AN ACTIVE SAFETY SURVEILLANCE PROGRAM TO MONITOR SELECTED EVENTS IN PATIENTS WITH LONG-TERM VORICONAZOLE USE

PASS PROTOCOL NUMBER: A1501103

Final Study Report

29 April 2022

This report was prepared by the Centre for Pharmacoepidemiology (CPE), Department of Medicine, Solna, Karolinska Institutet for Pfizer, Inc.

NON-INTERVENTIONAL (NI) STUDY REPORT

PASS information

Title	An Active Safety Surveillance Program to Monitor Selected Events in Patients With Long-Term Voriconazole Use.
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Research question and objectives	To estimate the incidence rate of hepatic disorders, phototoxicity, squamous cell carcinoma (SCC) of the skin, visual disorders and periostitis among adult and paediatric patients receiving voriconazole, particularly with long-term use.
Country of study	Sweden
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1. **ABSTRACT (STAND-ALONE DOCUMENT)**

2. **LIST OF ABBREVIATIONS**

Abbreviation	**Definition**
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CDR	Cause of Death Register
CHMP	Committee for Medical Products for Human Use
CI	Confidence Interval
DDD	Defined Daily Dose
EMA	European Medicines Agency
EMR	Electronic Medical Record
EU	European Union
FAS	Full Analysis Set
GPP	Good Pharmacoepidemiology Practices
GvHD	Graft-versus-host disease
GVP	Good Pharmacovigilance Practice
HIV	Human Immunodeficiency Virus
HSCT	Haematopoietic Stem Cell Transplantation
IA	Invasive Aspergillosis
ICD	International Classification of Diseases
IDSA	Infectious Diseases Society of America
IFI	Invasive Fungal Infection
IQR	Inter Quartile Range
IR	Incidence Rate
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology

MAH	Marketing Authorization Holder
NCSP	Nordic Classification of Surgical and Medical Procedures
NIS	Non-Interventional Study
NOMESCO	Nordic Medico-Statistical Committee
NPR	National Patient Register
OTC	Over The Counter
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PIN	Personal Identity Number
PPV	Positive Predictive Value
PSUR	Periodic Safety Update Report
PDR	Swedish Prescribed Drug Register
RA	Rheumatoid Arthritis
RMP	Risk Management Plan
SCB	Statistiska Centralbyrån (Statistics Sweden)
SCC	Squamous Cell Carcinoma
SCR	Swedish Cancer Register
SD	Standard Deviation
SLE	Systemic Lupus Erythematosus
SmPC	Summary of Product Characteristics
SOT	Solid Organ Transplant
VOLD	Veno-occlusive Liver Disease

3. INVESTIGATORS

Name, degree(s)	Title	Affiliation
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Muhammad Younus, MBBS, PhD	Senior Director, Safety Surveillance Research, Worldwide Medical and Safety	Pfizer Inc.

4. OTHER RESPONSIBLE PARTIES

Not Applicable

5. **MILESTONES**

Study milestones comprise three interim reports during the conduct of the study and the present final report.

Milestone	Planned date	Actual date
Completion of study feasibility assessment	-	30 April 2014 (Report submitted to the EMA)
Endorsement of the study protocol by the CHMP	-	24 September 2015
IRB/Ethic Committee's approval of the protocol	-	23 March 2016 (supplement application was approved on 15 July 2016)
Start of data collection/abstraction from Swedish National Registers	2Q 2016	12 April 2016
End of data collection/ dataset finalization for analysis	3Q 2021	15 December 2021
Registration in the EU PAS register	Before the start of data collection	EUPAS12624 (Date of Registration: 03 March 2016)
Interim report I	30 Sep, 2017	04 May 2018* (submitted with PSUR 2018)
Interim report II	31 Dec, 2018	19 December 2018
Interim report III	4Q 2020	16 November 2020
Final Report of Study Results	2Q 2022	

* The EMA had advised to submit the first interim analysis report with the PSUR 2018.

6. RATIONALE AND BACKGROUND

Voriconazole (Vfend®) is a broad spectrum triazole antifungal agent, which has been approved in the European Union (EU) since 2002 for the treatment of invasive aspergillosis (IA), candidaemia in non-neutropenic patients, fluconazole-resistant serious invasive Candida infections (including *C. krusei*), and serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp. 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, voriconazole was approved on 24 June 2014 in the EU for prophylaxis of invasive fungal infections (IFI) in high-risk haematopoietic stem cell transplantation (HSCT) recipients. In addition to the approved indications, voriconazole is also being used as prophylaxis to prevent IFI in patients with immunocompromised status such as solid organ transplant (SOT) recipients [1, 2].

In the EU, voriconazole is indicated in adult and paediatric patients for the above indications. Clinical data demonstrated that the safety and efficacy in paediatric patients were generally similar to those observed in adult patients in therapeutic studies. However, a higher frequency of hepatic related adverse events (AEs), mainly associated with increased liver enzymes, was observed in the paediatric population compared to adults [3]. 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 [4-8]. These potential risks are described in more detail below:

- **Hepatic disorders:** Hepatic disorder is an important identified risk in the voriconazole Risk Management Plan (RMP). In clinical trials, there have been cases of serious hepatic adverse reactions during treatment with voriconazole (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities)[4-8]. 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 [7, 8].

- **Visual disorders:** Visual disorder is an important identified risk in the voriconazole RMP. In clinical trials, visual impairments (including blurred vision, photophobia, chloropsia, chromatopsia, colour blindness, cyanopsia, eye disorder, halo vision, night blindness, oscillopsia, photopsia, scintillating scotoma, visual acuity reduced, visual brightness, visual field defect, vitreous floaters, and xanthopsia) with voriconazole were very common. These visual impairments were generally mild, transient and fully reversible, with the majority spontaneously resolving within 60 minutes and no clinically significant long-term visual effects observed. There was evidence of attenuation with repeated doses of voriconazole. The visual impairments rarely resulted in discontinuation and were not associated with long-term sequelae.

- **Phototoxicity and squamous cell carcinoma (SCC) of the skin:** Phototoxicity and SCC of the skin are important identified risks in the voriconazole RMP. Voriconazole has been associated with phototoxicity including reactions such as ephelides, lentigo, actinic keratosis, and pseudoporphyria. There have been reports of SCC of the skin in patients treated with voriconazole for long periods of time; the mechanism has not been established. Some patients who reported SCC of the skin had prior phototoxic reactions.

- **Periostitis:** Periostitis has been reported with prolonged (i.e., 6 months to several years) use of voriconazole, mainly in patients with lung transplant [6]. If a patient develops skeletal pain and radiologic findings compatible with periostitis, voriconazole discontinuation should be considered after multidisciplinary advice.

This non-interventional (NI) study was designed to monitor selected safety outcomes in patients receiving voriconazole in routine clinical care. This study is designated as a post-authorisation safety study (PASS) and is a commitment to the European Medicines Agency (EMA).

This final study report includes data from 1 January 2006 through 31 December 2019.

7. **RESEARCH QUESTION AND OBJECTIVES**

The overall objective of this study was to monitor selected safety outcomes in patients receiving voriconazole in the real-world setting, particularly with long-term use (i.e. ≥180 days).

Specifically, the primary study objective was to estimate the incidence rate of hepatic disorders, phototoxicity, SCC of the skin, visual disorders and periostitis among adult and paediatric patients receiving voriconazole by duration of use including patients with long-term use (≥180 days). The secondary objective was to estimate the incidence rate of gastrointestinal disorders and all-cause mortality.

8. **AMENDMENTS AND UPDATES**

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1	18 June 2015	Substantial	Section 5.0, Section 8.4, Section 8.7	A revised timeline for submission of the first and second interim reports to the EMA. A third interim report for submission to the EMA was added. Information on additional risk factors included confounding variables and effect modifiers were added. Revised to classify cumulative duration of voriconazole use and summarized incidence of safety outcomes within the following voriconazole treatment intervals: ≤3 months, >3 to ≤6 months, >6 to ≤9 months, >9 to ≤ 12 months, or >12 months. Added analysis of cumulative dose over time and description on how missing data will be handled.	Updated to address comments from the EMA (Assessment Report dated: 23 April 2015)

9. RESEARCH METHODS

9.1. Study design

This is an observational, population-based cohort study using data from the Swedish national registers to evaluate safety outcomes among patients receiving voriconazole (Vfend®) in the real-world setting, particularly with long term use (≥180 days).

9.2. Setting

Patients, both adult and paediatric, who filled at least one prescription of voriconazole constituted the study population. Data on eligible patients were collected between 1 January 2006 and 31 December 2017 from existing population-based national health registers in Sweden including the Swedish prescribed drug register (PDR), the Swedish cancer register (SCR), the National patient register (NPR), and the Causes of death register (CDR).

9.3. Subjects

Patients meeting the following inclusion criterion were eligible for inclusion in the study:

- At least one filled prescription of voriconazole identified from the PDR in the recruitment period, between 1 January 2006 and 31 December 2017.

All patients who met the study eligibility criterion in the PDR were included and followed until the end of 2019 as described in the following section. There were no exclusion criteria for this study other than those implied by the inclusion criteria above.

9.3.1. Index Date and Follow up

The index date was defined as the date of the first filled prescription of voriconazole during the recruitment period. Follow up and exposure was defined between the index date until the administrative end of follow up on the 31 December 2019, as recorded in the PDR.

Study eligible patients were followed from the index date to whichever of the following occurred first:

- Death
- Emigration
- 31 December 2019 at which time all surviving patients were censored (administrative censoring).

9.3.2. Full Analysis Set

The full analysis set (FAS) includes all study patients. The primary analyses were performed on the FAS.

9.4. Variables

9.4.1. Exposure of voriconazole

The exposure to voriconazole was ascertained using the information on filled prescriptions in the PDR. The PDR provides information on the date of the filling and on the amount dispensed (number of packs, size of packs and the number of defined daily dose [DDD] per pack). The DDD for voriconazole is 400 mg per day. As information on exact dose was not

available, it was assumed that all patients who were dispensed voriconazole were dosed 400mg per day.

For example, the last dose for a patient who filled a prescription with 1 pack of 56 tablets of 200 mg[1], was assumed to be taken on the morning of day 28 (where the first dose was taken in the evening of the day of the filling of the prescription = day 0). If the patient refilled the prescription before the last dose of the pack was taken, day 0 of the new pack was assumed to occur on day 28 of the previous pack, i.e. the new filling was shifted forward in time.

Thus, the number of available DDDs was estimated for each patient, on any given date, all under the assumption that the patient takes one DDD (400 mg) every day, during the interval the drug was prescribed. The cumulative dose at a particular point in time was the sum of DDDs assumed taken from the index date until that time.

In the statistical analyses, the time at risk was divided into the following intervals based on the cumulative dose:

Short term intervals:

- ≤ 1 month (index date to the day before DDD number 30)
- >1 to ≤3 months (DDD number 30 to the day before DDD number 90)
- >3 to ≤6 months (DDD number 90 to the day before DDD number 180)

Long term intervals:

- >6 to ≤9 months (DDD number 180 to the day before DDD number 271)
- >9 to ≤12 months (DDD number 271 to the day before DDD number 366)
- >12 months (DDD number 366 until end of follow-up)

At an outcome occurrence the following exposure measures were defined:

- T, Time since the index date, regardless of drug intake, defined as outcome date minus index date.
- D, Number of DDDs taken before the outcome
- A, Average number of DDDs per day since the index date, defined as A=D/T.

9.4.2. Safety Outcomes

There were five primary and two secondary safety outcomes in this study.

[1] An up to date list of available packages of voriconazole in Sweden is on the following webpage: http://www.fass.se/LIF/product?3&userType=2&nplId=20020319000021&docType=30&scrollTopPosition=245&docTypeDynTab=30

Primary safety outcomes:

- Hepatic disorder (acute onset)
- Phototoxicity (acute onset)
- Visual disorder (acute onset)
- Periostitis (delayed onset)
- SCC of the skin (delayed onset)

Secondary outcomes:

- All-cause mortality (death due to any cause) (both acute and delayed onset)
- Gastrointestinal disorder (acute onset)

International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Swedish Edition (ICD-10-SE) codes pertaining to the primary and secondary outcomes are listed in Table S1 Appendix 8.1. ICD-10-SE codes for both main and secondary diagnoses were used in the NPR (Table S1 Appendix 8.1). SCC of the skin was identified using International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) codes in the SCR (Table S1 Appendix 8.1). Death was identified using the CDR (Table S1 Appendix 8.1). All-cause mortality, rather than cause-specific mortality, was studied. Gastrointestinal disorders were identified using ICD-10-SE codes in the NPR (Table S1 Appendix 8.1).

Only safety outcomes occurring after the index date and prior to censoring (i.e. during the time at risk) were considered as outcomes. The time of an outcome was assumed to be the first date it was recorded in the registers. That may be the date of a visit or admission or discharge from a hospital.

As described in the statistical analysis plan (SAP) (Appendix 4), study outcomes were classified into two categories, based on the general timing of the safety outcomes as described below in Section 9.4.3 Time at risk. These categories were:

- **Acute onset outcomes**: Generally, these safety outcomes might be triggered during treatment or soon (e.g., within days/weeks) after treatment discontinuation. The following outcomes were classified as acute onset outcomes: hepatic disorders, phototoxicity, visual disorders and gastrointestinal disorders.
- **Delayed onset outcomes**: Generally, these safety outcomes take time to develop and report. The following outcomes were classified as delayed onset outcomes: periostitis and SCC of the skin.

All-cause mortality was classified as both an acute and a delayed onset outcome.

9.4.3. Time at Risk

The time at risk started on the index date, and ended at whichever of the following occurred first:

- Death
- 31 December 2019 at which time all surviving patients were censored (administrative censoring)
- Study outcomes, i.e., diagnosis of hepatic disorders, phototoxicity, visual disorders, SCC of the skin, or periostitis, gastrointestinal disorders recorded in the national health registers. The follow-up was continued for other outcomes if the patient developed one outcome.

Further, time at risk was calculated differently for acute onset outcomes and for delayed onset outcomes:

Acute onset outcomes: For the acute onset outcomes the time at risk was the interval between 1 and 90 days prior to the date of safety outcome diagnosis i.e., within 90 days prior to outcome diagnosis date (assuming the patient was taking the medication as prescribed). If there were more than 90 days between the last dose of a filled prescription and the first dose of the next filling, then the first 90 days were considered as time at risk and the following days until the next filled prescription were disregarded.

Only the first occurrence of each safety outcome after the index date was considered in the analysis. If the first safety outcome of any acute outcome occurred during the "not at risk" period, the patient was censored for that outcome.

Delayed onset outcomes*:* All days after the index date until the end of follow-up were counted as at-risk period.

9.4.4. Covariates

All additional covariates, including concomitant medications or treatment, underlying conditions, and comorbidities were obtained from national health registers in Sweden, including the NPR and PDR:

Demographics

- Age
- Sex
- Geographical region
- Country of birth
- Occupation

Concomitant medication/treatment

- Immunosuppressant and antineoplastic drugs

- Radiotherapy ultraviolet light A and B

Underlying conditions

- Solid organ transplant
- Bone marrow transplant
- HIV infection
- Cystic fibrosis
- Haematological conditions

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)
- Hemodialysis
- History of other skin malignancy

Occupations were classified according to the Swedish Classification of Occupations by Statistics Sweden. Considering the potential sunlight exposure, a specialist in dermatology divided different occupations into two categories based on whether the work is mainly done indoors or outdoors. This categorization was done to provide additional descriptive information for the patients included in the study.

Underlying conditions were defined as clinical conditions associated with the indications for voriconazole and which are thought to carry a higher risk of fungal infections or which have an indication of fungal infection prophylaxis. The category co-morbid conditions included

selected diseases or clinical conditions considered to be relevant research to the research question in a broad sense.

The details of each variable definition with their ICD-10-SE, ATC and classification of care measures (KVÅ) codes are available in Table S2, Appendix 8.1.

9.5. Data sources and measurement

Data were obtained from the Swedish national registers, including the PDR, the SCR, the NPR, and the CDR. The national healthcare registers cover all residents of Sweden (10.3 million in 2019 - https://www.statistikdatabasen.scb.se/pxweb/en/ssd/). Several validation studies for a variety of exposures and outcomes have been conducted using these data sources [9-11].

A unique personal identity number (PIN) is issued to all residents of Sweden upon birth or immigration and is used throughout life. The PIN is used to link patient-level data from the various registers [12]. All citizens, independent of socioeconomic status, have unrestricted access to health services including partial or complete reimbursement of purchased medicines due to the tax-supported public health service with universal coverage.

Below is a brief description of the major national healthcare databases/registers in Sweden used in this study.

The Swedish Prescribed Drug Register (PDR): The PDR is a nationwide database covering all filled prescriptions for the entire Swedish population [13]. 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, the amount in DDD, the prescribing date, and the date when the prescription was filled. The information is updated monthly. It does not include 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 PDR.

The Swedish National Patient Register (NPR) The NPR includes more than 99% of all somatic (including surgery) and psychiatric hospital discharges and visits [14]. It is mandatory for all physicians, private and publicly funded, to report 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 [15]. Since 1997, ICD-10-SE 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), has been used since 1997. Since 2001 all out-patients visits (non-hospitalisations) are recorded, prior to that, only the day surgeries were recorded. In this study, only data from 2001 and onwards were used.

The Swedish Cause of Death Register (CDR): The CDR 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-SE [16]. The NPR can be linked and matched with the CDR 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 SCR was founded in 1958 and contains information about clinical and histological diagnoses and date and place of living at diagnosis [17]. 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-3 version into ICD 7 in order to facilitate comparisons over time. The database is updated annually.

The Population Register (Statistics Sweden): The Population Register holds 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).

9.6. Bias

In this study, all participants that filled a prescription of voriconazole between 1 January 2006 and 31 December 2017 for ambulatory use were included, without any exclusion criteria. Two additional sub-studies 1) validation of hepatic disorder diagnosis and 2) hospital time exposure to voriconazole, were performed and are described in the following Section 9.6.1 Validation sub-studies.

For additional discussion on potential bias, please see 11.2. Limitations in the Discussion section.

9.6.1. Validation sub-studies

9.6.1.1. Validation of hepatic disorder diagnoses in users of systemic antimycotics

The aim was to estimate the positive predictive value of the clinical ICD-10-SE codes to identify patients with hepatic disorders using medical records revision as gold standard, among patients with any systemic antimycotic treatment. The results are presented in Section 10.5.2.1 Validation of hepatic disorder diagnosis. A complete study report about this validation process is presented in Appendix 8.2.

The cross-sectional validation study included patients that 1) had at least one filled prescription for any systemic antimycotic drug (ATC-code J02A) recorded in the PDR representing seven or more defined daily doses (DDD) and 2) were identified by having at least one of ICD-10-SE codes representing toxic liver disease (K71.0, K71.1, K71.2, K71.6, K71.8, K71.9), hepatic failure (K72.0, K72.9), and jaundice (R17) as a primary or secondary diagnosis in the NPR, after the first filled prescription of the antimycotic drug. Time between filling of a prescription of antimycotic drug (ATC code J02A) and the hepatic diagnosis was required to be less than 6 months.

With the aim to review at least 100 patients with inclusion criteria, stratified random sampling was used, aiming to draw 40% of the total sample from the patients with toxic liver disease, 40% from patients with hepatic failure, and 20% from the patients with jaundice and voriconazole treatment. This approach was used to get a reasonable representation of cases with the three diagnostic categories for the validation study to give informative results.

Trained data abstractors reviewed medical records to systematically collect relevant information about the three diagnoses of interest recorded from hospitalizations and outpatient visits, using structure forms.

9.6.1.2. Validation of in-hospital time exposure to systemic antimycotics

The aim was to estimate the average in-hospital duration of voriconazole use among approximately 150 adult and paediatric patients. The results are presented in Section 10.5.2.2 Estimating duration of voriconazole treatment use in hospital. A complete study report about this validation process is presented in Appendix 8.3.

The study included a simple random sample of all patients with a prescription of voriconazole in an out-patient setting who had a hospital discharge date within 7 days prior to or on the date of first filling of a voriconazole prescription, between 2006 and 2017.

A registered nurse and a medical doctor systematically reviewed all medical records to identify the date on which voriconazole was initiated during inpatient treatment.

In-hospital duration of voriconazole use were estimated according to the information retrieved. In situations, where there was insufficient information in the medical record to know the exact date for start of voriconazole use, four different methods were used to estimate the durations of uncertain episodes of voriconazole use (in days):

1. **Patients with uncertain duration omitted:** Duration = 0;
2. **Minimum duration imputed:** Duration = 1;
3. **Mean episode duration imputed:** Duration = End day – (Admission + End)/2 + 1;
4. **Maximum episode duration imputed:** Duration= End day – Admission day + 1.

9.7. Study Size

The protocol (Appendix 2 Section 8.5.2) and the SAP (Appendix 4 Section 4.7.2) presents details on the precision of estimate for a range of sample sizes. For example, with a sample size of 500 patients treated with voriconazole for long-term use (≥ 180 days), the estimated 95% of CI around the estimate 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.

9.8. Data transformation

Raw data obtained from the National Board of Health and Welfare (NBHW) were transformed and harmonized into a common data model (minimal informative datasets for demographics, drugs, diagnoses and demographic characteristics) developed at the Centre for Pharmacoepidemiology, Karolinska Institute. Analysis datasets were derived from these data.

9.9. Statistical methods

Descriptive analyses (no formal hypothesis-testing) were conducted to describe patient characteristics, concomitant medications/treatments, and underlying co-morbid conditions (Table S2 Appendix 8.1) in the study cohort.

The crude incidence rates per 1,000 person-years of hepatic disorders, phototoxicity, SCC of the skin, visual disorders, periostitis and gastrointestinal disorders, among adult and paediatric patients receiving voriconazole were calculated. Rates were calculated for all patients (i.e. incident and prevalent), for patients without any history of the outcome (i.e. incident patients

only), and for patients with a history of the outcome. Given the interest in duration of use, incidence rates for different cumulative dose intervals of voriconazole were also calculated.

The incidence rates are presented in a similar way for the acute and delayed onset outcomes. For the acute onset outcomes, the earlier cumulative dose intervals are most relevant, whereas the later cumulative dose intervals may be more important for the delayed onset outcomes. Less than 30 days of cumulative dose may not be considered clinically relevant for a delayed onset outcome. Death could occur both as an acute and as a delayed onset outcome, so it was analysed in both categories.

All data summaries and statistical analyses were performed using SAS® version 9.4.

9.9.1. Main summary measures

Continuous variables were summarized with the mean and standard deviation (SD) or median with inter quartile range (IQR) where appropriate. Categorical variables were summarized with counts and percentage.

The following exposure measures were summarised for each study outcome:

- The time since index date
- The number of DDDs taken before the safety outcome
- The average number of DDDs of voriconazole per day since the index date

9.9.2. Main statistical methods

The complete Statistical Analysis Plan (SAP) is presented in the Appendix 4.

9.9.2.1. Estimation of Incidence Rates

The incidence rates of safety outcomes were estimated among adult and paediatric patients receiving voriconazole using a piecewise exponential model.

The treatment intervals were based on cumulative dose, that is the cumulative sum of assumed taken doses, expressed in DDDs (Section 9.4.1). Within a cumulative dosing interval, the total time at risk was the sum of the individual time at risk for patients that belonged to the interval.

The incidence rate for a cumulative dosing interval was calculated as the number of patients with the safety outcome in the interval divided by the total person-time at risk for that interval.

9.9.2.2. Subgroup Analyses

Subgroup analyses were performed using the FAS dataset to estimate the incidence rates of the five primary outcomes across various demographic and baseline characteristics. The piecewise exponential model was used to calculate incidence rates separately within the categories of subgroups (Table S3 Appendix 8.1), including:

- Age group (i.e. 2 months to <18 years and adults ≥18 years)
- Use of voriconazole (e.g. for approved indications, or unclear indication)

- Co-morbid/underlying conditions (e.g. SOT recipients)

- History of outcome prior to the index date

The PDR does not provide systematic information on the indication of a treatment and therefore, it was not possible to directly assess on-label/off-label use. Instead, diagnostic codes in the NPR served as proxies for approved indications for voriconazole. This information was classified into two categories:

- **Voriconazole use for an approved indication of voriconazole recorded in the NPR.** Patients with a code for a potential diagnosis corresponding to an approved indication 7 days prior to the first filled prescription. The following were considered as approved indications (ICD-10-SE) aspergillosis (B44), candidal sepsis (B37.7), pulmonary candidiasis (B37.1), candidal meningitis (B37.5), candidal endocarditis (B37.6), candidiasis of other sites (B37.8), disseminated candida infection (B37.8C), candida esophagitis (B37.8D), opportunistic mycoses (B48.7) as well as the procedure codes DR021 Control before and after allogeneic bone marrow transplantation or peripheral stem cell transplantation and DR022 Control before and after high-dose treatment with autologous stem cell transplantation.

- **Voriconazole use with unclear indication.** This is the compliment set to the above subgroups. All patients that did not have a specific code for a potential diagnosis corresponding to an approved indication were included in this category, and those patients that had a code but with a recording date outside the 7 days prior to the first filled prescription. Thus, the category includes: indications that are before the 7 days window, non-approved/off label use, and unknown indications.

9.9.3. Missing values

Given that the Swedish national registers collect comprehensive data on each patient, the amount of missing data on important study variables such as voriconazole exposure and safety outcomes was minimal. Therefore, the missing data were not imputed. All variables included a category for missing values, where applicable.

9.9.4. Sensitivity analyses

Sensitivity analysis was not planned.

9.9.5. Amendments to the statistical analysis plan

Amendment to the March 31, 2017 version of SAP.

The definition of long-term use was changed in order to be consistent with the definition of "long term use", i.e. >=180 days, the old definition was > 180 days. Thus day 180 is moved from the interval >3 to <=6 months to >6 to <=9 months.

To address the feedback on the second interim analysis report from PRAC (EMA/CHMP/PRAC/406357/2019) dated 19 September 2019, the following additional analyses were included in this report:

1. Annual number of patients treated with voriconazole from 2006 through 2017 to examine variations in the number of patients by year.

2. Rates of safety outcomes were calculated in patients with a history of diagnoses for the respective safety outcome prior to the index date. Additionally, subgroup analyses were conducted, for patients with a history of primary outcomes prior to the index date, and for patients without a history of primary outcomes.

3. Incidence rate of outcomes by DDD category.

9.10. Quality control

The data were managed and analysed in accordance with the Guidelines for Quality Control at the Centre for Pharmacoepidemiology, Karolinska Institutet. The statistical analyses, the output, and the report were reviewed by the project epidemiologists and project statisticians.

9.11. Protection of human subjects

Ethical conduct of the study: The study was 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), and the Guidelines for Good Pharmacovigilance Practice (GVP), issued by the EMA (International Society for Pharmacoepidemiology, 2015, The European Medicines Agency, 2016) [18, 19].

Independent Ethics Committee (IEC)/ Institutional Review Board (IRB): This study was approved by the regional ethical board in Stockholm, Sweden, on 23 March 2016 (record number 2016/397-31), and a supplement application was approved on 15 July 2016 (record number 2016/1328-32).

Patient information and consent: Not applicable. Given that this study utilized anonymized data from secondary data sources, informed consent from the individual patients was not required.

10. RESULTS

10.1. Participants

In total, 2,416 patients filled at least one prescription of voriconazole in Sweden between 1 January 2006 and 31 December 2017. Since no exclusion criteria were applied, all 2,416 patients were included in the study cohort. The number of patients with a prescription of voriconazole by year decreased from 280 in 2006 to 150 in 2017 (Table S4 in Appendix 8.1).

10.2. Descriptive data

Of the study cohort, 1,352 (56.0%) were males and 1,064 (44.0%) were females. The median age on the index date was 60 years (first quartile [q1]: 42, and third quartile [q3]: 69) and the mean age was 53.7 years (SD: 21.2). There were 239 (9.8%) paediatric patients (aged <18 years) and 2,177 (90.1%) adults (Table 2).

The most common underlying conditions were haematological conditions (n=1,136, 47%) and solid organ transplant (n=381, 15.8%). The most common comorbid conditions were hypertension (n=1,056, 43.7%), sepsis (n=697, 28.8%) and autoimmune disease (n=472, 19.5%) (Table 2).

Table 2. Patient demographic and baseline characteristics

		n	%
Total		**2,416**	**100.0**
Demographics			
Age (year)	≤1	18	0.7
	2-17	221	9.1
	18-39	309	12.8
	40-59	637	26.4
	60-69	684	28.3
	70+	547	22.6
	Mean (sd)	53.7 (21.2)	
	Median (Q1 – Q2)	60 (42 - 69)	
Sex	Male	1,352	56.0
	Female	1,064	44.0
Geographical region	1: Northern Sweden	302	12.5
	2: Southern/Coastal Sweden	1,489	61.6
	3: Central Sweden	623	25.8
	Missing	2	0.1
Country of birth	Sweden	1,999	82.7
	Europe, outside Sweden	245	10.1
	Outside Europe	172	7.1
Occupation	Mainly indoor	1,268	52.5
	Mainly outdoor	140	5.8
	Missing*	1,008	41.7

	n	%
Underlying conditions		
Solid organ transplant	381	15.8
Bone marrow transplant	14	0.6
HIV infection	16	0.7
Cystic fibrosis	82	3.4
Hematological conditions	1,136	47.0
Co-morbid conditions		
Diabetes	345	14.3
Hypertension	1,056	43.7
Osteoarthritis	165	6.8
Cytomegalovirus (CMV)	24	1.0
Liver disease (infectious and non-infectious)	186	7.7
Psoriasis	62	2.6
Atopic dermatitis	29	1.2
Autoimmune disease (i.e. Rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE))	472	19.5
Sepsis	697	28.8
Veno-occlusive liver disease (VOLD)	6	0.2
Graft-versus-host disease (GvHD)	96	4.0
Other		
Hemodialysis	30	1.2
History of other skin malignancy	1	0.0
Concomitant medication/treatment		
Immunosuppressant and antineoplastic drugs	644	26.7
Radiotherapy ultraviolet light A and B	2	0.1

Source: Appendix 8.1 Table S17 and S18
* all patients in age categories ≤1 and 2-17 are classified as missing considering occupation status.

Considering the primary acute onset outcomes, patients with previous history of hepatic disorder were 32 (1.3%), the patients with previous history of phototoxicity were 96 (4.0%) and the patients with history of visual disorders were 190 (7.9%). For the primary delayed onset outcomes, the patients with history of periostitis were 18 (0.7%) and the patients with history of SCC of the skin were 30 (1.2%) (Table S5 in Appendix 8.1).

The patient demographics and background characteristics by different prespecified subgroups are presented in the Appendix 8.1: A) Paediatric patients (Tables S23 and S24), B) Adults (Tables S28 and S29), C) Voriconazole use, with an approved indication of voriconazole treatment (Tables S33 and S34), D) Voriconazole use unclear indication (Tables S38 and S39), E) Patients with any co-morbid/underlying condition (Tables S43 and S44), F) History of Hepatic disorders (Tables S48 and S49), G) History of Visual disorders (Tables S53 and

S54); H) History of Periostitis (Tables S58 and S59); I) History SCC of the skin (Tables S63 and S64); J) History of Phototoxicity (Tables S68 and S69); K) No history of Hepatic disorders (Tables S73 and S74); L) No history of Visual disorders (Tables S78 and S79); M) No history of Periostitis (Tables S83 and S84); N) No history SCC of the skin (Tables S88 and S89); O) No history of Phototoxicity (Tables S93 and S94). A brief description of these descriptive characteristics is provided in the following Section 10.5.1 Subgroup analysis.

The median follow-up time for acute onset outcomes was 146.0 days (q1: 104.0, q3: 244.0), and for delayed onset outcomes was 1,268.0 days (q1: 282.0, q3; 2,926.5) (Table S15 Appendix 8.1). Total cumulative dose (DDD) had a median of 56.0 (q1: 20.5, q3: 112) in both acute and delayed onset outcomes.

10.3. Outcome data

See following section.

10.4. Main results

10.4.1. Primary acute onset outcomes

Among patients without a history of the outcome of interest, who filled at least one prescription of voriconazole, for the primary acute onset outcomes the total number of hepatic disorders outcomes was 11, the total number of phototoxicity outcomes was 35, and the total number of visual disorders outcomes was 34 (Table S11 Appendix 8.1). The incidence rates were 6.4 per 1,000 person-years (95% CI: 3.2-11.4) for hepatic disorders, 21.0 (95% CI: 14.7-29.3) for phototoxicity, and 21.5 (95% CI: 14.9-30.1) for visual disorders (Table 3).

Among patients without a history of the outcome of interest, the highest incidence rate for the three primary acute onset outcomes was noted: in the 1-29 DDD interval for hepatic disorders, phototoxicity and visual disorders, and in the 30-89 DDD interval for visual disorders. Additionally, a higher incidence rate was observed in the >365 DDD interval for hepatic and visual disorders and in the 271-365 DDD interval for phototoxicity. All incidence rates within each DDD interval had wide and overlapping confidence intervals (CIs). No clear trend was observed for higher incidence rates with longer use of voriconazole for any of the acute onset outcomes (Table 3).

Table 3. Incidence rates (95 % confidence interval) acute onset outcomes (per 1,000 patient year), for patients not experiencing the outcome in the previous cumulative dosing periods. Patients without a history of the outcome of interest.

	Hepatic disorders					Phototoxicity					Visual disorders				
Cumulative dose interval	Patients	Time at risk (years)	Events	**IR**	95 % CI	Patients	Time at risk (years)	Events	**IR**	95 % CI	Patients	Time at risk (years)	Events	**IR**	95 % CI
Overall	2,384	1,725	11	**6.4**	3.2 - 11.4	2,320	1,663	35	**21.0**	14.7 - 29.3	2,226	1,578	34	**21.5**	14.9 - 30.1
Short term															
1-29 DDD	2,384	507	5	**9.9**	3.2 - 23.0	2,320	497	16	**32.2**	18.4 - 52.2	2,226	475	13	**27.4**	14.6 - 46.8
30-89 DDD	1,384	497	3	**6.0**	1.2 - 17.6	1,335	478	11	**23.0**	11.5 - 41.2	1,288	457	13	**28.5**	15.2 - 48.7
90-179 DDD	705	318	2	**6.3**	0.8 - 22.7	676	300	3	**10.0**	2.1 - 29.2	649	292	5	**17.1**	5.6 - 39.9
Long term															
180-270 DDD	307	140	0	**0.0**	0.0 - 26.3	298	134	2	**14.9**	1.8 - 53.7	280	128	0	**0.0**	0.0 - 28.7
271-365 DDD	165	96	0	**0.0**	0.0 - 38.3	158	92	3	**32.6**	6.7 - 95.1	153	87	0	**0.0**	0.0 - 42.6
>365 DDD	104	159	1	**6.3**	0.2 - 35.0	98	154	0	**0.0**	0.0 - 23.9	94	132	3	**22.7**	4.7 - 66.3

Source: Appendix 8.1 Table S7, S11, and S21

Incidence rates, overall and by DDD intervals, for primary acute onset outcomes in patients with or without history of the outcome of interest, are presented in Table S9 Appendix 8.1. The overall estimated incidence rates were 7.5 per 1,000 person-years (95% CI: 4.0-12.7) for hepatic disorders, 21.4 (95% CI: 15.1-29.6) for phototoxicity, and 29.7 (95% CI: 22.0-39.1) for visual disorders. The incidence rates were similar to the incidence rates in patients without history of the outcome of interest, and all CIs were overlapping.

Corresponding overall incidence rates for primary acute onset outcomes in patients with history of the outcome of interest, are presented in Table S12 Appendix 8.1. The overall estimated incidence rates were 102.2 per 1,000 person-years (95% CI: 12.4-369.3) for hepatic disorders, 32.0 (95% CI: 3.9-115.4) for phototoxicity, and 148.3 (95% CI: 84.8-240.9) for visual disorders. Even though the groups are small and the CIs are wide and overlapping, hepatic and visual disorders have higher incidence rates among those who have a history of the outcome of interest, compared to those patients without a history of the outcome of interest.

10.4.2. Primary Delayed onset outcomes

For the primary delayed onset outcomes in patients without a history of the outcome of interest, the total number of periostitis outcomes was 12, and the total number of SCC of the skin outcomes was 36 (Table S11 Appendix 8.1). The overall incidence rates were 1.1 per 1,000 person-years (95% CI: 0.6-1.9) for periostitis and 3.2 (95% CI: 2.3-4.5) for SCC of the skin (Table 4).

Considering the incidence rates for each DDD interval shown in Table 3, for the primary delayed onset outcomes, the point estimates were in the same range for the various DDD intervals, with wide and overlapping CIs in patients without a history of the outcome of interest. Although, no clear trends for incidence rates were observed with increased DDD intervals, a higher incidence rate was observed for > 365 DDD interval compared to other DDD intervals for periostitis 4.0 (95% CI: 0.5-14.5) and SCC of the skin 10.1 (95% CI: 3.3-23.7) (Table 4).

Table 4. Incidence rates (95 % confidence interval), delayed onset outcomes (per 1,000 patient year), for patients not experiencing the outcome in the previous cumulative dosing periods. Patients without a history of the outcome of interest.

	Periostitis					SCC of the skin				
Cumulative dose interval	Patients	Time at risk (years)	Events	**IR**	95 % CI	Patients	Time at risk (years)	Events	**IR**	95 % CI
Overall	2,398	11,237	12	**1.1**	0.6 - 1.9	2,386	11,188	36	**3.2**	2.3 - 4.5
Short term										
1-29 DDD	2,398	4,614	5	**1.1**	0.4 - 2.5	2,386	4,566	11	**2.4**	1.2 - 4.3
30-89 DDD	1,387	3,158	2	**0.6**	0.1 - 2.3	1,383	3,142	12	**3.8**	2.0 - 6.7
90-179 DDD	705	1,957	3	**1.5**	0.3 - 4.5	705	1,963	6	**3.1**	1.1 - 6.7
Long term										
180-270 DDD	310	704	0	**0.0**	0.0 - 5.2	308	718	2	**2.8**	0.3 - 10.1
271-365 DDD	167	300	0	**0.0**	0.0 - 12.3	165	299	0	**0.0**	0.0 - 12.3

	Periostitis					SCC of the skin				
Cumulative dose interval	Patients	Time at risk (years)	Events	**IR**	95 % CI	Patients	Time at risk (years)	Events	**IR**	95 % CI
>365 DDD	104	497	2	**4.0**	0.5 - 14.5	103	493	5	**10.1**	3.3 - 23.7

Source: Appendix 8.1 Table S8, S11, and S21

Incidence rates, overall and by DDD intervals, for primary delayed onset outcomes in patients with or without history of the outcome of interest, are presented in Table S10 Appendix 8.1. The overall incidence rates were 1.3 per 1,000 person-years (95% CI: 0.7-2.2) for periostitis and 3.6 (95% CI: 2.6-5.0) for SCC of the skin. The incidence rates are similar to the incidence rates in patients without a history of the outcome of interest, and all CIs are overlapping.

Corresponding overall incidence rates for patients with history of the outcome of interest, are presented in Table S12 Appendix 8.1. The overall incidence rates were 45.6 per 1,000 person-years (95% CI: 9.4-133.3) for periostitis and 104.3 (95% CI: 33.9-243.3) for SCC of the skin. Even though the groups are small and the CIs are wide, primary delayed onset outcomes have higher incidence rates among those who have a history of the outcome of interest, compared to those patients without a history of the outcome of interest.

10.4.3. Secondary outcomes

The incidence rates per 1,000 person-years for the secondary acute onset outcomes were 17.9 (95% CI: 12.0-25.7) for gastritis and duodenitis, 11.5 (95% CI: 6.9-17.9) for gastro-oesophageal reflux disease, 8.2 (95% CI: 4.5-13.8) for esophagitis, and 6.5 (95% CI: 3.2-11.6) for gastric ulcer. All other secondary acute onset outcomes are shown in Table 5. There were no incident outcomes of disorders of esophagus in diseases classified elsewhere, peptic ulcer or gastro jejunal ulcer.

The incidence rate (per 1,000 person-years) of all-cause mortality was 319.0 (95% CI: 293.1-346.6) when analysed as a secondary acute onset outcome whereas the incidence rate went down to 122.3 (95% CI: 115.9-128.9) when analysed as a secondary delayed onset outcome (Table 5).

Table 5. Risk estimates per 1,000 patient years for secondary outcomes - patients without history of the outcome of interest. Population: All patients

Secondary Outcomes	Patients	Time at risk (years)	Events	**IR**	Lower 95% CI	Upper 95% CI
Acute onset outcomes						
All-cause mortality	2,416	1,749	558	**319.0**	293.1	346.6
Oesophagitis	2,355	1,698	14	**8.2**	4.5	13.8
Gastro-oesophageal reflux disease	2,294	1,657	19	**11.5**	6.9	17.9
Other diseases of oesophagus	2,370	1,704	11	**6.5**	3.2	11.6
Disorders of oesophagus in diseases classified elsewhere	2,414	1,751	0	**0.0**	0.0	2.1
Gastric ulcer	2,344	1,699	11	**6.5**	3.2	11.6

Secondary Outcomes	Patients	Time at risk (years)	Events	IR	Lower 95% CI	Upper 95% CI
Duodenal ulcer	2,386	1,736	9	**5.2**	2.4	9.8
Peptic ulcer, site unspecified	2,409	1,745	0	**0.0**	0.0	2.1
Gastrojejunal ulcer	2,414	1,751	0	**0.0**	0.0	2.1
Gastritis and duodenitis	2,269	1,619	29	**17.9**	12.0	25.7
Acute appendicitis	2,379	1,730	1	**0.6**	0.0	3.2
Delayed onset outcomes						
All-cause mortality	2,416	11,190	1,368	**122.3**	115.9	128.9

Source: Appendix 8.1 Table S20

10.5. Other analyses

10.5.1. Subgroups analyses

A summary of all overall incidence rates is presented in Tables S13 and S14 Appendix 8.1 for primary acute and delayed onset outcomes respectively, in all prespecified subgroup analysis.

All tables corresponding to all subgroup analysis are available in the Appendix 8.1: A) Paediatric patients (Tables from S23 to S27), B) Adults (Tables from S28 to S32), C) Voriconazole use, with an approved indication of voriconazole treatment (Tables from S33 to S37), D) Voriconazole use with unclear indications of voriconazole treatment (Tables from S38 to S42), E) Patients with any co-morbid/underlying condition (Tables from S43 to S47), F) History of Hepatic disorders (Tables from S48 to S52), G) History of Visual disorders (Tables from S53 to S57); H) History of Periostitis (Tables from S58 to S62); I) History SCC of the skin (Tables from S63 to S67); J) History of Phototoxicity (Tables from S68 and S72); K) No history of Hepatic disorders (Tables from S73 to S77); L) No history of Visual disorders (Tables from S78 to S82); M) No history of Periostitis (Tables from S83 to S87); N) No history SCC of the skin (Tables from S88 to S92); O) No history of Phototoxicity (Tables from S93 to S97). Descriptions of these tables are provided in the following sections.

10.5.1.1. (A) Paediatric patients

Of all 239 (9.9%) included paediatric patients, 131 (54.8%) were males and 108 (45.2%) were females. The median age at the index date was 9 years (q1: 4-q3: 14) and the mean age was 9.1 years (SD: 5.3). The most common underlying conditions were haematological conditions (n=149, 62.3%) and solid organ transplant (n=58, 24.3%). The most common comorbid conditions were sepsis (n=101, 42.3%), hypertension (n=22, 9.2%), and autoimmune disease (n=20, 8.4%) (Tables S23 and S24 Appendix 8.1).

Amongst patients without a history of the outcome of interest, who filled at least one prescription of voriconazole for the primary acute onset outcomes, the overall incidence rates were 15.0 per 1,000 person-years (95% CI: 3.1-43.8) for hepatic disorders, 48.2 (95% CI: 22.0-91.5) for phototoxicity, and 31.1 (95% CI: 11.4-67.7) for visual disorders. For the primary delayed onset outcomes, the overall incidence rates were 1.8 per 1,000 person-years (95% CI: 0.4-5.3) for periostitis and 0.6 (95% CI: 0.0-3.3) for SCC of the skin (Table S25 Appendix 8.1).

The incidence rates estimated for the DDD intervals are shown in Table 6 for the primary acute and delayed onset outcomes. For primary acute onset outcomes in the paediatric population, higher incidence rates in the 30-89 DDD interval for hepatic disorders and visual disorders, and in the 180-270 DDD interval for phototoxicity were observed, compared to other DDD intervals. In the primary delayed onset outcomes, the highest incidence rate was observed for the >365 DDD interval. Due to very low number of outcomes within each DDD interval and wide CIs, it is not possible to describe a clear pattern between DDD intervals and the incidence rates of primary acute and delayed onset outcomes in the paediatric population.

Table 6. Risk estimates per 1,000 patient years for primary outcomes, by cumulative dose intervals - patients without history of the outcome of interest. Population: A) Paediatrics

Outcome	Cumulative dose interval	Patients	Time at risk (years)	Events	IR	Lower 95% CI	Upper 95% CI
Acute onset outcomes							
Hepatic disorders	1-29 DDD	238	54	1	**18.4**	0.5	102.2
	30-89 DDD	142	47	2	**43.0**	5.2	155.2
	90-179 DDD	76	49	0	**0.0**	0.0	75.6
	180-270 DDD	39	15	0	**0.0**	0.0	246.0
	271-365 DDD	23	14	0	**0.0**	0.0	270.1
	>365 DDD	16	21	0	**0.0**	0.0	178.0
Phototoxicity	1-29 DDD	231	53	3	**56.9**	11.7	166.3
	30-89 DDD	136	44	3	**68.9**	14.2	201.5
	90-179 DDD	73	44	1	**22.7**	0.6	126.6
	180-270 DDD	37	14	2	**147.4**	17.9	532.6
	271-365 DDD	21	12	0	**0.0**	0.0	312.4
	>365 DDD	15	20	0	**0.0**	0.0	181.3
Visual disorders	1-29 DDD	229	51	2	**39.1**	4.7	141.4
	30-89 DDD	136	44	3	**68.1**	14.0	199.0
	90-179 DDD	73	48	1	**21.0**	0.5	116.8
	180-270 DDD	39	15	0	**0.0**	0.0	246.0
	271-365 DDD	23	14	0	**0.0**	0.0	270.1
	>365 DDD	16	21	0	**0.0**	0.0	178.0
Delayed onset outcomes							
Periostitis	1-29 DDD	235	688	0	**0.0**	0.0	5.4
	30-89 DDD	139	431	0	**0.0**	0.0	8.6
	90-179 DDD	74	280	2	**7.2**	0.9	25.8
	180-270 DDD	38	96	0	**0.0**	0.0	38.3
	271-365 DDD	23	68	0	**0.0**	0.0	54.5
	>365 DDD	16	97	1	**10.3**	0.3	57.6
SCC of the skin	1-29 DDD	239	689	0	**0.0**	0.0	5.4
	30-89 DDD	142	432	0	**0.0**	0.0	8.5

Outcome	Cumulative dose interval	Patients	Time at risk (years)	Events	IR	Lower 95% CI	Upper 95% CI
	90-179 DDD	76	291	0	**0.0**	0.0	12.7
	180-270 DDD	39	109	0	**0.0**	0.0	33.8
	271-365 DDD	23	68	0	**0.0**	0.0	54.5
	>365 DDD	16	100	1	**10.0**	0.3	56.0

Source: Appendix 8.1 Table S26

10.5.1.2. (B) Adult patients

Of all 2,177 (90.1%) adult patients, 1,221 (56.1%) were males and 956 (43.9%) were females. The median age at the index date was 62 years (q1: 49-q3: 70) and the mean age was 58.6 years (SD: 15.9). The most common underlying conditions were haematological conditions (n=987, 45.3%) and solid organ transplant (n=323, 14.8%). The most common comorbid conditions were hypertension (n=1,034, 47.5%), sepsis (n=596, 27.4%), and autoimmune disease (n= 452, 20.8%) (Tables S28 and S29 Appendix 8.1).

Amongst patients without a history of the outcome of interest, who filled at least one prescription of voriconazole for the primary acute onset outcomes, the overall incidence rates were 5.2 per 1,000 person-years (95% CI: 2.3-10.3) for hepatic disorders, 17.6 (95% CI: 11.5-25.8) for phototoxicity, and 20.2 (95% CI: 13.4-29.2) for visual disorders. For the primary delayed onset outcomes, the overall incidence rates were 0.9 per 1,000 person-years (95% CI: 0.4-1.8) for periostitis and 3.7 (95% CI: 2.6-5.1) for SCC of the skin (Table S30 Appendix 8.1).

The incidence rates estimated for each DDD interval are shown in Table 7 for the primary acute and delayed onset outcomes in patients without previous outcomes in the category. Due to low number of outcomes and wide CIs, it is not possible to describe a clear pattern between DDD intervals and the incidence rates of primary acute and delayed onset outcomes.

Table 7. Risk estimates per 1,000 patient years for primary outcomes, by cumulative dose intervals - patients without history of the outcome of interest. Population: B) Adults

Outcome	Cumulative dose interval	Patients	Time at risk (years)	Events	IR	Lower 95% CI	Upper 95% CI
Acute onset outcomes							
Hepatic disorders	1-29 DDD	2,146	453	4	**8.8**	2.4	22.6
	30-89 DDD	1,242	450	1	**2.2**	0.1	12.4
	90-179 DDD	629	269	2	**7.4**	0.9	26.9
	180-270 DDD	268	125	0	**0.0**	0.0	29.4
	271-365 DDD	142	83	0	**0.0**	0.0	44.6
	>365 DDD	88	139	1	**7.2**	0.2	40.2
Visual disorders	1-29 DDD	1,997	424	11	**25.9**	13.0	46.4
	30-89 DDD	1,152	413	10	**24.2**	11.6	44.6
	90-179 DDD	576	244	4	**16.4**	4.5	41.9

Outcome	Cumulative dose interval	Patients	Time at risk (years)	Events	**IR**	Lower 95% CI	Upper 95% CI
	180-270 DDD	241	113	0	**0.0**	0.0	32.5
	271-365 DDD	130	73	0	**0.0**	0.0	50.5
	>365 DDD	78	112	3	**26.9**	5.5	78.6
Phototoxicity	1-29 DDD	2,089	445	13	**29.2**	15.6	50.0
	30-89 DDD	1,199	434	8	**18.4**	8.0	36.3
	90-179 DDD	603	256	2	**7.8**	0.9	28.2
	180-270 DDD	261	121	0	**0.0**	0.0	30.5
	271-365 DDD	137	80	3	**37.3**	7.7	109.1
	>365 DDD	83	134	0	**0.0**	0.0	27.5
Delayed onset outcomes							
Periostitis	1-29 DDD	2,163	3,925	5	**1.3**	0.4	3.0
	30-89 DDD	1,248	2,727	2	**0.7**	0.1	2.6
	90-179 DDD	631	1,677	1	**0.6**	0.0	3.3
	180-270 DDD	272	607	0	**0.0**	0.0	6.1
	271-365 DDD	144	232	0	**0.0**	0.0	15.9
	>365 DDD	88	401	1	**2.5**	0.1	13.9
SCC of the skin	1-29 DDD	2,147	3,877	11	**2.8**	1.4	5.1
	30-89 DDD	1,241	2,710	12	**4.4**	2.3	7.7
	90-179 DDD	629	1,671	6	**3.6**	1.3	7.8
	180-270 DDD	269	609	2	**3.3**	0.4	11.9
	271-365 DDD	142	232	0	**0.0**	0.0	15.9
	>365 DDD	87	393	4	**10.2**	2.8	26.0

Source: Appendix 8.1 Table S31

10.5.1.3. (C) Voriconazole use with an approved indication

Of 707 (29.3%) included patients with approved indication, 425 (60.1%) were males and 282 (39.9%) were females. The median age at the index date was 62 years (q1: 49-q3: 71) and the mean age was 58.2 years (SD: 17.9). The most common underlying conditions were haematological conditions (n=361, 51.1%) and solid organ transplant (n=116, 16.4%). The most common comorbid conditions were hypertension (n=331, 46.8%), sepsis (n=246, 34.8%), and autoimmune disease (n= 139,19.7%) (Tables S33 and S34 Appendix 8.1).

Amongst patients without a history of the outcome of interest, who filled at least one prescription of voriconazole for the primary acute onset outcomes, the overall incidence rates were 5.6 per 1,000 person-years (95% CI: 1.2-16.5) for hepatic disorders, 15.4 (95% CI: 6.7-30.4) for phototoxicity, and 35.9 (95% CI: 21.3-56.7) for visual disorders. For the primary delayed onset outcomes, the overall incidence rates were 1.0 per 1,000 person-years (95% CI: 0.2- 3.0) for periostitis and 5.2 (95% CI: 2.9-8.5) for SCC of the skin (Table S35 Appendix 8.1). The incidence rates estimated for each DDD interval are shown in Table S36 Appendix

8.1 for primary acute and delayed onset outcomes in patients without a history of the outcome of interest.

10.5.1.4. (D) Voriconazole use with unclear indications

Of 1,709 (70.7%) patients with unclear indications, 927 (54.2 %) were males and 782 (45.8%) were females. The median age at the index date was 59 years (q1: 39-q3: 68) and the mean age was 51.9 years (SD: 22.1). The most common underlying conditions were haematological conditions (n=775, 45.3%) and solid organ transplant (n=265, 15.5%). The most common comorbid conditions were hypertension (n=725, 42.4%), sepsis (n=451, 26.4%), and autoimmune disease (n= 333, 19.5%) (Tables S38 and S39 Appendix 8.1).

Amongst patients without a history of the outcome of interest, who filled at least one prescription of voriconazole for the primary acute onset outcomes, the overall incidence rates were 6.7 per 1,000 person-years (95% CI: 2.9-13.2) for hepatic disorders, 23.6 (95% CI: 15.6-34.3) for phototoxicity, and 14.9 (95% CI: 8.5-24.1) for visual disorders. For the primary delayed onset outcomes, the overall incidence rates were 1.1 per 1,000 person-years (95% CI: 0.5-2.1) for periostitis and 2.5 (95% CI: 1.6-3.9) for SCC of the skin (Table S40 Appendix 8.1). The incidence rates estimated for each DDD interval are shown in Table S41 Appendix 8.1 for acute and delayed onset outcomes in patients without a history of the outcome of interest.

10.5.1.5. (E) Patients with any comorbid/underlying condition

Of all 2,085 (86.3%) patients with any comorbid/underlying condition, 1,192 (57.2%) were males and 893 (42.8%) were females. The median age at the index date was 60 years (q1: 43-q3: 69) and the mean age was 54.0 years (SD: 21.4). The most common underlying conditions were haematological conditions (n=1,136, 54.5%) and solid organ transplant (n=381, 18.3%). The most common comorbid conditions were hypertension (n=1,056, 50.6%), sepsis (n=697, 33.4%), and autoimmune disease (n= 472, 22.6%) (Tables S43 and S44 Appendix 8.1).

Amongst patients without a history of the outcome of interest, who filled at least one prescription of voriconazole for the primary acute onset outcomes, the overall incidence rates were 7.0 per 1,000 person-years (95% CI: 3.4-12.9) for hepatic disorders, 24.9 (95% CI: 17.2-34.8) for phototoxicity, and 23.3 (95% CI: 15.8-33.1) for visual disorders. For the primary delayed onset outcomes, the overall incidence rates were 1.3 per 1,000 person-years (95% CI: 0.7-2.3) for periostitis and 3.6 (95% CI: 2.5-5.0) for SCC of the skin (Table S45 Appendix 8.1). The incidence rates estimated for each DDD interval are shown in Table S46 Appendix 8.1 for primary acute and delayed onset outcomes in patients without a history of the outcome of interest.

10.5.2. Validation sub studies

10.5.2.1. Validation of hepatic disorder diagnoses in users of systemic antimycotics

This study included 115 patients, using stratified random sampling as described in methods section, that filled at least one prescription for any antimycotic drug between July 1st, 2005 and September 30th, 2016 of whom 26 had toxic liver disease, 58 had hepatic failure and 31 with jaundice. The complete report of this validation process is presented in Appendix 8.2.

Toxic liver disease. The medical records of 26 patients with an ICD-10-SE code for toxic liver disease were reviewed. In total, the diagnosis was confirmed for 14 patients, yielding a

PPV of 53.8% (95% CI 33.4% - 73.4%). Of these, 7 patients had undergone liver biopsy, which supported the diagnosis of toxic liver disease in 6 cases.

Hepatic failure. In total, 58 patient records with an ICD-10-SE code for hepatic failure were reviewed. Of these, 38 patients could be fully classified through the electronic algorithm in combination with the review by the specialist in hepatology and26 out of the 38 diagnoses were confirmed. In 20 cases the abstracted data was discussed with a second physician and it was concluded that an additional 10 cases fulfilled the criteria for hepatic failure. Thus, 36 patients were classified as confirmed cases and 22 patients were classified as non-confirmed cases. The PPV for having a confirmed ICD-10-SE code for any hepatic failure was 62.1% (95% CI 48.4% - 74.5%). As for subgroups of hepatic failure according to our classification, the PPV was highest for liver synthetic dysfunction followed by the international definition of hepatic failure and liver synthetic dysfunction with ascites. However, the CIs were overlapping.

Since the ICD-10-SE code K71.1 represents hepatic toxic liver injury causing hepatic failure, these patients were included in a sub-analysis. From the 3 patients with the diagnosis K71.1 only one patient was confirmed to meet diagnostic criteria for liver failure in our validation study. The PPV for having a confirmed ICD-10-SE code for any hepatic failure including K71.1 was 60.7%. The pattern of PPVs for diagnostic subgroups was similar as for the analyses where K71.1 was not included.

Jaundice. A total of 31 patients with a jaundice diagnosis were reviewed. Only one of the 31 patients had a diagnosis that could not be confirmed, which resulted in a PPV of 96.8% (95% CI 83.3% - 99.9%).

10.5.2.2. Estimating duration of in-hospital use of voriconazole treatment

The study included 135 patients with documented dispensation of voriconazole during hospitalization, of whom 128 patients had information available to define the initiation date. A registered nurse and a medical doctor systematically reviewed all medical records to identify the date on which voriconazole was initiated during inpatient treatment. The complete report of this validation process is presented in Appendix 8.3.

For patients who were receiving voriconazole during the inpatients stay and who had unclear start and/or stop dates for voriconazole use, four different definitions of duration were used as described in the methods section.

The first approach was to omit patients with uncertain episodes from the analyses, meaning that all those patients with episodes when the duration of voriconazole use was uncertain during inpatient treatment were omitted. When seven such patients were omitted, the remaining 128 patients had a mean duration of hospitalization of 29.6 days and a median of 23 days. For all the 135 patients, their mean duration of hospitalization was 29.0 days, and median 23 days.

When the patients with uncertain episodes were omitted, the mean inpatient duration of voriconazole treatment was 16.2 days, with a median of 10 days. When the episodes with uncertain duration of voriconazole treatment were imputed, the method of imputing minimum duration resulted in a mean duration of 15.5 days and a median duration of 9 days; the method of imputing mid duration resulted in mean duration gave a mean of 16.0 days and a median of 9 days; and the method of imputing the maximum duration resulted in a mean duration of 16.6 days with a median of 10 days. Thus, all estimations of in-hospital voriconazole treatment

duration had a mean around 16, and the use of different definitions and scenarios did not change the estimation substantially. The estimations for the four different definitions are presented in Table 8.

Table 8. Duration of voriconazole treatments during hospitalization (days)

	Voriconazole in hospital treatment duration in days	
	Mean (standard deviation - sd)	Median (interquartile range - IQR)
1. Patients with uncertain duration omitted	16.2 (sd 17.2)	10 (IQR 4-22.5)
2. Minimum duration imputed	15.5 (sd 17.1)	9 (IQR 4-22.0)
3. Mean episode duration imputed	16.0 (sd 16.9)	9 (IQR 4-22.0)
4. Maximum episode duration imputed	16.6 (sd 17.1)	10 (IQR 4-23.0)

Source: Appendix 8.3 Table 3

10.6. Adverse events / adverse reactions

As described in the protocol (Appendix 2 Section 10), "*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)".*

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. Hence, according to the Swedish law, it is not possible to report any individual adverse events. Therefore, adverse events were not reported to Pfizer Inc. in this study.

The Karolinska Institutet follows pertinent guidance about adverse events reporting in accordance with the GVP Module VI and VIII.

11. DISCUSSION

11.1. Key results

This final study report is based on data from 2,416 patients who had filled a prescription of voriconazole in Sweden between 1 January 2006 and 31 December 2017 (including all patients included in the three previous interim reports) and followed up until December 2019.

The overall estimated incidence rates (per 1000 person-year) for the primary acute onset outcomes were 6.4 (95% CI: 3.2-11.4) for hepatic disorders, 21.0 (95% CI: 14.7-29.3) for phototoxicity, and 21.5 (95% CI: 14.9-30.1) for visual disorders among patients without a history of the outcome of interest. Overall, no clear trends for incidence rates were observed with increasing DDD intervals, including ≥ 180 DDD interval (i.e., long-term voriconazole use) for the primary acute onset outcomes Although high incidence rates were observed with short term treatment and in high DDD intervals, the IR were in similar range for the various follow-up periods.

The overall incidence rates (per 1000 person-years) for the primary delayed onset outcomes were 1.1 (95% CI: 0.6-1.9) for periostitis and 3.2 (95% CI: 2.3-4.5) for SCC of the skin, for patients without a history of the outcome of interest. The point estimates were in the same range for the various follow-up periods with wide and overlapping CIs in patients without a history of the outcome of interest. No clear trends for incidence rates were observed with increasing DDD intervals however higher IRs were noted for > 365 DDD interval compared to other DDD intervals for periostitis and SCC of the skin.

As expected, for hepatic, visual disorders, periostitis and SCC of the skin, the incidence rates were higher among those who had a history of the outcome of interest, compared to those patients that did not have a history of the outcome of interest. Overall, the estimated incidence rates of primary acute and delayed onset outcomes were comparable with the previous interim analysis report submitted to the EMA in 2019.

The secondary outcomes had a low frequency and there were no incident outcomes of disorders of oesophagus in diseases classified elsewhere, peptic ulcer, gastro jejunal ulcer or acute appendicitis. The incidence rate for all-cause mortality was 319.0 (95% CI: 293.1-346.6) per 1,000 person-years when analysed as a secondary acute onset outcome and 122.3 (95% CI: 115.9-128.9) when analysed as a secondary delayed onset outcome. These incidence rates of all-cause- mortality were also comparable with the incidence rates reported in the previous interim reports.

Expected study sample size as described in the protocol versus sample size in the interim and final study reports

In accordance with the protocol, the study included all patients with at least one filled prescription of voriconazole accrued over time in the NPR during the study period. However, it is to be noted that the number of patients treated with voriconazole per year decreased gradually from the beginning to the end of the study recruiting period, which resulted in a lower number of included patients than the planned pre-specified sample size in the study protocol. The discordance between the expected numbers and the observed numbers per year may be explained by two reasons, as follows:

- First, the protocol presented preliminary counts of patients with at least one filled prescription of voriconazole by year based on the historical data (2006-2012) in the

Swedish Prescribed Drug Register without excluding duplicate patients (i.e, patients receiving voriconazole for more than one year were counted in multiple years) as described in the protocol (Appendix 2. Protocol - Section 8.5.1: Historical counts of patients treated with voriconazole in the Swedish Prescribed Drug Register). In contrast, a patient treated with voriconazole was counted only once in all interim analysis and also final analysis in line with the study objective to estimate the incidence rates of safety outcomes. Therefore, the numbers of patients in the 1st, 2nd, and 3rd interim and final analysis represent counts of unique patients.

- Second, the number of patients with at least one filled prescription of voriconazole by year appears to be decreasing over time. As presented in the protocol, the annual average number of patients (without removing duplicates) was 305 based on 2006-2012 data. However, the average annual number of patients (without removing duplicates) decreased to 218 between 2013 and 2017 in the Swedish Prescribed Drug Register (Table 9). Therefore, this may also explain why the total number of patients included in the final report is lower than the number of patients expected in the study as described in the protocol.

Table 9. Number of patients with at least one filled prescription of voriconazole by year from the protocol (2006-2017), Swedish Prescribed Drug Register (2006-2017), 1st interim analysis report (2006-2014), 2nd interim analysis report (2006-2015), 3rd interim analysis report and final report (2006-2017)

Year	Number of Patients presented in the protocol [1] (2006-2012)	Number of Patients in the Swedish Prescribed Drug Register [2] (2006-2017)	Number of Patients in the 1st Interim analysis report[3] (2006-2014)	Number of Patients in the 2nd Interim analysis report[3] (2006-2015)	Number of Patients in the 3rd Interim analysis report[4] (2006-2017)	Number of Patients in the Final analysis report[5] (2006-2017)
2006	280	280	280	280	280	280
2007	290	290	221	221	221	221
2008	334	333	250	250	250	250
2009	323	314	227	227	227	227
2010	327	327	234	234	234	234
2011	312	312	229	229	229	229
2012	270	270	194	194	194	194
2013	-	259	180	180	180	180
2014	-	207	148	148	148	148
2015	-	209	-	146	146	146
2016	-	209	-	-	157	157
2017	-	206	-	-	150	150

[1] Annual average number of patients with at least one filled prescription of voriconazole (including duplicates) based on 2006-2012 data presented in the protocol= 305 [(280+290+334+323+327+312+270) ÷ 7]
[2] Patients counts from the National Board of Health and Welfare website/Swedish Prescribed Drug Register, downloaded February 1, 2021. Annual average number of patients with at least one filled prescription of voriconazole (including duplicates) based on 2013-2017= 218 (259+207+209+209+206) ÷ 5]
[3] Excluding duplicate patients
[4] Total number of patients (excluding duplicates) with at least one filled prescription of voriconazole (2006-2017)=2416
[5] Source: Appendix 8.1 Table S4 (excluding duplicates)

Discussion on the incidence rates of safety outcomes estimated in this study in relation to frequencies of these outcomes presented in section 4.8 of Voriconazole Summary of Product Characteristics (SmPC) [20]

Due to different methodologies used for estimating rates of safety, it is of investigators' opinion that the incidence rates (per 1000 person-year) of acute and delayed onset outcomes estimated in this study are not directly comparable to the frequencies of adverse reactions/clinical events presented in the voriconazole SmPC Section 4.8 Undesirable effects. Specifically:

- In this study, safety outcomes were identified using ICD-10-SE codes pertinent to each outcome in the Swedish National Healthcare registries. Each of these outcomes is a composite of several distinct clinical events based on ICD-10-SE diagnosis and procedural codes. For example, the outcome of "hepatic disorders" encompasses several ICD-10-SE codes, including hepatic failure, hepatitis/toxic liver diseases and hepatic encephalopathy. In contrast, the SmPC Section 4.8 presents cumulative proportion of individual clinical events such as hepatic failure, hepatomegaly, jaundice, liver function test abnormal which were coded using MedDRA terms in clinical trials. Additionally, these clinical events are presented in the SmPC using the following pre-defined frequency categories: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

- In this study, the occurrence of safety outcomes was measured by incidence rates (per 1,000-person years) which takes into account duration/time at risk whereas in the SmPC Section 4.8, occurrence is measured using cumulative proportions (%) without taking the duration of exposure into account — therefore these two quantitative measures are not directly comparable. Further, the assessment of safety outcomes with long term use of voriconazole was the focus of this study and therefore patients were followed up for up to 14 years. In contrast, cumulative proportion of safety outcomes are reported in the SmPC from clinical trial data where the overall duration of patient follow was substantially shorter than this study.

Due to the reasons described above, the incidence rates of safety outcomes reported in this study are not comparable to the frequencies presented in the SmPC Section 4.8.

11.2. Study Limitations

A potential limitation of this study is that the PDR only provides information on filled prescriptions and therefore information on actual medication use and discontinuation dates are not available. Adherence to medication is difficult to assess using a secondary database that captures data on filled prescription.

Moreover, the available registers do not contain information on medication use in hospitals or in nursing homes, which are administered without an individual dispensation. Given that the focus of this study is to monitor safety events with long-term voriconazole treatment, it is expected that the data obtained from the PDR adequately address the study objectives in the absence of in-patient data on voriconazole use. It was estimated that a mean around 16 additional days (or a median of 10 days) should be added to the total duration of voriconazole use for those patients that began treatment during a hospitalization. This additional time of voriconazole exposure is not believed to have a major impact on the safety outcomes over a long-term period.

All events were identified using secondary databases with ICD codes. Even though these data sources are considered to have a high ability to capture the outcomes under study, the quality of the diagnoses may vary between different outcomes. This may have introduced

misclassification of outcomes that may affect the rate estimation. In the validation sub-study of hepatic disorder diagnosis, a PPV within the expected range as reported in similar studies [21-23] was estimated. It is possible that this potential misclassification may have a higher impact in less clinically relevant diagnostics.

The time for each safety outcome in this study was the earliest date among all the outcomes belonging to the same category. This first record in the registers may not represent exactly the date of the event depending on the outcome (i.e., however this does not affect mortality dates). Outcomes that occur during a hospitalization may be recorded at discharge. Outcomes that occur in the outpatient setting may also have a delay until the patient decides to consult and the diagnosis is recorded.

Caution should be exercised when interpreting the incidence rates reported for some of the outcomes (e.g., periostitis and SCC of the skin) as they are based on a small number of cases. As such, the incidence rates are numerically "unstable" and an addition or removal of 1 or 2 cases to or from the numerator could substantially change the rates. Further, wide CIs around the incidence estimates indicate less precision and greater potential for random error.

All prescriptions in Sweden are ordered by physicians and it is not possible to purchase voriconazole without a prescription. Nevertheless, the indication for each prescription is recorded in free text in the medical records which was not available for this study. The percentage of unclear indications may represent some conditions not covered by the indication definition and codes that were used, or the 7 day window between the indication date registry and the first filling of the prescription in the ambulatory setting used to define indications, or off-label use including prevention of potential life threating fungal infections in other immunocompromised conditions like anti-aspergillus prophylaxis in lung transplant patients [7]. With the available information, it was not possible to explore these potential unclear indications within this category.

11.3. Interpretation

In this long-term study, the safety of voriconazole in relation to different length of exposure was examined. As described in the previous sections, the results do not suggest a clear cumulative dose effect since a higher incidence for those patients exposed for longer time compared to those patients that were exposed for shorter time was not observed. As such, some incidence rates are numerically "unstable" and an addition or removal of 1 or 2 cases to or from the numerator could substantially change the rates. Further, wide CIs around the incidence rate estimates indicate less precision and greater potential for random error. Additionally, the final sample size was lower than the expected as discussed in the previous sections.

Patients exposed to voriconazole usually present with high comorbidity or severe medical conditions. They are also frequently administered several concomitant medications, which may impair the possibility of evaluating potentially causal associations between exposure to voriconazole and adverse outcomes [24].

The results are expressed as incidence rates whereas almost all published results use cumulative incidences [25-33]. Incidence rates or incidence density are appropriate frequency measures when time of exposure is variable, like in the present study. Moreover, all our safety outcomes were measured in the real-world setting using codes assigned to diagnoses made by physicians in a clinical context, in different increasing DDDs with the main aim to estimate long-term incidence of safety outcomes. Frequently, adverse safety outcome incidences

reported in the literature are measured prospectively in the context of clinical trials, using structured definitions, for shorter exposure periods. Because of these differences between incidence estimates, the comparison of our results and previous published studies is difficult in most cases, as discuss in the following sections.

Additionally, the incidence rate estimates are based on a small number of incident cases and the number of observed outcomes is low. Hence, wide CIs around the incidence rates indicate less precision and greater potential for sampling variability and random error, particularly affecting stratified and subgroup analyses with smaller sample sizes. Therefore, caution must be applied when interpreting these incidence rates with wide CIs based on few incident outcomes.

11.3.1. Hepatic disorders

An overall incidence rate of hepatic disorders of 6.4 per 1,000 person-years was estimated. Overall, no clear trend in incidence rates of hepatic disorders with DDD interval was observed. As expected, all incidence rates were higher in the patients with a history of hepatic disorders.

In the validation study of diagnosis of hepatic disorders presented as a sub-study in this report, the validity of ICD-10-SE diagnoses of toxic liver disease, hepatic failure and jaundice among patients treated with antimycotics, the PPV was found to be 53.8% (95% CI 33.4% - 73.4%) for toxic liver disease, 62.1% (95% CI 48.4% - 74.5%) for liver failure, and 96.8% (95% CI 83.3% - 99.9%) for jaundice. The study focused on incident liver injury, since diagnoses before the beginning of the systemic antimycotic drugs were excluded. These estimates are similar to findings in other validation studies of liver diagnoses performed in Europe [21-23].

Varying estimates for hepatic disorders show that hepatic disorders are common in this high comorbidity and polymedicated population. The definition of hepatic toxicity is variable between different studies, but mostly includes altered laboratory results, generally including aspartate aminotransferase, alanine aminotransferase with additional variation in cut points. As laboratory results were not available, ICD-10-SE codes representing clinical diagnosis that were validated in the validation sub study were used. The variability observed in the different estimates below may be related to different populations, different comorbidities, different voriconazole indications, duration and context [8].

The incidence rates can be compared to findings from a retrospective cohort study of inpatients and outpatients voriconazole initiators who used voriconazole for 30 days [24]. They estimated an incidence rate for severe acute liver injury of 80.2 (9.7-289.8) and 0.0 (0.0-38.8) per 1,000 person-years in patients with and without chronic liver disease, respectively. The incidence rate of liver aminotransferases >200 U/L was 185.6 (108.1-297.2) and 167.4 (45.6-428.5) per 1,000 person-years in patients without and with chronic liver disease respectively. However, since those results were based on fewer voriconazole users (478 patients) during a short exposure time, and with different definitions of hepatic injury outcomes, care should be taken when comparing with the incidence rates presented in this report.

The following examples show cumulative incidence estimates that vary in magnitude, indication, population and exposure time. In a meta-analysis including clinical trials that mainly enrolled adult patients who had suspected or documented invasive fungal infections with aspergillosis or candidiasis or persistent febrile neutropenia and who were receiving

antifungal therapy, the pooled risk of an elevation of liver enzyme levels requiring the cessation of treatment was 9.5% for voriconazole, and the risk of elevation of liver enzyme levels not requiring stopping of treatment was 19.7% [25]. To highlight the possible heterogeneity in the studies included, one example included in that meta-analysis reported a cumulative incidence of hepatic events of 23%, in non-neutropenic patients with candidemia older than 12 years, from 2 to 8 weeks of treatment with voriconazole [26]. In a different meta-analysis of mostly retrospective observational studies assessing the relationship between voriconazole serum concentration and clinical outcomes of success and toxicity, the pooled incidence rate of hepatotoxicity was 5.7% [27]. Some other studies not included in the meta-analyses, estimated cumulative incidence within similar range. A cohort of hematopoietic cell transplant adult recipients who received voriconazole as a primary antifungal prophylaxis had a biochemical hepatotoxicity of 22.8% as the most common reason for premature treatment discontinuation [28]. In a prospective study of in patients with empirical prophylaxis treatment with voriconazole, hepatotoxicity was observed in 6.3% [29]. Because these are cumulative incidence rates and due to the described heterogeneity between studies, population, definitions, duration and indication, direct comparisons with our results are not possible.

11.3.2. Phototoxicity

An overall incidence rate of phototoxicity of 21.0 per 1,000 person-years was estimated. The incidence rate appears to decrease from a high incidence rate in the 1-90 DDD interval, but with a high incidence rate in the 279-365 DDD interval as well. However, all these estimates were unadjusted and had overlapping CIs.

All studies describing phototoxicity associated with voriconazole present cumulative incidences and hence the results presented in this report are not directly comparable. As an example, a study of acute invasive aspergillosis in immunocompromised patients older than 12 years found that during 12 weeks of treatment with voriconazole, 8.2% of patients had skin reactions, including rash, pruritus, or photosensitivity [30]. In another prospective study of inpatients with empirical prophylaxis treatment with voriconazole, photosensitivity was observed in 10.5% [29]. However, in the above-mentioned studies, photosensitivity definitions varied.

11.3.3. Visual disorders

An overall incidence rate of visual disorders of 21.5 per 1,000 person-years was estimated. The incidence rate seemed to be highest in the 1-90 DDD interval, but with a high incidence rate in the >365 DDD interval as well, although all estimates were unadjusted and the CIs were overlapping. As expected, all incidence rates were higher in the patients with previous visual disorders.

There is considerable variability in previously published incidence of visual disorders associated with voriconazole treatment. For example, a cumulative incidence of visual events of 4% was reported in non-neutropenic patients with candidemia older than 12 years from 2 to 8 weeks of treatment with voriconazole [26]. In a study of acute invasive aspergillosis in 144 immunocompromised patients older than 12 years, the incidence of visual disturbances (defined as blurred vision, altered visual perception, altered colour perception, and photophobia) was 44.8% [30]. In a prospective study of 95 patients receiving empirical prophylaxis treatment with voriconazole, visual changes (defined as blurred vision, a sense of brighter light, or a sense of more intense colours) occurred in 17.7% of the patients [29]. Finally, in a retrospective study of patients with haematological malignancies treated with

voriconazole for a fungal infection, the incidence of visual hallucinations was 14.6% [31]. Because of differences in estimates including large variability in outcome definitions, the results presented in this report are not directly comparable.

11.3.4. Periostitis

An overall incidence rate of periostitis of 1.1 per 1,000 person-years was estimated. The incidence rate appears to be stable through the short term DDD intervals, and has a high incidence rate in the >365 DDD interval. However, all these estimates were unadjusted and CIs are overlapping. As expected, all incidence rates were higher in the patients with previous periostitis. Because of differences in estimates, the results presented in this report are not directly comparable to cumulative incidence reported in previous studies.

Voriconazole-induced periostitis is related to elevated plasma fluoride level and seems to have a high cumulative incidence between 15% and 50% [6, 7, 34]. These adverse event estimations are frequent and primarily related to higher dosages or prolonged exposure in immunocompromised and transplant patient populations.

For example, in a retrospective cohort of 195 patients who received treatment with voriconazole due to an outbreak of Exserohilum infection as a result of contaminated methylprednisolone injections, 25% reported skeletal pain, and the incidence of confirmed periostitis was 10.7%. The diagnosis of periostitis was done with the presence of skeletal pain and a positive bone scan with technetium-99 m labeled methyl diphosphonate [32]. In another small cohort of adult post-transplant patients who received voriconazole for at least 6 months, 50% developed periostitis [33]. Voriconazole related skeletal pain had a higher incidence than periostitis in all studies. Because of differences in estimates including large variability in outcome definitions, the results presented in this report are not directly comparable.

11.3.5. SCC of the skin

This study estimated an overall incidence rate of SCC of 3.2 per 1,000 person-years. The incidence rate seems to be stable from 1 through 270 DDDs, with a high rate in the >365 DDD interval. All these estimates are unadjusted and CIs are overlapping. As expected, all incidence rates were higher in patients with a history of SCC.

A literature search identified several published studies that assessed the risk of SCC of the skin in voriconazole treated patients however the majority of the studies were conducted in special patient population such as solid organ transplant recipients including lung transplant and bone marrow transplant recipients in the US. Three studies that were conducted or included EU patients are described here. The first was a case series of potentially 19 voriconazole-associated SCC cases in France. The study suggested that voriconazole exposure may be associated with a multi-step phototoxic process i.e., acute phototoxicity during the first year of voriconazole therapy, actinic keratosis of the same sun-exposed skin area in the second/third year, followed by SCC of the skin during the third year or later. This study did not report incidence of SCC of the skin in voriconazole exposed patients [35].The second was a retrospective cohort study of patients with chronic pulmonary aspergillosis treated with voriconazole in the UK. The mean duration of voriconazole use was 36.7 months. This study reported SCC of the skin incidence rate of 4.88 per 1,000 person/years [36] which was comparable to the incidence rate observed in this study.

The third was a multicenter retrospective cohort of adults with lung transplant conducted in 9 countries including France, Germany, Italy, the Netherlands, Spain and Switzerland. Exposure

to voriconazole for at least 30 days had an incidence rate of SCC of 33.4 (28/837) per 1,000 person-years [37].

11.4. Generalisability

This study utilized nationwide data from Swedish national registers which collects complete information from all residents in Sweden. The study includes a long recruitment period of 12 years and almost complete follow up for the study cohort. Therefore, the study findings are likely to be generalizable to voriconazole treated patients in Sweden and in settings with similar populations. Based on biological plausibility, there is no reason to suspect non-generalizability of these results to other populations.

12. **OTHER INFORMATION**

Not Applicable.

13. **CONCLUSIONS**

This final study report included data on 2,416 patients who filled a prescription of voriconazole in Sweden between 1 January 2006 and 31 December 2017 and were followed up until 31 December 2019.

In this cohort of adult and paediatric patients with at least one filled prescription of voriconazole, although no clear trends for incidence rates were observed, the incidence rates for the primary acute onset outcomes were not increased over time with short- and- long term voriconazole use. However, for primary delayed onset outcomes, a high incidence rate was observed for periostitis and SCC of the skin in the > 365 DDD interval compared to other DDD intervals. Published studies have suggested increased risk of SCC of the skin with long-term exposure to voriconazole in immunocompromised patients such as solid organ transplant recipients. Care should be taken when interpreting the incidence rates reported for periostitis and SCC of the skin as they are unadjusted and based on a small number of outcomes. Further, wide CIs around the incidence estimates indicate less precision and greater potential for random error.

Overall, findings from this long-term study are consistent with the known safety profile of voriconazole. This study utilizes data from the Swedish national registers which collects data from all residents in Sweden. Therefore, the study findings are likely to be generalizable to all voriconazole treated patients in Sweden and in similar settings.

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15. **LIST OF SOURCE TABLES AND FIGURES**

Supplementary tables in Appendix 8.1 – Additional Study Tables