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

Study Protocol – Version 5.0
EU PAS Register Number: ENCEPP/SDPP/4357

June 30, 2017

Prepared for

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PASS Information

Title	Risk of Skin Cancer and Lymphoma in Users of Topical Tacrolimus, Pimecrolimus, and Corticosteroids Protopic JOint European Longitudinal Lymphoma and skin cancer Evaluation (JOELLE) Study
Protocol version identifier	Version 5.0
Date of last version of protocol	June 30, 2017
EU PAS Register number	ENCEPP/SDPP/4357
Active substance	Topical tacrolimus (ATC code: D11AH01) Topical pimecrolimus (ATC code: D11AH02)
Medicinal product	Protopic® Elidel®
Product reference	EU/1/02/201 (PROTOPIC®)
Procedure number	EMEA/H/C/000374 (PROTOPIC®)
Marketing authorization holder(s)	LEO Pharma A/S
Joint PASS	No
Research question and 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 with a diagnosis of atopic dermatitis or with at least two prescriptions of moderate- to high-potency topical corticosteroids within a period of 12 months ▪ New users of topical pimecrolimus compared with users of moderate- to high-potency topical corticosteroids with a diagnosis of atopic dermatitis or with at least two prescriptions of moderate- to high-potency topical corticosteroids within a period of 12 months
Country(-ies) of study	United Kingdom; The Netherlands; Denmark; Sweden
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Project Title: Risk of Skin Cancer and Lymphoma in Users of Topical Tacrolimus, Pimecrolimus, and Corticosteroids—Protopic JOint European Longitudinal Lymphoma and skin cancer Evaluation (JOELLE) Study

Protocol ID Number: F506-CL-5810

LEO Pharma Protocol ID Number: NIS-PROTOPIC-1306

Version and date: Version 5.0, June 30, 2017

The following people have reviewed the protocol and give their approval:

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Protocol ID Number: F506-CL-5810

LEO Pharma Protocol ID Number: NIS-PROTOPIC-1306

Version and date: Version 5.0, June 30, 2017

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Project Title: Risk of Skin Cancer and Lymphoma in Users of Topical Tacrolimus, Pimecrolimus, and Corticosteroids—Protopic Joint European Longitudinal Lymphoma and skin cancer Evaluation (JOELLE) Study

Protocol ID Number: F506-CL-5810

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Version and date: Version 5.0, June 30, 2017

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Protocol ID Number: F506-CL-5810

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Protocol ID Number: F506-CL-5810

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Version and date: Version 5.0, June 30, 2017

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Protocol ID Number: F506-CL-5810

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1 Table of Contents

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2 List of 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
NCR	Netherlands Cancer Registry
NHS	National Health Service
NK	natural killer (a type of white blood cell)
NMSC	non-melanoma 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

The analysis of Phase I involved the period from the date of first availability of topical tacrolimus and topical pimecrolimus in each study population through December 31, 2011. In the JOELLE Extension, the study period is extended for 4 years, with a period of inclusion of new users from the date of first availability of topical tacrolimus and topical pimecrolimus in each study population through December 31, 2014, and a follow-up of all new users through December 31, 2015. This ensures a follow-up of at least 6 months of all new users after applying a 6-month induction period. In some databases, data beyond 2015 may be available and will be included in the study.

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.

Because prescription data in Sweden are available only since 2015, the users of topical tacrolimus and topical pimecrolimus in Sweden could be past users of the study medications.

Moderate- to high-potency corticosteroids cohorts:

1. Individuals with a recorded diagnosis of atopic dermatitis at any time before the start date who received a prescription for moderate- to high-potency topical corticosteroids during the study period after the eligibility date.
2. Individuals without a recorded diagnosis of atopic dermatitis before the start date who received a prescription for moderate- to high-potency topical corticosteroids during the study period and at least one other prescription (for moderate- to high-potency topical corticosteroids) within the 12 months before the start 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.

Untreated 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 recorded prescription for topical tacrolimus
- Pimecrolimus cohort: date of first recorded prescription for topical pimecrolimus
- Corticosteroids cohorts: the start date for the corticosteroids cohorts will depend on the availability of a recorded diagnosis of atopic dermatitis, as follows:
    1. Patients with a recorded diagnosis of atopic dermatitis: date of first prescription for moderate- to high-potency topical corticosteroids recorded during the study period after the eligibility date.
    2. Patients without a recorded diagnosis of atopic dermatitis: date of first prescription for moderate- to high-potency topical corticosteroids recorded during the study period after the eligibility date and after having another recorded prescription within the prior 12 months.
- Untreated 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.

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4 Abstract

Title: Risk of Skin Cancer and Lymphoma in Users of Topical Tacrolimus, Pimecrolimus, and Corticosteroids—Protopic JOint European Longitudinal Lymphoma and skin cancer Evaluation (JOELLE) Study

Rationale and background: Topical tacrolimus is indicated for the treatment of moderate to severe atopic dermatitis, and topical pimecrolimus for the treatment of mild to moderate atopic dermatitis. Safety data from animal studies, systemic use in patients with organ transplants, and case reports have raised concerns about a potential increase in the risk of lymphoma and skin cancer associated with the use of these agents, especially in children. The study is listed in the Protopic® Risk Management Plan as an ongoing additional pharmacovigilance activity (formerly, Committee for Medicinal Products for Human Use [CHMP] follow-up measure [FUM-039], merged into follow-up measure RMP052 which is now closed). The requirement was issued upon the approval of the additional indication of maintenance therapy for tacrolimus ointment in February 2009.

Research question and objectives: 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 untreated population.

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. 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 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.

Study design: The study design is a multinational collaborative cohort study evaluating populations enrolled in four European population-based data sources.

Population: The study will be conducted following a common protocol in populations covered in population-based health databases and cancer registries in four countries in Europe that are available for research and that provide access to health-related data including prescription drug data: the PHARMO Database Network in the Netherlands, the Danish health databases, the Swedish health databases, and the Clinical Practice Research Datalink (CPRD) in the UK.

The study population is all individuals of any age registered in the study databases from the date topical tacrolimus became available in each country through 31 December 2014

(period of inclusion), and who have at least 12 months of continuous enrollment in the study databases, except for children 0 to 12 months of age.

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.

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 untreated patients.

Variables: 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 untreated cohort will be individually matched to the corticosteroids cohort identified for comparison with users of tacrolimus.

The study endpoints are any skin malignancy, non-melanoma 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 or pathology registries, complemented with hospital and general practitioner data.

Data sources: Automated health databases in four countries: the PHARMO Database Network in the Netherlands; Danish health databases (accessed through partnership with the Southern Denmark University); Swedish health databases (accessed through partnership with Karolinska Institutet); and the CPRD in the UK. The study is coordinated by RTI Health Solutions in Spain and the United States.

Study size:

The table below shows the number of patients studied in Phase I of the study (data collection through December 31, 2011), and the total number of patients expected to be included in the JOELLE Extension.

Table Abstract-1. Number of New Users of Tacrolimus and Person-years of Follow-up in Phase I (2002–2011) and Estimated Total Number in the JOELLE Extension (2002-2015)

	Phase I[a]		JOELLE Extension[b]	
	Total Number of New Users	Person-years of Follow-up	Estimated Number of New Users	Estimated Person-years of Follow-up
Children aged < 18 years	19,948	50,316	24,412	133,285
Adults aged ≥ 18 years	66,127	198,400	98,788	551,369

[a] Actual values.

[b] Assumes 3 additional years of inclusion of new users (through December 31, 2014) and at least 1 year of follow-up (through December 31, 2015). Depending on data availability, the extension may be longer in some of the study databases.

Data analysis: 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 related 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 exposures of interest will be the cumulative dose of topical tacrolimus and pimecrolimus and time since first exposure.

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 patient and person-time counts by exposure category, endpoint, deciles of exposure propensity scores, age, sex, data source, and type of prescriber of first prescription when available. 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 untreated patients. Sensitivity analyses will be conducted to evaluate protopathic and surveillance bias. Separate analyses will be conducted for the pediatric and adult populations.

Milestones:

The study protocol version 4.0 dated April 10, 2013, was approved by the EMA.

The study was registered in the EU PAS Register in July 30, 2013 (http://www.encepp.eu/encepp/viewResource.htm?id=4358).

Phase I of the study was completed November 30, 2015. The study report was submitted to the EMA on December 11, 2015.

The JOELLE Extension involves the inclusion of 4 years of additional data. Depending on data availability, the extension may be longer in some of the study databases. The start of data collection is planned between Q3 2017 and Q1 2018. The final study report is expected to be completed in Q3 2019.

5 Amendments and Updates

The protocol version 4.0 dated April 10, 2013, was the protocol endorsed by the EMA and first posted in the EU PAS Register. This protocol was developed prior to release of the EMA guidance on protocol format.

The protocol version 5.0, dated June 30, 2017 is the protocol amended to reflect nonsubstantial changes proposed for implementing the JOELLE Extension after finalization of Phase I. This protocol follows EMA guidance on protocol format.

Summary of Amendments and Updates

Version Number	Date	Section(s) of Study Protocol	Amendment or Update	Reason
5.0	30 Jun 2017	All sections	Use of EMA template	Follow EMA guidance on protocol format
5.0	30 Jun 2017	PASS Information Approval pages	Updated author, MAH, MAH contact person, approvals	Added protocol amendment author; change in MAH; changes in approvals
5.0	30 Jun 2017	3. Responsible Parties	Addition of LEO Pharma A/S; Updated responsible parties	Change in MAH and responsible parties
5.0	30 Jun 2017	6. Milestones and Timelines	Revised timelines for completing JOELLE Extension	Based on data management needs and patient accrual
5.0	30 Jun 2017	Abstract 9.2.1 Study period	Included study period for JOELLE Extension	Precision based on Phase I results
5.0	30 Jun 2017	9.3.3 New users	Clarification of definition of new users in Sweden	Prescription drug data in Sweden are available only since 2005
5.0	30 Jun 2017	9.3.6 Case Identification and Validation 9.4 Data Sources	Linkage to National Cancer Registry in Netherlands will be used to identify stage of melanoma skin cancer for sensitivity analysis	Linkage available for staging of malignant melanoma for JOELLE Extension
5.0	30 Jun 2017	9.3.6.1 Assessment of Protopathic Bias for CTCL	Extended to Sweden. Questionnaire to be sent to general practitioners in CPRD.	Review of medical records available in Sweden. Free-text no longer available in CPRD. Improved evaluation of protopathic bias.
5.0	30 Jun 2017	9.6 Study Size 9.9 Limitations of Research Methods Annex 6 Annex 7	Estimation based on Phase I data and 4-year follow-up; removed Annex 6 and Annex 7	Improved estimation
5.0	30 Jun 2017	9.3.7 Confounding Factors 9.7.1.1 Description of the Study Cohorts; 9.7.1.2 Description of Cases	Update availability of variables and information in data sources	Updated information obtained

Version Number	Date	Section(s) of Study Protocol	Amendment or Update	Reason
5.0	30 Jun 2017	9.7.1.3 Estimation of Propensity Scores Annex 5.	Described methods for selection of variables; description of population before and after matching; description of trimmed-out population; replaced preliminary list of variables with the final list	Improve analysis
5.0	30 Jun 2017	9.7.2.1 Stratification by type of prescriber	Type of prescriber available in Denmark. Overall effect of type of prescriber will be evaluated in PHARMO, Denmark, and Sweden.	Increased data availability; improved analysis
5.0	30 Jun 2017	9.7.2 Pooled Analysis	Aggregated data from all databases will be centralized in Statistics Denmark servers. Pooled analysis will be conducted remotely within these servers.	Data confidentiality regulations in Denmark
5.0	30 Jun 2017	9.7.2.5 Sensitivity Analysis 9.3 Endpoints	Included additional sensitivity analyses; availability of stage of non-melanoma skin cancer and malignant melanoma will be explored in all databases to address surveillance bias; removed stratification by utilization of health resources; alternative definition of severity of atopic dermatitis.	Improve analysis and interpretation of results. Data on utilization of health care resources is very limited in the study databases.
5.0	30 Jun 2017	9.7.2.6 Secondary Analysis	Corticosteroids vs. untreated patients: increased matching ratio; stratification by time since first prescription and type of prescriber.	Improved analysis to assess reverse causation and severity of atopic dermatitis in users of topical corticosteroids.
5.0	30 Jun 2017	10. Protection of Human Subjects	Updated to reflect review of medical records in Sweden and questionnaires to general practitioners in CPRD.	Individual data collection will be conducted by researchers in Sweden and general practitioners in CPRD.
5.0	30 Jun 2017	10.1 Approvals	Specification of approvals needed for JOELLE Extension	New approvals needed for JOELLE Extension

Version Number	Date	Section(s) of Study Protocol	Amendment or Update	Reason
5.0	30 Jun 2017	11. Management and Reporting of Adverse Events/ Adverse Reactions	Updated text from EMA reporting guidelines for noninterventional studies (GVP Module VI)	Adapted text to source (GVP Module VI)
5.0	30 Jun 2017	12. Plans for Disseminating and Communicating Study Results	Included Phase I dissemination activities	Phase I publications available
4.4	09 Mar 2015	6. Milestones and Timelines	Revised timelines for completing study	Delay in obtaining cancer data from cancer registries in Denmark and the CPRD. Need to conduct exploratory analyses for estimating exposure propensity scores
4.4	09 Mar 2015	3.5.1.3, Estimation of Propensity Scores Annex 5. Estimation of Propensity Scores: Preliminary List of Variables	Exclusion of variables ”prior use of topical corticosteroids” and “type of prescriber of first prescription” from the estimation of propensity scores	Poor overlapping of propensity scores between the study cohorts**,** leading to a low number of eligible patients for matching
			Stratification of analyses by variable “type of prescriber of first prescription” in data sources where this variable is available	Potential confounding effect of type of prescriber of first prescription
4.3	06 Jun 2014	3.3.1, Identification of atopic dermatitis; 3.5.1.1, Description of the study cohorts	Clarification of definition of cohort of users of moderate- to high-potency topical corticosteroids. Inclusion of full analysis plan for the description of the study cohorts.	EMA request

Version Number	Date	Section(s) of Study Protocol	Amendment or Update	Reason
4.2	09 Jan 2014	Key Definitions, Abstract, 1.3 Research Objectives, 3 Research Methods, 3.2.3 Study Cohorts, 3.2.3.2 Corticosteroids Cohorts, 3.3.1 Identification of Atopic Dermatitis, 3.3.3.6 and 3.3.4.6 Cohort of Users of Corticosteroids with a Diagnosis of or a Proxy for Atopic Dermatitis, Appendix B	Modifications to criteria for identification of corticosteroids cohorts. Ascertainment of proxy for atopic dermatitis and application of clinical algorithm were discarded. Deletion of Appendix B (Exclusion of Diagnoses and Medications for Identification of Atopic Dermatitis)	Reflect final decisions on modified criteria for identification of corticosteroids cohorts
4.2	09 Jan 2014	3.1. Data Sources, 3.3.1 Identification of Atopic Dermatitis	Deleted mention of using the primary care database in Sweden to identify atopic dermatitis in children	Identification of corticosteroids cohorts in Sweden will be based on diagnoses recorded in the national patient registry and prescription data
4.2	09 Jan 2014	3.3.5 Endpoints, new Annex 4	Specifications of ICD-O-3 topography code for skin MM and NMSC (C44) and inclusion of in situ skin carcinomas	Addition of topography code for skin cancers for further clarity and PRAC request to include in situ skin carcinomas as study outcomes
4.2	09 Jan 2014	3.3.6 Case Identification and Validation	Specification of ICD-10 nomenclature for identification of study malignancies in the cancer registry in the UK	UK cancer registry coding practices
4.2	09 Jan 2014	3.5.3. Sensitivity Analysis	Addition of sensitivity analysis for in situ skin carcinomas	Analysis of invasive skin malignancies excluding in situ skin carcinomas
4.2	11 Nov 2013	Annex 5. Estimation of Propensity Scores: Preliminary List of Variables	ATC code for oral antidiabetics is A10B instead of A101B	Coding error
4.2	29 Oct 2013	Annex 6. Incidence Rates of Study Malignancies and Population in Nordic Countries	Evaluation of severity of atopic dermatitis. Visits to physician or pediatrician should be for atopic dermatitis.	Diagnosis of atopic dermatitis was missing in original description

Version Number	Date	Section(s) of Study Protocol	Amendment or Update	Reason
4.1	30 Sep 2013	Abstract, 1.3 Research Objectives, 3 Research Methods, 3.2.3 Study Cohorts, 3.2.3.2 Corticosteroids Cohorts, 3.3.1 Identification of Atopic Dermatitis, 3.3.3.6 Cohort of Users of Corticosteroids with a Diagnosis of or a Proxy for Atopic Dermatitis, Appendix B	Modified criteria for identification of atopic dermatitis	Reflect final definition of atopic dermatitis or proxies following low positive predictive value found in the prediction models
4.1	30 Sep 2013	3.1 Data Sources; 3.3.1 Identification of Atopic Dermatitis; 3.8 Limitations, Appendix B	Update on access to primary care data in Sweden	Reflect availability of primary care data in Sweden
4.1	30 Sep 2013	6 Milestones and Timelines	Adding details on study registration to EMA PAS registry	Reflect EMA PAS study registration
4.1	30 Sep 2013	Section 8 Dated Amendments to the Protocol	Moved to Section 7 before references	Align with EMA guidance on protocol format
4.1	17 Oct 2013	Annex 5. Estimation of Propensity Scores: Preliminary List of Variables, Morphology codes for the definition of non-melanoma skin cancer	Exclusion of codes 8050/2, 8052/2, 8070/2, 8076/2, and 8081/2	Codes for in situ, precancerous malignancies
4.1	17 Oct 2013	Annex 5. Estimation of Propensity Scores: Preliminary List of Variables, Morphology codes for the definition of melanoma skin cancer	Exclusion of codes 8720/2, 8741/2, and 8742/2	Codes for in situ, precancerous malignancies

6 Milestones

Phase I and JOELLE Extension milestones, initial target timelines, and actual/revised timelines according to this protocol amendment (see Section 5) are provided in Table 1. Ranges reflect differences in data availability start times across databases.

Table 1. Milestones and Timelines for Phase I and JOELLE Extension

Study Milestones	Target Timeline Protocol V4.4, March 9, 2015	Actual/Revised Timeline
Phase I		
EMA protocol endorsement	NA	Apr 2013
Registration in EU PAS Register	July 30, 2013 http://www.encepp.eu/encepp/viewResource.htm?id=4358	July 30, 2013
Start of data collection[a]	Q4 2012	3Q 2013
End of data collection[b]	Q4 2013 – Q2 2014	March 2015
End core site analysis	Q2-Q3 2014	July 2015
End pooled analysis	Q4 2014	August 2015
Draft study report	Q1-Q4 2015	October 15, 2015
Final study report	Q2 2015	November 30, 2015[c]
JOELLE Extension		
Submission of nonsubstantial protocol amendment to the EMA	NA	3Q 2017
Data accumulation	Dec 31, 2014[d]	Dec 31, 2015[e]
Start of data collection[a]	Q2-Q4 2015	Q3 2017 – Q1 2018
End of data collection[b]	Q4 2015 – Q3 2016	Q2–Q3 2018
End core site analysis	Q2 2016 - Q1 2017	Q1 2019
End pooled analysis	Q2 2017	Q2 2019
Draft study report	Q3 2017	Q3 2019
Final study report	Q4 2017	Q3 2019

NA = not applicable.

[a] Start of data collection is "the date from which information on the first study patient is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts" [1].

[b] End of data collection is "the date from which the analytical data set is completely available" [1].

[c] Final report submitted to the European Medicines Agency.

[d] Assumed 3 years of data accumulation since December 31, 2011. Duration of the data accumulation period was considered dependent on the use of the study medications in each country and study size calculations according to results from phase I.

[e] Assumed 4 years of data accumulation since December 31, 2011. Data beyond 4 years may be available in some of the study databases.

Note: Contracts between the sponsor and research organization(s) and approvals by data protection, data custodian, ethics, and scientific review bodies are pending for the JOELLE Extension. Timelines may be impacted by approvals of these bodies, duration of contract reviews, and availability of data and staff at research institutions once contracts and approvals are finalized.

7 Rationale and Background

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 untreated population. The study will evaluate populations covered by automated health databases in four countries: the Netherlands, Denmark, Sweden, and the United Kingdom (UK).

7.1 Rationale

The long-term safety profile of tacrolimus ointment and pimecrolimus cream requires further evaluation. Concerns about a potential increased risk of 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 [2,3]. 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 et al. [4], 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. [5], 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, which limits the interpretation of the results about TCI use and risk of all lymphoma. The study by Schneeweiss et al. [5] 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. [5] 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 [6]. 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. [5] 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. [6] 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 non-melanoma skin cancer (NMSC) and use of TCIs as 0.5 (95% CI, 0.4–0.7) [7]. 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) [6].

A number of concerns have been expressed about the methods applied in these nonexperimental studies [8]. Claims-based cohort studies so far have not included long-term 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 skin monitoring of patients under regular treatment by a dermatologist, e.g., individuals with atopic dermatitis, is likely to result in earlier and increased ascertainment of melanoma and NMSC diagnoses and thereby artificially increase the RR. 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 [4,9,10]. 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 [4,9]. 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 misdiagnosed and treated as atopic dermatitis [6]. 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. [9]. 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 multinational epidemiologic study that will evaluate the risk of skin malignancies and lymphomas in pediatric (focus of the follow-up measure FUM-039, later merged into FUM-RMP052) and adult patients exposed to TCIs in Europe.

Phase I of the study, involving the period 2002-2011, has been completed and the report was submitted to the EMA in December 2015. The study has been extended for 4 years (JOELLE Extension) in order to increase the number of exposed patients and the length of follow-up.

7.2 Background

Topical tacrolimus 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 cream, and moderate to severe disease for tacrolimus ointment.

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 adolescents aged more than 16 years and 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 Authorization 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 2.

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 726/2004*, 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 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 [11]. 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 planned to address the issues highlighted in the report by performing this multinational

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

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 include all ages. In 2013, FUM-039 was integrated into the Protopic® Risk Management Plan as FUM-RMP052.

In 2016, Astellas transferred the Marketing Authorization for Protopic® to LEO Pharma A/S, including the sponsorship for JOELLE.

Table 2. Approved Indications and Regulatory Status of Topical Calcineurin Inhibitors in Study Countries (2011)

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.
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

Specifications of Indication	Tacrolimus Ointment		Pimecrolimus Cream
	First Indication	Second Indication	
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.

8 Research Question and Objectives

The study aims to investigate the magnitude of the association, if any, between the use of topical tacrolimus or topical pimecrolimus and an increased risk of skin cancer and lymphoma in children and adults.

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 with a diagnosis of atopic dermatitis or with at least two prescriptions of moderate- to high-potency topical corticosteroids within a period of 12 months
- New users of topical pimecrolimus compared with users of moderate- to high-potency topical corticosteroids with a diagnosis of atopic dermatitis or with at least two prescriptions of moderate- to high-potency topical corticosteroids within a period of 12 months

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 with a diagnosis of atopic dermatitis or with at least two prescriptions of moderate- to high-potency topical corticosteroids within a period of 12 months 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 a diagnosis of atopic dermatitis or with at least two prescriptions of moderate- to high-potency topical corticosteroids within a period of 12 months.

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 among the untreated population, the atopic dermatitis cohort treated with moderate- to high-potency corticosteroids (see Section 9.3.1, Identification of Atopic Dermatitis, for further details on atopic dermatitis criteria), and the tacrolimus cohort.

9 Research Methods

This is a multinational cohort study of new users of topical tacrolimus, new users of topical pimecrolimus, users of topical corticosteroids with a diagnosis of atopic dermatitis or with at least two prescriptions of moderate- to high-potency corticosteroids within a period of 12 months, 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 [12]. 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 data sources.

It is convenient when trying to take into account induction periods to follow an inception cohort, in which only initiators of the medication of interest are followed. 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-user 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.

9.1 Study Design

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, Southern Denmark University in Denmark, the Karolinska Institutet in Sweden, and the Clinical Practice Research Datalink (CPRD) in the UK. 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 development 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

The sponsor will have the following primary roles and responsibilities:

- Provide funding for the study
- Provide input into the development of this core protocol
- Review and provide input during the study implementation phase

The study will be conducted in two phases:

- Phase I. Completed on December 11, 2015. The study included the period from the date of first availability of topical tacrolimus and topical pimecrolimus in each study population through December 31, 2011.
- JOELLE Extension. The study will be extended for a period of 4 years from January 1, 2012, through December 31, 2015, according to the use of the study medications and precision estimates based on the results from Phase I. Data beyond 2015 may be available in some databases and will be included in the analysis.

9.2 Setting

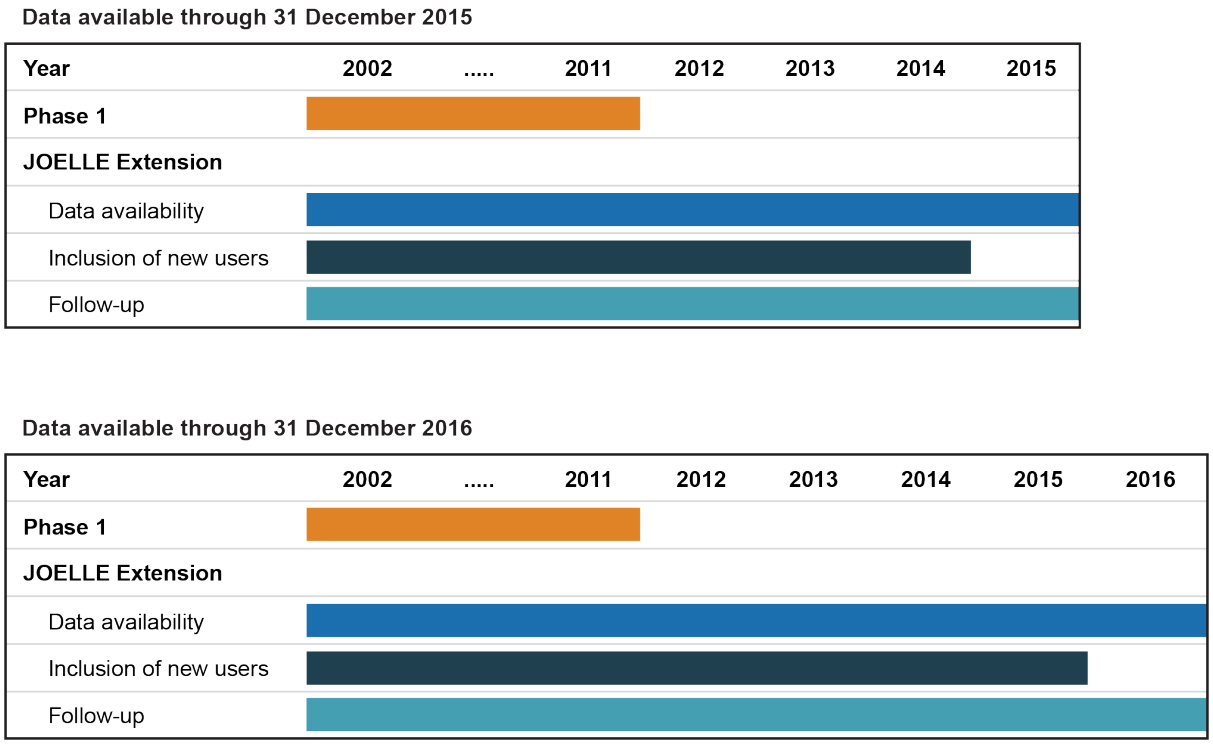
The study will be conducted following a common protocol in populations covered in population-based health databases and cancer registries in four countries in Europe that are available for research and that provide access to health-related data (including prescription drug data). Data will be obtained from the following data sources:

- The PHARMO Database Network in the Netherlands
- The Danish health databases
- The Swedish health databases
- The Clinical Practice Research Datalink (CPRD) in the UK

9.2.1 Study Period

The study Phase I covered the period from the date of first availability of topical tacrolimus and topical pimecrolimus in each study population through December 31, 2011. In the JOELLE Extension, the study period is extended for 4 years, with a period of inclusion of new users from the date of first availability of topical tacrolimus and topical pimecrolimus in each study population to December 31, 2014, and a follow-up of all new users through December 31, 2015. This ensures a follow-up of at least 6 months of all new users after applying a 6-month induction period. In some databases data beyond 2015 may be available and will be included in the study. In these databases, the study period will cover a period from the date of first availability of topical tacrolimus and topical pimecrolimus in each study population to 12 months before the end of data availability, and a follow-up of all new users up to the last date of data availability. Figure 1 shows the study period for Phase I and the JOELLE Extension for two scenarios of data availability: through December 31, 2015, and through December 31, 2016.

Figure 1. Study Period According to Two Scenarios of Data Availability



9.2.2 Eligibility Criteria

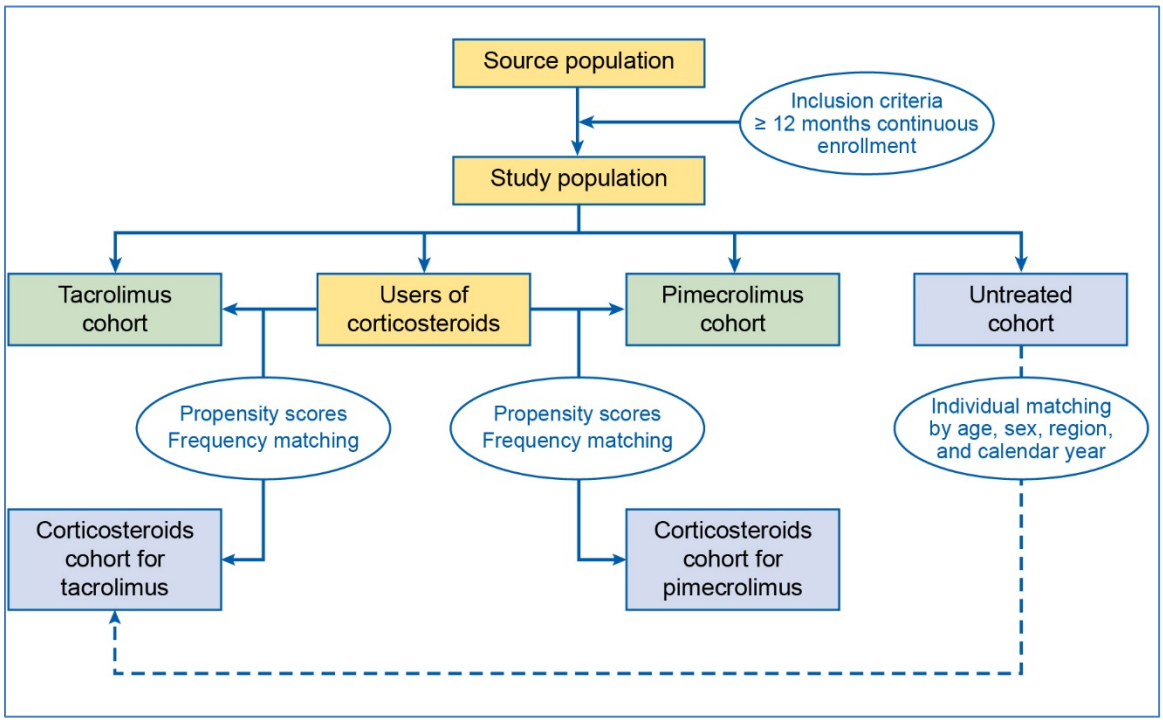
To be eligible for inclusion in the study population, individuals should have at least 12 months of continuous enrollment in the study databases, except for children 0 to 12 months of age. Thus, a person becomes eligible for study inclusion the day after this 12-month enrollment period has been completed (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.

9.2.3 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 untreated patients (Figure 2).

Figure 2. 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* **(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 meeting *one* of the following criteria:
  - Individuals with a recorded diagnosis of atopic dermatitis at any time before the start date who received a prescription for moderate- to high-potency corticosteroids during the study period after the eligibility date.
  - Individuals without a recorded diagnosis of atopic dermatitis before the start date who received a prescription for moderate- to high-potency corticosteroids during the study period after the eligibility date and at least one other prescription (for moderate- to high-potency topical corticosteroids) within the 12 months before the start 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 untreated

population, attempting to put in population perspective the magnitude of any changes in risk observed between the study cohorts:

- *Untreated 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 untreated 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.

9.2.3.1 Tacrolimus Cohort and Pimecrolimus Cohort

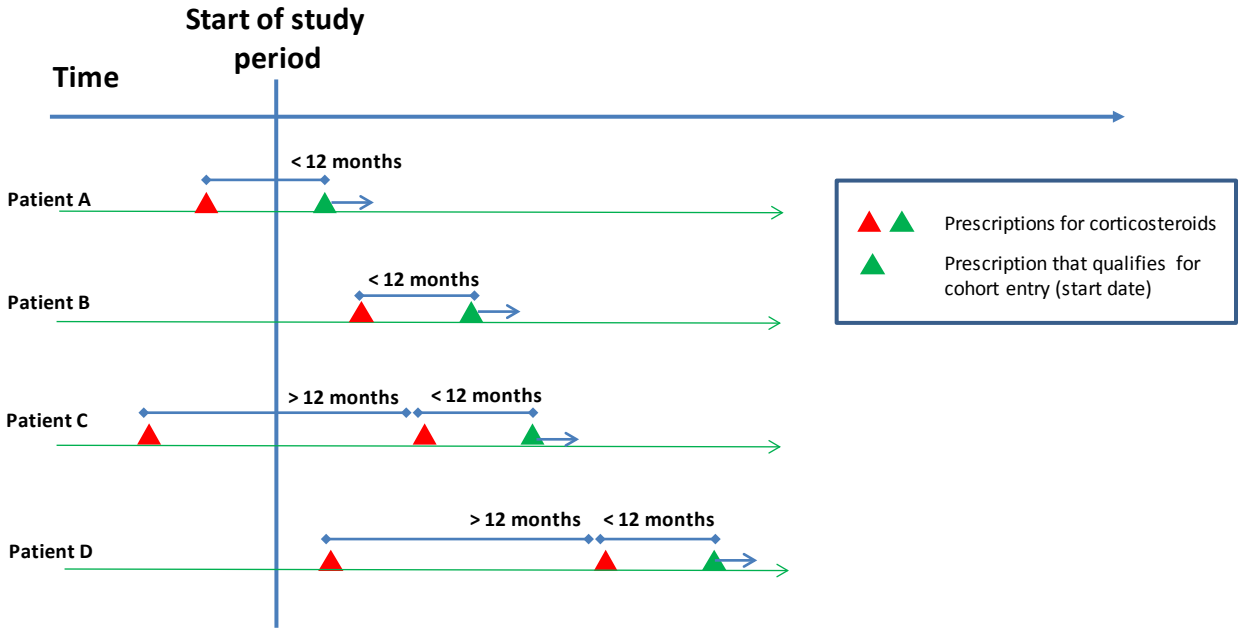
Patients will be included in the tacrolimus cohort or the pimecrolimus cohort according to the first medication prescribed during the study period. If the first prescription a patient receives is for topical tacrolimus, that patient will be included in the tacrolimus cohort. The date of that first prescription 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 9.3.4, 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 have 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).

9.2.3.2 Corticosteroids Cohorts

Topical corticosteroids have multiple indications of use. The two corticosteroids cohorts will be identified in each database from (1) all eligible individuals from the study population who have a diagnosis of atopic dermatitis at any time before the start date and received a prescription for moderate- to high-potency corticosteroids and (2) all eligible individuals without a diagnosis of atopic dermatitis any time before the start date who received a prescription for moderate- to high-potency corticosteroids during the study period and at least one other prescription within the prior 12 months (Figure 3). (See Section 9.3.1, Identification of Atopic Dermatitis, for further details on the atopic dermatitis criteria.)

Figure 3. Users of Moderate- to High-Potency Corticosteroids With Two Prescriptions Within a Period of 12 Months



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 criteria either for atopic dermatitis or for the number of corticosteroids prescriptions at the time of receiving the first prescription for moderate- to high-potency corticosteroids (Figure 3) (see Section 9.3.1, Identification of Atopic Dermatitis, for further details). 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.

9.2.3.3 Untreated Cohort

The untreated cohort will be identified from all eligible patients from the study population and will be used as the reference in the comparison with the corticosteroids cohort identified for users of tacrolimus (Figure 2). Individuals in the untreated cohort are not

required to have a diagnosis of atopic dermatitis. The untreated 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 matching ratio up to 4:1. The selected match in the untreated cohort must be eligible on the start date of the matched corticosteroids cohort member; the untreated cohort member will be assigned the start date of the matched corticosteroids cohort member.

Patients in the untreated cohort can contribute person-time to any of the other four study cohorts during follow-up and will be censored from the untreated cohort at the date of receiving a prescription for tacrolimus, pimecrolimus, or a moderate- to high-potency corticosteroid.

In Phase I, we evaluated the feasibility of conducting a sensitivity analysis to include an untreated 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.

Results from Phase I showed that the prevalence of recorded atopic dermatitis in the study databases, except the CPRD, was very low. Therefore, the sensitivity analysis restricted to patients with atopic dermatitis was not conducted. This analysis will also not be conducted in the JOELLE Extension.

9.2.4 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.

9.3 Variables

9.3.1 Identification of Atopic Dermatitis

Ascertainment of atopic dermatitis based on recorded diagnoses will be performed in a first step for the identification of members of the corticosteroids cohorts across databases.

PHARMO, Denmark, and Sweden

In the databases of PHARMO, Denmark, and Sweden, hospital inpatient and/or outpatient ICD-10 diagnoses are available for the full cohorts of users of corticosteroids.

In Phase I, the application of an algorithm, originally planned to predict atopic dermatitis status (yes/no) in the corticosteroids cohorts, was discarded due to the low positive predictive value found in the prediction models. Subsequently, application of clinical algorithm criteria to ascertain atopic dermatitis was considered based on (1) individuals with a primary or secondary hospital outpatient or inpatient discharge diagnosis of atopic dermatitis at any time before the start date or (2) individuals with at least two prescriptions for moderate- to high-potency topical corticosteroids within a period of 12 months AND who do not have any prescription for specific exclusion medications (e.g., topical or systemic antipsoriatic drugs, topical salicylic acid preparations) or any hospital discharge or outpatient diagnosis for a specific disease (e.g., psoriasis and similar disorders, vitiligo, scleroderma) within 12 months prior to the start date. These exclusion criteria were also applied to the tacrolimus and pimecrolimus cohorts to achieve comparable cohorts. An exploratory analysis was performed in the databases of Sweden and PHARMO to assess the impact that the exclusion of specific medications or diagnoses would have in the tacrolimus and pimecrolimus cohorts. The results showed that approximately 50% of the members of the tacrolimus and pimecrolimus cohorts would be excluded. Such a substantial reduction in these study cohorts was considered not acceptable. Therefore, these exclusion criteria will not be applied to the corticosteroids cohorts or to the tacrolimus and pimecrolimus cohorts. The corticosteroids cohorts will be defined as (1) individuals with a recorded diagnosis of atopic dermatitis who are users of moderate- to high-potency corticosteroids during the study period and (2) individuals without a recorded diagnosis of atopic dermatitis who received at least two prescriptions of moderate- to high-potency topical corticosteroids within a period of 12 months. This definition of the corticosteroids cohorts improves their comparability with the tacrolimus and pimecrolimus cohorts as the inclusion criteria are expanded to include patients without a recorded diagnosis of atopic dermatitis, so they are similar to the inclusion criteria for the tacrolimus and pimecrolimus cohorts.

It should be noted that the absence of a recorded diagnosis of atopic dermatitis in the study databases does not indicate by itself off-label use of tacrolimus or pimecrolimus. The extent to which diagnoses are recorded depends on the type of database, whether it is based on primary care or hospital diagnoses, compliance of physicians with local recording requirements, type of diagnoses, and other parameters. The indication of medications is usually not recorded in most databases. In some primary care databases (e.g., the CPRD) physicians are encouraged to record the indication of new medications. Evaluation of the indication and off-label prescribing of medications usually requires the clinical review and assessment of diagnoses, free text, and medical records when these are available.

CPRD

In the CPRD, patients with atopic dermatitis within the corticosteroids cohorts will be identified using Read codes, the standard clinical terminology system used in general practice in the UK. In Phase I, the diagnosis of atopic dermatitis was validated in a random sample of 60 children and 40 adult patients by reviewing free-text comments and the computerized medical history. The positive predictive value of using Read codes to identify these patients was 95.0% in children and 87.5% in adults.

9.3.2 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 as 0.03% and 0.1% ointment
- Pimecrolimus (D11AH02); available as 1% cream

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.

9.3.3 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 data sources, 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. Because the prescription register in Sweden is available only since July 2005, in this data source, new users are defined as those patients who did not fill any prescription for topical tacrolimus or topical pimecrolimus between July 1, 2005, and July 1, 2016. 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.

9.3.4 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.

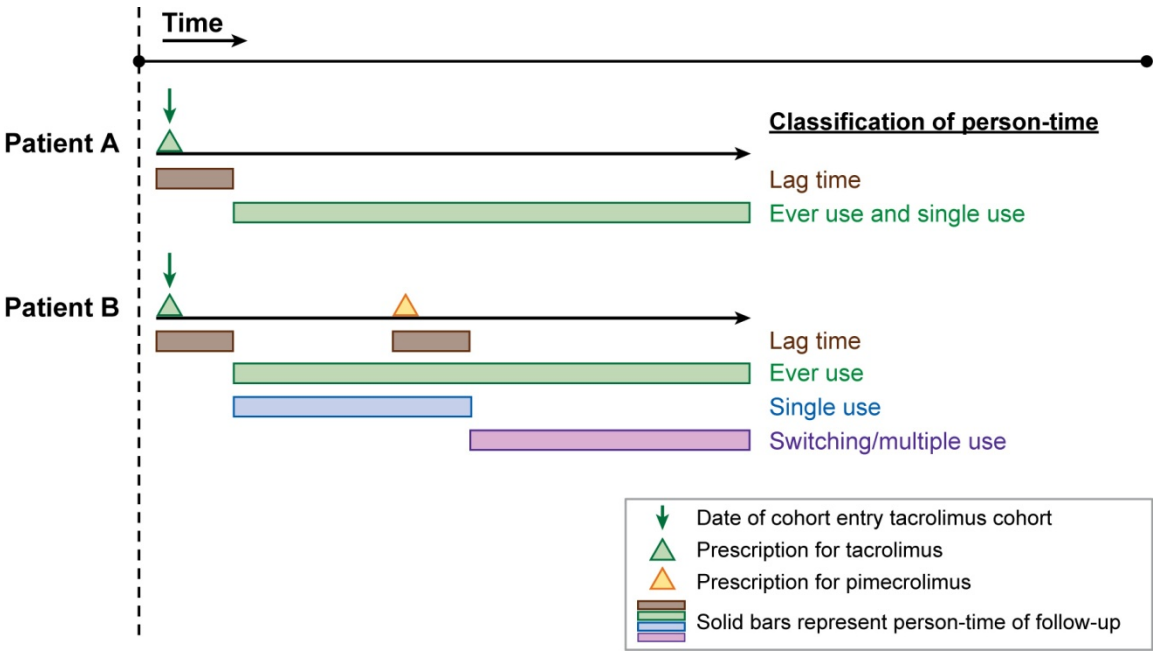
9.3.4.1 Exposure to Topical Tacrolimus

- *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 4). 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 4):

- *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 4. Exposure Assessment: Example for Exposure to Topical Tacrolimus



9.3.4.2 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.

9.3.4.3 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.

9.3.4.4 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. The average duration of prescriptions used in Phase I will be used in the JOELLE Extension.

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 9.3.4.1 (ever use, single use, and switching/multiple use) and for combined multiple use of both tacrolimus and pimecrolimus (Section 9.3.4.3).

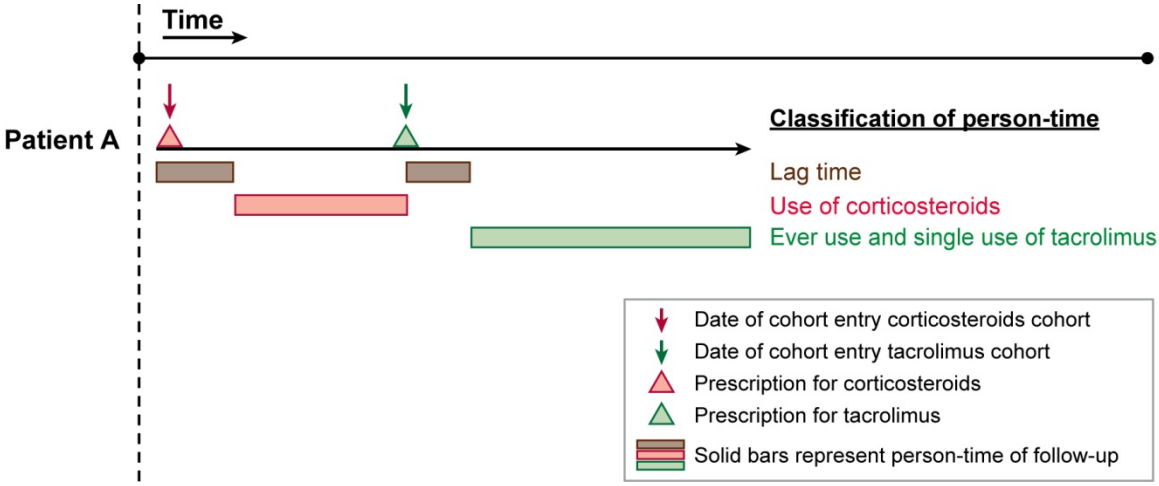
9.3.4.5 Duration of Exposure

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.

9.3.4.6 Cohort of Users of Corticosteroids

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 5).

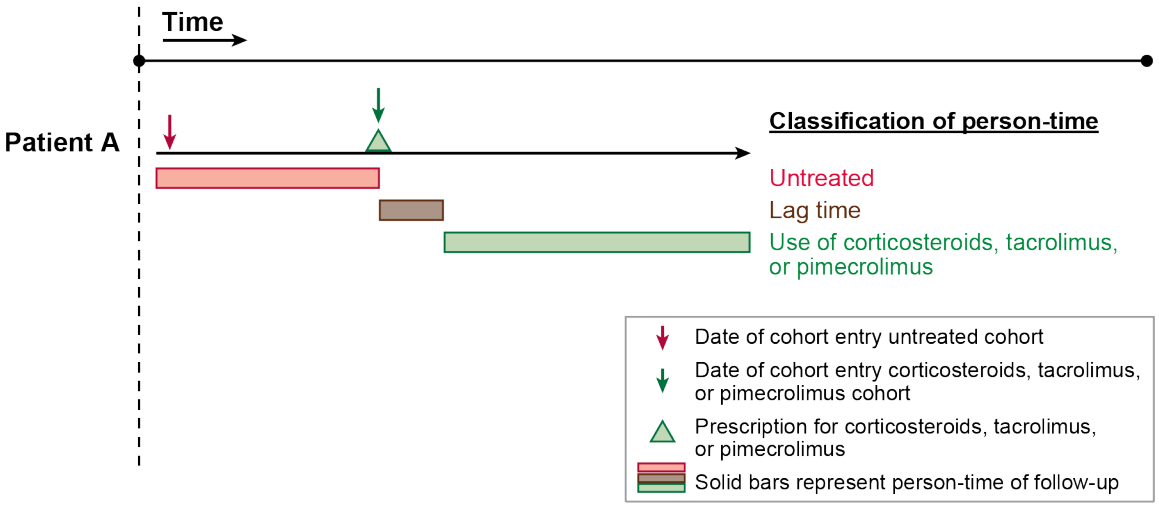
Figure 5. Exposure Assessment: Example for Patients Contributing Person-time to Both the Corticosteroids Cohort and the Tacrolimus Cohort



9.3.4.7 Untreated Cohort

Person-time will be accumulated from the start date (see Section 9.2.3.3) 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 6).

Figure 6. Exposure Assessment: Example for Patients Contributing Person-time to the Untreated Cohort and Any Other Cohort



9.3.5 Endpoints

Incident malignancies are defined as the first occurrence of one of the malignancies of interest occurring in study patients 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 ICD-O-3 topography code C44 (skin) will be used together with the corresponding morphology codes to identify malignant melanomas (MM) and non-melanoma skin cancers (NMSC). The complete lists of ICD-O-3 codes for the malignancies of interest are presented in Annex 4.

The following incident malignancies will be included in the study.

Skin Malignancies

- Malignant melanoma, including in situ carcinomas (MM)
- Non-melanoma skin cancer (NMSC), including in situ carcinomas (i.e., squamous cell and basal cell carcinomas, Merkel cell carcinoma, and adnexal and skin appendages neoplasms)

Skin malignancies will be evaluated as a group ("Any skin malignancy") and by individual malignancy type—i.e., melanoma, NMSC. In a sensitivity analysis, NMSC will be further subclassified as basal cell carcinoma and squamous cell carcinoma.

Lymphomas

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

Lymphomas will be analyzed as a group ("Any lymphoma") and by specific lymphoma type—cutaneous T-cell lymphoma, Hodgkin lymphoma, and non-Hodgkin lymphoma (excluding CTCL). In a sensitivity analysis, lymphomas will be grouped as cutaneous or noncutaneous lymphomas.

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 [13]. 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 [13,14]. 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 Annex 4, Table A4-3). 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.

9.3.6 Case Identification and Validation

Potential cases of the targeted malignancies will be identified in PHARMO, Denmark, and Sweden using the list of ICD-O-3 codes shown in Annex 4. 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, electronical medical records). 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

In, Denmark, and Sweden, cases will be identified through cancer registries and will not require validation [15].

In PHARMO, as in Phase I, cases will be identified in the pathology database (PALGA), which is mapped to the ICD-O-3 classification. Cases identified will be validated by an independent pathologist by reviewing the pathology excerpts of all pediatric cases, a random sample of adult cases, and all cases of CTCL. Staging information is not directly available in PALGA. In order to conduct the sensitivity analysis to assess surveillance bias (Section 9.7.2.5), staging information will be obtained from the Netherlands Cancer Registry (NCR). The sensitivity analysis will include all malignant melanoma cases identified in PALGA for which data from the NCR are available. Data from the NCR are currently available through 2014 and might be available through 2015 in 2018.

In the CPRD, for practices linked to the cancer registry, cases will be identified using ICD-10 codes. For practices not linked to the cancer registry, cases will be identified through the CPRD records and linkage to Hospital Episode Statistics (HES) data. The linkage of CPRD data to cancer registry data will be performed in the study. Note that the linkage is partial, and there is a lag of 2 years for obtaining data from the cancer registry. Cases from linked practices for which cancer registry information is not available will be identified through CPRD records and HES, as for practices not linked to the cancer registry. The ICD-O-3 coding system is not used for coding neoplasms in the CPRD. 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 9.3.5. For cases identified

through the CPRD or the Hospital Episodes Statistics linkage, validation of all pediatric cases, a random sample of adult cases of melanoma skin cancers and lymphomas (number of cases to be determined based on the final number of cases identified), and all cases of non-melanoma skin cancer and CTCL will be performed by reviewing the computerized information.

9.3.6.1 Assessment of Protopathic Bias for CTCL

Evaluation of potential protopathic bias for CTCL cases will be conducted in the CPRD and Sweden.

In the CPRD, pending ISAC approval, researchers will send questionnaires to general practitioners requesting 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).

Similarly, in the JOELLE Extension in Sweden, pending ethics approval, researchers will aim to review the medical records of cases of CTCL with the purpose of identifying information indicating whether CTCL symptoms were already present at the time of the start of the exposure.

9.3.7 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 [5,9,16]. Atopic dermatitis and severity of atopic dermatitis have been associated with an increased risk of skin cancer and lymphoma [8], 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 demographic variables, lifestyle habits, medical history, use of medications, and utilization of health care services. A detailed list of variables is presented in Annex 5.

In Phase I, to assess unmeasured confounding, researchers at PHARMO and the CPRD explored the feasibility of obtaining additional 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]). The clinical review of patient profiles and free-text comments of a sample of users in PHARMO-GP and the CPRD did not provide any additional relevant information on unmeasured confounding factors.

9.4 Data Sources

The study will be conducted following a common protocol in populations covered by population-based health databases and cancer registries in four countries 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 Annex 3. Data will be obtained from the following databases:

- The PHARMO Database Network in the Netherlands
- The Danish health databases
- The Swedish health databases
- The Clinical Practice Research Datalink (CPRD) in the UK

The PHARMO Institute in the Netherlands (http://www.pharmo.com/) has access to the PHARMO Database Network, a patient-centric data network that includes high-quality and complete information on (among others) patient demographics, drug dispensings, hospital morbidity, and pathology for more than 4 million residents of a well-defined population in the Netherlands for an average of 10 years. For a subset, clinical laboratory and GP information is also available. For the JOELLE Extension, data from the NCR, maintained by the Netherlands Comprehensive Cancer Organisation, are now available in the PHARMO Database Network and will be used to identify the stage of malignant melanoma, which will be used for a sensitivity analysis to assess surveillance bias (Section 9.7.2.5). 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 (5.7 million inhabitants in Denmark and 9.7 million inhabitants in Sweden in 2015). 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 with drug dispensings, register of causes of death, and population registers [17]. Data collected in these registers can be made available for research purposes under the principles for protection and release of sensitive data [18,19].

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 4.4 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 data sets (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 [20]; CPRD Web site, http://www.cprd.com/intro.asp).

9.5 Study Size

We have updated the study size calculations for conducting the JOELLE Extension based on the incidence rates of each malignancy observed in Phase I and the updated annual number of users of tacrolimus in each data source. Calculations assume an extension of 4 years (through December 31, 2015), with a period of 3 years of inclusion of users and 1 year of follow-up. This ensures all users are followed for at least 6 months after applying a 6-month induction period. The total number of users in Phase I and the estimated number of users in the JOELLE Extension and the corresponding person-years of follow-up are presented in Table 3. In some databases, data beyond 2015 may be available and will be included in the study.

Table 3. Number of New Users of Tacrolimus and Person-years of Follow-up in Phase I (2002–2011) and Estimated Number in the JOELLE Extension (2002-2015)

	Phase I[a]		Extension[b]	
	Number of New Users	Person-years of Follow-up	Estimated Number of New Users	Estimated Person-years of Follow-up
Children aged < 18 years	19,948	50,316	24,412	133,285
Adults aged ≥ 18 years	66,127	198,400	98,788	551,369

[a] Actual values.

[b] Based on a 4-year extension (additional 3-year period of inclusion plus 1 year of follow-up) accounting for 6-month induction period.

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 estimated number of users of tacrolimus, assuming a 4-year extension (additional 3-year period of inclusion plus 1 year of follow-up) and the incidence rates observed in Phase I.

For the pediatric population, the probabilities, although higher than in Phase I, are still low. The highest probability is for any lymphoma, with a 70% probability for having an upper limit of the 95% CI of the rate ratio below 8.

For the adult population, probabilities, already high in Phase I, have increased for the JOELLE Extension. The probability is 95% or higher 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 and CTCL, the probabilities are 95% and 85%, respectively, for having an upper limit below 4.

Table 4. For Each Study Outcome, Probability That the Upper Limit of the 95% Confidence Interval of the Incidence Ratio is Below 2, 4, 8, or 16; JOELLE Extension (2002-2015)

Cancer Type by Age Group	Incidence per 100,000 Person-years[a]	Probability That Upper Limit of the 95% CI of the Rate Ratio is Below			
		2	4	8	16
Age < 18 years					
Skin, non-melanoma	0.5	0.05	0.09	0.15	0.23
Melanoma of skin	1.0	0.06	0.14	0.25	0.40
Lymphoma	2.1	0.09	0.24	0.46	0.70
Non-Hodgkin lymphoma	0.5	0.05	0.09	0.15	0.23
Hodgkin lymphoma	1.6	0.08	0.19	0.37	0.58
CTCL[b]	0.2	0.04	0.06	0.08	0.11
Age ≥ 18 years					
Skin, non-melanoma	286.2	1.00	1.00	1.00	1.00
Melanoma of skin	34.7	1.00	1.00	1.00	1.00
Lymphoma	25.6	0.99	1.00	1.00	1.00
Non-Hodgkin lymphoma	18.1	0.95	1.00	1.00	1.00
Hodgkin lymphoma	4.4	0.43	0.95	1.00	1.00
CTCL	3.1	0.33	0.85	0.99	1.00

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

Note: Based on a 4-year extension (additional 3-year period of inclusion plus 1 year of follow-up) accounting for 6-month induction period.

[a] Incidence rates based on results from Phase I.

[b] Calculations could not be based on Phase I results because there were no cases of CTCL in children unexposed to topical tacrolimus. Incidence rates are from the age- and sex-specific incidences rates from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute in the United States (SEER*Stat version 7.05).

9.5.1 Estimated Distribution of Follow-up

Table 5 and Table 6 show the estimated distribution of follow-up of users of tacrolimus assuming a 4-year extension (2002-2015) with a period of inclusion of new users from the date of first availability of topical tacrolimus and topical pimecrolimus in each study population through December 31, 2014, and a follow-up of all new users through December 31, 2015. Numbers are presented for children aged 0 to less than 18 years (Table 5) and adults aged 18 years or older (Table 6). Overall, it is estimated that approximately 14,000 children and 59,000 adults will be followed for at least 5 years.

Table 5. Estimated Number of Users by Years of Follow-up, Among New Users of Tacrolimus, Children Aged Less Than 18 Years; JOELLE Extension (2002-2015)

Years of Follow-up	Number of Users by Years of Follow-up		Cumulative Number of Users by Years of Follow-up	
	n	(%)	n	(%)
< 1	254	(1)	25,479	(100)
1 to < 2	2,345	(9)	25,225	(99)
2 to < 3	2,584	(10)	22,880	(90)
3 to < 4	2,903	(11)	20,296	(80)
4 to < 5	3,146	(12)	17,393	(68)
5 to < 6	3,115	(12)	14,247	(56)
6 to < 7	2,784	(11)	11,132	(44)
7 to < 8	2,098	(8)	8,348	(33)
8 to < 9	2,338	(9)	6,250	(25)
9 to < 10	2,144	(8)	3,912	(15)
10 to < 11	618	(2)	1,768	(7)
11 to < 12	578	(2)	1,150	(5)
12 to < 13	464	(2)	572	(2)
13 to < 14	108	(0)	108	(0)

Table 6. Estimated Number of Users by Years of Follow-up, Among New Users of Tacrolimus, Adults Aged 18 Years or Older; JOELLE Extension (2002-2015)

Years of Follow-up	Number of Users by Years of Follow-up		Cumulative Number of Users by Years of Follow-up	
	n	(%)	n	(%)
< 1	1,032	(1)	103,175	(100)
1 to < 2	9,640	(9)	102,143	(99)
2 to < 3	10,100	(10)	92,503	(90)
3 to < 4	11,020	(11)	82,403	(80)
4 to < 5	11,527	(11)	71,383	(69)
5 to < 6	11,386	(11)	59,856	(58)
6 to < 7	10,947	(11)	48,470	(47)
7 to < 8	9,729	(9)	37,523	(36)
8 to < 9	10,582	(10)	27,794	(27)
9 to < 10	10,956	(11)	17,212	(17)
10 to < 11	2,353	(2)	6,256	(6)
11 to < 12	2,168	(2)	3,903	(4)
12 to < 13	1,550	(2)	1,735	(2)
13 to < 14	185	(0)	185	(0)

9.6 Data Collection

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.

9.7 Data Analysis

This analysis section provides an overview of the analyses that were conducted for this study during Phase I and will be repeated for the JOELLE Extension (final analysis) except when indicated otherwise.

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 by the coordinating center, after combining stratified data from each database. 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 patient and person-time counts by exposure category, endpoint, deciles of propensity scores, and type of prescriber. To estimate overall measures of effect, the coordinating center will analyze these stratified data using Mantel-Haenszel methods.

For the JOELLE extension, because of data confidentiality requirements, data from Denmark cannot be shared outside the country. Therefore, stratified data from all databases will be centralized on the servers of Statistics Denmark through the University of Southern Denmark, and the coordinating center will conduct the pooled analysis remotely within these servers.

A common 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.

9.7.1 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 data set based on counts of patients, person-years, and outcome events according to the strata of propensity scores.

9.7.1.1 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 patient flow diagram showing the impact that each step of applying the study criteria had on the study size. Once the study population is identified, members of each study cohort (tacrolimus cohort, pimecrolimus cohort, two corticosteroids cohorts, and untreated cohort) will be described as of the start date, with separate analyses performed for children (0 to < 18 years) and adults (≥ 18 years) according to the variables detailed below. In addition, each study cohort will be described for children aged ≥ 2 to < 16 years.

Variables for Description of Study Cohort

Variables for the description of the study cohort are those included in Annex 5 for the estimation of propensity scores. In addition, the following variables will be described:

- Duration of available history in the database up to the start date in years: mean (SD), median (P25, P75), and frequency distribution of duration of medical history (for endpoint, use date of first endpoint): ≤1, 2-4, 5+
- Duration of follow-up in years: mean (SD), median (P25, P75), and frequency distribution of duration of follow-up (for endpoint, use date of first endpoint): ≤1, 2-4, 5+
- Number of years since first recorded diagnosis of atopic dermatitis: Mean (SD); median (P25, P75); and frequency distribution: ≤1, 2-4, 5-9, 10-14, 15+
- Number of years since first prescription of topical corticosteroids of any potency plain or combined: Mean (SD); median (P25, P75); and frequency distribution: ≤1, 2-4, 5-9, 10-14, 15+
- Total number of prescriptions for topical corticosteroids in the 12 months before the start date: 0, 1, 2-3, 4+
  - Topical corticosteroids, plain
    - Weak
    - Moderately potent
    - Potent
    - Very potent

- Topical corticosteroids, combinations with other agents
  - Weak
  - Moderately potent
  - Potent
  - Very potent

9.7.1.2 Description of Patterns of Use

Patterns of use of topical tacrolimus, topical pimecrolimus, and topical corticosteroids during follow-up will also be described for all users included in the study. The analysis of patterns of use will include the total number of prescriptions received, the distribution of prescriptions, and the distribution of total number of grams of active substance per person.

9.7.1.3 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.

9.7.1.4 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. Covariates are measured before initiating treatment with the study medications. A list of covariates to be evaluated is presented in Annex 5. Selection of variables will be conducted using a high-dimensional propensity score algorithm [21]. This algorithm has been shown to perform well in the Danish databases [22]. 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.

From the fitted propensity score model, a propensity score will be estimated for each patient (twice for any patient 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). Trimming (excluding) nonoverlapping regions of propensity scores will be performed prior to any propensity score implementation.

After trimming, strata of propensity scores will be used to frequency match users of corticosteroids with users of tacrolimus and pimecrolimus. A matching ratio up to 4:1 (corticosteroids to tacrolimus or pimecrolimus), depending on available matches, will be used across strata.

In the JOELLE Extension, the patient characteristics will be described for the study cohorts before and after matching. This will allow the investigators to evaluate the efficiency of the frequency matching conducted. In addition, the baseline characteristics of patients excluded after trimming will be also described to identify subgroups (e.g. more severe patients) for whom the results of the study cannot be generalized.

The strata of propensity scores will be used to stratify person-time of follow-up and number of events for each defined exposure category. This will allow investigators to conduct a stratified analysis with aggregated data from each data source. Mantel-Haenszel methods for stratified data will be used to estimate pooled measures of effect. Additional stratification by type of prescriber of first prescription as a proxy for severity of atopic dermatitis was conducted in PHARMO and Sweden in Phase I and will be conducted in PHARMO, Sweden, and Denmark in the JOELLE Extension, the study data sources where this variable is available. 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.

9.7.2 Pooled Analysis

The coordinating center will conduct an analysis of the propensity score–stratified data from each individual database and an overall analysis combining the data across all database research partners. For the JOELLE Extension, because data from Denmark cannot be shared outside the country, data from each data source will be centralized on the servers of Statistics Denmark through the University of Southern Denmark, and the coordinating center will conduct the pooled analysis remotely within these servers. 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. Data source will be retained as a stratification variable, and the effect within each data source 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.

9.7.2.1 Stratification by Type of Prescriber (Dermatologist vs. Other Prescribers)

Data from prior studies and from Phase I of the JOELLE study have shown that type of prescriber of the first prescription (e.g., dermatologist versus nondermatologist) can be a confounder of the association between study medications and skin cancer [23]. In Phase I, information on type of prescriber was available in PHARMO and Sweden but not in Denmark or the CPRD. We evaluated the confounding effect of type of prescriber through a quantitative bias analysis for unmeasured confounders to account for the lack of information in Denmark and CPRD. In the JOELLE Extension, information on type of prescriber is also available in Denmark. To evaluate the potential bias for the uncontrolled effect of type of prescriber in the CPRD, an additional analysis restricted to users in PHARMO, Denmark, and Sweden will be conducted in the JOELLE Extension. Based on the number of users included in Phase I, this additional analysis is estimated to include approximately 90% of children and 79% of adults from the whole study cohort (including the CPRD).

9.7.2.2 Estimation of Incidence Rates

Incidence rates will be estimated separately for children and adults. Crude incidence rates will be calculated for each data source and overall across all data sources 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 data source. 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.

9.7.2.3 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, age categories, sex, 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.

9.7.2.4 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.

9.7.2.5 Sensitivity Analysis

Sensitivity analyses will be conducted for single use of topical tacrolimus and topical pimecrolimus. The following sensitivity analyses 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. Incidence rates and incidence rate ratios will be estimated for the occurrence of all MMs and NMSCs excluding in situ carcinomas, to evaluate the role, if any, of the inclusion of noninvasive skin carcinomas.
4. Incidence rates and incidence rate ratios will be estimated for basal cell carcinoma and squamous cell carcinoma separately.
5. Incidence rates and incidence rate ratios will be estimated for cutaneous and noncutaneous lymphomas separately.
6. Incidence rates and incidence rate ratios will be estimated by strata of propensity scores to explore effect modification.
7. 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, 48 months) in addition to the predefined lag time of 6 months.
8. To explore potential surveillance bias, incidence rates of malignant melanoma and non-melanoma skin cancer will be stratified by stage of malignancy at the time of diagnosis in those data sources where information on stage is available. Data on stage of cancer at diagnosis can be useful to assess the potential role of a higher medical surveillance in the detection of cases (if lower stages are found, higher medical surveillance is likely to have occurred).
9. Incidence rates and incidence rate ratios will be estimated by severity of atopic dermatitis. In Phase I, definition of severity of atopic dermatitis was based on the utilization of health care resources. However, information was only partially available in the study data sources. In the JOELLE Extension, severity of atopic dermatitis will be defined according to the type of prescriber of the first prescription (dermatologist or nondermatologist) as a proxy for severity.

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

9.7.2.6 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 untreated patients. The analyses will be conducted using the corticosteroids cohort identified in the comparison with users of tacrolimus. Each database research partner will individually match untreated patients with the corticosteroids cohort by year of birth, sex, calendar year of start date, and primary care general practice/region, at a matching ratio up to 4:1. 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. To assess potential reverse causation among users of topical corticosteroids, incidence rate ratios will be estimated by time since first exposure to topical corticosteroids. Also, to evaluate the effect of severity of atopic dermatitis, the analysis will be stratified by type of prescriber of the first prescription (dermatologist or nondermatologist) of topical corticosteroids.

9.8 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.

A quality-assurance audit of this study may be conducted by the sponsor or the sponsor’s designees.

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 to restore files in the event of a hardware or software failure at each research center.

9.9 Limitations of the Research Methods

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 Phase I was the low precision of the estimated relative risks for most malignancies in the pediatric population and for lymphoma, particularly for CTCL, in adults. The JOELLE Extension study was planned to

improve the precision of the study through the inclusion of 4 additional years of data. Updated study size calculations show that the estimated precision of the effect estimates is improved, although it remains low in the pediatric population.

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 [24]. 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 [25,26]. Other disorders such as pyoderma gangrenosum, cutaneous lupus erythematosus, and oral lichen are even rarer in children [27-29]. Lichen sclerosus et atrophicus (LSA) is also uncommon in children [30]. LSA usually responds very well to treatment with very potent topical corticosteroids (clobetasol propionate), which reduces the need for topical tacrolimus or pimecrolimus [30]. 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. Several databases capture only partial information about the occurrence or severity of atopic dermatitis. During the JOELLE Extension, we plan to use type of prescribing physician (dermatologist or nondermatologist) as a proxy for severity of atopic dermatitis.

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, Denmark, Sweden) are based on diagnoses when discharged from the hospital or in connection with a hospital outpatient clinic visit, whereas the CPRD is based on information from GPs (in Sweden, data from primary care have also recently become available). 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.

Non-melanoma 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.

9.10 Other Aspects

This study adheres to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)* [31] and has been designed in line with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological*

Standards in Pharmacoepidemiology [32]. The *ENCePP Checklist for Study Protocols* [33] has been completed (Annex 2).

This study is a noninterventional post-authorization safety study according to the EMA *Guideline on Good Pharmacovigilance Practices: Module VIII – Post-authorisation safety studies* [1]. The study will comply with the study reporting requirements specified in Module VIII section VIII.B.4.3.1. "Progress reports" and VIII.B.4.3.2. "Final Study Report" of the *Guideline on Good Pharmacovigilance Practices* [1].

The study was registered in the ENCePP electronic register of studies [34] before the study implementation commenced, with registration ID ENCEPP/SDPP/4357 of July 30, 2013. The study will be conducted in alignment with the ENCePP Code of Conduct, and for the JOELLE Extension, the study team will apply for the ENCePP Study Seal [35].*

10 Protection of Human Subjects

This is a retrospective, noninterventional study based on data already collected in automated health care databases. All data collected in PHARMO and Denmark will be de-identified regarding personal identifiers associated with health information. In the CPRD and Sweden, data to evaluate reverse causation for CTCL cases will require individual patient identifiers. In the CPRD, questionnaires to the general practitioners are managed by a third party, and researchers do not have access to personal identifiers. In Sweden, review of medical records will require the use of individual patient identifiers.

10.1 Approvals

The RTI-HS study team received approval for exemption from review by the RTI International institutional review board on August 5, 2013.

Ethics approval is not required for anonymized database research in the Netherlands. However, this study fulfilled the requirements as checked by the PHARMO Compliance Commission on October 7, 2011, to use data from the PHARMO Database Network for this specific study. Permission for the use of data from the Pathology Registry was received on April 23, 2013. Approval from the Netherlands Cancer Registry will be requested for the JOELLE Extension.

The study was approved by the Danish Data Protection Agency via Statistics Denmark. According to Danish law, studies based solely on register data do not require approval from an ethics review board [36]. New approval for the JOELLE Extension will be requested through the University of Southern Denmark.

The Centre for Pharmacoepidemiology at Karolinska Institutet received approval from the Regional Ethical review board of Stockholm on September 26, 2012, and October 12,

* During phase I, the financial sponsor of this study was Astellas, the manufacturer of Protopic®. Astellas' contractual agreements with research partners reflected Astellas' 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 recommendations of the International Committee of Medical Journal Editors (http://www.icmje.org/)

2012. New ethical approval will be requested for the review of medical records to assess CTCL cases.

Approval of the Clinical Practice Research Datalink (CPRD) Independent Scientific Advisory Committee was received on September 26, 2013 (protocol number 13_121R), and approval of the United Kingdom (UK) National Cancer Intelligence Network of the same study protocol was received on December 6, 2013. For the JOELLE Extension, a protocol amendment will be submitted to ISAC and the National Cancer Intelligence Network for approval.

11 Management and Reporting of Adverse Events/Adverse Reactions

Given the information in the four data sources available for this study (see Annex 3, Summary of Characteristics of Databases), other than the outcome variables, collection of information about adverse events in relation to the study medications is not possible. Based on current guidelines from the European Medicines Agency [1] and the International Society for Pharmacoepidemiology [37], noninterventional post-authorization studies based on secondary use of data (e.g., medical chart reviews, electronic health care records), do not require the reporting of adverse reactions in the form of individual case safety reports. Any unexpected potential safety issues discovered during the analysis of the data will without delay be reported to the sponsor by e-mail to drug.safety@leo-pharma.com.

12 Plans for Disseminating and Communicating Study Results

Phase I of the study was completed November 30, 2015, and the study report was submitted to the EMA on December 11, 2015. The final JOELLE Extension study report will be submitted to the EMA. Study report finalization is planned for Q3 2019.

Authorship will follow guidelines established by the International Committee of Medical Journal Editors [38]. See also, Section V, Communication, in the *Guidelines for Good Pharmacoepidemiology Practices* [37] and the ENCePP Code of Conduct (http://www.encepp.eu/).

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist [39] will be followed when reporting results of this study (http://www.strobe-statement.org/index.php?id=available-checklists).

Dissemination of phase 1 results includes four presentations at the International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE) and two manuscripts currently in editorial review:

- Castellsague J, Kuiper J, Pottegård A, Anveden-Berglind I, Dedman D, Gutierrez L, Calingaert B, van Herk-Sukel M, Hallas J, Sundström A, Gallagher A, Kaye JA, Pardo C, Rothman KJ, Perez-Gutthann S. Risk of lymphoma risk in users of topical tacrolimus, pimecrolimus, and corticosteroids (JOELLE study). Pharmacoepidemiol Drug Saf. 2016 Aug;25(S3):494-5.

- Castellsague J, van Herk-Sukel M, Hallas J, Sundström A, Gallagher A, Gutierrez L, Calingaert B, Kuiper J, Pottegård A, Berglind I, Dedman D, Kaye JA, Pardo C, Rothman KJ, Perez-Gutthann S. Risk of skin cancer in users of topical tacrolimus, pimecrolimus, and corticosteroids. JOint European Longitudinal Lymphoma and skin cancer Evaluation (JOELLE) study. Pharmacoepidemiol Drug Saf. 2016 Aug;25(S3):527.
- Castellsague J, Calingaert B, Rothman KJ, Gutierrez L, van Herk-Sukel M, Kuiper J, Pottegård A, Hallas J, Berglind, Sundström A, Dedman D, Gallagher A, Kaye JA, Pardo C, Perez-Gutthann S. Probabilistic bias analysis for unmeasured confounders in a study of users of topical tacrolimus, pimecrolimus and corticosteroids (JOELLE) study. Pharmacoepidemiol Drug Saf. 2016 Aug;25(S3):142-3.
- Kuiper J, van Herk-Sukel M, Castellsague J, Potttegard A, Berglind I, Dedman D, Gutierrez L, Calingaert B, Hallas J, Sundström A, Gallagher A, Kaye JA, Pardo C, Rothman KJ, Perez-Gutthann S. Utilization of tacrolimus and pimecrolimus in Europe: results from the Joint European Longitudinal Lymphoma and skin cancer Evaluation (JOELLE) study. Pharmacoepidemiol Drug Saf. 2016 Aug;25(S3):632.
- Castellsague J, Kuiper J, Pottegård A, Anveden-Berglind I, Dedman D, Gutierrez L, Calingaert B, van Herk-Sukel M, Hallas J, Sundström A, Gallagher A, Kaye JA, Pardo C, Rothman KJ, Perez-Gutthann S. A cohort study on the risk of lymphoma and skin cancer in users of topical tacrolimus, pimecrolimus, and corticosteroids (JOint European Longitudinal Lymphoma and skin cancer Evaluation – JOELLE Study). Under review 2017.
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Annex 1.
List of Stand-Alone Documents

None.

Annex 2.
ENCePP Checklist for Study Protocols

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

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 section number 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). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection*	☒	☐	☐	6
1.1.2 End of data collection†	☒	☐	☐	
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS Register	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

* Date from which information on the first study is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts.

† Date from which the analytical data set is completely available.

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
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)	☒	☐	☐	7.1-7.2
	2.1.2 The objective(s) 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)	☒	☐	☐	8
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☒	☐	

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1-9.4
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.7.2.2
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.7.2.3 9.7.2.4
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	9.2.1
	4.2.2 Age and sex?	☒	☐	☐	8
	4.2.3 Country of origin?	☒	☐	☐	9.2
	4.2.4 Disease/indication?	☒	☐	☐	9.2.3
	4.2.5 Duration of follow-up?	☒	☐	☐	9.2.4

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.3

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.4
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.3.4
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.4.4

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☐	☐	☒	
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.5
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3.6
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.3.7

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.7.1.4
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.7.1.4
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.7.2.5
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.4

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.2.1 9.7.2.5

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4 Annex 3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4 Annex 3
9.1.3 Covariates?	☒	☐	☐	9.4 Annex 3
9.2 Does the protocol describe the information available from the data source(s) on:				9.4 Annex 3
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4 Annex 3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4 Annex 3
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, comorbidity, co-medications, lifestyle)	☒	☐	☐	9.4 Annex 3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.2
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Annex 4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.3 Covariates?	☒	☐	☐	Annex 5
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7.2
10.2 Are descriptive analyses included?	☒	☐	☐	9.7.1.1
10.3 Are stratified analyses included?	☒	☐	☐	9.7.2 9.7.2.5
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7.2
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2.1
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.8

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Jordi Castellsague

Date: 30/June/2017

Signature: [redacted]

Annex 3.
Summary of Characteristics of Databases

Table A3-1. Protopic and Malignancies: Main Features of Databases and Data Availability

Characteristic	CPRD, UK	PHARMO Netherlands	Danish Health Databases	Swedish National Registers
Database population in 2015 (million)	4.4	4.0	5.7	9.7
Database type	Primary health care electronic medical record database plus linkage to hospital data (Hospital Episodes Statistics [HES]) and cancer registry data	PHARMO Database Network holds several databases, linked on patient level. For this study, outpatient pharmacy data (dispensed drugs), hospitalization data, GP data, pathology data (PALGA), and Netherlands Cancer Registry (JOELLE Extension) 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) and primary care database 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 Database Network are probabilistically linked: pharmacy and hospitalization are core databases, Netherlands Cancer Registry, 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)	Yes	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	https://www.farmacotherapeutischkompas.nl/	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, in JOELLE Extension	Yes
Inpatient drugs (cytostatics)	Pending	Indirectly (based on hospitalization for chemotherapy); no specific drug names 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)

Characteristic	CPRD, UK	PHARMO Netherlands	Danish Health Databases	Swedish National Registers
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 and ICD-10 discharge diagnoses PALGA: PALGA codes based on SNOMED ICD-O-3 coding Netherlands Cancer Registry: ICD-10	ICD-10	ICD-9 and ICD-10
Outpatient diagnoses	Yes	Yes (subset in GP database)	Yes (only at hospitals)	Yes (at hospitals and primary care setting)
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) and primary care data
Atopic dermatitis	Read codes, specialist-reported diagnosis, free text	Algorithm: based on hospital outpatient or inpatient diagnosis and medications	Algorithm: based on hospital outpatient or inpatient diagnosis and medications	Algorithm: based on primary care and hospital (outpatient or inpatient) diagnoses and medications
Atopic dermatitis severity	Algorithm: specifications pending	Algorithm: specifications pending	Algorithm: specifications pending	Algorithm: specifications pending

Characteristic	CPRD, UK	PHARMO Netherlands	Danish Health Databases	Swedish National Registers
Validation atopic dermatitis diagnosis	Review of patients records and physician's questionnaires.	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)
Sun exposure (intensity), ultraviolet light therapy	Regional sun exposure estimates as proxy	Hospital codes for ultraviolet (UV) light therapy available but number treated is low (about 40 patients)	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 Netherlands Cancer Registry coding based on ICD-10	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

Characteristic	CPRD, UK	PHARMO Netherlands	Danish Health Databases	Swedish National Registers
Cancer data linkage	Partial	Yes	Yes	Yes
Specific issues/needs	Underreporting NMSC	Underreporting NMSC Basal cell carcinoma is not captured in the Netherlands Cancer Registry, and records need to be reviewed by a 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 = non-melanoma skin cancer; PALGA = pathology data.

Annex 4.
Coding of Malignancies

Table A4-1. Morphology Codes for the Definition of Non-melanoma Skin Cancers (Topography Code C44)

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	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	"
Squamous cell carcinoma in situ with questionable stroma invasion	M 8076/2
Epidermoid carcinoma in situ with questionable stroma invasion	"
Squamous cell carcinoma, microinvasive	M 8076/3

Description	ICD-O-3 codes
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	"
Matrical carcinoma	"
Merkel cell carcinoma	M 8247/3
Merkel cell tumor	"
Primary cutaneous neuroendocrine carcinoma	"

Description	ICD-O-3 codes
ADNEXAL AND SKIN APPENDAGE NEOPLASMS	
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 A4-2. Morphology Codes for the Definition of Skin Melanoma (Topography Code C44)

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
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 A4-3. 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 A4-4. 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	"

Cancer Description	**ICD-O-3 codes**
Hodgkin lymphoma, nodular sclerosis, grade 2	M 9667/3
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	"
Malignant lymphoma, histiocytic, NOS	"

Cancer Description	ICD-O-3 codes
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	"
Follicular lymphoma, NOS	M 9690/3
Malignant lymphoma, follicular, NOS	"
Malignant lymphoma, follicle center, follicular	"
Malignant lymphoma, follicle center, NOS	"

Cancer Description	**ICD-O-3 codes**
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	"
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	"

Cancer Description	ICD-O-3 codes
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	"
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	"

Cancer Description	ICD-O-3 codes
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 A4-3 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 A4-4 are limited to those that have not already been listed in Table A4-3.

Annex 5.
List of Variables for the Estimation of Propensity Scores and Description of the Study Cohorts

Note: Additional variables to be included in the description of the study cohorts are detailed in section 9.7.1.1

Demographics and Lifestyle Habits

- Age
  - Children (years): 0-1, 2-4, 5-9, 10-14, 15-17
  - Adults (years): 18-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, 85+
- Sex
- Smoking history at the start date: current nonsmoker, current smoker, former smoker, unknown (CPRD)
- Body mass index at the start date: <20, 20-25, >25, unknown (CPRD)
- Socioeconomic status (PHARMO and CPRD)
- Calendar year of the start date: 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014 (additional years to be included if available)
- Primary care health practice/geographic region or outpatient pharmacy geographic region code (PHARMO)

Atopic Dermatitis

- Outpatient diagnosis of atopic dermatitis at any time before the start date
- Hospital discharge diagnosis of atopic dermatitis at any time before the start date
- Severe atopic dermatitis (yes/no):
  Based on the use of health care resources in the year before the start date, severe atopic dermatitis is defined as any patient meeting any one of the following criteria [4,40,41]:
  - At least one visit to the dermatologist for patients aged younger than 3 years
  - At least four physician or pediatrician visits for atopic dermatitis in patients aged 3 years or older
  - At least one hospitalization with a primary discharge diagnosis for atopic dermatitis
- Type of prescriber of first prescription of study medications: dermatologist versus nondermatologist (PHARMO, Denmark, Sweden)

Medical History

Medical history ascertained by outpatient (GP, specialist, hospital outpatient) and/or hospital discharge diagnosis recorded at any time before the start date (yes/no).

Disease Classification	Individual Variables to be Evaluated (ICD-9)
Disease interacting with the immune system	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)
	Diseases of the immune system (279)
Skin disease (excluding atopic dermatitis, eczema and psoriasis)	Inflammatory skin diseases (690, 691.0, 692.0-692.8, 693-695, 697, 698)
	Other skin diseases (700-709)
Chronic disease	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)
	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)
	Organ transplantation (V42, V43.2, 996.8)
	HIV infection or AIDS (042, V08)

Use of Medications

At least one prescription recorded within 1 year before the start date (yes/no, unless other parameters are specified)

Medication Category	Individual Variables To Be Evaluated (ATC code)
Use of immunosuppressant, immunostimulant and cytostatic drugs	Systemic corticosteroids (H02AB, H02B)
	Systemic tacrolimus (L04AD02)
	Azathioprine (L04AX01)
	Methotrexate (L01BA01, L04AX03)
	Ciclosporin (L04AD01)
	Other antineoplastic agents excluding methotrexate (L01 except L01BA01)
	Other immunosuppressants (L04AA, L04AB, L04AC, L04AD03, L04AX02, L04AX04, L04AX05, L04AX06)
	Immunostimulants (L03)
	Systemic antivirals (J05)
Antipsoriatics for topical use	Tars (D05AA)
	Antracen derivatives (D05AC) (dithranol and dithranol combinations)
	Psoralens for topical use (D05AD) (trioxsalen, methoxsalen)
	Other antipsoriatics for topical use (D05AX) (fumaric acid, calcipotriol, calcitriol, tacalcitol, tazarotene, calcipotriol combinations)
Antipsoriatics for systemic use	Psoralens for systemic use (D05BA) (trioxsalen, methoxsalen, bergapten)
	Retinoids (D05BB) (etretinate, acitretin)
	Other antipsoriatics (D05BX) (fumaric acid derivatives, combinations)
Other dermatological preparations excluding topical corticosteroids	Topical salicylic acid preparations (D02AF, D01AE12)
	Other dermatological agents (D01-D04, D06, D08-D11)
Other drugs	Cardiovascular system drugs (excluding lipid-modifying agents) (C01-C09)
	Anti-inflammatory and antirheumatic agents, nonsteroidal (M01A)
	Other antirheumatic agents (M01B, M01C)
	Hormone-replacement therapy (G03C, G03E, G03F)
	Lipid-modifying agents (C10)
	Insulins (A10A)
	Oral antidiabetics (A10B)
	Antiepileptics (N03)
	Drugs for asthma and obstructive airways disease excluding inhaled corticosteroids (R03A, R03BB, R03BC, R03BX, R03C, R03D)
	Inhaled corticosteroids (R03BA)

Utilization of Health Care Resources

Utilization of health care resources in the year before the start date.

Resource Category	Individual Variables to be Evaluated
Outpatient	Number of visits to general practitioner: 0, 1, 2-3, 4+
	Number of visits to dermatologist: 0, 1, 2-3, 4+
	Number of visits to pediatrician: 0, 1, 2-3, 4+
	Number of emergency department visits: 0, 1, 2-3, 4+
	Number of outpatient hospital visits: 0, 1, 2-3, 4+
Inpatient	Number of hospitalizations (excluding emergency department visits and hospital outpatient visits): 0, 1, 2-3, 4+
Prescriptions	Number of prescriptions: 0, 1, 2-4, 5-9, 10+