NON-INTERVENTIONAL (NI) DRUG STUDY PROTOCOL

Evaluation of the Potential Association Between Voriconazole Use and Squamous Cell Carcinoma (SCC) of Skin Among Patients With Lung or Lung/Heart Transplants

Compound Name:	Voriconazole
Study Number:	A1501097
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LIST OF ABBREVIATIONS

BCC	Basal Cell Carcinoma
COPD	Chronic Obstructive Pulmonary Disease
CMV	Cytomegalovirus
EU	European Union
EMR	Electronic Medical Records
EMA	European Medicines Agency
GPP	Good Pharmacoepidemiology Practices
HIV	Human Immunodeficiency Virus
IA	Invasive Aspergillosis
ICU	Intensive Care Unit
IRB/EC	Institutional Review Board/Ethics Committee
IFI	Invasive Fungal Infection
IQR	Inter Quartile Range
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LT	Lung or Lung or Heart Transplant
PhRMA	Pharmaceutical Research and Manufacturers Association
PASS	Post Authorization Safety Study
RR	Relative Risk
SOPs	Standard Operating Procedures
SCC	Squamous Cell Carcinomas
SAE	Serious Adverse Event
SOT	Solid Organ Transplant
UK	United Kingdom
US	United States of America

1. INTRODUCTION

Voriconazole (Vfend®) is approved for the treatment of invasive aspergillosis (IA) and other systemic fungal infections. In addition to the approved indications, published reports indicate that voriconazole is used as prophylaxis to prevent IA in solid organ transplant (SOT), primarily lung or lung/heart transplantation (LT) [1, 2].

Patients undergoing LT typically receive immunosuppressive medications for a period of time after the transplantation to prevent organ rejection. This prolonged immunosuppression renders these patients highly susceptible to invasive fungal infections (IFIs) such as IA [3]. As a result, antifungal prophylaxis is commonly prescribed for patients after LT in many transplant centers worldwide. Some transplant centers prefer universal antifungal prophylaxis for all patients, while others use "targeted" prophylaxis in only the highest risk patients. The data from a recent worldwide survey showed that voriconazole is the preferred antifungal for prophylaxis either as monotherapy or in combination with another antifungal agent[4]. It is important to note, however, that there have been no prospective comparative clinical trials conducted to evaluate the safety and efficacy of voriconazole prophylaxis in this clinical situation, and voriconazole has not been approved by any regulatory authority for this use.

Squamous cell carcinomas (SCC) is the second most common skin cancer in the general population after the basal cell carcinoma (BCC), and it is the most common cancer in immunocompromised patients with SOT. Overall, the incidence of SCC in SOT patients is 65 to 250 times that of the general population [5], and varies by type of organ transplant. Furthermore, SCC has been reported to be more aggressive and has been associated with a high mortality in immunocompromised patients [6]. The recognized risk factors for the development of SCC include old age, prolonged sunlight exposure, long duration of immunosuppressive therapy, infection with human papillomavirus (HPV) and lower CD4 cell counts, and certain host factors such as White race and Fitzpatrick skin types I, II, or III [7-9].

Recently, single case reports [10-12] and small case series [13-15] of SCC in patients with immunocompromised status such as patients with SOT, hematological malignancy or with human immunodeficiency virus (HIV) infection using voriconazole have been reported. Two retrospective observational studies were conducted in the US which investigated the risk of SCC during voriconazole therapy in patients with LT. In a retrospective cohort study, Feist et al. [16] reported a higher incidence of SCC and/or BCC in LT patients who received voriconazole for prophylaxis or treatment of aspergillosis compared to those who received other antifungals or no treatment (42.9% vs. 9.9%)[1]. In another study, Vadnerkar et al. [17] evaluated risk factors for SCC in LT patients receiving voriconazole prophylaxis (i.e., all patients received voriconazole) and concluded that prolonged duration of voriconazole therapy and residence in locations with high-levels of sun exposure were independent risk factors for SCC in patients with LT receiving voriconazole. However, severe immunosuppression has been recognized as an independent risk factor for SCC in several published studies [5]. Neither Feist nor Vadnerkar adequately

[1] As of February 10, 2012, full text of Feist et al. paper is not available and the information is based on the abstract only. The study examined combined endpoint of SCC and/or BCC, and did not report separate incidence estimates for SCC and BCC.

controlled for patient immune status in their studies. It is possible that LT patients who receive voriconazole prophylaxis, particularly for longer durations, may be more immunosuppressed compared to patients who do not receive voriconazole. Therefore, the association between voriconazole use and SCC reported in these studies may be biased due to "confounding by indication."

In addition to the reports of SCC, there have been several reports of melanoma in immunocompromised patients receiving prolonged voriconazole therapy [18]. To date, there have been no published studies that have investigated the association between voriconazole use and the development of melanoma.

The potential association between voriconazole use and the development of SCC or melanoma in patients can be evaluated either by a retrospective cohort or a case-control study design. In this context, a retrospective cohort study design has several advantages over a case-control study design. A retrospective cohort study will enable us to estimate the incidence of SCC in patients who received voriconazole and compare this to the incidence in patients who did not receive voriconazole. This study design will allow us to describe a broad range of potential risk factors for SCC (demographics, comorbid conditions, concomitant medications including immunosuppressive agents) in patients who received voriconazole and compare these to patients who did not receive voriconazole. In addition, this study design will enable us to evaluate multiple endpoints (e.g., SCC and melanoma).

Based on the recently conducted comprehensive study feasibility assessment of existing EU and US databases, we concluded that an adequately powered retrospective cohort study in the overall voriconazole-treated population would not be feasible because of the low incidence of SCC[2]. However, the background incidence of SCC has been reported to be relatively high in the LT patient population, and the majority of cases of SCC reported in patients receiving voriconazole have been in LT patients. By focusing on LT patients, we will be more likely to identify a sufficient number of patients to be able to conduct an adequately powered retrospective cohort study.

A recently completed study feasibility assessment in LT centers by the Principal Investigator (PI) (See section 3.6) indicated that it is feasible to conduct a retrospective cohort study with an adequate power using data from multiple LT centers in the EU, US and Australia.

This proposed retrospective cohort study evaluating the potential association between voriconazole use and the development of SCC of skin in patients with LT is a post-authorization safety study (PASS) committed to the European Medicines Agency (EMA).

[2] Report submitted to the EMA on 20 September, 2010

2. STUDY OBJECTIVES

2.1. Primary objective

- To assess the potential association between voriconazole use and the development of SCC of skin in patients with lung or heart/lung transplant.

2.2. Secondary objective

- To assess the potential association between voriconazole use and the development of melanoma in patients with lung or heart/lung transplant.

3. METHODS

3.1. Study design

This will be a non-interventional observational study. The study objectives will be accomplished by means of a retrospective cohort study design.

3.2. Study population

Lung or lung/heart transplant recipients constitute the study population and will be identified from a multicenter, multinational retrospective database of patients with LT. The study database is being developed and will include retrospective patient-level data from several lung transplant centers in the EU, North America and Australia.

3.3. Definition of exposed and unexposed cohorts

Voriconazole exposed cohort: Patients with LT who receive at least one dose of voriconazole regardless whether they also receive other antifungals will be included in this cohort.

Unexposed cohort: Patients with LT who did not receive voriconazole will be included in this cohort.

3.4. Inclusion and exclusion criteria

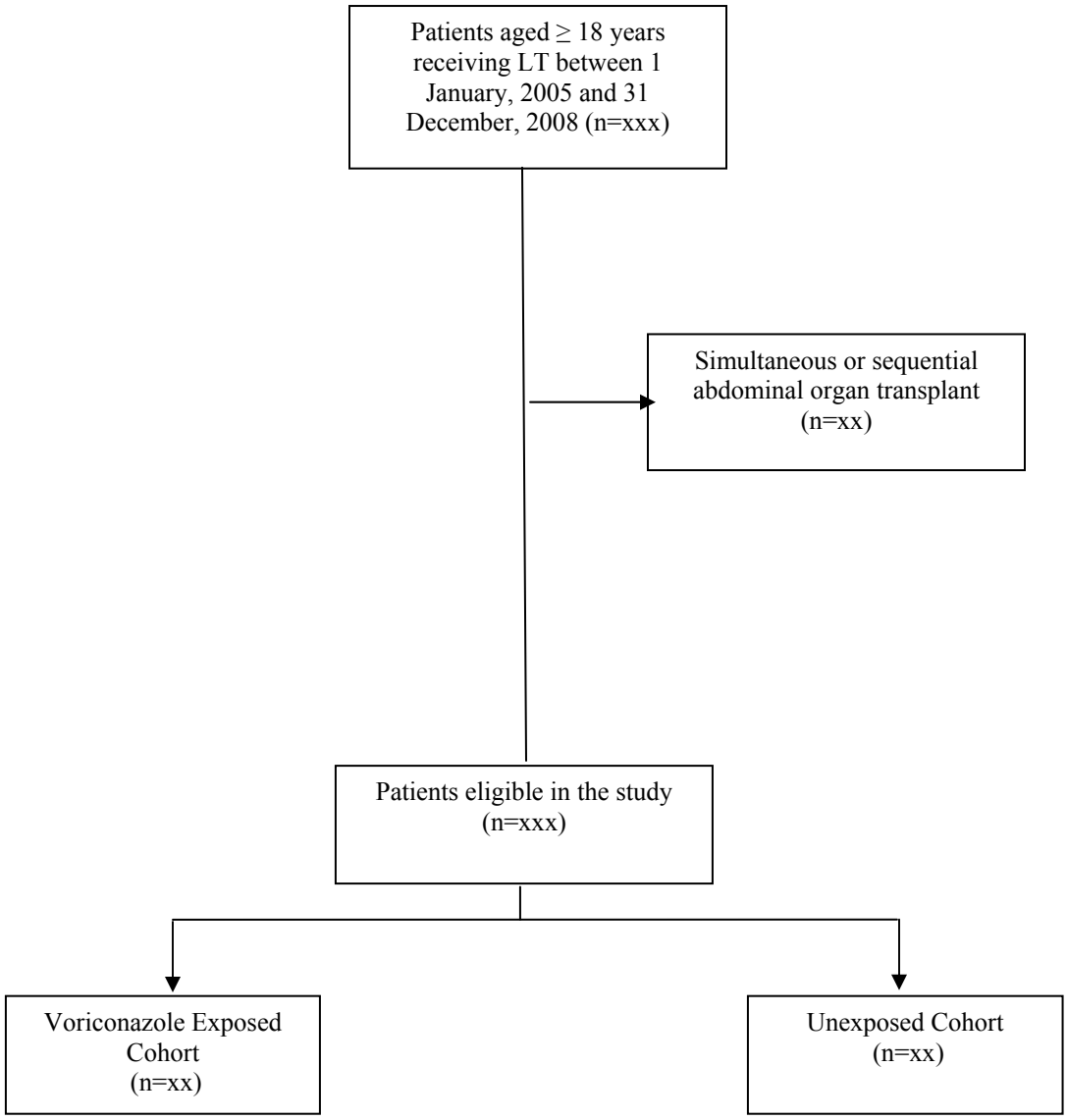
Inclusion criteria

- Patient aged ≥ 18 years at the time of LT
- Patient received LT between 1 January, 2005 and 31 December, 2008

Exclusion criteria

- Patient with simultaneous or sequential abdominal organ transplant (Note. Bone marrow transplant recipients who undergo LT will not be excluded)

Figure 1. Eligibility in the study assessing the potential association between voriconazole use and SCC of skin and melanoma in patients with LT



3.5. Index date and follow up

The index date will be the "date of LT". The study eligible patients will be followed from the index date to whichever of the following occurs first:

- Occurrence of SCC of skin or melanoma (follow up will be continued for the occurrence of a second endpoint if the patient develop one endpoint)
- Death
- Last patient visit or 31 December , 2012, at which time all surviving patients will be censored, whichever occurs first.

3.6. Data source

Patients will be identified from a multicenter, multinational LT patient database, which is being developed at the University of Toronto, Canada. This new database will contain retrospective patient-level data from several lung transplant centers in the EU, North America and Australia that agree to contribute patient-level data to the database under development.

A recently completed site feasibility assessment by the PI showed that some transplant centers use 'complete electronic medical records' (EMR) i.e., maintaining all medical records such as medication use, diagnosis, pathology reports in both inpatient and outpatient settings in EMR, some use 'partial EMR', i.e., some data in EMR and others in paper-based records, and some use 'paper records only' i.e., maintaining all data in paper charts only. Of the 19 transplant centers contacted by the PI, 16 completed the site feasibility assessment questionnaire. Of these 16 centers, six centers have complete EMR (four in EU and two in North America), eight centers have partial EMR (four in EU, three in North America and one in Australia) and two centers have paper records only. The feasibility assessment data suggest that it is feasible to conduct a retrospective cohort study with an adequate power in transplant centers that either have complete EMR or have partial EMR. To minimize the time needed to compile the new database, the study will mainly target the centers with complete EMR. Centers with partial EMR will be enrolled if needed to ensure enough number of LT patients is included in the database.

As of 10 February 2011, three centers in North America have been enrolled in the study (two with complete EMR and one with partial EMR data). The PI is in the process of enrolling additional centers who have expressed interest to participate in the study. These centers are based in Germany (1 center), Italy (1), Belgium (1), UK (1), Switzerland (2), Spain (2), US (2), and Australia (1).

3.7. Patient selection

Consecutive eligible patients undergoing LT at the study transplant centers between 1 January, 2005 and 31 December, 2008 will be included. An attempt will be made to collect post transplant follow up data for all surviving patients until the end 2012.

3.8. Sample size and power

Appendix 1 describes the sample size estimations of a retrospective cohort study addressing the study primary objective based on different assumptions. Assuming a p_0 value (i.e., incidence of SCC of skin in LT patients unexposed to voriconazole) of 5% and voriconazole exposed-to-unexposed ratio of 1:2, the study would require at least 157 patients in the voriconazole exposed cohort and 314 patients in the unexposed exposed cohort to detect a relative risk (RR) of 2.5 with 80% power at a 5% significance level.

3.9. Data collection

The data will be abstracted from EMR at centers with complete EMR. At transplant centers with partial EMR, the data elements in EMR will be linked to data in paper records using a "patient medical record number." Extracted data from each center will be compiled in the study database. The study database will only contain the encrypted identification of the patients and will be protected by a firewall and a password. The following data will be collected.

3.9.1. Voriconazole and other antifungal treatment

Data on voriconazole therapy will include:

- Indication:
    - Prophylaxis of IFIs
    - Treatment of IFIs
- Dose and frequency
- Duration of therapy (will be calculated by using the treatment start and stop dates)

Data on antifungl agents other than voricoanzole (e.g., itraconazole, posaconazole, amphotericin B) will also be collected.

3.9.2. Outcomes

Data on the diagnosis of SCC of skin and melanoma will be obtained from the medical records. Information on the biopsy report confirming the diagnosis will also be collected, when available. In addition, data on other serious skin related events, including phototoxicity will be collected.

3.9.3. Risk factors and potential confounders for SCC of skin

The following data will be collected:

- Age
- Gender
- Race/ethnicity
- Occupation
- Skin phototype
- Geographical location of residence (surrogate for sun exposure)

- History of immune disorder or malignancy prior to transplant.
- Type of transplant (lung vs. heart-lung, single vs. double lung, re-transplant)
- Cytomegalovirus (CMV) serostatus (donor and recipient)
- Reason for transplant (chronic obstructive pulmonary disease (COPD), cystic fibrosis, other)
- Days in intensive care unit (ICU), days in hospital at the time of transplant, need for readmission
- Need for hemodialysis during transplant admission
- Number of transplant rejection episodes
- Number of episodes of neutropenia after transplant
- Use of immunosuppressive agents after transplant
    - Interleukin (IL)-2 inhibitors (i.e., basiliximab, daclizumab, alemtuzumab).
    - Alemtuzumab (Campath)
    - Thymoglobulin
    - Calcineurin inhibitors (CNIs) (tacrolimus, cyclosporine) – with number of episodes with elevated levels
    - Sirolimus, everolimus
    - Mycophenolate
    - Corticosteroids
- Use of phototoxic agents after transplant
- Presence or absence of phototoxicity after the LT as documented in medical records
- History of SCC

3.9.4. Quality control

Data collected will be periodically checked for consistency by the study coordinator. The study investigators will follow their own Standard Operating Procedures (SOPs) for data collection and management.

4. ADVERSE EVENT REPORTING

This study protocol requires review of the patient medical chart and/or a narrative field in the dataset. Review of patient medical charts and narratives for specific attribution of SAEs to Pfizer drugs will not be actively pursued. However, while the primary purpose of this study does not encompass assessment of drug-related effects in individuals, the reviewer may identify an SAE with explicit attribution to a Pfizer drug via patient chart and/or narrative review (and with an identifiable reporter). Such SAEs must be reported to Pfizer or its representative for submission to regulatory authorities. Explicit attribution is not inferred by a temporal relationship between drug administration and an SAE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the SAE.

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- results in death;

- is life-threatening (i.e., at immediate risk of death due to the event);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

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

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

If there is a written notation in the medical chart/narrative field indicating that a physician attributed a serious adverse event to a Pfizer drug, the abstractor will complete an SAE form within 24 hours of identification of the event and submit it to Pfizer Safety. Since patients are de-identified, such information will not include any patient or physician identifying information such as name, address, or phone number.

5. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices such as *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidances, Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines and similar.

5.1. Institutional Review Board (IRB)/Ethics Committee (EC) Approval

Ethics approval from each study center's IRB/EC will be sought before implementing the study at each center.

5.2. Confidentiality of the data

Confidentiality of the data will be maintained at all times. The database will only contain the encrypted identification of the patients. The database will be protected by a firewall, and stored in a password protected computer. All analyses will be conducted on appropriately de-identified data and reported only in aggregate form.

5.3. Informed consent

This study will utilize retrospective (i.e., existing data from medical charts) unidentified data after appropriate IRB/EC approvals. Therefore, informed consent from each patient is not required in this study.

6. DATA MANAGEMENT

There will be one final analytic dataset containing data from all study transplant centers. The final dataset will be maintained at the principal study center in secure servers that transmit information only over encrypted connections. Access to raw data bypassing record level protection will be given only to the PI, study coordinator and database administrator. For analyses, de-identified data will be used and kept in a password protected computer with limited physical access.

6.1. Missing values

There will be no imputation of missing values. All variables will include a category for missing values, where applicable.

7. STATISTICAL ANALYSES

Detailed statistical analyses is outlined in the statistical analysis plan (SAP). Briefly, the following analyses will be conducted.

7.1. Descriptive analyses

Descriptive statistics will be presented to describe patient characteristics such as age at transplant, sex, race/ethnicity, occupation, geographical location of residence, reasons for transplant, co-morbid conditions and immunosuppressive agents used in the voriconazole exposed and unexposed cohorts.

Counts and percentages to describe categorical variables, and mean and standard deviations (or median with inter quartile range (IQR), where appropriate) for continuous variables will be calculated.

7.2. Incidence estimates

Incidence rates of SCC of skin and melanoma by voriconazole exposed cohort and unexposed cohort will be calculated. Patients with a history of SCC will be excluded, when estimating the SCC incidence, and patients with a history of melanoma will be excluded when estimating the melanoma incidence.

The incidence estimates will be stratified by selected variables such as:

- Age at transplant

- Gender
- Race/ethnicity
- Occupation
- Skin phototype
- Geographical location
- Exposure to sunlight
- Reason for transplant
- Co-morbid conditions
- Immunosuppressive agents used
- Number of transplant rejection episodes
- Number of episodes of neutropenia after transplant

If there are sufficient number of patients with previous SCC in LT patients, incidence of recurrent SCC will be estimated among patients with history of SCC and the risk factors for recurrent SCC will be evaluated in univariate and multivariate analyses.

7.3. Univariate and multivariate analyses

The regression analyses will be performed separately for the study primary and secondary objectives.

7.3.1. Analyses to address primary objective

Comparison of voriconazole exposed cohort and unexposed cohort: A univariate Cox proportional hazard regression analysis will be conducted to assess the association between voriconazole and SCC of skin. Based on the results of the univariate analysis, a multivariate Cox proportional hazard regression model will be developed to evaluate the independent effect of voriconazole use on the risk of SCC of skin while controlling for effects of major confounding variables such as exposure to sunlight (using geographical location of residence as a proxy variable), immune status (using immunosuppressive medications as a proxy variable) and confounding by indication (using underlying medical conditions as a proxy variable). In addition to multivariate regression analyses, other analytic methods will be considered in order to control for major confounders such as patients' immune status and exposure to sunlight.

Further, depending on the number of patients, subgroup analyses such as comparison of patients who receive voriconazole but no other antifungals (i.e., 'voriconazole only cohort') with patients who did not receive voriconazole (i.e., unexposed cohort) will be considered to assess the association between voriconazole and SCC of skin.

7.3.2. Analysis to address secondary objective

In order to assess the potential association between voriconazole use and the development of melanoma, a similar analytic approach, described in section 7.3.1, will be used.

8. STRENGTHS AND LIMITATIONS

Strengths:

- **Control for potential confounders:** This study will attempt to control for the confounding effect of patient immune status, which is a well known confounder, when assessing the potential association between voriconazole use and SCC of skin and melanoma among patients with LT. Multivariate Cox proportional hazard regression and other analytic methods, as appropriate, will be used to evaluate the independent effect of voriconazole use on the risk of SCC of skin while controlling for effects of confounders.

- **Use of a retrospective cohort study design:** A retrospective cohort study design will be used to address the research question. One of the major advantages of a retrospective cohort study over a case-control study is that the incidence of SCC of skin in LT patients receiving voriconazole can be estimated and compared with LT patients who did not receive voriconazole, and compare the characteristics of the two groups such as demographic variables, comorbid conditions, concomitant medication use, especially immunosuppressive agents. Further, in addition to the SCC of skin, other endpoints (e.g., melanoma) can be studied using a retrospective cohort study design.

- **Use of real world data:** This study evaluates the potential association between voriconazole use and SCC of skin and melanoma in patients with LT in a real-world setting using data from multiple transplant centers.

- **Generalizibility of findings**: This study will include patients with LT from several transplant centers in the EU, North America and Australia. Therefore, the results are likely to be generalizable to patients who underwent LT with regards to the risk of SCC of skin and melanoma.

Potential limitations:

- **Confounding by indication:** Confounding by indication is likely to take place in this study if a physician's decision to initiate a particular antifungal (s) for prophylaxis is influenced by the clinical status of the patient. This is of particular concern for voriconazole, which is a preferred antifungal agent in many transplant centers, as physicians are more likely to use voriconazole if patients are severely ill or are at high risk of acquiring IFIs. This could result in an association of voriconazole use with untoward outcomes including SCC of skin or melanoma. Although complete control of confounding by indication may not be possible, data on co-morbid conditions and laboratory tests will be collected and used in the statistical analyses (i.e., multivariate regression) for controlling its confounding effect.

- **Generalizibility of study findings to voriconazole treated patients overall:**
  It should be noted that the findings from such a study may not be generalizable to all voriconazole-treated patients with regards to the risk of SCC of skin as patients with LT are a special patient population with unique factors that make them more susceptible to SCC of skin.

- **Confounding by study center:** This study will include data from several transplant centers in the EU, North America and Australia. Therefore, factors such as sun exposure levels, and management and treatment of patients with LT will vary by study centers. The potential confounding effect by study center will be accounted for in the statistical analyses.

- **Misclassification of exposure:** The data on medication use more than three months prior to the transplant may not be available for most patients. which may result in misclassification of exposure. However, since the majority of patients receive antifungals at the time of transplant, the proportion of patients who may have received antifungal(s) three months before LT would be very small.

- **Exposure to sunlight:** Patients' exposure to sunlight has been identified as a risk factor for the SCC of skin. Exposure to sunlight or use of sun protective measures is not routinely documented in medical charts for all patients with LT. A proxy variable based on a patient's area of residence (e.g., highly exposed to sunlight versus not) will be developed and used in the analyses in the absence of individual-level data on exposure to sunlight.

9. ANTICIPATED STUDY TIMELINE

The estimated completion time of this retrospective cohort study is approximately two and a half years after the protocol endorsement. It will take approximately four months to recruit transplant centers including obtaining IRB/EC approvals, three months for development of the study database structure, 12 months for data collection/compilation, three months for data cleaning/verification, and nine months for statistical analyses and the study report development. The final study report is expected in the third quarter of 2015. The updates on the progress of the study will be provided to the EMA annually.

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11. APPENDIX:

1. Sample size calculations

This section describes sample size estimations of a retrospective cohort study addressing the primary objective. The calculations are based on the following assumptions:

- Two sided hypothesis tests with Alpha (α) level of 5%
- Power (i.e., the ability to statistically detect a difference between the two cohorts [i.e., voriconazole exposed cohort and unexposed cohort] when a statistical difference exists) is 80%.
- *Exposed-to- unexposed* (i.e., voriconazole exposed cohort-to- unexposed cohort) ratio ranges from 1:1, 1:2 to 1:3. The study feasibility assessment data suggest that there will be less number of patients with voriconazole exposure t than patients without voriconazole exposure. For sample size estimations, it is reasonable to assume that voriconazole exposed -to- unexposed ratio will range from 1:1, 1:2 to 1:3.
- Minimal detectable relative risk (RR) comparing voriconazole exposed cohort to unexposed cohort ranges from 2.0 to 3.0.
- Incidence of SCC of skin in LT patients unexposed to voriconazole (p_0) ranges from 3.0% to 15.0%. In order to estimate the sample size for a cohort study, it is necessary to specify the value of p_0, the rate of SCC of skin in patients unexposed to voriconazole, from the same source population (i.e., patients with LT) from which the voriconazole cohort will be drawn. The data on p_0 in the published literature is limited. Only one study was identified that reported an incidence of 9.9% for SCC and/or BCC of skin in patients with LT [16]. However, several published papers reported SCC of skin incidence in similar patient populations (i.e., renal, heart, or liver transplant patients) [19-22].[3] For sample size calculations, it is reasonable to assume that the value of p_0 will range from 3.0% to 15.0%.

Table 1. Sample size estimations for a retrospective cohort study of LT patients with a range of p_0, detectable RRs, and voriconazole exposed-to-unexposed cohort ratios, with 80% power at a 5% significance level

[3] The incidence of SCC of skin in other organ transplant patients (i.e., other than lung or lung/heart transplant patients) is reported to range from 3.45% in patients with renal transplant patients in UK, 4.6% in patients with renal liver, heart, lung or pancreas transplant in Sweden, 12.6% in patients with liver transplant in the US, to 12.6% in patients with renal transplant in Spain.

p_0	RR to be detected	Minimum number of patients required in voriconazole exposed cohort and unexposed cohort for various *exposed-to-unexposed* ratios:					
		1:1		1:2		1:3	
		Voriconazole Cohort	Non Voriconazole Cohort	Voriconazole Cohort	Non Voriconazole Cohort	Voriconazole Cohort	Non Voriconazole Cohort
3.0	2.0	749	749	536	1072	464	1392
	2.5	385	385	272	544	233	699
	3.0	245	245	171	342	146	438
4.0	2.0	552	552	396	792	343	1029
	2.5	283	283	200	400	172	516
	3.0	179	179	125	250	107	321
5.0	2.0	435	435	312	624	270	810
	2.5	222	222	157	314	135	405
	3.0	140	140	98	196	84	252
6.0	2.0	356	356	256	512	222	666
	2.5	181	181	128	256	110	330
	3.0	114	114	80	160	68	204
8.0	2.0	258	258	185	370	161	483
	2.5	130	130	92	184	79	237
	3.0	81	81	57	114	49	147
10.0	2.0	199	199	143	286	124	372
	2.5	100	100	71	142	61	183
	3.0	62	62	44	88	37	111
13.0	2.0	145	145	104	208	91	273
	2.5	71	71	51	102	44	132
	3.0	43	43	31	62	27	81
15.0	2.0	120	120	87	174	76	228
	2.5	59	59	42	84	36	108
	3.0	35	35	25	50	22	66

Notes: Sample size was calculated using the method described by Dupont and Plummer (1990) and specifying an unmatched cohort design: Software implementing this method (PS power and sample size is available at: http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize

Table 1 shows required number of subjects in voriconazole exposed cohort and other antifungal(s) exposed cohort with different values of the parameters described above. For example, assuming that the rate of p_0 is 5.0% and the voriconazole exposed–to unexposed cohort ratio is 1:2, the study would require at least 157 patients in the voriconazole exposed cohort and 314 patients in the unexposed cohort to detect a rate ratio of 2.5 with 80% power at a 5% significance level.