Risk of Skin Cancer and Lymphoma in Users of Topical Tacrolimus, Pimecrolimus, and Corticosteroids

Protopic **JO**int **E**uropean **L**ongitudinal **L**ymphoma and skin cancer **E**valuation (JOELLE) Study

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ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
ATC	Anatomical Therapeutic Chemical classification
CBCL	cutaneous B-cell lymphomas
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPR	Civil Personal Registration (number)
CPRD	Clinical Practice Research Datalink (formerly GPRD, General Practice Research Database)
CTCL	cutaneous T-cell lymphoma
EC	European Commission
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
FDA	US Food and Drug Administration
FUM	Follow-up Measure (regulatory term)
GP	general practitioners
HES	Hospital Episode Statistics
HIV	human immunodeficiency virus
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ICD-9	International Classification of Diseases, 9th Revision
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-O-3	International Classification of Diseases for Oncology, Third Edition
ID	identification
MM	malignant melanoma
NHS	National Health Service
NK	natural killer (a type of white blood cell)
NMSC	nonmelanoma skin cancer
NORDCAN	Association of the Nordic Cancer Registries
NOS	not otherwise specified
OPED	Odense University Pharmacoepidemiological Database
OR	odds ratio
PALGA	The Dutch National Pathology Registry
PHARMO	PHARMO Institute for Drug Outcomes Research in the Netherlands
RR	relative risk

SAP	statistical analysis plan
SNOMED	Systematized Nomenclature of Medicine
STROBE	Strengthening the reporting of observational studies in epidemiology (statement)
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
UK	United Kingdom
WHO	World Health Organization

KEY DEFINITIONS

Study period

Phase I. From the date of first availability of topical tacrolimus and topical pimecrolimus in each study population through December 31, 2011.

Phase II. The study will be extended to include the follow-up of each study population from January 1, 2012, onward to a date to be determined according to the use of the study medications and statistical power estimates based on the results from phase I.

Eligibility criteria

To be eligible for inclusion in the study population, individuals should have at least 12 months of continuous enrollment in the study databases, except for children 0 to 12 months of age.

Eligibility date

The day after 12 months of continuous enrollment in a study database. For children 0 to 12 months of age, the eligibility date is the date of enrollment in the database. The eligibility date can occur before or during the study period.

Study cohorts

Tacrolimus-exposed cohort: patients receiving a first prescription for topical tacrolimus during the study period after the eligibility date. These are new users of topical tacrolimus defined as not having any prescription for either topical tacrolimus or topical pimecrolimus at any time before cohort entry.

Pimecrolimus-exposed cohort: patients receiving a first prescription for topical pimecrolimus during the study period after the eligibility date. These are new users of topical pimecrolimus defined as not having any prescription for either topical tacrolimus or topical pimecrolimus at any time before cohort entry.

Moderate- to high-potency corticosteroids cohorts: patients with atopic dermatitis receiving a prescription for moderate- to high-potency topical corticosteroids during the study period after the eligibility date. Patients can be past, prevalent, or new users of moderate- to high-potency corticosteroids. Users of corticosteroids will be frequency matched to users of tacrolimus and pimecrolimus according to categories of percentiles of propensity scores estimated for each exposed cohort

Not-treated cohort: eligible patients not receiving treatment with topical tacrolimus, topical pimecrolimus, or moderate- to high-potency topical corticosteroids

Start date

Date of cohort entry and start of follow-up. The start date is defined for each study cohort as follows:

- Tacrolimus cohort: date of first prescription for topical tacrolimus
- Pimecrolimus cohort: date of first prescription for topical pimecrolimus
- Corticosteroids cohorts: date of first prescription for moderate- to high-potency topical corticosteroids received during the study period after the eligibility date.
- Not-treated cohort: start date of the matching member of the corticosteroids cohort.

End date

Date of end of follow-up. Follow-up after start date will continue until the earliest occurrence of one of the following events: first occurrence of any one of the study endpoints, death, disenrollment from the study databases, or end of the study period.

ABSTRACT

The Protopic JOint European Longitudinal Lymphoma and skin cancer Evaluation (JOELLE) Study is a European, multinational cohort study to assess the risk of skin cancer and lymphoma in the pediatric and adult population treated with topical tacrolimus, pimecrolimus, and corticosteroids and in the not-treated population. The study is part of the Protopic Risk Management Plan RMP052 (formerly, Committee for Medicinal Products for Human Use [CHMP] follow-up measure [FUM-039]) to the approval of the additional indication of maintenance therapy for tacrolimus ointment initiated in February 2009.

The primary objective of the study is to estimate the incidence rate ratios of skin cancer and lymphoma in the pediatric and adult populations for new users of topical tacrolimus and topical pimecrolimus compared with users of moderate- to high-potency topical corticosteroids diagnosed with atopic dermatitis. Secondary objectives of the study are (1) to estimate the incidence rate ratios of skin cancer and lymphoma in users of moderate- to high-potency topical corticosteroids diagnosed with atopic dermatitis compared with persons not treated with topical tacrolimus, pimecrolimus, or corticosteroids and (2) to describe the patterns of use and the characteristics of users of topical tacrolimus, pimecrolimus, and corticosteroids.

The study design is a multinational collaborative retrospective cohort study evaluating populations covered in four automated health databases: the PHARMO Record Linkage System in the Netherlands; Clinical Practice Research Datalink (CPRD), formerly the General Practice Research Database (GPRD) in the UK; Southern Denmark University in Denmark; and Karolinska Institutet in Sweden. The study will be coordinated by RTI Health Solutions in Spain and the United States.

Exposure propensity scores will be used to frequency match users of tacrolimus and users of pimecrolimus with users of moderate- to high-potency topical corticosteroids. The not-treated cohort will be individually matched to the corticosteroids cohort identified for comparison with users of tacrolimus.

The study endpoints are any skin malignancy, nonmelanoma skin cancer, malignant melanoma, any lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, and cutaneous T-cell lymphoma. Information on the study endpoints will be obtained from cancer registries, complemented with hospital and general practitioner data and review of medical records in one of the databases (CPRD).

The study cohorts will be followed from the start date for the first occurrence of any one of the study endpoints. A minimum lag time of 6 months will be assumed between the start of exposure and the occurrence of the study endpoints. Person-years of follow-up will be

classified according to ever use, single use, and switching/multiple use of tacrolimus and pimecrolimus and to cumulative dose and duration of exposure. The main exposure of interest will be the cumulative dose of topical tacrolimus and pimecrolimus.

The analysis will be conducted at two levels: a country-specific analysis conducted at each database research partner and an overall analysis conducted at the coordinating center. The approach is for each database research partner to create stratified tables with cross-classifications of subject and person-time counts by exposure category, endpoint, and deciles of exposure propensity scores. The coordinating center will estimate overall measures of effect through a stratified analysis of the data from the database research partners. Mantel-Haenszel methods will be used to summarize effects across strata. Crude and adjusted incidence rate ratios for each study endpoint and exposure category will be estimated comparing users of tacrolimus and users of pimecrolimus with users of corticosteroids. A secondary analysis will compare users of corticosteroids with not-treated subjects. Sensitivity analyses will be conducted to evaluate protopathic and surveillance bias. Separate analyses will be conducted for the pediatric and adult populations.

This study is a non-interventional Post-Authorization Safety Study according to *Module VIII of the Guideline on Good Pharmacovigilance Practice.* This study adheres to the *Guidelines for Good Pharmacoepidemiology Practices* and has been designed in line with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology*. The ENCePP Study Protocol Checklist has been completed. The study will be registered in the ENCePP registry before study implementation commences.

1 INTRODUCTION

This document describes the core protocol for conducting a European, multinational cohort study to assess the risk of skin cancer and lymphoma in pediatric and adult users of topical tacrolimus, pimecrolimus, and corticosteroids and in the not-treated population. The study will evaluate populations covered in four automated health databases, one each in Denmark, the Netherlands, Sweden, and the United Kingdom (UK).

1.1 Background

Topical tacrolimus ointment and pimecrolimus belong to the topical calcineurin inhibitor (TCI) class and have approved licenses for use in patients with atopic dermatitis; mild to moderate disease for pimecrolimus, and moderate to severe disease for tacrolimus.

In the European Union (EU), the use of tacrolimus ointment for the treatment of moderate to severe atopic dermatitis in children aged 2 years and older (Protopic® 0.03% ointment) and in adults (Protopic® 0.1% and 0.03% ointment) not responding to or intolerant of conventional therapies such as topical corticosteroids was approved by the European Medicines Agency (EMA) in February 2002 through the centralized procedure (EU/1/02/201). Subsequently, in February 2009, the EMA granted Astellas, the Marketing Authorisation Holder (MAH), an extension to the license of tacrolimus ointment to add the indication of "maintenance treatment" of atopic dermatitis. Pimecrolimus (Elidel® cream 10 mg/g) was approved by the EMA in October 2002 for the treatment of mild to moderate atopic dermatitis in patients aged 2 years and older through the mutual recognition procedure. An overview of indications and regulatory status of tacrolimus ointment and pimecrolimus cream in selected countries in the EU is summarized in Table 1.

As part of the Review Procedure initiated by the European Commission (EC) in April 2005 and concluded in June 2006 following Article 20 of EC Regulation No 726/20041, the Committee for Medicinal Products for Human Use (CHMP) considered that there was a positive benefit-risk relationship for tacrolimus ointment, 0.03% and 0.1% for the treatment of atopic dermatitis; however, CHMP recommended that Astellas further investigate whether atopic dermatitis patients are at an increased risk of developing skin malignancies following exposure to tacrolimus ointment—FUM (Follow-up Measure)-030, March 2006. In response to this request, Astellas conducted drug utilization studies in the Record Linkage System of the PHARMO Institute for Drug Outcomes Research in the Netherlands (PHARMO) and in the

[1] Corresponding to Art. 18 of the Council Regulation (EEC) No 2309/93 of July 22, 1993, for procedures before November 20, 2005.

General Practice Research Database (GPRD) in the UK—FUM-030, March 2006. The aim was to characterize how Protopic was used in Europe, to assess the level of exposure to tacrolimus ointment in the EU, and to explore the incidence of skin cancer in the users of this drug—prior to developing a proposal for a protocol for the requested epidemiological study. Subsequently and as part of the approval in Europe of the Protopic maintenance indication, CHMP mandated another FUM (FUM-039, February 2009), follow-up of children on maintenance treatment. In reply, RTI Health Solutions (RTI-HS) and a group of experts in the Nordic countries explored the feasibility of using the Nordic prescription and cancer registries for the follow-up of children receiving maintenance treatment (Perez-Gutthann et al., 2010). Based on the conclusions in the Rapporteur Assessment Report dated August 10, 2010, endorsed by the CHMP, from the review of the documentation submitted by Astellas in response to FUM-039, Astellas plans to address the issues highlighted in the report by performing this multinational observational study in several European countries to better explore the risk of malignancies in the context of therapeutic use. Due to the low number of children exposed to topical tacrolimus and the low rates of the study endpoints, the study will also include the adult population. In 2013, FUM-039 was integrated into the Protopic Risk Management Plan as RMP052.

Table 1. Approved Indications and Regulatory Status of Topical Calcineurin Inhibitors in Study Countries

Specifications of Indication	Tacrolimus Ointment		Pimecrolimus Cream
	First Indication	Second Indication	
Indication	Moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies and in children (aged 2 years and older) who failed to respond adequately to conventional therapies such as topical corticosteroids.	Moderate to severe atopic dermatitis. Maintenance treatment for flare prevention or prolongation of flare-free intervals in patients experiencing a high frequency of disease exacerbations (i.e., occurring ≥ 4 times per year) who have had an initial response to a maximum of 6 weeks of twice-daily treatment with tacrolimus ointment (lesions cleared, almost cleared, or were mildly affected).	Mild or moderate atopic dermatitis.

Specifications of Indication	Tacrolimus Ointment		Pimecrolimus Cream
	First Indication	Second Indication	
Target population	Adults not adequately responsive to or intolerant to conventional therapies such as topical corticosteroids (TCS) and children aged ≥ 2 to < 16 years who failed to respond adequately to conventional therapies such as TCS.	Adults and children aged 2 years and older who had an initial response to a maximum of 6 weeks of twice-daily treatment with tacrolimus ointment (lesions cleared, almost cleared, or were mildly affected).	Patients aged 2 years and older when treatment with TCS is either inadvisable or not possible: ▪ Intolerance to TCSs ▪ Lack of effect of TCS ▪ Use on the face and neck where prolonged intermittent treatment with TCS may be inappropriate.
Dosage	Adults: 0.1% or 0.03% Children: 0.03%	Adults: 0.1% or 0.03% Children: 0.03%	10 mg/g (i.e., 1%)
Regulatory Approvals			
EMA	EC decision Feb 28, 2002	EC decision Feb 26, 2009	Mutual Recognition Procedure Approval Oct 3, 2002
Netherlands			
Approved date	Feb 28, 2002	Feb 26, 2009	April 28, 2003[a]
Denmark			
Approved date	Feb 28, 2002	Feb 26, 2009	March 15, 2002[b]
Sweden			
Approved date	Feb 28, 2002	Feb 26, 2009	April 17, 2003[c]
UK			
Approved date	Feb 28, 2002	Feb 26, 2009	October 3, 2002

EC = European Commission; EMA = European Medicines Agency; TCS = topical corticosteroids; UK = United Kingdom.

[a] Source: Dutch College for the Evaluation of Medicinal Products/Medical Evaluation Board. Available at: http://www.cbg-meb.nl/CBG/en/. Accessed Nov 30, 2011.

[b] Source: Danish Medicines Agency. Available at: http://laegemiddelstyrelsen.dk/en. Accessed Nov 30, 2011.

[c] Source: Swedish Medical Products Agency. Available at: http://www.lakemedelsverket.se/english/. Accessed Nov 30, 2011.

1.2 Rationale

The long-term safety profile of tacrolimus ointment and pimecrolimus cream requires further evaluation. Concerns about a potential increased risk of cancer, particularly for cancers such as skin cancers and lymphoma, from use of tacrolimus and pimecrolimus result primarily from the increased cancer risk observed with the systemic use of tacrolimus in organ transplantation and from data from animal studies and case reports in a small number of patients (US Food and Drug Administration [FDA], 2005a; FDA, 2005b). There is a particular concern about these risks in the pediatric population.

Published data from studies that have evaluated the relative risk (RR) of lymphomas or cutaneous lymphomas associated with use of TCIs are sparse, and studies have often been limited by the small number of cases, short follow-up, low exposure levels to TCIs, and the complexity required to take into account a large number of potential confounding factors when using databases. Two studies that evaluated the risk of lymphoma following TCI use reported opposite results: Arellano and colleagues (2007), who were unable to validate outcomes among individuals with claims related to atopic dermatitis, reported the odds ratio (OR) to be less than 1.0, and Schneeweiss et al. (2009), who used data from a large health insurance claims database in which individuals with untreated dermatitis served as the reference group and who validated outcome by chart review, reported the RR to be greater than 1.0. Both studies had wide confidence intervals around RRs of all lymphoma, a finding that limits the interpretation of the results about TCI use and risk of all lymphoma. The study by Schneeweiss et al. (2009) compared users of pimecrolimus with users of topical corticosteroids (TCS) and reported a RR for all lymphoma of 1.2 (95% confidence interval [CI], 0.7-1.8). Schneeweiss et al. (2009) also assessed the risk of cutaneous lymphomas and reported RRs of 1.5 (95% CI, 0.4–6.2) for pimecrolimus users and 2.5 (95% CI, 0.5–12.6) for tacrolimus users versus patients with untreated atopic dermatitis. Another study that used automated electronic medical records to ascertain T-cell lymphomas, 80% of which were cutaneous, in individuals with atopic dermatitis or eczema identified RRs of 3.1 (95% CI, 1.4–6.9) among tacrolimus users and 1.9 (95% CI, 0.7–4.9) among pimecrolimus users compared with nonusers (Hui et al., 2009). In this study, 4 of 16 identified T-cell lymphoma cases had suspected cutaneous T-cell lymphoma (CTCL) at the time of TCI initiation, an observation consistent with the hypothesis that the association between TCI use and lymphoma may be related at least partially to TCI treatment of symptoms from yet-to-be-diagnosed CTCL (known as protopathic bias).

In the Schneeweiss et al. (2009) study, the RR of Hodgkin lymphoma among tacrolimus users compared with patients with untreated dermatitis was 5.3 (95% CI, 0.5–59); among pimecrolimus users, the RR was 3.5 (95% CI, 0.4-31.0). The relative risk of non-Hodgkin lymphoma among tacrolimus users compared with patients with untreated dermatitis was 1.4 (95% CI, 0.5–4.0); among pimecrolimus users, the RR was 1.6 (95% CI, 0.8-3.5). The

Hui et al. (2009) study reported the RR of B-cell lymphoma in patients with atopic dermatitis or eczema among tacrolimus users as 1.1 (95% CI, 0.6–2.1) and among pimecrolimus users as 1.6 (95% CI,1.0–2.6), compared with nonusers.

There is little quantitative evidence that TCI use is associated with skin malignancies. One clinic-based case-control study reported an OR for nonmelanoma skin cancer (NMSC) and use of TCIs as 0.5 (95% CI, 0.4–0.7) (Margolis et al., 2007). In another study in patients with atopic dermatitis or eczema, the RR of melanoma with use of tacrolimus was 0.3 (95% CI 0.1–0.8) and with use of pimecrolimus was 0.7 (95% CI, 0.4– 1.3) (Hui et al., 2009).

A number of concerns have been expressed about the methods applied in these nonexperimental studies (Tennis et al., 2011). Claims-based cohort studies so far have not included long TCI exposure or follow-up times, and even in large data sources, the total number of cases of specific neoplasias is small. Cases and controls from dermatology clinic–based case-control studies are likely to have differential medical history details because controls are likely to have been at the clinic for longer periods of time than patients reaching the clinic due to a skin malignancy. This may tend to underestimate the exposures among cases and correspondingly underestimate the RR associated with dermatologic treatments. It has also been suggested that increased screening of patients under regular treatment by a dermatologist, e.g., individuals with atopic dermatitis, is likely to result in early and increased ascertainment of melanoma and NMSC and artificially increase the RR of cutaneous neoplasias among these patients. On the other hand, dermatologists may be less likely to prescribe treatments potentially associated with cutaneous cancers to patients at high risk of these cancers.

There is some evidence to suggest that atopic dermatitis or eczema is associated with increased risk of lymphomas, with RR ranging from 0.7 to 1.8 (Arellano et al., 2009; Arellano et al., 2007; Hagströmer et al., 2005). Severity of atopic dermatitis has also been associated with an increased risk of lymphomas, with RRs of 2.4 and 3.7 reported for severe atopic dermatitis (Arellano et al., 2007; Arellano et al., 2009). Thus, comparisons of treatments most likely to be used in patients with severe or recalcitrant disease to the general population or to patients with mild disease may be confounded by indication for the treatments. As mentioned above, undiagnosed CTCL or even noncutaneous lymphomas may in early stages produce cutaneous symptoms that may be treated with treatments for atopic dermatitis (Hui et al., 2009). This phenomenon and confounding by indication could explain the very high RRs observed for lymphomas with skin involvement and TCS treatment found by Arellano et al. (2009). In this study, RRs of lymphomas with skin involvement for TCS use compared with nonuse among individuals with atopic dermatitis or using topical immunosuppressants, stratified by duration of TCS use, were as follows:

- < 30 days use, 3.8 (95% CI, 2.2–6.7)
- 1–6 months use, 14.8 (95% CI, 8.3–26.6)
- 6 months–1 year use, 25.8 (95% CI, 9.5–69.7)
- 1–2 years use, 12.9 (95% CI, 4.0–41.9)
- > 2 years use, 82.9 (95% CI, 9.3–740.2).

These potential sources of bias, as well as the challenges of obtaining sufficient study sizes, have resulted in the need for further research on this topic.

This protocol describes the design and methodology of a multicountry epidemiologic study that will evaluate the risk of skin malignancies and lymphomas in pediatric (focus of the RMP052) and adult patients exposed to TCIs in Europe.

1.3 Research Objectives

The primary objective of the study is to estimate the incidence rate ratios of skin cancer and lymphoma in the pediatric (aged < 18 years) and adult (aged ≥ 18 years) populations for the following groups:

- New users of topical tacrolimus compared with users of moderate- to high-potency topical corticosteroids diagnosed with atopic dermatitis
- New users of topical pimecrolimus compared with users of moderate- to high-potency topical corticosteroids diagnosed with atopic dermatitis

Secondary objectives of the study are as follows:

- To estimate the incidence rate ratios of skin cancer and lymphoma in users of moderate- to high-potency topical corticosteroids diagnosed with atopic dermatitis compared with persons not treated with topical tacrolimus, pimecrolimus, or moderate- to high-potency corticosteroids.
- To describe, over time and across countries, the patterns of use and the characteristics of users of topical tacrolimus, users of topical pimecrolimus, and users of moderate- to high-potency topical corticosteroids with atopic dermatitis.

In a sensitivity analysis, incidence rate ratios of skin cancer and lymphoma will be estimated for children aged ≥ 2 to < 16 years, the pediatric age range specified in the labeling of topical tacrolimus.

When estimating incidence rates we will assume a minimum lag time of 6 months between the start of treatment and the occurrence of the study endpoints. This implies that person-time for the interval of the first 6 months since start of treatment will be excluded, along

with any events that occur within this time period. This lag time encompasses a period of drug utilization and dose accumulation, a period of induction time (from causal action of exposure to disease initiation), and a latency period (from disease initiation to disease detection). The induction time for the occurrence of skin cancer and lymphomas associated with the use of tacrolimus and pimecrolimus is unknown. Therefore, we will conduct sensitivity analyses to estimate incidence rates within the first 6 months of treatment and for several lag times longer than the initial 6 months. The lag time analysis will also be used to explore potential protopathic bias if early symptoms of skin cancer or lymphoma are erroneously treated as atopic dermatitis and therefore the reason for starting treatment.

The goal of the first secondary objective is to obtain background rates among persons not treated with the study medications and to put in perspective potential differences between the not-treated population, the atopic dermatitis cohort treated with moderate- to high-potency corticosteroids, and the tacrolimus cohort.

2 STUDY STRUCTURE

The study will be conducted as a collaborative study involving five research centers: one coordinating center, RTI Health Solutions in Spain and the United States, and four database research partners—the PHARMO Institute for Drug Outcomes Research in the Netherlands, the Clinical Practice Research Datalink (CPRD) in the UK, Southern Denmark University in Denmark, and Karolinska Institutet in Sweden. Each participating database research partner will adapt this core protocol to the specific needs of the local database.

The coordinating center will have the following primary roles and responsibilities:

- Serve as the coordinating center for the study
- Lead preparation of the final version of this core study protocol with input from all research partners
- Guide database-specific adaptation of the protocol, with a focus on consistency with the core protocol of variable definitions and other methodological aspects across adapted protocols
- Provide scientific support to the study implementation phase, including case validation efforts
- Support integration of study results by analyzing stratified data from each database research partner to estimate overall measures of effect
- Facilitate research network communications, study reporting, and dissemination of study results

The database research partners will have the following primary roles and responsibilities:

- Provide input into the final version of this core protocol
- Develop the protocol adaptation to each database
- Implement the study in the respective database
- Liaise with the coordinating center during study implementation as needed
- Contribute to the preparation of study reports and dissemination of results

Astellas will have the following primary roles and responsibilities:

- Serve as the study sponsor
- Astellas staff will provide input into the final version of this core protocol
- Astellas staff will review and provide input during the study implementation phase

The study will be conducted in two phases:

- Phase I. The study will include the period from the date of first availability of topical tacrolimus and topical pimecrolimus in each study population through December 31, 2011.
- Phase II. The study will be extended to include the follow-up of each study population from January 1, 2012, onward to a date to be determined (depending on data availability in each database) according to the use of the study medications and statistical power estimates based on the results from phase I.

3 RESEARCH METHODS

This is a multinational cohort study of new users of topical tacrolimus, new users of topical pimecrolimus, users of topical corticosteroids diagnosed with atopic dermatitis, and nonusers of these medications. The study will be conducted with data from automated databases; cancer registries; and, for a subgroup, medical records. Stratification by exposure propensity scores will be used to control for confounding, including confounding by indication. An exposure propensity score estimates the probability that a given patient will receive a treatment conditional on measured covariates and can serve as a summary confounder variable. Because exposure propensity scores focus on the indication for use and nonuse of medications, they can be useful to control for confounding by indication. Propensity scores can perform better than conventional regression methods when the number of events relative to the number of potential confounders is small because rather than having to model the events with many variables, one can instead model the exposure, which may have ample data to accommodate a rich model (Cepeda et al., 2003). This advantage may be important in this study, given the low number of events for each study

endpoint expected in the pediatric population. Data aggregated by strata of propensity scores estimated in each database will be used to estimate overall effects across the four databases.

In general, estimation of causal effects should incorporate a specific time interval between the start of exposure and the onset of disease. In the case of exposure to drugs, this requires the use of a new-user design, in which only initiators of the medication of interest are followed (inception cohort). A new-user design also prevents potential survival bias secondary to the inclusion of prevalent users who are "survivors" of earlier periods of treatment. In addition, a new-users design allows a more accurate estimation of propensity scores and control of confounding by indication, as covariates are measured at the initiation of therapy and are not affected by the exposure itself.

3.1 Data Sources

The study will be conducted following a common core protocol in populations covered in four population-based health databases and cancer registries in Europe that are available for research and that provide access to health-related data (including prescription drug data). A summary of the characteristics and availability of data on study variables is presented in Appendix A. Data will be obtained from the following databases:

- The Clinical Practice Research Datalink (CPRD) in the UK
- The PHARMO Record Linkage System in the Netherlands
- The Danish health databases
- The Swedish health databases

The CPRD contains data recorded by general practitioners (GPs), who play a key role in the UK health care system as they are responsible for primary health care and referrals to specialists. The CPRD currently has research-quality records for over 5 million active patients known to represent over 8% of the general population in the UK; it contains diagnostic and prescribing information recorded by the GPs as part of their routine clinical practice. Currently, over half of the CPRD has been linked to other UK health care datasets (e.g., National Cancer Registration Dataset, National Hospital Episodes Statistics, national mortality data), via the patient's National Health Service (NHS) number, sex, date of birth, and postal code (Gelfand et al., 2005; CPRD Web site, http://www.cprd.com/intro.asp).

The PHARMO Institute in the Netherlands (http://www.pharmo.com/) has access to the PHARMO Record Linkage System, a patient-centric data network that includes high-quality and complete information on (amongst others) patient demographics, drug dispensings, hospital morbidity, and pathology for more than 3.2 million community-dwelling inhabitants

of 65 geodemographic areas in the Netherlands. For a subset, clinical laboratory and GP information is also available. Some of the databases (e.g., pathology database—PALGA) are partnership databases; permissions on a per-project basis are required to access data. Access to medical charts and other clinical data is available within the prerequisites of the Dutch privacy regulations.

In Denmark and Sweden, each national health care system provides universal coverage to all residents (5.5 million inhabitants in Denmark and 9.2 million inhabitants in Sweden). Health care coverage includes visits to GPs, specialists, hospital admissions, and hospital outpatient visits; drug costs are either partially or completely covered. A centralized civil registration system has been in place in each country for many years, allowing for personal identification of each person in the entire population and for the possibility of linkage to all national registers containing civil registration numbers, e.g., patient register, cancer register, prescription databases, register of causes of death, and population registers (Furu et al., 2010). Visits to GPs and specialists outside the hospitals are not included in the registers. Data collected in these registers can be made available for research purposes under the principles for protection and release of sensitive data (Danish National Board of Health, 2011; Swedish National Board of Health and Welfare, 2009).

3.2 Population

3.2.1 Study Population

All individuals of any age registered in the study databases from the date topical tacrolimus became available in each country through December 31, 2011.

3.2.2 Eligibility Criteria

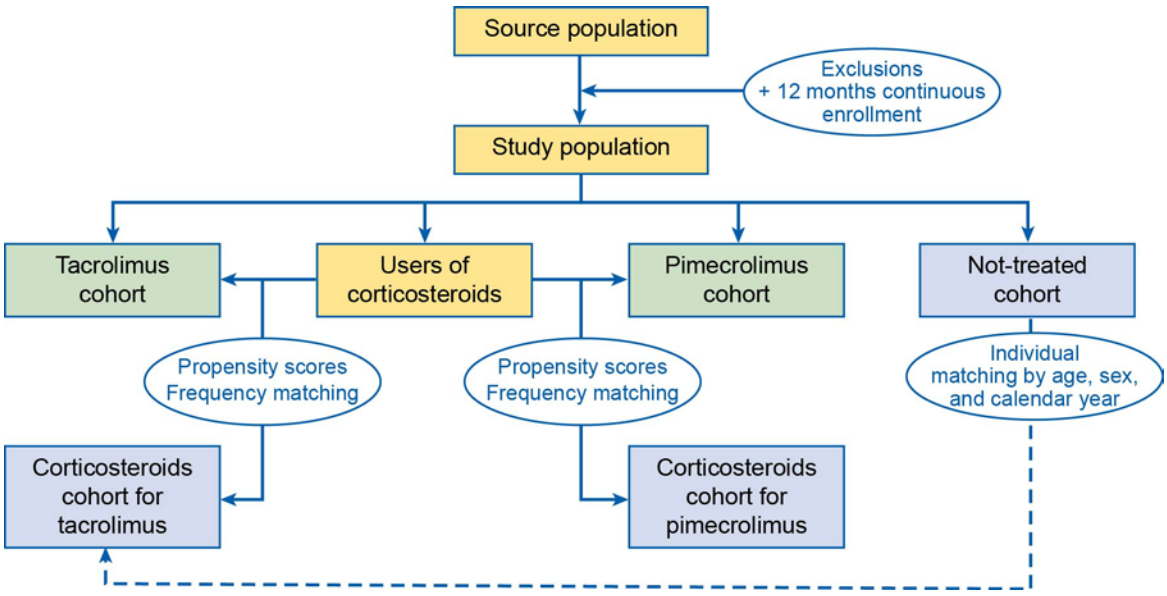
To be eligible for inclusion in the study population, individuals should have at least 12 months of continuous enrollment in the study databases, except for children 0 to 12 months of age. Thus, a person becomes eligible for study inclusion the day after this 12-month enrollment period has been completed (eligibility date) or, for children 0 to 12 months of age, from the date of enrollment in the database. The eligibility date can occur before or during the study period.

Because the study is focused on incident cases of skin cancer and lymphoma, patients with a history of any of these conditions any time before the start date (date of cohort entry) will be excluded from the study population.

3.2.3 Study Cohorts

The study will include four primary cohorts identified from all eligible individuals in the study population who are prescribed topical tacrolimus, topical pimecrolimus, or moderate- to high-potency topical corticosteroids during the study period, and one secondary cohort of not-treated patients (Figure 1).

Figure 1. Selection of Study Cohorts



The primary study cohorts are defined as follows:

- *Tacrolimus-exposed cohort* **(tacrolimus cohort)**: patients receiving a first prescription for topical tacrolimus during the study period after the eligibility date
- *Pimecrolimus-exposed cohort* **(pimecrolimus cohort)**: patients receiving a first prescription for topical pimecrolimus during the study period after the eligibility date
- *Two cohorts of users of moderate- to high-potency topical corticosteroids with atopic dermatitis* **(corticosteroids cohorts).** Two comparative cohorts, one for the tacrolimus cohort and one for the pimecrolimus cohort, will be identified from all eligible individuals from the study population who have atopic dermatitis and receive a prescription for moderate- to high-potency corticosteroids during the study period after the eligibility date. To identify the two corticosteroids cohorts, propensity scores will be estimated separately for the tacrolimus cohort and the pimecrolimus cohort. Users of corticosteroids will be frequency matched to users of tacrolimus and

pimecrolimus according to categories of percentiles of propensity scores estimated for each exposed cohort.

The study will include a secondary cohort to address the secondary study objective of comparing users of moderate- to high-potency corticosteroids versus the not-treated population, attempting to put in population perspective the magnitude of any changes in risk observed between the study cohorts:

- *Not-treated cohort*. A comparative cohort of patients not receiving treatment with any of the study medications will be identified among all eligible individuals from the study population. The not-treated cohort will be matched to the corticosteroids cohort that was identified as the comparative cohort for users of tacrolimus. Individual matching will be conducted on year of birth, sex, primary care general practice/region, and calendar year of start date.

Each of these study cohorts is described in more detail below.

3.2.3.1 Tacrolimus Cohort and Pimecrolimus Cohort

Patients will be included in the tacrolimus cohort or the pimecrolimus cohort according to the first medication prescribed during the study period. If the first prescription a patient receives is for topical tacrolimus, that patient will be included in the tacrolimus cohort. The date of that first prescription is defined as the start date, the date of cohort entry. Once a patient enters one of the exposed cohorts (tacrolimus cohort or pimecrolimus cohort) that patient remains in that cohort until the end of follow-up. Therefore, patients entering the tacrolimus cohort or the pimecrolimus cohort cannot contribute person-time to the other study cohorts after becoming exposed (see Section 3.3.4, Exposure Assessment, for further details on the classification of person-time).

The indication for topical tacrolimus and topical pimecrolimus is restricted to the treatment of atopic dermatitis. However, these medications might be used to treat other skin conditions such as psoriasis or other inflammatory skin diseases. For the purpose of this study, we assume that all patients included in the tacrolimus cohort and the pimecrolimus cohort suffer from atopic dermatitis whether or not a diagnosis of atopic dermatitis is recorded in the study databases. To characterize users of tacrolimus and pimecrolimus, we will ascertain at the start date diagnosis of atopic dermatitis, diagnosis of other skin conditions, and prior treatments (e.g., topical corticosteroids).

3.2.3.2 Corticosteroids Cohorts

Topical corticosteroids have multiple indications of use. Therefore, the two corticosteroids cohorts will be identified in each database from all eligible individuals from the study population who have atopic dermatitis and receive a prescription for moderate- to high-

potency corticosteroids during the study. Individuals meeting these criteria will be used to estimate propensity scores separately for the tacrolimus cohort and the pimecrolimus cohort. A person can be included in both corticosteroids cohorts, the comparative cohort for tacrolimus and the comparative cohort for pimecrolimus. The propensity score represents the predicted probability of receiving each corresponding treatment instead of receiving moderate- to high-potency topical corticosteroids. The percentiles of propensity scores estimated for each exposed cohort will be classified in 20 strata (twentiles). Users of corticosteroids will be frequency matched to users of tacrolimus and pimecrolimus according to the strata of propensity scores of each exposed cohort. A matching ratio (corticosteroids to tacrolimus or pimecrolimus) up to 4:1, depending on available matches, will be used across strata. The strata of propensity scores will be used to conduct an overall stratified analysis combining the data from the study databases. Separate propensity scores and strata of propensity scores will be calculated for the pediatric and adult populations.

Patients in the two corticosteroids cohorts should meet the diagnostic criteria for atopic dermatitis at the time of receiving the first prescription for moderate- to high-potency corticosteroids (see Section 3.3.1 for atopic dermatitis diagnostic criteria). The date of the first prescription during the study period for moderate- to high-potency corticosteroids is defined as the start date. Patients in the corticosteroids cohorts can be prevalent or new users of moderate- to high-potency corticosteroids. Patients in the corticosteroids cohorts can contribute person-time to the tacrolimus cohort or the pimecrolimus cohort during follow-up should they receive a prescription for tacrolimus or pimecrolimus. In that situation, patients will be censored from the corticosteroids cohort at the date of receiving a prescription for tacrolimus or pimecrolimus.

3.2.3.3 Not-Treated Cohort

The not-treated cohort will be identified from all eligible subjects from the study population and will be used as the reference in the comparison with the corticosteroids cohort identified for users of tacrolimus (Figure 1). Individuals in the not-treated cohort are not required to have a diagnosis of atopic dermatitis. The not-treated cohort will be individually matched to the corticosteroids cohort on year of birth, sex, primary care general practice/region, and calendar year of start date, with a 1:1 matching ratio. The selected match in the not-treated cohort must be eligible on the start date of the matched corticosteroids cohort member; the not-treated cohort member will be assigned the start date of the matched corticosteroids cohort member.

Patients in the not-treated cohort can contribute person-time to any of the other four study cohorts during follow-up and will be censored from the not-treated cohort at the date of receiving a prescription for tacrolimus, pimecrolimus, or a moderate- to high-potency corticosteroid.

We will evaluate the feasibility of conducting a sensitivity analysis to include a not-treated cohort with atopic dermatitis. The identification of individuals with atopic dermatitis not treated with the study medications is difficult because most of these patients would have been treated with topical medications at some point during the natural course of their disease. Because we are studying a long-term effect (malignancy), we do not know the impact that early treatments could have on the study endpoint. In addition, early treatments might not be captured in the study databases. For example, the prescription register in Sweden is quite recent and includes medications dispensed only since 2005. Another limitation is that untreated patients might include those who are at the initial stage of the disease when a diagnosis of atopic dermatitis might not yet have been confirmed. Some of these patients might be diagnosed with atopic dermatitis at a later time, but others might be diagnosed with other skin disease or with an acute or transitory skin condition. Therefore, a potential untreated cohort might include patients with heterogeneous skin conditions.

3.2.4 Follow-up

Follow-up after entry into each cohort (start date) will continue until the earliest of occurrence of one of the following: first occurrence of any one of the study endpoints, death, disenrollment from the study databases, or end of the study period.

In a sensitivity analysis, patients will be followed for the occurrence of each specific endpoint regardless of a prior occurrence of any of the other study endpoints during the study period.

3.3 Definitions

3.3.1 Identification of Atopic Dermatitis

A diagnosis of atopic dermatitis is required for members of the corticosteroids cohorts. The methods to ascertain atopic dermatitis will vary between databases according to the information available in each one.

In the CPRD, patients with atopic dermatitis will be identified using Read codes, and the diagnosis of atopic dermatitis will be validated in a random sample of patients by reviewing free-text comments and the computerized medical history. (Read codes are the standard clinical terminology system used in general practice in the United Kingdom.)

In the databases of PHARMO, Denmark, and Sweden, only hospital inpatient and/or outpatient diagnoses are available for the full cohorts of users of corticosteroids. However, a

subset of the data in PHARMO can be linked to an additional database, the PHARMO-GP, which includes GP diagnoses and indication of treatment, in addition to prescriptions. These data will be used to determine the atopic dermatitis status (yes/no) of the subset of members of the corticosteroids cohort who are also included in the PHARMO-GP database. Ascertainment of atopic dermatitis status will be based on GP diagnosis codes. Data from this subset will be used to construct an algorithm to predict the atopic dermatitis status of the rest of patients in the corticosteroids cohort (those not included in the PHARMO-GP database). The algorithm will be constructed by selecting a set of covariates available in the corticosteroids cohort (hospital inpatient and/or outpatient diagnoses and prescriptions) from the subset of patients for whom the atopic dermatitis status was determined. We will fit a logistic regression model on these patients to predict the adjudicated atopic dermatitis status. The parameter estimates from this model will be applied to the covariate data of the members of the corticosteroids cohort not included in the PHARMO-GP. The cut point used for the prediction algorithm will be based on a balance of the sensitivity and specificity of the resulting algorithm. Separate prediction algorithms will be fit for children and adults.

The prediction algorithm generated in PHARMO will be applied to the data of Sweden and Denmark to determine the atopic dermatitis status of users of corticosteroids at the start date.

In Sweden, in addition to the prediction algorithm, a clinical algorithm will be used to identify atopic dermatitis in children. According to clinical empirical information, children with atopic dermatitis in Sweden can be identified through prescriptions of topical calcineurin inhibitors or topical corticosteroids in the absence of prescriptions for salicylic acid or other antipsoriatics for topical use. The results from the two algorithms will be compared, and discrepant cases will be reviewed manually.

3.3.2 Study Medications

The study medications of interest are topical tacrolimus, topical pimecrolimus, and topical corticosteroids. The Anatomical Therapeutic Chemical (ATC) classification for topical tacrolimus and topical pimecrolimus is as follows:

- Tacrolimus (D11AH01); available in two concentrations: 0.03% and 0.1%
- Pimecrolimus (D11AH02); available in one concentration: 1%

Topical corticosteroids will be classified according to their potency. The ATC classification for topical corticosteroids is as follows:

- Topical corticosteroids, plain
  - Weak (D07AA)

  - Moderately potent (D07AB)
  - Potent (D07AC)
  - Very potent (D07AD)
- Topical corticosteroids, combinations with other agents
  - Weak (D07BA, D07CA, D07XA)
  - Moderately potent (D07BB, D07CB, D07XB)
  - Potent (D07BC, D07CC, D07XC)
  - Very potent (D07BD, D07CD, D07XD)

Corticosteroids with an ATC classification of moderately potent, potent, or very potent are the corticosteroids of interest to this study and will be classified together as moderate- to high-potency corticosteroids.

Children with atopic dermatitis may be prescribed moderate- to high-potency corticosteroids infrequently, which may impact the inclusion of pediatric patients using these medications. Before identification of the study cohorts, descriptive analysis will be conducted to ascertain the number of users of each type of corticosteroid. If the number of children using moderate- to high-potency corticosteroids is insufficient, we will include children using topical corticosteroids of any potency, from weak to very potent corticosteroids. In that situation, further increased risk of potential residual confounding should be considered in the interpretation of results.

3.3.3 New Users

A new user of topical tacrolimus or topical pimecrolimus is defined as any user that has not been prescribed either topical tacrolimus or topical pimecrolimus at any time before the date of cohort entry. New users can be identified in the four study databases, although some degree of misclassification of prevalent users as new users is possible in the CPRD and Sweden. In the CPRD, prescriptions initiated by a specialist (e.g., dermatologist) may not be recorded in the database. Although subsequent prescriptions are managed by the GP, some patients might be prevalent users at the time of the first recorded prescription in the CPRD and be misclassified as new users.

In Sweden, the prescription register includes all drugs prescribed and dispensed since July 2005. This implies that users of topical tacrolimus or pimecrolimus entering the study cohort might be past users of these medications because topical tacrolimus was approved in 2002 and topical pimecrolimus in 2003. The eligibility criterion of 12 months of continuous enrollment will result in the exclusion of patients receiving a prescription for the study

medications during that period. The validity of using that time period of 12 months for the eligibility criteria will be evaluated using data from Denmark, where the prescription registry includes information since 1995. In case of important misclassification (cut-off point to be determined), an algorithm based on data from Denmark will be developed to identify new users in Sweden.

3.3.4 Exposure Assessment

To assess the effect of exposure to topical tacrolimus and topical pimecrolimus, we assume that exposure to either of the two medications results in a lifetime change in risk for the effects of that specific medication. That is, if a patient is exposed to topical tacrolimus (tacrolimus cohort), the status of exposure to tacrolimus is maintained throughout follow-up even after stopping therapy with tacrolimus. However, time at risk will start after the lag time of 6 months is completed.

Accordingly, person-time of follow-up of each cohort (topical tacrolimus and topical pimecrolimus) will be classified in several categories of exposure.

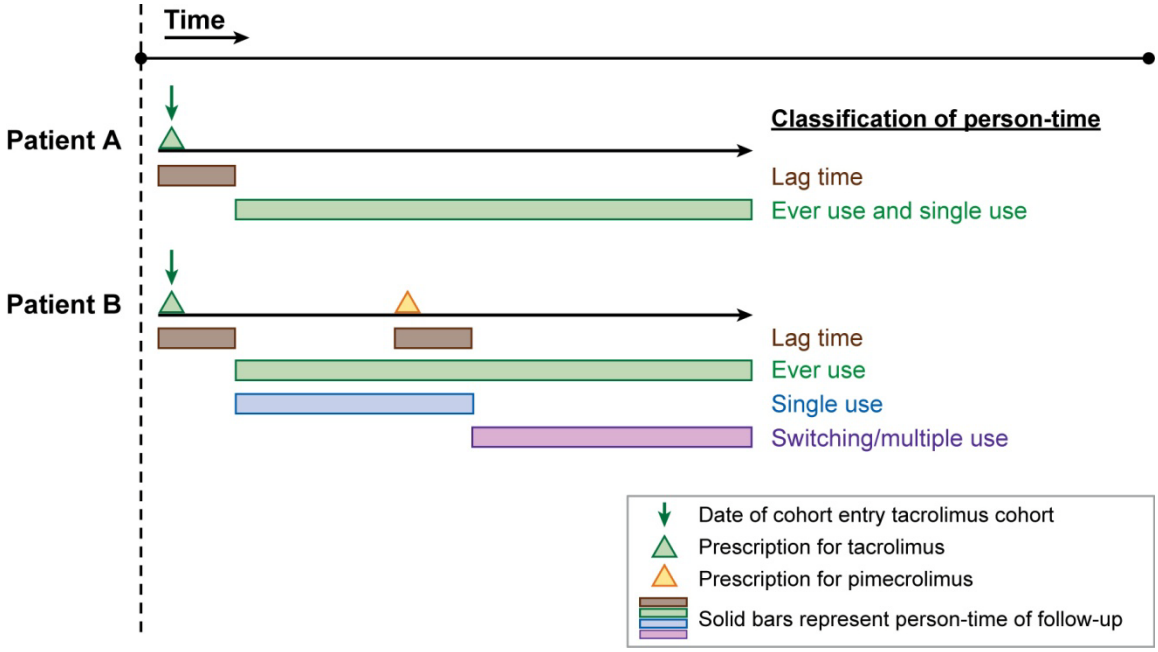
3.3.4.1 Exposure to Topical Tacrolimus

- *Ever use of topical tacrolimus:* person-time starting 6 months after the date of the first prescription for topical tacrolimus to the end of follow-up (Figure 2). In this exposure category, any potential switching to topical pimecrolimus is ignored (all person-time of follow-up is allocated to topical tacrolimus).

In addition, the overall person-time of follow-up of topical tacrolimus will be classified in two mutually exclusive categories (Figure 2):

- *Single use of topical tacrolimus (monotherapy with topical tacrolimus):* person-time starting 6 months after the date of the first prescription for topical tacrolimus to the earliest of the following dates: 6 months after the date of receiving a prescription for topical pimecrolimus or date of end of follow-up.
- *Switching (from topical tacrolimus to topical pimecrolimus)/multiple use:* person-time starting 6 months after the date of receiving a prescription for topical pimecrolimus to the end of follow-up.

Figure 2. Exposure Assessment: Example for Exposure to Topical Tacrolimus



3.3.4.2 Exposure to Topical Pimecrolimus

The same exposure rationale described for topical tacrolimus will be implemented for defining exposure to topical pimecrolimus, with pimecrolimus as the first exposure and tacrolimus as the second or additional exposure.

3.3.4.3 Exposure to Both Topical Tacrolimus and Topical Pimecrolimus

- *Combined multiple use:* in addition, person-time starting 6 months after switching between the two study drugs will be combined in a single overall category of switching/multiple use to assess the effect of the overall exposure to both drugs after switching.

3.3.4.4 Cumulative Exposure

Cumulative exposure will be used as the main measure of exposure in the analysis and will be calculated as the cumulative dose of tacrolimus or pimecrolimus a patient receives during follow-up. Dose will be accumulated daily according to the milligrams prescribed and the estimated average duration of prescriptions. The milligrams prescribed will be calculated according to the strength of the formulation and the package size. The average duration of prescriptions will be estimated separately for children and adults from preliminary descriptive analysis of the time between consecutive prescriptions.

Cumulative exposure will be categorized in levels of exposure (e.g., low, medium, and high) according to the distribution of cumulative exposure in the study databases. The number of levels of cumulative exposure and cut-off values will be decided after examining the distribution of cumulative exposure across databases. Patients will contribute time of follow-up to each level of cumulative exposure according to the cumulative dose received. For each level of cumulative exposure, we will assume an induction period of 6 months for the start of exposure effects. Thus, the time at risk will start 6 months after reaching the cut-off value of each cumulative exposure category. Cumulative exposure will be assessed for tacrolimus and for pimecrolimus for each of the exposure categories described in Section 3.3.4.1 (ever use, single use, and switching/multiple use) and for combined multiple use of both tacrolimus and pimecrolimus (Section 3.3.4.3).

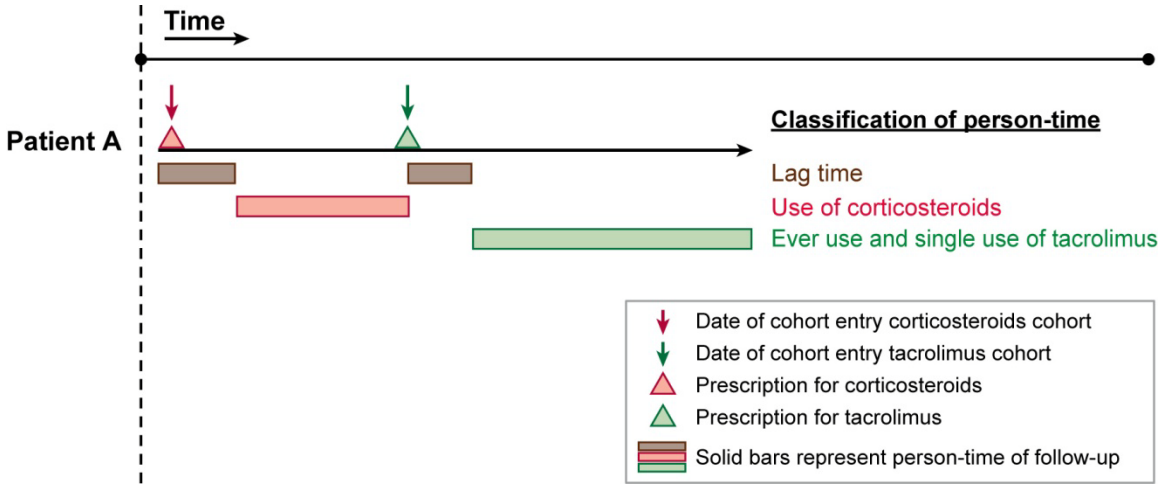
3.3.4.5 Duration of Exposure

Duration of exposure will be calculated as the total time of use of topical tacrolimus or pimecrolimus. A maximum time interval between prescriptions will be estimated from preliminary descriptive analysis to define consecutive prescriptions. Duration of exposure will be categorized after examining the duration distribution of each database.

3.3.4.6 Cohort of Users of Corticosteroids With Atopic Dermatitis

Person-time will be accumulated from the date of cohort entry to the earliest of the following dates: prescription for topical tacrolimus, prescription for topical pimecrolimus, or end of follow-up (Figure 3).

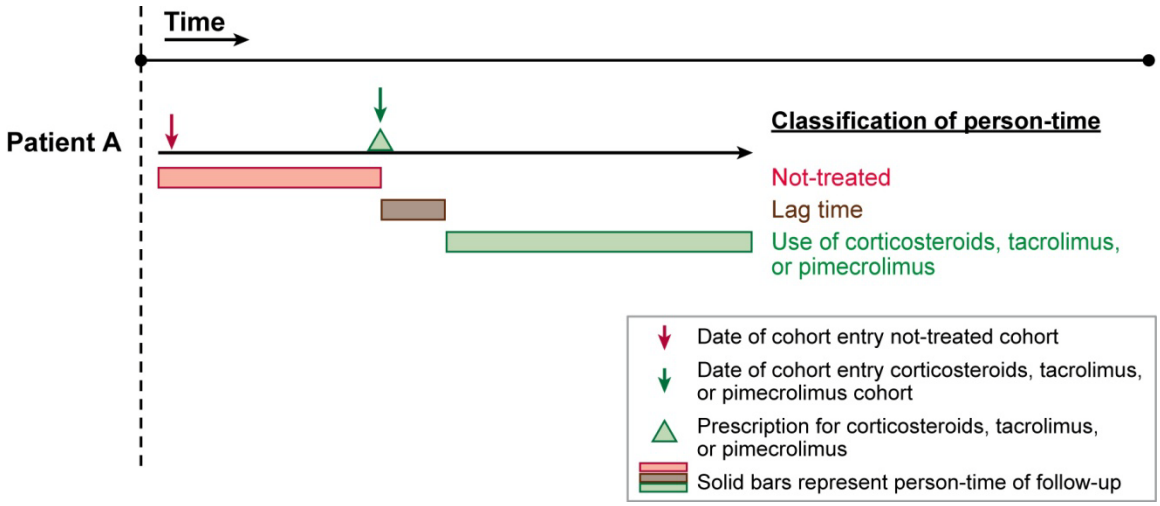
Figure 3. Exposure Assessment: Example for Patients Contributing Person-time to Both the Corticosteroids Cohort and the Tacrolimus Cohort



3.3.4.7 Not-Treated Cohort

Person-time will be accumulated from the start date (see Section 3.2.3.3) to the earliest of the following dates: prescription for moderate- to high-potency topical corticosteroids, prescription for topical tacrolimus, prescription for topical pimecrolimus, or end of follow-up (Figure 4).

Figure 4. Exposure Assessment: Example for Patients Contributing Person-time to the Not-Treated Cohort and Any Other Cohort



3.3.5 Endpoints

Incident malignancies are defined as the first occurrence of one of the malignancies of interest occurring in study subjects during study follow-up. If a person develops more than one primary malignancy of interest (i.e., a malignant melanoma and a lymphoma), only the first malignancy will be included and counted as an individual record. In a sensitivity analysis, the occurrence of each endpoint will be evaluated regardless of a prior occurrence of any of the other study endpoints during the study period.

The third version of the International Classification of Diseases for Oncology (ICD-O-3), which provides site (topography) and histology (morphology) codes for neoplasms, will be used to define malignancies in the study. The complete lists of ICD-O-3 codes for the malignancies of interest are presented in Appendix B.

The following incident malignancies will be included in the study.

Skin Malignancies

- Malignant melanoma (MM)

- Nonmelanoma skin cancer (NMSC) (i.e., squamous cell and basal cell carcinomas, Merkel cell carcinoma, and adnexal and skin appendages neoplasms)

Lymphomas

- Cutaneous T-cell lymphomas (CTCL)
- Hodgkin lymphomas (HL)
- Non-Hodgkin lymphomas (excluding CTCL)

Skin malignancies will be evaluated as a group ("Any skin malignancy") and by individual malignancy type—i.e., melanoma, NMSC. Lymphomas will be also analyzed as a group ("Any lymphoma") and by specific lymphoma type—cutaneous T-cell lymphoma, Hodgkin lymphoma, and non-Hodgkin lymphoma (excluding CTCL).

The classification of lymphomas has undergone several revisions during the last decade, and the most recent revised classification published by the World Health Organization (WHO) in 2008 represents a worldwide consensus on the diagnosis of these tumors (Swerdlow et al., 2008). A variety of T-cell and B-cell neoplasms can involve the skin, either primarily or secondarily. The term "primary cutaneous lymphoma" refers to CTCLs and cutaneous B-cell lymphomas (CBCLs) that either frequently present first in the skin (before there is evidence of systemic disease) or commonly involve the skin relatively early in their natural history. Because primary cutaneous lymphomas are clinically distinct from other lymphomas (which involve skin only uncommonly or only in patients with advanced disease) and may require distinct approaches to treatment, recent classification systems for non-Hodgkin lymphomas such as the European Organisation for Research and Treatment of Cancer (EORTC) classification for primary cutaneous lymphomas and the WHO 2008 classification for tumors of hematopoietic and lymphoid tissues included primary cutaneous lymphomas as a distinct category (Swerdlow et al., 2008; Willemze et al., 2005). However, the ICD-O-3 classification, which was published in 2001, does not incorporate these recent revisions to the classification of lymphomas.

Aiming to have the most up-to-date, standardized approach that incorporates as much as possible the recent changes in the classification of malignant cutaneous lymphomas and that can be implemented across all databases, we reviewed the ICD-O-3 codes for cutaneous lymphomas under "Mature T- and NK-cell Lymphomas" against the WHO 2008 classification for cutaneous lymphomas under "Mature T-cell and NK-cell Neoplasms" and selected the ICD-O-3 codes that matched the definition and codes of cutaneous lymphomas in the WHO 2008 classification (see Appendix B, Table B-3). This approach did not pose any problem for the identification of CTCLs. However, the identification of CBCLs (classified as a separate entity in WHO 2008) was not possible as the WHO 2008 codes for these tumors do not have correspondence in ICD-O-3. Therefore CBCLs (which occur considerably less frequently than CTCLs) will not be included within the cutaneous lymphomas group in this

study although they are still expected to be identified as non-Hodgkin lymphomas in the study databases and would count toward that endpoint. Moreover, certain other rare lymphomas that were newly included with provisional codes in the WHO 2008 classification (and which are proposed for inclusion in the next edition of ICD-O), for example, primary cutaneous gamma-delta T-cell lymphoma, will not be explicitly included in this study. However, such lymphomas, if any occur in the study population and are coded less specifically, would be included in the non-Hodgkin lymphoma endpoint.

3.3.6 Case Identification and Validation

Potential cases of the targeted malignancies will be identified in PHARMO, Sweden, and Denmark using the list of ICD-O-3 codes shown in Appendix B. The development of a case validation approach will depend on whether validation of cases of neoplasms had been performed as part of the standard validation procedures by the data source from which cases originate (e.g., cancer registries, pathology registries).

In the Danish and Swedish databases, case validation will not be needed as the cases will be identified through cancer registries (Barlow et al., 2009).

In PHARMO, coding in the pathology database (PALGA) is based on the ICD-O-3 classification. Mapping of PALGA codes is expected to perform well in the study based on examination of PALGA codes against the ICD-O-3 list of targeted neoplasms. In cases where the ICD-O-3 code descriptions do not match exactly the PALGA codes, a coding expert from PALGA will be consulted. Case validation will be performed by an independent pathologist who will review the pathology excerpts of all pediatric cases, a random sample of adult cases, and all cases of CTCL.

In the CPRD, the ICD-O-3 coding system is not used for coding neoplasms. Therefore, the standard reference medical terminology or diagnostic coding systems used in the database (Read/OXMIS) will be mapped to the ICD-O-3 topography and morphology codes for each endpoint. CTCLs will be identified using the selected ICD-O-3 codes that matched the definition and codes of cutaneous lymphomas in the WHO 2008 classification of lymphomas as described in Section 3.3.5. For potential cases identified through the CPRD or the Hospital Episodes Statistics linkage, validation of all pediatric cases, a random sample of adult cases, and all cases of CTCL will be performed by reviewing the computerized information (codes, free text) and through a questionnaire to be sent to the GPs requesting information from medical records (hospital discharge letters, pathology reports, etc.).

The linkage of CPRD data to cancer registry data will be explored in the study. Note that the linkage is partial, and for the practices linked by the end of 2012 (study phase 1), the linkage will cover potential cases through 2010. Cases that are identified and recorded in

the cancer registries will not require further validation because of the standard validation procedures used by the cancer registries.

3.3.6.1 Assessment of Protopathic Bias for CTCL in CPRD

As part of the validation of cases of CTCL in the CPRD, we will request additional information to assess protopathic bias. Information may include date of CTCL diagnosis; date of start of symptoms; reasons for prescribing topical tacrolimus, pimecrolimus, or corticosteroids; physician suspicion of CTCL before start of treatment; skin conditions before start of treatment (e.g., psoriasis); location and extent of CTCL; biopsy results; date of onset of symptoms of atopic dermatitis; location and extent of atopic dermatitis; and details of topical treatment (amount, frequency, duration).

3.3.7 Confounding and Risk Factors

A number of diseases and conditions have been associated with the risk of skin cancer and lymphoma. The main risk factors are age, sex, immunosuppressive disease and use of immunosuppressive agents, chronic disease, severe skin diseases, frailty and general health status, intensity of sun exposure, and skin phenotype (Arellano et al., 2009; Jensen et al., 2008; Scheneweiss et al., 2009). Atopic dermatitis and severity of atopic dermatitis have been associated with an increased risk of skin cancer and lymphoma (Tennis et al., 2011), which can lead to confounding by indication as tacrolimus, pimecrolimus, and corticosteroids are indicated for the treatment of atopic dermatitis.

We will use propensity scores and stratification by categories of propensity scores to control for confounding and confounding by indication, in particular. Ascertainment of confounders and risk factors will be based on the information available in each database. Estimation of propensity scores at the start date will include the following factors (a more detailed list of variables is presented in Appendix C; the final list will appear in the statistical analysis plan [SAP]):

- Age
- Sex
- Calendar year
- Duration of atopic dermatitis: time since first recorded diagnosis; time since first prescription for topical corticosteroids
- Severity of atopic dermatitis based on the use of health care resources in the 12 months before the start date (Arellano et al., 2007; Emerson et al., 1998; Margolis et al., 2001)

- History of inflammatory and other skin disease (other than atopic dermatitis and eczema)
- History of diseases involving the immune system: psoriasis, rheumatoid arthritis, other
- History of chronic disease: malignancy, disease of the immune system, organ transplantation, HIV infection,[1] severe renal disease, liver disease, cardiovascular disease, diabetes, chronic obstructive pulmonary disease, musculoskeletal disorders
- Prior use of topical corticosteroids
- Prior use of immunosuppressive agents and cytostatic drugs: systemic corticosteroids, immunosuppressants, systemic antivirals, anticancer drugs
- Prior use of dermatological agents
- Prior use of other drugs
- Type of prescriber of first prescription of study medications (general practitioner, pediatrician, dermatologist, other specialist)
- Prior use of health care resources: number of visits to general practitioner, referrals to specialists, hospitalizations, and prescriptions.
- Geographic region of primary care general practice

Information on some factors (e.g., visits to a general practitioner) may not be available in all the study databases or may be ascertained through different methods across databases (e.g., hospital discharge diagnosis vs. information from general practitioners). Depending on the available information, we will combine variables. In addition, the effect of each database will be evaluated in the overall analysis.

To assess unmeasured confounding, in the CPRD and PHARMO-GP, for a random sample of users of tacrolimus, pimecrolimus, and corticosteroids, we will explore obtaining information on risk factors that are known to be of relevance but are not captured in databases (e.g., severity of atopic dermatitis, history of sun exposure, or treatment with ultraviolet A phototherapy (UVA). If feasible, the clinical information obtained on severity of atopic dermatitis will be used to validate the definition of severity based on the use of health services.

3.4 Study Size

In Table 2, we present, for each study endpoint and for the overall and pediatric populations, the number of patients exposed to tacrolimus or to pimecrolimus that are needed to have, with a 80% probability, an upper limit for the two-sided 95% CI of the rate

[1] Information on HIV/AIDS is not available in the Swedish database.

ratio below the specific values of 2, 4, 8, and 16. The calculations are based on the following assumptions: two-sided confidence level of 95%, expected rate ratio of 1, an equal number of exposed and unexposed (allocation ratio of 1:1), and incidence among the unexposed is the same as the incidence in the general population. Calculations using these assumptions yield the maximum study sizes required for a given probability. Increasing the ratio of unexposed to exposed or assuming a higher incidence of malignancies in patients with atopic dermatitis will reduce the required study size.

The incidence rates for all endpoints, with the exception of CTCL, have been calculated using age-specific incidence rates from the Association of the Nordic Cancer Registries, which collects cancer incidence data from Sweden, Denmark, Norway, Finland, and Iceland (NORDCAN, 2011). The incidence rates for CTCL are based on the age- and sex-specific incidences rates for CTCL from the Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute in the US (SEER*Stat version 7.05). The incidence rates for each type of cancer (Table D-1) and the population from NORDCAN countries (Table D-2) are presented in Appendix D.

Table 2. Estimated Number of Person-Years Exposed to Tacrolimus Needed to Have an 80% Probability That the Upper Limit for the 95% Confidence Interval of the Rate Ratio is Below 2, 4, 8, or 16[a]

Cancer Type by Age Group	Incidence per 100,000 Person-years	Upper Limit for the 95% CI of the Rate Ratio is Below			
		2	4	8	16
All ages					
Skin, nonmelanoma	30.08	109,000	27,250	12,100	6,805
Melanoma of skin	25.17	130,750	32,700	14,550	8,175
Non-Hodgkin lymphoma	18.03	181,500	45,400	20,175	11,350
Hodgkin lymphoma	2.31	1,421,000	355,500	158,000	88,800
CTCL	1.48	2,208,000	552,000	245,500	138,000
Age 0-19 years[b]					
Skin, nonmelanoma	0.05	62,850,000	15,712,500	6,982,500	3,927,500
Melanoma of skin	0.44	7,430,000	1,857,500	825,500	464,500
Non-Hodgkin lymphoma	0.90	3,632,500	908,000	403,500	227,000
Hodgkin lymphoma	1.35	2,425,000	606,000	269,250	151,500
CTCL	0.19	17,200,000	4,300,000	1,911,000	1,075,000
Age 20+ years					
Skin, nonmelanoma	39.65	82,000	20,500	9,100	5,125
Melanoma of skin	33.05	99,000	24,750	11,000	6,190
Non-Hodgkin lymphoma	23.48	139,000	34,750	15,450	8,690
Hodgkin lymphoma	2.62	1,250,000	312,500	139,000	78,115
CTCL	1.89	1,730,000	432,500	192,200	108,110

CI = confidence interval; CTCL = cutaneous T-cell lymphoma.

Note: Calculations were obtained using Episheet (study size sheet) (Rothman, 2011).

[a] Allocation ratio 1:1

[b] For statistical power calculations, the upper limit of age in children was set at 19 years. However, the age of children for the study implementation is < 18 years in accordance with the regulatory definition.

Preliminary information on the number of users of tacrolimus and pimecrolimus for all age groups and for the pediatric population that are available in each database from the time of market availability in each country to the latest data cut-off is summarized in Table 3. There are a total of approximately 114,216 users of tacrolimus of all ages, and 28,455 users aged 0 to 19 years.

Table 3. Preliminary Number of Users of Tacrolimus and Pimecrolimus in the Study Database

Data Source	Tacrolimus	Pimecrolimus
All ages		
PHARMO	15,971	7,735
CPRD	12,597	7,241
Denmark[a]	42,639	61,220
Sweden	43,009	5,519
Total[a]	114,216	81,715
Age 0-19 years[b]		
PHARMO	3,636	2,676
CPRD	3,436	2,745
Denmark[a]	12,771	24,656
Sweden	8,612	1,343
Total[a]	28,455	31,420
Age 20+ years		
PHARMO	12,335	5,059
CPRD	9,161	4,496
Denmark[a]	29,868	36,564
Sweden	34,397	4,176
Total[a]	85,761	50,295

CPRD = Clinical Practice Research Datalink (United Kingdom).

[a] Potential overestimate.

[b] For statistical power calculations the upper limit of age in children was set at 19 years. However, the age of children for the study implementation is < 18 years in accordance with the regulatory definition.

In Table 4, we present the probability for each study endpoint to have an upper limit for the two-sided 95% CI of the rate ratio below the specific values of 2, 4, 8, and 16, according to the preliminary number of users of tacrolimus available in the study databases. Calculations assume that each person that was prescribed tacrolimus in a given year contributed 1 year of follow-up. For the adult population, the probability is above 80% for having an upper limit of the 95% CI of the rate ratio below 2 for NMSC, melanoma of skin, and non-Hodgkin lymphoma. For Hodgkin lymphoma, the probability is about 83% for having an upper limit below 8. For CTCL, the probability ranges from 13% for an upper limit below 2 to 91% for an upper limit below 16.

For the pediatric population, the probabilities are low. The highest probability is for Hodgkin lymphoma, with a 36.3% probability for having an upper limit of the 95% CI of the rate ratio below 16.

Table 4. For Each Study Endpoint, Probability That the Upper Limit for the 95% Confidence Interval of the Rate Ratio is Below 2, 4, 8, or 16[a]

Cancer Type by Age Group	Incidence per 100,000 Person-years	Upper Limit for the 95% CI of the Rate Ratio is Below			
		2	4	8	16
All ages					
Skin, nonmelanoma	30.08	0.97	1.00	1.00	1.00
Melanoma of skin	25.17	0.93	1.00	1.00	1.00
Non-Hodgkin lymphoma	18.03	0.84	1.00	1.00	1.00
Hodgkin lymphoma	2.31	0.18	0.56	0.88	0.99
CTCL	1.48	0.13	0.39	0.72	0.92
Ages 0-19 years[b]					
Skin, nonmelanoma	0.05	0.030	0.036	0.042	0.050
Melanoma of skin	0.44	0.042	0.067	0.102	0.149
Non-Hodgkin lymphoma	0.90	0.051	0.096	0.165	0.260
Hodgkin lymphoma	1.35	0.060	0.124	0.226	0.363
CTCL	0.19	0.035	0.049	0.066	0.088
Ages 20+ years					
Skin, nonmelanoma	39.65	0.97	1.00	1.00	1.00
Melanoma of skin	33.05	0.93	1.00	1.00	1.00
Non-Hodgkin lymphoma	23.48	0.83	1.00	1.00	1.00
Hodgkin lymphoma	2.61	0.16	0.49	0.83	0.97
CTCL	1.89	0.13	0.38	0.70	0.91

CI = confidence interval; CTCL = cutaneous T-cell lymphoma.

Note: Calculations obtained using Episheet (study size sheet) (Rothman, 2011) and based on 50,000 person-years in the 0-19 years age group and 150,000 person-years in the 20+ years age group.

[a] Allocation ratio 1:1.

[b] For statistical power calculations the upper limit of age in children was set at 19 years. However, the age of children for the study implementation is < 18 years in accordance with the regulatory definition.

For the primary study objective, we will use a matching ratio (corticosteroids to tacrolimus or pimecrolimus) up to 4:1, depending on available matches across strata. Therefore, we present in Appendix E study size calculations (Table E-1) and precision (Table E-2) using a matching ratio of 4:1. For HL (all ages), the probability that the upper limit of the 95% CI of

the rate ratio is below 4 increases from 0.56 (matching ratio 1:1) to 0.76 (matching ratio 4:1). For CTCL the probability increases from 0.39 to 0.57, respectively.

3.5 Data Analysis

This analysis section provides an overview of the analyses that will be conducted for this study during phase 1.

Data analyses will occur in two stages: (1) a country-specific analysis by each of the database research partners and (2) a pooled analysis conducted at the coordinating center, where summary data from the collaborating database research partners will be combined. The database research partners have organization-specific restrictions on the level and type of information that can be shared externally. This two-stage analysis is designed to meet those restrictions while nevertheless accomplishing the goal of assimilating the data from the collaborating database research partners into one summary analysis. The basic approach is for each database research partner to create stratified tables with cross-classifications of subject and person-time counts by exposure category, endpoint, and deciles of propensity scores. To estimate overall measures of effect, the coordinating center will analyze these stratified data.

A core statistical analysis plan will be developed separately and will describe methods for the creation of the study cohorts, the descriptive analyses, variable creation including propensity scores, and the incidence rate and rate ratio analyses. The statistical analysis plan will also detail the required input data from the individual database research partner that will be used to perform the pooled analysis. Calculation of person-years, incidence and rate ratios, and confidence intervals will be documented. A description of the planned pooled analyses and table shells will be included. Appendices to the analysis plan will document all diagnostic, procedure, and medication codes to be used in defining the outcomes, exposures, and covariates. The core statistical analysis plan will be adapted to the specifications of each database.

3.5.1 Country-Specific Analysis

Each database research partner will conduct country-specific analyses to (1) describe the study cohorts at the start date; (2) describe the characteristics of cases; and (3) estimate exposure propensity scores within its data, conduct frequency matching of the tacrolimus and pimecrolimus cohort with the corticosteroids cohorts across strata of propensity scores, and create a summary dataset based on counts of patients, person-years, and outcome events according to the strata of propensity scores.

3.5.1.1 Description of the Study Cohorts

Each database research partner will first apply the study inclusion/exclusion criteria to select the study population. During this process, each database research partner will create a table showing the impact that each step of applying the study criteria has on the study size. Once the study population is identified each study cohort (tacrolimus cohort, pimecrolimus cohort, two corticosteroids cohorts, and not-treated cohort) will be described at the time of cohort entry. The study cohorts will be characterized according to confounding and risk factors, including the following variables (see Section 3.3.7 and Appendix C, Table C-1):

- Age
- Sex
- Calendar year of the start date
- Distribution of person-time between eligibility date and start date
- Medical history including atopic dermatitis, risk factors, and confounders at any time before the start date
- Duration of atopic dermatitis: time since first recorded diagnosis; time since first prescription for topical corticosteroids
- Severity of atopic dermatitis based on the use of health care resources in the 12 months before the start date (Arellano et al., 2007; Emerson et al., 1998; Margolis et al., 2001)
- Use of medications, including topical corticosteroids, in the 12 months before the start date.
- Duration of follow-up

A detailed description of the characterization variables will be presented in the SAP; the characterization variables will be based on the preliminary list of variables presented in Appendix C, Table C-1, for the estimation of propensity scores.

Patterns of use of topical tacrolimus, topical pimecrolimus, and topical corticosteroids during follow-up will also be explored and described. The analysis of patterns of use will include number of prescriptions received, total number of milligrams, time between prescriptions, switching between study drugs, number of children using topical corticosteroids by potency, and other parameters to be determined.

These descriptive analyses will be informative for defining several aspects of the study design including estimation of the average duration of prescriptions and assessment of cumulative exposure and duration of use of topical tacrolimus and topical pimecrolimus.

3.5.1.2 Description of Cases

Characteristics of cases at the time of diagnosis will be described for each study endpoint. Characteristics will include age, sex, cancer subtype (e.g., type of NMSC, type of lymphoma), stage of cancer if available, medication exposure category, and selected medical history.

3.5.1.3 Estimation of Propensity Scores

Estimation of propensity scores will be conducted separately for children and adults. For each age group, each database research partner will estimate two separate sets of propensity scores, one set for the analyses comparing users of tacrolimus with users of corticosteroids and another set for the analyses comparing users of pimecrolimus with users of corticosteroids.

The propensity scores, which are based on the values of the covariates at treatment initiation, will estimate the probability that each patient is prescribed the study drug (tacrolimus or pimecrolimus) rather than moderate- to high-potency topical corticosteroids. The propensity score will serve as a within–database variable that summarizes the confounding from a large set of variables. Propensity scores will be estimated using multiple logistic regression models. Covariates to be used for the estimation of propensity scores are those related to the probability of receiving treatment with tacrolimus or pimecrolimus and those associated with the risk of skin cancer and lymphoma. A preliminary list of covariates to be included in the logistic model is presented in Section 3.3.7 and in Appendix C, Table C-1. Patients who contribute follow-up time to both the corticosteroids cohort and one of the exposed cohorts (tacrolimus or pimecrolimus) will be included twice in the model used to estimate propensity scores—once in the corticosteroids cohort, using covariate data values at the time of initiating corticosteroids, and once in the tacrolimus or pimecrolimus cohorts, using covariate data values at the time of initiating tacrolimus or pimecrolimus. General estimating equations will be used to account for within-individual correlation.

From the fitted propensity score model, a propensity score will be estimated for each subject (twice for any subject who contributes follow-up time to both a study drug cohort and the corticosteroids cohort). The database research partners will categorize exposure propensity scores in 20 strata (twentiles). These strata will be used to frequency match users of corticosteroids with users of tacrolimus and pimecrolimus. A matching ratio (corticosteroids to tacrolimus or pimecrolimus) up to 4:1, depending on available matches, will be used across strata.

The strata of propensity scores will be used to stratify person-time of follow-up and endpoint counts for each defined exposure category. Initially, the propensity scores and counts will be summarized into deciles by combining data from contiguous strata; if this

results in cell counts that are too small, some deciles may be further combined, resulting in fewer strata.

Each database research partner will apply the study definitions to calculate person-time of exposure and number of events associated with each exposure category and endpoint definition. Using these data in conjunction with propensity scores, each database research partner will create an exposure summary table containing the essential data for measuring the effect of exposure on the study outcomes while adhering to the restrictions that are imposed on the release of individual-level data from each site.

3.5.2 Pooled Analysis

After receiving the site-specific, propensity-score stratified tables from each database research partner, the coordinating center will conduct an analysis of the data from each individual database research partner and an overall analysis combining the data across all database research partners. The overall analysis will be designed to estimate the effect of the exposure while controlling for confounding using the data stratified on propensity scores. Mantel-Haenszel methods will be used to summarize effects across strata. Database research partner, that is, data source, will be retained as a stratification variable and the effect within each database will be estimated. If some strata have zero cases, it may be possible to collapse neighboring propensity score strata within sites without introducing confounding, yielding fewer than 10 strata per site in the final stratified analysis. Before the final analysis, the amount of confounding reintroduced by collapsing of neighboring strata will be evaluated.

3.5.2.1 Estimation of Incidence Rates

Incidence rates will be estimated separately for children and adults. Crude incidence rates will be calculated for each country and overall across all countries as the number of outcome events divided by the person-time at risk. The Poisson distribution will be used to calculate exact 95% CIs for the incidence rates within each database research partner's data. Standardized incidence rates will be estimated using the distribution of person-time across deciles of propensity scores of the cohort exposed to tacrolimus as the standard. Crude and standardized incidence rates for each study endpoint will be estimated for each exposure category of each study cohort: tacrolimus cohort, pimecrolimus cohort, and the two corticosteroids cohorts. Crude and standardized incidence rates for exposure to tacrolimus and pimecrolimus will be estimated initially for ever use, single use, and switching/multiple use. The main exposure of interest will be cumulative dose, which will be estimated for each exposure category (ever use, single use, and switcher/multiple use). Crude and standardized incidence rates will be also estimated by duration of exposure.

3.5.2.2 Estimation of Incidence Rate Ratios

The coordinating center will use Mantel-Haenszel methods for the pooled analysis. Incidence rate ratios and 95% CIs will be estimated, stratifying by deciles of propensity scores and database research partner. To control for confounding, the Mantel-Haenszel analysis will provide pooled estimators that summarize the effect of exposure across strata of propensity scores and database partner. Incidence rate ratios will be estimated separately for children and adults. Crude and adjusted incidence rate ratios and 95% CIs for each study endpoint will be estimated, comparing the incidence rates for each exposure category (ever use, single use, and switcher/multiple use) of topical tacrolimus and topical pimecrolimus with the rates in the corresponding corticosteroids cohort. The analysis will focus on the estimation of incidence rate ratios comparing the incidence rates for each category of cumulative dose and duration of exposure to tacrolimus and pimecrolimus (e.g., low, medium, high) with the rates in the corresponding corticosteroids cohort. These rate ratios will be estimated separately for the periods of ever use, single use, switching/multiple use, and combined multiple use.

3.5.2.3 Estimation of Incidence Rate Differences

The main analysis is based on incidence rate ratios; however, additional analyses may be performed looking at incidence rate differences and numbers needed to harm.

3.5.3 Sensitivity Analysis

A number of sensitivity analysis will be conducted.

1. Incidence rates and incidence rate ratios will be estimated for the subgroup of children aged ≥ 2 to < 16 years, which is the age range for children specified in the labeling of topical tacrolimus.
2. Incidence rates and incidence rate ratios will be estimated for the occurrence of each specific endpoint regardless of a prior occurrence of any of the other study endpoints during the study period.
3. To evaluate protopathic bias, incidence rates and incidence rate ratios will be estimated for the first 6 months after the first exposure (ignoring lag time), and for other lag times (e.g., 12 months, 18 months, 24 months) in addition to the predefined lag time of 6 months.
4. To explore potential surveillance bias, incidence rates will be stratified by the following variables when available:
   - Type of prescriber of first prescription (general practitioner, pediatrician, dermatologist, other specialties)

- Utilization of health services within the year before the start date. Categorized as 0, 1, and 2 or more.
  - Number of visits to general practitioner
  - Number of visits to dermatologist
  - Number of visits to pediatrician
  - Number of outpatient hospital visits
  - Number of hospitalizations
- Stage of malignancy at the time of diagnosis

Data for the sensitivity analyses will be generated by each database research partner, and the overall analysis will be conducted by the coordinating center.

3.5.4 Secondary Analysis

The secondary analysis will address the secondary study objective of estimating incidence rates and incidence rate ratios of skin cancer and lymphoma in users of topical corticosteroids compared with not-treated subjects. The analyses will be conducted using the corticosteroids cohort identified in the comparison with users of tacrolimus. Each database research partner will individually match not-treated subjects with the corticosteroids cohort by year of birth, sex, calendar year of start date, and primary care general practice/region, at a matching ratio of 1:1. Each database research partner will stratify the data simultaneously by year of birth, sex, calendar year of start date, and primary care general practice/region and will compute person-time and endpoint counts for each stratum. The coordinating center will estimate crude and standardized incidence rates and will use Mantel-Haenszel methods to estimate crude and adjusted incidence rate ratios for each database and overall across databases.

In addition, we will evaluate the feasibility of conducting a sensitivity analysis comparing the incidence rates and incidence rate ratios between users of topical moderate- to high-potency corticosteroids and patients diagnosed with atopic dermatitis who are not treated with the study medications.

3.6 Data Management

Routine procedures include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality control checks of all programs. Each database research partner will maintain any patient-identifying information securely onsite according to internal standard operating procedures.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed (i.e., storage on CD-ROM and DVD), with periodic backup of files to tape. Standard procedures will be in place at each location handling the data to restore files in the event of a hardware or software failure.

3.7 Quality Assurance and Quality Control

The standard operating procedures of each database research partner will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

All programming written by one study analyst will be independently reviewed by a different analyst, with oversight by a senior statistician. All key study documents, such as the statistical epidemiological analysis plan, abstraction forms, and study reports will undergo quality-control review, senior scientific review, and editorial review.

At the coordinating center, an independent Office of Quality Assurance performs audits and assessments that involve various aspects of its projects, including but not limited to documentation of education and training, data entry, data transfer, and RTI International institutional review board approval. Such audits in RTI will be conducted by the Office of Quality Assurance according to established criteria in standard operating procedures and other applicable procedures. Each of the database research centers will follow its own quality and audit trail procedures. The quality and audit trails at each center may be different.

3.8 Limitations

As in all safety studies, the relevant parameters to consider for the interpretation of the results focus on the point estimate, the upper limit of the confidence interval, and the absolute excess risk. A limitation of the study is the low precision of the estimated relative risks for most malignancies in the pediatric population and for HL and CTCL in adults. We estimate that for HL in the whole population (children and adults), there is a 56% probability that the upper limit of the 95% confidence interval of the observed rate ratio will be below 4. Thus, even if there is no effect of tacrolimus on the risk of HL, it is likely that the upper limit of the CI around the rate ratio estimate will be high enough to include large

multiples of the rate. In terms of absolute risk, a 95% upper limit of 4 translates to an increase of about 9 additional cases per 100,000 person-years of treatment. Although precision may be low, with findings that are compatible with high multiples of risk, the risk is very low for this outcome, and even a multiple of 4 in the rate would correspond to a small absolute increase in risk for HL. For CTCL, the incidence is 1.48 cases per 100,000 person-years, which is lower than for HL. Assuming a rate ratio of 1, about 2 cases are expected in the tacrolimus cohort. The precision of the effect estimate for CTCL is lower than that for HL, with only a 39% probability that the 95% upper limit will be below 4. This upper limit would correspond to about 6 additional cases per 100,000 person-years of treatment. Thus, the anticipated study size for phase I of the study will result in some effect estimates with considerable random variability, although the risks for these rare outcomes are generally low, even when multiplied several-fold. Nevertheless, to reduce the random error of these estimates, the study will be extended in phase II to include additional new users of topical tacrolimus and to increase the time of follow-up.

We assumed that topical tacrolimus and topical pimecrolimus are prescribed only for atopic dermatitis and that members of these cohorts are not required to have a recorded diagnosis of atopic dermatitis. However, some patients may be prescribed these medications for skin disease other than atopic dermatitis. Bias from misclassification of atopic dermatitis among these patients could be present if the risk of skin malignancies associated with the underlying skin disease for which these medications are prescribed differs from the risk associated with atopic dermatitis. The magnitude of the bias would depend on the proportion of patients prescribed topical tacrolimus or topical pimecrolimus to treat skin disease other than atopic dermatitis. However, skin diseases that could be treated with these medications are infrequent, particularly in children, and may include inverse psoriasis (flexural psoriasis) and facial psoriasis (Morris et al., 2001). For other skin diseases, such as vitiligo and alopecia areata, there seems to be limited effect of topical tacrolimus or pimecrolimus, and both diseases are slightly more common among children with atopic dermatitis (Alikhan et al., 2011; Chu et al., 2011). Other disorders such as pyoderma gangrenosum, cutaneous lupus erythematosus, and oral lichen are even rarer in children (Bansal et al., 2008; Laeijendecker et al., 2005; Langan et al., 2012). Lichen sclerosus et atrophicus (LSA) is also uncommon in children (Jensen and Bygum, 2012). LSA usually responds very well to treatment with very potent topical corticosteroids (clobetasol propionate), which reduces the need for topical tacrolimus or pimecrolimus (Jensen and Bygum, 2012). Overall, these data indicate that the magnitude of a potential bias caused by misclassification of atopic dermatitis in users of topical tacrolimus and topical pimecrolimus will probably be low. To minimize potential bias, we will include in the estimation of propensity scores individual variables for specific skin diseases that potentially can be treated with topical tacrolimus or topical pimecrolimus.

The study will combine results from different databases with heterogeneity between databases regarding exposure information (prescribed vs. dispensed medications) and ascertainment of risk factors and confounders. Three of the study databases (PHARMO, Sweden, Denmark) are based on diagnoses when discharged from the hospital or in connection with an hospital outpatient clinic visit, whereas the CPRD is based on information from general practitioners. Ascertainment of covariates using hospital discharge diagnoses might result in the identification of individuals with more severe comorbidity. The effect of each database will be adjusted for in the overall stratified analysis.

Nonmelanoma skin cancer is most probably underreported in cancer registries because reporting is not required or reporting has been required only in recent years. Although underreporting will result in underestimation of incidence rates, it is expected to have a nondifferential effect between users of tacrolimus and pimecrolimus and users of corticosteroids.

3.9 Human Subjects Protection

This is a retrospective noninterventional study and does not pose any risks for patients. All data collected in the study will be de-identified with no breach of confidentiality with regard to personal identifiers or health information. Each database research partner will apply for an independent ethics committee review according to local regulations; in addition, RTI Health Solutions as the coordinating center will obtain approval from the RTI International institutional review board.

Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

3.10 Other Good Research Practice

This study adheres to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)* (International Society for Pharmacoepidemiology, 2008) and has been designed in line with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2012). The *ENCePP Checklist for Study Protocols* (ENCePP, 2013) has been completed (Appendix F).

This study is a non-interventional Post-Authorization Safety Study according to the EMA *Guideline on Good Pharmacovigilance Practices: Module VIII – Post-authorisation safety studies* (EMA, 2012a). The study will comply with the study reporting requirements specified

in Module VIII section VIII.B.6.3.1. “Progress reports” and VIII.B.6.3.2. “Final study Report” of the *Guideline on Good Pharmacovigilance Practices* (EMA 2012a).

The study will be registered in the ENCePP electronic register of studies (ENCePP, 2010) before the study implementation commences. The research team and study sponsor adhere to the general principles of transparency and independence in the ENCePP *Code of Conduct* (ENCePP, 2011). Given the limitations in data access at several research centers related to patient data protection and local governance, research independence and research transparency will be approached as follows:

- Research Independence: The financial sponsor of this study is Astellas, the manufacturer of Protopic. Astellas has agreed that contractual agreements with research partners will reflect Astellas’s commitment to maintain its role as financial sponsor, while giving the research partners—RTI-HS, PHARMO, CPRD, Southern Denmark University, Karolinska Institutet—scientific independence, including independent publication of manuscripts consistent with the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org/).
- Research Transparency and Audits: For requests to access for audit purposes, only aggregated data from all research centers at the coordinating center will be available. The audit trail will consist of a detailed description of the methods to extract and process the electronic health records or claims data, as applicable. Access to raw data at each database research center will require the data requestor to obtain a license or apply for approval at a research committee and to fulfill the conditions required under the governance rules of each database research center.

4 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Based on current guidelines from ISPE (2008, Section VI) and the EMA (2012b, Section VI:C.1.2.1), noninterventional studies such as the one described in this protocol, conducted using medical chart reviews or electronic claims and health care records, do not require expedited reporting of suspected adverse events/reactions. Based on the data used for this study, no suspected adverse events/reactions are expected.

5 DISSEMINATION OF STUDY RESULTS

There is an ethical obligation to disseminate findings of potential scientific or public health importance (e.g., results pertaining to the safety of a marketed medication). The research team has agreed to pursue publications on the following topics: study core protocol, drug utilization study in each database in separate publications, and a single publication on the

overall study results, with online appendixes for presenting additional information and results.

Authorship will follow guidelines established by the International Committee of Medical Journal Editors (2010). See also, Section V, Communication, in the *Guidelines for Good Pharmacoepidemiology Practices* (International Society for Pharmacoepidemiology, 2008) and the ENCePP Code of Conduct (http://www.encepp.eu/).

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (STROBE, 2007) will be followed when reporting results of this study (http://www.strobe-statement.org/index.php?id=available-checklists).

6 MILESTONES AND TIMELINES

Milestones and tentative timelines for the implementation of phase I of the study are provided in Table 5. Ranges reflect differences in data availability start times across databases.

Table 5. Phase I Milestones and Timelines

Study Milestones	Target Timeline Range	
Start of data extraction	Q4 2012	NA
End of data collection[a]	Q4 2012	Q3 2013
End core site analysis	Q3 2013	Q4 2013
End pooled analysis	NA	Q1 2014
Draft study report	NA	Q3 2014
Final study report	NA	Q3 2014

NA = not applicable.

[a] The date on which the analytical dataset is completely available.

Tentative timelines for the implementation of phase II of the study are provided in Table 6.

Table 6. Tentative Timelines for Phase II

Study Milestones	Target Timeline Range	
Estimated finalization phase I	NA	Q3 2014
Data accumulation[a]	NA	Dec 31, 2014
Start of data extraction	Q2 2015	Q 2015
End of data collection[b]	Q3 2015	Q1 2016
End core site analysis	Q1 2016	Q3 2016
End pooled analysis	NA	Q1 2017
Draft study report	NA	Q2 2017
Final study report	NA	Q3 2017

NA = not applicable.

[a] Assumes 3 years of data accumulation since December 31, 2011. Duration of the data accumulation period will depend on the use of the study medications in each country and study size calculations according to results from phase I.

[b] The date on which the analytical dataset is completely available.

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8 DATED AMENDMENTS TO THE PROTOCOL

Significant deviations from the protocol, such as any changes in the population or sample that were implemented after the beginning of the study, along with the rationale, should be documented in writing. Any changes made after data analysis has begun should be documented as such and the rationale provided.

Appendix A.
Summary of Characteristics of Databases

Table A-1. Protopic and Malignancies: Main Features of Databases and Data Availability

Characteristic	CPRD UK	PHARMO Netherlands	Danish Health Databases	Swedish National Registers
Database population	5,100,000	3,200,000	5,500,000	9,000,000
Database type	Primary health care electronic medical record database plus linkage to hospital data (Hospital Episodes Statistics [HES]) and cancer registry data	PHARMO Record Linkage System holds several databases, linked on patient level. For this study, outpatient pharmacy data (dispensed drugs),hospitalization data, GP data, and pathology data (PALGA) data will be used	▪ Prescription registry (all reimbursed drugs dispensed by prescription since 1995) ▪ Danish National Registry of Patients (hospital admissions, outpatient visits, and emergency department visits) ▪ Cancer registry	▪ Prescribed Drug Register (all drugs dispensed by prescription since July 1, 2005) ▪ Patient registers (hospital admissions and outpatient visits) ▪ Cancer Register ▪ Register of the Total Population
Tacrolimus reimbursement approval	April 2002	November 2002	June 2002 Change in December 2008 (can be prescribed by MDs other than dermatologists)	June 2002
Study data: phase 1 availability timelines	2011 Data: ▪ CPRD: 1Q 2012 (data updated every 3-4 months; lag time 6-12 weeks) ▪ CPRD-HES: 3Q 2012 ▪ CPRD-cancer data: 2014	2011 Data: 3Q 2012 ▪ Hospital data: yearly available (7 months lag time) ▪ Complete database update: annually Q3, includes hospitalization data available up to previous year December (7 months lag time) ▪ Pharmacy, GP, PALGA available up to Q3	2011 Data: ▪ Mid 2012 ▪ Prescription data: annually available at midyear (lag time 6-18 months)	2011 data: ▪ Rx data: 3Q 2012 ▪ Cancer data: 1Q 2013 ▪ Prescription data (since July 1, 2005): 1 month lag time ▪ Cancer Register: 1 year lag time ▪ Patient Register: Up to 8 months lag time

Characteristic	CPRD UK	PHARMO Netherlands	Danish Health Databases	Swedish National Registers
Linkages	▪ Half of CPRD practices (England) linked to HES database through NHS ID. Linkage update every 3 months (4-7 months delay) ▪ CPRD linkage to Cancer Regional Registries (partial) through NHS ID (2 years delay)	All databases in PHARMO Record Linkage System are probabilistically linked: pharmacy and hospitalization are core databases, PALGA database and GP database need permission for use. ▪ GP Data: 8%	Linkage through Civil Personal Registration (CPR) number	Linkage of databases through CPR
Restrictions/ Regulations			Individual prescription data cannot be transferred to researchers	
Demographics				
Unique identifier	Yes (patient NHS ID)	No	Yes (CPR)	Yes (CPR)
Registration date	Yes (GP practice registration)	Yes		
Date of birth	Yes	Yes	Yes	Yes
Gender	Yes	Yes	Yes	Yes
Date of death	Yes	Yes	Yes	Yes
Drugs				
Unique product code	Yes	Yes	Yes	Yes
Drug coding classification	Multilex/British National Formulary	ATC	ATC	ATC
Online drug formularies	By registration only http://bnf.org/bnf/index.htm	Pending	http://dkma.medstat.dk	http://formulary.drugplan.health.gov.sk.ca/

Characteristic	CPRD UK	PHARMO Netherlands	Danish Health Databases	Swedish National Registers
Prescribed/ dispensed drugs	GP prescriptions	Dispensed (independent of reimbursement)	Danish prescription registry (reimbursed drugs dispensed by prescription)	Swedish prescription drug register (all drugs dispensed by prescription since 2005 independent of reimbursement)
Date drug prescribed/ dispensed	Yes	Yes, date dispensed	Yes	Yes
Drug indication	Associated with new courses of medications, but completeness is variable.	No	No	No
Dose	Yes (Prescribed dose)	Yes	Yes (cumulative dose)	Yes
Formulation	Yes	Yes	Yes	Yes
Treatment duration	As indicated by the prescription	Yes, as indicated on the dispensing	No	No
Type of prescriber	GP	Yes	Yes (but laborious)	Yes
Inpatient drugs (cytostatics)	Pending	Indirectly (based on hospitalization for chemotherapy) no drug specific. For a small subset, inpatient data available including information on type (ATC code)	Drug-specific codes available	Mostly administered at hospitals. Drug-specific codes available (underreported but improving)
Study variables and data validation				
Disease and procedures dictionary codes	▪ CPRD: Read ▪ HES: ICD-9-CM discharge diagnoses ▪ Cancer registry: ICD-10	Hospitalization: ICD-9-CM discharge diagnoses PALGA: PALGA codes based on SNOMED ICD-O-3 coding	ICD-10	ICD-9 and ICD-10

Characteristic	CPRD UK	PHARMO Netherlands	Danish Health Databases	Swedish National Registers
Outpatient diagnoses	Yes	Yes (subset in GP database)	Yes (only at hospitals)	Yes (only at hospitals)
Hospital diagnoses	Recorded by GPs and partial linkage to HES	Yes	Yes	Yes
Outpatient specialist care	Specialists referral letters	Yes for subset GP database with specialist referral letters	Yes (only at hospitals)	Yes (only at hospitals)
Medical history/ comorbidities	GP data and hospital diagnoses (partially through HES linkage)	Available as hospital discharge diagnoses for hospitalized patients. For a subset, available in GP database.	Hospital (inpatient and outpatient data	Hospital (in- and outpatient data)
Atopic dermatitis	Algorithm: CPRD Review pending (Read codes, specialists reported diagnosis, free text)	Algorithm: Hospital diagnosis and medications	Algorithm: specifications pending, based on hospital diagnosis and medications	Algorithm: specifications pending; based on hospital diagnosis and medications
Atopic dermatitis severity	Algorithm: specifications pending	Algorithm: specifications pending	Algorithm: specifications pending	Algorithm: specifications pending
Validation atopic dermatitis diagnosis	▪ Review of patients records and physicians questionnaires. ▪ Computerized free text information available for review	Linkage to GP data (about 8% of patients) possible but very intensive effort	Outpatient diagnosis available at national level but not able to be validated	▪ No link to patients available ▪ Record review for patients seen at hospitals possible but difficult for patients seen by GPs ▪ Review of free text in prescription register
Immunosuppressive diseases (HIV, AIDS)	Yes	Yes (pharmacy and hospitalizations data used as proxies)	Not available (confidential data)	Not available (confidential data)

Characteristic	CPRD UK	PHARMO Netherlands	Danish Health Databases	Swedish National Registers
Sun exposure (intensity), ultraviolet light therapy	Regional sun exposure estimates as proxy	UV light therapy data potentially available in GP database. Awaiting confirmation if intensity of sun exposure is recorded	No	Information on ultraviolet light therapy is available (procedure codes in the patient register)
Access to patients' records	GPs and partial linkage to HES	Possible	▪ Possible Cancer registry cannot be linked to patients, but regional databases can be linked to patients	No link to patients possible
Study endpoints				
Coding of neoplasms	▪ CPRD: Read ▪ HES and Cancer Registry: ICD-10	PALGA coding based on ICD-O-3	ICD-10 and ICD-O-3	All diagnoses are coded by ICD-7, ICD-9, ICD-10, ICD-O-2 and ICD-O-3
Case identification	▪ CPRD: OXMIS/Read ▪ HES and Cancer Registry: ICD-10 ▪ Optional (physician reviewed codes)	Dutch National Pathology Registry (PALGA)	Danish Cancer Registry (accessible through Danish Health Board)	Swedish Cancer Register
Cancer data linkage	Partial	Yes (PALGA Registry)	Yes	Yes
Specific issues/needs	Underreporting NMSC	▪ Underreporting NMSC ▪ Lymphoma records need to be reviewed by pathologist	Underreporting NMSC	▪ Underreporting NMSC ▪ Basal cell carcinoma recorded since 2005
Case validation	All available information plus physician questionnaire	PALGA: Pathology database	Linkage to cancer registry	Linkage to cancer register

CPR = Civil Personal Registration (number); CPRD = Clinical Practice Research Datalink; HES = Hospital Episode Statistics; ID = identification; NHS = National Health Service; NMSC = nonmelanoma skin cancer; PALGA = pathology data.

Appendix B.
Coding of Malignancies

Table B-1. Morphology Codes for the Definition of Nonmelanoma Skin Cancers

Description	ICD-O-3 codes
SQUAMOUS CELL NEOPLASMS	
Papillary carcinoma, in situ	M 8050/2
Papillary carcinoma, NOS	M 8050/3
Verrucous carcinoma, NOS	M 8051/3
Condylomatous carcinoma	"
Verrucous squamous cell carcinoma	"
Verrucous epidermoid carcinoma	"
Warty carcinoma	"
Papillary squamous cell carcinoma, noninvasive	M 8052/2
Papillary squamous cell carcinoma, noninvasive	"
Papillary squamous cell carcinoma	M 8052/3
Papillary epidermoid carcinoma	"
Squamous cell carcinoma in situ, NOS	M 8070/2
Epidermoid carcinoma in situ, NOS	"
Intraepidermal carcinoma, NOS	"
Intraepithelial squamous cell carcinoma	"
Squamous cell carcinoma, NOS	M 8070/3
Epidermoid carcinoma, NOS	"
Squamous carcinoma	"
Squamous cell epithelioma	"
Squamous cell carcinoma, keratinizing, NOS	M 8071/3
Squamous cell carcinoma, large cell, keratinizing	"
Epidermoid carcinoma, keratinizing	"
Squamous cell carcinoma, large cell, nonkeratinizing, NOS	M 8072/3
Squamous cell carcinoma, large cell, nonkeratinizing, NOS	"
Epidermoid carcinoma, large cell, nonkeratinizing	"
Squamous cell carcinoma, small cell, nonkeratinizing	M 8073/3
Epidermoid carcinoma, small cell, nonkeratinizing	"
Squamous cell carcinoma, spindle cell	M 8074/3
Epidermoid carcinoma, spindle cell	"
Squamous cell carcinoma, sarcomatoid	"
Squamous cell carcinoma, adenoid	M 8075/3
Squamous cell carcinoma, pseudoglandular	"
Squamous cell carcinoma, acantholytic	"

Description	ICD-O-3 codes
Squamous cell carcinoma in situ with questionable stromal invasion	M 8076/2
Epidermoid carcinoma in situ with questionable stromal invasion	"
Squamous cell carcinoma, microinvasive	M 8076/3
Squamous cell carcinoma, with horn formation	M 8078/3
Bowen's disease	M 8081/2
Intraepidermal squamous cell carcinoma, Bowen type	"
Basaloid squamous cell carcinoma	M 8083/3
Squamous cell carcinoma 'clear cell-type'	M 8084/3
BASAL CELL NEOPLASMS	
Basal cell carcinoma, NOS	M 8090/3
Basal cell epithelioma	"
Rodent ulcer	"
Pigmented basal cell carcinoma	"
Multifocal superficial basal cell carcinoma	M 8091/3
Multicentric basal cell carcinoma	"
Infiltrating basal cell carcinoma, NOS	M 8092/3
Infiltrating basal cell carcinoma, nonsclerosing	"
Infiltrating basal cell carcinoma, sclerosing	"
Basal cell carcinoma, morpheic	"
Basal cell carcinoma, desmoplastic type	"
Basal cell carcinoma, fibroepithelial	M 8093/3
Fibroepithelioma of Pinkus type	"
Fibroepithelial basal cell carcinoma, Pinkus type	"
Pinkus tumor	"
Fibroepithelioma, NOS	"
Basosquamous carcinoma	M 8094/3
Mixed basal-squamous cell carcinoma	"
Metatypical carcinoma	M 8095/3
Basal cell carcinoma, nodular	M 8097/3
Basal cell carcinoma, micronodular	"
Trichilemmal carcinoma	M 8102/3
Trichilemmal carcinoma	"
Pilomatrix carcinoma	M 8110/3
Pilomatrixoma, malignant	"
Pilomatricoma, malignant	"

Description	ICD-O-3 codes
Matrical carcinoma	"
Merkel cell carcinoma	M 8247/3
Merkel cell tumor	"
Primary cutaneous neuroendocrine carcinoma	"
ADNEXAL AND SKIN APPENDAGE NEOPLAMS	
Skin appendage carcinoma	M 8390/3
Adnexal carcinoma	"
Sweat gland adenocarcinoma	M 8400/3
Sweat gland carcinoma	"
Sweat gland tumor, malignant	"
Apocrine adenocarcinoma	M 8401/3
Nodular hidradenoma, malignant	M 8402/3
Hidradenocarcinoma	"
Malignant eccrine spiradenoma	M 8403/3
Sclerosing sweat duct carcinoma	M 8407/3
Syringomatous carcinoma	"
Microcystic adnexal carcinoma	"
Eccrine papillary adenocarcinoma	M 8408/3
Digital papillary adenocarcinoma	"
Eccrine poroma, malignant	M 8409/3
Porocarcinoma	"
Sebaceous adenocarcinoma	M 8410/3
Sebaceous carcinoma	"
Eccrine adenocarcinoma	M 8413/3
Ceruminous adenocarcinoma	M 8420/3
Ceruminous carcinoma	"

NOS = not otherwise specified.

Source: International Classification of Diseases for Oncology- Third Edition (ICD-O-3)

Table B-2. Morphology Codes for the Definition of Skin Melanoma

Cancer Description	ICD-O-3 codes
Melanoma in situ	M 8720/2
Malignant melanoma, NOS (except juvenile melanoma M-8770/0)	M 8720/3
Nodular melanoma	M 8721/3
Balloon cell melanoma	M 8722/3
Malignant melanoma, regressing	M 8723/3
Amelanotic melanoma	M 8730/3
Malignant melanoma in junctional naevus	M 8740/3
Precancerous melanosis, NOS	M 8741/2
Malignant melanoma in precancerous melanosis	M 8741/3
Lentigo maligna	M 8742/2
Hutchinson melanotic freckle, NOS	"
Lentigo maligna melanoma	M 8742/3
Malignant melanoma in Hutchinson melanotic freckle	"
Superficial spreading melanoma	M 8743/3
Acral lentiginous melanoma, malignant	M 8744/3
Desmoplastic melanoma, malignant	M 8745/3
Neurotropic melanoma, malignant	"
Desmoplastic melanoma, amelanotic	"
Mucosal lentiginous melanoma	M 8746/3
Malignant melanoma in giant pigmented nevus	M 8761/3
Malignant melanoma in congenital melanocytic nevus	"
Mixed epithelioid and spindle cell melanoma	M 8770/3
Epithelioid cell melanoma	M 8771/3
Spindle cell melanoma, NOS	M 8772/3
Blue nevus, malignant	M 8780/3

NOS = not otherwise specified.

Source: International Classification of Diseases for Oncology- Third Edition (ICD-O-3)

Table B-3. Morphology Codes for the Definition of Cutaneous Lymphomas With Primary Cutaneous Manifestations

Cancer Description	ICD-O-3 codes
Mature T-cell and Natural Killer Cell Lymphomas	970-971
Mycosis fungoides	M 9700/3
Pagetoid reticulosis	"
Sézary's syndrome	M 9701/3
Angioimmunoblastic T-cell lymphoma	M 9705/3
Peripheral T-cell lymphoma AILD	"
Angioimmunoblastic lymphoma	"
Subcutaneous panniculitis-like T-cell lymphoma	M 9708/3
Cutaneous T-cell lymphoma, NOS	M 9709/3
Cutaneous lymphoma, NOS	"
Anaplastic large cell lymphoma, T cell and Null cell type	M 9714/3
Large cell (Ki-1+) lymphoma	"
Anaplastic large cell lymphoma, NOS	"
Anaplastic large cell lymphoma, CD30+	"
Primary cutaneous CD30+ T-cell lymphoproliferative disorder	M 9718/3
Lymphomatoid papulosis	"
Primary cutaneous anaplastic large cell lymphoma	"
Primary cutaneous CD30+ large T-cell lymphoma	"
NK/T-cell lymphoma, nasal and nasal type	M 9719/3
T/NK-cell lymphoma	"
Angiocentric T-cell lymphoma	"
Malignant reticulosis, NOS	"
Polymorphic reticulosis	"

AILD = angioimmunoblastic lymphadenopathy-type T-cell lymphoma; NOS = not otherwise specified.

Source: International Classification of Diseases for Oncology- Third Edition (ICD-O-3)

Table B-4. Morphology Codes for the Definition of Hodgkin and Non-Hodgkin Lymphomas

Cancer Description	ICD-O-3 codes
HODGKIN LYMPHOMA	**M 965-966**
Hodgkin lymphoma, NOS	M 9650/3
Hodgkin disease, NOS	"
Malignant lymphoma, Hodgkin	"
Hodgkin lymphoma, lymphocyte-rich	M 9651/3
Classical Hodgkin lymphoma, lymphocyte-rich	"
Hodgkin disease, lymphocyte predominance, NOS	"
Hodgkin disease, lymphocytic-histiocytic predominance	"
Hodgkin disease, lymphocyte predominance, diffuse	"
Hodgkin lymphoma, mixed cellularity, NOS	M 9652/3
Classical Hodgkin lymphoma, mixed cellularity, NOS	"
Hodgkin lymphoma, lymphocyte depletion, NOS	M 9653/3
Classical Hodgkin lymphoma, lymphocyte depletion, NOS	"
Hodgkin lymphoma, lymphocyte depletion, diffuse fibrosis	M 9654/3
Classical Hodgkin lymphoma, lymphocyte depletion, diffuse fibrosis	"
Hodgkin lymphoma, lymphocyte depletion, reticular	M 9655/3
Classical Hodgkin lymphoma, lymphocyte depletion, reticular	"
Hodgkin lymphoma, nodular lymphocyte predominance	M 9659/3
Hodgkin lymphoma, lymphocyte predominance, nodular	"
Hodgkin paragranuloma, NOS	"
Hodgkin paragranuloma, nodular	"
Hodgkin granuloma	M 9661/3
Hodgkin sarcoma	M 9662/3
Hodgkin lymphoma, nodular sclerosis, NOS	M 9663/3
Classical Hodgkin lymphoma, nodular sclerosis, NOS	"
Hodgkin disease, nodular sclerosis, NOS	"
Hodgkin lymphoma, nodular sclerosis, cellular phase	M 9664/3
Classical Hodgkin lymphoma, nodular sclerosis, cellular phase	"
Hodgkin lymphoma, nodular sclerosis, grade 1	M 9665/3
Classical Hodgkin lymphoma, nodular sclerosis, grade 1	"
Hodgkin disease, nodular sclerosis, lymphocyte predominance	"
Hodgkin disease, nodular sclerosis, mixed cellularity	"
Hodgkin lymphoma, nodular sclerosis, grade 2	M 9667/3

Cancer Description	ICD-O-3 codes
Classical Hodgkin lymphoma, nodular sclerosis, grade 2	"
Hodgkin disease, nodular sclerosis, lymphocyte depletion	"
Hodgkin disease, nodular sclerosis, syncytial variant	"
NON-HODGKIN LYMPHOMAS	**M 967-972**
Mature B-cell Lymphomas	**M967-969**
Malignant lymphoma, small B lymphocytic, NOS	M 9670/3
Malignant lymphoma, small lymphocytic, NOS	"
Malignant lymphoma, lymphocytic, well differentiated diffuse	"
Malignant lymphoma, lymphocytic, NOS	"
Malignant lymphoma, lymphocytic, diffuse, NOS	"
Malignant lymphoma, small cell, NOS	"
Malignant lymphoma, small lymphocytic, diffuse	"
Malignant lymphoma small cell diffuse	"
Malignant lymphoma, lymphoplasmacytic	M 9671/3
Malignant lymphoma, lymphoplasmacytoid	"
Immunocytoma	"
Malignant lymphoma, plasmacytoid	"
Plasmacytic lymphoma	"
Mantle cell lymphoma	M 9673/3
Mantle zone lymphoma	"
Malignant lymphoma, lymphocytic intermediate differentiation, diffuse	"
Malignant lymphoma, centrocytic	"
Malignant lymphomatous polyposis	"
Malignant lymphoma, mixed small and large cell, diffuse	M 9675/3
Malignant lymphoma, mixed lymphocytic-histiocytic, diffuse	"
Malignant lymphoma, mixed cell type, diffuse	"
Malignant lymphoma, centroblastic-centrolytic	"
Malignant lymphoma, centroblastic-centrolytic, diffuse	"
Primary effusion lymphoma	M 9678/3
Mediastinal large B-cell lymphoma	M 9679/3
Thymic large B-cell lymphoma	"
Malignant lymphoma, large B-cell, diffuse, NOS	M 9680/3
Diffuse large B-cell lymphoma, NOS	"
Malignant lymphoma, large cell, NOS	"
Malignant lymphoma, large B-cell, NOS	"

Cancer Description	ICD-O-3 codes
Malignant lymphoma, histiocytic, NOS	"
Malignant lymphoma, histiocytic, diffuse	"
Malignant lymphoma, large cell, cleaved and noncleaved	"
Malignant lymphoma, large cell, diffuse, NOS	"
Malignant lymphoma, large cleaved cell, NOS	"
Malignant lymphoma, large cell, cleaved, diffuse	"
Malignant lymphoma, large cell, cleaved, NOS	"
Malignant lymphoma, large cell, noncleaved, diffuse	"
Malignant lymphoma, large cell noncleaved, NOS	"
Malignant lymphoma, noncleaved, diffuse, NOS	"
Malignant lymphoma, noncleaved, NOS	"
Malignant lymphoma, large B-cell, diffuse, centroblastic, NOS	"
Malignant lymphoma, centroblastic, NOS	"
Malignant lymphoma, centroblastic, diffuse	"
Intravascular large B-cell lymphoma	"
Intravascular B-cell lymphoma	"
Angioendotheliomatosis	"
Angiotropic lymphoma	"
T-cell rich large B-cell lymphoma	"
Histiocyte-rich large B-cell lymphoma	"
T-cell rich/histiocyte-rich large B-cell lymphoma	"
Anaplastic large B-cell lymphoma	"
Malignant lymphoma, large B-cell diffuse, immunoblastic, NOS	M 9684/3
Malignant lymphoma, immunoblastic, NOS	"
Immunoblastic sarcoma	"
Malignant lymphoma, large cell, immunoblastic	"
Plasmablastic lymphoma	"
Burkitt lymphoma, NOS	M 9687/3
Burkitt tumor	"
Malignant lymphoma, undifferentiated, Burkitt type	"
Malignant lymphoma, small noncleaved, Burkitt type	"
Burkitt like lymphoma	"
Splenic marginal zone B-cell lymphoma	M 9689/3
Splenic marginal zone lymphoma, NOS	"
Splenic lymphoma with villous lymphocytes	"

Cancer Description	ICD-O-3 codes
Follicular lymphoma, NOS	M 9690/3
Malignant lymphoma, follicular, NOS	"
Malignant lymphoma, follicle center, follicular	"
Malignant lymphoma, follicle center, NOS	"
Malignant lymphoma, centroblastic-centrocytic, follicular	"
Malignant lymphoma, nodular, NOS	"
Malignant lymphoma, lymphocytic, nodular, NOS	"
Follicular lymphoma, grade 2	M 9691/3
Malignant lymphoma, mixed small cleaved and large cell, follicular	"
Malignant lymphoma, mixed lymphocytic-histiocytic, nodular	"
Malignant lymphoma, mixed cell type, follicular	"
Malignant lymphoma, mixed cell type, nodular	"
Follicular lymphoma, grade 1	M 9695/3
Malignant lymphoma, small cleaved cell, follicular	"
Follicular lymphoma, small cleaved cell	"
Malignant lymphoma, lymphocytic, poorly differentiated, nodular	"
Follicular lymphoma, grade 3	M 9698/3
Malignant lymphoma, large cell, follicular, NOS	"
Malignant lymphoma, large cell, noncleaved, follicular	"
Malignant lymphoma, histiocytic, nodular	"
Malignant lymphoma, noncleaved cell, follicular, NOS	"
Malignant lymphoma, large cleaved cell, follicular	"
Malignant lymphoma, centroblastic, follicular	"
Malignant lymphoma, lymphocytic, well differentiated, nodular	"
Marginal zone B-cell lymphoma NOS	M 9699/3
Marginal zone lymphoma, NOS	"
Mucosal-associated lymphoid tissue (MALT) lymphoma	"
MALT lymphoma	"
Bronchial-associated lymphoid tissue (BALT) lymphoma	"
BALT lymphoma	"
Skin-associated lymphoid tissue (SALT) lymphoma	"
SALT lymphoma	"
Monocytoid B-cell lymphoma	"
Nodal marginal zone lymphoma	"

Cancer Description	ICD-O-3 codes
MATURE T AND NK-CELL LYMPHOMAS	**M970-971**
Mature T-cell lymphoma, NOS	M 9702/3
Peripheral T-cell lymphoma, NOS	"
T-cell lymphoma, NOS	"
Peripheral T-cell lymphoma, pleomorphic small cell	"
Peripheral T-cell lymphoma, pleomorphic medium and large cell	"
Peripheral T-cell lymphoma, large cell	"
T-zone lymphoma	"
Lymphoepithelioid lymphoma	"
Lennert lymphoma	"
Hepatosplenic γ/δ (gamma-delta) cell lymphoma	M 9716/3
Intestinal T-cell lymphoma	M 9717/3
Enteropathy type intestinal T-cell lymphoma	"
Enteropathy associated T-cell lymphoma	"
PRECURSOR CELL LYMPHOBLASTIC LYMPHOMA	**972**
Precursor cell lymphoblastic lymphoma, NOS	M 9727/3
Malignant lymphoma, lymphoblastic, NOS	"
Malignant lymphoma, convoluted cell	"
Lymphoblastoma	"
Precursor B-cell lymphoblastic lymphoma	M 9728/3
Precursor T-cell lymphoblastic lymphoma	M 9729/3
MALIGNANT LYMPHOMAS, NOS OR DIFFUSE	M959
Malignant lymphoma, NOS	M 9590/3
Lymphoma, NOS	"
Microglioma	"
Malignant lymphoma, non-Hodgkin, NOS	M 9591/3
Non-Hodgkin lymphoma, NOS	"
B cell lymphoma, NOS	"
Malignant lymphoma, noncleaved cell, NOS	"
Malignant lymphoma diffuse, NOS	"
Malignant lymphoma, lymphocytic, intermediate differentiation, nodular	"
Malignant lymphoma, small cell, noncleaved, diffuse	"
Malignant lymphoma, undifferentiated cell, non-Burkitt	"
Malignant lymphoma, undifferentiated cell type, NOS	"
Lymphosarcoma, NOS	"

Cancer Description	ICD-O-3 codes
Lymphosarcoma, diffuse	"
Reticulum cell sarcoma, NOS	"
Reticulum cell sarcoma, diffuse	"
Reticulosarcoma, NOS	"
Reticulosarcoma, diffuse	"
Malignant lymphoma, small cleaved cell, diffuse	"
Malignant lymphoma, lymphocytic, poorly differentiated, diffuse	"
Malignant lymphoma, small cleaved cell, NOS	"
Malignant lymphoma, cleaved cell, NOS	"
Composite Hodgkin and non-Hodgkin lymphoma	M 9596/3

NOS = not otherwise specified.

Source: International Classification of Diseases for Oncology- Third Edition (ICD-O-3)

Note: All the cutaneous lymphomas listed in Table B-3 will also be counted toward the “non-Hodgkin lymphoma” endpoint and toward the “Any lymphoma” endpoint but for simplicity purposes the diagnoses listed in Table B-4 are limited to those that have not already been listed in Table B-3.

Appendix C.
Estimation of Propensity Scores: Preliminary List of Variables

Table C-1. Preliminary List of Covariates to be Included in the Logistic Model for the Estimation of Propensity Scores and in the Analysis to Characterize Users of the Study Medications

Coding of variables is ICD-9-CM; however, each database research partner will adapt these descriptive codes to the specific classification of disease used in each database (e.g., OXMIS or Read codes in CPRD; ICD-10 in Sweden).

- Age at start date of each study cohort
- Sex
- Calendar year at start date of each study cohort
- Severity of atopic dermatitis. Based on the use of health care resources in the 12 months before the start date (Arellano et al., 2007; Margolis et al., 2001)
  - At least one visit to the dermatologist for patients younger than 3 years old, or
  - At least four physician or pediatrician visits for patients 3 years old and older, or
  - At least one hospitalization with a primary discharge diagnosis for atopic dermatitis
- Disease potentially interacting with the immune system[a] (ICD-9-CM codes)
  - Psoriasis (696)
  - Epstein-Barr virus infection (075)
  - Rheumatoid arthritis (714)
  - Systemic lupus erythematosus (710.0)
  - Sjögren's syndrome (710.2)
  - Celiac sprue (579.0)
  - Asthma (493)
  - Allergic rhinitis (477)
- Skin disease (excluding atopic dermatitis, eczema and psoriasis)[a] (ICD-9-CM codes)
  - Inflammatory skin diseases (690, 691.0, 692.0-692.8, 693-695, 697, 698)
  - Other skin diseases (700-709)
- Chronic disease[a] (ICD-9-CM codes)
  - Malignancy (140-171, 174-199, 203-208, 230-231, 232-238.1, 238.3-238.9) excluding skin cancer (172,173, 232, 238.2) and lymphoma (200-202)
  - Diseases of the immune system (279)
  - Organ transplantation (V42, V43.2, 996.8)
  - HIV infection or AIDS (042, V08)
  - Renal failure (584)
  - Chronic liver disease and hepatic failure (570, 571, 572.2, 572.3, 572.4, 573)

  - Ischemic heart disease (410-414)
  - Hypertensive disease (401-405)
  - Heart failure (428)
  - Other cardiovascular diseases (390-398, 415-417, 420, 427,429, 440-448)
  - Cerebrovascular diseases (430-438)
  - Diabetes mellitus (250)
  - Chronic obstructive pulmonary disease (COPD), emphysema, respiratory insufficiency (491, 492, 496, 518.8)
  - Musculoskeletal system and connective disease (excluding rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's syndrome) (710.1, 710.3-710.9, 711-713, 715-739)
- Use of topical corticosteroids (ATC). Total number of prescriptions within 12 months before the start date. Categorized as 0, 1, 2, and 3 or more.
  - Topical corticosteroids, plain
    - Weak (D07AA)
    - Moderately potent (D07AB)
    - Potent (D07AC)
    - Very potent (D07AD)
  - Topical corticosteroids, combinations with other agents
    - Weak (D07BA, D07CA, D07XA)
    - Moderately potent (D07BB, D07CB, D07XB)
    - Potent (D07BC, D07CC, D07XC)
    - Very potent (D07BD, D07CD, D07XD)
- Use of immunosuppressant and cytostatic drugs[b] (ATC)
  - Systemic corticosteroids (H02AB, H02B)
  - Systemic tacrolimus (L04AD02)
  - Immunosuppressants and immunomodulating agents (excluding systemic tacrolimus) (L03, L04AA, L04AB, L04AC, L04AD01, L04AX)
  - Systemic antivirals (J05)
  - Anticancer drugs (L01)
- Use of dermatological agents[b] (excluding topical corticosteroids) (ATC)
  - Antipsoriatics
    - Antipsoriatics for topical use (D05A)
    - Antipsoriatics for systemic use (D05B)
  - Other dermatological agents (D01-D04, D06, D08-D11)

- Use of other drugs[b] (ATC)
  - Cardiovascular system drugs (excluding lipid modifying agents) (C01-C09)
  - Anti-inflammatory and anti-rheumatic agents, nonsteroidal (M01A)
  - Other anti-rheumatic agents (M01B, M01C)
  - Hormone replacement therapy (G03C, G03E, G03F)
  - Lipid modifying agents (C10)
  - Insulins (A10A)
  - Oral antidiabetics (A101B)
  - Antiepileptics (N03)
  - Drugs for obstructive airways disease (excluding inhaled corticosteroids) (R03A, R03BB, R03BC, R03BX, R03C, R03D)
  - Inhaled corticosteroids (R03BA)
- Type of prescriber of first prescription of study medications (general practitioner, pediatrician, dermatologist, other specialist)
- Utilization of health care resources in the in the 365 days before the start date. Categorized as 0, 1, and 2 or more (where available)
  - Number of visits to general practitioner
  - Number of visits to dermatologist
  - Number of visits to pediatrician
  - Number of outpatient hospital visits
  - Number of hospitalizations (excluding hospital outpatient visits)

[a] Hospitalization, specialist referral, or general practitioner diagnosis in the five years before the start date: yes/no.

[b] Prescription at the start date or within the 365 days before the start date: yes/no.

Appendix D.
Incidence Rates of Study Malignancies and Population in Nordic Countries

Table D-1. Incidence Rates (per 100,000 Population) of Study Malignancies in the General Population for the year 2008

		Cancer Type				
Sex	Age (Years)	Skin, Nonmelanoma	Melanoma of Skin	Non-Hodgkin Lymphoma	Hodgkin Lymphoma	Cutaneous T-cell Lymphoma[a]
Male	0-4	0.1	0	1.5	0	0.1
	5-9	0.1	0	1.4	0.4	0.1
	10-14	0	0.4	0.8	2.2	0.4
	15-19	0.1	0.8	0.9	2.6	0.4
	20-24	0	2.7	1.5	3.6	0.4
	25-29	0.4	5	2	3.3	0.4
	30-34	1.7	10.1	4.3	4.2	0.8
	35-39	1.7	14.7	5.7	2.9	0.7
	40-44	2.9	19.3	8.5	2.8	1.1
	45-49	5.4	20.3	11.2	2.4	1.8
	50-54	7.3	28	20.3	3	1.6
	55-59	18.3	37.1	29	1.8	2.4
	60-64	37.3	56.9	45.1	4.2	3.5
	65-69	69.2	62.4	55	3.1	4.3
	70-74	124.3	81.1	69.9	4.3	5.9
	75-79	217.4	101.5	94.2	4.4	7.7
	80-84	343.6	84.9	92	3.3	5.9
	85+	573.4	115.7	94.7	4.1	6.4
Female	0-4	0	0	0.3	0	0.1
	5-9	0	0	0.1	0	0
	10-14	0	0.4	1.1	0.8	0.1
	15-19	0.1	1.7	1	4.2	0.3
	20-24	1.3	8.1	1.3	3.5	0.3
	25-29	0.1	12.7	2.8	3	0.5
	30-34	1	17.5	3.3	2.9	0.5
	35-39	1.9	23.8	3.2	2	0.6
	40-44	3.9	30.7	4.4	0.9	0.9
	45-49	5.7	27.7	8.6	1.4	1.2
	50-54	10.3	29.9	13.3	0.8	1.6
	55-59	12.9	34.4	20.5	1.3	1.2

		Cancer Type				
Sex	**Age (Years)**	**Skin, Nonmelanoma**	**Melanoma of Skin**	**Non-Hodgkin Lymphoma**	**Hodgkin Lymphoma**	**Cutaneous T-cell Lymphoma[a]**
	60-64	28.4	44.8	32.7	1	2.1
	65-69	41.1	47	41.5	2.4	2.6
	70-74	72.1	51.5	54.6	3.8	3.7
	75-79	113.3	57.5	68	2.2	3.4
	80-84	169.8	53.9	71	3.2	4
	85+	284.2	66.6	54.6	1.3	2.9
Overall	0-4	0.05	0.00	0.91	0.00	0.07
	5-9	0.05	0.00	0.77	0.20	0.06
	10-14	0.00	0.40	0.95	1.52	0.24
	15-19	0.10	1.24	0.95	3.38	0.37
	20-24	0.64	5.34	1.40	3.55	0.36
	25-29	0.25	8.78	2.39	3.15	0.49
	30-34	1.36	13.73	3.81	3.56	0.66
	35-39	1.80	19.17	4.47	2.46	0.65
	40-44	3.39	24.88	6.49	1.87	1.01
	45-49	5.55	23.94	9.92	1.91	1.47
	50-54	8.79	28.94	16.83	1.91	1.59
	55-59	15.61	35.75	24.76	1.55	1.74
	60-64	32.84	50.83	38.88	2.60	2.76
	65-69	54.78	54.50	48.07	2.74	3.44
	70-74	96.38	65.27	61.72	4.03	4.73
	75-79	158.32	76.53	79.33	3.15	5.26
	80-84	237.10	65.90	79.13	3.24	4.76
	85+	372.08	81.52	66.79	2.15	4.04

Source (except for cutaneous T-cell lymphoma): NORDCAN: cancer incidence, mortality, prevalence and survival in the Nordic countries, version 4.0. Updated Jun 2011. Association of the Nordic Cancer Registries. Danish Cancer Society. Available at: http://www.ancr.nu. Accessed November 4, 2011.

[a] Source (for cutaneous T-cell lymphoma): Surveillance Epidemiology and End Results (SEER) program in the US. Surveillance Research Program, National Cancer Institute SEER*Stat software (www.seer.cancer.gov/seerstat) version 7.0.5.

Table D-2. Population in NORDCAN Countries, 2008

Age (Years)	Male	Female	Total
0-4	752,915	716,693	1,469,608
5-9	727,218	693,462	1,420,680
10-14	782,844	745,763	1,528,607
15-19	847,172	803,960	1,651,132
20-24	774,738	741,157	1,515,895
25-29	782,771	754,349	1,537,120
30-34	827,688	798,692	1,626,380
35-39	872,893	842,093	1,714,986
40-44	944,124	905,833	1,849,957
45-49	864,905	837,727	1,702,632
50-54	838,518	825,119	1,663,637
55-59	830,231	824,832	1,655,063
60-64	829,492	834,130	1,663,622
65-69	583,523	614,897	1,198,420
70-74	437,476	503,216	940,692
75-79	341,769	448,543	790,312
80-84	239,238	378,618	617,856
85+	171,097	391,958	563,055
Total	12,448,612	12,661,042	25,109,654

Source: NORDCAN: cancer incidence, mortality, prevalence and survival in the Nordic countries, version 4.0. Updated Jun 2011. Association of the Nordic Cancer Registries. Danish Cancer Society. Available at: http://www.ancr.nu. Accessed November 4, 2011.

Appendix E. Study Size and Precision

Calculations for Table E-1 and Table E-2 used a matching ratio (corticosteroids to tacrolimus or pimecrolimus) of 4:1.

Table E-1. Estimated Number of Person-Years Exposed to Tacrolimus Needed to Have an 80% Probability That the Upper Limit for the 95% Confidence Interval of the Rate Ratio is Below 2, 4, 8, or 16[a]

Cancer Type by Age Group	Incidence per 100,000 Person-years	Upper Limit for the 95% CI of the Rate Ratio is Below			
		2	4	8	16
All ages					
Skin, nonmelanoma	30.08	67,900	17,000	7,600	4,300
Melanoma of skin	25.17	81,200	20,300	9,100	5,100
Non-Hodgkin lymphoma	18.03	113,300	28,400	12,600	7,100
Hodgkin lymphoma	2.31	884,000	221,000	98,300	55,300
CTCL	1.48	1,379,800	345,000	153,400	86,300
Age 0-19 years[b]					
Skin, nonmelanoma	0.05	39,270,300	9,817,600	4,363,400	2,454,400
Melanoma of skin	0.44	4,662,200	1,165,600	518,100	291,400
Non-Hodgkin lymphoma	0.90	2,276,600	569,200	253,000	142,300
Hodgkin lymphoma	1.35	1,513,800	378,500	168,200	94,700
CTCL	0.19	10,635,700	2,659,000	1,181,800	664,800
Age 20+ years					
Skin, nonmelanoma	39.65	51,500	12,900	5,800	3,300
Melanoma of skin	33.05	61,800	15,500	6,900	3,900
Non-Hodgkin lymphoma	23.48	87,000	21,800	9,700	5,500
Hodgkin lymphoma	2.62	780,900	195,300	86,800	48,900
CTCL	1.89	1,081,600	270,400	120,200	67,600

CI = confidence interval; CTCL = cutaneous T-cell lymphoma.

Note: Calculations were obtained using Episheet (study size sheet) (Rothman, 2011).

[a] Allocation ratio 4:1.

[b] For statistical power calculations, the upper limit of age in children was set at 19 years. However, the age of children for the study implementation is < 18 years in accordance with the regulatory definition.

Table E-2. For Each Study Endpoint, Probability That the Upper Limit for the 95% Confidence Interval of the Rate Ratio is Below 2, 4, 8, or 16[a]

Cancer Type by Age Group	Incidence per 100,000 Person-years	Upper Limit for the 95% CI of the Rate Ratio is Below			
		2	4	8	16
All ages					
Skin, nonmelanoma	30.08	1.00	1.00	1.00	1.00
Melanoma of skin	25.17	0.99	1.00	1.00	1.00
Non-Hodgkin lymphoma	18.03	0.96	1.00	1.00	1.00
Hodgkin lymphoma	2.31	0.27	0.76	0.98	1.00
CTCL	1.48	0.19	0.57	0.89	0.99
Ages 0-19 years[b]					
Skin, nonmelanoma	0.05	0.031	0.039	0.048	0.058
Melanoma of skin	0.44	0.048	0.084	0.138	0.213
Non-Hodgkin lymphoma	0.90	0.061	0.130	0.238	0.383
Hodgkin lymphoma	1.35	0.073	0.173	0.333	0.531
CTCL	0.19	0.038	0.057	0.083	0.116
Ages 20+ years					
Skin, nonmelanoma	39.65	1.00	1.00	1.00	1.00
Melanoma of skin	33.05	0.99	1.00	1.00	1.00
Non-Hodgkin lymphoma	23.48	0.96	1.00	1.00	1.00
Hodgkin lymphoma	2.61	0.23	0.69	0.96	1.00
CTCL	1.89	0.18	0.55	0.88	0.99

CI = confidence interval; CTCL = cutaneous T-cell lymphoma.

Note: Calculations were obtained using Episheet (study size sheet) (Rothman, 2011) and based on 50,000 person-years in the 0-19 years age group and 150,000 person-years in the 20+ years age group.

[a] Allocation ratio 4:1.

[b] For statistical power calculations the upper limit of age in children was set at 19 years. However, the age of children for the study implementation is < 18 years in accordance with the regulatory definition.

Appendix F.
ENCePP Study Protocol Checklist

Doc.Ref. EMEA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2)

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

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

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

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

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	41-42
1.1.2 End of data collection[2]	☒	☐	☐	41-42

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

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

1.1.3 Study progress report(s)	☒	☐	☐	40
1.1.4 Interim progress report(s)	☒	☐	☐	40
1.1.5 Registration in the EU PAS register	☒	☐	☐	40
1.1.6 Final report of study results	☒	☐	☐	41-42

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	4
2.1.2 The objectives of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	12
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 if applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Rather than testing a statistical difference between treatments with a priori hypothesis the study aims at measuring and comparing risk estimates among groups.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	10
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	22
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	33

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	11
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	10
4.2.2 Age and sex?	☒	☐	☐	12
4.2.3 Country of origin?	☒	☐	☐	11
4.2.4 Disease/indication?	☒	☐	☐	13
4.2.5 Co-morbidity?	☒	☐	☐	24
4.2.6 Seasonality?	☐	☒	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	12

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	18
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	18, 19
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	19
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	20

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	22
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	23

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	24
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	31

Comments:

Design attempts to address confounding by indication/severity, potential differential information and surveillance across exposure groups

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	13
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	23
8.1.3 Covariates?	☒	☐	☐	24
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	Appendix A
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Appendix A
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	Appendix A

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	Appendix C
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☒	☐	☐	Appendix B
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	17
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	Appendix A

Comments:

See Appendix A: Summary of characteristics of databases

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	26-31

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	35
10.2 Is the choice of statistical techniques described?	☒	☐	☐	29
10.3 Are descriptive analyses included?	☒	☐	☐	30
10.4 Are stratified analyses included?	☒	☐	☐	31
10.5 Does the plan describe the methods for adjusting for confounding?	☒	☐	☐	24
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	32

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	16-17

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	35
11.3 Are methods of quality assurance described?	☒	☐	☐	36
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	36
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	14
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	34
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	27
12.3 Does the protocol address other limitations?	☒	☐	☐	36

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/ Institutional Review Board approval been described?	☒	☐	☐	38
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	38

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	44

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	40
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	39

Comments:

Name of the main author of the protocol: Susana Perez-Gutthann, MD, PhD

Date: 10/Apr/2013

Signature: _____