual disorders, SCC of the skin, periostitis) will be summarized using a piecewise exponential model that permits separate estimation of the hazard within the following voriconazole treatment intervals:

- ≤3 months
- >3 to ≤6 months
- >6 to ≤9 months
- >9 to ≤12 months
- > 12 month

The piecewise model will be used to calculate incidence rates (e.g., per 1,000 person days, person months or person years of follow-up), as well as cumulative incidence rates. The model will also be used to construct 95% confidence intervals for the incidence rates. Further, the piecewise exponential model will be used to calculate incidence rates separately within the categories of subgroups such as age group (i.e., paediatrics aged 2 months to 18 years and adults >18 years) and co-morbid/underlying conditions (e.g., SOT recipients) when there exist enough data within the subgroup to support a meaningful statistical summary.

Milestones

The study will be registered in the 'EU PAS Register' after the protocol endorsement by the Committee for Medicinal Products for Human Use (CHMP).

Three interim reports during the conduct of the study and the final report after the study completion will be prepared. It should be noted that there is a lag of about 1.5 years for data updates in the select Swedish registries that will be utilized for this study. For example: on 31 December, 2015 which is the data cut-off date for the first interim report, the registries are expected to contain data from 1 Jan, 2006 through 30 June, 2013. Further, the availability of study data is dependent on receiving permission by the National Board of Health and Welfare, and Statistics Sweden and is beyond the control of the study investigators. Therefore the report submission timeline may be affected by any delay in the availability of study data to the investigators by the relevant authorities.

The table below provides detail about the data cut-off date, expected inclusion of data from the Swedish National Registries, and estimated timeline for submission of the interim and final reports to the EMA.

Report*	**Data cut- off date** (Data abstraction will begin after this date)	**Expected data availability in Swedish National Registries** (Accounting for approx. 1.5 years of data lag-time)	**Expected report submission to the EMA**
1st Interim Report	31 Dec, 2015	1 Jan, 2006 through 30 June, 2013	4Q 2016
2nd Interim Report	31 Dec, 2017	1 Jan, 2006 through 30 June, 2015	4Q 2018
3rd Interim Report	31 Dec, 2019	1 Jan, 2006 through 30 June, 2017	4Q 2020
Final Clinical Study Report	30 June, 2021	1 Jan, 2006 through 31 Dec, 2019	2Q 2022

The first interim report will include analysis of the available data on all 4 safety events from 2006 through the data cut-off 31 December, 2015. The second, third interim reports and the final report will include available data from 2006 through the specific data cut-offs as listed in the table.

4. AMENDMENTS AND UPDATES

#	Protocol section	Major changes
1.	5.0 Milestones	• Timeline for submission of the first and second interim reports to the EMA has been revised. • A third interim report for submission of the EMA has been added.
2.	8.4 Variables	Information on additional risk factors including confounding variables and effect modifiers have been added.
3.	8.7 Data analysis	Revised to classify cumulative duration of voriconazole use and summarize incidence of safety events within the following voriconazole treatment intervals: • 3 ≤ months • >3 to ≤6 months • >6 to ≤9 months • >9 to ≤12 months • >12 month Added analysis of cumulative dose over time by using cumulative average dose at each time point during the study as a time-dependent covariate. A categorical version of cumulative average dose using tertiles or quartiles will also be explored. Added the description how Missing data will be handled.

5. MILESTONES

Milestone	**Planned Quarter/date**	**Actual date** ***dd/mm/yyyy***
Completion of study feasibility assessment	-	30 April, 2014 (Report submitted to the EMA)
Protocol endorsement by the CHMP/EMA	-	
Registration in the EU PAS register	After the final protocol endorsement by the CHMP and prior to start of data collection	
Start of data collection/abstraction from Swedish National Registries	2Q 2016	
End of data collection/abstraction from Swedish National Registries	3Q 2021	
Interim and Final Reports:		
Interim report- I	4Q 2016	
Interim report-II	4Q 2018	
Interim report-III	4Q 2020	
Final study report	2Q 2022	

6. RATIONALE AND BACKGROUND

Voriconazole (Vfend®), a broad spectrum triazole antifungal agent, has been available since 2002 for the treatment of invasive aspergillosis (IA), candidemia in non-neutropenic patients, fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*), serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp. in the EU. Voriconazole has shown superior efficacy compared to other antifungal agents and is currently recommended as the drug of choice for IA by the Infectious Diseases Society of America (IDSA).[1] Also, on 24 June, 2014, voriconazole was approved for prophylaxis of invasive fungal infections (IFI) in high risk haematopoietic stem cell transplantations (HSCT) recipients in the EU. In addition to the approved indications, published reports indicate that voriconazole is being used as prophylaxis to prevent IFI in patients with immunocompromised status such as solid organ transplant (SOT) recipients.[2,3]

In the EU, voriconazole is indicated in adult and paediatric patients (aged 2 years to 18 years) for the above indications. Safety and efficacy data of voriconazole in paediatric patients for the treatment of IA, candidiasis including candidemia (ICC) and esophageal candidiasis (EC) have been available only in a limited number of adolescents (n=52) that were included in the therapeutic studies. An additional 53 paediatric patients were observed in the two recently completed paediatric therapeutic studies (A1501080 &A1501085) (Pfizer data on file). Clinical data demonstrated that the safety and efficacy in paediatrics patients were generally similar to those observed in adult patients in therapeutic studies. Only a higher frequency of hepatic related adverse events (AEs), mainly associated to increased liver enzymes, in the paediatrics population compared to adults was observed. The type and severity of the hepatic related AEs, however, was similar to that in adults. No cases of liver failure or cases with a fatal outcome were reported. Further, the safety profile of voriconazole in paediatrics patients, as shown by data in additional pharmacokinetics studies and from the analysis of post-marketing Safety database of the Marketing Authorisation Holder (MAH), is generally consistent with the known safety profile of voriconazole (Pfizer data on file).

Voriconazole is initiated in the inpatient setting (ie., during hospitalisation) in the majority of patients and long-term use (≥ 180 days) of voriconazole, when needed, is usually continued in the outpatient setting. Recently, concerns have been raised about potential increased risks of hepatic disorders, squamous cell carcinoma (SCC) of the skin, visual disorders and periostitis with long-term use of voriconazole. Each of these risks is briefly described below:

Hepatic disorders: Hepatic disorder is an important identified risk with voriconazole use in the Risk Management Plan (RMP). In clinical trials, there have been uncommon cases of serious hepatic adverse reactions during treatment with voriconazole (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities). Instances of hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly haematological malignancy). Transient hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. Liver dysfunction has usually been reversible on discontinuation of therapy (voriconazole Summary of Product Characteristics [SmPC]). Hepatic disorder analysis over

time in the pivotal prophylaxis study (A1501073) showed that the majority of hepatic AEs occurred at the early stages following administration of voriconazole and the risk did not increase over time. Similar observation was made in therapeutic clinical trials.

The SmPC instructs prescribers on how to monitor the risk of hepatic disorders during treatment with voriconazole and was recently updated to further provide guidance to manage this risk. In addition, the MAH has initiated a comprehensive additional risk minimisation measures (RMMs) in the EU which constitute a comprehensive educational program that includes a Healthcare Professional (HCP) Checklist, HCP Questions and Answer (Q&A) Brochure, and Patient Alert Card aimed to educate and remind prescribers and patients of the risks of hepatic disorders and how to minimise them. The additional RMMs haven been endorsed by the Committee for Medicinal Products for Human Use (CHMP). Further, the effectiveness of the additional RMMs will be evaluated in a post-authorisation safety study (PASS) A1501102.

Visual disorders: In therapeutic studies, voriconazole treatment-related visual disturbances were very common. In these studies, with short-term as well as long-term treatment, approximately 21% of subjects experienced altered/enhanced visual perception, blurred vision, colour vision change or photophobia during treatment with voriconazole. These visual disturbances were transient and fully reversible, with the majority spontaneously resolving within 60 minutes and no clinically significant long-term visual effects observed. The mechanism of action is unknown, although the site of action is most likely to be within the retina. In a study in healthy volunteers investigating the impact of voriconazole on retinal function, voriconazole caused a decrease in the electroretinogram (ERG) waveform amplitude. The ERG measures electrical currents in the retina. The ERG changes did not progress over 29 days of treatment and were fully reversible on withdrawal of voriconazole (voriconazole SmPC). In addition, in the pivotal prophylaxis study (A1501073), the majority of visual disorders occurred at early stages of the administration of voriconazole. Nevertheless, prescribers are warned about these events in the SmPC.

Phototoxicity and squamous cell carcinoma (SCC) of the skin: Phototoxicity and SCC of the skin are important identified risks in the voriconazole RMP. Dermatological reactions were common in patients treated with voriconazole in clinical trials, but these patients had serious underlying diseases and were receiving multiple concomitant medicinal products. The majority of rashes were of mild to moderate severity. Voriconazole has been associated with phototoxicity and pseudoporphyria. It is recommended that all patients, including children, avoid exposure to direct sunlight during voriconazole treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF).

In the clinical program, only one case of SCC of the skin treated with voriconazole was reported. The case was a 4- year male patient infected with human immunodeficiency virus (HIV) receiving antiviral treatment; other concomitant medications included were sulphonamides and trimethoprim. Post-marketing single case reports, and small case series of SCC of the skin in patients with immunocompromised status such as patients with SOT, haematological malignancy or patients infected with human immunodeficiency virus (HIV) infection using voriconazole for long-term have been reported. In addition, a few analytical

studies using retrospective data in lung transplant recipients have been published suggesting an increased risk of SCC of the skin with voriconazole use.[4, 5] A review of cumulative cases of skin cancer/SCC reported to the MAH (from international birth date (IBD) to 28 February, 2014 in adults and paediatrics) did not provide sufficient evidence to support a causal association between SCC and administration of voriconazole. The mechanism and causal association of SCC to administration of voriconazole remains unclear. In the majority of reported cases with long-term voriconazole use (i.e., >180 days), immunosuppressed condition was the main confounding factor (Pfizer data on file). In order to assess the risk of SCC of the skin in adults, the MAH is conducting a multinational, multicenter, non-interventional PASS (A1501097) to evaluate the risk of SCC of the skin with voriconazole use in lung transplant recipients.

To ensure the risks of phototoxicity and SCC of the skin are adequately managed, the MAH has already in place routine and additional RMMs in the EU. The voriconazole SmPC Sections 4.4 and 4.8.'Warnings and Precautions' and "undesirable effects" warns prescribers of the risk of phototoxicity and SCC of the skin, recommends the use of sun protection measures during treatment with voriconazole, and recommends early discontinuation in cases of phototoxicity, premalignant skin lesions or the onset of SCC. The additional RMMs, described earlier, will also educate and remind prescribers and patients of the risks of phototoxicity and SCC of the skin with voriconazole use and how to minimise them.

Periostitis: Periostitis has been reported with prolonged (i.e., 6 months to several years) use of voriconazole mainly in patients with lung transplant (Pfizer data on file). Prescribers are warned about the risk of periostitis in the SmPC and are advised to limit exposure to voriconazole and to consider discontinuation of voriconazole if skeletal pain and radiologic findings compatible with periostitis develop. The SmPC also recommends limited duration of voriconazole therapy and indicates that long-term treatment requires careful assessment of the benefit-risk balance.

The MAH monitors the safety profile of voriconazole via routine pharmacovigilance activities. To further strengthen the safety monitoring for the risks of hepatic disorders, phototoxicity, SCC of the skin, visual disorders and periostitis (hereafter referred to as 'safety events') with voriconazole exposure particularly with long-term use, the MAH has planned an 'active safety surveillance program'. In the case of rare exposures such as voriconazole use and a rare safety outcomes such as SCC of the skin and periostitis, an active surveillance program using existing healthcare data source(s) permits collection of safety data in an efficient and timely manner and thereby allows monitoring of targeted safety events by periodically estimating the incidence of these events. A recently completed study feasibility assessment by the MAH showed that it is feasible to establish an active safety surveillance program for voriconazole using existing population-based registers in Sweden (Study Feasibility Assessment Report submitted to the EMA on 30 April, 2014).

This non-interventional (NI) study is designated as a post-authorisation safety study (PASS) and is a commitment to the European Medicines Agency (EMA).

7. RESEARCH QUESTION AND OBJECTIVES

The overall objective of this study is to monitor selected safety events in patients receiving voriconazole in the real world setting, particularly with long-term use.

Specifically:

To estimate the incidence rate of hepatic disorders, phototoxicity, SCC of the skin, visual disorders and periostitis among adult and paediatric patients receiving voriconazole, particularly with long-term use.

8. RESEARCH METHODS

8.1. Study design

In this observational cohort study, eligible patients will be identified from population-based Swedish National Registers.

One of the strengths of this observational study is the use of large existing health care data from routine clinical care that allow monitoring of selected safety events among patients exposed to voriconazole particularly with long-term in a reasonable period of time. It is expected that findings from this population-based study would have greater generalizability than those from clinical trials because of the less stringent study eligibility criteria than generally used in clinical trials. It is to be noted that in Sweden individual level data from the whole population is routinely collected and recorded in several registers. It has been suggested that data from Nordic registers including Sweden can be used for long term surveillance of drug safety. [6,7]

8.2. Setting

Patients treated with voriconazole will constitute the study population. Study eligible patients will be identified from existing population-based national health registers in Sweden. The study will utilize retrospective data (i.e., already accumulated data since January 2006 through 2015) as well as prospective data accumulated in future years (i.e., by the data cut-off date of 30 June, 2021) from the Swedish National Registries (further described in Section 8.3 Data Sources).

8.2.1. Inclusion criteria

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

- At least one filled prescription of voriconazole (identified from the Swedish Prescribed Drug Register) between 2006 and 2017.

Note: Although the study will include patients with at least one filled prescription of voriconazole to be inclusive for safety reporting purposes, the analysis for the study objective will mainly focus on patients treated with long-term voriconazole use.

8.2.2. Exclusion criteria

There are no exclusion criteria for this study.

8.2.3. Index date and follow up

The index date will be the "date of first filled voriconazole" as recorded in the Swedish Prescribed Dug Register. The study eligible patients will be followed from the index date to whichever of the following occurs first:

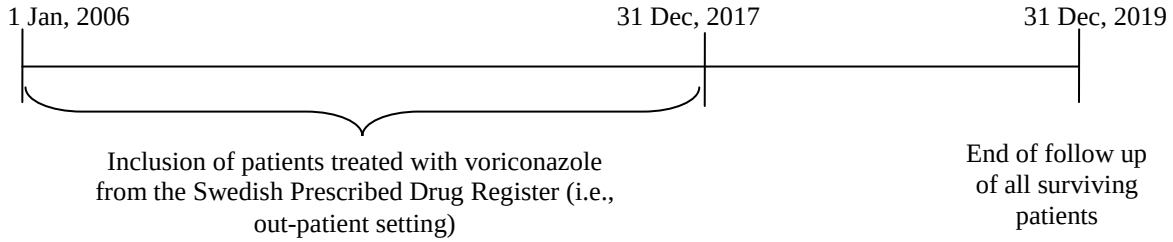
- Death
- Emigration, or
- 31 December, 2019 at which time all surviving patients will be censored.

Note: Patients once exposed to voriconazole will be considered 'at risk' for developing the safety event(s) until the end of follow up regardless of voriconazole discontinuation.

8.2.4. Patient selection

Given that patients typically receive voriconazole in the out-patient setting, all patients meeting the study eligibility criteria in the Swedish Prescribed Drug Register will be included. Additional relevant information (e.g., demographic information, comorbid/underlying conditions) will be obtained from other population-based registers in Sweden (further described in Section 8.3 Data Sources). Figure 1 describes inclusion and follow up period timelines.

Figure 1. Patients inclusion and follow up period



8.3. Data sources

Data will be obtained from the Swedish National Registers, including the Swedish Prescribed Drug Register (SPDR), the Swedish Cancer Register (SCR), the National Patient Register (NPR), the Causes of Death Register (CDR), and the Registers of Statistics Sweden. The national healthcare registers cover all residents of Sweden (9.6 million in 2013). A unique personal identity number is issued to all residents of Sweden upon birth or immigration and is used throughout life which will be used to link patient-level data from the different registers. All citizens independent of socioeconomic status have unrestricted access to health services including partial or complete reimbursement of purchased medicines because of a tax-supported public health service with universal coverage. Below is the description of major national healthcare databases/registers in Sweden.

The Swedish Prescribed Drug Registry: The Swedish Prescribed Drug Registry is a nationwide database covering all prescribed dispensed medications for the entire Swedish population. It includes data that fall into four main categories: (1) patient-specific data,(2) prescriber data, (3) drug data, and (4) pharmacy data. Drug data include the trade name, pharmaceutical form, strength and package size, number of packages, Anatomical Therapeutic Chemical (ATC) classification code, amount in defined daily doses (DDD), and the prescribing and dispensing date. The information is updated monthly. It does not include the majority of sales of non-prescription over-the-counter (OTC) medicines.

It is to be noted that the data on medications administered during hospitalisation are not available in the Prescribed Drug Register but are maintained in hospitals' medical records (either as electronic medical records [EMR] and/or paper charts) and can be accessed and collected after approvals from relevant authorities.

The Swedish National Patient Register: The Swedish National Patient Register (NPR) includes more than 99% of all somatic (including surgery) and psychiatric hospital discharges and visits. It is mandatory for all physicians, private and publicly funded, to deliver data to the NPR (except for visits in primary care). Previous validation of the NPR by the National Board of Health and Welfare showed that 85 % to 95 % of all diagnoses in the NPR are valid. Since 1997 ICD-10 codes have been used. A Swedish version of the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures has been used since 1997. Current procedures are listed in the Nordic Classification of Surgical and Medical Procedures (NCSP).

The Swedish Cause of Death Register (CDR): The Swedish Cause of Death Register comprises all deaths among Swedish residents, whether occurring in Sweden or abroad. The causes of death are coded centrally at Statistics Sweden according to the international (English) version of ICD-10. The NPR can be linked and matched with the cause-of-death register to attain an even better coverage of disease events and, to some extent, to include patients managed outside hospitals.

The Swedish Cancer Register (SCR): The Swedish Cancer Register was founded in 1958 and contains information about clinical and histological diagnoses and date and place of living at diagnosis. It reports valid information on more than 97% of all patients with cancer. The Cancer Register converts all diagnoses recorded by the current ICD and ICD-O version into ICD 7 in order to facilitate comparisons over time. The database is updated annually.

The Population Registers (Statistics Sweden): The registers hold data on socioeconomic status such as: income, education, immigration, emigration and country of birth. The Swedish Standard Classification of Occupations is used for classification of occupations (SSYK, Statistics Sweden 1996).

8.4. Variables

Table 1 describes the exposure variable, outcomes variables, potential confounders and effect modifiers, their roles and operational definitions.

Table 1. Study variables, their roles and operational definitions

Variable	Role	Operational definition
Exposure variables		
Voriconazole use (yes/no)	Main exposure	ATC code and drug name in Swedish Prescribed Drug Register
Duration of voriconazole therapy For example • ≤ 3 months • >3 to ≤6 months • >6 to ≤9 months • >9 to ≤12 months • >12 months	Main exposure	Duration of voriconazole treatment will be calculated from daily defined dose (DDD), and multiplied with the number of filled prescriptions. Data on duration will be obtained from the Swedish Prescribed Drug Register
Use of voriconazole for: • Approved indications E.g.,: Invasive aspergillosis, Candidemia • Non approved use	Other exposure	ATC code and drug name in Swedish Prescribed Drug Register Note: Information on indication for medication use is not available/directly captured in the Prescribed Drug Register. An algorithm will be developed based on diagnoses recorded around the time of the prescription to use as the proxy variable. There may be some misclassification since patients without any specific ICD code may have used voriconazole either for a non-approved use or for prophylaxis.
Use of voriconazole for : • Prophylaxis of IFIs • Treatment of IFIs • Unknown cause	Other exposure	ATC code and drug name in Swedish Prescribed Drug Register Note: Information on use of voriconazole for prophylaxis and/or treatment may not available/directly captured in the Prescribed Drug Register. An algorithm will be developed based on diagnoses recorded around the time of the prescription to use as the proxy variable.
Outcome variables		
• Hepatic disorders (Selected clinical liver conditions identifiable using relevant ICD codes will be included)	Primary outcome	ICD-10 codes in Swedish Patient Register (Appendix I)
• SCC of the skin	Primary outcome	ICD-10/ICD-0/3 codes in the Swedish Cancer Register (Appendix I)
• Visual disorders	Primary outcome	ICD-10 codes in Swedish Patient Register (Appendix I)
• Periostitis	Primary outcome	ICD-10 codes in Swedish Patient Register (Appendix I)

Table 1. Study variables, their roles and operational definitions

Variable	Role	Operational definition
• Phototoxicity	Primary outcome	ICD-10 codes in Swedish Patient Register (Appendix I)
Other safety events • Gastrointestinal disorders • Nausea • Vomiting • Abdominal pain • Abdominal discomfort • Diarrhea • Dyspepsia • Flatulence • Non-infective gastroenteritis	Other outcome	ICD-10 codes in Swedish Patient Register
Potential confounders and effect modifiers		
Demographics For example • Age • Sex • Geographical region • Country of birth • Occupation	Baseline characteristic, Sub-group identifier	Patient Register and Statistics Sweden
Concomitant medications/treatment For example: • Immunosuppressants • Other concomitant medications Radiotherapy ultraviolet light A and B	Sub-group identifier	ATC code and drug name in Swedish Prescribed Drug Register Procedure codes in the Patient Register
Underlying conditions For example • Solid organ transplant • Bone marrow transplant • HIV infection • Cystic fibrosis • Haematological conditions	Sub-group identifier	ICD-10 codes in the Patient register, and /or Prescribed Drug Register

Table 1. Study variables, their roles and operational definitions

Variable	Role	Operational definition
Co-morbid conditions • Diabetes • Hypertension • Osteoarthritis • Cytomegalovirus (CMV) • liver disease (infectious and non-infectious) • Psoriasis • Atopic dermatitis • Autoimmune disease (i.e. Rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE)) • Sepsis • Veno-occlusive liver disease (VOLD) • Graft-versus-host disease (GvHD) Other • Hemodialysis • History of SCC • History of other skin malignancy		
Death	Other outcome	Causes of Death Register

8.4.1. Review of medical records to assess and describe the accuracy of ICD-10 codes used to identify patients with hepatic disorders

Patients with ICD-10 diagnostic and procedural codes pertinent to hepatic disorders and with recorded use of any systemic antimycotic treatment (Appendix I) will be identified from the Swedish Patient Register and the Prescribed Drug Register. To assess and describe the accuracy of the ICD-10 codes to identify patients with hepatic disorders, medical records of a subset of these patients (up to 100 medical records, randomly selected if feasible) will be reviewed by medically qualified research personnel provided that approval is granted by ethics committees and local and/or national governing bodies.

Trained data abstractors will review medical records to collect information pertinent to hepatic disorders. In addition to the diagnosis documented by the treating physicians or nurse (if available), the data abstractor will collect information on the date of diagnosis, clinical and diagnostic evidence based on progress notes, and relevant laboratory/radiology results from medical records as available. The information collected from medical records will be reviewed independently by two qualified medical professionals to confirm the diagnosis of hepatic disorder. In case of disagreement, a third qualified professional will be brought in to serve as a tie breaker.

Given that only biopsy confirmed cases of SCC of the skin are recorded in the Swedish Cancer Register, assessment of ICD-10 codes for the cases of SCC of the skin is not needed. The data in Swedish Cancer Register is generally considered to be of high quality.[8, 9] Assessment of ICD-10 codes for periostitis and visual disorders is not planned.

8.4.2. Data collection process

All data in this active safety surveillance study will be obtained from population based registers/data sources that routinely collect individual-level data in Sweden. For a sub-set of patients, information on duration of voriconazole treatment will include data from medical charts to cover treatment started during hospitalisation. In addition, medical charts will be reviewed in another sub-set of patients to validate diagnoses of hepatic disorders among patients treated with systemic antimycotics.

Healthcare data will be obtained from the National Registers at the National Board of Health and Welfare and Statistics Sweden. Socio-demographic characteristics, such as place of living by region (North, West or South of Sweden), country of birth, date of emigration and death will be obtained from the population registers held by Statistics Sweden. Data from the various registers can be merged through a unique identifier, the personal identification number (PIN) assigned to each resident at birth or immigration. Data on voriconazole in the out-patient setting will be obtained from the Swedish Prescribed Drug Register. A patient's co-morbid/underlying conditions (e.g., bone marrow transplant, hematologic malignancy, cystic fibrosis, lung transplant) will be obtained from the Swedish Patient Register (NPR). Data on malignancy will be obtained from the Cancer Register (using morphology codes). These registers are periodically updated with varying lag time/availability to researchers. The current lag time to obtain updated data is approximately 16 months for the Cancer Register and for the Cause of Death Register, 9 months for the Patient Register, and 2 months for the Swedish Prescribed Drug Register.

Given that the Swedish Prescribed Drug Register does not contain data on medications dispensed during hospitalisation, manual review of patients' charts will be performed to estimate the "mean duration of voriconazole use" in a subset of patients' dispensed voriconazole during hospitalisation. Medical charts of a subset of patients will be identified through key information (PIN, hospital, clinic, date of admittance and date of discharge) obtained from the National Board of Health and Welfare. Further, information on concentrations of voriconazole as noted in medical records or in laboratory databases will be obtained when available.

Considering the challenges to access individual medical charts and time to review/manually abstract the required data, the review of medical charts of <u>all</u> patients dispensed voriconazole during hospitalisation is not feasible. Therefore, approximately 150 eligible patient's charts (adults and paediatrics) will be reviewed to estimate the average duration of voriconazole use in hospital. Of patients with a prescription of voriconazole in the out-patient setting (identified from the Swedish Prescribed Drug Register) between 2006 and 2017, the subset of patients who presumably started their voriconazole treatment during hospitalisation would be the sampling frame. Treatment administered during hospitalisation is not recorded in the Prescribed Drug Register and in-hospital drug use can only be obtained through reviewing

medical charts. Overall, the mean duration of voriconazole during hospitalisation is estimated to be approximately 21 days (Pfizer data on file). Assuming a large standard deviation (SD) of 10 days, the review of 150 medical charts will yield a fairly precise estimate of the true population mean of the duration of voriconazole use during hospitalisation (i.e., within 2 days of the sample estimate).

8.5. Study size

8.5.1. Historical counts of patients treated with voriconazole in the Swedish Prescribed Drug Register

Table 2 presents the counts of patients receiving voriconazole by age group in the Swedish Prescribed Drug Register (2006 through 2012).

Table 2 Counts of patients exposed to voriconazole in the Swedish Prescribed Drug Register (2006 through 2012)

Age group	2006	2007	2008	2009	2010	2011	2012	Total
Paediatric	38	40	27	43	46	40	26	**260**
Adult	242	250	307	280	281	272	244	**1,876**
								2,136

Note: Counts do not exclude duplicate patients i.e, some patients receiving voriconazole for more than one year may have been counted in multiple years.

Preliminary counts of patients with at least one filled prescription of voriconazole in the Swedish Prescribed Drug Register showed 2,136 patients during the seven-year period 2006 through 2012; yielding an annual average of 305 patients (including 37 paediatric patients). With an average of 305 patients per year, approximately 3,660 (305x12) patients treated with voriconazole are expected in the Swedish Prescribed Drug Register from 1 January, 2006 through 31 December, 2017 (section 8.2.1 Inclusion criteria). It is to be noted that patients with long-term voriconazole use will be a subset of all patients exposed to voriconazole in the database.

8.5.2. Precision of estimate calculations

The study objective is to estimate the incidence of selected safety events among patients receiving voriconazole particularly with long-term use. The study is not intended to test a formal hypothesis such as to evaluate the association between voriconazole use and the selected safety events. Therefore, calculations of precision of incidence estimates are most appropriate.

The calculations of precision of estimates are based on the following assumptions:

- The confidence intervals (CI) around the estimate are 2-sided.
- The rate of selected safety events observed in patients exposed to voriconazole use is specified below:

Hepatic disorders[a] = 28.6%: The definition of hepatic disorders/toxicity varies vastly in the published literature. For the purpose of the precision of estimate calculations, the MAH used the rate of hepatic disorders estimated from the voriconazole clinical programme that included prophylaxis and therapeutic clinical trials in paediatric and adult patients (Pfizer data on file). It is to be noted that the patients with a diagnosis of hepatic disorders included both clinical cases of liver conditions and liver function test (LFT) abnormality. Therefore, the rate of hepatic disorders in this study, which is based on clinical liver conditions only, is likely to be lower than 28.6%. Further, the rate of hepatic disorders among patients with long-term voriconazole use is not available. Therefore, the rate of hepatic disorders from pooled data was used for the precision of estimate calculations.

Phototoxicity= 0.8%: In pooled analysis of therapeutic and prophylaxis clinical trials that included both paediatric and adult patients (n=2,161), approximately 0.8 % of adult patients exposed to voriconazole experienced phototoxicity. No case of phototoxicity was observed in paediatric patients. The rate of phototoxicity among patients with long-term voriconazole use is not available. Therefore, the rate of phototoxicity from pooled data from clinical trials was used for the precision of estimate calculations.

SCC of the skin = 3.1%: The incidence of SCC of the skin in overall voriconazole-treated patients is not available in the literature. However, SCC of the skin rate among lung transplant recipients exposed to voriconazole in retrospective observational studies has been reported to range from 3.1% (median follow up time of 36 months) to 39.5% (median follow up time of 34 months).[4,5] It is to be noted that SOT recipients including patients with lung transplant are at high risk of developing SCC of the skin.[10,11] Therefore, it is likely that the rate of SCC of the skin in overall voriconazole-treated patients in the active surveillance program will be lower than the lung transplant recipients. For the purpose of the precision of estimate calculations, the MAH used the conservative estimate of 3.1%.

Visual disorders[b]= 31.0%: In pooled analysis of therapeutic and prophylaxis clinical trials that included both paediatric and adult patients (n=2,161), the rate of visual

[a] RMP search criteria used to define hepatic toxicity in the RMP: Drug related hepatic disorders, comprehensive search (SMQ).

[b] RMP search criteria used to define visual disorders in the RMP: **System Organ Class:** Eye disorders **High level Group Terms:** Eye disorders congenital, Eye therapeutic procedures, Neurological disorders of the eye, or Ocular neoplasms. **High Level Terms:** Eye injuries NEC, Eye movement disorders, Ophthalmic function diagnostic procedures, or Ophthalmic histopathology and imaging procedures or Optic nerve disorders NEC. **Preferred Terms:** Acquired pigmented retinopathy, Floppy iris syndrome, Hepato-lenticular degeneration, Horner's syndrome, IIIrd nerve injury, IVth nerve injury, Intraocular lens dislocation, Intraocular lens opacity, Marfan's syndrome, Millard-Gubler syndrome, Miller Fisher syndrome, Nystagmus, Ophthalmological examination abnormal, Optic nerve injury, Optic pathway injury, Retinal arteriovenous malformation.

disorders was 31% (Pfizer data on file). The rate of visual disorders among patients with long-term voriconazole use is not available. Therefore, the rate of visual disorders from pooled data from clinical trials was used for the precision of estimate calculations.

Periostitis = 1.0%: The incidence of periostitis in patients treated with voriconazole (or the incidence in the general population) is not available. For the purpose of the precision of estimate calculations, the MAH used periostitis incidence of 1% among patients receiving voriconazole.

Based on the assumptions outlined above, Table 3 presents the precision of the estimate (width of 95% CI) for a range of sample sizes. For example, a sample size of 500 patients treated with voriconazole for long-term (≥ 180 days), the estimated width of 95% confidence interval (CI) would be (24.6%-32.6%) for hepatic disorders, (0%-1.6%) for phototoxicity, (1.6%-4.6%) for SCC of the skin, (27.0%-35.1%) for visual disorders and (0.1%-1.9%) for periostitis.

Table 3 Precision of estimate (width of 95% CI) for each safety event for a range of sample sizes

Sample Size [Number of Patients Treated With Voriconazole]	Event	Rate of Event in Patients Exposed to Voriconazole (%)	Estimated 95% CI Around the Point Estimate for Event
300	Hepatic disorders	28.6	23.5-33.7
	Phototoxicity	0.8	0-1.8
	SCC of the skin	3.1	1.1-5.1
	Visual disorders	31.0	25.8-36.2
	Periostitis	1.0	0-2.1
500	Hepatic disorders	28.6	24.6-32.6
	Phototoxicity	0.8	0-1.6
	SCC of the skin	3.1	1.6-4.6
	Visual disorders	31.0	27.0-35.1
	Periostitis	1.0	0.1-1.9
800	Hepatic disorders	28.6	25.5-31.7
	Phototoxicity	0.8	0.2-1.4
	SCC of the skin	3.1	1.9-4.3
	Visual disorders	31.0	27.8-34.2
	Periostitis	1.0	0.3-1.7
1000	Hepatic disorders	28.6	25.8-31.4
	Phototoxicity	0.8	0.3-1.4
	SCC of the skin	3.1	2.0-4.2
	Visual disorders	31.0	28.1-33.9

Table 3 Precision of estimate (width of 95% CI) for each safety event for a range of sample sizes

Sample Size [Number of Patients Treated With Voriconazole]	Event	Rate of Event in Patients Exposed to Voriconazole (%)	Estimated 95% CI Around the Point Estimate for Event
	Periostitis	1.0	0.4-1.6
1500	Hepatic disorders	28.6	26.3-30.9
	Phototoxicity	0.8	0.4-1.3
	SCC of the skin	3.1	2.2-4.0
	Visual disorders	31.0	28.7-33.3
	Periostitis	1.0	0.5-1.5

nQuery Advisor® was used for calculations.
CI = confidence interval; SCC = squamous cell carcinoma.
Note: These rates of selected safety events of hepatic disorder, visual disorder and phototoxicity among patients exposed to voriconazole were estimated from the pooled data from clinical trials. The rates with long-term voriconazole use (≥ 180 days) were not available therefore, the rates with any voriconazole exposure duration were used for the precision of estimate calculations.

As noted in section 8.5.1 'Historical counts of patients treated with voriconazole in the Swedish Prescribed Drug Register', with an average of 305 patients per year, approximately 3,660 (305x12) patients exposed to voriconazole are expected in the Swedish Prescribed Drug Register from 2006 through 2017. It is to be noted that patients with long-term (≥ 180 days) voriconazole use will be a subset of all patients exposed to voriconazole in the database – this subset of patients will provide information to address the focus on long-term usage in the study objective.

8.6. Data management

Data will be requested from the National Board of Health and Welfare, where all data is linked across the registers by the unique identifier. The study data will be stored at secure servers, and maintained by trained data managers ensuring compliance with national regulations. Frequency tables of variables of interest will be generated to check for plausibility and consistency. Logic checks comparing similar data points will be conducted on a regular basis. SAS® version 9.4 (SAS Institute, Cary, NC, USA) will be used for statistical analyses.

8.7. Data analysis

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

Briefly, descriptive analyses (no formal hypothesis-testing) will be conducted to address the objective. Counts and percentages to describe categorical variables, and mean and standard deviations (or median with IQR, where appropriate) for continuous variables will be calculated.

Figures and box plots will be used to supplement the descriptive statistics when appropriate. Given that the Swedish National Registries collect comprehensive data on each patient, the amount of missing data on important study variables such as voriconazole exposure and safety events is expected to be minimal. Therefore, imputation of missing data is not intended. All variables will include a category for missing values, where applicable. However, the extent of the missing data will be evaluated at the time of the first interim analysis. In case of substantial missing data, appropriate statistical techniques for imputing missing data will be considered and documented in the SAP.

Incidence estimates of safety events in patients treated with voriconazole

Safety events (i.e., hepatic disorders, phototoxicity, visual disorders, SCC of the skin, periostitis) will be summarized using a piecewise exponential model that permits separate estimation of the hazard within the following voriconazole treatment intervals 3 ≤ months, >3 to ≤6 months, >6 to ≤9 months, >9 to ≤12 months and > 12 months. The piecewise model will be used to calculate incidence rates (e.g., per person- days, person-months or person-years of follow-up), as well as cumulative incidence rates. The model will also be used to construct 95% CIs for the incidence rates.

Further, analysis of cumulative dose will be analysed over time by using cumulative average dose at each time point during the study as a time-dependent covariate. A categorical version of cumulative average dose using tertiles or quartiles will also be explored.

Additional summary statistics will include:

- Number of each new selected safety event reported during the follow up time
- Cumulative person-time at risk by safety event
- Total number of patients treated with voriconazole

Patients may provide more than one exposure period to voriconazole; if the percentage of patients with multiple exposures is greater than 5%, a robust variance estimate for the incidence rate will be used to account for the clustering of exposures within patients.

Sub-group analyses

Sub-group analyses will be performed to explore the incidence rates across various demographic and baseline characteristics. The piecewise exponential model will be used to calculate incidence rates separately within the categories of subgroups, including:

- Age group (i.e., paediatrics aged 2 months to 18 years and adults >18 years)
- Co-morbid/underlying conditions (e.g., SOT recipients)
- Use of voriconazole (e.g., for approved indications, non-approved/off label use)
- Existing/history of outcome prior to the index date (i.e., voriconazole initiation): E.g.,:

- SCC of the skin estimates will be presented by "history of SCC", i.e., incidence of SCC of the skin among patients with a history of SCC *and* patients without a history of SCC

- Phototoxicity estimates will be presented by "history of phototoxicity ", i.e., incidence of phototoxicity among patients with a history of phototoxicity *and* patients without a history of phototoxicity

- Visual disorders estimates will be presented by "history of visual disorders" i.e., incidence among patients with a history of visual disorders 3 months prior to the index date *and* patients without a history of visual disorders[c]

- Periostitis estimates will be presented by "history of periostitis" i.e., incidence among patients with a history of periostitis 3 months prior to the index date *and* patients without a history of periostitis.

Subgroups analyses will only be performed when there exist enough data within the subgroup to support a meaningful statistical summary.

8.8. Quality control

The investigators will follow 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, and description of available data.

8.9. Limitations of the research methods

Following are the study limitations:

- First, the dependency on drug dispensing from Swedish Prescribed Drug Register as a measure for 'actual use' of the drug. It is possible that a patient dispensed voriconazole or other select azoles might not have actually taken it. However, considering the patient population it is reasonable to assume that all patients who receive a prescription would actually take it until they experience an adverse reaction that is not tolerable or determined by the physician to warrant discontinuation.

- Second, as described earlier, it is not feasible to review charts of all study eligible patients with hospitalisation to obtain data on voriconazole dispensing during hospitalisation. Therefore, the review of approximately 150 eligible patients charts selected by age groups (adults, paediatrics) would be performed to estimate the duration of voriconazole use during hospitalisation. It is expected that selection of a subset of patients will provide a representative estimate of average duration of voriconazole use during hospitalisation.

Further, patients developing safety events who received voriconazole only during hospitalisation will not be included in this study because such patients cannot be identified through the Swedish Prescribed Drug Register. Given that the focus of this study is to monitor safety events with long term voriconazole treatment, it is expected that the data obtained will adequately address the study objectives in the absence of data from patients treated with voriconazole only in the in-patient setting.

8.10. Other aspects

Not applicable

9. PROTECTION OF HUMAN SUBJECTS

Information concerning individuals in a register study is protected by Swedish laws. Before the research begins, an ethical approval is needed (**The Ethical Review Act**).

Karolinska Institutet has, in accordance with decisions by the Regional Ethical Review Board in Stockholm, been granted permission to conduct research studies. In order to carry out research studies, Karolinska Institutet will request access to information from the national health data registers held by the National Board of Health and Welfare. This information is subject to what is known as statistical confidentiality in accordance with Chapter 24, Section 8 of the Public Access to Information and Secrecy Act (OSL), which means that confidentiality applies to any such specific activities of an authority that relate to the production of statistics for information relating to an individual's personal or financial circumstances and that can be attributed to the individual.

After a public interest test, the National Board of Health and Welfare will disclose the information including the socio-demographic information provided by Statistics Sweden requested to Karolinska Institutet, to be used in research studies. The information will be disclosed to Karolinska Institutet in an anonymised state, with a code key retained by the National Board of Health and Welfare. The information disclosed may only be used within the present research study. In accordance with Section 6 of the Official Statistics Act (2001:99), it is not permitted to take action for the purpose of attempting to ascertain the identity of individuals. The publication of statistical results based on the released material may only take place in such a way that the identities of individuals are not divulged.

Confidentiality based on Chapter 24, Section 8 OSL is, under the main rule, absolute. This means that the information cannot be disclosed. However, exemptions from this absolute confidentiality are granted since, in order to meet the needs of research data, an opening has been introduced in the Section in question for disclosing information for research purposes, provided that it has been established that the information can be disclosed without the individual or someone close to him/her suffering prejudice or harm. It is on the basis of this exemption that the National Board of Health and Welfare, after a prejudice test, has decided to disclose the requested information to Karolinska Institutet.

In cases where the information is disclosed by an authority responsible for official statistics, in this case by the National Board of Health and Welfare, for research purposes, confidentiality is transferred in accordance with Chapter 11, Section 3 OSL to the recipient

authority. The information disclosed is thereby subject to confidentiality in accordance with Chapter 24, Section 8 OSL at the recipient authority, i.e., at Karolinska Institutet.

9.1. Patient Information and Consent

Not applicable

9.2. Patient withdrawal

Not Applicable

9.3. Institutional review board (IRB)/Independent ethics committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (eg recruitment advertisements), if applicable, from the Institutional Review Board/Independent Ethics Committees (IRB/IEC).

Protocol review and approval by IEC, 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.

9.4. Ethical conduct of the study

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

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study uses existing health care databases, 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.

In addition, a sub-study requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. If allowed by local legislation,

the reviewer is to report AE with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

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

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

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

For these safety events with an explicit attribution to or associated with use of, respectively, a Pfizer product, the data captured in the medical record will constitute all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

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

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This study will be registered in the EU post-authorisation studies (PAS) after the protocol endorsement by the CHMP.

Three interim reports during the conduct of the study and the final report after the study completion will be developed. It should be noted that there is a lag of about 1.5 years for data updates in the select Swedish registries that will be utilized for this study. For example: on 31 December, 2015 which is the data cut-off date for the first interim report, the registries are expected to contain data from 1 Jan, 2006 through 30 June, 2013. Further, the availability of study data is dependent on receiving permission by the National Board of Health and Welfare and Statistics Sweden and is beyond the control of the study investigators. Therefore the report submission timeline may be affected by any delay in the availability of study data to the investigators by the relevant authorities.

Table 4 below provides detail about the data cut-off date, expected inclusion of data from the Swedish National Registries and estimated timeline for submission of the interim and final reports to the EMA.

Table 4 Data cut-off date, exepected inclusion of data from the registries and estimated timeline for submission of the interim and final reports to the EMA

Report*	Data cut- off date (Data abstraction will begin after this date)	Expected data availability in Swedish registries (Accounting for approx. 1.5 years of data lag-time)	Expected report submission to the EMA
1st Interim Report	31 Dec, 2015	1 Jan, 2006 through 30 June, 2013	4Q 2016
2nd Interim Report	31 Dec, 2017	1 Jan, 2006 through 30 June, 2015	4Q 2018
3rd Interim Report	31 Dec, 2019	1 Jan, 2006 through 30 June, 2017	4Q 2020
Final CSR	30 June, 2021	1 Jan, 2006 through 31 Dec, 2019	2Q 2022

*The first interim report will include analysis of the available data on all 4 safety events from 2006 through the data cut-off 31 December, 2015. The second, third interim reports and the final report will include available data from 2006 through the specific data cut-offs as listed in the table.

The final study results will be disclosed through the EU PAS register as well.

COMMUNICATION OF ISSUES

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

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13. .LIST OF FIGURES

14. LIST OF TABLES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

ICD-10, procedure and morphology codes for the study endpoints

Note: The list of ICD-10 codes includes all major codes for each of the safety events however the list might not be exhaustive. Additional relevant codes for the study endpoints (if identified) during the data collection will also be included. List of all codes used to define each of the safety events will be documented in the Statistical Analysis Plan (SAP) and also included in the interim and final study reports.

Description of term	**ICD-10, Procedure and morphology codes**
Hepatic disorders	
Hepatic failure	K72, K72.00, K72.10, K72.11, K72.01, K72.90, K72.91
Hepatic encephalopathy	G92
Hepatitis / toxic liver disease	K71.0, K71.1, K71.2, K,71.3, K71.4, K71, 4, K71,5, K71.6, K71.7, K71.8, K71.9
Hepatorenal syndrome	K76.7
Jaundice	R17
Toxic liver Necrosis (hepatic failure)	K71.1
Procedures: Hepatic disorders	**Procedure codes**
Liver dialysis	DJ020
Liver transplant	Z94.4 Procedure codes: JJC 00, JJC 20, JJC 30, JJC 40, JJC 50, JJC 60, JJC 96, DJ005, DJ006
Visual disorders	**ICD-10 codes**
Diplopia	H53.2
Photopsia (or visual	H53.1

disturbance)	H53.1, H53.3
Blurred vision (or visual disturbances)	H53.8, H53.9, H53.1
Visual field defect	H53.4 (without diagnoses of brain metastases)
Vitreous floaters	H43.3, H43.8, H43.9
Photophobia (light sensitivity)	H53.7, L56.0, L56.1, L56.8 (except L56.8A, L56.9, E80.2
Maculopathy	H35.3AND NOT (Chloroquine OR Tamoxifen)
Retinal haemorrhage	H35.6 and not (ocular OR retinal metastases)
Retinal edema	H35.8 and not (ocular OR retinal metastases)
Miscellaneous	H35.9
Periostitis	H05.0, M86.6, M86.9, M87.1, M90. 1 K10.2, M46.2 (note: there is no clear distinction of periostitis, with or without osteomyelitis)
SCC of the skin ICD-0/3 code C44	**Morphology codes**
Papillary carcinoma, NOS	M 8050/3
Verrucous carcinoma, NOS	M 8051/3
Papillary squamous cell carcinoma	M 8052/3
Squamous cell carcinoma, NOS	M 8070/3
Squamous cell carcinoma, keratinizing, NOS	M 8071/3
Squamous cell carcinoma, large cell, nonkeratinizing, NOS	M 8072/3
Squamous cell carcinoma, small cell, nonkeratinizing	M 8073/3
Squamous cell carcinoma, spindle cell	M 8074/3
Squamous cell carcinoma, adenoid	M 8075/3
Squamous cell carcinoma, microinvasive	M 8076/3
Squamous cell carcinoma, with horn	M 8078/3

formation	
Basaloid squamous cell carcinoma	M 8083/3
Squamous cell carcinoma 'clear cell-type'	M 8084/3
Phototoxicity	L56.8, E80.0, L59.8, Q82.1, E80.1, H53.1, E72.0, Q87.1 L56.0, L56.2, L27, L57.8

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Study reference number:
A1501103

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[4]	☒	☐	☐	13
1.1.2 End of data collection[5]	☒	☐	☐	13
1.1.3 Study progress report(s)	☐	☐	☒	-
1.1.4 Interim progress report(s)	☒	☐	☐	13
1.1.5 Registration in the EU PAS register	☒	☐	☐	13
1.1.6 Final report of study results.	☒	☐	☐	13

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	16,17
2.1.2 The objective(s) of the study?	☒	☐	☐	17
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	17
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	-
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	-

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	17
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	20, 21
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000	☒	☐	☐	27

[4] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[5] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)				

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	17, 18
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	18
4.2.2 Age and sex?	☒	☐	☐	18
4.2.3 Country of origin?	☒	☐	☐	18
4.2.4 Disease/indication?	☒	☐	☐	18
4.2.5 Co-morbidity?	☒	☐	☐	18
4.2.6 Seasonality?	☐	☐	☒	-
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	18

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	20, 21
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	19, 20, 21
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	20
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	-
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	20

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	20, 21
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	20, 21, 22

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	21, 27, 28
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	-

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	19, 20, 21
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	19, 20, 21
8.1.3 Covariates?	☒	☐	☐	19, 20, 21
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	19, 18
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	19, 18
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	19, 18
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	19, 20, 21
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	9, 20, 21
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical				

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	19, 20, 21
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	24, 25, 26

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	-
10.2 Is the choice of statistical techniques described?	☒	☐	☐	27
10.3 Are descriptive analyses included?	☒	☐	☐	27
10.4 Are stratified analyses included?	☒	☐	☐	27
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	27
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	-

Comments:

The protocol provides the outline of the data analysis. Detailed data analysis to address the study objective will be documented in a separate statistical analysis plan (SAP).

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☒	☐	-
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	27
11.3 Are methods of quality assurance described?	☒	☐	☐	28
11.4 Does the protocol describe possible quality	☒	☐	☐	28

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
issues related to the data source(s)?				
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	-

Comments:

The management of missing data will be described in the statistical analysis plan

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	29
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	-
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	23, 24, 25
12.3 Does the protocol address other limitations?	☒	☐	☐	28

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	29, 30
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	-
13.3 Have data protection requirements been described?	☒	☐	☐	27, 29

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	12

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	31
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	31, 32

Comments:

Name of the main author of the protocol: Muhammad Younus

_____

Date: 25/11/2014

Signature: _____  _____