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): Extension Phase

Final Report Version 1.2

5-Mar-2020

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PASS Information

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Date of last version of the final study report	5-March-2020
EU PAS Register number	ENCEPP/SDPP/21769
Active substance	▪ Tacrolimus (D11AH01) ▪ Pimecrolimus (D11AH02) ▪ Corticosteroids (topical corticosteroids, plain): Moderately potent (D07AB), Potent (D07AC), Very potent (D07AD); Topical corticosteroids, combinations with other agents: Moderately potent (D07BB, D07CB, D07XB), Potent (D07BC, D07CC, D07XC), Very potent (D07BD, D07CD, D07XD)
Medicinal product	Tacrolimus (Protopic®)
Product reference	EU/1/02/201 (Protopic®)
Procedure number	EMEA/H/C/000374 (Protopic®)
Marketing authorisation holder(s)	LEO Pharma A/S, Denmark
Joint PASS	No
Research question and objectives	The Protopic® JOELLE study is a European, multinational cohort study that assessed the risk of skin cancer and lymphoma in the paediatric and adult populations treated with topical tacrolimus, pimecrolimus, and corticosteroids and in the untreated population. The primary objective was to estimate the incidence rate ratios of skin cancer and lymphoma in the paediatric (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	The Netherlands Denmark Sweden United Kingdom

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1 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: Extension Phase

Alejandro Arana, MD, MSc; RTI Health Solutions, on behalf of the Protopic® JOELLE research team

Keywords: Atopic dermatitis, multinational cohort study, long-term safety, long-term follow-up, topical tacrolimus, topical pimecrolimus, topical calcineurin inhibitors, topical corticosteroids, skin cancer, lymphoma

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 conduct of this study was requested by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) to further evaluate the incidence of skin cancer and lymphoma in children treated with topical tacrolimus. The JOELLE Phase I study analysed observed data from 2002 through 31-Dec-2011, and the study report dated 30-Nov-2015, was endorsed by the EMA on 21-Jul-2016. In the JOELLE study extension phase, the additional study period started 1-Jan-2012 in all databases and was prolonged for 4-6 years. The JOELLE study extension phase analysed observed data from 2002 through 31-Dec-2017 in the Clinical Practice Research Datalink in the United Kingdom (UK-CPRD) and the PHARMO Database Network in the Netherlands (NL-PHARMO), through 31-Dec-2016 in the Danish nationwide health registers (Denmark), and through 31-Dec-2015 in the Swedish health care registers (Sweden). This report summarises the results of the JOELLE study, including the extension phase, with re-created cohorts covering up to an additional 6 years of data, allowing for evaluation of longer latency period for the development of skin cancers and lymphomas.

Research question and objectives: The primary objective was to estimate the incidence rate ratios (IRRs) of malignant melanoma, non-melanoma skin cancer (NMSC), non-Hodgkin lymphoma [except cutaneous T-cell lymphoma (CTCL)], Hodgkin lymphoma, CTCL, and any type of lymphoma in the paediatric and adult populations, comparing new users of topical tacrolimus and topical pimecrolimus with users of moderate- to high-potency topical corticosteroids. The secondary objective was to estimate the IRRs of these malignancies

comparing users of moderate- to high-potency topical corticosteroids with the untreated population.

Study design: JOELLE is a multinational cohort study of new users of topical tacrolimus and new users of topical pimecrolimus, frequency matched to users of moderate- to high-potency topical corticosteroids[*] on twentiles of propensity scores, and of users of moderate- to high-potency topical corticosteroids individually matched at a ratio of 1 study medication user to 4 untreated patients from the general population on age, sex, geographic region, and calendar year of start date.

Setting: Information recorded in health databases in four European countries on prescriptions dispensed in community pharmacies or prescribed in the primary care setting and diagnoses from hospitalisations, primary health care, and cancer registries. Researchers with access to such databases in Denmark, the Netherlands, Sweden, and the United Kingdom collaborated with RTI Health Solutions (Spain and the United States) as the coordinating centre.

Subjects and study size, including dropouts: The study cohort sizes before propensity score matching were 40,786 children (aged less than 18 years) and 153,257 adults (age 18 years or older) initiating treatment with topical tacrolimus, and 38,168 children and 76,549 adults initiating treatment with topical pimecrolimus. After trimming, the study included 32,605 children and 126,908 adults initiating treatment with topical tacrolimus matched to 117,592 children and 452,996 adults treated with topical corticosteroids; 27,961 children and 61,841 adults initiating treatment with topical pimecrolimus matched to 111,024 children and 244,572 adults treated with topical corticosteroids. Compared with JOELLE Phase I, the final cohort numbers represent a 39% and 48% increase for new users of tacrolimus and 15% and 39% for new users of pimecrolimus, for children and adults, respectively. The untreated cohort comprised 361,585 children and 1,291,042 adults.

Variables and data sources: Data sources were UK-CPRD, NL-PHARMO, and the Danish and Swedish national registers (Denmark and Sweden, respectively). The coordinating centre was RTI Health Solutions in Spain and the United States. In Denmark, NL-PHARMO, and Sweden, outcomes were identified in cancer or pathology registries. In UK-CPRD, outcomes were identified through general practice, hospital, and cancer register data. In NL-PHARMO and UK-CPRD, case validation was performed. Exposure to topical tacrolimus and topical pimecrolimus was defined as ever use (topical tacrolimus or topical pimecrolimus) and single use (topical tacrolimus or topical pimecrolimus but not both) of each of these medications. The effect of cumulative dose and duration of use of each medication was also evaluated. In

[*] Use of the term “topical corticosteroids” refers to moderate- to high-potency topical corticosteroids unless otherwise specified.

each data source, data were collapsed and stratified by deciles of propensity scores. The coordinating centre conducted a central stratified analysis, using Mantel-Haenszel methods to estimate overall IRRs and incidence rate differences for children and adults across the study data sources. Incidence rate ratios were adjusted by the type of prescriber of the first prescription, as a proxy for severity of the underlying cutaneous condition, in Denmark, NL-PHARMO, and Sweden. A sensitivity analyses were conducted to evaluate the potential for a protopathic bias (reverse causation) for CTCL cases in UK-CPRD by obtaining additional information from questionnaires sent to general practitioners of individual cases and in Sweden by reviewing medical records of the cases.

Results: Denmark and Sweden contributed the largest number of users of topical tacrolimus: together, they contributed 72.1% of all children and 73.5% of all adults. Denmark contributed the largest number of users of topical pimecrolimus: 72.8% of children and 69.6% of adults.

Among users of topical tacrolimus, the median follow-up period ranged from 4.0 years in UK-CPRD to 6.8 years in NL-PHARMO in children and from 3.7 years in UK-CPRD to 6.1 years in NL-PHARMO in adults. Among users of topical pimecrolimus, the median follow-up ranged from 5.5 years in the UK-CPRD and Sweden to 8.1 years in Denmark in children and from 4.6 years in UK-CPRD to 7.0 years in Denmark in adults.

JOELLE study extension phase follow-up was longer than the follow-up in any other study of topical calcineurin inhibitors and malignancies. Among children, the proportion of topical tacrolimus users with a duration of follow-up of at least 10 years was 45.1% in Denmark, 34.1% in NL-PHARMO, and 25.3% in UK-CPRD. Among adults, the proportion of users with a duration of follow-up of at least 10 years was 29.6% in Denmark, 26.5% in NL-PHARMO, and 18.4% in UK-CPRD. In Sweden, the study period started on 1-Jan-2006, and the proportion of users with at least 10 years of follow-up was minimal.

Among children treated with topical tacrolimus, the median number of prescriptions was one prescription in Denmark and Sweden, and two prescriptions in UK-CPRD and NL-PHARMO. The mean number of grams of active substance (1 tube of 30 grams at 0.03% contains 0.09 grams of tacrolimus), was 0.11 grams in UK-CPRD, 0.10 grams in Denmark, 0.09 grams in NL-PHARMO, and 0.05 grams in Sweden.

Among adults treated with topical tacrolimus, the median number of prescriptions was one prescription in all the study databases. The mean number of grams of active substance was 0.12 grams in UK-CPRD, 0.10 grams in Demark, 0.11 grams in NL-PHARMO, and 0.07 grams in Sweden.

In children, there were few cases of lymphoma. The pooled adjusted IRRs comparing single use of topical tacrolimus versus topical corticosteroids for malignant melanoma and NMSC were lower than 1. The IRR comparing single use of topical tacrolimus versus topical corticosteroids was 2.19 (95% confidence interval [CI], 0.81-5.97) for non-Hodgkin lymphoma (excluding CTCL), 2.37 (95% CI, 0.99-5.68) for Hodgkin lymphoma, and 7.77 (95% CI, 0.50-121.45) for CTCL. The IRR for each type of lymphoma was based on a low number of events and was elevated for low cumulative doses, but not for medium and high cumulative doses, in the case of non-Hodgkin lymphoma, and not for medium doses in Hodgkin lymphoma. In children, the relative risk for each study outcome, skin cancers and lymphomas, for topical pimecrolimus compared with topical corticosteroids was also based on a low number of events and did not suggest an increased risk.

In adults, compared with topical corticosteroids, users of topical tacrolimus had an IRR for NMSC of 1.04 (95% CI, 1.00-1.09), and the IRRs for non-Hodgkin lymphoma and Hodgkin lymphoma (excluding CTCL) were lower than 1. For adults, the adjusted IRR of CTCL for single use of topical tacrolimus was 1.80 (95% CI, 1.25-2.58); there was a dose-response relationship of increased incidence with increasing dose. Adjusted IRRs of CTCL for single use of topical tacrolimus were 0.81 (95% CI, 0.45-1.47) for a cumulative dose of 0.05 gram or less, 2.11 (95% CI, 1.13-3.95) for a cumulative dose from 0.05 to 0.10 gram, and 5.25 (95% CI, 3.21-8.56) for a cumulative dose greater than 0.10 gram.

In the sensitivity analysis, the possibility of protopathic bias present in the estimation of the association of topical tacrolimus or pimecrolimus with cutaneous lymphoma (compared with topical corticosteroids) was investigated by calculating the IRR in different time windows after first exposure. For tacrolimus, the IRR of CTCL for time since exposure > 5 years was 0.25 (95% CI, 0.03-1.87), suggesting that the risk is confined to the first years after the start of the medication. For the same purpose, the analyses were restricted to cases with unknown or no evidence of protopathic bias. In other words, these analyses included cases without documented evidence of symptoms or signs of a previous skin condition in the same location as the subsequently diagnosed cutaneous lymphoma. The result of this sensitivity analysis did not provide evidence for protopathic bias contributing to the observed association between topical tacrolimus and CTCL.

The adjusted IRR of malignant melanoma for single use of topical pimecrolimus in adults was 1.21 (95% CI, 1.03-1.41). Adjusted IRRs were higher in the highest category of cumulative dose. The adjusted IRR for single use with a cumulative dose greater than 1 gram was 1.59 (95% CI, 1.14-2.22).

The adjusted IRR of NMSC for single use of topical pimecrolimus in adults was 1.28 (95% CI, 1.20-1.35). Crude and adjusted IRRs were higher in the highest category of cumulative dose. The adjusted IRR for single use with a cumulative dose greater than 1 gram was 1.43 (95% CI, 1.26-1.62). In adults, the IRRs for non-Hodgkin lymphoma (excluding CTCL), Hodgkin lymphoma, and CTCL for users of topical pimecrolimus compared with users of topical corticosteroids were lower than 1.

Except for malignant melanoma, the IRRs for all other outcomes were elevated in the cohort of users of topical corticosteroids compared with non-users of any study medication. In adults, the IRR for CTCL was 5.42 (95% CI, 3.77-7.79). In the sensitivity analyses performed by time since exposure to the study medications, IRRs for periods of 5 years or longer after first exposure to topical tacrolimus or topical pimecrolimus were not increased compared to the main analyses.

Discussion: Results from the JOELLE study extension phase are similar to those from Phase I of JOELLE and add a longer follow-up to the existing knowledge on the matter. JOELLE study extension phase follow-up was longer than follow-up in any other study of topical calcineurin inhibitors and malignancies, with more than 20% of the study population followed for more than 10 years. When analysing the risk of malignancies associated with long-term follow-up in the sensitivity analyses performed by time since exposure to the study medications, no evidence for the relative risk of skin cancer or lymphoma increasing with increasing duration of follow-up was observed.

Severity of atopic dermatitis is associated with increased risk of malignancies; to control for severity, we used a variable based on the type of prescriber of the first prescription. Nevertheless, type of prescriber is not equivalent to severity of atopic dermatitis, and the lack of more accurate measures of the severity of atopic dermatitis (e.g., clinical assessment) could have resulted in residual confounding and overestimation of the effect of the study medications, especially for topical tacrolimus, which is indicated for more severe forms of atopic dermatitis.

In one sensitivity analysis for protopathic bias, the elevated relative risk of CTCL associated with topical tacrolimus was confined to the first years after starting the medication, which suggests the presence of protopathic bias. However, in the other sensitivity analysis, there was no effect on the elevated relative risk of CTCL associated with topical tacrolimus when cases with manifestations of a previous skin condition in the same location as the subsequently diagnosed cutaneous lymphoma were omitted, which implies there was no substantial protopathic bias. In summary, the results of different analyses addressing protopathic bias are inconclusive.

Conclusions: To date, this is the largest study and the one with the longest follow-up evaluating the risk of skin cancer and lymphoma in users of topical tacrolimus and topical pimecrolimus, although half of them received only one prescription/dispensing.

The results of this study are in line with prior studies and could be consistent with an increased risk with topical tacrolimus of CTCL in adults or any lymphoma in children and an increased risk with topical pimecrolimus of skin cancer in adults. However, the interpretation of these findings is complicated by alternative explanations, mainly confounding by indication, protopathic bias, and surveillance bias, which cannot be ruled out. The excess risk of CTCL associated with the use of topical tacrolimus versus the use of moderate- to high-potency topical corticosteroids in adults was 3 cases of CTCL per 100,000 person-years of follow-up (95% CI, 1 to 6). The public health impact associated with such excess risk, if causal, would be low.

In the JOELLE study extension phase, follow-up was longer than in any other study of its kind. The evaluation of a longer latency period for the development of skin cancers and lymphomas in the sensitivity analyses performed by time since exposure to the study medications did not show evidence of malignancies associated with new use of topical tacrolimus or pimecrolimus with long-term follow-up.

Marketing Authorisation Holder(s): LEO Pharma A/S

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2 List of Abbreviations

ATC	Anatomical Therapeutic Chemical classification
BCC	basal cell carcinoma
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	cutaneous lymphoma
COPD	chronic obstructive pulmonary disease
CTCL	cutaneous T-cell lymphoma
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS	European Union electronic register of post-authorisation studies
FUM	Follow-up Measure (regulatory term)
GP	general practitioner
GOLD	General Practitioner Online Database; online database containing data collected in primary care practices; part of UK-CPRD
HES	Hospital Episode Statistics
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
ICD-10	International Classification of Diseases, 10th Revision
ICD-O-3	International Classification of Diseases for Oncology, Third Edition
IR	incidence rate
IRR	incidence rate ratio
ISAC	Independent Scientific Advisory Committee
ISPE	International Society for Pharmacoepidemiology
JOELLE	**JO**int **E**uropean **L**ongitudinal **L**ymphoma and skin cancer **E**valuation
MM	malignant melanoma
N/E	not estimable
NCRAS	National Cancer Registration and Analysis Service (UK)
NHL	non-Hodgkin lymphoma
NL-PHARMO	PHARMO Database Network (the Netherlands)
NMSC	non-melanoma skin cancer
NR	not reportable
OR	odds ratio
PALGA	Dutch National Pathology Registry (Pathologisch Anatomisch Landelijk Geautomatiseerd Archief), the Netherlands
PASS	post-authorisation safety study
PPV	positive predictive value
Q*n*	quarter of the calendar year
RR	relative risk
RTI-HS	RTI Health Solutions
SAP	statistical analysis plan
SC	skin cancer

SCC	squamous cell carcinoma
SD	standard deviation
SEER	Surveillance, Epidemiology, and End Results (programme of the US National Cancer Institute)
TCI	topical calcineurin inhibitor
UK	United Kingdom
UK-CPRD	Clinical Practice Research Datalink (United Kingdom)
US or USA	United States of America

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* Data analyst Huub Straatman passed away in March 2019.

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The research team chose the acronym JOELLE to honour of Dr. Joelle Erkens, pharmacoepidemiologist at Astellas and formerly at PHARMO Institute, who was lost to the research team in June 2011 following her untimely death.

4 Other Responsible Parties

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LEO Pharma A/S (hereafter LEO Pharma), marketing authorisation holder of Protopic®, established contractual agreements with research partners reflecting its role as financial sponsor, while giving the research partners—RTI Health Solutions, PHARMO, University of Southern Denmark, Karolinska Institutet, and CPRD—scientific independence, including independent publication of manuscripts consistent with the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org/) and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Study Seal. As per the study protocol, LEO Pharma has served as the study sponsor. LEO Pharma staff provided input to the protocol and reviewed and provided input to the study report. LEO Pharma was not involved in data extraction and analysis. The interpretation of the results is from the JOELLE research partners.

5 Milestones

Milestones and timelines for the implementation of the JOELLE study extension phase are provided in Table 1.

Table 1. Milestones and Timelines

Study Milestones	Planned Timeline (Range)	Actual Timeline	Comments
Submission of non-substantial protocol amendment to the EMA	Q3 2017	10-Jul-2017	EMA endorsed the protocol on 22-Sep-2017
Registration in EU PAS Register		17-Jan-2018	ENCePP seal obtained
End of cohort follow-up	31-Dec-2015[a]	31-Dec-2015 (Sweden) 31-Dec-2016 (Denmark) 31-Dec-2017 (NL-PHARMO and UK-CPRD)	
Start of data collection[b]	Q3 2017–Q1 2018	Oct 2017-Jun 2018	
End of data collection[c]	Q2–Q3 2018	Apr 2019	
End site analysis	Q1 2019	Jun 2019	
End pooled analysis	Q3 2019	Jul 2019	
Final study report	Q3 2019	20-Sep-2019	
Final study report V1.2		5-March-2020	Corrections after submission to EMA

EMA = European Medicines Agency; ENCePP = European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; EU PAS Register = European Union electronic register of post-authorisation studies; Q*n* = quarter of the calendar year.

[a] Assumed 4 years of data accumulation since 31-Dec-2011. Data beyond 4 years was available in 2 of 4 of the study countries.

[b] The date from which data extraction started (European Medicines Agency. *Guideline on Good Pharmacovigilance Practices (GVP). Module VIII – Post-authorisation Safety Studies*).[1]

[c] The date on which the analytical data set was completely available (European Medicines Agency. *Guideline on Good Pharmacovigilance Practices (GVP). Module VIII – Post-authorisation Safety Studies*).[1]

6 Rationale and Background

Topical tacrolimus ointment and pimecrolimus cream belong to the topical calcineurin inhibitor (TCI) class and have marketing authorisation for use in patients with atopic dermatitis: for moderate to severe disease for topical tacrolimus and for mild to moderate disease for topical pimecrolimus.

Tacrolimus ointment was approved by the European Medicines Agency (EMA) in February 2002 for the treatment of moderate to severe atopic dermatitis in children aged 2 years and older who failed to respond adequately to conventional therapies such as topical corticosteroids (Protopic® 0.03% ointment) and in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids (Protopic® 0.1% and 0.03% ointment). In February 2009, the EMA granted Astellas an extension to the licence 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 patients aged 2 years and over with mild or moderate atopic dermatitis where treatment with topical corticosteroids is either inadvisable or not possible. These situations may include intolerance to topical corticosteroids, lack of effect of topical corticosteroids, or use on the face and neck where prolonged intermittent treatment with topical corticosteroids may be inappropriate.

In 2006, the EMA Committee for Medicinal Products for Human Use (CHMP) considered that there was a positive benefit-risk balance for tacrolimus ointment, 0.03% and 0.1%, for the treatment of atopic dermatitis. However, further evaluation of the long-term safety profile of tacrolimus ointment was recommended due to concerns about a potential increased risk of cancer, particularly for skin cancers and lymphoma, observed with the systemic use of tacrolimus in organ transplantation and in data from animal studies and case reports on a small number of patients treated with topical tacrolimus or topical pimecrolimus.[2,3] There was a particular concern about these risks in the paediatric population.

As part of the approval in Europe of the maintenance indication for Protopic®, the CHMP mandated a Follow-up Measure (FUM-039, February 2009) for the long-term follow-up of children on maintenance treatment. A feasibility evaluation was conducted by RTI Health Solutions (RTI-HS) and a group of experts in the Nordic countries to explore the feasibility of using the Nordic prescription and cancer registries for the follow-up of children receiving maintenance treatment; the report of this evaluation described multiple challenges for the proposed study.[4] Astellas agreed to perform a European multinational observational study to 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 outcomes, the study was

planned to also include the adult population. In 2013, FUM-039 was integrated into the Protopic® Risk Management Plan as RMP052. On 16-Jul-2016, LEO Pharma became the marketing authorisation holder.

Published data from observational studies that have evaluated the relative risk (RR) of lymphomas or cutaneous lymphomas associated with use of TCIs are sparse, and a number of concerns have been raised on the limitations of available studies.[5,6] To date, observational cohort studies have not included long-term TCI exposure or follow-up times, and even in large data sources, the total number of cases of specific neoplasms is small. Before JOELLE, four studies had evaluated the risk of lymphoma following TCI use[7,8,9,10,11]; Arellano et al.[7] published results from a nested case-control study in a cohort of patients with atopic dermatitis in the United States (US) PharMetrics database with data through early 2004. The odds ratio (OR) was reported to be less than 1.0 based on cases not validated through medical chart reviews. Arana et al.[10,12] extended the study in PharMetrics until March 2009. The adjusted OR for overall lymphoma associated with pimecrolimus was 0.76 (95% confidence interval [CI], 0.54-1.08), and for tacrolimus was 1.24 (95% CI, 0.80-1.91). Pimecrolimus was not associated with any specific type of lymphoma, whereas tacrolimus was associated with an increased risk for T-cell lymphoma (OR, 4.95; 95% CI, 1.86-13.19).[6]

Schneeweiss and colleagues,[9] 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 incidence rate ratios (IRRs) greater than 1.0. For any type of lymphoma, IRRs were 1.97 (95% CI, 0.87-4.50) for topical tacrolimus, 1.79 (95% CI, 0.92-3.48) for topical pimecrolimus, and 1.33 (95% CI, 0.73-2.38) for topical corticosteroids. For cutaneous forms of lymphoma, IRRs were 2.53 (95% CI, 0.51-12.6) for topical tacrolimus, 1.49 (95% CI, 0.36-6.24) for topical pimecrolimus, and 1.27 (95% CI, 0.37-4.37) for topical corticosteroids. These effect estimates are imprecise, which limits the interpretation of the results about TCI use and the risk of lymphoma. In a third study conducted in the US in patients with atopic dermatitis, the IRR for cutaneous T-cell lymphoma (CTCL) comparing treated and untreated patients was 3.13 (95% CI, 1.41-6.94) for the use of topical tacrolimus and 1.86 (95% CI, 0.71-4.87) for the use of topical pimecrolimus.[8]

Margolis et al.[11] published findings on the risk of malignancies using data from a longitudinal cohort study of 7,457 children who had a history of atopic dermatitis and pimecrolimus use and who were enrolled in the nationwide Paediatric Eczema Elective Registry. Rates were compared with those expected using data from the Surveillance, Epidemiology, and End Results (SEER) programme of the US National Cancer Institute. The age-standardised (to the SEER population) IRR for all malignancies was 1.2 (95% CI, 0.5-2.8). The standardised IRR

for lymphoma (based on two cases in children exposed to pimecrolimus) was 2.9 (95% CI, 0.7-11.7). No skin cancers were identified. The authors noted that the data were unlikely to reflect continuous use of pimecrolimus, as demonstrated by the increasing proportion of children reporting not having used the drug at all in the previous 6-month period as the study progressed.

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).[13] In another study, in patients with atopic dermatitis or eczema, the RR of malignant melanoma with use of tacrolimus compared with non-use was 0.3 (95% CI, 0.1-0.8) and with use of pimecrolimus compared with non-use was 0.7 (95% CI, 0.4-1.3).[8]

There is some evidence suggesting that atopic dermatitis, eczema, and increasing severity of atopic dermatitis are associated with an increased risk of lymphomas, with RRs around 3 reported for severe atopic dermatitis.[7,14,15] 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. In addition, undiagnosed CTCL or even non-cutaneous forms of lymphomas may in early stages produce cutaneous symptoms that may lead to the incorrect diagnosis of atopic dermatitis, and lead to treatment with topical corticosteroids and, if not effective TCIs.[8] This phenomenon, termed protopathic bias or reverse causation, could explain the associations observed for lymphomas with skin involvement and the use of TCIs.

The objective of JOELLE and its extension was to compare the incidence rates of NMSC, malignant melanoma, and lymphoma between patients initiating treatment with TCIs and users of moderate- to high-potency topical corticosteroids. In the first phase of JOELLE, with data from 2002 through 2011, incidence rates of lymphoma per 100,000 person-years were 10.4 in children (aged less than 18 years) and 41.0 in adults (aged 18 years or older) using tacrolimus, and 3.0 in children and 27.0 in adults using pimecrolimus. The IRR of tacrolimus versus topical corticosteroids for lymphoma was 3.74 (95% CI, 1.00-14.06) in children and 1.27 (95% CI, 0.94-1.71) in adults. For specific types of lymphoma, the highest IRR was 3.17 (95% CI, 0.58-17.23) for Hodgkin lymphoma in children and 1.76 (95% CI, 0.81-3.79) for CTCL in adults. For pimecrolimus versus topical corticosteroids, the highest IRR was 1.31 (95% CI, 0.33-5.14) for CTCL in adults. Residual confounding by severity of atopic dermatitis, increased monitoring of severe patients, and protopathic bias could have affected the results.[16]

This study is an extension of JOELLE to further evaluate the long-term safety profile of tacrolimus ointment and pimecrolimus cream, designed with longer follow-up, and including sensitivity analyses to minimise confounding by severity of atopic dermatitis and protopathic bias that may affect the results.

6.1 Ethics Approvals

The RTI-HS study team received approval for exemption from review by the RTI International institutional review board on 22-Nov-2017.

Ethics approval is not required for anonymised database research in the Netherlands. However, this study fulfilled the requirements, as checked by the PHARMO Compliance Commission on 7-Oct-2011, to use data from the PHARMO Database Network (NL-PHARMO) for this specific study. Permission for the use of data from the Dutch National Pathology Registry (PALGA) was received on 23-Apr-2013. Approval for access to the Netherlands Cancer Registry staging data for malignant melanoma cases was received on 9-Aug-2018.

The study extension was approved by the Danish Data Protection Agency via Statistics Denmark on 13-Mar-2018. According to Danish law, studies based solely on register data do not require approval from an ethics review board.[17]

The Centre for Pharmacoepidemiology at Karolinska Institutet received ethics approval for the JOELLE study extension phase and for the medical record review of cutaneous lymphoma cases on 12-Jul-2017, and approval to use data from the Swedish registers from the National Board of Health and Welfare on 24-Nov-2017.

Approval of the Clinical Practice Research Datalink (CPRD) Independent Scientific Advisory Committee was received on 26-Mar-2018 (protocol number, 13_121RAR).

7 Research Question and Objectives

The primary objective of the study was to estimate the IRRs of skin cancer and lymphoma in the paediatric (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 were as follows:

- To estimate the IRRs 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.

8 Amendments and Updates

The protocol for the JOELLE study extension phase, protocol version 5.0, dated 30-Jun-2017, was the protocol amended to reflect non-substantial changes proposed for implementing the JOELLE study extension phase after finalisation of JOELLE Phase I (final study report dated 30-Nov-2015, endorsed by the EMA on 21-Jul-2016). The protocol was endorsed by the EMA on 22-Sep-2017. The protocol was also posted in the EU PAS Register, EUPAS21769. No amendments to the protocol version 5.0 have been made.

* Use of the term “topical corticosteroids” refers to moderate- to high-potency topical corticosteroids unless otherwise specified.

9 Research Methods

9.1 Study Design

This was 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 non-users of any of these medications (with or without atopic dermatitis). The study design used access to automated population-based health databases from multiple 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 very low rates of the study outcomes in children, the study also included the adult population.

The new-user design (1) allowed evaluation of potential effects of exposure to drugs that incorporated a specific time interval between the start of exposure and the onset of disease; (2) prevented potential survival bias secondary to the inclusion of prevalent users who were "survivors" of earlier periods of treatment; and (3) allowed a more accurate estimation of propensity scores and control of confounding by indication, as covariates were measured at the initiation of therapy and were not affected by the exposure itself. However, while the users of topical tacrolimus and topical pimecrolimus were new users only, the users of topical corticosteroids included both new users and prevalent users. In agreement with the labelling of TCIs, most users of topical tacrolimus and topical pimecrolimus are expected to be prior users of topical corticosteroids.

The four primary cohorts consisted of all patients with at least 12 months of continuous enrolment in the study databases who received a first prescription of topical tacrolimus, first prescription of topical pimecrolimus, or a prescription of moderate- to high-potency topical corticosteroids during the study period after the eligibility date, plus one secondary cohort of individuals not treated with any of the study medications ("untreated cohort"). Exposure propensity scores were used to frequency match users of tacrolimus and users of pimecrolimus with users of moderate- to high-potency topical corticosteroids. Patients in the untreated cohort were selected from the general population in each database and individually matched to patients in the corticosteroids cohort that was identified for comparison with users of tacrolimus on year of birth, sex, primary care general practice/region (in the United Kingdom, Netherlands, and Sweden); they were assigned a cohort entry date identical to the treated patient (all data sources). A diagnosis of atopic dermatitis was not required to be in the untreated cohort.

The study outcomes comprised (1) NMSC including in situ carcinoma; (2) malignant melanoma, including in situ melanoma; (3) any skin cancer (NMSC or malignant melanoma); (4) non-Hodgkin lymphoma, other than CTCL; (5) Hodgkin lymphoma; (6) CTCL; and (7) any lymphoma (non-Hodgkin, Hodgkin lymphoma, and CTCL).

This study adheres to the International Society for Pharmacoepidemiology (ISPE) *Guidelines for Good Pharmacoepidemiology Practices*[18]; the EMA *Guidelines on Good Pharmacovigilance Practices (GVP), Module VIII – Postauthorization Safety Studies*;[1] and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology*.[19] The study protocol and ENCePP checklist of the original study were registered in the EU PAS Register[20] prior to the start of data collection, with the registration number ENCEPP/SDPP/4357 of 30-Jul-2013 (http://www.encepp.eu/encepp/viewResource.htm?id=4358. Accessed 13-Nov-2015). The JOELLE study extension phase and its protocol were registered in the EU PAS Register and obtained the ENCePP Study Seal on 17-Jan-2018 (EUPAS21769).

9.2 Setting

The study was conducted following a common core protocol in population-based health databases and cancer registries/pathology databases 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 (NL-PHARMO)
- The Danish health care registers (Denmark)
- The Swedish health care registers (Sweden)
- The Clinical Practice Research Datalink in the United Kingdom (UK-CPRD)

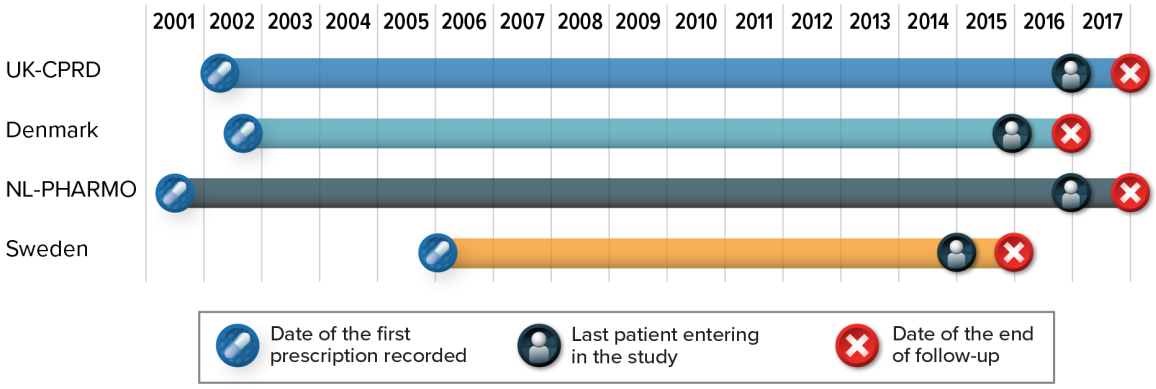
Selection of these data sources was based on their previous work on the evaluation of the risk of cancer among users of topical tacrolimus and topical pimecrolimus and their linkage capabilities to cancer registries. Specifically, the two Nordic databases participated in the feasibility exploratory phase of the study conducted in 2010, which was linked to the EMA request to Astellas to “explore the feasibility of using the Nordic prescription and cancer registries for the follow-up of children receiving maintenance treatment,” as a Follow-up Measure to the approval of the additional indication of maintenance therapy for topical tacrolimus (FUM-039, May 2009). Researchers at UK-CPRD and NL-PHARMO conducted drug utilisation studies in 2006 on the use of topical tacrolimus and topical pimecrolimus and performed exploratory analysis on the risk of cancer.[21,22] These databases have been used

extensively in the field of pharmacoepidemiology in the conduct of landmark studies in epidemiologic and pharmacoepidemiologic research.

For the JOELLE study extension phase, all study cohorts were re-created using the data available at the time of data extraction. The study period started from the date of first availability of topical tacrolimus and topical pimecrolimus in each data source. Topical tacrolimus was available in the market in 2002 in all the study countries. Topical pimecrolimus was available in 2002 in Denmark and in 2003 in the rest of the countries in the study. In Sweden, prescription data were available only since 2005, and the study period for Sweden started on 1-Jan-2006.

In the JOELLE study extension phase, the additional study period started 1-Jan-2012 in all databases and was prolonged for 6 years in UK-CPRD and NL-PHARMO, allowing enrolment of new patients through 31-Dec-2016. In these two databases, follow-up of all new users was conducted through 31-Dec-2017. In Denmark, the study period was extended for 5 years, allowing enrolment of new patients through 31-Dec-2015, and follow-up of all users was conducted through 31-Dec-2016. In Sweden, the study period was extended for 4 years, allowing enrolment of new patients through 31-Dec-2014, and follow-up of all users was conducted through 31-Dec-2015 (Figure 1). In Sweden, the shorter study period is related to the yearly update of the national registers and the lag time of up to 18 months before data are available for research.

Figure 1. JOELLE Study Extension Phase: Study Period for Each Data Source



NL-PHARMO = PHARMO Database Network (the Netherlands); UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

9.3 Subjects

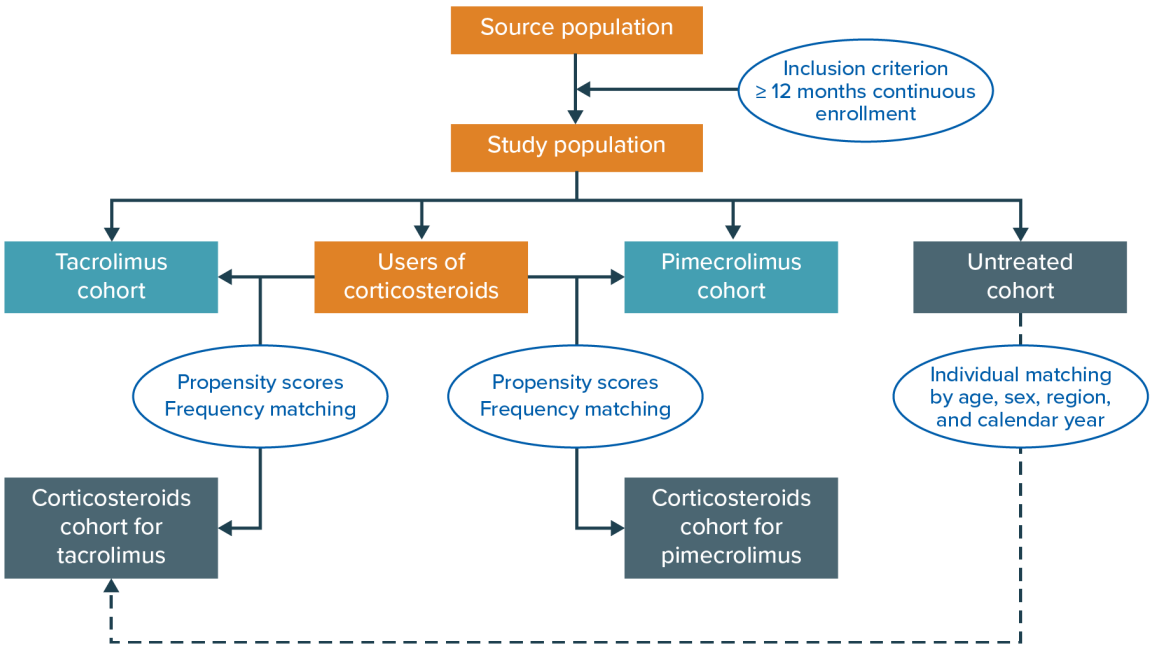
The study included four primary cohorts identified from all eligible patients who were prescribed or dispensed topical tacrolimus, topical pimecrolimus, or moderate- to high-potency topical corticosteroids during the study period, and one secondary cohort of untreated patients.

To be eligible for inclusion in the study cohorts, patients were required to have at least 12 months of continuous enrolment in the study databases, except for children 0 to 12 months of age who were eligible from the date of enrolment in each database. The eligibility date was defined as the date at which patients reached 12 months of continuous enrolment, which could occur before or during the study period. The study focused on incident cases of skin cancer and lymphoma; therefore, patients with a history of any of these conditions any time before cohort entry were excluded. This exclusion aimed to avoid potential misclassification of outcomes linked to the difficulties to distinguish, in some data sources, diagnoses of a new malignancy of a given type (first-ever diagnosis) from diagnoses of cancer recurrences or second malignancies of the same type.

9.3.1 Study Cohorts

Figure 2 contains a diagram summarising the process whereby study cohorts were selected in each data source and Figure 3 a graphical depiction of the longitudinal study design.

Figure 2. Selection of Study Cohorts



- *Tacrolimus-exposed cohort*: patients receiving a first-ever prescription for topical tacrolimus during the study enrolment period after the eligibility date.
- *Pimecrolimus-exposed cohort*: patients receiving a first-ever prescription for topical pimecrolimus during the study enrolment period after the eligibility date.
- *Moderate- to high-potency corticosteroids cohorts*:
  Two comparative cohorts of users of moderate- to high-potency corticosteroids, one for the tacrolimus cohort and one for the pimecrolimus cohort, were identified from all eligible patients from the study database. Inclusion criteria for the two corticosteroids cohorts were the following:

  1. Patients with a recorded diagnosis of atopic dermatitis who received a prescription for moderate- to high-potency topical corticosteroids during the study enrolment period after the eligibility date, or
  2. Patients without a recorded diagnosis of atopic dermatitis who received a prescription for moderate- to high-potency topical corticosteroids during the study enrolment period and at least one other prescription (for moderate- to high-potency topical corticosteroids) within the prior 12 months.

     Users of corticosteroids were frequency matched to users of tacrolimus and pimecrolimus according to twentiles of propensity scores estimated for each exposed cohort. An overall frequency matching ratio (corticosteroids to tacrolimus or pimecrolimus) up to 4:1, depending on available matches, was used across strata (See Section 9.9.2.1, Estimation of Propensity Scores).
- *Untreated cohort*: eligible patients with or without atopic dermatitis not receiving treatment with topical tacrolimus, topical pimecrolimus, or moderate- to high-potency topical corticosteroids. Eligible untreated patients were matched in a 4:1 ratio to users of corticosteroids (comparative cohort for tacrolimus) on year of birth, sex, primary care general practice/region (in NL-PHARMO, Sweden, and UK-CPRD), and were assigned a cohort entry date identical to that of the treated patient (all data sources).

9.3.2 Start of Follow-up

Follow-up started at the date of cohort entry (start date), which was defined for each study cohort as follows:

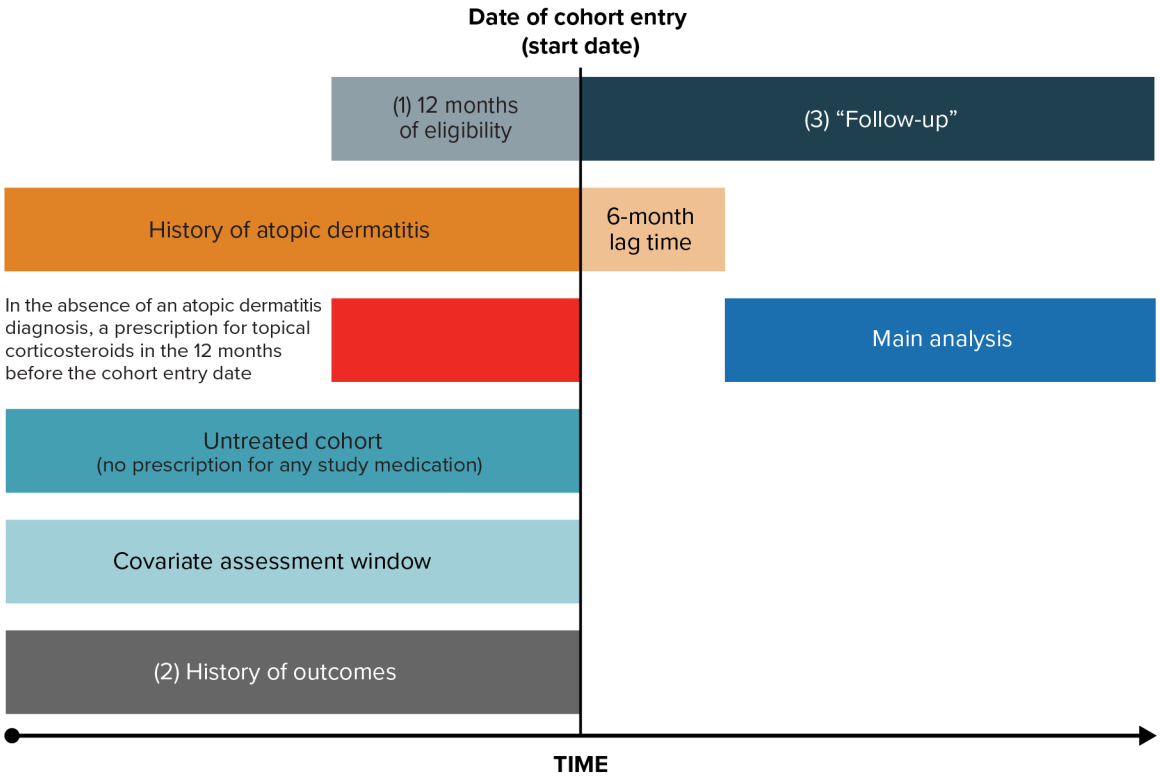
- Tacrolimus cohort: date of first prescription for topical tacrolimus received after the eligibility date
- Pimecrolimus cohort: date of first prescription for topical pimecrolimus received after the eligibility date

- Corticosteroids cohorts:
  - Patients with a diagnosis of atopic dermatitis recorded: date of first prescription for moderate- to high-potency topical corticosteroids received during the study period after the eligibility date
  - Patients without a recorded diagnosis of atopic dermatitis: date of first prescription for moderate- to high-potency topical corticosteroids received during the study period after the eligibility date and after having received another prescription within the prior 12 months
- Untreated cohort: start date of the matching member of the corticosteroids cohort

9.3.3 End of Follow-up

Follow-up after the start date continued until the earliest occurrence of any one of the study outcomes (except for certain sensitivity analyses), death, disenrolment from the study database, or end of the study period (UK-CPRD and NL-PHARMO, 31-Dec-2017; Denmark, 31-Dec-2016; Sweden, 31-Dec-2015).

Figure 3. Study Design



9.4 Variables

9.4.1 Outcome Variables

The following malignancies were the primary outcomes of interest:

- Malignant melanoma, including in situ melanoma
- Non-melanoma skin cancer, including in situ carcinoma (i.e., squamous cell carcinoma [SCC] and basal cell carcinoma [BCC], Merkel cell carcinoma, and adnexal and skin appendage neoplasms)
  - In a sensitivity analysis, the common forms of NMSC were classified separately as SCC or BCC
- Skin malignancies (malignant melanoma or NMSC)
- Non-Hodgkin lymphoma (excluding CTCL)
- Hodgkin lymphoma
- Cutaneous T-cell lymphoma (CTCL)
- Any lymphoma: non-Hodgkin lymphoma, Hodgkin lymphoma, or CTCL
  - In a sensitivity analysis, non-Hodgkin lymphomas were subclassified as cutaneous and non-cutaneous lymphomas

Malignancy outcomes were defined as the first time a diagnosis of one of the malignancies of interest was recorded in a study patient during follow-up. If a person developed more than one primary malignancy of interest, only the first malignancy was included and counted as an individual record in the main analysis. In a sensitivity analysis, patients were followed for the occurrence of each study outcome regardless of a prior occurrence of any other study outcome during the study period (see Section 9.9.4).

9.4.1.1 Outcome Identification

The ICD-O-3 (International Classification of Diseases for Oncology, Third Edition) coding system, which provides site (topography) and histology (morphology) codes for neoplasms, was used to identify malignancies. The ICD-O-3 topography code C44 (skin) was used together with the corresponding morphology codes to identify malignant melanomas, NMSCs, and cutaneous lymphomas other than CTCL. Cutaneous T-cell lymphomas were identified using the selected ICD-O-3 codes that matched the definition and codes of cutaneous lymphomas in the World Health Organization 2008 classification of lymphomas.[23] The complete lists of ICD-O-3 codes for the malignancies of interest are presented in the study protocol in Annex 4.

- In NL-PHARMO, coding in PALGA is based on ICD-O-3 coding. Mapping of PALGA codes performed well in the study based on examination of PALGA codes against the ICD-O-3 list of targeted neoplasms. If an ICD-O-3 code description did not exactly match a PALGA code, advice from a coding expert from PALGA was sought. For the sensitivity analysis on staging (Section 9.9.4), staging information for the cases of malignant melanomas was obtained from the Netherlands Cancer Registry.
- ICD-O-3 coding has been used to code neoplasms consistently in Denmark since 2000 and in Sweden since 2005. Cancer staging data for the cases of malignant melanomas are available in Denmark and Sweden.
- In the Danish Cancer Registry, ICD-O-3 topography codes were not available, but ICD-10 (International Classification of Diseases, 10th Revision) codes were available; "C43" was used for malignant melanomas and "C44" for NMSC. However, the specific ICD-10 codes for in situ neoplasms of skin are not captured. Non-Hodgkin lymphomas other than CTCL could not be classified reliably as cutaneous or non-cutaneous in Denmark.
- In UK-CPRD, the ICD-O-3 coding system is not used for coding neoplasms. Read codes are the standard clinical terminology system used in general practice in the UK and recorded in UK-CPRD GOLD (GOLD is an online database containing data collected in primary care practices). For practices linked to the cancer register and to the Hospital Episode Statistics (HES) data, cases were identified using ICD-10 codes. Therefore, in UK-CPRD, Read and ICD-10 codes were mapped to ICD-O-3 topography and morphology codes for each outcome. Mapping of Read codes used clinical diagnosis codes for the specific cancer outcomes of interest from the Read medical code chapter for malignant neoplasms followed by at least one numeric character (i.e., B….00 [Neoplasms]) and additional codes designated for skin neoplasm from the By* ("[X]") and BB* ("[M]") chapters of the Read medical code listing. Clinical diagnosis codes for in situ carcinomas of skin beginning with characters "B8" were also included. Mapping of ICD-10 codes was performed based on the equivalent topography (site) ICD-O-3 code. The specific ICD-10 codes for in situ carcinomas of skin were also included. In creating these code lists, advice was obtained from UK-CPRD coding experts; the resulting code lists were also reviewed by a medical oncologist/haematologist (Dr. James Kaye).

9.4.1.2 Outcome Confirmation and Validation

- *NL-PHARMO*. Cases were identified through the PALGA diagnosis code. Validation of all paediatric cases, of all CTCL cases, and of a random sample of adult cases up to a total of 150 was performed by an independent pathologist by reviewing the event data of the pathology excerpts. Note that cases from the year 2017 were not validated due to the inaccessibility of data at the time of validation. The independent pathologist received the complete event data from NL-PHARMO, as delivered by PALGA, to check the exactness of the diagnosis of each patient as identified by NL-PHARMO.

The PALGA system automatically generates an excerpt from the reports received from the pathologist who reviewed the data initially submitted to PALGA; the excerpt contains the following information:

  - Report identifier: laboratory, year of investigation, type of investigation, PALGA number, date of investigation
  - Patient identifiers (name up to eight characters, encrypted), initials, age at investigation, date of birth, place of birth, place of birth code, sex, residence, residence code, postal code
  - Event data (conclusion with maximal 1,000 characters, free text) and the "PALGA diagnosis," a coded diagnosis line based upon standard pathology terminology.

- *Denmark and Sweden*. Case confirmation and validation was not required because cancer cases were identified through the national cancer registries in each country, which report cases based on tumour site and histology type and implement various data quality and control procedures.[24,25,26]
- *UK-CPRD*. Outcomes were identified in the cancer register, HES data, and UK-CPRD GOLD for practices that were linked to the register and/or to HES and in UK-CPRD GOLD only for unlinked practices. Validation was performed through a clinical review of the patient profiles for the following type of outcomes: (1) all paediatric outcomes, (2) all CTCL, (3) a sample of those identified in UK-CPRD GOLD not linked to the cancer register or to the HES data, and (4) those with a discordant type of cancer recorded in UK-CPRD GOLD and the cancer register or HES data.

9.4.2 Study Exposures

The Anatomical Therapeutic Chemical (ATC) classification was used to identify study exposures in Denmark, NL-PHARMO, and Sweden: tacrolimus (D11AH01), available in two concentrations (0.03% and 0.1%), and pimecrolimus (D11AH02), available in one concentration (1%). Topical corticosteroids of interest to this study—moderately potent (D07AB), potent (D07AC), or very potent (D07AD)—were classified together as moderate- to high-potency corticosteroids. In addition, topical corticosteroids in combination with other agents—moderately potent (D07BB, D07CB, D07XB), potent (D07BC, D07CC, D07XC), and very potent (D07BD, D07CD, D07XD)—were also classified as moderate- to high-potency corticosteroids. In UK-CPRD, Gemscript codes and the British National Formulary are used by general practitioners (GPs) in primary care to code prescriptions. The National Health Service Dictionary of Medicines and Devices codes were mapped to ATC codes via SafeScript (www.safescript.com) in a multistep process, followed by manual revision of each code individually. The linkage occurs at the ingredient level, and there are various checks throughout the process using the requirements for process control identified in DSCN14 (ISB

0129).[27] The mapping is approached from several directions and sources; therefore, the likelihood of false positive matches was expected to be low.

9.4.2.1 Topical Tacrolimus and Topical Pimecrolimus

To assess the effect of topical tacrolimus and topical pimecrolimus, we assumed for the main analysis a lag time of 6 months for the occurrence of the study outcomes. This lag time conceptually encompasses a period of drug utilisation 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 potential induction time for the occurrence of skin cancer and lymphomas associated with the use of tacrolimus and pimecrolimus is unknown. Therefore, we also conducted sensitivity analyses using lag times of 0 months, 12 months, 24 months, and 48 months (Section 9.9.4).

To assess the risk associated with the use of topical tacrolimus and topical pimecrolimus, we assumed that exposure to either of the two medications resulted in a lifetime change in risk for the effects of that specific medication (i.e., for a patient exposed to topical tacrolimus or topical pimecrolimus, the status of exposure was maintained throughout follow-up, even after stopping therapy). However, for the main analysis, time at risk started after the lag time of 6 months was completed. Person-time of follow-up for each cohort (e.g., topical tacrolimus) was classified into exposure categories, as follows:

- ***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. Any switching from tacrolimus to pimecrolimus was ignored.

In addition, the overall person-time of follow-up of topical tacrolimus use was classified into two mutually exclusive categories:

- ***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 earlier 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 or multiple use): person-time starting 6 months after the date of receiving a prescription for topical pimecrolimus to the end of follow-up.

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

In addition, any ***combined*** use of topical tacrolimus and topical pimecrolimus was aggregated into a single overall category of switching/multiple use to assess the effect of the overall exposure to both drugs after switching.

Cumulative Dose

Cumulative exposure, the main measure of exposure in the analysis, was calculated as the cumulative dose of active substance of topical tacrolimus or pimecrolimus that a patient received during follow-up. The cumulative dose of each drug was estimated separately for ever use, single use, and switching/multiple use of both tacrolimus and pimecrolimus. Cumulative dose of active substance was measured in grams calculated from the strength of the formulation and the package size and was categorised in levels of exposure and cutoff values based on the distribution of cumulative dose from the JOELLE Phase I descriptive analysis (Table 2). The same cutoff values were applied to children and adults.

Table 2. Categorisation of Cumulative Dose of Active Substance

Category of Cumulative Dose of Active Substance	Topical Tacrolimus	Topical Pimecrolimus[a]
Low	≤ 0.05 g	≤ 0.5 g
Medium	> 0.05 g to ≤ 0.10 g	> 0.5 g to ≤ 1 g
High	> 0.10 g	> 1 g

[a] The cutoff values for pimecrolimus are those for tacrolimus multiplied by a factor of 10 to provide strength equivalence.

For each level of cumulative dose, we assumed an induction period of 6 months for the start of exposure effects. Thus, the time at risk started 6 months after reaching the cutoff value of each level of cumulative dose. Patients contributed follow-up time to each level of cumulative dose according to the daily cumulative dose until the end of follow-up. Thus, for each patient, dose was accumulated daily according to the grams prescribed and the assumed duration of prescriptions. The cumulative dose for the combined use of tacrolimus and pimecrolimus was classified in two levels: low-medium (collapsing low and medium categories) and high. Cumulative dose after switching continued to accumulate daily for patients in the combined category.

Duration of Use

Duration of use was defined as the total time of use of topical tacrolimus or pimecrolimus during follow-up. For each patient, duration of use was accumulated daily according to the assumed duration of prescriptions, calculated on the basis of JOELLE Phase I descriptive analysis: 60 days for topical tacrolimus and 70 days for topical pimecrolimus. Total duration was estimated separately for children and adults.

Duration was categorised according to the median of the distribution of total duration. A common median was used as the cutoff point in all the data sources: 60 days for topical tacrolimus and 70 days for topical pimecrolimus. Duration categories were as follows:

- Short: 1 to 120 days for topical tacrolimus and 1 to 140 days for topical pimecrolimus
- Medium: 121 to 240 days for topical tacrolimus and 141 to 280 days for topical pimecrolimus
- Long: > 240 days for topical tacrolimus and > 280 days for topical pimecrolimus

The same duration categories were used for children and adults. For each category of duration of use, we assumed an induction period of 6 months for the start of exposure effects. Thus, the time at risk started 6 months after reaching the cutoff value of each duration category.

9.4.2.2 Topical Corticosteroids

Time at risk for the effects of exposure to moderate- to high-potency corticosteroids was defined as the person-time starting 6 months after cohort entry to the earliest of the date of (1) a prescription for topical tacrolimus, (2) a prescription for topical pimecrolimus, or (3) end of follow-up.

9.4.3 Covariates

To control for confounding, we used frequency matching by twentiles of propensity scores. The methods used to estimate propensity scores and the covariates that were evaluated are described in Section 9.9.2.1. The covariates included in the regression models for the estimation of propensity scores were those that were associated with the study outcomes and included age, sex, immunosuppressive disease and use of immunosuppressive agents, chronic disease, severe skin diseases, atopic dermatitis, severity of atopic dermatitis, and measures of health care resource utilisation.

Because information on severity of atopic dermatitis was very limited in all the study sources, we evaluated the effect of type of prescriber of the first prescription as a proxy for severity of atopic dermatitis. The underlying assumption considered that patients with more severe atopic dermatitis would have been seen and treated first by a dermatologist and patients with less severe atopic dermatitis would have been seen and treated first by a GP. Information on this variable was available in Denmark, NL-PHARMO, and Sweden; it was not available in UK-CPRD.

9.5 Data Sources and Measurement

The study was conducted following a common core protocol in the populations covered in the four population-based health databases and cancer registries in Europe listed in Section 9.2. Summary information on main characteristics of the data sources is presented in Table 3.

Table 3. Selected Characteristics of the Data Sources Used in This Study

Characteristic	UK-CPRD GOLD	NL-PHARMO	Danish Health Registers	Swedish National Registers
Database population	15,500,000 (total coverage) 2,300,000 persons registered and alive	3,200,000	5,500,000	9,700,000
Database type	Database of electronic health records from primary care plus linkage to cancer register data and Hospital Episode Statistics in English practices	The PHARMO Database Network holds several databases, linked on patient level. For this study, outpatient pharmacy data, hospitalisation data, and pathology data (PALGA) was used. Malignant melanoma staging data was obtained from the Netherlands Cancer Registry.	Prescription register since 1995 Danish National Registry of Patients: hospital admissions, hospital outpatient visits, and emergency department visits. Cancer register	Prescribed Drug Register since 1-Jul-2005 Patient registers: hospital admissions and hospital outpatient visits Register of the total population Cancer register
Drugs				
Prescribed/ dispensed drugs	GP prescriptions No inpatient prescribing data	Dispensed in community pharmacies (reimbursed and not reimbursed medications) No inpatient data used in this study	Dispensed in community pharmacies (reimbursed and not reimbursed medications) No inpatient data	Drugs dispensed by prescription in community pharmacies since 2005 (reimbursed and not reimbursed medications) No inpatient data
Drug indication	Associated with new courses of medications, but completeness is variable	Not available	Not available	Not available
Type of prescriber info	GP only	Yes	Yes	Yes
Study variables and data validation				
Outpatient diagnoses	Yes	Not used for this study	Yes, hospital outpatient clinics	Yes, hospital outpatient clinics
Hospital diagnoses	Recorded by GPs in primary care and available from linked Hospital Episode Statistics for admitted patients	Yes	Yes	Yes

Characteristic	UK-CPRD GOLD	NL-PHARMO	Danish Health Registers	Swedish National Registers
Study endpoints				
Cancer data linkage	Partial, for a defined subset of practices in England only	Yes, PALGA (pathology register) and the Netherlands Cancer Registry	Yes	Yes
Outcome validation	Clinical review of patient profiles and for cutaneous lymphomas as part of the assessment of protopathic bias, additional information through GP questionnaires	PALGA (pathology register)	Linkage to cancer register	Linkage to cancer register and for cutaneous lymphomas as part of the assessment of protopathic bias, access to medical records for review and abstraction of additional information

GOLD = General Practitioner Online Database; online database containing data collected in primary care practices; part of UK CPRD; GP = general practitioner; NL-PHARMO = PHARMO Institute for Drug Outcomes Research in the Netherlands; PALGA = Dutch National Pathology Registry; UK-CPRD = Clinical Practice Research Datalink, United Kingdom.

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 patient demographics, outpatient 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, inpatient drug dispensings, cancer diagnosis, and GP information is also available. Some of the databases (e.g., pathology database—PALGA) are partnership databases; permissions on a per-project basis are required to access data. Access to medical charts and other clinical data is available within the parameters of the Dutch privacy regulations. For this study, data from the Outpatient Pharmacy Database, the Hospitalisation Database, and PALGA were used. Data from the Netherlands Cancer Registry was used to identify the stage of malignant melanomas for a sensitivity analysis.

In Denmark and Sweden, each national health care system provides universal coverage to all residents. Health care coverage includes visits to GPs, specialists, hospital admissions, and hospital outpatient visits; for reimbursement-approved drugs, costs are either partially or completely covered. A centralised civil registration system has been in place in both countries for many years, allowing for personal identification of each individual person in the entire population and for the possibility of linkage to all national registers containing civil registration numbers, e.g., patient register, cancer register, prescription databases, register of causes of death, and population registers.[28] Data from the primary care setting are not available. Data collected in these registers can be made available for research purposes under the principles for protection and release of sensitive data.[29,30]

UK-CPRD GOLD primary care database contains data recorded by GPs, who are responsible for primary health care and referrals to specialists in the UK. The database currently has research-quality records for over 2.3 million active patients known to represent over 3% of the general population in the UK. Data are collected on demographic information (year of birth, sex, region), prescription details (dosage, quantity), clinical events (symptoms, diagnoses), preventative care provided, tests, immunisations, lifestyle (body mass index, smoking status), specialist referrals, hospital admissions and their major outcomes, and details relating to death. UK-CPRD GOLD does not contain information on dispensing of prescriptions or information on hospital-based medications. A subset of English practices (currently 75%, representing 58% of all UK-CPRD practices) has been linked to other UK health care data sets (e.g., National Cancer Registration and Analysis Service [NCRAS], Cancer Registry, HES, Office for National Statistics mortality data) via the patient's National Health Service number, sex, date of birth, and postal code. Validation of UK-CPRD has shown high positive predictive value (PPV) of some diagnoses and, where evaluated, comparisons of incidence to other UK data sources are also broadly similar.[31,32,33,34] This study used data from the July 2018 database build for UK-CPRD GOLD primary care data, linkage set 16, and the linked cancer register and HES data covering the period to 31-Dec-2015, (UK-CPRD GOLD + cancer register) and 31-Dec-2017 (UK-CPRD GOLD + HES).

9.6 Bias

We conducted sensitivity analyses to evaluate the effect of the following potential sources of bias:

- Confounding by indication (i.e., by severity)
- Protopathic bias (reverse causation)
- Surveillance bias

9.6.1 Confounding by Indication (Severity)

For the whole JOELLE study (Phase I plus the extension), information on type of prescriber was available in the study populations of NL-PHARMO, Sweden, and Denmark.

The main analyses were stratified by type of prescriber in NL-PHARMO, Sweden, and Denmark; the Mantel-Haenszel adjusted IRR was estimated in each of these populations (i.e., IRR was adjusted by type of prescriber in Denmark, NL-PHARMO, and Sweden).

This adjustment was not possible in UK-CPRD, and the IRR was not adjusted for the effect of type of prescriber in UK-CPRD. Researchers at UK-CPRD investigated the possibility of using referrals to dermatology around the time of first prescription as a proxy for first

prescriber. Although it was possible to identify referrals in some patient records, UK-CPRD researchers considered that the evidence was not strong enough to stratify data in the analysis.

9.6.2 Protopathic Bias (Reverse Causation)

Protopathic bias could be present if the signs and symptoms of the outcome are the reason for initiating treatment with the study medications. This is particularly relevant for CTCL, which can be misdiagnosed and treated as atopic dermatitis for up to 10 years before the correct diagnosis is made.[35,36]

Evaluation of potential protopathic bias for CTCL cases was conducted in UK-CPRD and Sweden.

In UK-CPRD, after approval of the Independent Scientific Advisory Committee (ISAC), researchers sent questionnaires to GPs requesting additional information to assess protopathic bias. Information included 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 Sweden, after ethics approval, researchers reviewed the medical records of cases of CTCL with the purpose of identifying information indicating whether symptoms that may have been caused by CTCL were already present at the time of the start of the exposure.

Furthermore, we attempted to limit the effect of protopathic bias by assuming in the main analysis an induction period of 6 months. In addition, we conducted a lag-time analysis with lag times of 0 months, 12 months, 24 months and 48 months.

To further evaluate protopathic bias, we estimated IRRs by time since the start of the exposure. Time was categorised as follows: first 6 months after the start of treatment, 6 months up to 2 years, 2 years up to 5 years, and 5 years and longer. Higher incidence rates in the periods immediately following exposure (e.g., first 6 months) than in later periods would be consistent with protopathic bias.

9.6.3 Surveillance Bias

Surveillance bias could be present if patients with severe atopic dermatitis were monitored more frequently and/or more thoroughly than patients with non-severe atopic dermatitis.

Increased surveillance could lead to an earlier detection of outcomes, which would result in higher incidence rates shortly after the beginning of the exposure and to the detection of early-stage malignancies. This was evaluated by the lag-time analysis and the analysis of incidence rates by time since the start of exposure.

9.7 Study Size

As detailed in the protocol for the JOELLE study extension phase, the study size calculations were derived from the incidence rates of each malignancy observed in the JOELLE Phase I and updated numbers of annual users of tacrolimus in each data source. The calculations assumed an extension of 4 years (through 31-Dec-2015), with a period of 3 years of inclusion and 1 year of follow-up to ensure that all users were followed for at least 6 months after applying the 6-month induction period. In most databases, data beyond 2015 were available. The estimated annual numbers of tacrolimus users across all data sources were as follows: for children (aged < 18 years), 24,412 new users contributing 133,285 person-years of follow-up; and for adults (aged ≥ 18 years), 98,788 new users contributing 551,369 person-years of follow-up.

In Table 4, we present the probability for each study outcome to have an upper limit for the two-sided 95% CI of the IRR below the specific values of 2, 4, 8, and 16, according to the estimated number of users of tacrolimus, assuming a 4-year extension across all study data sources and the incidence rates observed in JOELLE Phase I. The calculations were based on the following assumptions: two-sided confidence level of 95%, expected rate ratio of 1, an equal number of exposed and unexposed (allocation ratio of 1:1), and incidence among the unexposed is the same as the incidence in the general population. Calculations assumed that each person that was prescribed tacrolimus in a given year contributed 1 year of follow-up.

For the adult population, the probability was 95% or higher for having an upper limit of the 95% CI of the IRR below 2 for NMSC, melanoma of skin, and non-Hodgkin lymphoma. For Hodgkin lymphoma and CTCL, the probabilities were 95% and 85%, respectively, for having an upper limit below 4.

For the paediatric population, the probabilities for having an upper limit of the 95% CI of the IRR below specific values ranging from 2 to 16 were overall low for all outcomes. The highest probability was for any lymphoma, with a 70% probability for having an upper limit of the 95% CI of the IRR below 16.

Table 4. For Each Study Outcome, Probability That the Upper Limit for the 95% Confidence Interval of the Incidence Rate Ratio is Below 2, 4, 8, or 16[a]; JOELLE Study Extension Phase (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 JOELLE Phase I.

[b] Calculations could not be based on JOELLE 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 incidence rates from the Surveillance, Epidemiology, and End Results (SEER) programme of the National Cancer Institute in the United States (SEER*Stat version 7.05).

9.8 Data Transformation

Categorisation of continuous variables used in the estimation of propensity scores was detailed in the statistical analysis plan (SAP).

9.9 Statistical Methods

Analysis were conducted as prespecified in the SAP, V1.0, 25-Jul-2017. Amendments to and deviations from the SAP are described in Section 9.9.5.

Data analyses occurred in two stages: (1) an analysis conducted in each data source and (2) a pooled analysis conducted by the coordinating centre, where summary data from each data source were combined. In the first stage, for the comparison of topical tacrolimus and topical

pimecrolimus versus topical corticosteroids, each data source produced stratified tables with cross-classifications of person-time and outcome counts by exposure category, age, type of prescriber (where available), and deciles of propensity scores. For the comparison of topical corticosteroids versus the untreated population, the data were stratified by levels of each matching variable, prescriber type (where available for the corticosteroids cohort), and time since cohort entry. In the second stage, the coordinating centre conducted stratified analyses to estimate pooled measures of effect.

This two-stage analysis was designed to meet data source–specific restrictions on the level and type of information that can be shared externally while accomplishing the goal of assimilating the data from multiple study data sources into one summary analysis.

Data protection rules in Denmark do not allow reporting of values from 1 to 4 or cells that allow a value of 1 to 4 to be derived from other reported cells. In this report, any values that could aid in deriving another value of 1 to 4 have been suppressed and appear as "not reportable" (NR).

[redacted]

9.9.1 Main Summary Measures

Members of each of the four study cohorts were characterised at the start date and separately for children (aged 0 to < 18 years) and adults (aged ≥ 18 years). Description of cohort members included the age and sex distribution, duration of follow-up, medical history, concurrent use of medications at the start date, and utilisation of health care resources.

Pooled incidence rates and IRRs across the study databases were estimated for each study outcome and for each type of exposure, as described in Section 9.4.2.

The JOELLE research team approached the study design and the interpretation of results based on the evaluation of point estimates, precision, and validity considerations, rather than statistical significance. Confidence intervals are interpreted as quantitative measures indicating magnitude of effect size and degree of precision, rather than as surrogates of significance tests. This is in agreement with the recommendations from the International Committee of Medical Journals Editors to "when possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals), and the statement of the American Statistical Association.[37] Avoid relying solely on statistical hypothesis testing, such as *P* values, which fail to convey important information about effect size and precision of estimates."

9.9.2 Main Statistical Methods

9.9.2.1 Estimation of Propensity Scores

To control for confounding, each data source frequency matched two comparative cohorts of users of moderate- to high-potency topical corticosteroids, one to the topical tacrolimus cohort and one to the topical pimecrolimus cohort, by twentiles of propensity scores. The exposure propensity scores were estimated as the probability of initiating treatment with topical tacrolimus or topical pimecrolimus rather than receiving moderate- to high-potency topical corticosteroids given a set of baseline covariates. Propensity scores were estimated in each data source separately for the topical tacrolimus and the topical pimecrolimus cohorts, and separately for children and adults.

The propensity scores were estimated using a two-step approach. In the first step, each data source fit outcome models to identify predictors of the study outcomes. In the second step, these predictors were included in the estimation of exposure propensity scores. Logistic regression models were used in each step. For the outcome models, three regression models were fit for each outcome—one for melanoma skin cancer, one for NMSC, and one for lymphoma—in the combined study database of users of topical tacrolimus, topical pimecrolimus, and topical corticosteroids. Because the number of outcomes in children was very low, these outcome models were fit in adults only. In the second step, variables from the fitted outcome models with a RR greater than 1.25 or less than 0.80 for any of the three outcomes were selected and included in the exposure propensity score regression models separately for topical tacrolimus and topical pimecrolimus, and separately for children and adults. When fitting a propensity score model, it is important to avoid including in the model strong predictors of exposure that are unrelated to the outcome (such variables are known as "instrumental variables," or "instruments"), because their inclusion may adversely affect the efficiency of the analysis, i.e., reduce precision.[38]

To account for patients with nonoverlapping propensity scores, each data source excluded from each study cohort all patients below the first percentile and above the 99.0th percentile of the distribution of propensity scores in the exposed cohorts (topical tacrolimus, or topical pimecrolimus) (i.e., data trimming). The resulting distributions of propensity scores in the topical tacrolimus and the topical pimecrolimus cohorts after trimming were used to identify twentiles of propensity score. Then, separately for the topical tacrolimus cohort and for the topical pimecrolimus cohort, users of topical corticosteroids were matched to each TCI user by twentiles of propensity scores at a ratio up to 4:1. Within each stratum, frequency matching was conducted by randomly selecting users of topical corticosteroids from the eligible pool until the matching ratio was met. It should be noted that the adjusted analyses were designed to handle different ratios between strata. All of the standardised rates were standardised by centre-specific strata of propensity scores, so the rates were calculated within the individual strata before being combined through the standardisation. Mantel-Haenszel techniques were used to calculate adjusted IRRs. The Mantel-Haenszel method basically calculates separate IRRs for each individual stratum and then takes a weighted average of stratum-specific IRRs with weights inversely proportional to the null-effect variance.

9.9.2.2 Data Stratification

After the matching, each data source collapsed twentiles of propensity scores into deciles and produced person-time and outcome counts by exposure category, type of prescriber (where available), age, sex, and decile of propensity scores. Because of privacy requirements, data from Denmark could not be shared outside the country.[17] Therefore, the stratified tables with cross-classifications of person-time and number of cases created by each data source except Denmark were sent to the coordinating centre. After performing quality checks, the coordinating centre uploaded the study data to Statistics Denmark and conducted the pooled analysis remotely within their servers.

9.9.2.3 Pooled Analysis

After receiving the data source–specific, age, sex, and propensity score–stratified tables, the coordinating centre conducted an analysis of the data from each individual data source and an overall analysis combining the data across all data sources. The overall analysis was designed to estimate the effect of the exposure while controlling for confounding using the data stratified on propensity scores. Data source was retained as a stratification variable, and the effect within each data source was estimated.

Estimation of Incidence Rates

Incidence rates were estimated separately for children and adults. Crude incidence rates were calculated for each data source and overall across all study data sources as the number of outcome events divided by the person-time at risk. The Poisson distribution was used to calculate exact 95% CIs for the incidence rates within each data source. Standardised incidence rates and 95% CIs were estimated using the distribution of person-time across deciles of propensity scores of the cohort exposed to tacrolimus as the standard.[39] Crude and standardised incidence rates for each study outcome were estimated for each exposure category (ever use, single use, and switching/multiple use) of each study cohort, and for cumulative dose and duration of use.

Estimation of Incidence Rate Ratios

Mantel-Haenszel methods were used to estimate pooled IRRs and 95% CIs across data sources and deciles of propensity scores. Incidence rate ratios were estimated separately for children and adults. Crude and adjusted IRRs and 95% CIs for each study outcome were estimated, comparing the incidence rates for each exposure category of topical tacrolimus and topical pimecrolimus (ever use, single use, and switching/multiple use) with the rates in the corresponding corticosteroids cohort.[40,41] The analysis focused on estimation of IRRs comparing the incidence rates for each exposure category (ever use, single use, switching/multiple use), levels of cumulative dose and duration of exposure to tacrolimus and pimecrolimus (e.g., low, medium, high) with the rates in the corresponding corticosteroids cohort.

Estimation of Incidence Rate Differences

Incidence rate differences were estimated for the same comparisons as those performed for the calculation of IRRs described above.

9.9.2.4 Effect of Type of Prescriber of First Prescription

In the JOELLE study extension phase, additional analyses stratifying by type of prescriber in NL-PHARMO, Sweden, and Denmark were performed as part of the sensitivity analyses (Section 9.9.4); the Mantel-Haenszel adjusted rate ratio was estimated in each of these populations (i.e., the IRR was adjusted by type of prescriber in Denmark, NL-PHARMO, and Sweden).

9.9.2.5 Secondary Analysis

The secondary analysis addressed the secondary study objective of estimating incidence rates and IRRs of skin cancer and lymphoma in users of topical corticosteroids compared with

untreated individuals. The analyses were conducted using the corticosteroids cohort identified in the comparison with users of tacrolimus. Each database research partner created a untreated cohort by individually matching patients not treated with any study medication with the corticosteroids cohort for topical tacrolimus, by year of birth, sex, calendar year of start date, and primary care general practice/region (where available), at a matching ratio up to 4:1. Patients in the corticosteroids cohort who could not be matched were excluded from this analysis. Each database research partner stratified the data simultaneously by age, sex, and primary care general practice/region (where available) and computed person-time and outcome counts for each stratum. The coordinating centre estimated crude and standardised incidence rates and used Mantel-Haenszel methods to estimate crude and adjusted IRRs for each data source and overall across data sources.

9.9.3 Missing Values

Information on some covariates (e.g., visits to a GP) was not available in all the study data sources or had been ascertained through different methods across data sources (e.g., hospital discharge diagnosis vs. information from GPs). When information on a variable was not available in a study data source, this variable was not evaluated.

Information on type of prescriber of first prescription was not available in UK-CPRD.

9.9.4 Sensitivity Analyses

To assess potential bias (see Section 9.6) and to evaluate different exposure and outcome definitions, we conducted the following sensitivity analyses:

- Analysis of first occurrence of each type of malignancy. In this analysis, follow-up continued after the first occurrence of a study outcome, allowing patients to have more than one study malignancy.
- Analysis of first occurrence of each type of malignancy in children aged 2 years but less than 16 years.
- Analysis of the occurrence of all malignant melanomas and NMSCs, excluding in situ carcinomas.
- Analysis of the occurrence of BCC and SCC, separately.
- Analysis of the occurrence of cutaneous and non-cutaneous lymphomas, separately.
- Analysis of the occurrence of each malignancy by strata of propensity scores to explore effect modification.
- Lag-time analysis with additional lag times of 0 months, 12 months, 24 months and 48 months.

- Time since the start of exposure: first 6 months, 6 months up to 2 years, 2 years up to 5 years; and 5 years and longer.
- Analysis by severity of atopic dermatitis. Severity of atopic dermatitis was approximated by the type of prescriber (dermatologist, non-dermatologist) of the first prescription which was available in NL-PHARMO; Denmark, and Sweden (see Section 9.9.2.4).
- Analysis by stage of cancer. Information on stage of cancer was available only for malignant melanoma. Analysis of the occurrence of malignant melanoma by stage of the malignancy was planned in Denmark, NL-PHARMO, and in Sweden.

9.9.5 Amendments to the Statistical Analysis Plan

The SAP version 1.0, 25-Jul-2017, for the JOELLE study extension phase, has been amended and is replaced by the SAP version 1.1, dated 15-Mar-2019, according to the specification detailed in Table 5.

Table 5. Summary of Amendments and Updates to the Statistical Analysis Plan

SAP Version	Date	Section of SAP	Amendment or Update	Reason
1.1	15-Mar-2019	Section 5.1.3.1; Estimation of propensity scores	Change in the method of selecting variables to be included in the propensity score models, from high dimensional propensity score variable selection to two-step selection as in JOELLE Phase I	Alignment of all centres with their analytical skills and familiarity with the method
1.1	15-Mar-2019	Section 5.3.1.2; Cumulative dose	Deletion of reference to sensitivity analysis with extension of duration of prescriptions by 60 days for cumulative dose and duration of use	Results in JOELLE Phase I were similar to those of main analysis; research team agreed that this analysis was not necessary

SAP = statistical analysis plan.

9.9.5.1 Deviations From the Statistical Analysis Plan

Information on stage of malignant melanoma of the skin was available only in Sweden, where about 50% of tumours were classified as “unknown” stage. In UK-CPRD, staging data were available from the cancer register for only 9% of all identified malignant melanoma cases. In Denmark, a two-stage classification (localised and non-localised) is used, which differed from the three-stage categorisation proposed for this study: stage I, II, and III/IV. In NL-PHARMO, a large number of cases were found with stage “unknown.” Given these limitations, the research team considered that this analysis would not provide useful results; therefore, the analysis by stage of malignant melanoma was not performed.

9.10 Quality Control

The standard operating procedures of each database research partner were used to guide the conduct of the study. These procedures included 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 was 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, underwent quality-control review, senior scientific review, and editorial review.

The quality and audit trails are centre specific, and each research partner followed its own quality and audit trail procedures. During Phase I, the marketing authorisation holder Astellas audited RTI-HS, Southern Denmark University, Karolinska's Clinical Pharmacoepidemiology department, and PHARMO Institute.

10 Results

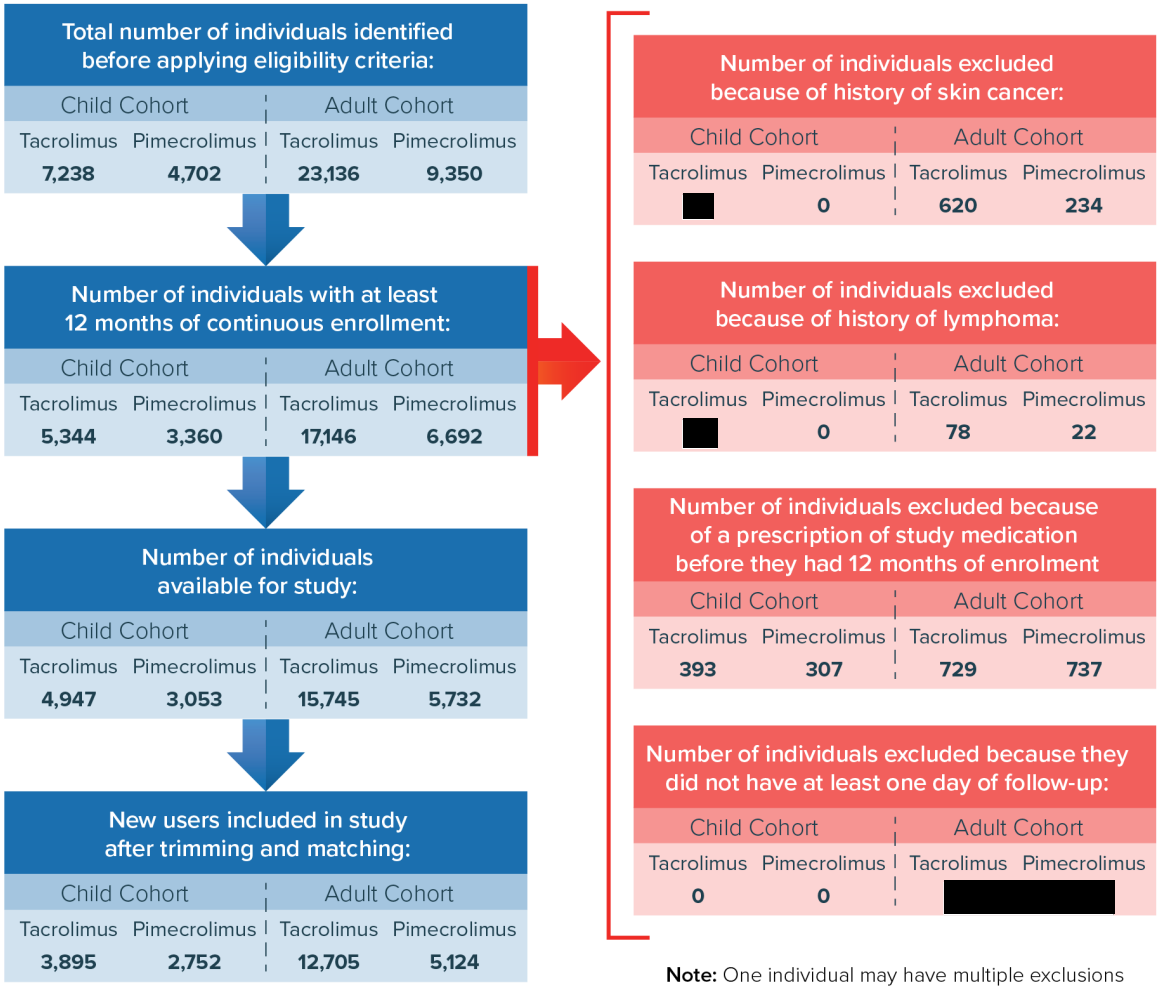
[redacted]

Due to the limited number of events and the reporting restrictions linked to cell counts below 5 for Denmark, we do not report data source–specific incidence estimates for any of the study outcomes in children and instead present in Section 10.4.2 the data source–specific number of events, from data sources where it is allowed, and the pooled estimates.

Detailed results for each data source are presented in Annex 2.

Cohort attrition for each population is described in Figure 4 through Figure 7.

Figure 4. Cohort Attrition, UK-CPRD



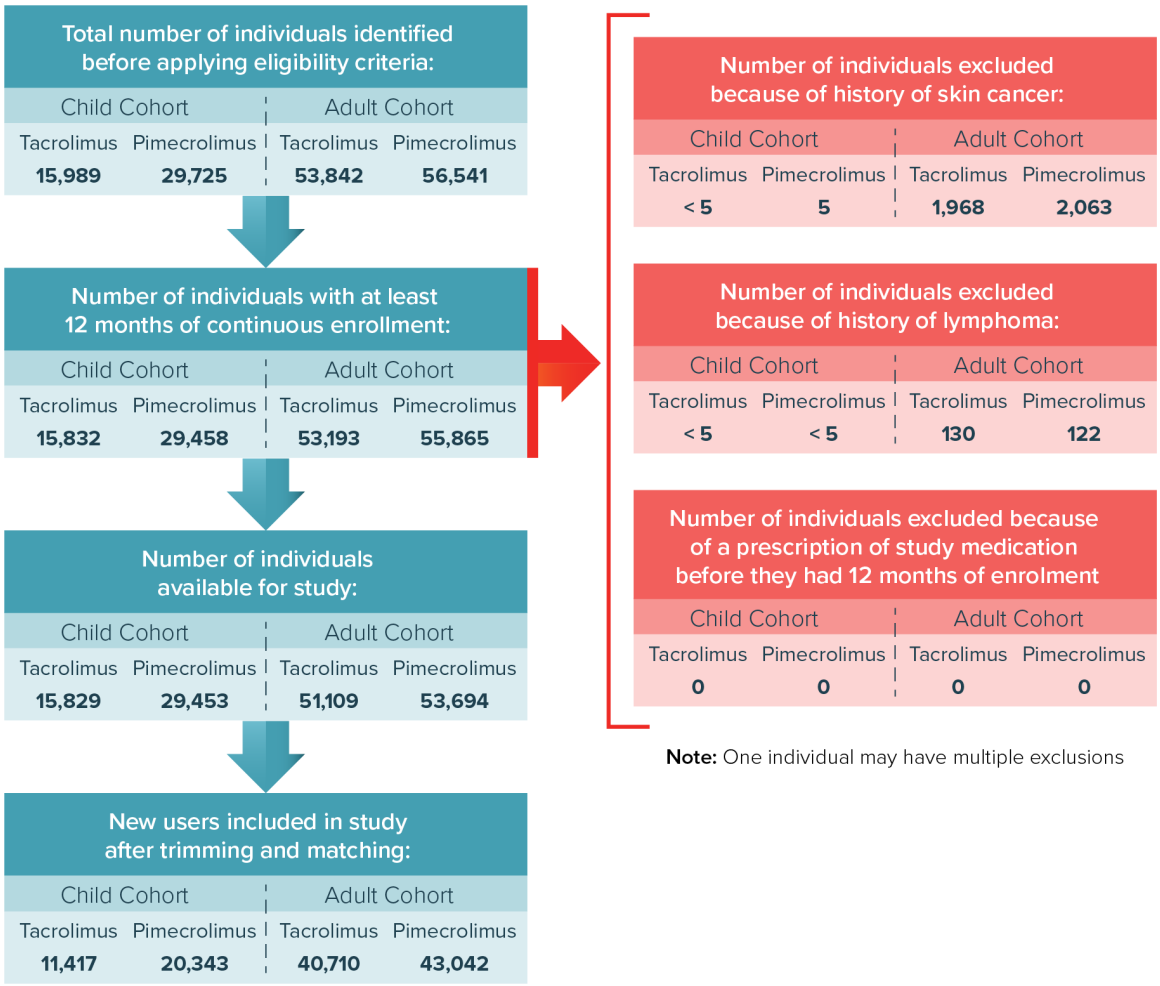
Note: One individual may have multiple exclusions

UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

Figure 5. Cohort Attrition, NL-PHARMO

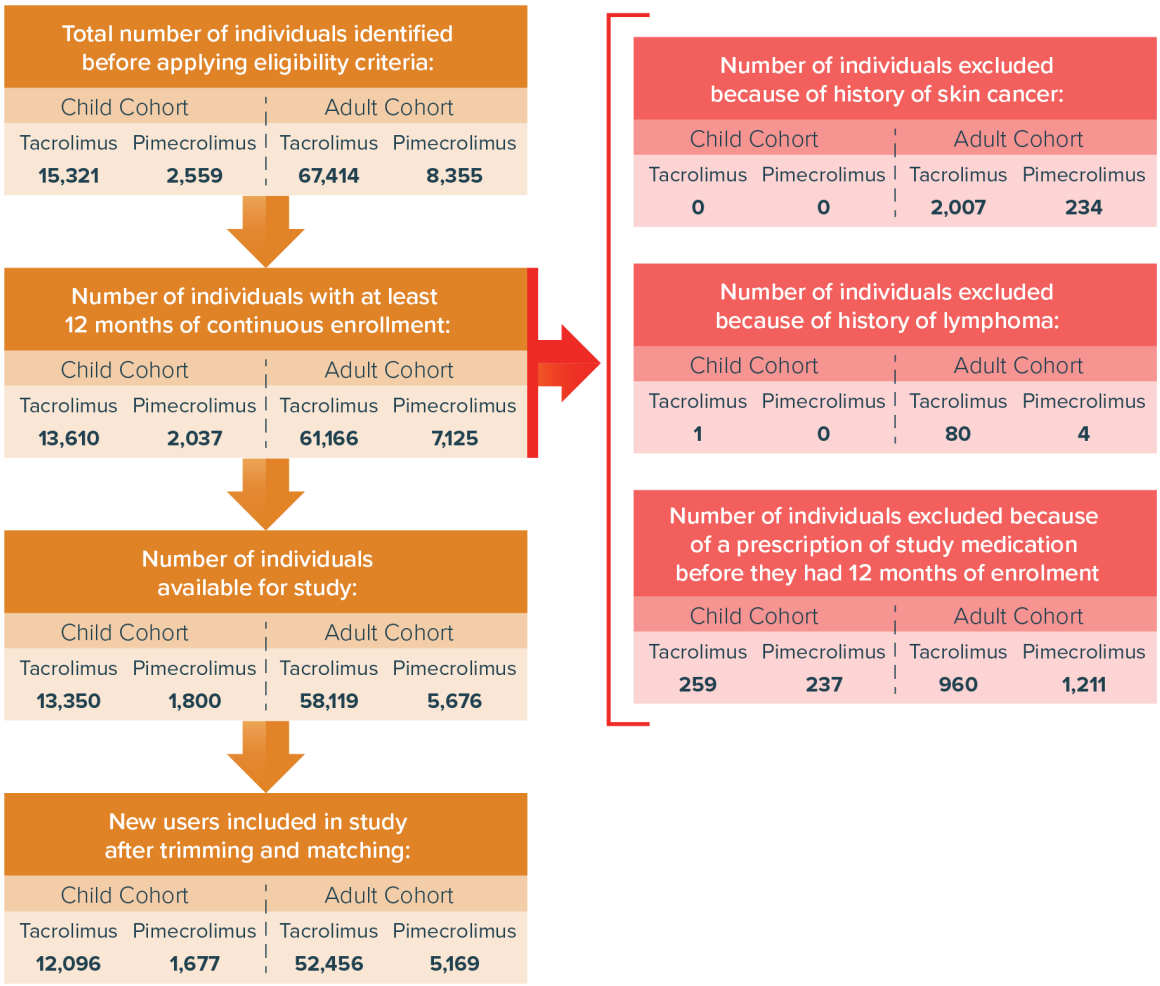
NL-PHARMO = PHARMO Database Network (the Netherlands).

Figure 6. Cohort Attrition, Denmark



Note: One individual may have multiple exclusions

Figure 7. Cohort Attrition, Sweden



10.1 Participants

After propensity score trimming and matching, the study included 32,605 children (age < 18 years) and 126,908 adults (age ≥ 18 years) initiating treatment with topical tacrolimus, and 27,961 children and 61,841 adults initiating treatment with topical pimecrolimus (Table 6).

Users of moderate- to high-potency topical corticosteroids were frequency matched to each exposed cohort on twentiles of propensity scores at a 4:1 unexposed:exposed ratio: 117,592 children and 452,996 adults were matched to users of tacrolimus and 111,024 children and 244,572 adults to users of pimecrolimus. The 4:1 ratio was attained or was very close to being attained for the pimecrolimus comparative cohort across all databases. For the tacrolimus comparative cohort, the ratio was close to 4:1 in the UK-CPRD and deviated from an overall 4:1 match in NL-PHARMO (2.87:1 in children and 3.20:1 in adults); Denmark

(3.83:1 in children and 3.67:1 in adults), and in Sweden (3.62:1 in children and 3.54:1 in adults).

The untreated cohort comprised 361,584 children and 1,291,042 adults matched on age and sex to users of topical corticosteroids included in the comparative cohort for topical tacrolimus.

Denmark and Sweden contributed the largest number of users of topical tacrolimus: together, they contributed 72.1% of all children and 73.5% of all adults. Denmark contributed the largest number of users of topical pimecrolimus: 72.8% of children and 69.6% of adults.

For users of topical tacrolimus, the median follow-up in children was 4.0 years in UK-CPRD, 6.6 years in Denmark, 6.8 years in NL-PHARMO, and 4.9 years in Sweden. In adults, the median follow-up was 3.7 years in UK-CPRD, 5.5 years in Denmark, 6.1 years in NL-PHARMO, and 4.5 years in Sweden. An estimate of the overall median was 5.7 years in children and 5.0 in adults.

For users of topical pimecrolimus, the median follow-up in children was 5.5 years in UK-CPRD, 9.8 years in Denmark, 7.6 years in NL-PHARMO, and 5.5 years in Sweden. In adults, the median follow-up was 4.7 years in UK-CPRD, 7.0 years in Denmark, 6.1 years in NL-PHARMO, and 4.9 years in Sweden. An estimate of the overall median was 8.9 years in children and 6.5 in adults.

The distribution of users by yearly categories of follow-up are presented for tacrolimus and pimecrolimus combined for children (Figure 8) and adults (Figure 11), for tacrolimus (Figure 9 and Figure 12), and for pimecrolimus (Figure 10 and Figure 13). Overall, for both children and adults, there were relevant differences among study populations in the proportion of users in the categories of longer duration of follow-up, with the lowest proportions found in Sweden.

The results for the categories of longer duration of follow-up, i.e., at least 10 years was of particular interest to the JOELLE study extension phase. Among children, the proportion of users with a duration of follow-up of 10 years or more was 45.1% in Denmark, 34.1% in NL-PHARMO, 25.3% in the UK-CPRD and 3.4% in Sweden. An estimate of the overall percentage of children with a duration of follow-up of 10 years or more was 31.9%. The results for a duration of follow-up of 5 years or more ranged from 56.4% in UK-CPRD to 80.3% in Denmark.

Among adults, the proportion of users with a duration of follow-up of 10 years or more was 29.6% in Denmark, 26.5% in NL-PHARMO, 18.4% in the UK-CPRD and 2.7% in Sweden.

An estimate of the overall percentage of adults with a duration of follow-up of 10 years or more was 19.4%. Adult users with a duration of follow-up of 5 years or more ranged from 50.9% in UK-CPRD to 69.2% in Denmark.

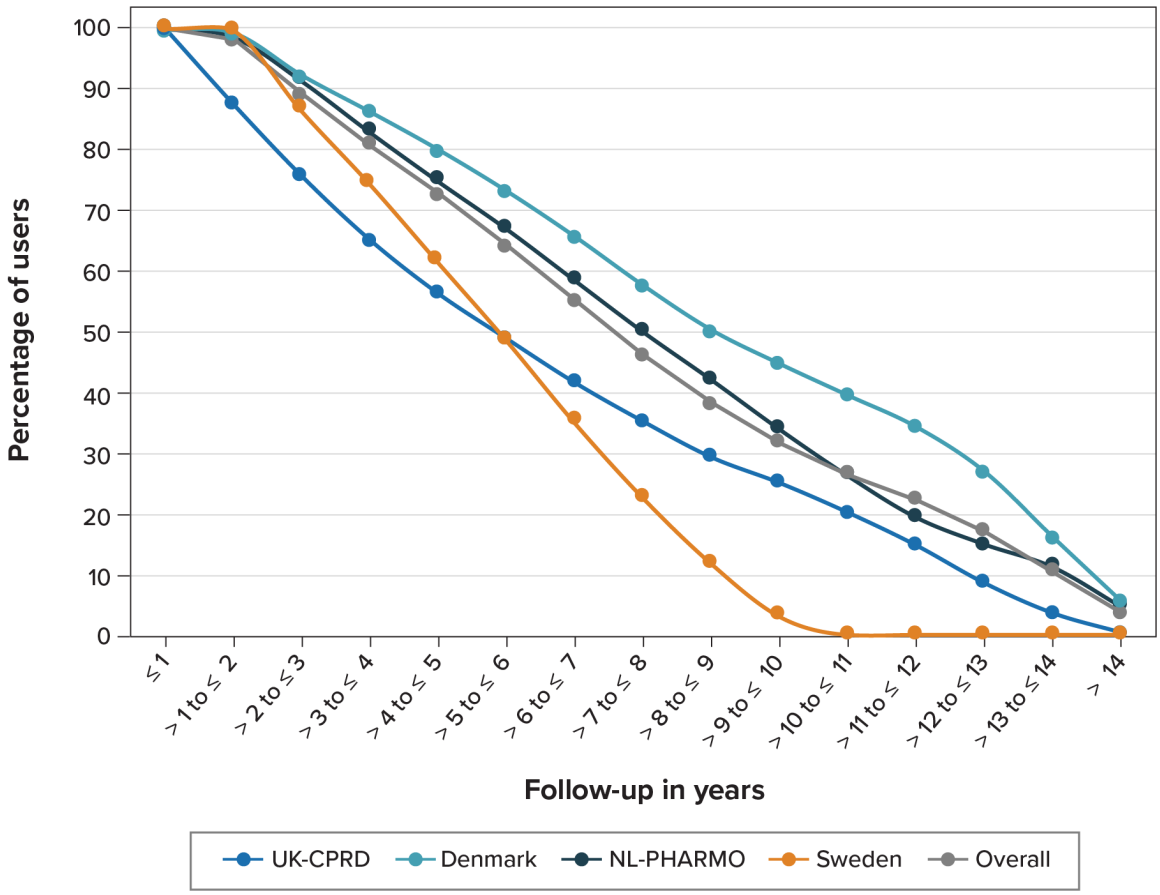
Table 6. Distribution of Users by Study Cohort and Population

Study Database	Topical Tacrolimus n (%)	Topical Corticosteroids n (%)	Topical Pimecrolimus n (%)	Topical Corticosteroids n (%)	Untreated Cohort[a] n (%)	Topical Corticosteroids n (%)
Children 0 to < 18 years						
UK-CPRD	3,895 (11.9)	15,253 (13.0)	2,752 (9.8)	11,008 (9.9)	61,001 (16.9)	15,253 (13.0)
Denmark	11,417 (35.0)	43,673 (37.1)	20,343 (72.8)	81,140 (73.1)	158,089 (43.7)	43,673 (37.1)
NL-PHARMO	5,197 (15.9)	14,904 (12.7)	3,189 (11.4)	12,168 (11.0)	58,424 (16.2)	14,904 (12.7)
Sweden	12,096 (37.1)	43,762 (37.2)	1,677 (6.0)	6,708 (6.0)	84,070 (23.3)	43,762 (37.2)
Total	32,605 (100)	117,592 (100)	27,961 (100)	111,024 (100)	361,584 (100)	117,592 (100)
Adults ≥ 18 years						
UK-CPRD	12,705 (10.0)	50,822 (11.2)	5,124 (8.3)	20,496 (8.4)	202,459 (15.7)	50,822 (11.2)
Denmark	40,710 (32.1)	149,242 (32.9)	43,042 (69.6)	169,559 (69.3)	484,789 (37.6)	149,242 (32.9)
NL-PHARMO	21,037 (16.6)	67,293 (14.9)	8,506 (13.8)	33,841 (13.9)	264,378 (20.5)	67,293 (14.9)
Sweden	52,456 (41.4)	185,639 (41.4)	5,169 (8.4)	20,676 (8.5)	339,416 (26.3)	185,639 (41.4)
Total	126,908 (100)	452,996 (100)	61,841 (100)	244,572 (100)	1,291,042 (100)	452,996 (100)

NL-PHARMO = PHARMO Database Network (the Netherlands); UK-CPRD = Clinical Practice Research Database (United Kingdom).

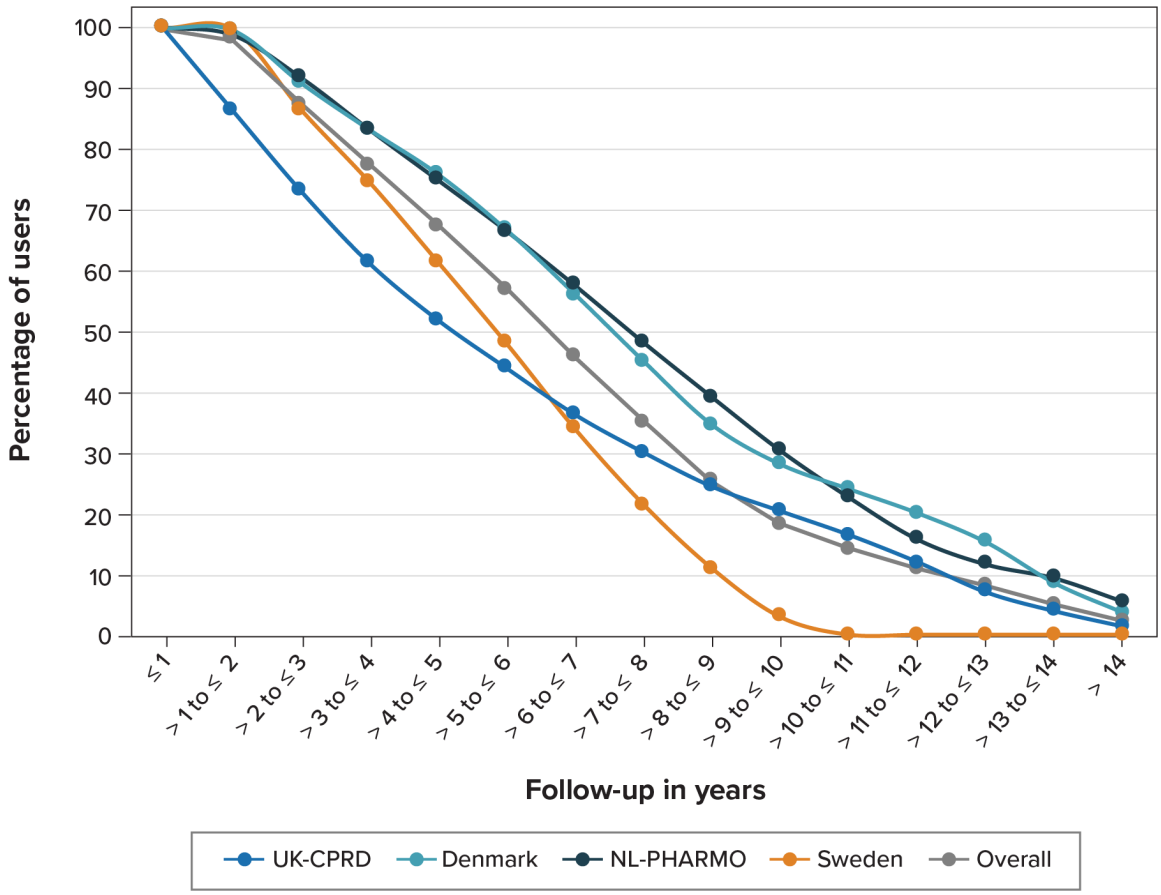
[a] Untreated cohort members were matched 4:1 to corticosteroid users on year of birth, sex and general practice/geographic region. In Sweden, the matching ratio was of approximately 2:1; however, in UK-CPRD and Denmark, age at cohort entry date (defined as date of first qualifying corticosteroid prescription) was estimated from the YEAR and MONTH of birth, where possible). This resulted in a small number of matched pairs being split across age bands.

Figure 8. Distribution of Tacrolimus and Pimecrolimus Combined Users by Yearly Categories of Duration of Follow-up—Children



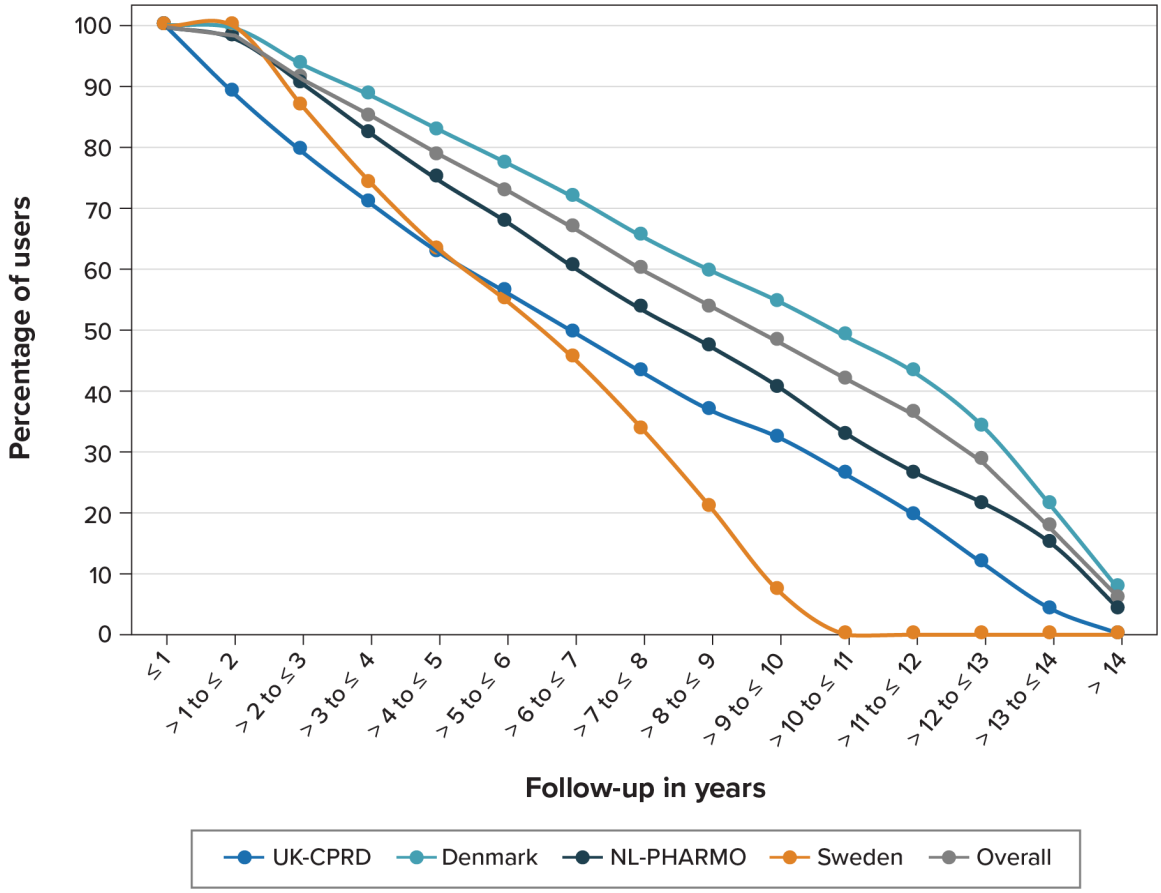
NL-PHARMO = PHARMO Database Network (the Netherlands); UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

Figure 9. Distribution of Tacrolimus Users by Yearly Categories of Duration of Follow-up—Children



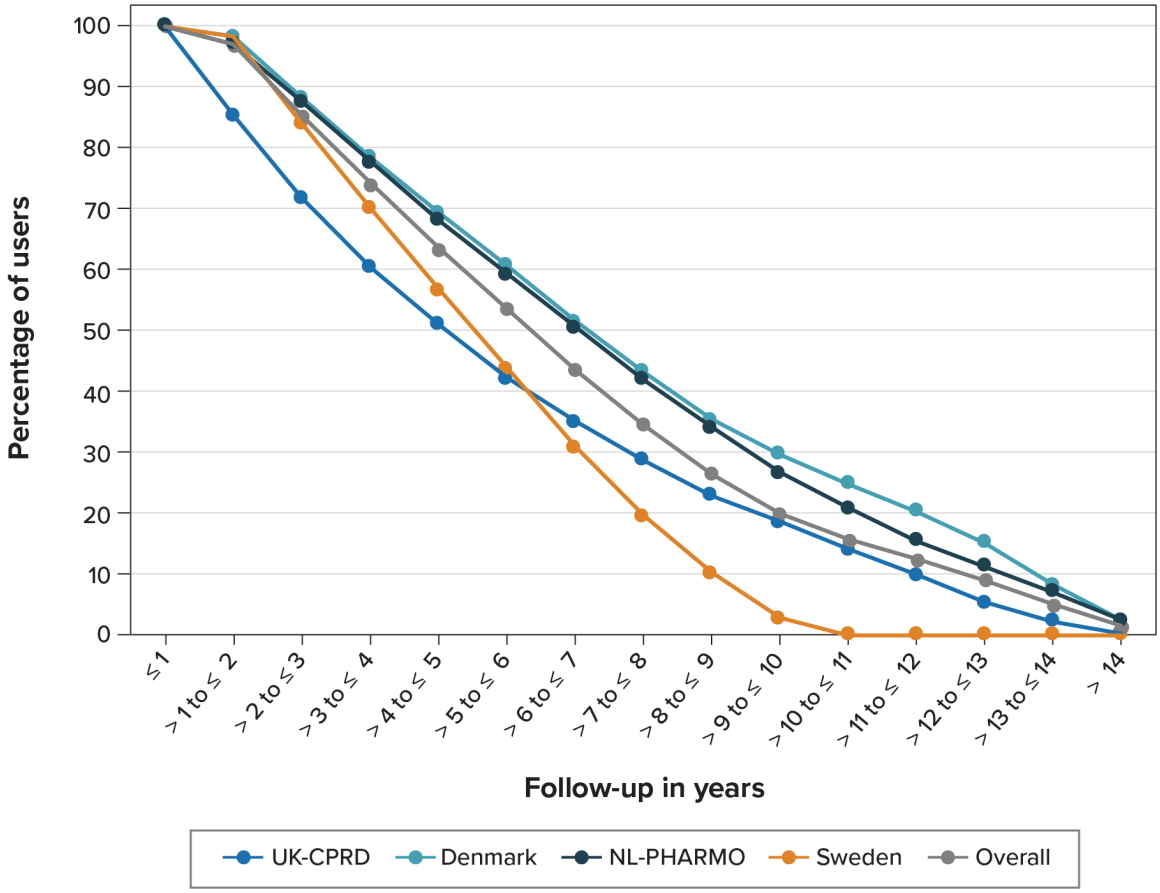
NL-PHARMO = PHARMO Database Network (the Netherlands); UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

Figure 10. Distribution of Pimecrolimus Users by Yearly Categories of Duration of Follow-up—Children



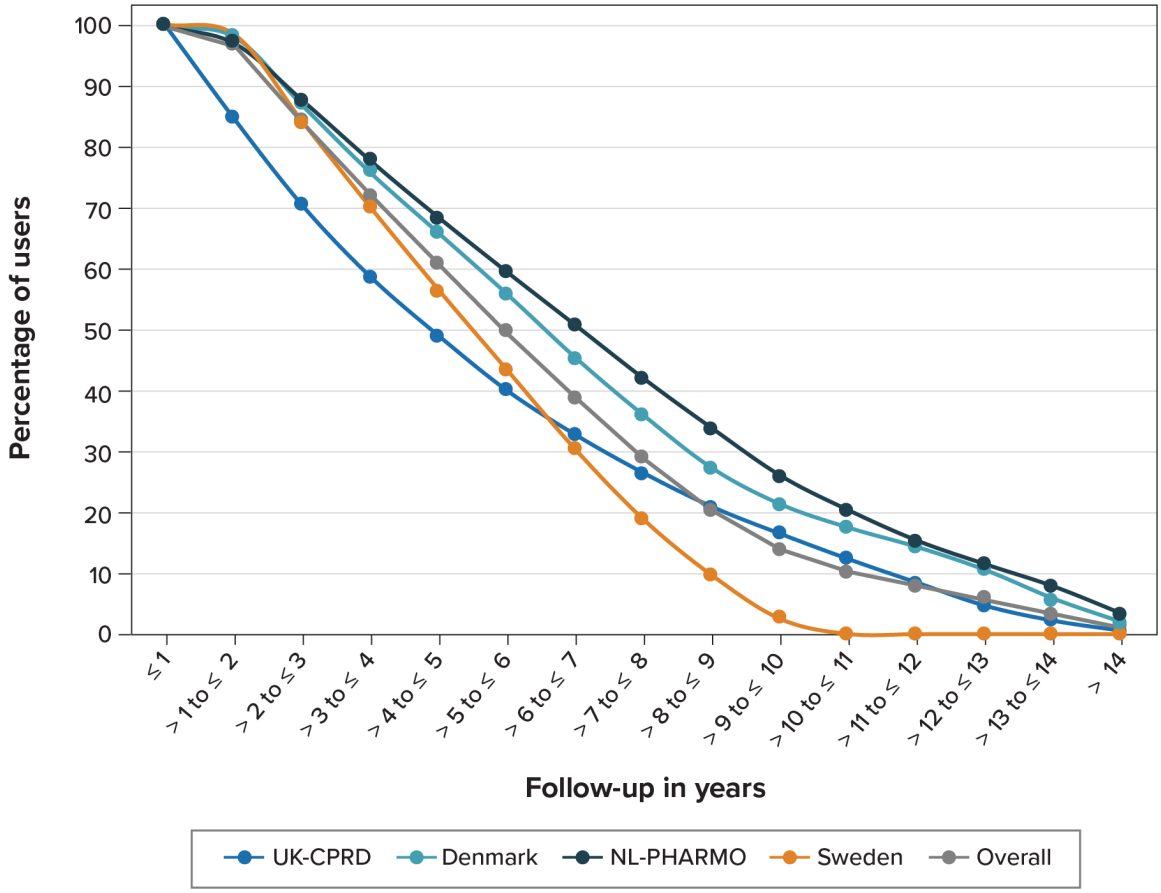
NL-PHARMO = PHARMO Database Network (the Netherlands); UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

Figure 11. Distribution of Tacrolimus and Pimecrolimus Combined Users by Yearly Categories of Duration of Follow-up—Adults



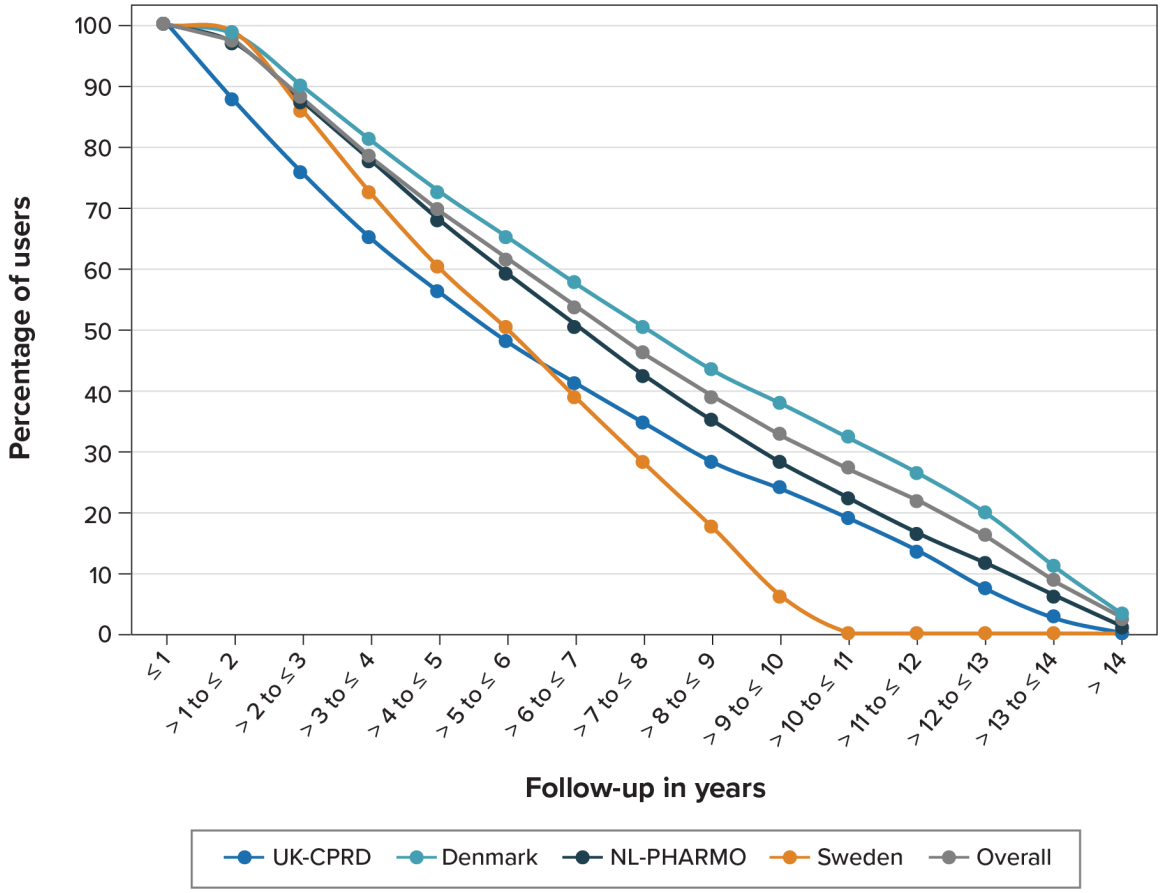
NL-PHARMO = PHARMO Database Network (the Netherlands); UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

Figure 12. Distribution of Tacrolimus Users by Yearly Categories of Duration of Follow-up—Adults



NL-PHARMO = PHARMO Database Network (the Netherlands); UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

Figure 13. Distribution of Pimecrolimus Users by Yearly Categories of Duration of Follow-up—Adults



NL-PHARMO = PHARMO Database Network (the Netherlands); UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

10.2 Descriptive Data

10.2.1 Utilisation Patterns

The utilisation patterns of topical tacrolimus and topical pimecrolimus are presented in Table 7 on page 70.

Among children treated with topical tacrolimus, the median number of prescriptions was one prescription in Denmark and Sweden and two prescriptions in the UK-CPRD and NL-PHARMO. The mean number of grams of active substance (one tube of 30 grams at 0.03% contains 0.09 grams of tacrolimus) was 0.11 grams in the UK-CPRD, 0.10 grams in Denmark, 0.09 in NL-PHARMO and 0.05 grams in Sweden.

Among adults treated with topical tacrolimus, the median number of prescriptions was one prescription in all the study databases. The mean number of grams of active substance was

0.12 grams in the UK-CPRD, 0.10 grams in Demark, 0.11 grams in NL-PHARMO and 0.07 grams in Sweden.

The median number of prescriptions for topical pimecrolimus was similar to the median for topical tacrolimus in both children and adults in all databases (median, 1).

The distribution of the number of prescriptions/dispensings in children (Figure 14) and adults (Figure 15) during follow-up are presented for tacrolimus and pimecrolimus combined and for tacrolimus and pimecrolimus separately. Complete results for each study population are presented in Annex 2 Table 25 through Annex 2 Table 36.

For tacrolimus, across all databases, most children had only one prescription/dispensing, ranging from 48.5% in NL-PHARMO to 57.8% in the UK-CPRD. Overall, approximately 80% of children had 1 to 3 prescriptions during follow-up across all databases. For the highest category of number of prescriptions (≥ 10 prescriptions/dispensings), the proportions ranged from 2.6% in Sweden to 6.0% in NL-PHARMO. Among adults, similar results were observed, with most adults having only one prescription, ranging from 46.1% receiving a single prescription in the UK-CPRD to 58.3% with only one dispensing in Denmark. Approximately 20% of adult patients had two prescriptions: from 16.3% in the UK-CPRD to 19.6% in Sweden. Adults with ≥ 10 prescriptions ranged from 2.4% in Sweden to 10.3% in UK-CPRD.

For pimecrolimus, slightly higher proportions of children and adults had one prescription during follow-up compared with tacrolimus; children with only one prescription ranged from 55.5% in Denmark to 68.3% in UK-CPRD, children with two prescriptions ranged from 14.6% in the UK-CPRD to 17.5% in Denmark and NL-PHARMO, and children with ≥ 10 prescriptions ranged from 1.5% in Sweden to 4.2% in Denmark. Among adults, pimecrolimus users with only one prescription ranged from 57.8% in UK-CPRD to 64.0% with one dispensing in Sweden; adults with two prescriptions/dispensings ranged from 16.3% in Denmark to 17.5% in Sweden, and adults with ≥ 10 prescriptions/dispensings ranged from 2.4% in Sweden to 6.2% in the UK-CPRD.

The number of users switching between topical tacrolimus and pimecrolimus during follow-up are presented in Annex 2 Table 12 for each study population. Summary results are presented in Table 8. The percentage of tacrolimus users switching to pimecrolimus ranged from 2.3% in Sweden to 10.6% in Denmark in children and from 1.9% in Sweden to 7.6% in Denmark in adults. The percentage of pimecrolimus users switching to tacrolimus ranged from 11.8% in NL-PHARMO to 15.7% in Denmark in children and from 10.7% in NL-PHARMO to 14.2% in Sweden in adults.

Table 7. Utilisation Patterns of Users of Topical Tacrolimus and Topical Pimecrolimus

	Topical Tacrolimus Cohort				Topical Pimecrolimus Cohort			
	UK-CPRD	**Denmark**	**NL-PHARMO**	**Sweden**	**UK-CPRD**	**Denmark**	**NL-PHARMO**	**Sweden**
Children (< 18 Years)	(N=32,605)				(N=27,961)			
Number of users	3,895	11,417	5,197	12,096	2,752	20,343	3,189	1,677
Number of prescriptions per patient								
Mean (SD)	4.03 (6.80)	2.80 (4.80)	3.20 (4.70)	2.26 (2.76)	2.76 (4.89)	2.60 (3.80)	2.40 (3.40)	1.83 (2.28)
20th percentile	1	1	1	1	1	1	1	1
50th percentile	2	1	2	1	1	1	1	1
80th percentile	5	3	4	3	3	3	3	2
Number of grams of active substance per patient[a], mean (SD)	0.11 (0.35)	0.10 (0.3)	0.09 (0.36)	0.05 (0.10)	1.25 (3.56)	0.80 (2.30)	0.91 (1.94)	0.57 (1.06)
Adults (≥ 18 Years)	(N=126,908)				(N=61,841)			
Number of users	12,705	40,710	21,037	52,456	5,124	43,042	8,506	5,169
Number of prescriptions per patient								
Mean (SD)	3.04 (6.38)	2.50 (4.20)	2.70 (4.50)	2.26 (2.97)	2.21 (4.05)	2.40 (4.00)	2.20 (3.80)	2.00 (2.63)
20th percentile	1	1	1	1	1	1	1	1
50th percentile	1	1	1	1	1	1	1	1
80th percentile	3	3	3	3	2	3	3	2
Number of grams of active substance per patient, mean (SD)	0.12 (0.49)	0.10 (0.30)	0.11 (0.64)	0.07 (0.14)	0.96 (2.98)	0.70 (2.00)	0.83 (2.29)	0.59 (1.07)

NL-PHARMO = PHARMO Database Network (the Netherlands); SD = standard deviation; UK-CPRD = Clinical Practice Research Database (United Kingdom).

[a] Calculated as strength x quantity (size of tube in grams).

Table 8. Utilisation Patterns of Users Who Switched Treatment Between Topical Tacrolimus and Topical Pimecrolimus

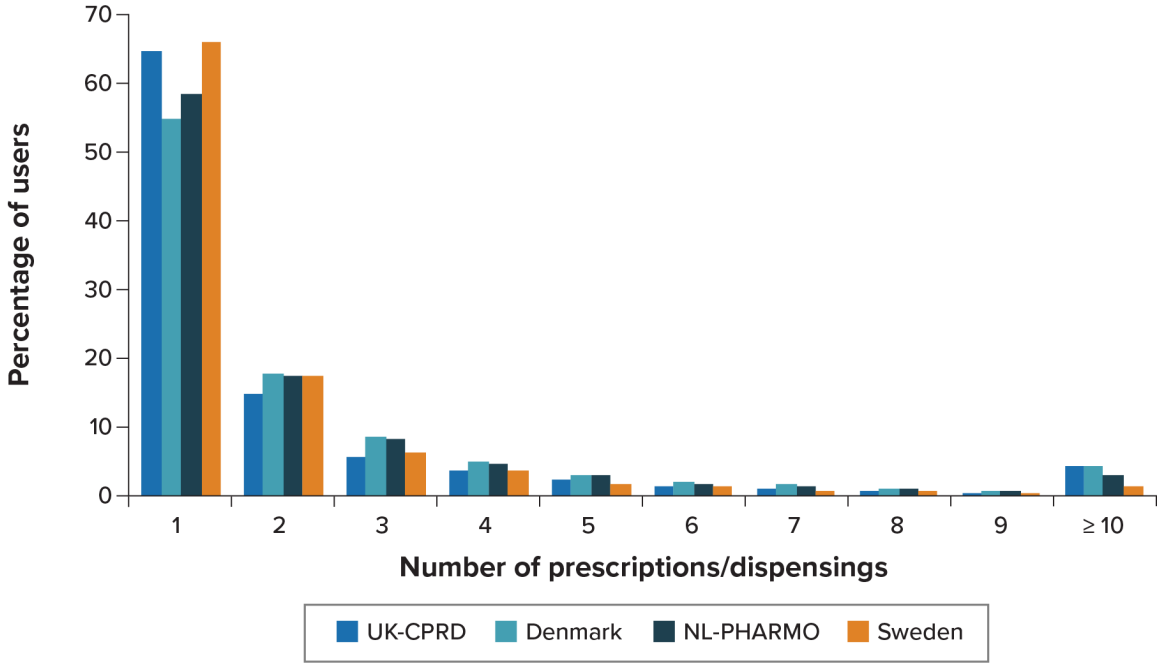
	Switched From Topical Tacrolimus to Topical Pimecrolimus				Switched From Topical Pimecrolimus to Topical Tacrolimus			
	UK-CPRD	**Denmark**	**NL-PHARMO**	**Sweden**	**UK-CPRD**	**Denmark**	**NL-PHARMO**	**Sweden**
Children								
Number of users at the start	3,895	11,417	5,197	12,096	2,752	20,343	3,189	1,677
Number (%) of users switching during follow-up[a]	268 (6.9)	1,211 (10.6)	396 /7.6)	277 (2.3)	340 (12.4)	3,199 (15.7)	377 (11.8)	241 (14.4)
Adults								
Number of users at the start	12,705	40,710	21,037	52,456	5,124	43,042	8,506	5,169
Number (%) of users switching during follow-up[a]	549 (4.3)	3,104 (7.6)	1,137 (5.4)	977 (1.9)	571 (11.1)	5,752 (13.4%)	913 (10.7)	734 (14.2)

NL-PHARMO = PHARMO Database Network (the Netherlands); UK-CPRD = Clinical Practice Research Database (United Kingdom).

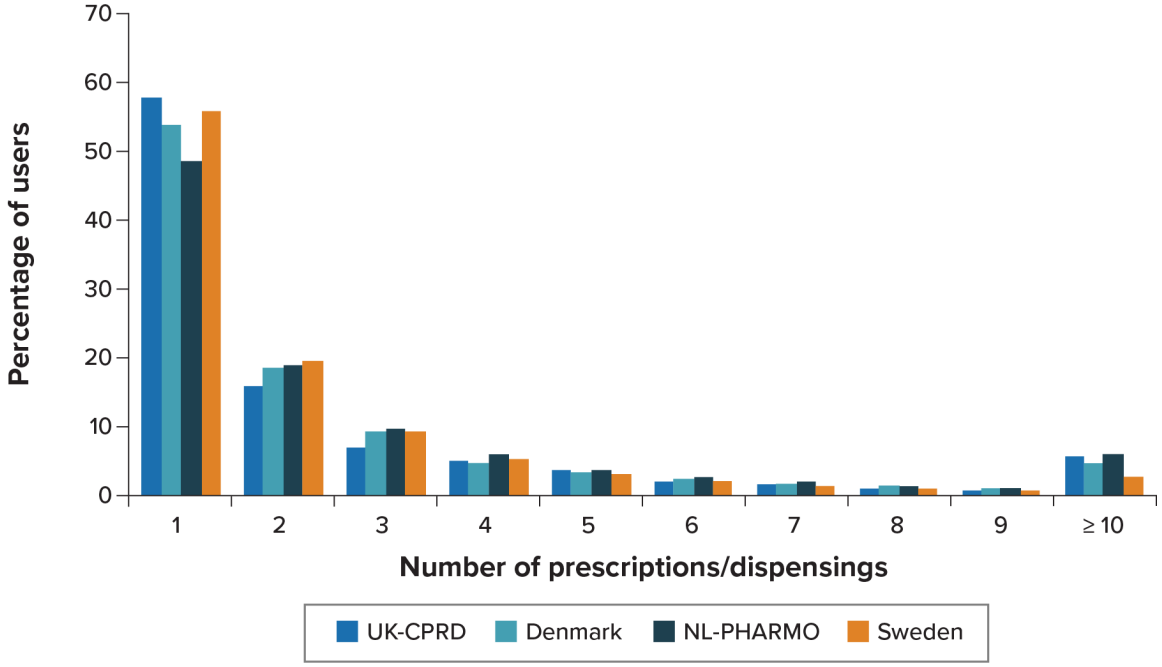
[a] Follow-up stopped at first study outcome.

Figure 14. Distribution of Number of Prescriptions/Dispensings of Tacrolimus or Pimecrolimus or Either—Children

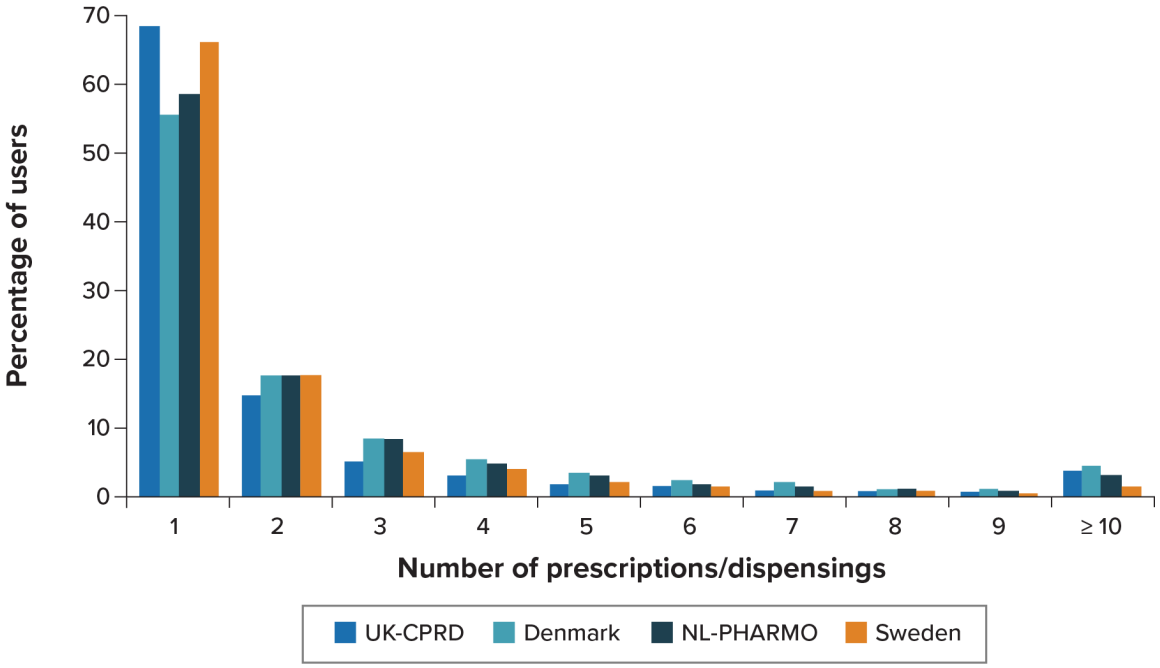
a. Either Tacrolimus or Pimecrolimus



b. Tacrolimus



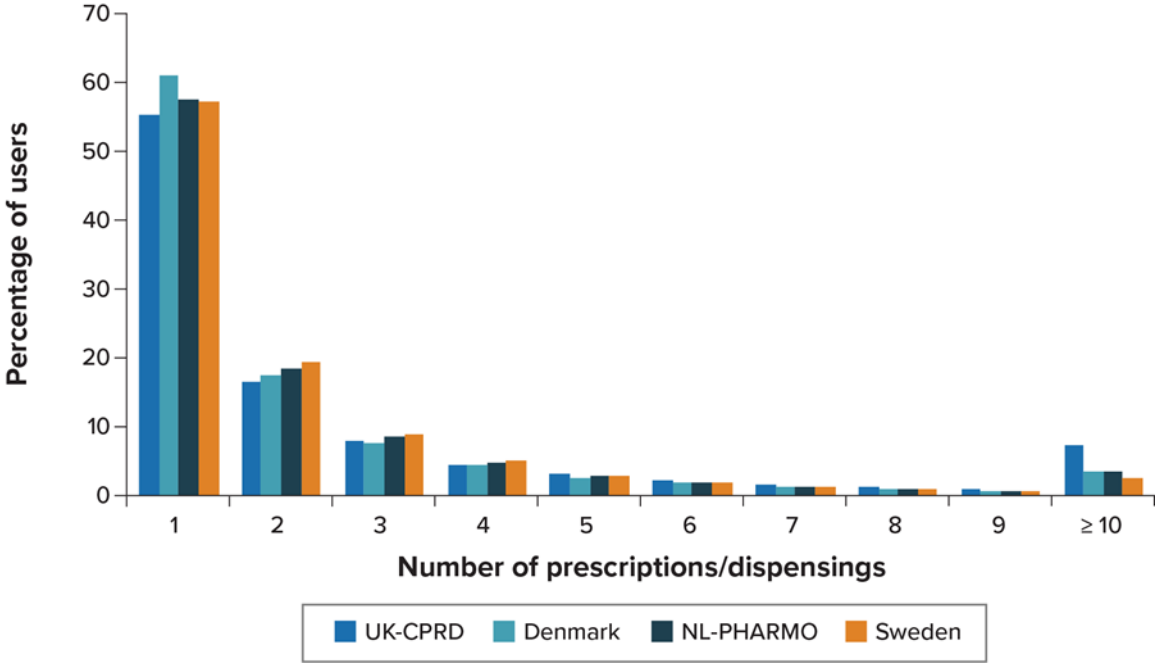
c. Pimecrolimus



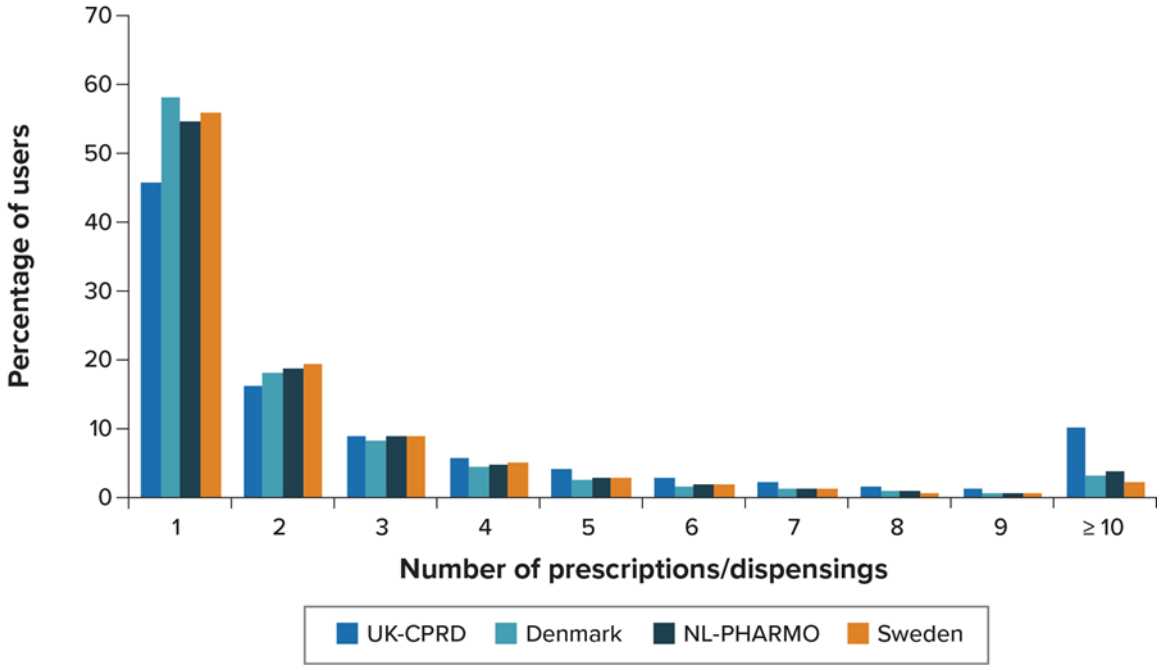
NL-PHARMO = PHARMO Database Network (the Netherlands); UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

Figure 15. Distribution of Number of Prescriptions/Dispensings of Tacrolimus or Pimecrolimus or Either—Adults

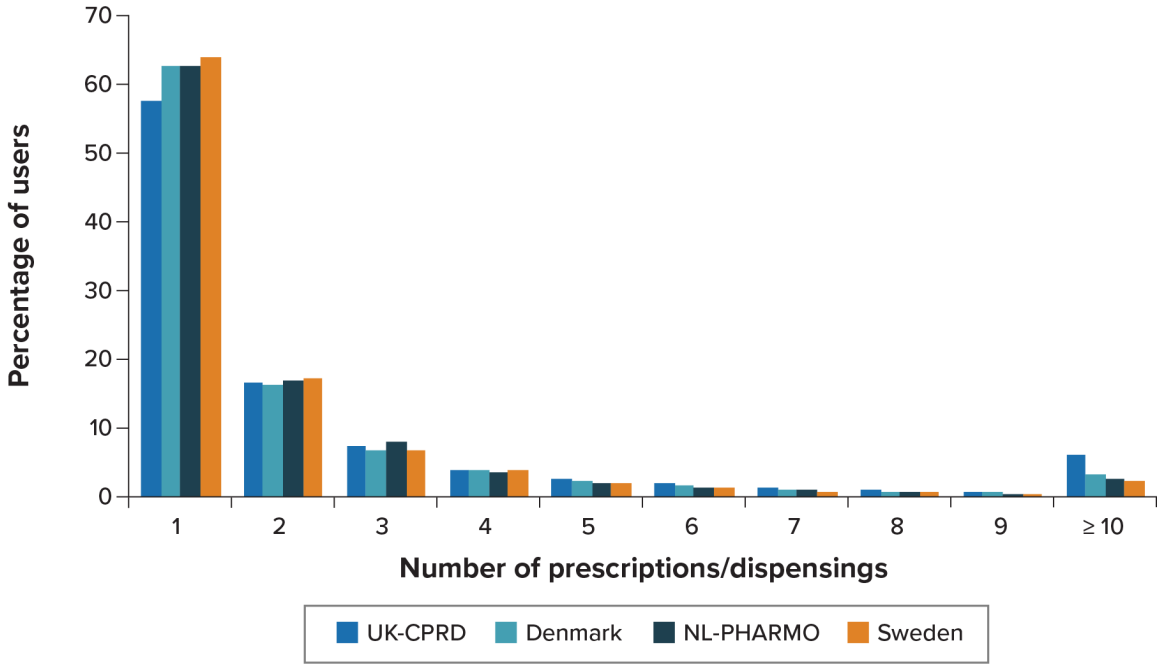
a. Either Tacrolimus or Pimecrolimus



b. Tacrolimus



c. Pimecrolimus



NL-PHARMO = PHARMO Database Network (the Netherlands); UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

10.2.2 Baseline Characteristics of Users

The baseline characteristics of patients included in each study cohort, by study population, are presented in Annex 3. Of note, the number of visits to the GP, dermatologist, paediatrician, specialist, and outpatient visits were available in UK-CPRD. Sweden did not have information about the actual number of visits; therefore, a proxy was used based on the

number of unique prescriptions made by GPs from the prescriber drug register. The number of emergency department visits was available only in UK-CPRD and Denmark. Finally, type of prescriber was not available in UK-CPRD.

The percentage of patients in the different topical tacrolimus and pimecrolimus cohorts *without* a recorded diagnosis of atopic dermatitis varied widely, 48%-78% in Sweden, 26%-61% in UK-CPRD, 90%-95% in Denmark, and greater than 99% NL-PHARMO (see Annex 4).

10.2.2.1 Topical Tacrolimus and Topical Pimecrolimus Versus Topical Corticosteroids—Children

Baseline characteristics in children treated with topical tacrolimus and topical pimecrolimus are presented in Annex 3 Table 1 and Annex 3 Table 3, respectively.

- The distributions by age and sex were similar in all study populations. However, in Denmark, the group aged 0-1 years was larger than in the rest of the study populations.
- The median duration of follow-up was shorter in the UK-CPRD than in the other study populations.
- The baseline prevalence of “Diseases interacting with the immune system” and “Skin diseases” for children treated with topical tacrolimus and topical pimecrolimus was highest in the UK-CPRD followed by Sweden, and at some distance, Denmark and NL-PHARMO. The distribution of “Chronic diseases” was similar among the study populations, with overall low prevalence observed across all assessed conditions, although in NL-PHARMO, the prevalence was somewhat lower.
- Regarding the use of medications, some differences were observed. The use of “Immunosuppressant and cytostatics” was much higher in UK-CPRD than in the rest of the populations, whereas the use of “Other medications” was similar across the study populations.
- The number of hospitalisations was similar in the four study populations. The number of visits to GPs was higher in UK-CPRD than in Sweden, whereas the number of visits to paediatricians was higher in Sweden than in UK-CPRD; the number of dermatologist and specialist visits was similar in both populations. Finally, the number of outpatient visits was higher in Sweden than in UK-CPRD. The number of emergency department visits was similar in UK-CPRD and Denmark.
- The percentage of patients with 5 or more prescriptions in the 12 months before the start date was highest in UK-CPRD, followed by NL-PHARMO and Sweden, and at some distance, Denmark.
- The distribution of patients by type of prescriber of the first prescription varied slightly between study populations. The most common prescribers were GPs in

NL-PHARMO; dermatologists in Sweden; and "Others" in Denmark, a category that contains hospital prescriptions that are not issued from a paediatric or dermatological department/ward, prescriptions from specialists who are not paediatricians or dermatologists, and prescriptions from other private practices.

- The prior use of topical corticosteroids, either plain or combined, was higher in UK-CPRD compared with the rest of the study populations.

In general, the frequency matching by twentiles of propensity scores achieved a good balance for most covariates in all the study populations, except for the variable "Prior use of topical corticosteroids plain."

The number of GP visits and number of prescriptions in UK-CPRD was larger for tacrolimus and pimecrolimus than for the corticosteroids cohorts. Finally, the variable "Type of prescriber of first prescription" also showed different distributions between tacrolimus and pimecrolimus versus corticosteroids cohorts in Denmark, NL-PHARMO, and Sweden.

10.2.2.2 Topical Tacrolimus and Topical Pimecrolimus Versus Topical Corticosteroids—Adults

Baseline characteristics in adults treated with topical tacrolimus and pimecrolimus are presented in Annex 3 Table 2 and Annex 3 Table 4, respectively.

- The distributions by age and sex were similar in all the study populations.
- As observed in children, the duration of follow-up was shorter in UK-CPRD than in the rest of the study populations.
- The baseline prevalence of recorded comorbidity was higher in UK-CPRD than in the rest of the study populations. These differences observed were higher for "Diseases interacting with the immune system" and "Skin diseases" than for "Chronic diseases."
- The use of "Immunosuppressant and cytostatics" and "Antipsoriatics topical" was higher in UK-CPRD than in the rest of the study populations. The distribution of use of "Other medications" was similar among the four data sources.
- We observed similar distributions among the four study populations regarding the number of hospitalisations in the 12 months before the index date.
- The distribution of visits to the GP was different between UK-CPRD and Sweden, being higher in UK-CPRD. Conversely, the number of outpatient visits was higher in Sweden than in UK-CPRD.
- The variable number of prescriptions in the 12 months before the start date showed different distributions among the study populations, as observed for children. The percentage of patients with five or more prescriptions was higher in UK-CPRD than in the rest of the study populations, particularly in comparison with Denmark.

- The most common prescriber of the first prescription in Sweden and NL-PHARMO was the dermatologist, whereas in Denmark, "Other" prescribers were most common (this category contains hospital prescriptions that are not issued from a paediatric or dermatological department/ward, prescriptions from specialists who are not paediatricians or dermatologists, and prescriptions from other private practices).
- Finally, "Prior use of topical corticosteroids plain" was somewhat higher in UK-CPRD than in the rest of the study populations.

As observed for children, the frequency matching by twentiles of propensity scores achieved a good balance for most covariates in all the study populations, except for the variable "Prior use of topical corticosteroids plain."

Of note, the distribution of "Immunosuppressants and cytostatics" and of systemic corticosteroids showed differences between tacrolimus and corticosteroids cohorts, only in UK-CPRD. The distribution of "Type of prescriber of first prescription" was different between the two cohorts in Denmark, NL-PHARMO, and Sweden.

10.2.2.3 Topical Corticosteroids Versus Untreated Population—Children

Baseline characteristics of children in the topical corticosteroids cohort and the untreated cohort are presented in Annex 3 Table 5.

- The age and sex distribution of the corticosteroids cohort and the untreated cohort was almost the same. As observed for topical tacrolimus and pimecrolimus, in Denmark, a higher percentage of children aged 0 to 1 years was observed.
- The follow-up was slightly shorter in UK-CPRD than in the rest of the study populations.
- Regarding the prevalence of comorbidities, in UK-CPRD, a higher percentage of comorbidities was observed than in the rest of the study populations. We also observed a higher prevalence of comorbidities among users of corticosteroids compared with untreated children. A similar pattern was observed for prior use of medications, utilisation of health care resources, and prescriptions.

10.2.2.4 Topical Corticosteroids Versus Untreated Population—Adults

Baseline characteristics of adults in the topical corticosteroids cohort and the untreated cohort are presented in Annex 3 Table 6. The patterns observed for adults are essentially the same as the ones observed for children: similarities between cohorts and study populations in the age and sex distribution; shorter follow-up in UK-CPRD than in the rest of the study populations; and higher percentage of comorbidities, prior use of medications, utilisation of health care resources, and prescriptions in UK-CPRD than in the rest of the study populations and in the corticosteroids cohort than in the untreated cohort.

10.2.2.5 Matched and Trimmed Study Cohort Population

In the JOELLE study extension phase, patient characteristics are described for the study cohorts before and after matching and trimming (see Annex 4). The frequency matching conducted was efficient, and populations were comparable in terms of distribution according to study variables.

The percentage of patients trimmed out after the matching process varies by study population, being greatest in children in the Danish population (around 30% for pimecrolimus), and lowest in the Swedish population, around 7% for pimecrolimus. Among adults, the population with largest percentage of patients trimmed out was NL-PHARMO, around 25%, and the population with the lowest percentage was Sweden, with around 10% of the patients trimmed out. The baseline characteristics of patients excluded after trimming showed that there were no subgroups (e.g., more severe patients) identified to whom the results of the study cannot be generalised.

10.3 Outcome Data

The overall distribution of outcomes in the main analysis (with a lag time of 6 months) by study data source are presented in Table 9.

A total of 150-153 events were identified in children across all cohorts (a range is reported due to small cell count reporting restrictions). The number of cases in children was scarce, especially for NMSC and CTCL. A total of 11 CTCL events were identified in children across all data sources. The Danish registries contributed 66 to 69 events (44%-45%); NL-PHARMO, 44 events (about 29%); the Swedish registries, 22 events (14%-15%); and UK-CPRD, 18 events (about 12%).

Among the adult cohorts, a total of 45,481 events were identified: 5,924 malignant melanoma, 36,317 NMSC, 2,595 non-Hodgkin lymphoma, 415 Hodgkin lymphoma and 230 CTCLs. The Danish registries contributed 21,899 events (48%), the Swedish registries, 11,195 events (about 25%); NL-PHARMO, 7,859 events (17%); and UK-CPRD, 4,528 events (about 10%).

Table 9. Distribution of Outcomes in All Study Cohorts by Study Data Source

Study Outcome	Study Data Source	Number and Percentage of Outcomes: Children < 18 Years n (%)	Number and Percentage of Outcomes: Adults ≥ 18 Years n (%)
Malignant melanoma	NL-PHARMO	13 (41.9)	892 (15.1)
	Denmark	9 (29.0)	2,936 (49.6)
	Sweden	[redacted]	1,525 (25.7)
	UK-CPRD	[redacted]	571 (9.6)
	Total	**31**	**5,924**
Non-melanoma skin cancer	NL-PHARMO	7 (70-53.8)	6,414 (17.7)
	Denmark	NR[b]	17,302 (47.6)
	Sweden	1 (10-7.7)	9,063 (25.0)
	UK-CPRD	[redacted]	3,538 (9.7)
	Total	**10-13**	**36,317**
Skin cancer	NL-PHARMO	20 (64.5)	7,306 (17.3)
	Denmark	NR[b]	20,238 (47.9)
	Sweden	6 (19.4)	10,588 (25.1)
	UK-CPRD	5 (16.1)	4,109 (9.7)
	Total	**41-44**	**42,241**
Non-Hodgkin lymphoma	NL-PHARMO	10 (23.8)	458 (17.6)
	Denmark	23 (54.8)	1,340 (51.6)
	Sweden	4 (9.5)	470 (18.1)
	UK-CPRD	5 (11.9)	327 (12.6)
	Total	**42**	**2,595**
Hodgkin lymphoma	NL-PHARMO	12 (21.4)	57 (13.7)
	Denmark	28 (50.0)	225 (54.2)
	Sweden	10 (17.9)	80 (19.3)
	UK-CPRD	6 (10.7)	53 (12.8)
	Total	**56**	**415**
Cutaneous T-cell lymphoma	NL-PHARMO	2 (18.2)	38 (16.5)
	Denmark	[redacted]	96 (41.7)
	Sweden	2 (18.2)	57 (24.8)
	UK-CPRD	[redacted]	39 (17.0)
	Total	**11**	**230**
Lymphoma	NL-PHARMO	24 (22.0)	553 (17.1)
	Denmark	56 (51.4)	1,661 (51.3)
	Sweden	16 (14.7)	607 (18.7)
	UK-CPRD	13 (11.9)	419 (12.9)
	Total	**109**	**3,240**

NL-PHARMO = PHARMO Database Network (the Netherlands); NR = not reportable; UK-CPRD = Clinical Practice Research Database (United Kingdom).

Note: Outcomes are with a lag time of 6 months.

[a] UK-CPRD counts below 5 will need to be redacted if shared outside of the regulatory environment.

[b] Data counts below 5 are not reported to comply with Danish data protection rules.

10.3.1 Outcome Validation

10.3.1.1 United Kingdom, UK-CPRD

In UK-CPRD, 715 potential cases were selected for patient profile review. Four patients had two different malignancies on the same date; for these patients one cancer was selected for the PPV calculation, giving priority to the cancer register first, then HES, and lastly to UK-CPRD GOLD. The PPVs (95% CIs) estimated separately for the Read codes and ICD-10 codes used to identify cases for each study outcome are presented in Annex 5, UK-CPRD table.

For malignant melanoma, including in situ tumours, based on 118 potential cases identified by Read codes and 97 confirmed cases, the estimated PPV was 82.2% (95% CI, 74.1%-88.6%) and for cases identified through ICD-10 codes based on 42 potential malignant melanoma cases identified and 40 confirmed cases the PPV was 95.2% (95% CI, 83.8%-99.4%).

For NMSC, including in situ tumours, based on 439 potential cases identified by Read codes and 397 confirmed cases, the estimated PPV was 90.4% (95% CI, 87.3%-93.0%) and for cases identified through ICD-10 codes based on 38 potential cases and 32 confirmed cases the PPV was 84.2% (95% CI, 68.7%-94.0%).

For non-Hodgkin lymphoma, excluding CTCL, based on 8 potential cases identified by Read codes and 7 confirmed cases, the estimated PPV was 87.5% (95% CI, 47.3%-99.7%) and for cases identified through ICD-10 codes based on 14 potential cases and 10 confirmed cases the PPV was 71.4% (95% CI, 41.9%-91.6%).

For Hodgkin lymphoma, based on 12 potential cases identified by ICD-10 codes and 11 confirmed cases the estimated PPV was 91.7% (95% CI, 61.5%-99.8%).

For CTCL, the estimated PPV based on 31 cases identified by Read codes and 22 confirmed cases was 71.0% (95% CI, 52.0%- 85.8%) and 23.1% (95% CI, 5.0%-53.8%) based on [redacted] potential cases identified through ICD-10 codes and [redacted] confirmed cases. It is notable that the 8 potential cases identified through ICD-10 code C84.4 (Peripheral T-cell lymphoma, not elsewhere classified) were not confirmed to be cutaneous lymphomas. Diseases designated by this code may involve skin directly (i.e., infiltration of lymphoma cells) or indirectly (inflammatory rash without infiltration by lymphoma cells), which supported its inclusion among the “cutaneous lymphomas” definition. However, a substantial proportion of peripheral T-cell lymphomas are confined to the lymph nodes and do not involve the skin.

10.3.1.2 Netherlands, NL-PHARMO

Validation was performed for all paediatric potential cases, a selected random sample of adult potential cases of malignant melanoma, NMSC (BCC and SCC cases), Hodgkin lymphoma and non-Hodgkin lymphoma outcomes, and for all potential CTCL cases identified (paediatric and adult). Results of the validation indicated that the diagnosis was confirmed as "definite" for 100% of the BCC & SCC NMSC cases, 87% of malignant melanoma cases, 83% of Hodgkin lymphoma cases, 76% of non-Hodgkin lymphoma cases and 50% of CTCL cases. The results of the validation are presented in Annex 5 Table 2.

A definite diagnosis could not be established but was considered as "likely correct" in 26% of CTCL potential cases, 18% of non-Hodgkin lymphoma potential cases, 13% of malignant melanoma potential cases and, 6% of Hodgkin lymphoma potential cases.

The diagnosis was considered as "likely incorrect" for 24% of CTCL potential cases and 11% of Hodgkin lymphoma potential cases.

10.4 Main Results

10.4.1 Study Population–Specific and Pooled Incidence Rates and Incidence Rate Ratios—Children

Due to the limited number of events and the reporting restrictions linked to cell counts below 5 for Denmark, we do not report data source–specific incidence estimates for any of the study outcomes in children and instead present in the following Sections 10.4.1.1 and 10.4.1.2 the data source–specific number of events, from data sources where it is allowed, and the pooled estimates.

10.4.1.1 Topical Tacrolimus Compared With Topical Corticosteroids in Children

The pooled results for the number of events, person-time, crude incidence rates, and adjusted IRRs for each study outcome comparing single use of tacrolimus with use of corticosteroids in children are presented in Table 10.

The number of skin malignancies for this analysis cannot be reported because they did not reach 5 events exposed to tacrolimus. The RR for single exposure to topical tacrolimus and malignant melanoma is 0.93 (95% CI, 0.30-2.82) and for NMSC is 0.46 (95% CI, 0.06-3.73).

A total of 40 lymphoma events were identified, 16 in users of topical tacrolimus ([redacted] in UK-CPRD, 5 in Denmark, [redacted] in NL-PHARMO, and 5 in Sweden), and 24 in users of topical corticosteroids (6 in UK-CPRD, 12 in Denmark, 3 in NL-PHARMO, and 3 in Sweden). The crude incidence rate of any lymphoma per 1,000 person-years was 0.095 events in single users of tacrolimus and 0.039 events in users of topical corticosteroids. The pooled adjusted IRR comparing single topical tacrolimus use with topical corticosteroids was 2.49 (95% CI, 1.32-4.70).

By type of lymphoma, there were 17 events of non-Hodgkin lymphoma, 6 in users of topical tacrolimus (data source–specific numbers cannot be reported due to small cell counts reporting restrictions in Denmark), and 11 in users of corticosteroids ([redacted] in UK-CPRD, 6 in Denmark, [redacted] in NL-PHARMO, and 1 in Sweden); 20 events of Hodgkin lymphoma, 8 in users of topical tacrolimus (data source–specific numbers cannot be reported due to small cell counts reporting restrictions in Denmark), and 12 in users of topical corticosteroids ([redacted] in UK-CPRD, 5 in Denmark, [redacted] in NL-PHARMO, and 2 in Sweden); and < 5 events of CTCL in users of topical tacrolimus (data source–specific numbers cannot be reported due to small cell counts reporting restrictions in Denmark). The pooled adjusted IRR comparing single use of topical tacrolimus versus topical corticosteroids was 2.19 (95% CI, 0.81-5.97) for non-Hodgkin lymphoma, 2.37 (95% CI, 0.99-5.68) for Hodgkin lymphoma, and 7.77 (95% CI, 0.50-121.45) for CTCL.

Table 11 and Table 12 show the results of the analysis of topical tacrolimus versus topical corticosteroids by type of lymphoma and cumulative dose categories. The IRR for both types of lymphoma are elevated for low cumulative doses, but not for medium and high cumulative doses in the case of Hodgkin lymphoma and not for medium doses in non-Hodgkin lymphoma.

Table 10. Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios for All Study Malignancies in Users of Topical Tacrolimus Compared With Users of Topical Corticosteroids—Children

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Malignant melanoma					
Topical corticosteroids	18	616,666	0.029 (0.017-0.046)	1.00 (reference)	1.00 (reference)
Topical tacrolimus					
Ever use	NR	NR	0.022 (0.006-0.057)	0.77 (0.19-2.33)	0.85 (0.28-2.59)
Single use	NR	NR	0.024 (0.006-0.061)	0.81 (0.20-2.47)	0.93 (0.30-2.82)
Non-melanoma skin cancer					
Topical corticosteroids	8	616,666	0.013 (0.006-0.026)	1.00 (reference)	1.00 (reference)
Topical tacrolimus					
Ever use	NR	NR	0.011 (0.001-0.041)	0.86 (0.09-4.33)	0.87 (0.19-4.04)
Single use	NR	NR	0.006 (0.000-0.033)	0.46 (0.01-3.41)	0.46 (0.06-3.73)
Skin cancer					
Topical corticosteroids	26	616,666	0.042 (0.028-0.062)	1.00 (reference)	1.00 (reference)
Topical tacrolimus					
Ever use	6	178,330	0.034 (0.012-0.073)	0.80 (0.27-1.98)	0.86 (0.35-2.11)
Single use	5	168,674	0.030 (0.010-0.069)	0.70 (0.21-1.86)	0.77 (0.29-2.04)
Non-Hodgkin lymphoma					
Topical corticosteroids	11	616,666	0.018 (0.009-0.032)	1.00 (reference)	1.00 (reference)
Topical tacrolimus					
Ever use	6	178,330	0.034 (0.012-0.073)	1.89 (0.57-5.56)	2.05 (0.75-5.59)
Single use	6	168,674	0.036 (0.013-0.077)	1.99 (0.61-5.88)	2.19 (0.81-5.97)
Hodgkin lymphoma					
Topical corticosteroids	12	616,666	0.019 (0.010-0.034)	1.00 (reference)	1.00 (reference)
Topical tacrolimus					
Ever use	9	178,330	0.050 (0.023-0.096)	2.59 (0.97-6.71)	2.41 (1.02-5.73)
Single use	8	168,674	0.047 (0.020-0.093)	2.44 (0.86-6.48)	2.37 (0.99-5.68)

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Cutaneous T-cell lymphoma					
Topical corticosteroids	NR	NR	0.002 (0.000-0.009)	1.00 (reference)	1.00 (reference)
Topical tacrolimus					
Ever use	NR	NR	0.011 (0.001-0.041)	6.92 (0.36-408.03)	7.42 (0.49-112.31)
Single use	NR	NR	0.012 (0.001-0.043)	7.31 (0.38-431.38)	7.77 (0.50-121.45)
Lymphoma					
Topical corticosteroids	24	616,666	0.039 (0.025-0.058)	1.00 (reference)	1.00 (reference)
Topical tacrolimus					
Ever use	17	178,330	0.095 (0.056-0.153)	2.45 (1.24-4.75)	2.44 (1.30-4.59)
Single use	16	168,674	0.095 (0.054-0.154)	2.44 (1.21-4.78)	2.49 (1.32-4.70)

CI = confidence interval; NL PHARMO = PHARMO Database Network (the Netherlands); NR = not reportable.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in NL-PHARMO, Denmark, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

Table 11. Non-Hodgkin Lymphoma: Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios, Overall and by Cumulative Dose, in Users of Topical Tacrolimus Compared With Users of Topical Corticosteroids—Children

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)a
Topical corticosteroids	11	616,666	0.018 (0.009-0.032)	1.00 (reference)	1.00 (reference)
Topical tacrolimus					
Ever use	6	178,330	0.034 (0.012-0.073)	1.89 (0.57-5.56)	2.05 (0.75-5.59)
Single use	6	168,674	0.036 (0.013-0.077)	1.99 (0.61-5.88)	2.19 (0.81-5.97)
Cumulative dose (grams)[b]					
Single use					
≤ 0.05	NR	NR	0.033 (0.009-0.083)	1.82 (0.42-6.15)	2.13 (0.69-6.60)
> 0.05 to 0.10	0	25,541	0.000 (0.000-0.144)	0.00 (0.00-9.62)	0.00 (0.00-N/E)
> 0.10	NR	NR	0.099 (0.012-0.359)	5.58 (0.60-25.56)	4.79 (1.03-22.16)

CI = confidence interval; N/E = not estimable; NL-PHARMO = PHARMO Database Network (the Netherlands); NR = not reportable.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Table 12. Hodgkin Lymphoma: Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios, Overall and by Cumulative Dose, in Users of Topical Tacrolimus Compared With Users of Topical Corticosteroids—Children

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Topical corticosteroids	12	616,666	0.019 (0.010-0.034)	1.00 (reference)	1.00 (reference)
Topical tacrolimus					
Ever use	9	178,330	0.050 (0.023-0.096)	2.59 (0.97-6.71)	2.41 (1.02-5.73)
Single use	8	168,674	0.047 (0.020-0.093)	2.44 (0.86-6.48)	2.37 (0.99-5.68)
Cumulative dose (grams)[b]					
Single use					
≤ 0.05	8	123,032	0.065 (0.028-0.128)	3.34 (1.18-8.89)	3.26 (1.35-7.89)
> 0.05 to 0.10	0	25,541	0.000 (0.000-0.144)	0.00 (0.00-8.69)	0.00 (0.00-N/E)
> 0.10	0	20,101	0.000 (0.000-0.184)	0.00 (0.00-11.04)	0.00 (0.00-N/E)

CI = confidence interval; N/E = not estimable; NL-PHARMO = PHARMO Database Network (the Netherlands).

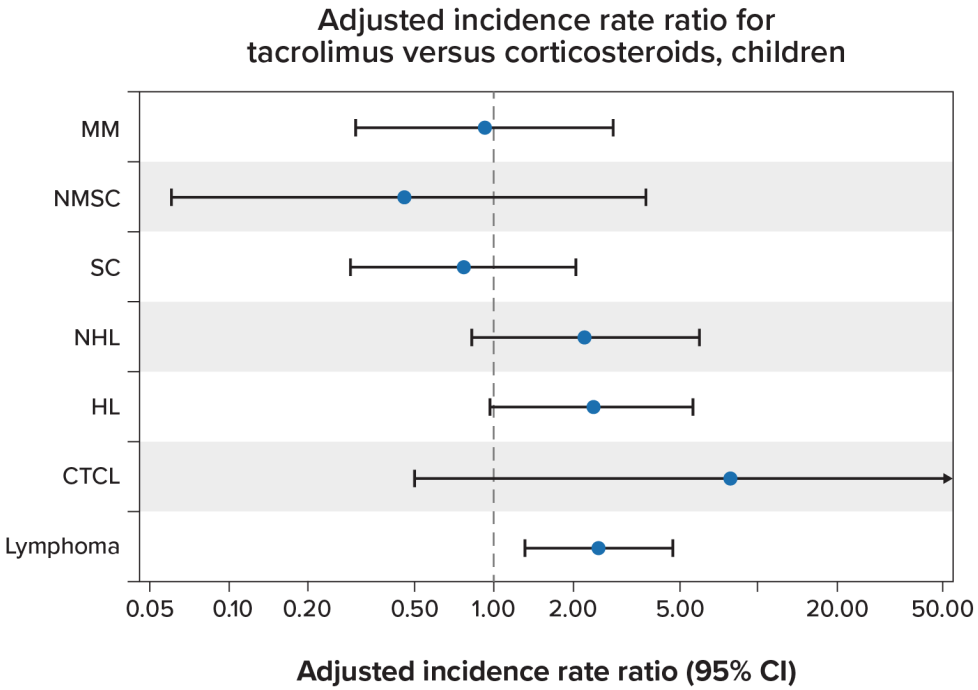
[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Summary of Results for the Comparison of Topical Tacrolimus With Topical Corticosteroids in Children

Figure 16 shows the summary results for topical tacrolimus and topical corticosteroid in children.

Figure 16. Summary Results for Topical Tacrolimus and Topical Corticosteroids—Children



CI = confidence interval; CTCL = cutaneous T-cell lymphoma; HL = Hodgkin lymphoma; MM = malignant melanoma; NHL = non-Hodgkin lymphoma; NMSC = non-melanoma skin cancer; SC = skin cancer.

***Summary of results*. In children, the IRR for each study outcome for topical tacrolimus compared with topical corticosteroids was based on a low number of events. There was an increase in the IRR for Hodgkin lymphoma and non-Hodgkin lymphoma. For Hodgkin lymphoma, this was only present at low doses. The increase in risk seen for CTCL is not very precise due the low number of events.**

10.4.1.2 Topical Pimecrolimus Compared With Topical Corticosteroids in Children

The pooled results for the number of events, person-time, crude incidence rates, and adjusted IRRs for each study outcome comparing single use of pimecrolimus with use of corticosteroids in children are presented in Table 13.

The number of skin malignancies for this analysis cannot be reported because they did not reach 5 events exposed to pimecrolimus. The IRR for single exposure to topical pimecrolimus and malignant melanoma is 0.69 (95% CI, 0.20-2.31) and for NMSC is 0.63 (95% CI, 0.13-3.13).

For the “any lymphoma” outcome, there were < 5 lymphoma events identified in users of topical pimecrolimus (data source–specific numbers are not reported due to small cell counts reporting restrictions in Denmark) and 34 events in users of topical corticosteroids ([redacted] in UK-CPRD, 25 in Denmark, 4 in NL-PHARMO, and [redacted] in Sweden). The crude incidence rate of any lymphoma per 1,000 person-years was 0.02 events in single users of topical pimecrolimus and 0.04 events in users of topical corticosteroids. The pooled adjusted IRR comparing single topical pimecrolimus use with topical corticosteroids was 0.48 (95% CI, 0.17-1.36).

By type of lymphoma, for non-Hodgkin lymphoma, were < 5 events in users of topical pimecrolimus (data source–specific numbers are not reported due to small cell counts reporting restrictions in Denmark), and 13 events in users of corticosteroids ([redacted] in Denmark and [redacted] in UK-CPRD); for Hodgkin lymphoma, < 5 events in users of topical pimecrolimus (data source–specific numbers cannot be reported due to small cell counts reporting restrictions in Denmark), and 18 events in users of topical corticosteroids ([redacted] in UK-CPRD, 12 in Denmark, [redacted] in NL-PHARMO, and 1 in Sweden); and for CTCLs, there were no events identified in users of topical pimecrolimus and < 5 events in users of topical corticosteroids. The pooled adjusted IRR comparing single use of topical pimecrolimus versus topical corticosteroids was 0.30 (95% CI, 0.04-2.28) for non-Hodgkin lymphoma, 0.71 (95% CI, 0.21-2.38) for Hodgkin lymphoma and not estimable for CTCL.

Table 13. Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios for All Study Malignancies in Users of Topical Pimecrolimus Compared With Users of Topical Corticosteroids—Children

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Malignant melanoma					
Topical corticosteroids	18	776,023	0.023 (0.014-0.037)	1.00 (reference)	1.00 (reference)
Topical pimecrolimus					
Ever use	NR	NR	0.014 (0.003-0.040)	0.59 (0.11-2.03)	0.62 (0.18-2.06)
Single use	NR	NR	0.015 (0.003-0.045)	0.66 (0.12-2.27)	0.69 (0.20-2.31)
Non-melanoma skin cancer					
Topical corticosteroids	11	776,023	0.014 (0.007-0.025)	1.00 (reference)	1.00 (reference)
Topical pimecrolimus					
Ever use	NR	NR	0.009 (0.001-0.033)	0.65 (0.07-2.96)	0.56 (0.11-2.79)
Single use	NR	NR	0.010 (0.001-0.037)	0.72 (0.08-3.31)	0.63 (0.13-3.13)
Skin cancer					
Topical corticosteroids	29	776,023	0.037 (0.025-0.054)	1.00 (reference)	1.00 (reference)
Topical pimecrolimus					
Ever use	5	218,434	0.023 (0.007-0.053)	0.61 (0.19-1.60)	0.60 (0.23-1.56)
Single use	5	195,272	0.026 (0.008-0.060)	0.69 (0.21-1.79)	0.67 (0.25-1.75)
Non-Hodgkin lymphoma					
Topical corticosteroids	13	776,023	0.017 (0.009-0.029)	1.00 (reference)	1.00 (reference)
Topical pimecrolimus					
Ever use	NR	NR	0.005 (0.000-0.026)	0.27 (0.01-1.82)	0.27 (0.04-2.02)
Single use	NR	NR	0.005 (0.000-0.029)	0.31 (0.01-2.04)	0.30 (0.04-2.28)
Hodgkin lymphoma					
Topical corticosteroids	18	776,023	0.023 (0.014-0.037)	1.00 (reference)	1.00 (reference)
Topical pimecrolimus					
Ever use	NR	NR	0.014 (0.003-0.040)	0.59 (0.11-2.03)	0.64 (0.19-2.15)
Single use	NR	NR	0.015 (0.003-0.045)	0.66 (0.12-2.27)	0.71 (0.21-2.38)
Cutaneous T-cell lymphoma					
Topical corticosteroids	NR	NR	0.004 (0.001-0.011)	1.00 (reference)	1.00 (reference)
Topical pimecrolimus					
Ever use	NR	NR	0.009 (0.001-0.033)	2.37 (0.20-20.68)	2.58 (0.44-15.27)
Single use	0	195,272	0.000 (0.000-0.019)	0.00 (0.00-9.62)	0.00 (0.00-N/E)
Lymphoma					
Topical corticosteroids	34	776,023	0.044 (0.030-0.061)	1.00 (reference)	1.00 (reference)
Topical pimecrolimus					
Ever use	6	218,434	0.027 (0.010-0.060)	0.63 (0.22-1.51)	0.65 (0.28-1.55)
Single use	NR	NR	0.020 (0.006-0.052)	0.47 (0.12-1.31)	0.48 (0.17-1.36)

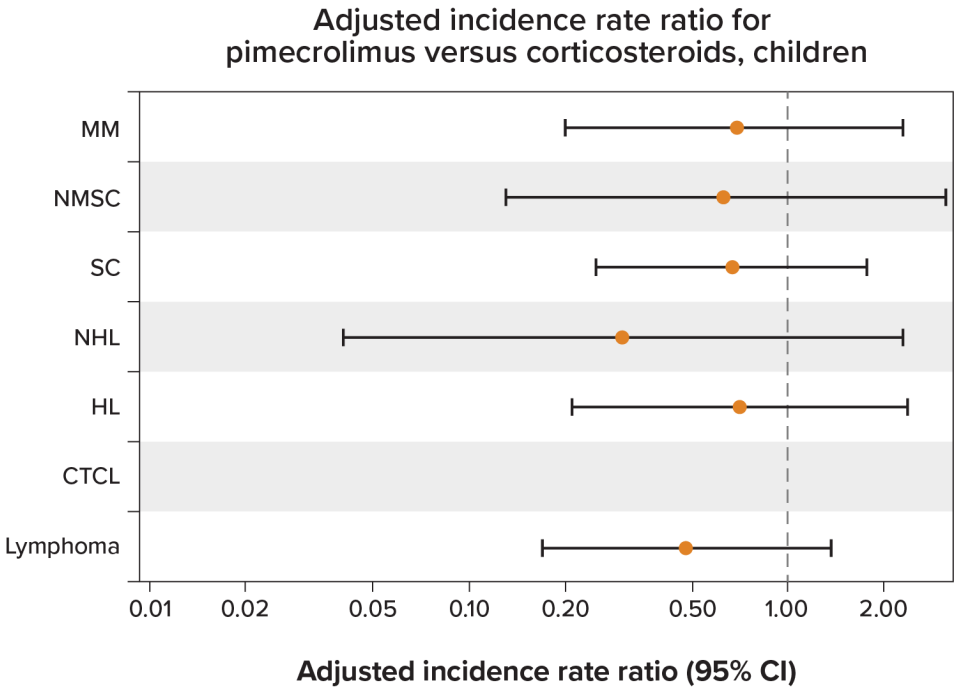
CI = confidence interval; N/E = not estimable; NL PHARMO = PHARMO Database Network (the Netherlands); NR = not reportable.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

Summary of Results for the Comparison of Topical Pimecrolimus With Topical Corticosteroids in Children

Figure 17 shows the summary results for topical pimecrolimus and topical corticosteroid in children.

Figure 17. Summary Results for Topical Pimecrolimus and Topical Corticosteroids—Children



CI = confidence interval; CTCL = cutaneous T-cell lymphoma; HL = Hodgkin lymphoma; MM = malignant melanoma; NHL = non-Hodgkin lymphoma; NMSC = non-melanoma skin cancer; SC = skin cancer.

Summary of results: **In children, the IRR for each study outcome for topical pimecrolimus compared with topical corticosteroids are based on a low number of events and do not suggest an increased risk.**

10.4.1.3 Topical Tacrolimus and Topical Pimecrolimus Combined Compared With Topical Corticosteroids: Skin Malignancies

Due to the low number of skin cancers in patients exposed to topical tacrolimus or pimecrolimus we evaluated the association of exposure to any TCIs and skin cancer (Table 14). The adjusted IRR of skin cancer associated with the use of TCIs was 0.72 (95% CI, 0.37-1.38).

Table 14. Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios in Users of Topical Tacrolimus or Pimecrolimus Compared With Users of Topical Corticosteroids—Children

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Malignant melanoma					
Corticosteroids	36	1,392,689	0.026 (0.018-0.036)	1.00 (reference)	1.00 (reference)
Tacrolimus or pimecrolimus	7	396,764	0.018 (0.007-0.036)	0.68 (0.26-1.56)	0.73 (0.32-1.65)
Non-melanoma skin cancer					
Corticosteroids	19	1,392,689	0.014 (0.008-0.021)	1.00 (reference)	1.00 (reference)
Tacrolimus or pimecrolimus	NR	NR	0.010 (0.003-0.026)	0.74 (0.18-2.22)	0.69 (0.23-2.09)
Skin cancer					
Corticosteroids	55	1,392,689	0.039 (0.030-0.051)	1.00 (reference)	1.00 (reference)
Tacrolimus or pimecrolimus	11	396,764	0.028 (0.014-0.050)	0.70 (0.33-1.36)	0.72 (0.37-1.38)

CI = confidence interval; NL PHARMO = PHARMO Database Network (the Netherlands); NR = not reportable.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

10.4.2 Study Population–Specific Incidence Rates and Incidence Rate Ratios—Adults

10.4.2.1 Topical Tacrolimus Compared With Topical Corticosteroids in Adults

The number of events, person-time, crude incidence rates, and adjusted IRRs for each study outcome and study data source comparing use of tacrolimus with use of corticosteroids in adults are presented in Table 15.

Incidence rates of skin cancers among topical corticosteroids exposed patients ranged from 3.86 per 1,000 person-years in Denmark to 5.19 in Sweden. The adjusted IRR for skin cancer for topical tacrolimus compared with topical corticosteroids ranged from 0.76 (95% CI, 0.65-0.89) in UK-CPRD to 1.14 (95% CI, 1.06-1.23) in Denmark (Figure 18).

Table 15. Incidence Rates and Crude and Adjusted Incidence Rate Ratios for All Study Malignancies for Ever Use and Single Use of Topical Tacrolimus Versus Topical Corticosteroids, by Study Population—Adults

Exposure	Study Database	Number of Cases	Person-years	Crude Incidence Rate per 1,000 Person-years (95% CI)	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio [a] (95% CI)
Malignant melanoma						
Corticosteroids	NL-PHARMO	176	383,824	0.459 (0.393-0.532)	1.00 (reference)	1.00 (reference)
	Denmark	373	791,713	0.471 (0.425-0.521)	1.00 (reference)	1.00 (reference)
	Sweden	451	752,796	0.599 (0.545-0.657)	1.00 (reference)	1.00 (reference)
	UK-CPRD	107	207,173	0.516 (0.423-0.624)	1.00 (reference)	1.00 (reference)
Tacrolimus						
Ever use	NL-PHARMO	54	125,701	0.430 (0.323-0.561)	0.94 (0.68-1.28)	0.93 (0.68-1.27)
	Denmark	104	227,486	0.457 (0.374-0.554)	0.97 (0.77-1.21)	0.97 (0.78-1.21)
	Sweden	133	214,684	0.620 (0.519-0.734)	1.03 (0.85-1.26)	1.07 (0.88-1.30)
	UK-CPRD	21	54,048	0.389 (0.241-0.594)	0.75 (0.45-1.21)	0.75 (0.47-1.20)
Single use	NL-PHARMO	52	120,094	0.433 (0.323-0.568)	0.94 (0.68-1.29)	0.94 (0.69-1.29)
	Denmark	102	214,099	0.476 (0.388-0.578)	1.01 (0.80-1.26)	1.01 (0.81-1.26)
	Sweden	132	211,909	0.623 (0.521-0.739)	1.04 (0.85-1.26)	1.07 (0.88-1.30)
	UK-CPRD	20	51,814	0.386 (0.236-0.596)	0.75 (0.44-1.21)	0.75 (0.46-1.20)
Non-melanoma skin cancer						
Corticosteroids	NL-PHARMO	1,552	383,824	4.044 (3.845-4.250)	1.00 (reference)	1.00 (reference)
	Denmark	2,685	791,713	3.391 (3.264-3.522)	1.00 (reference)	1.00 (reference)
	Sweden	3,465	752,796	4.603 (4.451-4.759)	1.00 (reference)	1.00 (reference)
	UK-CPRD	834	207,173	4.026 (3.757-4.308)	1.00 (reference)	1.00 (reference)
Tacrolimus						
Ever use	NL-PHARMO	489	125,701	3.890 (3.553-4.251)	0.96 (0.87-1.07)	0.97 (0.87-1.07)
	Denmark	876	227,486	3.851 (3.600-4.114)	1.14 (1.05-1.23)	1.15 (1.06-1.24)
	Sweden	998	214,684	4.649 (4.365-4.946)	1.01 (0.94-1.08)	1.06 (0.99-1.14)
	UK-CPRD	170	54,048	3.145 (2.690-3.655)	0.78 (0.66-0.92)	0.78 (0.66-0.92)

Exposure	Study Database	Number of Cases	Person-years	Crude Incidence Rate per 1,000 Person-years (95% CI)	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio [a] (95% CI)
Single use	NL-PHARMO	468	120,094	3.897 (3.552-4.267)	0.96 (0.87-1.07)	0.97 (0.88-1.08)
	Denmark	833	214,099	3.891 (3.631-4.164)	1.15 (1.06-1.24)	1.16 (1.07-1.25)
	Sweden	976	211,909	4.606 (4.321-4.904)	1.00 (0.93-1.07)	1.05 (0.98-1.13)
	UK-CPRD	160	51,814	3.088 (2.628-3.605)	0.77 (0.64-0.91)	0.76 (0.64-0.90)
Skin cancer						
Corticosteroids	NL-PHARMO	1,728	383,824	4.502 (4.292-4.719)	1.00 (reference)	1.00 (reference)
	Denmark	3,058	791,713	3.863 (3.727-4.002)	1.00 (reference)	1.00 (reference)
	Sweden	3,910	752,796	5.194 (5.032-5.359)	1.00 (reference)	1.00 (reference)
	UK-CPRD	939	207,173	4.532 (4.247-4.832)	1.00 (reference)	1.00 (reference)
Tacrolimus						
Ever use	NL-PHARMO	543	125,701	4.320 (3.964-4.699)	0.96 (0.87-1.06)	0.97 (0.88-1.06)
	Denmark	980	227,486	4.308 (4.042-4.586)	1.12 (1.04-1.20)	1.12 (1.05-1.21)
	Sweden	1,129	214,684	5.259 (4.957-5.575)	1.01 (0.95-1.08)	1.06 (0.99-1.13)
	UK-CPRD	191	54,048	3.534 (3.050-4.072)	0.78 (0.66-0.91)	0.78 (0.66-0.91)
Single use	NL-PHARMO	520	120,094	4.330 (3.966-4.719)	0.96 (0.87-1.06)	0.97 (0.88-1.07)
	Denmark	935	214,099	4.367 (4.092-4.656)	1.13 (1.05-1.22)	1.14 (1.06-1.23)
	Sweden	1,106	211,909	5.219 (4.916-5.536)	1.00 (0.94-1.07)	1.05 (0.98-1.13)
	UK-CPRD	180	51,814	3.474 (2.985-4.020)	0.77 (0.65-0.90)	0.76 (0.65-0.89)
Non-Hodgkin lymphoma						
Corticosteroids	NL-PHARMO	111	383,824	0.289 (0.238-0.348)	1.00 (reference)	1.00 (reference)
	Denmark	239	791,713	0.302 (0.265-0.343)	1.00 (reference)	1.00 (reference)
	Sweden	184	752,796	0.244 (0.210-0.282)	1.00 (reference)	1.00 (reference)
	UK-CPRD	60	207,173	0.290 (0.221-0.373)	1.00 (reference)	1.00 (reference)
Tacrolimus						
Ever use	NL-PHARMO	36	125,701	0.286 (0.201-0.396)	0.99 (0.66-1.45)	0.99 (0.68-1.45)
	Denmark	66	227,486	0.290 (0.224-0.369)	0.96 (0.72-1.27)	0.96 (0.73-1.26)
	Sweden	34	214,684	0.158 (0.110-0.221)	0.65 (0.44-0.94)	0.69 (0.48-0.99)
	UK-CPRD	27	54,048	0.500 (0.329-0.727)	1.72 (1.05-2.76)	1.73 (1.10-2.72)

Exposure	Study Database	Number of Cases	Person-years	Crude Incidence Rate per 1,000 Person-years (95% CI)	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio [a] (95% CI)
Single use	NL-PHARMO	35	120,094	0.291 (0.203-0.405)	1.01 (0.67-1.49)	1.01 (0.69-1.48)
	Denmark	62	214,099	0.290 (0.222-0.371)	0.96 (0.71-1.27)	0.96 (0.73-1.27)
	Sweden	34	211,909	0.160 (0.111-0.224)	0.66 (0.44-0.95)	0.70 (0.48-1.00)
	UK-CPRD	25	51,814	0.482 (0.312-0.712)	1.67 (1.00-2.70)	1.66 (1.04-2.66)
Hodgkin lymphoma						
Corticosteroids	NL-PHARMO	11	383,824	0.029 (0.014-0.051)	1.00 (reference)	1.00 (reference)
	Denmark	47	791,713	0.059 (0.044-0.079)	1.00 (reference)	1.00 (reference)
	Sweden	44	752,796	0.058 (0.042-0.078)	1.00 (reference)	1.00 (reference)
	UK-CPRD	10	207,173	0.048 (0.023-0.089)	1.00 (reference)	1.00 (reference)
Tacrolimus						
Ever use	NL-PHARMO	[redacted]	[redacted]	0.040 (0.013-0.093)	1.39 (0.38-4.33)	1.38 (0.44-4.26)
	Denmark	15	227,486	0.066 (0.037-0.109)	1.11 (0.58-2.02)	1.09 (0.61-1.95)
	Sweden	6	214,684	0.028 (0.010-0.061)	0.48 (0.17-1.13)	0.48 (0.20-1.12)
	UK-CPRD	[redacted]	[redacted]	0.074 (0.020-0.189)	1.53 (0.35-5.32)	1.51 (0.47-4.86)
Single use	NL-PHARMO	[redacted]	[redacted]	0.042 (0.014-0.097)	1.45 (0.40-4.54)	1.44 (0.47-4.45)
	Denmark	13	214,099	0.061 (0.032-0.104)	1.02 (0.51-1.92)	1.00 (0.54-1.85)
	Sweden	6	211,909	0.028 (0.010-0.062)	0.48 (0.17-1.14)	0.48 (0.20-1.14)
	UK-CPRD	[redacted]	[redacted]	0.077 (0.021-0.198)	1.60 (0.37-5.55)	1.58 (0.49-5.08)
Cutaneous T-cell lymphoma						
Corticosteroids	NL-PHARMO	13	383,824	0.034 (0.018-0.058)	1.00 (reference)	1.00 (reference)
	Denmark	27	791,713	0.034 (0.022-0.050)	1.00 (reference)	1.00 (reference)
	Sweden	30	752,796	0.040 (0.027-0.057)	1.00 (reference)	1.00 (reference)
	UK-CPRD	16	207,173	0.077 (0.044-0.125)	1.00 (reference)	1.00 (reference)
Tacrolimus						
Ever use	NL-PHARMO	6	125,701	0.048 (0.018-0.104)	1.41 (0.44-3.97)	1.33 (0.50-3.52)
	Denmark	10	227,486	0.044 (0.021-0.081)	1.29 (0.56-2.75)	1.28 (0.63-2.63)
	Sweden	15	214,684	0.070 (0.039-0.115)	1.75 (0.88-3.36)	1.75 (0.94-3.25)
	UK-CPRD	13	54,048	0.241 (0.128-0.411)	3.11 (1.38-6.91)	3.12 (1.49-6.53)

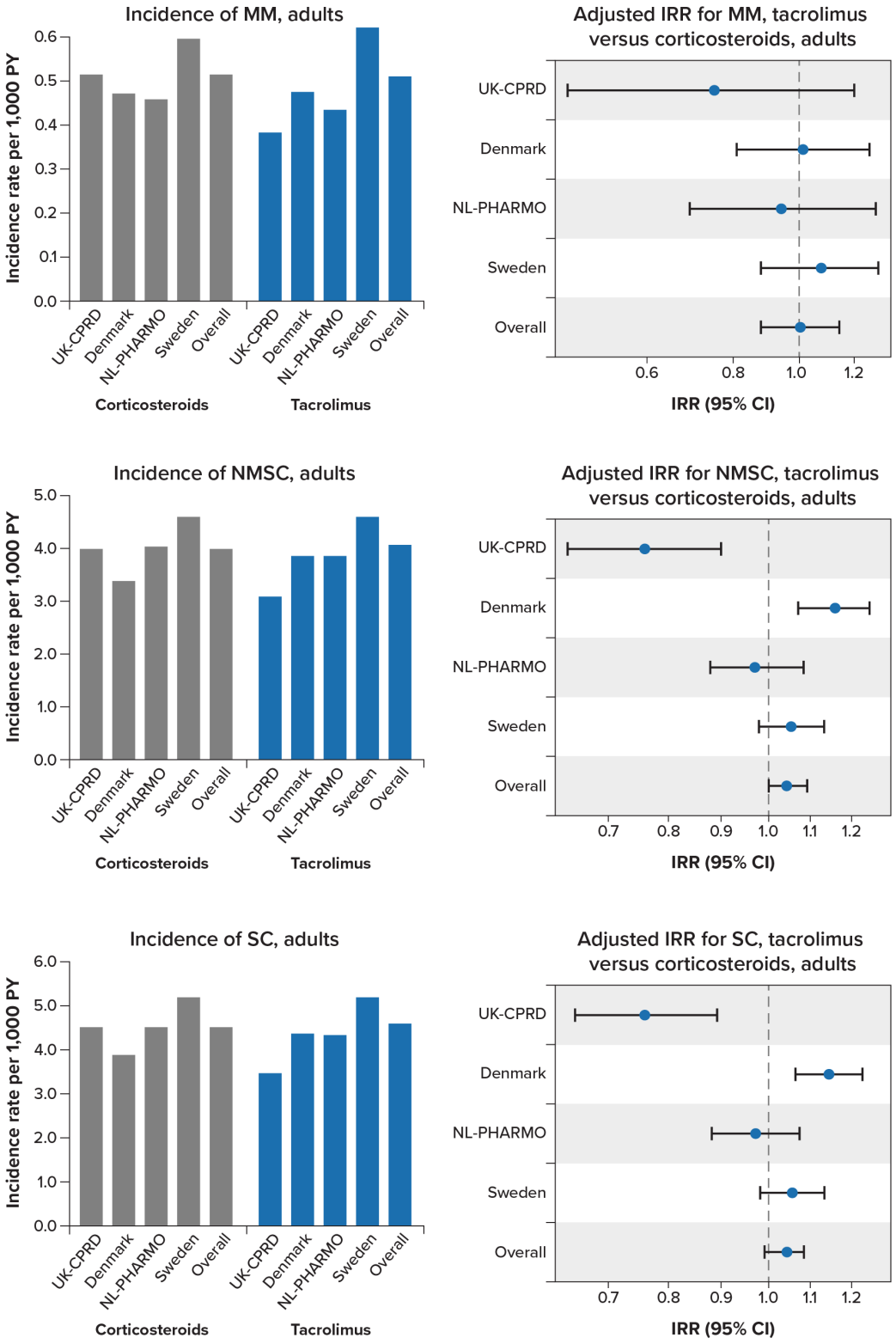
Exposure	Study Database	Number of Cases	Person-years	Crude Incidence Rate per 1,000 Person-years (95% CI)	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio [a] (95% CI)
Single use	NL-PHARMO	6	120,094	0.050 (0.018-0.109)	1.48 (0.46-4.16)	1.40 (0.53-3.69)
	Denmark	10	214,099	0.047 (0.022-0.086)	1.37 (0.59-2.92)	1.36 (0.66-2.78)
	Sweden	14	211,909	0.066 (0.036-0.111)	1.66 (0.81-3.22)	1.67 (0.89-3.13)
	UK-CPRD	13	51,814	0.251 (0.134-0.429)	3.25 (1.44-7.20)	3.27 (1.56-6.83)
Lymphoma						
Corticosteroids	NL-PHARMO	135	383,824	0.352 (0.295-0.416)	1.00 (reference)	1.00 (reference)
	Denmark	313	791,713	0.395 (0.353-0.442)	1.00 (reference)	1.00 (reference)
	Sweden	258	752,796	0.343 (0.302-0.387)	1.00 (reference)	1.00 (reference)
	UK-CPRD	86	207,173	0.415 (0.332-0.513)	1.00 (reference)	1.00 (reference)
Tacrolimus						
Ever use	NL-PHARMO	47	125,701	0.374 (0.275-0.497)	1.06 (0.75-1.49)	1.06 (0.76-1.48)
	Denmark	91	227,486	0.400 (0.322-0.491)	1.01 (0.79-1.28)	1.01 (0.80-1.27)
	Sweden	55	214,684	0.256 (0.193-0.333)	0.75 (0.55-1.00)	0.78 (0.58-1.04)
	UK-CPRD	44	54,048	0.814 (0.592-1.093)	1.96 (1.33-2.85)	1.96 (1.36-2.82)
Single use	NL-PHARMO	46	120,094	0.383 (0.280-0.511)	1.09 (0.76-1.53)	1.08 (0.77-1.52)
	Denmark	85	214,099	0.397 (0.317-0.491)	1.00 (0.78-1.28)	1.00 (0.79-1.27)
	Sweden	54	211,909	0.255 (0.191-0.332)	0.74 (0.54-1.00)	0.77 (0.58-1.04)
	UK-CPRD	42	51,814	0.811 (0.584-1.096)	1.95 (1.32-2.86)	1.95 (1.35-2.82)

CI = confidence interval; NL-PHARMO = PHARMO Database Network (the Netherlands); UK-CPRD = Clinical Practice Research Database.

[a] Adjusted by deciles of propensity scores and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] UK-CPRD counts below 5 will need to be redacted if shared outside of the regulatory environment.

Figure 18. Incidence Rate and Adjusted Incidence Rate Ratio of Skin Cancers for Single Use of Topical Tacrolimus Versus Topical Corticosteroids, by Study Population—Adults

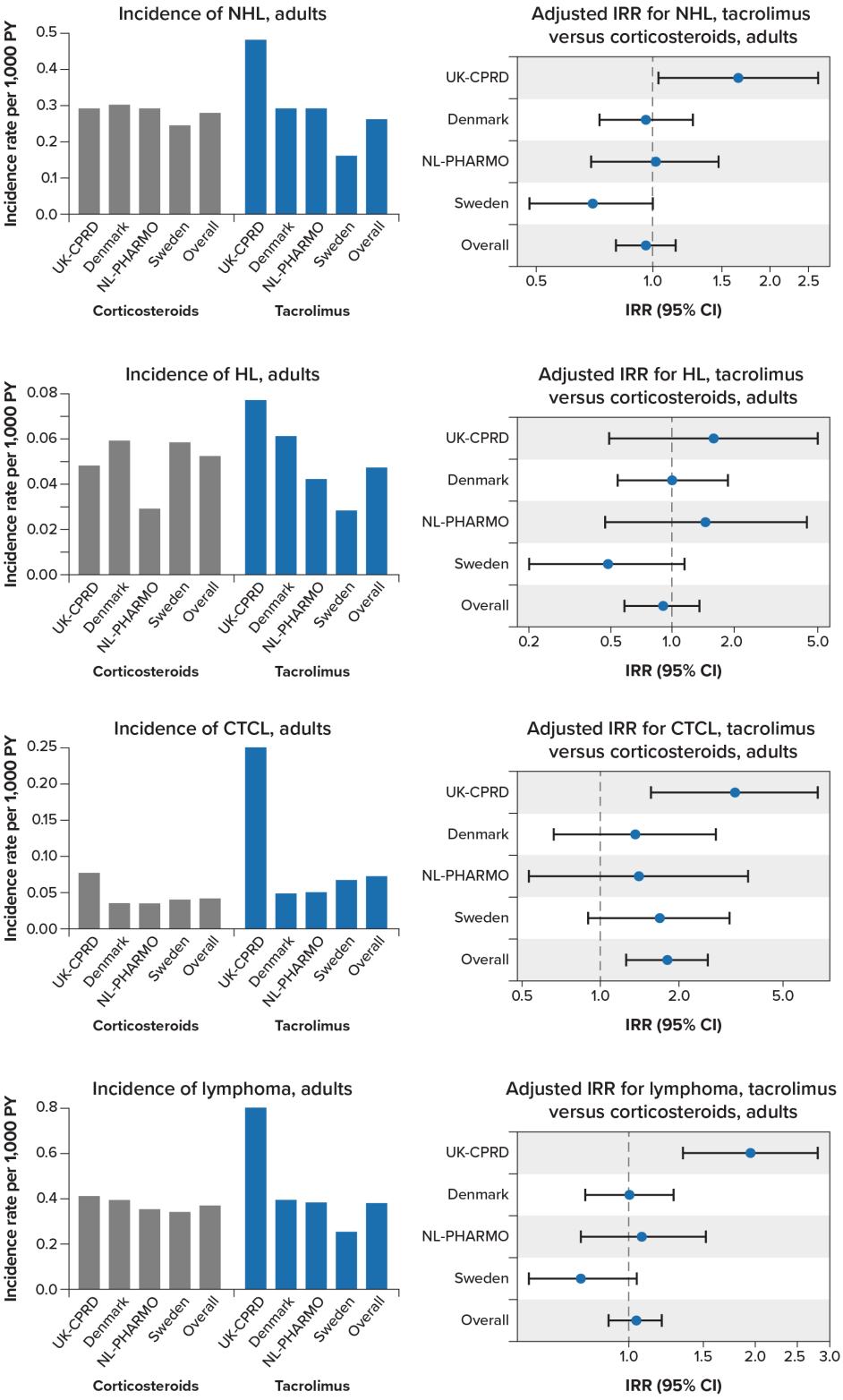


CI = confidence interval; IRR = incidence rate ratio; MM = malignant melanoma; NL-PHARMO = PHARMO Database Network (the Netherlands); NMSC = non-melanoma skin cancer; SC = skin cancer; UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

Incidence rates of lymphomas were similar among the study databases in users of corticosteroids, and lower in Sweden and higher in UK-CPRD than in the rest of populations among users of tacrolimus. The high incidence of lymphoma in the tacrolimus cohort in the UK-CPRD population is noticeable. The incidences of non-Hodgkin lymphoma, Hodgkin lymphoma, and CTCL are elevated, especially in the tacrolimus cohort in UK-CPRD.

The adjusted IRR for any lymphoma ranged from 0.77 (95% CI, 0.58-1.04) in Sweden to 1.95 (95% CI, 1.35-2.82) in UK-CPRD. For CTCL, the adjusted IRR ranged from 1.36 (95% CI, 0.66-2.78) in Denmark to 3.27 (95% CI, 1.56-6.83) in UK-CPRD (Figure 19).

Figure 19. Incidence Rate and Adjusted Incidence Rate Ratio of Lymphomas for Single Use of Topical Tacrolimus Versus Topical Corticosteroids, by Study Population—Adults



CI = confidence interval; CTCL = cutaneous T-cell lymphoma; HL = Hodgkin lymphoma; IRR = incidence rate ratio; NHL = non-Hodgkin lymphoma; NL-PHARMO = PHARMO Database Network (the Netherlands); UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

10.4.2.2 Topical Pimecrolimus Compared With Topical Corticosteroids in Adults

The number of events, person-time, crude incidence rates, and adjusted IRRs for each study outcome and study data source comparing use of pimecrolimus with use of corticosteroids in adults are presented in Table 16.

Incidence rates of skin cancers among topical corticosteroids exposed patients matched to pimecrolimus ranged from 3.56 per 1,000 person-years in Denmark to 4.51 in Sweden. The adjusted IRR for skin cancer for topical pimecrolimus compared with topical corticosteroids ranged from 1.03 (95% CI, 0.83-1.29) in UK-CPRD to 1.40 (95% CI, 1.15-1.71) in Sweden (Figure 20).

Table 16. Incidence Rates and Crude and Adjusted Incidence Rate Ratios of All Study Malignancies for Ever Use and Single Use of Topical Pimecrolimus Versus Topical Corticosteroids, by Study Population—Adults

Exposure	Study Database	Number of Cases	Person-years	Crude Incidence Rate per 1,000 Person-years (95% CI)	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)
Malignant melanoma						
Corticosteroids	NL-PHARMO	91	193,502	0.470 (0.379-0.577)	1.00 (reference)	1.00 (reference)
	Denmark	509	1,108,188	0.459 (0.420-0.501)	1.00 (reference)	1.00 (reference)
	Sweden	49	90,046	0.544 (0.403-0.719)	1.00 (reference)	1.00 (reference)
	UK-CPRD	43	100,616	0.427 (0.309-0.576)	1.00 (reference)	1.00 (reference)
Pimecrolimus						
Ever use	NL-PHARMO	28	50,506	0.554 (0.368-0.801)	1.18 (0.74-1.82)	1.17 (0.77-1.79)
	Denmark	153	294,490	0.520 (0.440-0.609)	1.13 (0.94-1.36)	1.14 (0.95-1.36)
	Sweden	21	23,224	0.904 (0.560-1.382)	1.66 (0.95-2.82)	1.67 (1.00-2.77)
	UK-CPRD	10	25,319	0.395 (0.189-0.726)	0.92 (0.41-1.87)	0.93 (0.47-1.86)
Single use	NL-PHARMO	27	46,239	0.584 (0.385-0.850)	1.24 (0.78-1.93)	1.23 (0.80-1.89)
	Denmark	141	265,399	0.531 (0.447-0.627)	1.16 (0.95-1.40)	1.17 (0.97-1.40)
	Sweden	21	20,798	1.010 (0.625-1.543)	1.86 (1.06-3.15)	1.87 (1.12-3.11)
	UK-CPRD	9	23,319	0.386 (0.176-0.733)	0.90 (0.39-1.88)	0.91 (0.44-1.87)
Non-melanoma skin cancer						
Corticosteroids	NL-PHARMO	757	193,502	3.912 (3.638-4.201)	1.00 (reference)	1.00 (reference)
	Denmark	3,440	1,108,188	3.104 (3.001-3.210)	1.00 (reference)	1.00 (reference)
	Sweden	357	90,046	3.965 (3.564-4.398)	1.00 (reference)	1.00 (reference)
	UK-CPRD	361	100,616	3.588 (3.227-3.978)	1.00 (reference)	1.00 (reference)
Pimecrolimus						
Ever use	NL-PHARMO	222	50,506	4.396 (3.836-5.013)	1.12 (0.96-1.31)	1.15 (0.99-1.33)
	Denmark	1,195	294,490	4.058 (3.831-4.295)	1.31 (1.22-1.40)	1.30 (1.22-1.39)
	Sweden	113	23,224	4.866 (4.010-5.850)	1.23 (0.98-1.52)	1.26 (1.02-1.55)
	UK-CPRD	98	25,319	3.871 (3.142-4.717)	1.08 (0.85-1.35)	1.08 (0.86-1.35)

Exposure	Study Database	Number of Cases	Person-years	Crude Incidence Rate per 1,000 Person-years (95% CI)	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)
Single use	NL-PHARMO	204	46,239	4.412 (3.827-5.061)	1.13 (0.96-1.32)	1.15 (0.98-1.34)
	Denmark	1,093	265,399	4.118 (3.878-4.370)	1.33 (1.24-1.42)	1.32 (1.23-1.41)
	Sweden	107	20,798	5.145 (4.216-6.217)	1.30 (1.04-1.61)	1.33 (1.07-1.65)
	UK-CPRD	88	23,319	3.774 (3.027-4.649)	1.05 (0.82-1.33)	1.05 (0.83-1.32)
Skin cancer						
Corticosteroids	NL-PHARMO	848	193,502	4.382 (4.092-4.688)	1.00 (reference)	1.00 (reference)
	Denmark	3,949	1,108,188	3.563 (3.453-3.676)	1.00 (reference)	1.00 (reference)
	Sweden	406	90,046	4.509 (4.081-4.969)	1.00 (reference)	1.00 (reference)
	UK-CPRD	404	100,616	4.015 (3.633-4.427)	1.00 (reference)	1.00 (reference)
Pimecrolimus						
Ever use	NL-PHARMO	250	50,506	4.950 (4.355-5.603)	1.13 (0.98-1.30)	1.15 (1.00-1.32)
	Denmark	1,348	294,490	4.577 (4.336-4.828)	1.28 (1.21-1.37)	1.28 (1.20-1.36)
	Sweden	134	23,224	5.770 (4.834-6.834)	1.28 (1.04-1.56)	1.31 (1.08-1.59)
	UK-CPRD	108	25,319	4.266 (3.499-5.150)	1.06 (0.85-1.32)	1.06 (0.86-1.31)
Single use	NL-PHARMO	231	46,239	4.996 (4.372-5.683)	1.14 (0.98-1.32)	1.16 (1.00-1.34)
	Denmark	1,234	265,399	4.650 (4.394-4.916)	1.30 (1.22-1.39)	1.30 (1.22-1.39)
	Sweden	128	20,798	6.154 (5.135-7.318)	1.36 (1.11-1.67)	1.40 (1.15-1.71)
	UK-CPRD	97	23,319	4.160 (3.373-5.074)	1.04 (0.82-1.30)	1.03 (0.83-1.29)
Non-Hodgkin lymphoma						
Corticosteroids	NL-PHARMO	57	193,502	0.295 (0.223-0.382)	1.00 (reference)	1.00 (reference)
	Denmark	255	1,108,188	0.230 (0.203-0.260)	1.00 (reference)	1.00 (reference)
	Sweden	14	90,046	0.155 (0.085-0.261)	1.00 (reference)	1.00 (reference)
	UK-CPRD	17	100,616	0.169 (0.098-0.271)	1.00 (reference)	1.00 (reference)
Pimecrolimus						
Ever use	NL-PHARMO	17	50,506	0.337 (0.196-0.539)	1.14 (0.62-1.99)	1.19 (0.69-2.05)
	Denmark	63	294,490	0.214 (0.164-0.274)	0.93 (0.69-1.23)	0.93 (0.70-1.22)
	Sweden	5	23,224	0.215 (0.070-0.502)	1.38 (0.39-4.07)	1.35 (0.49-3.71)
	UK-CPRD	9	25,319	0.355 (0.163-0.675)	2.10 (0.83-4.99)	2.02 (0.91-4.49)

Exposure	Study Database	Number of Cases	Person-years	Crude Incidence Rate per 1,000 Person-years (95% CI)	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)
Single use	NL-PHARMO	14	46,239	0.303 (0.166-0.508)	1.03 (0.53-1.87)	1.07 (0.60-1.92)
	Denmark	55	265,399	0.207 (0.156-0.270)	0.90 (0.66-1.21)	0.90 (0.67-1.21)
	Sweden	4	20,798	0.192 (0.052-0.492)	1.24 (0.30-3.94)	1.21 (0.40-3.68)
	UK-CPRD	9	23,319	0.386 (0.176-0.733)	2.28 (0.90-5.42)	2.18 (0.98-4.86)
Hodgkin lymphoma						
Corticosteroids	NL-PHARMO	7	193,502	0.036 (0.015-0.075)	1.00 (reference)	1.00 (reference)
	Denmark	67	1,108,188	0.060 (0.047-0.077)	1.00 (reference)	1.00 (reference)
	Sweden	[redacted]	[redacted]	0.056 (0.018-0.130)	1.00 (reference)	1.00 (reference)
	UK-CPRD	[redacted]	[redacted]	0.040 (0.011-0.102)	1.00 (reference)	1.00 (reference)
Pimecrolimus						
Ever use	NL-PHARMO	5	50,506	0.099 (0.032-0.231)	2.74 (0.68-10.02)	2.78 (0.88-8.75)
	Denmark	8	294,490	0.027 (0.012-0.054)	0.45 (0.19-0.94)	0.45 (0.22-0.93)
	Sweden	[redacted]	[redacted]	0.000 (0.000-0.159)	0.00 (0.00-4.23)	0.00 (0.00-N/E)
	UK-CPRD	[redacted]	[redacted]	0.158 (0.043-0.405)	3.97 (0.74-21.34)	3.87 (0.98-15.23)
Single use	NL-PHARMO	5	46,239	0.108 (0.035-0.252)	2.99 (0.75-10.94)	3.03 (0.95-9.62)
	Denmark	8	265,399	0.030 (0.013-0.059)	0.50 (0.21-1.04)	0.50 (0.24-1.04)
	Sweden	[redacted]	[redacted]	0.000 (0.000-0.177)	0.00 (0.00-4.72)	0.00 (0.00-N/E)
	UK-CPRD	[redacted]	[redacted]	0.129 (0.027-0.376)	3.24 (0.47-19.13)	3.17 (0.73-13.66)
Cutaneous T-cell lymphoma						
Corticosteroids	NL-PHARMO	7	193,502	0.036 (0.015-0.075)	1.00 (reference)	1.00 (reference)
	Denmark	31	1,108,188	0.028 (0.019-0.040)	1.00 (reference)	1.00 (reference)
	Sweden	[redacted]	[redacted]	0.011 (0.000-0.062)	1.00 (reference)	1.00 (reference)
	UK-CPRD	[redacted]	[redacted]	0.040 (0.011-0.102)	1.00 (reference)	1.00 (reference)
Pimecrolimus						
Ever use	NL-PHARMO	[redacted]	[redacted]	0.040 (0.005-0.143)	1.09 (0.11-5.75)	1.06 (0.23-4.96)
	Denmark	6	294,490	0.020 (0.007-0.044)	0.73 (0.25-1.77)	0.72 (0.30-1.70)
	Sweden	0	23,224	0.000 (0.000-0.159)	0.00 (0.00-151.22)	0.00 (0.00-N/E)
	UK-CPRD	[redacted]	[redacted]	0.039 (0.001-0.220)	0.99 (0.02-10.04)	0.96 (0.11-8.40)

[redacted]

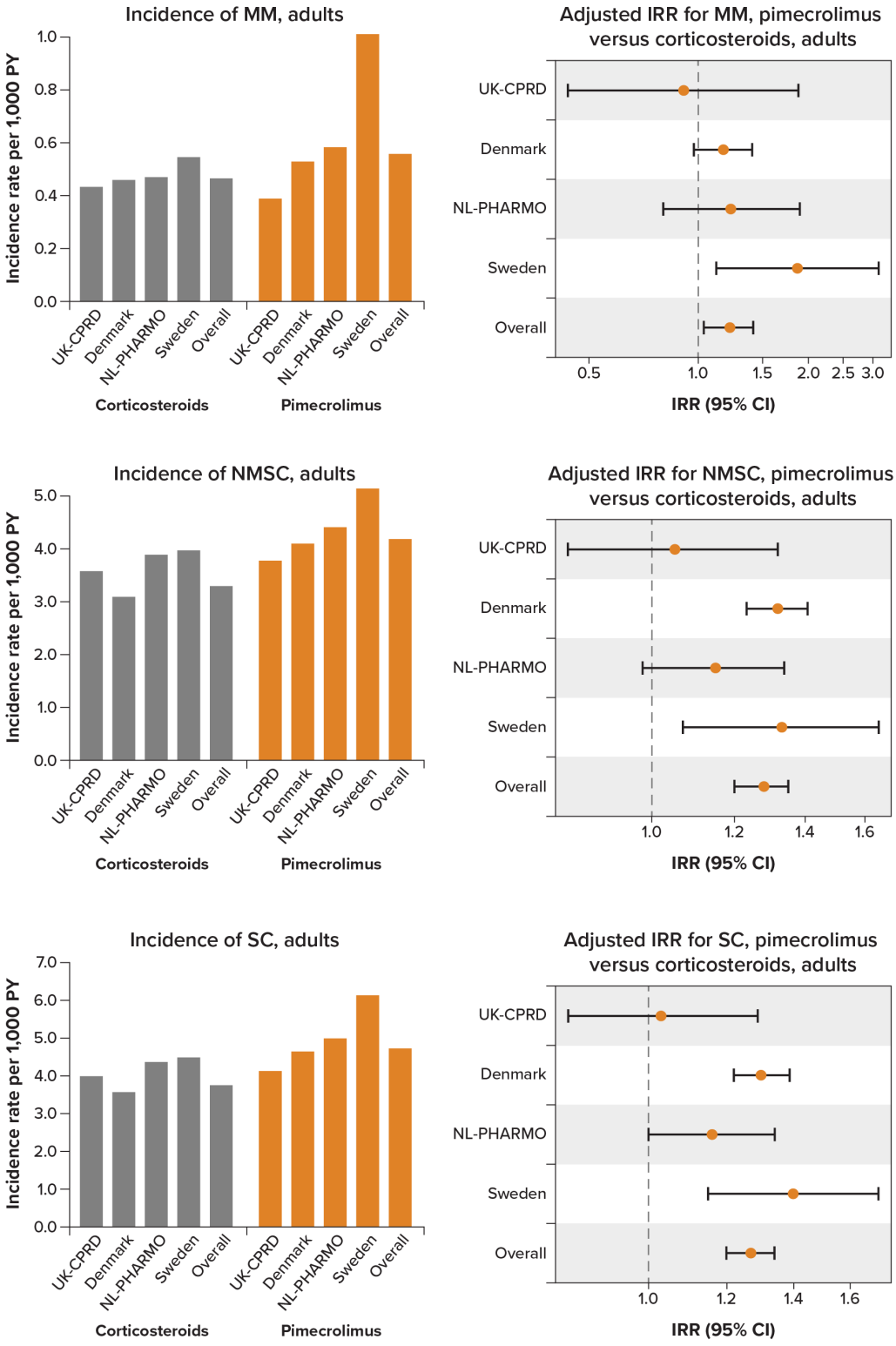
Exposure	Study Database	Number of Cases	Person-years	Crude Incidence Rate per 1,000 Person-years (95% CI)	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)
Single use	NL-PHARMO	1	46,239	0.022 (0.001-0.120)	0.60 (0.01-4.65)	0.58 (0.07-4.66)
	Denmark	NR	NR	0.015 (0.004-0.039)	0.54 (0.14-1.52)	0.53 (0.19-1.49)
	Sweden	0	20,798	0.000 (0.000-0.177)	0.00 (0.00-168.85)	0.00 (0.00-N/E)
	UK-CPRD	[redacted]	[redacted]	0.043 (0.001-0.239)	1.08 (0.02-10.90)	1.09 (0.12-9.82)
Lymphoma						
Corticosteroids	NL-PHARMO	71	193,502	0.367 (0.287-0.463)	1.00 (reference)	1.00 (reference)
	Denmark	353	1,108,188	0.319 (0.286-0.354)	1.00 (reference)	1.00 (reference)
	Sweden	20	90,046	0.222 (0.136-0.343)	1.00 (reference)	1.00 (reference)
	UK-CPRD	25	100,616	0.248 (0.161-0.367)	1.00 (reference)	1.00 (reference)
Pimecrolimus						
Ever use	NL-PHARMO	24	50,506	0.475 (0.304-0.707)	1.30 (0.78-2.08)	1.34 (0.84-2.12)
	Denmark	77	294,490	0.261 (0.206-0.327)	0.82 (0.63-1.05)	0.82 (0.64-1.05)
	Sweden	5	23,224	0.215 (0.070-0.502)	0.97 (0.28-2.66)	0.94 (0.36-2.48)
	UK-CPRD	14	25,319	0.553 (0.302-0.928)	2.23 (1.07-4.45)	2.14 (1.12-4.09)
Single use	NL-PHARMO	20	46,239	0.433 (0.264-0.668)	1.18 (0.68-1.96)	1.22 (0.74-2.00)
	Denmark	67	265,399	0.252 (0.196-0.321)	0.79 (0.60-1.03)	0.79 (0.61-1.03)
	Sweden	4	20,798	0.192 (0.052-0.492)	0.87 (0.22-2.58)	0.84 (0.29-2.46)
	UK-CPRD	13	23,319	0.557 (0.297-0.953)	2.24 (1.05-4.55)	2.17 (1.12-4.22)

CI = confidence interval; N/E = not estimable; NL-PHARMO = PHARMO Database Network (the Netherlands); NR = not reportable; UK-CPRD = Clinical Practice Research Database (United Kingdom).

[a] Adjusted by deciles of propensity scores and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] UK-CPRD counts below 5 will need to be redacted if shared outside of the regulatory environment.

Figure 20. Incidence Rate and Adjusted Incidence Rate Ratio of Skin Cancers for Single Use of Topical Pimecrolimus Versus Topical Corticosteroids, by Study Population—Adults

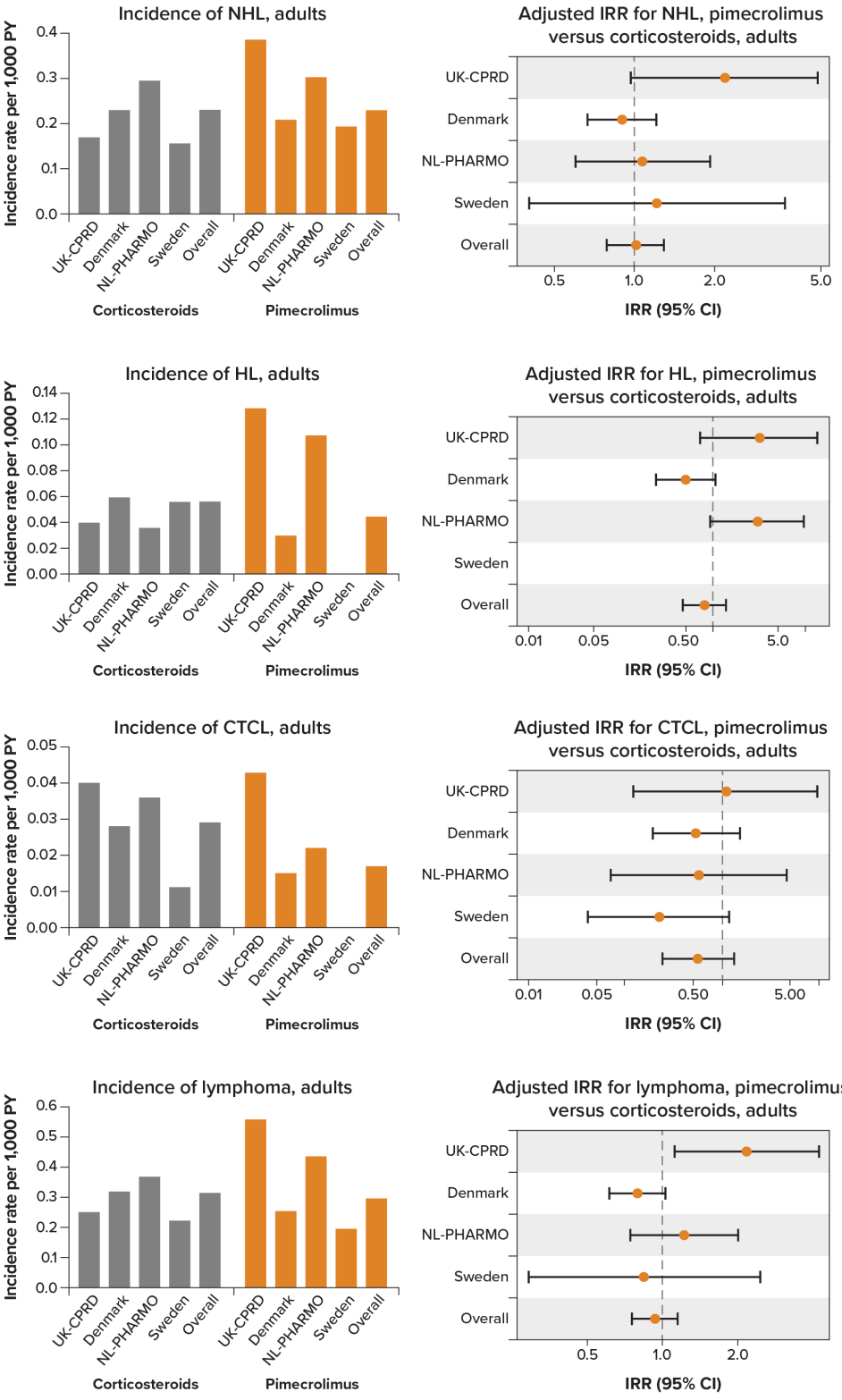


CI = confidence interval; IRR = incidence rate ratio; MM = malignant melanoma; NL-PHARMO = PHARMO Database Network (the Netherlands); NMSC = non-melanoma skin cancer; SC = skin cancer; UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

Incidence rates of lymphomas were similar between the study databases among users of corticosteroids. Among users of pimecrolimus incidence rates were lower in Sweden and higher in UK-CPRD than in the rest of populations. In UK-CPRD, as in the tacrolimus-exposed cohort, the incidence rate of non-Hodgkin lymphoma, Hodgkin lymphoma, and CTCL were higher than in the other study populations.

The adjusted IRR for any lymphoma for topical pimecrolimus compared with topical corticosteroids ranged from 0.79 (95% CI, 0.61-1.03) in Denmark to 2.17 (95% CI, 1.12-4.22) in UK-CPRD. For CTCL, the adjusted IRR ranged from 0.00 (no cases were observed) in Sweden to 1.09 (95% CI, 0.12-9.82) in UK-CPRD (Figure 21).

Figure 21. Incidence Rate and Adjusted Incidence Rate Ratio of Lymphomas for Single Use of Topical Pimecrolimus Versus Topical Corticosteroids, by Study Population—Adults



CI = confidence interval; CTCL = cutaneous T-cell lymphoma; HL = Hodgkin lymphoma; IRR = incidence rate ratio; NHL = non-Hodgkin lymphoma; NL-PHARMO = PHARMO Database Network (the Netherlands); UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

10.4.3 Pooled Incidence Rates and Incidence Rate Ratios—Adults

10.4.3.1 Topical Tacrolimus Compared With Topical Corticosteroids in Adults

The results of pooled analyses comparing use of tacrolimus versus use of corticosteroids for each study outcome in adults aged 18 years or older are presented in Table 17 on page 106 through Table 23 on page 114. An overview of IRRs and incidence rate differences for all outcomes is presented in Overview of Pooled Analysis Results for the Comparison of Topical Tacrolimus With Topical Corticosteroids in Adults on page 115.

Malignant Melanoma

A total of 312 events of malignant melanoma were identified in ever users of topical tacrolimus, and 1,107 events were identified in users of topical corticosteroids (Table 17). Of the 312 events in ever users, 306 (98.1%) were identified for single use of topical tacrolimus. The crude incidence rate per 1,000 person-years of malignant melanoma was 0.51 in single users of topical tacrolimus and 0.52 in users of corticosteroids. The crude IRR for single use of tacrolimus was 0.99 (95% CI, 0.87-1.12), and the adjusted IRR was 1.00 (95% CI, 0.88-1.14). The adjusted IRR for single use with a cumulative dose greater than 0.10 gram was 1.09 (95% CI, 0.82-1.45).

Table 17. Malignant Melanoma, Including In Situ: Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios, Overall and by Cumulative Dose, in Users of Topical Tacrolimus Compared With Users of Topical Corticosteroids—Adults

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Topical corticosteroids	1,107	2,135,506	0.518 (0.488-0.550)	1.00 (reference)	1.00 (reference)
Topical tacrolimus					
Ever use	312	621,919	0.502 (0.448-0.561)	0.97 (0.85-1.10)	0.98 (0.87-1.12)
Single use	306	597,916	0.512 (0.456-0.572)	0.99 (0.87-1.12)	1.00 (0.88-1.14)
Switching/multiple use	6	24,003	0.250 (0.092-0.544)	0.48 (0.18-1.05)	0.51 (0.23-1.14)
Cumulative dose (grams)[b]					
Ever use					
≤ 0.05	200	401,841	0.498 (0.431-0.572)	0.96 (0.82-1.12)	1.00 (0.86-1.16)
> 0.05 to 0.10	62	128,978	0.481 (0.369-0.616)	0.93 (0.71-1.20)	0.92 (0.71-1.19)
> 0.10	50	91,101	0.549 (0.407-0.724)	1.06 (0.78-1.41)	1.04 (0.78-1.39)
Single use					
≤ 0.05	197	389,261	0.506 (0.438-0.582)	0.98 (0.83-1.14)	1.01 (0.87-1.18)
> 0.05 to 0.10	60	123,598	0.485 (0.370-0.625)	0.94 (0.71-1.21)	0.92 (0.71-1.20)
> 0.10	49	85,057	0.576 (0.426-0.762)	1.11 (0.82-1.48)	1.09 (0.82-1.45)

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Switching/multiple use					
≤ 0.05	NR	NR	0.238 (0.049-0.697)	0.46 (0.09-1.35)	0.50 (0.16-1.54)
> 0.05 to 0.10	NR	NR	0.372 (0.045-1.343)	0.72 (0.09-2.60)	0.76 (0.19-3.06)
> 0.10	NR	NR	0.165 (0.004-0.922)	0.32 (0.01-1.78)	0.33 (0.05-2.33)
Duration of use (days)					
1-120	221	455,091	0.486 (0.424-0.554)	0.94 (0.81-1.08)	0.95 (0.82-1.10)
121-240	57	113,013	0.504 (0.382-0.653)	0.97 (0.73-1.27)	1.00 (0.76-1.31)
> 240	34	53,815	0.632 (0.438-0.883)	1.22 (0.84-1.71)	1.23 (0.88-1.74)

CI = confidence interval; NL PHARMO = PHARMO Database Network (the Netherlands); NR = not reportable.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Non-melanoma Skin Cancer

A total of 2,533 events of NMSC were identified in ever users of topical tacrolimus, and 8,536 events were identified in users of topical corticosteroids (Table 18). Of the 2,533 events in ever users, 2,437 (96.2%) were identified for single use of topical tacrolimus. The crude incidence rate per 1,000 person-years of NMSC was 4.08 in single users of topical tacrolimus and 4.00 in users of corticosteroids. The crude IRR for single use of tacrolimus was 1.02 (95% CI, 0.97-1.07), and the adjusted IRR was 1.04 (95% CI, 1.00-1.09). Although the trend in the cumulative dose-response relationship is not monotonically increasing in the adjusted IRR analysis, both crude and adjusted IRRs were highest in the highest category of cumulative dose. The adjusted IRR for single use with a cumulative dose greater than 0.10 gram was 1.12 (95% CI, 1.02-1.23).

Table 18. Non-melanoma Skin Cancer, Including in Situ: Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios, Overall and by Cumulative Dose, in Users of Topical Tacrolimus Compared With Users of Topical Corticosteroids—Adults

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Topical corticosteroids	8,536	2,135,506	3.997 (3.913-4.083)	1.00 (reference)	1.00 (reference)
Topical tacrolimus					
Ever use	2,533	621,919	4.073 (3.916-4.235)	1.02 (0.97-1.07)	1.04 (1.00-1.09)
Single use	2,437	597,916	4.076 (3.916-4.241)	1.02 (0.97-1.07)	1.04 (1.00-1.09)
Switching/multiple use	96	24,003	3.999 (3.240-4.884)	1.00 (0.81-1.22)	1.04 (0.85-1.27)

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Cumulative dose (grams)[b]					
Ever use					
≤ 0.05	1,562	401,841	3.887 (3.697-4.085)	0.97 (0.92-1.03)	1.04 (0.98-1.10)
> 0.05 to 0.10	526	128,978	4.078 (3.737-4.442)	1.02 (0.93-1.11)	0.99 (0.90-1.08)
> 0.10	445	91,101	4.885 (4.441-5.360)	1.22 (1.11-1.34)	1.12 (1.02-1.23)
Single use					
≤ 0.05	1,509	389,261	3.877 (3.683-4.077)	0.97 (0.92-1.02)	1.03 (0.98-1.09)
> 0.05 to 0.10	510	123,598	4.126 (3.776-4.500)	1.03 (0.94-1.13)	1.00 (0.91-1.09)
> 0.10	418	85,057	4.914 (4.454-5.409)	1.23 (1.11-1.36)	1.12 (1.02-1.24)
Switching/multiple use					
≤ 0.05	53	12,579	4.213 (3.156-5.511)	1.05 (0.79-1.38)	1.14 (0.87-1.50)
> 0.05 to 0.10	16	5,380	2.974 (1.700-4.830)	0.74 (0.43-1.21)	0.76 (0.47-1.25)
> 0.10	27	6,044	4.467 (2.944-6.500)	1.12 (0.74-1.63)	1.07 (0.73-1.56)
Duration of use (days)					
1-120	1,786	455,091	3.924 (3.745-4.111)	0.98 (0.93-1.03)	1.02 (0.97-1.07)
121-240	484	113,013	4.283 (3.910-4.682)	1.07 (0.98-1.17)	1.07 (0.98-1.18)
> 240	263	53,815	4.887 (4.314-5.515)	1.22 (1.08-1.38)	1.15 (1.02-1.30)

CI = confidence interval; NL PHARMO = PHARMO Database Network (the Netherlands).

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Skin Cancer

A total of 2,843 events of any skin cancer were identified in ever users of topical tacrolimus, and 9,635 events were identified in users of topical corticosteroids (Table 19). Of the 2,843 events in ever users, 2,741 (96.4%) were identified for single use of topical tacrolimus. The crude incidence rate per 1,000 person-years of any skin cancer was 4.58 in single users of topical tacrolimus and 4.51 in users of corticosteroids. The crude IRR for single use of tacrolimus was 1.02 (95% CI, 0.97-1.06), and the adjusted IRR was 1.04 (95% CI, 0.99-1.08). Although the trend in the cumulative dose-response relationship is not monotonically increasing in the adjusted IRR analysis, both crude and adjusted IRRs were higher in the highest category of cumulative dose. The adjusted IRR for single use with a cumulative dose greater than 0.10 gram was 1.12 (95% CI, 1.02-1.23).

Table 19. Skin Cancer, Including In Situ: Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios, Overall and by Cumulative Dose, in Users of Topical Tacrolimus Compared With Users of Topical Corticosteroids—Adults

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Topical corticosteroids	9,635	2,135,506	4.512 (4.422-4.603)	1.00 (reference)	1.00 (reference)
Topical tacrolimus					
Ever use	2,843	621,919	4.571 (4.405-4.743)	1.01 (0.97-1.06)	1.04 (0.99-1.08)
Single use	2,741	597,916	4.584 (4.414-4.759)	1.02 (0.97-1.06)	1.04 (0.99-1.08)
Switching/multiple use	102	24,003	4.249 (3.465-5.159)	0.94 (0.77-1.14)	0.98 (0.81-1.19)
Cumulative dose (grams)[b]					
Ever use					
≤ 0.05	1,762	401,841	4.385 (4.182-4.594)	0.97 (0.92-1.02)	1.03 (0.98-1.09)
> 0.05 to 0.10	587	128,978	4.551 (4.190-4.935)	1.01 (0.93-1.10)	0.98 (0.90-1.06)
> 0.10	494	91,101	5.423 (4.955-5.923)	1.20 (1.10-1.32)	1.11 (1.01-1.21)
Single use					
≤ 0.05	1,706	389,261	4.383 (4.177-4.596)	0.97 (0.92-1.02)	1.03 (0.98-1.09)
> 0.05 to 0.10	569	123,598	4.604 (4.233-4.998)	1.02 (0.94-1.11)	0.99 (0.91-1.07)
> 0.10	466	85,057	5.479 (4.992-5.999)	1.21 (1.10-1.33)	1.12 (1.02-1.23)
Switching/multiple use					
≤ 0.05	56	12,579	4.452 (3.363-5.781)	0.99 (0.74-1.28)	1.07 (0.82-1.39)
> 0.05 to 0.10	18	5,380	3.346 (1.983-5.288)	0.74 (0.44-1.17)	0.76 (0.48-1.21)
> 0.10	28	6,044	4.633 (3.078-6.696)	1.03 (0.68-1.48)	0.99 (0.68-1.43)
Duration of use (days)					
1-120	2,005	455,091	4.406 (4.215-4.603)	0.98 (0.93-1.02)	1.01 (0.96-1.06)
121-240	541	113,013	4.787 (4.392-5.208)	1.06 (0.97-1.16)	1.06 (0.98-1.16)
> 240	297	53,815	5.519 (4.909-6.184)	1.22 (1.09-1.37)	1.16 (1.03-1.30)

CI = confidence interval; NL PHARMO = PHARMO Database Network (the Netherlands).

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Non-Hodgkin Lymphoma

A total of 163 events of non-Hodgkin lymphoma were identified in ever users of topical tacrolimus, and 594 events were identified in users of topical corticosteroids (Table 20). Of the 163 events in ever users, 156 (95.7%) were identified for single use of topical tacrolimus. (Table 20). The crude incidence rate per 1,000 person-years of non-Hodgkin lymphoma was 0.26 in single users of topical tacrolimus and 0.28 in users of corticosteroids. The crude IRR

for single use of tacrolimus was 0.94 (95% CI, 0.78-1.12), and the adjusted IRR was 0.96 (95% CI, 0.80-1.14). Crude and adjusted IRRs were higher in the highest category of cumulative dose. The adjusted IRR for single use with a cumulative dose greater than 0.10 gram was 1.18 (95% CI, 0.82-1.69). There was a dose-response relationship with increasing duration of use. Adjusted IRRs by duration were 0.91 (95% CI, 0.74-1.11) for a duration of 1-120 days, 0.96 (95% CI, 0.67-1.37) for a duration of 121-240 days, and 1.28 (95% CI, 0.83-1.96) for a duration of more than 240 days.

Table 20. Non-Hodgkin Lymphoma: Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios, Overall and by Cumulative Dose, in Users of Topical Tacrolimus Compared With Users of Topical Corticosteroids—Adults

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Topical corticosteroids	594	2,135,506	0.278 (0.256-0.301)	1.00 (reference)	1.00 (reference)
Topical tacrolimus					
Ever use	163	621,919	0.262 (0.223-0.306)	0.94 (0.79-1.12)	0.96 (0.80-1.14)
Single use	156	597,916	0.261 (0.222-0.305)	0.94 (0.78-1.12)	0.96 (0.80-1.14)
Switching/multiple use	7	24,003	0.292 (0.117-0.601)	1.05 (0.42-2.17)	0.98 (0.46-2.06)
Cumulative dose (grams)[b]					
Ever use					
≤ 0.05	97	401,841	0.241 (0.196-0.294)	0.87 (0.69-1.08)	0.92 (0.74-1.13)
> 0.05 to 0.10	35	128,978	0.271 (0.189-0.377)	0.98 (0.67-1.37)	0.96 (0.69-1.36)
> 0.10	31	91,101	0.340 (0.231-0.483)	1.22 (0.82-1.76)	1.10 (0.76-1.57)
Single use					
≤ 0.05	95	389,261	0.244 (0.197-0.298)	0.88 (0.70-1.09)	0.93 (0.75-1.15)
> 0.05 to 0.10	30	123,598	0.243 (0.164-0.347)	0.87 (0.58-1.26)	0.86 (0.60-1.25)
> 0.10	31	85,057	0.364 (0.248-0.517)	1.31 (0.88-1.88)	1.18 (0.82-1.69)
Switching/multiple use					
≤ 0.05	NR	NR	0.159 (0.019-0.574)	0.57 (0.07-2.07)	0.55 (0.14-2.21)
> 0.05 to 0.10	NR	NR	0.929 (0.302-2.169)	3.34 (1.08-7.84)	3.19 (1.32-7.70)
> 0.10	0	6,044	0.000 (0.000-0.610)	0.00 (0.00-2.20)	0.00 (0.00-N/E)
Duration of use (days)					
1-120	109	455,091	0.240 (0.197-0.289)	0.86 (0.70-1.06)	0.91 (0.74-1.11)
121-240	32	113,013	0.283 (0.194-0.400)	1.02 (0.69-1.45)	0.96 (0.67-1.37)
> 240	22	53,815	0.409 (0.256-0.619)	1.47 (0.91-2.25)	1.28 (0.83-1.96)

CI = confidence interval; N/E = not estimable; NL PHARMO = PHARMO Database Network (the Netherlands); NR = not reportable.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Hodgkin Lymphoma

A total of 30 events of Hodgkin lymphoma were identified in ever users of topical tacrolimus, and 112 events were identified in users of topical corticosteroids (Table 21). Of the 30 events in ever users of topical tacrolimus, 28 (93.3%) were identified for single use. The crude incidence rate per 1,000 person-years of Hodgkin lymphoma was 0.05 in single users of topical tacrolimus and 0.05 in users of corticosteroids. The crude IRR for single use of tacrolimus was 0.89 (95% CI, 0.57-1.36) and the adjusted IRR was 0.89 (95% CI, 0.58-1.35). Crude and adjusted IRRs were higher in the highest category of cumulative dose and of duration of use. Adjusted IRRs for single use of tacrolimus were 1.48 (95% CI, 0.65-3.38) for a cumulative dose of more than 0.10 gram and 1.17 (95% CI, 0.37-3.67) for a duration of use of more than 240 days.

Table 21. Hodgkin Lymphoma: Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios, Overall and by Cumulative Dose, in Users of Topical Tacrolimus Compared With Users of Topical Corticosteroids—Adults

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Topical corticosteroids	112	2,135,506	0.052 (0.043-0.063)	1.00 (reference)	1.00 (reference)
Topical tacrolimus					
Ever use	30	621,919	0.048 (0.033-0.069)	0.92 (0.59-1.39)	0.92 (0.61-1.38)
Single use	28	597,916	0.047 (0.031-0.068)	0.89 (0.57-1.36)	0.89 (0.58-1.35)
Switching/multiple use	NR	NR	0.083 (0.010-0.301)	1.59 (0.19-5.87)	1.72 (0.42-7.05)
Cumulative dose (grams)[b]					
Ever use					
≤ 0.05	19	401,841	0.047 (0.028-0.074)	0.90 (0.52-1.47)	0.87 (0.53-1.42)
> 0.05 to 0.10	5	128,978	0.039 (0.013-0.090)	0.74 (0.24-1.78)	0.80 (0.33-1.94)
> 0.10	6	91,101	0.066 (0.024-0.143)	1.26 (0.45-2.82)	1.39 (0.61-3.17)
Single use					
≤ 0.05	18	389,261	0.046 (0.027-0.073)	0.88 (0.50-1.46)	0.85 (0.52-1.41)
> 0.05 to 0.10	NR	NR	0.032 (0.009-0.083)	0.62 (0.17-1.62)	0.66 (0.25-1.79)
> 0.10	6	85,057	0.071 (0.026-0.154)	1.35 (0.48-3.02)	1.48 (0.65-3.38)
Switching/multiple use					
≤ 0.05	NR	NR	0.079 (0.002-0.443)	1.52 (0.04-8.62)	1.53 (0.21-11.01)
> 0.05 to 0.10	NR	NR	0.186 (0.005-1.036)	3.54 (0.09-20.16)	4.12 (0.57-29.83)
> 0.10	0	6,044	0.000 (0.000-0.610)	0.00 (0.00-11.83)	0.00 (0.00-N/E)

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Duration of use (days)					
1-120	22	455,091	0.048 (0.030-0.073)	0.92 (0.56-1.47)	0.91 (0.58-1.45)
121-240	NR	NR	0.044 (0.014-0.103)	0.84 (0.27-2.03)	0.87 (0.35-2.15)
> 240	NR	NR	0.056 (0.011-0.163)	1.06 (0.22-3.19)	1.17 (0.37-3.67)

CI = confidence interval; N/E = not estimable; NL PHARMO = PHARMO Database Network (the Netherlands); NR = not reportable.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Cutaneous T-Cell Lymphoma

A total of 44 events of CTCL were identified in ever users of topical tacrolimus, and 86 events were identified in users of topical corticosteroids (Table 22). Of the 44 events in ever users of topical tacrolimus, 43 (97.7%) were identified for single use (Table 22). The incidence rate per 1,000 person-years of CTCL was 0.07 in single users of topical tacrolimus and 0.04 in users of corticosteroids. The crude IRR for single use of tacrolimus was 1.79 (95% CI, 1.21-2.60), and the adjusted IRR was 1.80 (95% CI, 1.25-2.58). There was a dose-response relationship with increasing dose. Adjusted IRRs for single use of tacrolimus were 0.81 (95% CI, 0.45-1.47) for a cumulative dose of 0.05 gram or less, 2.11 (95% CI, 1.13-3.95) for a cumulative dose from 0.05 to 0.10 gram, and 5.25 (95% CI, 3.21-8.56) for a cumulative dose greater than 0.10 gram. Adjusted IRRs for single use of topical tacrolimus by duration were 1.48 (95% CI, 0.96-2.28) for a duration of 1-120 days, 1.31 (95% CI, 0.57-3.01) for a duration of 121-240 days, and 4.68 (95% CI, 2.49-8.80) for a duration of more than 240 days.

Table 22. Cutaneous T-Cell Lymphoma: Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios, Overall and by Cumulative Dose, in Users of Topical Tacrolimus Compared With Users of Topical Corticosteroids—Adults

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Topical corticosteroids	86	2,135,506	0.040 (0.032-0.050)	1.00 (reference)	1.00 (reference)
Topical tacrolimus					
Ever use	44	621,919	0.071 (0.051-0.095)	1.76 (1.19-2.55)	1.76 (1.23-2.53)
Single use	43	597,916	0.072 (0.052-0.097)	1.79 (1.21-2.60)	1.80 (1.25-2.58)
Switching/multiple use	NR	NR	0.042 (0.001-0.232)	1.03 (0.03-5.92)	1.05 (0.15-7.42)

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Cumulative dose (grams)[b]					
Ever use					
≤ 0.05	13	401,841	0.032 (0.017-0.055)	0.80 (0.41-1.45)	0.85 (0.48-1.51)
> 0.05 to 0.10	11	128,978	0.085 (0.043-0.153)	2.12 (1.02-3.98)	2.03 (1.09-3.80)
> 0.10	20	91,101	0.220 (0.134-0.339)	5.45 (3.17-8.95)	4.92 (3.01-8.04)
Single use					
≤ 0.05	12	389,261	0.031 (0.016-0.054)	0.77 (0.38-1.41)	0.81 (0.45-1.47)
> 0.05 to 0.10	11	123,598	0.089 (0.044-0.159)	2.21 (1.06-4.15)	2.11 (1.13-3.95)
> 0.10	20	85,057	0.235 (0.144-0.363)	5.84 (3.40-9.58)	5.25 (3.21-8.56)
Switching/multiple use					
≤ 0.05	NR	NR	0.079 (0.002-0.443)	1.97 (0.05-11.30)	2.04 (0.29-14.44)
> 0.05 to 0.10	0	5,380	0.000 (0.000-0.686)	0.00 (0.00-17.40)	0.00 (0.00-N/E)
> 0.10	0	6,044	0.000 (0.000-0.610)	0.00 (0.00-15.49)	0.00 (0.00-N/E)
Duration of use (days)					
1-120	27	455,091	0.059 (0.039-0.086)	1.47 (0.92-2.29)	1.48 (0.96-2.28)
121-240	6	113,013	0.053 (0.019-0.116)	1.32 (0.47-2.99)	1.31 (0.57-3.01)
> 240	11	53,815	0.204 (0.102-0.366)	5.08 (2.44-9.54)	4.68 (2.49-8.80)

CI = confidence interval; N/E = not estimable; NL PHARMO = PHARMO Database Network (the Netherlands); NR = not reportable.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Lymphoma

A total of 237 events of any lymphoma were identified in ever users of topical tacrolimus, and 792 events were identified in users of topical corticosteroids (Table 23). Of the 237 events in ever users, 227 (95.8%) were identified for single use of topical tacrolimus. The crude incidence rate per 1,000 person-years of any type of lymphoma was 0.38 in single users of topical tacrolimus and 0.37 in users of corticosteroids. The crude IRR for single use of tacrolimus was 1.02 (95% CI, 0.88-1.19), and the adjusted IRR was 1.04 (95% CI, 0.90-1.20). Crude and adjusted IRRs were higher in the highest category of cumulative dose. The adjusted IRR for single use with a cumulative dose greater than 0.10 gram was 1.67 (95% CI, 1.27-2.18). There was a dose-response relationship with increasing duration of use. Adjusted IRRs for single use by duration were 0.97 (95% CI, 0.82-1.15) for a duration of 1-120 days, 0.99 (95% CI, 0.72-1.34) for a duration of 121-240 days, and 1.62 (95% CI, 1.16-2.27) for a duration of more than 240 days.

Table 23. Lymphoma: Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios, Overall and by Cumulative Dose, in Users of Topical Tacrolimus Compared With Users of Topical Corticosteroids—Adults

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Topical corticosteroids	792	2,135,506	0.371 (0.345-0.398)	1.00 (reference)	1.00 (reference)
Topical tacrolimus					
Ever use	237	621,919	0.381 (0.334-0.433)	1.03 (0.88-1.19)	1.04 (0.90-1.20)
Single use	227	597,916	0.380 (0.332-0.432)	1.02 (0.88-1.19)	1.04 (0.90-1.20)
Switching/multiple use	10	24,003	0.417 (0.200-0.766)	1.12 (0.54-2.08)	1.08 (0.58-2.01)
Cumulative dose (grams)[b]					
Ever use					
≤ 0.05	129	401,841	0.321 (0.268-0.381)	0.87 (0.71-1.04)	0.90 (0.75-1.09)
> 0.05 to 0.10	51	128,978	0.395 (0.294-0.520)	1.07 (0.79-1.42)	1.06 (0.80-1.41)
> 0.10	57	91,101	0.626 (0.474-0.811)	1.69 (1.27-2.21)	1.55 (1.19-2.04)
Single use					
≤ 0.05	125	389,261	0.321 (0.267-0.383)	0.87 (0.71-1.05)	0.90 (0.75-1.09)
> 0.05 to 0.10	45	123,598	0.364 (0.266-0.487)	0.98 (0.71-1.33)	0.98 (0.73-1.32)
> 0.10	57	85,057	0.670 (0.508-0.868)	1.81 (1.36-2.37)	1.67 (1.27-2.18)
Switching/multiple use					
≤ 0.05	NR	NR	0.318 (0.087-0.814)	0.86 (0.23-2.20)	0.84 (0.31-2.24)
> 0.05 to 0.10	NR	NR	1.115 (0.409-2.428)	3.01 (1.10-6.57)	2.96 (1.32-6.61)
> 0.10	0	6,044	0.000 (0.000-0.610)	0.00 (0.00-1.65)	0.00 (0.00-N/E)
Duration of use (days)					
1-120	158	455,091	0.347 (0.295-0.406)	0.94 (0.78-1.11)	0.97 (0.82-1.15)
121-240	43	113,013	0.380 (0.275-0.513)	1.03 (0.74-1.39)	0.99 (0.72-1.34)
> 240	36	53,815	0.669 (0.469-0.926)	1.80 (1.25-2.52)	1.62 (1.16-2.27)

CI = confidence interval; N/E = not estimable; NL PHARMO = PHARMO Database Network (the Netherlands); NR = not reportable.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Overview of Pooled Analysis Results for the Comparison of Topical Tacrolimus With Topical Corticosteroids in Adults

An overview of the adjusted IRRs and rate differences for each study malignancy in adults treated with topical tacrolimus versus adults treated with topical corticosteroids is presented in Table 24 and Table 25 and Figure 22.

Pooled adjusted IRRs for single use of topical tacrolimus compared with use of topical corticosteroids were 1.04 (95% CI, 0.99-1.08) for any skin cancer. 1.00 (95% CI, 0.88-1.14) for malignant melanoma, and 1.04 (95% CI, 1.00-1.09) for NMSC.

The pooled adjusted IRR for single use of topical tacrolimus compared with use of topical corticosteroids was 1.04 (95% CI, 0.90-1.20) for any lymphoma. By type of lymphoma, IRRs were 0.96 (95% CI, 0.80-1.14) for non-Hodgkin lymphoma, 0.89 (95% CI, 0.58-1.35) for Hodgkin lymphoma, and 1.80 (95% CI, 1.25-2.58) for CTCL. For any lymphoma, Hodgkin lymphoma, and CTCL, increased IRRs were observed with the highest cumulative doses.

In terms of absolute effects, the excess rate per 1,000 person-years of follow-up, comparing single use of topical tacrolimus with use of corticosteroids was, 0.17 (95% CI, −0.03 to 0.36) events for any skin cancer, 0.00 (95% CI, −0.06 to 0.07) events for malignant melanoma, 0.17 (95% CI, −0.02 to 0.35) events for NMSC, 0.01 (95% CI, −0.04 to 0.07) events for any lymphoma, −0.01 (95% CI, −0.06 to 0.04) events for non-Hodgkin lymphoma, −0.01 (95% CI, −0.03 to 0.01) events for Hodgkin lymphoma, and 0.03 (95% CI, 0.01 to 0.06) events for cutaneous T-cell lymphoma (Table 25).

Table 24. Overview of Pooled Adjusted Incidence Rate Ratios, Overall, by Cumulative Dose, and by Duration of Use, in Users of Topical Tacrolimus Compared With Users of Topical Corticosteroids—Adults

	Adjusted[a] Incidence Rate Ratio (95% CI)						
Exposure	**Malignant Melanoma**	**Non-melanoma Skin Cancer**	**Skin Cancer**	**Non-Hodgkin Lymphoma**	**Hodgkin Lymphoma**	**Cutaneus T-cell Lymphoma**	**Lymphoma**
Ever use	0.98 (0.87-1.12)	1.04 (1.00-1.09)	1.04 (0.99-1.08)	0.96 (0.80-1.14)	0.92 (0.61-1.38)	1.76 (1.23-2.53)	1.04 (0.90-1.20)
Single use	1.00 (0.88-1.14)	1.04 (1.00-1.09)	1.04 (0.99-1.08)	0.96 (0.80-1.14)	0.89 (0.58-1.35)	1.80 (1.25-2.58)	1.04 (0.90-1.20)
Cumulative dose (grams)[b]							
Ever use							
≤ 0.05	1.00 (0.86-1.16)	1.04 (0.98-1.10)	1.03 (0.98-1.09)	0.92 (0.74-1.13)	0.87 (0.53-1.42)	0.85 (0.48-1.51)	0.90 (0.75-1.09)
> 0.05 to 0.10	0.92 (0.71-1.19)	0.99 (0.90-1.08)	0.98 (0.90-1.06)	0.96 (0.69-1.36)	0.80 (0.33-1.94)	2.03 (1.09-3.80)	1.06 (0.80-1.41)
> 0.10	1.04 (0.78-1.39)	1.12 (1.02-1.23)	1.11 (1.01-1.21)	1.10 (0.76-1.57)	1.39 (0.61-3.17)	4.92 (3.01-8.04)	1.55 (1.19-2.04)
Single use							
≤ 0.05	1.01 (0.87-1.18)	1.03 (0.98-1.09)	1.03 (0.98-1.09)	0.93 (0.75-1.15)	0.85 (0.52-1.41)	0.81 (0.45-1.47)	0.90 (0.75-1.09)
> 0.05 to 0.10	0.92 (0.71-1.20)	1.00 (0.91-1.09)	0.99 (0.91-1.07)	0.86 (0.60-1.25)	0.66 (0.25-1.79)	2.11 (1.13-3.95)	0.98 (0.73-1.32)
> 0.10	1.09 (0.82-1.45)	1.12 (1.02-1.24)	1.12 (1.02-1.23)	1.18 (0.82-1.69)	1.48 (0.65-3.38)	5.25 (3.21-8.56)	1.67 (1.27-2.18)
Duration of use (days)							
1-120	0.95 (0.82-1.10)	1.02 (0.97-1.07)	1.01 (0.96-1.06)	0.91 (0.74-1.11)	0.91 (0.58-1.45)	1.48 (0.96-2.28)	0.97 (0.82-1.15)
121-240	1.00 (0.76-1.31)	1.07 (0.98-1.18)	1.06 (0.98-1.16)	0.96 (0.67-1.37)	0.87 (0.35-2.15)	1.31 (0.57-3.01)	0.99 (0.72-1.34)
> 240	1.23 (0.88-1.74)	1.15 (1.02-1.30)	1.16 (1.03-1.30)	1.28 (0.83-1.96)	1.17 (0.37-3.67)	4.68 (2.49-8.80)	1.62 (1.16-2.27)

CI = confidence interval; NL PHARMO = PHARMO Database Network (the Netherlands).

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Table 25. Overview of Pooled Adjusted Incidence Rate Differences per 1,000 Person-years in Users of Topical Tacrolimus Compared With Users of Topical Corticosteroids—Adults

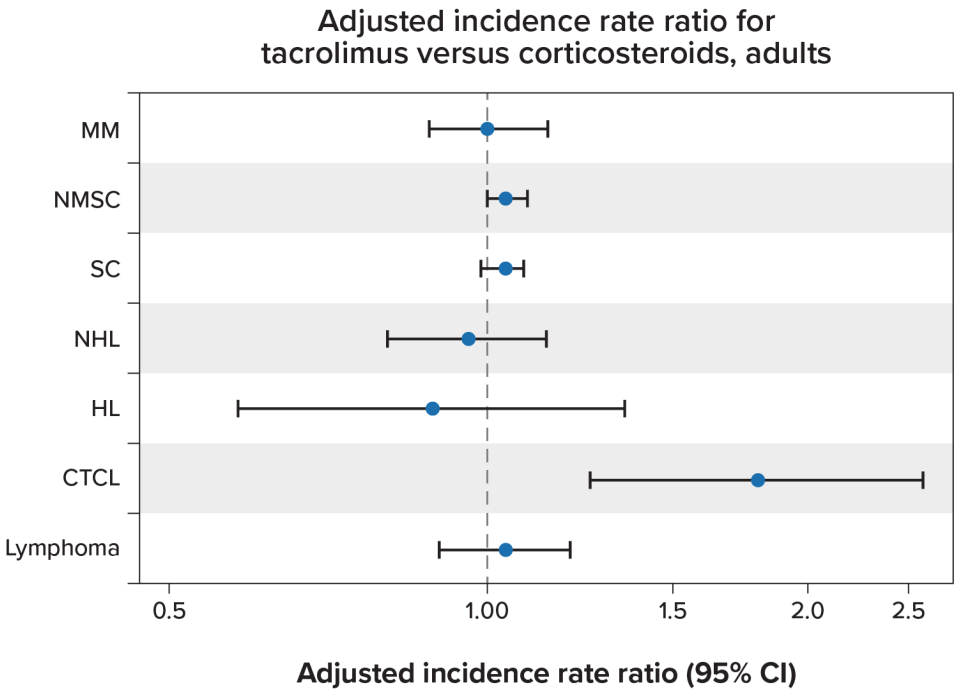
	Adjusted[a] Incidence Rate Difference (95% CI)						
Exposure	**Malignant Melanoma**	**Non-melanoma Skin Cancer**	**Skin Cancer**	**Non-Hodgkin Lymphoma**	**Hodgkin Lymphoma**	**Cutaneus T-cell Lymphoma**	**Lymphoma**
Ever use	-0.01 (−0.07 to 0.06)	0.17 (−0.02 to 0.35)	0.16 (−0.03 to 0.35)	−0.01 (−0.06 to 0.04)	0.00 (−0.02 to 0.02)	0.03 (0.01 to 0.05)	0.02 (−0.04 to 0.07)
Single use	0.00 (−0.06 to 0.07)	0.17 (−0.02 to 0.35)	0.17 (−0.03 to 0.36)	−0.01 (−0.06 to 0.04)	−0.01 (−0.03 to 0.01)	0.03 (0.01 to 0.06)	0.01 (−0.04 to 0.07)
Cumulative dose (grams)[b]							
Ever use							
≤ 0.05	0.00 (−0.08 to 0.07)	0.14 (−0.07 to 0.36)	0.15 (−0.08 to 0.37)	−0.02 (−0.08 to 0.03)	−0.01 (−0.03 to 0.02)	−0.01 (−0.03 to 0.01)	−0.04 (−0.10 to 0.03)
> 0.05 to 0.10	−0.04 (−0.17 to 0.08)	−0.06 (−0.42 to 0.31)	−0.10 (−0.49 to 0.28)	−0.01 (−0.10 to 0.08)	−0.01 (−0.05 to 0.03)	0.04 (−0.01 to 0.10)	0.02 (−0.09 to 0.14)
> 0.10	0.02 (−0.13 to 0.18)	0.52 (0.06 to 0.98)	0.54 (0.05 to 1.03)	0.03 (−0.09 to 0.15)	0.02 (−0.04 to 0.07)	0.18 (0.08 to 0.27)	0.22 (0.06 to 0.39)
Single use							
≤ 0.05	0.01 (−0.07 to 0.08)	0.13 (−0.09 to 0.34)	0.14 (−0.09 to 0.37)	−0.02 (−0.07 to 0.04)	−0.01 (−0.03 to 0.02)	−0.01 (−0.03 to 0.01)	−0.03 (−0.10 to 0.03)
> 0.05 to 0.10	−0.04 (−0.17 to 0.09)	−0.02 (−0.39 to 0.35)	−0.06 (−0.46 to 0.33)	−0.04 (−0.13 to 0.05)	−0.02 (−0.05 to 0.02)	0.05 (−0.01 to 0.10)	−0.01 (−0.12 to 0.10)
> 0.10	0.05 (−0.12 to 0.21)	0.54 (0.06 to 1.02)	0.58 (0.07 to 1.09)	0.06 (−0.08 to 0.19)	0.02 (−0.04 to 0.08)	0.19 (0.09 to 0.29)	0.27 (0.09 to 0.45)
Duration of use (days)							
1 to 120	−0.02 (−0.10 to 0.05)	0.07 (−0.13 to 0.27)	0.05 (−0.17 to 0.26)	−0.03 (−0.08 to 0.03)	−0.01 (−0.03 to 0.02)	0.02 (−0.01 to 0.04)	−0.01 (−0.07 to 0.05)
121 to 240	0.00 (−0.14 to 0.13)	0.29 (−0.11 to 0.68)	0.29 (−0.13 to 0.71)	−0.01 (−0.11 to 0.09)	−0.01 (−0.05 to 0.03)	0.01 (−0.03 to 0.06)	−0.01 (−0.12 to 0.11)
> 240	0.12 (−0.10 to 0.34)	0.64 (0.04 to 1.24)	0.76 (0.13 to 1.40)	0.09 (−0.09 to 0.26)	0.01 (−0.06 to 0.07)	0.16 (0.04 to 0.28)	0.26 (0.04 to 0.48)

CI = confidence interval; NL PHARMO = PHARMO Database Network (the Netherlands).

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Figure 22. Summary of Results for the Comparison of Topical Tacrolimus With Topical Corticosteroids—Adults



CI = confidence interval; CTCL = cutaneous T-cell lymphoma; HL = Hodgkin lymphoma; MM = malignant melanoma; NHL = non-Hodgkin lymphoma; NMSC = non-melanoma skin cancer; SC = skin cancer.

Summary of results: **There was an increased IRR for CTCL and topical tacrolimus compared with topical corticosteroids in adults.**

10.4.3.2 Topical Pimecrolimus Compared With Topical Corticosteroids in Adults

Pooled analysis comparing use of pimecrolimus versus use of corticosteroids for each study outcome in adults aged 18 years or older are presented in Table 26 through Table 32. An overview of IRRs and incidence rate differences for all outcomes is presented in Overview of Pooled Analysis Results for the Comparison of Topical Pimecrolimus With Topical Corticosteroids on page 126.

Malignant Melanoma

A total of 212 events of malignant melanoma were identified in ever users of topical pimecrolimus, and 692 events were identified in users of topical corticosteroids (Table 26). Of the 212 events in ever users, 198 (93.4%) were identified for single use of topical pimecrolimus. The crude incidence rate per 1,000 person-years of malignant melanoma was 0.56 in single users of topical pimecrolimus and 0.46 in users of corticosteroids. The crude

IRR for single use of pimecrolimus was 1.20 (95% CI, 1.02-1.41), and the adjusted IRR was 1.21 (95% CI, 1.03-1.41). Crude and adjusted IRRs were higher in the highest category of cumulative dose. The adjusted IRR for single use with a cumulative dose greater than 1 gram was 1.59 (95% CI, 1.14-2.22).

Table 26. Malignant Melanoma, Including In Situ: Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios, Overall and by Cumulative Dose, in Users of Topical Pimecrolimus Compared With Users of Topical Corticosteroids—Adults

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Topical corticosteroids	692	1,492,352	0.464 (0.430-0.500)	1.00 (reference)	1.00 (reference)
Topical pimecrolimus					
Ever use	212	393,538	0.539 (0.469-0.616)	1.16 (0.99-1.36)	1.17 (1.00-1.36)
Single use	198	355,755	0.557 (0.482-0.640)	1.20 (1.02-1.41)	1.21 (1.03-1.41)
Switching/multiple use	14	37,783	0.371 (0.203-0.622)	0.80 (0.43-1.35)	0.79 (0.47-1.35)
Cumulative dose (grams)[b]					
Ever use					
≤ 0.5	142	281,936	0.504 (0.424-0.594)	1.09 (0.90-1.30)	1.10 (0.92-1.32)
> 0.5 to 1.0	25	52,069	0.480 (0.311-0.709)	1.04 (0.67-1.54)	1.04 (0.70-1.55)
> 1.0	45	59,533	0.756 (0.551-1.011)	1.63 (1.18-2.21)	1.54 (1.12-2.11)
Single use					
≤ 0.5	135	257,848	0.524 (0.439-0.620)	1.13 (0.93-1.36)	1.15 (0.95-1.38)
> 0.5 to 1.0	22	45,763	0.481 (0.301-0.728)	1.04 (0.65-1.58)	1.04 (0.68-1.60)
> 1.0	41	52,144	0.786 (0.564-1.067)	1.70 (1.21-2.32)	1.59 (1.14-2.22)
Switching/multiple use					
≤ 0.5	7	24,087	0.291 (0.117-0.599)	0.63 (0.25-1.30)	0.62 (0.30-1.31)
> 0.5 to 1.0	NR	NR	0.476 (0.098-1.390)	1.03 (0.21-3.01)	1.04 (0.33-3.22)
> 1.0	NR	NR	0.541 (0.147-1.386)	1.17 (0.32-3.00)	1.14 (0.43-3.06)
Duration of use (days)					
1-140	152	285,440	0.533 (0.451-0.624)	1.15 (0.96-1.37)	1.15 (0.97-1.37)
141-280	34	73,263	0.464 (0.321-0.649)	1.00 (0.69-1.41)	1.01 (0.72-1.42)
> 280	26	34,835	0.746 (0.488-1.094)	1.61 (1.04-2.38)	1.62 (1.10-2.40)

CI = confidence interval; NL PHARMO = PHARMO Database Network (the Netherlands); NR = not reportable.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

Non-melanoma Skin Cancer

A total of 1,628 events of NMSC were identified in ever users of topical pimecrolimus, and 4,915 events were identified in users of topical corticosteroids (Table 27). Of the 1,628 events in ever users, 1,492 (91.6%) were identified for single use of topical pimecrolimus. The crude incidence rate per 1,000 person-years of NMSC was 4.19 in single users of topical pimecrolimus and 3.29 in users of corticosteroids. The crude IRR (95% CI) for single use of pimecrolimus was 1.27 (95% CI, 1.20-1.35), and the adjusted IRR was 1.28 (95% CI, 1.20-1.35). Crude and adjusted IRRs were higher in the highest category of cumulative dose. The adjusted IRR for single use with a cumulative dose greater than 1 gram was 1.43 (95% CI, 1.26-1.62).

Table 27. Non-melanoma Skin Cancer, Including in Situ: Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios, Overall and by Cumulative Dose, in Users of Topical Pimecrolimus Compared With Users of Topical Corticosteroids—Adults

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Topical corticosteroids	4,915	1,492,352	3.293 (3.202-3.387)	1.00 (reference)	1.00 (reference)
Topical pimecrolimus					
Ever use	1,628	393,538	4.137 (3.938-4.343)	1.26 (1.19-1.33)	1.26 (1.19-1.33)
Single use	1,492	355,755	4.194 (3.984-4.412)	1.27 (1.20-1.35)	1.28 (1.20-1.35)
Switching/multiple use	136	37,783	3.599 (3.020-4.258)	1.09 (0.91-1.30)	1.07 (0.91-1.27)
Cumulative dose (grams)[b]					
Ever use					
≤ 0.5	1,109	281,936	3.934 (3.705-4.172)	1.19 (1.12-1.28)	1.23 (1.15-1.32)
> 0.5 to 1.0	232	52,069	4.456 (3.901-5.067)	1.35 (1.18-1.54)	1.29 (1.13-1.48)
> 1.0	287	59,533	4.821 (4.279-5.412)	1.46 (1.29-1.65)	1.33 (1.18-1.50)
Single use					
≤ 0.5	1,014	257,848	3.933 (3.694-4.182)	1.19 (1.11-1.28)	1.23 (1.15-1.32)
> 0.5 to 1.0	208	45,763	4.545 (3.948-5.207)	1.38 (1.20-1.59)	1.32 (1.15-1.52)
> 1.0	270	52,144	5.178 (4.579-5.834)	1.57 (1.39-1.78)	1.43 (1.26-1.62)
Switching/multiple use					
≤ 0.5	95	24,087	3.944 (3.191-4.821)	1.20 (0.97-1.47)	1.21 (0.99-1.48)
> 0.5 to 1.0	24	6,306	3.806 (2.438-5.663)	1.16 (0.74-1.72)	1.11 (0.74-1.66)
> 1.0	17	7,389	2.301 (1.340-3.683)	0.70 (0.41-1.12)	0.64 (0.40-1.03)
Duration of use (days)					
1-140	1,141	285,440	3.997 (3.769-4.236)	1.21 (1.14-1.29)	1.23 (1.15-1.31)
141-280	314	73,263	4.286 (3.825-4.787)	1.30 (1.16-1.46)	1.28 (1.14-1.44)
> 280	173	34,835	4.966 (4.254-5.764)	1.51 (1.29-1.76)	1.43 (1.23-1.66)

CI = confidence interval; NL PHARMO = PHARMO Database Network (the Netherlands).

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Skin Cancer

A total of 1,840 events of any skin cancer were identified in ever users of topical pimecrolimus, and 5,607 events were identified in users of topical corticosteroids (Table 28). Of the 1,840 events in ever users, 1,690 (91.8%) were identified for single use of topical pimecrolimus. The crude incidence rate per 1,000 person-years of any skin cancer was 4.75 in single users of topical pimecrolimus and 3.76 in users of corticosteroids. The crude IRR for single use of was 1.26 (95% CI, 1.20-1.34), and the adjusted IRR was 1.27 (95% CI, 1.20-1.34). Crude and adjusted IRRs were higher in the highest category of cumulative dose. The adjusted IRR for single use with a cumulative dose greater than 1 gram was 1.45 (95% CI, 1.29-1.63).

Table 28. Skin Cancer, Including In Situ: Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios, Overall and by Cumulative Dose, in Users of Topical Pimecrolimus Compared With Users of Topical Corticosteroids—Adults

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Topical corticosteroids	5,607	1,492,352	3.757 (3.659-3.857)	1.00 (reference)	1.00 (reference)
Topical pimecrolimus					
Ever use	1,840	393,538	4.676 (4.464-4.894)	1.24 (1.18-1.31)	1.25 (1.18-1.31)
Single use	1,690	355,755	4.750 (4.527-4.982)	1.26 (1.20-1.34)	1.27 (1.20-1.34)
Switching/multiple use	150	37,783	3.970 (3.360-4.659)	1.06 (0.89-1.24)	1.04 (0.88-1.22)
Cumulative dose (grams)[b]					
Ever use					
≤ 0.5	1,251	281,936	4.437 (4.195-4.690)	1.18 (1.11-1.26)	1.22 (1.14-1.29)
> 0.5 to 1.0	257	52,069	4.936 (4.351-5.578)	1.31 (1.15-1.49)	1.26 (1.11-1.43)
> 1.0	332	59,533	5.577 (4.993-6.210)	1.48 (1.32-1.66)	1.35 (1.21-1.52)
Single use					
≤ 0.5	1,149	257,848	4.456 (4.202-4.721)	1.19 (1.11-1.26)	1.22 (1.15-1.30)
> 0.5 to 1.0	230	45,763	5.026 (4.397-5.719)	1.34 (1.17-1.53)	1.29 (1.13-1.47)
> 1.0	311	52,144	5.964 (5.320-6.665)	1.59 (1.41-1.78)	1.45 (1.29-1.63)
Switching/multiple use					
≤ 0.5	102	24,087	4.235 (3.453-5.141)	1.13 (0.92-1.37)	1.14 (0.94-1.38)
> 0.5 to 1.0	27	6,306	4.281 (2.821-6.229)	1.14 (0.75-1.66)	1.10 (0.75-1.61)
> 1.0	21	7,389	2.842 (1.759-4.344)	0.76 (0.47-1.16)	0.70 (0.46-1.07)

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Duration of use (days)					
1-140	1,293	285,440	4.530 (4.286-4.784)	1.21 (1.13-1.28)	1.22 (1.15-1.30)
141-280	348	73,263	4.750 (4.264-5.276)	1.26 (1.13-1.41)	1.25 (1.12-1.39)
> 280	199	34,835	5.713 (4.946-6.564)	1.52 (1.31-1.75)	1.45 (1.26-1.67)

CI = confidence interval; NL PHARMO = PHARMO Database Network (the Netherlands).

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Non-Hodgkin Lymphoma

A total of 94 events of non-Hodgkin lymphoma were identified in ever users of topical pimecrolimus, and 343 events were identified in users of topical corticosteroids (Table 29). Of the 94 events in ever users, 82 (87.2%) were identified for single use of topical pimecrolimus. The incidence rate per 1,000 person-years of non-Hodgkin lymphoma was 0.23 both, in single users of topical pimecrolimus and users of corticosteroids. The crude IRR for single use of pimecrolimus was 1.00 (95% CI, 0.78-1.28), and the adjusted IRR was 1.01 (95% CI, 0.79-1.28). The IRR for medium cumulative doses > 0.5 to 1.0 gram was highest, and the same occurred for medium duration of use.

Table 29. Non-Hodgkin Lymphoma: Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios in Users of Topical Pimecrolimus Compared With Users of Topical Corticosteroids—Adults

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Topical corticosteroids	343	1,492,352	0.230 (0.206-0.255)	1.00 (reference)	1.00 (reference)
Topical pimecrolimus					
Ever use	94	393,538	0.239 (0.193-0.292)	1.04 (0.82-1.31)	1.04 (0.83-1.31)
Single use	82	355,755	0.230 (0.183-0.286)	1.00 (0.78-1.28)	1.01 (0.79-1.28)
Switching/multiple use	12	37,783	0.318 (0.164-0.555)	1.38 (0.71-2.45)	1.34 (0.75-2.39)
Cumulative dose (grams)[b]					
Ever use					
≤ 0.5	59	281,936	0.209 (0.159-0.270)	0.91 (0.68-1.20)	0.92 (0.69-1.21)
> 0.5 to 1.0	18	52,069	0.346 (0.205-0.546)	1.50 (0.88-2.41)	1.39 (0.86-2.23)
> 1.0	17	59,533	0.286 (0.166-0.457)	1.24 (0.72-2.02)	1.28 (0.78-2.11)
Single use					
≤ 0.5	50	257,848	0.194 (0.144-0.256)	0.84 (0.61-1.14)	0.85 (0.63-1.15)
> 0.5 to 1.0	16	45,763	0.350 (0.200-0.568)	1.52 (0.86-2.51)	1.41 (0.85-2.33)
> 1.0	16	52,144	0.307 (0.175-0.498)	1.34 (0.75-2.20)	1.39 (0.83-2.32)
Switching/multiple use					
≤ 0.5	9	24,087	0.374 (0.171-0.709)	1.63 (0.74-3.12)	1.61 (0.83-3.12)
> 0.5 to 1.0	NR	NR	0.317 (0.038-1.146)	1.38 (0.17-5.02)	1.25 (0.31-4.99)
> 1.0	NR	NR	0.135 (0.003-0.754)	0.59 (0.01-3.30)	0.57 (0.08-4.07)
Duration of use (days)					
1-140	65	285,440	0.228 (0.176-0.290)	0.99 (0.75-1.29)	1.02 (0.78-1.33)
141-280	20	73,263	0.273 (0.167-0.422)	1.19 (0.72-1.86)	1.12 (0.71-1.75)
> 280	9	34,835	0.258 (0.118-0.490)	1.12 (0.51-2.16)	0.99 (0.51-1.93)

CI = confidence interval; NL PHARMO = PHARMO Database Network (the Netherlands); NR = not reportable.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Hodgkin Lymphoma

A total of 17 events of Hodgkin lymphoma were identified in ever users of topical pimecrolimus, and 83 events were identified in users of topical corticosteroids (Table 30). Of the 17 events in ever users, 16 (94.1%) occurred with single use of topical pimecrolimus. The incidence rate per 1,000 person-years of Hodgkin lymphoma was 0.05 in single users of topical pimecrolimus and 0.06 in users of corticosteroids. The crude IRR for single use of pimecrolimus was 0.81 (95% CI, 0.44-1.39), and the adjusted IRR was 0.81 (95% CI, 0.47-1.38). No increased rate ratios were observed with increasing cumulative dose or duration of use of pimecrolimus.

Table 30. Hodgkin Lymphoma: Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios in Users of Topical Pimecrolimus Compared With Users of Topical Corticosteroids—Adults

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)[a]
Topical corticosteroids	83	1,492,352	0.056 (0.044-0.069)	1.00 (reference)	1.00 (reference)
Topical pimecrolimus					
Ever use	17	393,538	0.043 (0.025-0.069)	0.78 (0.43-1.32)	0.78 (0.46-1.31)
Single use	16	355,755	0.045 (0.026-0.073)	0.81 (0.44-1.39)	0.81 (0.47-1.38)
Switching/multiple use	NR	NR	0.026 (0.001-0.147)	0.48 (0.01-2.73)	0.47 (0.07-3.35)
Cumulative dose (grams)[b]					
Ever use					
≤ 0.5	9	281,936	0.032 (0.015-0.061)	0.57 (0.25-1.14)	0.58 (0.29-1.15)
> 0.5 to 1.0	NR	NR	0.115 (0.042-0.251)	2.07 (0.74-4.70)	2.13 (0.91-4.96)
> 1.0	NR	NR	0.034 (0.004-0.121)	0.60 (0.07-2.25)	0.63 (0.16-2.44)
Single use					
≤ 0.5	8	257,848	0.031 (0.013-0.061)	0.56 (0.23-1.15)	0.56 (0.27-1.16)
> 0.5 to 1.0	NR	NR	0.131 (0.048-0.285)	2.36 (0.84-5.35)	2.42 (1.04-5.64)
> 1.0	NR	NR	0.038 (0.005-0.139)	0.69 (0.08-2.57)	0.72 (0.18-2.78)
Switching/multiple use					
≤ 0.5	NR	NR	0.042 (0.001-0.231)	0.75 (0.02-4.28)	0.73 (0.10-5.17)
> 0.5 to 1.0	0	6,306	0.000 (0.000-0.585)	0.00 (0.00-10.75)	N/E!
> 1.0	0	7,389	0.000 (0.000-0.499)	0.00 (0.00-9.18)	N/E
Duration of use (days)					
1-140	13	285,440	0.046 (0.024-0.078)	0.82 (0.42-1.48)	0.83 (0.47-1.49)
141-280	NR	NR	0.027 (0.003-0.099)	0.49 (0.06-1.83)	0.48 (0.12-1.95)
> 280	NR	NR	0.057 (0.007-0.207)	1.03 (0.12-3.85)	0.95 (0.24-3.82)

CI = confidence interval; N/E = not estimable; NL PHARMO = PHARMO Database Network (the Netherlands); NR = not reportable.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Cutaneous T-Cell Lymphoma

A total of 9 events of CTCL were identified in single users of topical pimecrolimus, and 43 events were identified in users of topical corticosteroids (Table 31). Of the 9 events in ever users, 6 (66.7%) occurred with single use of topical pimecrolimus. The incidence rate per 1,000 person-years of CTCL was 0.012 in single users of topical pimecrolimus and 0.03 in users of corticosteroids. The crude IRR for single use of pimecrolimus compared with use of corticosteroids was 0.59 (95% CI, 0.20-1.38), and the adjusted IRR was 0.57 (95% CI, 0.25-1.33).

Table 31. Cutaneous T-Cell Lymphoma: Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios in Users of Topical Pimecrolimus Compared With Users of Topical Corticosteroids—Adults

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude IRR (95% CI)	Adjusted IRR (95% CI)[a]
Topical corticosteroids	43	1,492,352	0.029 (0.021-0.039)	1.00 (reference)	1.00 (reference)
Topical pimecrolimus					
Ever use	9	393,538	0.023 (0.010-0.043)	0.79 (0.34-1.65)	0.77 (0.38-1.57)
Single use	6	355,755	0.017 (0.006-0.037)	0.59 (0.20-1.38)	0.57 (0.25-1.33)
Switching/multiple use	NR	NR	0.079 (0.016-0.232)	2.76 (0.55-8.61)	2.49 (0.78-7.98)
Cumulative dose (grams)[b]					
Ever use					
≤ 0.5	NR	NR	0.018 (0.006-0.041)	0.62 (0.19-1.55)	0.61 (0.24-1.54)
> 0.5 to 1.0	0	52,069	0.000 (0.000-0.071)	0.00 (0.00-2.57)	0.00 (0.00-N/E)
> 1.0	NR	NR	0.067 (0.018-0.172)	2.33 (0.61-6.42)	2.44 (0.89-6.67)
Single use					
≤ 0.5	NR	NR	0.012 (0.002-0.034)	0.40 (0.08-1.26)	0.40 (0.12-1.29)
> 0.5 to 1.0	0	45,763	0.000 (0.000-0.081)	0.00 (0.00-2.92)	0.00 (0.00-N/E)
> 1.0	NR	NR	0.058 (0.012-0.168)	2.00 (0.40-6.24)	2.11 (0.66-6.71)
Switching/multiple use					
≤ 0.5	NR	NR	0.083 (0.010-0.300)	2.88 (0.34-11.06)	2.78 (0.68-11.45)
> 0.5 to 1.0	0	6,306	0.000 (0.000-0.585)	0.00 (0.00-21.20)	0.00 (0.00-N/E)
> 1.0	NR	NR	0.135 (0.003-0.754)	4.70 (0.12-27.60)	4.30 (0.60-31.09)
Duration of use (days)					
1-140	6	285,440	0.021 (0.008-0.046)	0.73 (0.25-1.72)	0.74 (0.32-1.71)
141-280	NR	NR	0.014 (0.000-0.076)	0.47 (0.01-2.78)	0.44 (0.06-3.10)
> 280	NR	NR	0.057 (0.007-0.207)	1.99 (0.23-7.65)	1.62 (0.39-6.75)

CI = confidence interval; IRR = incidence rate ratio; N/E = not estimable; NL PHARMO = PHARMO Database Network (the Netherlands); NR = not reportable.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Lymphoma

A total of 120 events of any lymphoma were identified in ever users of topical pimecrolimus, and 469 events were identified in users of topical corticosteroids (Table 32). Of the 120 events in ever users, 104 (86.7%) were identified for single use of topical pimecrolimus. The incidence rate per 1,000 person-years of any type of lymphoma was 0.29 in single users of topical pimecrolimus and 0.31 in users of topical corticosteroids. The crude IRR for single use of pimecrolimus was 0.93 (95% CI, 0.74-1.15) and the adjusted IRR was 0.93 (95% CI, 0.75-1.15).

Results for each type of lymphoma (non-Hodgkin lymphoma, Hodgkin lymphoma, and CTCL) are presented in Overview of Pooled Analysis Results for the Comparison of Topical Pimecrolimus With Topical Corticosteroids on page 126.

Table 32. Lymphoma: Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios in Users of Topical Pimecrolimus Compared With Users of Topical Corticosteroids—Adults

Exposure	Cases (n)	Person-years (n)	Crude Incidence Rate (95% CI) per 1,000 Person-years	Crude IRR (95% CI)	Adjusted IRR (95% CI)[a]
Topical corticosteroids	469	1,492,352	0.314 (0.286-0.344)	1.00 (reference)	1.00 (reference)
Topical pimecrolimus					
Ever use	120	393,538	0.305 (0.253-0.365)	0.97 (0.79-1.19)	0.97 (0.79-1.18)
Single use	104	355,755	0.292 (0.239-0.354)	0.93 (0.74-1.15)	0.93 (0.75-1.15)
Switching/multiple use	16	37,783	0.423 (0.242-0.688)	1.35 (0.76-2.21)	1.30 (0.79-2.14)
Cumulative dose (grams)[b]					
Ever use					
≤ 0.5	73	281,936	0.259 (0.203-0.326)	0.82 (0.63-1.06)	0.83 (0.65-1.06)
> 0.5 to 1.0	24	52,069	0.461 (0.295-0.686)	1.47 (0.93-2.21)	1.36 (0.90-2.05)
> 1.0	23	59,533	0.386 (0.245-0.580)	1.23 (0.77-1.87)	1.27 (0.83-1.94)
Single use					
≤ 0.5	61	257,848	0.237 (0.181-0.304)	0.75 (0.57-0.98)	0.76 (0.58-0.99)
> 0.5 to 1.0	22	45,763	0.481 (0.301-0.728)	1.53 (0.95-2.34)	1.42 (0.93-2.19)
> 1.0	21	52,144	0.403 (0.249-0.616)	1.28 (0.79-1.98)	1.33 (0.86-2.07)
Switching/multiple use					
≤ 0.5	12	24,087	0.498 (0.257-0.870)	1.59 (0.81-2.80)	1.56 (0.88-2.77)
> 0.5 to 1.0	NR	NR	0.317 (0.038-1.146)	1.01 (0.12-3.67)	0.91 (0.23-3.65)
> 1.0	NR	NR	0.271 (0.033-0.978)	0.86 (0.10-3.13)	0.83 (0.21-3.33)
Duration of use (days)					
1-140	84	285,440	0.294 (0.235-0.364)	0.94 (0.73-1.18)	0.96 (0.76-1.21)
141-280	23	73,263	0.314 (0.199-0.471)	1.00 (0.63-1.52)	0.94 (0.62-1.43)
> 280	13	34,835	0.373 (0.199-0.638)	1.19 (0.63-2.05)	1.05 (0.61-1.82)

CI = confidence interval; IRR = incidence rate ratio; NL PHARMO = PHARMO Database Network (the Netherlands); NR = not reportable.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Overview of Pooled Analysis Results for the Comparison of Topical Pimecrolimus With Topical Corticosteroids

An overview of the adjusted IRRs and rate differences for each study malignancy in adults treated with topical pimecrolimus versus adults treated with topical corticosteroids is presented in Table 33, Table 34, and Figure 23.

Pooled adjusted IRRs for single use of topical pimecrolimus compared with use of topical corticosteroids were 1.27 (95% CI, 1.20-1.34) for any skin cancer, 1.21 (95% CI, 1.03-1.41) for malignant melanoma, and 1.28 (95% CI, 1.20-1.35) for NMSC.

The pooled adjusted IRR for single use of topical pimecrolimus compared with use of topical corticosteroids was 0.93 (0.75-1.15) for any lymphoma. By type of lymphoma, IRRs were 1.01 (95% CI, 0.79-1.28) for non-Hodgkin lymphoma, 0.81 (95% CI, 0.47-1.38) for Hodgkin lymphoma, and 0.57 (95% CI, 0.25-1.33) for CTCL. For non-Hodgkin lymphoma, incidence was higher with higher cumulative doses. For CTCL, adjusted IRRs were higher for the highest cumulative dose, although effect estimates were based on < 5 exposed events.

In terms of absolute effects, the excess rate per 1,000 person-years of follow-up, comparing single use of topical pimecrolimus with use of corticosteroids was, 1.00 (95% CI, 0.76 to 1.25) event for any skin cancer, 0.10 (95% CI, 0.01 to 0.18) event for malignant melanoma, and 0.91 (95% CI, 0.68 to 1.14) event for NMSC, −0.02 (95% CI, −0.09 to 0.04) event for any lymphoma, 0.00 (95% CI, −0.05 to 0.06) events for non-Hodgkin lymphoma, −0.01 (95% CI, −0.04 to 0.02) event for Hodgkin lymphoma, and −0.01 (95% CI, −0.03 to 0.00) event for CTCL (Table 34).

Table 33. Overview of Pooled Adjusted Incidence Rate Ratios in Users of Topical Pimecrolimus Compared With Users of Topical Corticosteroids—Adults

	Adjusted[a] Incidence Rate Ratios (95% CI)						
Exposure	**Malignant Melanoma**	**Non-melanoma Skin Cancer**	**Skin Cancer**	**Non-Hodgkin Lymphoma**	**Hodgkin Lymphoma**	**Cutaneus T-cell Lymphoma**	**Lymphoma**
Ever use	1.17 (1.00-1.36)	1.26 (1.19-1.33)	1.25 (1.18-1.31)	1.04 (0.83-1.31)	0.78 (0.46-1.31)	0.77 (0.38-1.57)	0.97 (0.79-1.18)
Single use	1.21 (1.03-1.41)	1.28 (1.20-1.35)	1.27 (1.20-1.34)	1.01 (0.79-1.28)	0.81 (0.47-1.38)	0.57 (0.25-1.33)	0.93 (0.75-1.15)
Cumulative dose (grams)[b]							
Ever use							
≤ 0.5	1.10 (0.92-1.32)	1.23 (1.15-1.32)	1.22 (1.14-1.29)	0.92 (0.69-1.21)	0.58 (0.29-1.15)	0.61 (0.24-1.54)	0.83 (0.65-1.06)
> 0.5 to 1.0	1.04 (0.70-1.55)	1.29 (1.13-1.48)	1.26 (1.11-1.43)	1.39 (0.86-2.23)	2.13 (0.91-4.96)	0.00 (0.00-N/E)	1.36 (0.90-2.05)
> 1.0	1.54 (1.12-2.11)	1.33 (1.18-1.50)	1.35 (1.21-1.52)	1.28 (0.78-2.11)	0.63 (0.16-2.44)	2.44 (0.89-6.67)	1.27 (0.83-1.94)
Single use							
≤ 0.5	1.15 (0.95-1.38)	1.23 (1.15-1.32)	1.22 (1.15-1.30)	0.85 (0.63-1.15)	0.56 (0.27-1.16)	0.40 (0.12-1.29)	0.76 (0.58-0.99)
> 0.5 to 1.0	1.04 (0.68-1.60)	1.32 (1.15-1.52)	1.29 (1.13-1.47)	1.41 (0.85-2.33)	2.42 (1.04-5.64)	0.00 (0.00-N/E)	1.42 (0.93-2.19)
> 1.0	1.59 (1.14-2.22)	1.43 (1.26-1.62)	1.45 (1.29-1.63)	1.39 (0.83-2.32)	0.72 (0.18-2.78)	2.11 (0.66-6.71)	1.33 (0.86-2.07)
Duration of use (days)							
1-140	1.15 (0.97-1.37)	1.23 (1.15-1.31)	1.22 (1.15-1.30)	1.02 (0.78-1.33)	0.83 (0.47-1.49)	0.74 (0.32-1.71)	0.96 (0.76-1.21)
141-280	1.01 (0.72-1.42)	1.28 (1.14-1.44)	1.25 (1.12-1.39)	1.12 (0.71-1.75)	0.48 (0.12-1.95)	0.44 (0.06-3.10)	0.94 (0.62-1.43)
> 280	1.62 (1.10-2.40)	1.43 (1.23-1.66)	1.45 (1.26-1.67)	0.99 (0.51-1.93)	0.95 (0.24-3.82)	1.62 (0.39-6.75)	1.05 (0.61-1.82)

CI = confidence interval; N/E = not estimable; NL PHARMO = PHARMO Database Network (the Netherlands).

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Table 34. Overview of Pooled Adjusted Incidence Rate Differences per 1,000 Person-years in Users of Topical Pimecrolimus Compared With Users of Topical Corticosteroids—Adults

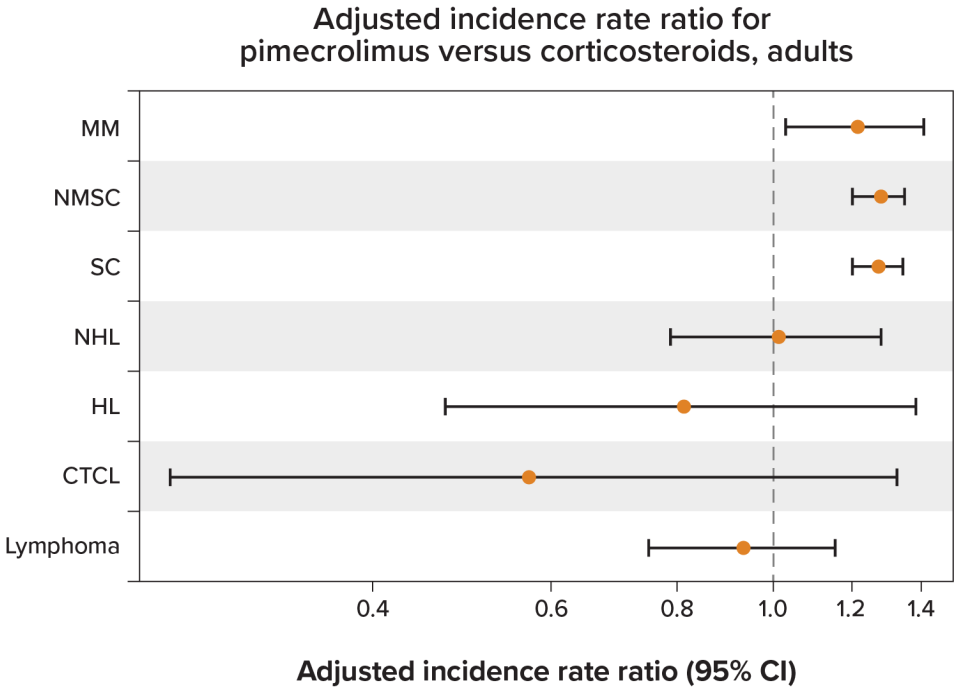
	Adjusted[a] Incidence Rate Difference (95% CI)						
Exposure	**Malignant Melanoma**	**Non−melanoma Skin Cancer**	**Skin Cancer**	**Non-Hodgkin Lymphoma**	**Hodgkin Lymphoma**	**Cutaneus T−cell Lymphoma**	**Lymphoma**
Ever use	0.08 (0.00 to 0.16)	0.85 (0.62 to 1.07)	0.92 (0.69 to 1.16)	0.01 (−0.05 to 0.06)	−0.01 (−0.04 to 0.01)	−0.01 (−0.02 to 0.01)	−0.01 (−0.07 to 0.05)
Single use	0.10 (0.01 to 0.18)	0.91 (0.68 to 1.14)	1.00 (0.76 to 1.25)	0.00 (−0.05 to 0.06)	−0.01 (−0.04 to 0.02)	−0.01 (−0.03 to 0.00)	−0.02 (−0.09 to 0.04)
Cumulative dose (grams)[b]							
Ever use							
≤ 0.5	0.05 (−0.04 to 0.14)	0.74 (0.49 to 0.99)	0.79 (0.52 to 1.06)	−0.02 (−0.08 to 0.04)	−0.02 (−0.05 to 0.00)	−0.01 (−0.03 to 0.01)	−0.05 (−0.12 to 0.01)
> 0.5 to 1.0	0.02 (−0.17 to 0.21)	1.01 (0.43 to 1.59)	1.03 (0.42 to 1.64)	0.10 (−0.07 to 0.26)	0.06 (−0.03 to 0.15)	N/E	0.12 (−0.07 to 0.31)
> 1.0	0.26 (0.04 to 0.49)	1.20 (0.62 to 1.78)	1.46 (0.83 to 2.08)	0.06 (−0.08 to 0.21)	−0.02 (−0.08 to 0.03)	0.04 (−0.03 to 0.11)	0.09 (−0.08 to 0.25)
Single use							
≤ 0.5	0.07 (−0.03 to 0.16)	0.75 (0.49 to 1.01)	0.82 (0.54 to 1.09)	−0.03 (−0.09 to 0.03)	−0.02 (−0.05 to 0.00)	−0.02 (−0.03 to 0.00)	−0.08 (−0.14 to −0.01)
> 0.5 to 1.0	0.02 (−0.19 to 0.23)	1.10 (0.47 to 1.72)	1.12 (0.46 to 1.78)	0.10 (−0.07 to 0.28)	0.08 (−0.03 to 0.18)	N/E	0.14 (−0.06 to 0.35)
> 1.0	0.29 (0.04 to 0.53)	1.55 (0.91 to 2.20)	1.84 (1.16 to 2.53)	0.09 (−0.07 to 0.25)	−0.02 (−0.08 to 0.04)	0.03 (−0.04 to 0.10)	0.10 (−0.08 to 0.29)
Duration of use (days)							
1 to 140	0.07 (−0.02 to 0.16)	0.75 (0.50 to 1.00)	0.82 (0.55 to 1.08)	0.01 (−0.06 to 0.07)	−0.01 (−0.04 to 0.02)	−0.01 (−0.03 to 0.01)	−0.01 (−0.08 to 0.06)
141 to 280	0.00 (−0.16 to 0.17)	0.94 (0.46 to 1.42)	0.94 (0.43 to 1.45)	0.03 (−0.09 to 0.15)	−0.03 (−0.07 to 0.01)	−0.02 (−0.05 to 0.01)	−0.02 (−0.15 to 0.11)
> 280	0.29 (0.00 to 0.58)	1.49 (0.74 to 2.24)	1.78 (0.98 to 2.58)	0.00 (−0.17 to 0.17)	0.00 (−0.09 to 0.08)	0.02 (−0.06 to 0.10)	0.02 (−0.19 to 0.22)

CI = confidence interval; N/E = not estimable; NL PHARMO = PHARMO Database Network (the Netherlands).

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

[b] Grams of active substance.

Figure 23. Summary of Results for the Comparison of Topical Pimecrolimus With Topical Corticosteroids—Adults



CI = confidence interval; CTCL = cutaneous T-cell lymphoma; HL = Hodgkin lymphoma; MM = malignant melanoma; NHL = non-Hodgkin lymphoma; NMSC = non-melanoma skin cancer; SC = skin cancer.

Summary of results: **There was an increase in the IRR of skin cancer including malignant melanoma and NMSC for adult patients exposed to topical pimecrolimus compared with adult patients exposed to topical corticosteroids.**

10.4.4 Topical Corticosteroids Compared With No Treatment—Children and Adults

A summary of the results for individual outcomes for topical corticosteroids compared with patients not treated with any of the study medications is presented in Table 35 for children (pooled across study populations) and Table 36 for adults (by study population). In children, the number of cases is small for estimating the IRR for the individual outcomes for patients exposed to topical corticosteroids compared with untreated patients.

Summary of results: **In children, the number of cases is small for estimating the IRR for the individual outcomes for patients exposed to topical corticosteroids compared with untreated patients.**

Table 35. Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios of Each Study Outcome in Users of Topical Corticosteroids Compared With Untreated Patients—Children

Exposure	Number of Cases	Person-years (n)	Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted[a] Incidence Rate Ratio (95% CI)
Malignant melanoma					
Untreated	14	1,498,595	0.009 (0.005-0.016)	1.00 (reference)	1.00 (reference)
Corticosteroids	NR	NR	0.007 (0.001-0.020)	0.72 (0.13-2.56)	0.77 (0.22-2.68)
Non-melanoma skin cancer					
Untreated	5	1,498,595	0.003 (0.001-0.008)	1.00 (reference)	1.00 (reference)
Corticosteroids	NR	NR	0.007 (0.001-0.020)	2.00 (0.31-10.30)	2.14 (0.50-9.11)
Skin cancer					
Untreated	19	1,498,595	0.013 (0.008-0.020)	1.00 (reference)	1.00 (reference)
Corticosteroids	6	448,780	0.013 (0.005-0.029)	1.05 (0.34-2.75)	1.13 (0.45-2.84)
Non-Hodgkin lymphoma					
Untreated	17	1,498,595	0.011 (0.007-0.018)	1.00 (reference)	1.00 (reference)
Corticosteroids	9	448,780	0.020 (0.009-0.038)	1.77 (0.69-4.19)	1.94 (0.86-4.41)
Hodgkin lymphoma					
Untreated	28	1,498,595	0.019 (0.012-0.027)	1.00 (reference)	1.00 (reference)
Corticosteroids	6	448,780	0.013 (0.005-0.029)	0.72 (0.24-1.76)	0.72 (0.30-1.75)
Cutaneous T-cell lymphoma					
Untreated	5	1,498,595	0.003 (0.001-0.008)	1.00 (reference)	1.00 (reference)
Corticosteroids	NR	NR	0.002 (0.000-0.012)	0.67 (0.01-5.97)	0.72 (0.08-6.48)
Lymphoma					
Untreated	50	1,498,595	0.033 (0.025-0.044)	1.00 (reference)	1.00 (reference)
Corticosteroids	16	448,780	0.036 (0.020-0.058)	1.07 (0.57-1.91)	1.12 (0.63-1.98)

CI = confidence interval; NR = not reportable.

[a] Adjusted by the Mantel-Haenszel method with strata formed by the cross-classification of the following variables: sex, age category, and region.

Incidence rates of each study outcome in untreated adult patients by study database are shown in Table 36. The incidence of each study outcome in untreated patients in Denmark is higher than in the rest of the study databases, leading to adjusted IRRs lower than in the rest of the databases. In adults, except in Denmark for skin malignancies, incidence rates of each study outcome were higher in the corticosteroids cohort than in the untreated cohort, and the IRR for use of topical corticosteroids compared with non-use of any study medication was elevated in all study populations. For lymphoma and its subtypes, the IRR for use of topical corticosteroids compared with non-use of any study medication was elevated in all study populations.

Summary of results: **In adults, for skin malignancies, the IRR for use of topical corticosteroids compared with non-use of any study medication was elevated in all study populations except in Denmark. For lymphoma and its subtypes, the IRR for use of topical corticosteroids compared with non-use of any study medication was elevated in all study populations.**

Table 36. Incidence Rates and Crude and Adjusted Incidence Rate Ratios of Each Study Outcome in Users of Topical Corticosteroids Compared With Untreated Patients, by Study Database—Adults

Exposure	Study Database	Number of Cases (n)	Person-years (n)	Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted[a] Incidence Rate Ratio (95% CI)
Malignant melanoma						
Untreated	NL-PHARMO	568	1,639,850	0.346 (0.318-0.376)	1.00 (reference)	1.00 (reference)
	Denmark	1,820	2,528,405	0.720 (0.687-0.754)	1.00 (reference)	1.00 (reference)
	Sweden	845	1,558,949	0.542 (0.506-0.580)	1.00 (reference)	1.00 (reference)
	UK-CPRD	378	822,692	0.459 (0.414-0.508)	1.00 (reference)	1.00 (reference)
Corticosteroids	NL-PHARMO	177	411,400	0.430 (0.369-0.499)	1.24 (1.04-1.47)	1.25 (1.05-1.47)
	Denmark	378	860,285	0.439 (0.396-0.486)	0.61 (0.54-0.68)	0.61 (0.54-0.68)
	Sweden	452	798,450	0.566 (0.515-0.621)	1.04 (0.93-1.17)	1.04 (0.93-1.17)
	UK-CPRD	112	222,876	0.503 (0.414-0.605)	1.09 (0.88-1.35)	1.09 (0.89-1.35)
Non-melanoma skin cancer						
Untreated	NL-PHARMO	3,943	1,639,850	2.404 (2.330-2.481)	1.00 (reference)	1.00 (reference)
	Denmark	9,658	2,528,405	3.820 (3.744-3.897)	1.00 (reference)	1.00 (reference)
	Sweden	4,468	1,558,949	2.866 (2.783-2.951)	1.00 (reference)	1.00 (reference)
	UK-CPRD	2,295	822,692	2.790 (2.677-2.906)	1.00 (reference)	1.00 (reference)
Corticosteroids	NL-PHARMO	1,552	411,400	3.772 (3.587-3.965)	1.57 (1.48-1.66)	1.57 (1.48-1.67)
	Denmark	2,655	860,285	3.086 (2.970-3.206)	0.81 (0.77-0.84)	0.81 (0.77-0.84)
	Sweden	3,465	798,450	4.340 (4.196-4.487)	1.51 (1.45-1.58)	1.51 (1.45-1.58)
	UK-CPRD	832	222,876	3.733 (3.484-3.996)	1.34 (1.23-1.45)	1.35 (1.25-1.46)
Skin cancer						
Untreated	NL-PHARMO	4,511	1,639,850	2.751 (2.671-2.832)	1.00 (reference)	1.00 (reference)
	Denmark	11,478	2,528,405	4.540 (4.457-4.623)	1.00 (reference)	1.00 (reference)
	Sweden	5,300	1,558,949	3.400 (3.309-3.493)	1.00 (reference)	1.00 (reference)
	UK-CPRD	2,669	822,692	3.244 (3.122-3.370)	1.00 (reference)	1.00 (reference)

Exposure	Study Database	Number of Cases (n)	Person-years (n)	Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted[a] Incidence Rate Ratio (95% CI)
Corticosteroids	NL-PHARMO	1,729	411,400	4.203 (4.007-4.406)	1.53 (1.44-1.62)	1.53 (1.45-1.62)
	Denmark	3,033	860,285	3.526 (3.401-3.653)	0.78 (0.75-0.81)	0.78 (0.75-0.81)
	Sweden	3,911	798,450	4.898 (4.746-5.054)	1.44 (1.38-1.50)	1.44 (1.38-1.50)
	UK-CPRD	942	222,876	4.227 (3.961-4.505)	1.30 (1.21-1.40)	1.31 (1.22-1.41)
Non-Hodgkin lymphoma						
Untreated	NL-PHARMO	251	1,639,850	0.153 (0.135-0.173)	1.00 (reference)	1.00 (reference)
	Denmark	744	2,528,405	0.294 (0.273-0.316)	1.00 (reference)	1.00 (reference)
	Sweden	242	1,558,949	0.155 (0.136-0.176)	1.00 (reference)	1.00 (reference)
	UK-CPRD	216	822,692	0.263 (0.229-0.300)	1.00 (reference)	1.00 (reference)
Corticosteroids	NL-PHARMO	112	411,400	0.272 (0.224-0.328)	1.78 (1.41-2.23)	1.79 (1.43-2.23)
	Denmark	238	860,285	0.277 (0.243-0.314)	0.94 (0.81-1.09)	0.94 (0.82-1.09)
	Sweden	184	798,450	0.230 (0.198-0.266)	1.48 (1.22-1.81)	1.49 (1.23-1.80)
	UK-CPRD	60	222,876	0.269 (0.205-0.347)	1.03 (0.76-1.37)	1.03 (0.78-1.37)
Hodgkin lymphoma						
Untreated	NL-PHARMO	26	1,639,850	0.016 (0.010-0.023)	1.00 (reference)	1.00 (reference)
	Denmark	91	2,528,405	0.036 (0.029-0.044)	1.00 (reference)	1.00 (reference)
	Sweden	29	1,558,949	0.019 (0.012-0.027)	1.00 (reference)	1.00 (reference)
	UK-CPRD	25	822,692	0.030 (0.020-0.045)	1.00 (reference)	1.00 (reference)
Corticosteroids	NL-PHARMO	12	411,400	0.029 (0.015-0.051)	1.84 (0.85-3.78)	1.84 (0.93-3.65)
	Denmark	50	860,285	0.058 (0.043-0.077)	1.61 (1.12-2.30)	1.63 (1.15-2.30)
	Sweden	44	798,450	0.055 (0.040-0.074)	2.96 (1.81-4.91)	2.99 (1.87-4.78)
	UK-CPRD	12	222,876	0.054 (0.028-0.094)	1.77 (0.81-3.66)	1.78 (0.90-3.52)
Cutaneous T-cell lymphoma						
Untreated	NL-PHARMO	[redacted]	[redacted]	0.004 (0.001-0.008)	1.00 (reference)	1.00 (reference)
	Denmark	23	2,528,405	0.009 (0.006-0.014)	1.00 (reference)	1.00 (reference)
	Sweden	11	1,558,949	0.007 (0.004-0.013)	1.00 (reference)	1.00 (reference)
	UK-CPRD	[redacted]	[redacted]	0.005 (0.001-0.012)	1.00 (reference)	1.00 (reference)

[redacted]

Exposure	Study Database	Number of Cases (n)	Person-years (n)	Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted[a] Incidence Rate Ratio (95% CI)
Corticosteroids	NL-PHARMO	13	411,400	0.032 (0.017-0.054)	8.64 (3.06-27.71)	8.61 (3.28-22.60)
	Denmark	26	860,285	0.030 (0.020-0.044)	3.32 (1.82-6.09)	3.39 (1.93-5.93)
	Sweden	30	798,450	0.038 (0.025-0.054)	5.32 (2.59-11.78)	5.37 (2.69-10.69)
	UK-CPRD	16	222,876	0.072 (0.041-0.117)	14.77 (4.76-60.69)	14.79 (4.98-43.96)
Lymphoma						
Untreated	NL-PHARMO	283	1,639,850	0.173 (0.153-0.194)	1.00 (reference)	1.00 (reference)
	Denmark	858	2,528,405	0.339 (0.317-0.363)	1.00 (reference)	1.00 (reference)
	Sweden	282	1,558,949	0.181 (0.160-0.203)	1.00 (reference)	1.00 (reference)
	UK-CPRD	245	822,692	0.298 (0.262-0.338)	1.00 (reference)	1.00 (reference)
Corticosteroids	NL-PHARMO	137	411,400	0.333 (0.280-0.394)	1.93 (1.56-2.37)	1.94 (1.58-2.38)
	Denmark	314	860,285	0.365 (0.326-0.408)	1.08 (0.94-1.23)	1.08 (0.95-1.23)
	Sweden	258	798,450	0.323 (0.285-0.365)	1.79 (1.50-2.12)	1.79 (1.51-2.12)
	UK-CPRD	88	222,876	0.395 (0.317-0.486)	1.33 (1.03-1.70)	1.34 (1.05-1.70)

CI = confidence interval; NL-PHARMO = PHARMO Database Network (the Netherlands); UK CPRD = Clinical Practice Research Datalink (United Kingdom).

[a] Adjusted by the Mantel-Haenszel method with strata formed by the cross-classification of the following variables: sex, age category, and region.

[b] UK-CPRD counts below 5 will need to be redacted if shared outside of the regulatory environment.

10.4.4.1 Pooled Analysis

Results of the pooled analysis of use of topical corticosteroids compared with non-use of any study medication are shown in Table 37 and Figure 24.

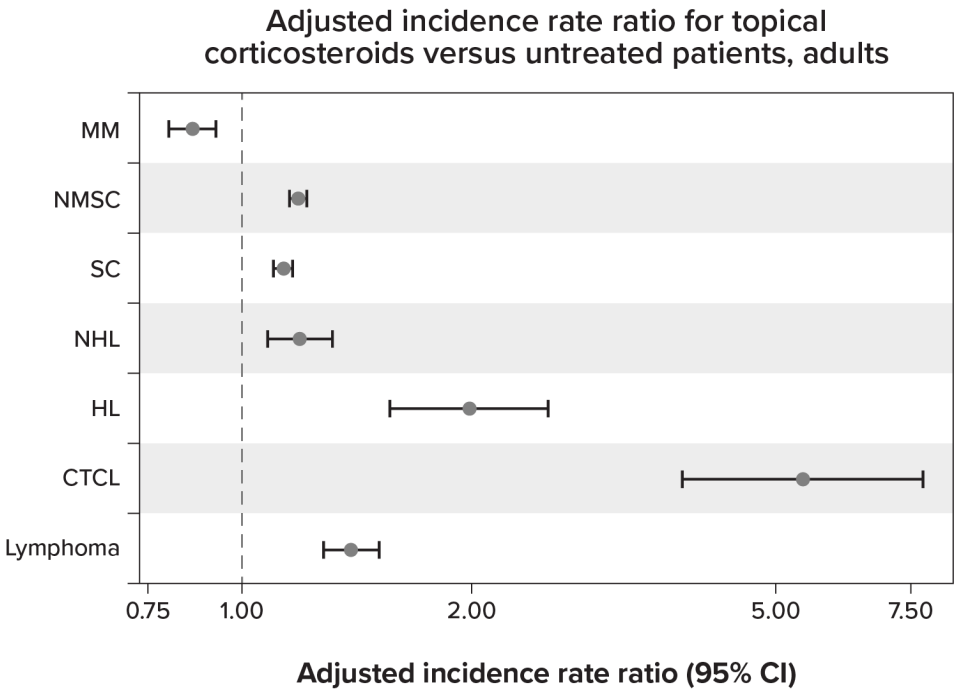
Table 37. Pooled Incidence Rates and Crude and Adjusted Incidence Rate Ratios in Users of Topical Corticosteroids Compared With Untreated Patients—Adults

Exposure	Number of Cases	Person-years (n)	Incidence Rate (95% CI) per 1,000 Person-years	Crude Incidence Rate Ratio (95% CI)	Adjusted[a] Incidence Rate Ratio (95% CI)
Malignant Melanoma					
Untreated	3,611	6,549,895	0.551 (0.533-0.570)	1.00 (reference)	1.00 (reference)
Corticosteroids	1,119	2,293,011	0.488 (0.460-0.517)	0.89 (0.83-0.95)	0.86 (0.80-0.92)
Non-melanoma skin cancer					
Untreated	20,364	6,549,895	3.109 (3.067-3.152)	1.00 (reference)	1.00 (reference)
Corticosteroids	8,504	2,293,011	3.709 (3.630-3.788)	1.19 (1.16-1.22)	1.18 (1.15-1.21)
Skin cancer					
Untreated	23,958	6,549,895	3.658 (3.612-3.704)	1.00 (reference)	1.00 (reference)
Corticosteroids	9,615	2,293,011	4.193 (4.110-4.278)	1.15 (1.12-1.17)	1.13 (1.10-1.16)
Non-Hodgkin lymphoma					
Untreated	1,453	6,549,895	0.222 (0.211-0.234)	1.00 (reference)	1.00 (reference)
Corticosteroids	594	2,293,011	0.259 (0.239-0.281)	1.17 (1.06-1.29)	1.19 (1.08-1.31)
Hodgkin lymphoma					
Untreated	171	6,549,895	0.026 (0.022-0.030)	1.00 (reference)	1.00 (reference)
Corticosteroids	118	2,293,011	0.051 (0.043-0.062)	1.97 (1.55-2.51)	1.98 (1.56-2.52)
Cutaneous T-cell lymphoma					
Untreated	44	6,549,895	0.007 (0.005-0.009)	1.00 (reference)	1.00 (reference)
Corticosteroids	85	2,293,011	0.037 (0.030-0.046)	5.52 (3.79-8.13)	5.42 (3.77-7.79)
Lymphoma					
Untreated	1,668	6,549,895	0.255 (0.243-0.267)	1.00 (reference)	1.00 (reference)
Corticosteroids	797	2,293,011	0.348 (0.324-0.373)	1.36 (1.25-1.49)	1.39 (1.28-1.51)

CI = confidence interval.

[a] Adjusted by the Mantel-Haenszel method with strata formed by the cross-classification of the following variables: sex, age category, and region.

Figure 24. Summary of Results for the Comparison of Users of Topical Corticosteroids With Untreated Patients—Adults



CI = confidence interval; CTCL = cutaneous T-cell lymphoma; HL = Hodgkin lymphoma; MM = malignant melanoma; NHL = non-Hodgkin lymphoma; NMSC = non-melanoma skin cancer; SC = skin cancer.

Except for malignant melanoma, all other outcomes were elevated in the cohort of users of topical corticosteroids compared with non-users of any study medication. The IRR for NMSC was 1.18 (95% CI, 1.15-1.21); for non-Hodgkin lymphoma (excluding CTCL), 1.19 (95% CI, 1.08-1.31); for Hodgkin lymphoma, 1.98 (95% CI, 1.56-2.52); and for CTCL, the adjusted IRR was calculated as 5.42 (95% CI, 3.77-7.79).

Summary of results: **Except for malignant melanoma, all other outcomes appeared elevated in the cohort of users of topical corticosteroids compared with non-users of any study medication. The IRRs were moderately increased except for CTCL, where the calculated IRR was greater than 5.**

10.5 Other Analyses

10.5.1 Exclusion of In Situ Tumours

Analysis of study outcomes with exclusion of in situ tumours for malignant melanoma and NMSC, as requested by the EMA, was performed. Please note that in Denmark, in situ cancers are not recorded the Danish Cancer Registry. Table 38 for tacrolimus and Table 39

for pimecrolimus show the results of the sensitivity analysis excluding in situ tumours and the main analysis including in situ tumours for comparison. Results are equivalent in both analyses, and exclusion of in situ tumours did not modify the effect estimate.

Table 38. Sensitivity Analysis Excluding In Situ Tumours: Pooled Crude Incidence Rates and Adjusted Incidence Rate Ratios in Users of Topical Tacrolimus Compared With Users of Topical Corticosteroids—Adults

Exposure Category by Outcome	Corticosteroids			Topical Tacrolimus (Single Use)			
	Cases (n)	Person-years (n)	Crude IR	Cases (n)	Person-years (n)	Crude IR	Adjusted IRR[a] (95% CI)
Malignant melanoma							
Main analysis	1,107	2,135,506	0.518	306	597,916	0.512	1.00 (0.88-1.14)
Exclusion in situ	875	2,139,099	0.409	236	598,836	0.394	0.98 (0.85-1.13)
Non-melanoma skin cancer							
Main analysis	8,536	2,135,506	3.997	2,437	597,916	4.076	1.04 (1.00-1.09)
Exclusion in situ	7,762	2,139,099	3.629	2,238	598,836	3.737	1.05 (1.00-1.10)

CI = confidence interval; IR = incidence rate; IRR = incidence rate ratio; NL PHARMO = PHARMO Database Network (the Netherlands).

Note: Incidence rates are per 1,000 person-years.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

Table 39. Sensitivity Analysis Excluding In Situ Tumours: Pooled Crude Incidence Rates and Adjusted Incidence Rate Ratios in Users of Topical Pimecrolimus Compared With Users of Topical Corticosteroids—Adults

Exposure Category by Outcome	Corticosteroids			Topical Pimecrolimus (Single Use)			
	Cases (n)	Person-years (n)	Crude IR	Cases (n)	Person-years (n)	Crude IR	Adjusted IRR[a] (95% CI)
Malignant melanoma							
Main analysis	692	1,492,352	0.464	198	355,755	0.557	1.21 (1.03-1.41)
Exclusion in situ	649	1,493,221	0.435	181	355,984	0.508	1.18 (1.00-1.39)
Non-melanoma skin cancer							
Main analysis	4,915	1,492,352	3.293	1,492	355,755	4.194	1.28 (1.20-1.35)
Exclusion in situ	4,751	1,493,221	3.182	1,453	355,984	4.082	1.28 (1.21-1.36)

CI = confidence interval; IR = incidence rate; IRR = incidence rate ratio; NL PHARMO = PHARMO Database Network (the Netherlands).

Note: Incidence rates are per 1,000 person-years.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

10.5.2 Analysis of First Occurrence of Each Type of Malignancy

Results of the sensitivity analysis for the first occurrence of each study outcome during follow-up, ignoring any previous occurrence of a different study outcome, are shown in Table 40 for tacrolimus and Table 41 for pimecrolimus. Results are similar for both medications.

Table 40. Sensitivity Analysis of First Occurrence of Each Type of Malignancy: Pooled Crude Incidence Rates and Adjusted Incidence Rate Ratios in Users of Topical Tacrolimus Compared With Users of Topical Corticosteroids—Adults

	Corticosteroids			Topical Tacrolimus (Single Use)			
Exposure Category by Outcome	**Cases (n)**	**Person-years (n)**	**Crude IR**	**Cases (n)**	**Person-years (n)**	**Crude IR**	**Adjusted IRR[a] (95% CI)**
Malignant melanoma							
Main analysis	1,107	2,135,506	0.518	306	597,916	0.512	1.00 (0.88-1.14)
First occurrence	1,218	2,171,431	0.561	327	607,855	0.538	0.97 (0.86-1.10)
Non-melanoma skin cancer							
Main analysis	8,536	2,135,506	3.997	2,437	597,916	4.076	1.04 (1.00-1.09)
First occurrence	8,685	2,142,009	4.055	2,487	599,621	4.148	1.05 (1.00-1.09)
Cutaneous T-cell lymphoma							
Main analysis	86	2,135,506	0.04	43	597,916	0.072	1.80 (1.25-2.58)
First occurrence	91	2,175,300	0.042	45	608,714	0.074	1.77 (1.24-2.52)

CI = confidence interval; IR = incidence rate; IRR = incidence rate ratio; NL PHARMO = PHARMO Database Network (the Netherlands).

Note: Incidence rates are per 1,000 person-years.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

Table 41. Sensitivity Analysis of First Occurrence of Each Type of Malignancy: Pooled Crude Incidence Rates and Adjusted Incidence Rate Ratios in Users of Topical Pimecrolimus Compared With Users of Topical Corticosteroids—Adults

	Corticosteroids			Topical Pimecrolimus (Single Use)			
Exposure Category by Outcome	Cases (n)	Person-years (n)	Crude IR	Cases (n)	Person-years (n)	Crude IR	Adjusted IRR[a] (95% CI)
Malignant melanoma							
Main analysis	692	1,492,352	0.464	198	355,755	0.557	1.21 (1.03-1.41)
First occurrence	749	1,515,771	0.494	215	362,773	0.593	1.21 (1.04-1.41)
Non-melanoma skin cancer							
Main analysis	4,915	1,492,352	3.293	1,492	355,755	4.194	1.28 (1.20-1.35)
First occurrence	5,001	1,496,918	3.341	1,522	356,977	4.264	1.28 (1.21-1.35)
Cutaneous T-cell lymphoma							
Main analysis	43	1,492,352	0.029	6	355,755	0.017	0.57 (0.25-1.33)
First occurrence	45	1,518,640	0.03	6	363,662	0.016	0.54 (0.23-1.26)

CI = confidence interval; IR = incidence rate; IRR = incidence rate ratio; NL PHARMO = PHARMO Database Network (the Netherlands).

Note: Incidence rates are per 1,000 person-years.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

10.5.3 Induction Time Analysis for Skin Malignancies

The analysis for lag times other than 6 months were performed to evaluate protopathic and surveillance bias: the analyses at zero, 12, 24, and 48 months are presented, together with the main analysis (lag time 6 months) for malignant melanoma, NMSC, and CTCL, in Table 42 for tacrolimus and Table 43 for pimecrolimus.

Results for the various lag times are not very different from the main analysis except for the analysis of tacrolimus and CTCL, where exclusion of the first 4 years after study entry reduced the IRR from 1.80 (95% CI, 1.25-2.58) to 0.77 (95% CI, 0.29-2.04), which could indicate protopathic bias.

Table 42. Sensitivity Analysis by Induction Time, by Each Type of Malignancy: Pooled Crude Incidence Rates and Adjusted Incidence Rate Ratios in Users of Topical Tacrolimus Compared With Users of Topical Corticosteroids—Adults

	Corticosteroids			Topical Tacrolimus (Single Use)			
Exposure Category by Outcome	**Cases (n)**	**Person-years (n)**	**Crude IR**	**Cases (n)**	**Person-years (n)**	**Crude IR**	**Adjusted IRR[a] (95% CI)**
Malignant melanoma							
Main analysis	1,107	2,135,506	0.518	306	597,916	0.512	1.00 (0.88-1.14)
By induction time							
0 months	1,277	2,357,290	0.542	348	658,260	0.529	0.99 (0.88-1.11)
12 months	1,012	1,917,987	0.528	270	538,361	0.502	0.96 (0.84-1.10)
24 months	841	1,519,895	0.553	226	428,451	0.527	0.97 (0.84-1.12)
48 months	528	890,360	0.593	131	252,812	0.518	0.89 (0.73-1.08)
Non-melanoma skin cancer							
Main analysis	8,536	2,135,506	3.997	2,437	597,916	4.076	1.04 (1.00-1.09)
By induction time							
0 months	9,983	2,357,290	4.235	2,813	658,260	4.273	1.03 (0.99-1.08)
12 months	7,678	1,917,987	4.003	2,191	538,361	4.07	1.04 (0.99-1.09)
24 months	6,166	1,519,895	4.057	1,751	428,451	4.087	1.03 (0.97-1.08)
48 months	3,640	890,360	4.088	1,069	252,812	4.228	1.05 (0.98-1.13)
Cutaneous T-cell lymphoma							
Main analysis	86	2,135,506	0.04	43	597,916	0.072	1.80 (1.25-2.58)
By induction time							
0 months	113	2,357,290	0.048	52	658,260	0.079	1.67 (1.20-2.31)
12 months	73	1,917,987	0.038	36	538,361	0.067	1.76 (1.18-2.62)
24 months	52	1,519,895	0.034	24	428,451	0.056	1.60 (0.99-2.59)
48 months	22	890,360	0.025	5	252,812	0.02	0.77 (0.29-2.04)

CI = confidence interval; IR = incidence rate; IRR = incidence rate ratio; NL PHARMO = PHARMO Database Network (the Netherlands).

Note: Incidence rates are per 1,000 person-years.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

Table 43. Sensitivity Analysis by Induction Time, by Each Type of Malignancy: Pooled Adjusted Incidence Rate Ratios in Users of Topical Pimecrolimus Compared With Users of Topical Corticosteroids—Adults

Exposure Category by Outcome	Corticosteroids			Topical Pimecrolimus (Single Use)			
	Cases (n)	Person-years (n)	Crude IR	Cases (n)	Person-years (n)	Crude IR	Adjusted IRR[a] (95% CI)
Malignant melanoma							
Main analysis	692	1,492,352	0.464	198	355,755	0.557	1.21 (1.03-1.41)
By induction time							
0 months	753	1,611,713	0.467	217	382,577	0.567	1.22 (1.05-1.42)
12 months	632	1,373,573	0.46	186	328,920	0.565	1.23 (1.05-1.45)
24 months	527	1,152,920	0.457	174	278,447	0.625	1.37 (1.16-1.63)
48 months	386	781,736	0.494	121	192,533	0.628	1.29 (1.05-1.58)
Non-melanoma skin cancer							
Main analysis	4,915	1,492,352	3.293	1,492	355,755	4.194	1.28 (1.20-1.35)
By induction time							
0 months	5,422	1,611,713	3.364	1,639	382,577	4.284	1.28 (1.21-1.35)
12 months	4,582	1,373,573	3.336	1,402	328,920	4.262	1.28 (1.21-1.36)
24 months	3,884	1,152,920	3.369	1,185	278,447	4.256	1.27 (1.19-1.35)
48 months	2,761	781,736	3.532	824	192,533	4.28	1.22 (1.13-1.32)
Cutaneous T-cell lymphoma							
Main analysis	43	1,492,352	0.029	6	355,755	0.017	0.57 (0.25-1.33)
By induction time							
0 months	56	1,611,713	0.035	7	382,577	0.018	0.51 (0.23-1.12)
12 months	41	1,373,573	0.03	6	328,920	0.018	0.60 (0.26-1.40)
24 months	31	1,152,920	0.027	NR	NR	0.011	0.40 (0.12-1.28)
48 months	18	781,736	0.023	NR	NR	0.016	0.70 (0.21-2.36)

CI = confidence interval; IR = incidence rate; IRR = incidence rate ratio; NL PHARMO = PHARMO Database Network (the Netherlands); NR = not reportable.

Note: Incidence rates are per 1,000 person-years.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

10.5.4 Analysis by Time Since Start of Exposure

The analyses by time since first exposure were performed to further evaluate protopathic and surveillance bias. The time periods since the start of exposure that were analysed were 6 months, > 6 months to 2 years, > 2 to 5 years, and > 5 years.

For tacrolimus, the IRR of CTCL for time since exposure > 5 years is 0.25 (95% CI, 0.03-1.87), suggesting (as in the previous sensitivity analysis) that the risk is confined to the first years after start of the medication. For pimecrolimus, the IRRs were equivalent in the

different time periods analysed, except for malignant melanoma, where the IRRs fluctuated, with no clear trend.

The analysis of the period with > 5 years since the start of exposure gives an idea of the long-term effect of exposure to tacrolimus and pimecrolimus. For > 5 years since exposure to tacrolimus, the IRR was 0.91 (95% CI, 0.73-1.14) for malignant melanoma, 1.00 (95% CI, 0.92-1.08) for NMSC, and 0.25 (95% CI, 0.03-1.87) for CTCL (Table 44). For > 5 years since exposure to pimecrolimus, the IRR was 1.18 (95% CI, 0.94-1.49) for malignant melanoma, 1.25 (95% CI, 1.15-1.36) for NMSC, and 1.33 (95% CI, 0.43-4.07) for CTCL (Table 45).

Table 44. Sensitivity Analysis by Time Since Start of Exposure, by Each Type of Malignancy: Pooled Crude Incidence Rates and Adjusted Incidence Rate Ratios in Users of Topical Tacrolimus Compared With Users of Topical Corticosteroids—Adults

	Corticosteroids			Topical Tacrolimus (Single Use)			
Exposure Category by Outcome	Cases (n)	Person-years (n)	Crude IR	Cases (n)	Person-years (n)	Crude IR	Adjusted IRR[a] (95% CI)
Malignant melanoma							
Main analysis	1,107	2,135,506	0.518	306	597,916	0.512	1.00 (0.88-1.14)
Time since exposure							
< 6 months	170	221,784	0.767	43	62,255	0.691	0.90 (0.64-1.27)
6-24 months	266	615,611	0.432	80	173,972	0.46	1.07 (0.83-1.38)
2-5 years	444	868,517	0.511	128	247,010	0.518	1.03 (0.84-1.25)
≥ 5 years	397	651,378	0.609	101	185,621	0.544	0.91 (0.73-1.14)
Non-melanoma skin cancer							
Main analysis	8,536	2,135,506	3.997	2,437	597,916	4.076	1.04 (1.00-1.09)
Time since exposure							
< 6 months	1,447	221,784	6.524	387	62,255	6.216	0.99 (0.88-1.11)
6-24 months	2,370	615,611	3.85	707	173,972	4.064	1.09 (1.00-1.19)
2-5 years	3,441	868,517	3.962	1,004	247,010	4.065	1.05 (0.98-1.13)
≥ 5 years	2,725	651,378	4.183	763	185,621	4.111	1.00 (0.92-1.08)
Cutaneous T-cell lymphoma							
Main analysis	86	2,135,506	0.04	43	597,916	0.072	1.80 (1.25-2.58)
Time since exposure							
< 6 months	27	221,784	0.122	10	62,255	0.161	1.34 (0.64-2.80)
6-24 months	34	615,611	0.055	19	173,972	0.109	2.07 (1.18-3.61)
2-5 years	38	868,517	0.044	23	247,010	0.093	2.09 (1.25-3.48)
≥ 5 years	14	651,378	0.021	NR	NR	0.005	0.25 (0.03-1.87)

CI = confidence interval; IR = incidence rate; IRR = incidence rate ratio; NR = not reportable; NL PHARMO = PHARMO Database Network (the Netherlands).

Note: Incidence rates are per 1,000 person-years.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

Table 45. Sensitivity Analysis by Time Since Start of Exposure, by Each Type of Malignancy: Pooled Crude Incidence Rates and Adjusted Incidence Rate Ratios in Users of Topical Pimecrolimus Compared With Users of Topical Corticosteroids—Adults

Exposure Category by Outcome	Corticosteroids			Topical Pimecrolimus (Single Use)			
	Cases (n)	Person-years (n)	Crude IR	Cases (n)	Person-years (n)	Crude IR	Adjusted IRR[a] (95% CI)
Malignant melanoma							
Main analysis	692	1,492,352	0.464	198	355,755	0.557	1.21 (1.03-1.41)
Time since exposure							
< 6 months	61	119,361	0.511	21	29,720	0.707	1.38 (0.84-2.25)
6-24 months	165	339,433	0.486	28	83,960	0.333	0.70 (0.47-1.04)
2-5 years	206	524,700	0.393	82	129,170	0.635	1.60 (1.24-2.07)
≥ 5 years	321	628,219	0.511	93	156,508	0.594	1.18 (0.94-1.49)
Non-melanoma skin cancer							
Main analysis	4,915	1,492,352	3.293	1,492	355,755	4.194	1.28 (1.20-1.35)
Time since exposure							
< 6 months	507	119,361	4.248	164	29,720	5.518	1.29 (1.08-1.54)
6-24 months	1,031	339,433	3.037	335	83,960	3.99	1.31 (1.15-1.48)
2-5 years	1,628	524,700	3.103	516	129,170	3.995	1.28 (1.16-1.42)
≥ 5 years	2,256	628,219	3.591	696	156,508	4.447	1.25 (1.15-1.36)
Cutaneous T-cell lymphoma							
Main analysis	43	1,492,352	0.029	6	355,755	0.017	0.57 (0.25-1.33)
Time since exposure							
< 6 months	13	119,361	0.109	NR	NR	0.034	0.28 (0.03-2.33)
6-24 months	12	339,433	0.035	NR	NR	0.036	0.96 (0.28-3.35)
2-5 years	19	524,700	0.036	NR	NR	0.008	0.21 (0.03-1.56)
≥ 5 years	12	628,219	0.019	NR	NR	0.026	1.33 (0.43-4.07)

CI = confidence interval; IR = incidence rate; IRR = incidence rate ratio; NL PHARMO = PHARMO Database Network (the Netherlands); NR = not reportable.

Note: Incidence rates are per 1,000 person-years.

[a] Adjusted by study database, deciles of propensity scores, and sex; and, in Denmark, NL-PHARMO, and Sweden, by type of prescriber (dermatologist, non-dermatologist) of the first prescription.

10.5.5 Analysis by Prescriber Type

Incidence rates and IRRs were estimated according to the type of prescriber of the first prescription (dermatologist or non-dermatologist) as a proxy for severity of atopic dermatitis. Table 46 shows the results for tacrolimus and Table 47 for pimecrolimus.

For topical tacrolimus, no differences were observed for malignant melanoma. However, for NMSC and CTCL the IRR was slightly higher if the prescriber was a non-dermatologist than if the prescriber was a dermatologist.

For topical pimecrolimus, the IRR for malignant melanoma was greater if the prescriber was a dermatologist, IRR 1.41 (95% CI, 1.09-1.82). For NMSC and CTCL, results were similar for both categories of prescribers.

Table 46. Sensitivity Analysis by Type of Prescriber, by Each Type of Malignancy: Pooled Crude Incidence Rates and Adjusted Incidence Rate Ratios in Users of Topical Tacrolimus Compared With Users of Topical Corticosteroids—Adults

	Corticosteroids			Topical Tacrolimus (Single Use)			
Exposure Category by Outcome	**Cases (n)**	**Person-years (n)**	**Crude IR**	**Cases (n)**	**Person-years (n)**	**Crude IR**	**Adjusted IRR[a] (95% CI)**
Malignant melanoma							
Main analysis	1,107	2,135,506	0.518	306	597,916	0.512	1.00 (0.88-1.14)
By prescriber type							
Dermatologist	568	1,014,405	0.56	168	307,616	0.546	1.02 (0.85-1.21)
Non-dermatologist	432	913,928	0.473	118	238,486	0.495	1.04 (0.85-1.28)
Non-melanoma skin cancer							
Main analysis	8,536	2,135,506	3.997	2,437	597,916	4.076	1.04 (1.00-1.09)
By prescriber type							
Dermatologist	4,628	1,014,405	4.562	1,321	307,616	4.294	1.00 (0.94-1.07)
Non-dermatologist	3,074	913,928	3.364	956	238,486	4.009	1.18 (1.10-1.27)
Cutaneous T-cell lymphoma							
Main analysis	86	2,135,506	0.04	43	597,916	0.072	1.80 (1.25-2.58)
By prescriber type							
Dermatologist	52	1,014,405	0.051	21	307,616	0.068	1.36 (0.82-2.25)
Non-dermatologist	18	913,928	0.02	9	238,486	0.038	1.94 (0.87-4.34)

CI = confidence interval; IR = incidence rate; IRR = incidence rate ratio.

Note: Incidence rates are per 1,000 person-years.

[a] Adjusted by study database, deciles of propensity scores, and sex.

Table 47. Sensitivity Analysis by Type of Prescriber, by Each Type of Malignancy: Pooled Crude Incidence Rates and Adjusted Incidence Rate Ratios in Users of Topical Pimecrolimus Compared With Users of Topical Corticosteroids—Adults

	Corticosteroids			Topical Pimecrolimus (Single Use)			
Exposure Category by Outcome	**Cases (n)**	**Person-years (n)**	**Crude IR**	**Cases (n)**	**Person-years (n)**	**Crude IR**	**Adjusted IRR[a] (95% CI)**
Malignant melanoma							
Main analysis	692	1,492,352	0.464	198	355,755	0.557	1.21 (1.03-1.41)
By prescriber type							
Dermatologist	240	484,606	0.495	77	112,560	0.684	1.41 (1.09-1.82)
Non-dermatologist	409	907,130	0.451	112	219,876	0.509	1.12 (0.91-1.39)
Non-melanoma skin cancer							
Main analysis	4,915	1,492,352	3.293	1,492	355,755	4.194	1.28 (1.20-1.35)
By prescriber type							
Dermatologist	1,749	484,606	3.609	516	112,560	4.584	1.31 (1.19-1.45)
Non-dermatologist	2,805	907,130	3.092	888	219,876	4.039	1.28 (1.19-1.38)
Cutaneous T-cell lymphoma							
Main analysis	43	1,492,352	0.029	6	355,755	0.017	0.57 (0.25-1.33)
By prescriber type							
Dermatologist	18	484,606	0.037	NR	NR	0.018	0.44 (0.10-1.88)
Non-dermatologist	21	907,130	0.023	NR	NR	0.014	0.60 (0.18-1.97)

CI = confidence interval; IR = incidence rate; IRR = incidence rate ratio; NR = not reportable.

Note: Incidence rates are per 1,000 person-years.

[a] Adjusted by study database, deciles of propensity scores, and sex.

10.5.6 Analysis by Stage of Malignant Melanoma of Skin

Data on stage of malignant melanoma either was not available or was partially available in the study populations. See Section 9.9.5.1, Deviations From the Statistical Analysis Plan. Data on stage of cancer at diagnosis could have been useful to assess the potential role of a higher medical surveillance in the detection of cases (if lower stages were found, higher medical surveillance was likely to have occurred).

10.5.7 Analysis by Type of NMSC

Although the risk of SCC and BCC are both elevated in association with immunosuppressive therapies in other settings (e.g., organ transplantation), the risk of SCC is increased to a greater degree than the risk of BCC. So, if the risk of NMSC in the present study is related to immunosuppression, one would expect the IRRs to be higher for SCC than for BCC.

Therefore, in this sensitivity analysis, NMSC cases were subclassified further as SCC or BCC, and IRRs were estimated separately for these two types of NMSC.

Incidence rates and IRRs were estimated for BCC and SCC separately and are presented in Table 48 and Table 49, respectively, pooling data from Denmark, NL-PHARMO, and Sweden. The adjusted IRR for tacrolimus was 1.09 (95% CI, 1.03-1.15) for BCC and 1.02 (95% CI, 0.94-1.11) for SCC. For pimecrolimus, the IRR was 1.34 (95% CI, 1.25-1.43) for BCC and 1.11 (95% CI, 0.98-1.27) for SCC.

The overall ratio of BCC to SCC of the skin was 2.1 to 1 for the topical tacrolimus cohort (single use) and the topical corticosteroids matched cohort. The overall BCC to SCC ratio was 3.9 to 1 for the topical pimecrolimus cohort (single use) and 3.2 to 1 for the topical corticosteroids matched cohort.

Table 48. Incidence Rates and Incidence Rate Ratios for Basal Cell Carcinoma, by Study Population: Adults

			Incidence Rate Per 1,000 Person-years						Incidence Rate Ratio					
			Crude			Standardised[a]			Crude			Adjusted[b]		
Exposure Category	Number of Cases	Person-years	IR	L95%	U95%	IR	L95%	U95%	IRR	L95%	U95%	IRR	L95%	U95%
Tacrolimus														
Corticosteroids[c]	5,247	1,928,677	2.721	2.647	2.795	2.603	2.531	2.674	1.00	(reference)		1.00	(reference)	
Single use	1,549	546,139	2.836	2.697	2.981	2.834	2.693	2.975	1.04	0.98	1.10	1.09	1.03	1.15
Pimecrolimus														
Corticosteroids[d]	3,486	1,391,905	2.504	2.422	2.589	2.527	2.443	2.612	1.00	(reference)		1.00	(reference)	
Single use	1,116	332,433	3.357	3.163	3.560	3.359	3.162	3.556	1.34	1.25	1.43	1.34	1.25	1.43

IR = incidence rate; IRR = incidence rate ratio; NL PHARMO = PHARMO Database Network (the Netherlands); UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

Note: Pooled results are from Denmark, NL-PHARMO, and Sweden; UK-CPRD data are not included.

[a] The tacrolimus section of the table is standardised to the tacrolimus person-time by decile and sex; similarly, the pimecrolimus section is standardised to pimecrolimus person-time distribution.

[b] Mantel-Haenszel with strata formed by the cross-classification of the following variables: propensity score decile, sex, and prescriber type.

[c] Comparative cohort of users of moderate- to high-potency topical corticosteroids for topical tacrolimus.

[d] Comparative cohort of users of moderate- to high-potency topical corticosteroids for topical pimecrolimus.

Table 49. Incidence Rates and Incidence Rate Ratios for Squamous Cell Carcinoma, by Study Population: Adults

Exposure Category	Number of Cases	Person-years	Incidence Rate Per 1,000 Person-years						Incidence Rate Ratio					
			Crude			Standardised[a]			Crude			Adjusted[b]		
			IR	L95%	U95%	IR	L95%	U95%	IRR	L95%	U95%	IRR	L95%	U95%
Tacrolimus														
Corticosteroids[c]	2,510	1,928,677	1.301	1.251	1.353	1.305	1.251	1.358	1.00	(reference)		1.00	(reference)	
Single use	733	546,139	1.342	1.247	1.443	1.340	1.243	1.437	1.03	0.95	1.12	1.02	0.94	1.11
Pimecrolimus														
Corticosteroids[d]	1,082	1,391,905	0.777	0.732	0.825	0.775	0.728	0.821	1.00	(reference)		1.00	(reference)	
Single use	285	332,433	0.857	0.761	0.963	0.851	0.752	0.950	1.10	0.96	1.26	1.11	0.98	1.27

IR = incidence rate; IRR = incidence rate ratio; NL PHARMO = PHARMO Database Network (the Netherlands); UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

Note: Pooled results are from Denmark, NL-PHARMO, and Sweden; UK-CPRD data are not included.

[a] The tacrolimus section of the table is standardised to the tacrolimus person-time by decile and sex; similarly, the pimecrolimus section is standardised to pimecrolimus person-time distribution.

[b] Mantel-Haenszel with strata formed by the cross-classification of the following variables: propensity score decile, sex, and prescriber type.

[c] Comparative cohort of users of moderate- to high-potency topical corticosteroids for topical tacrolimus.

[d] Comparative cohort of users of moderate- to high-potency topical corticosteroids for topical pimecrolimus.

10.5.8 Analysis of Lymphoma, *Cutaneous and Non-cutaneous*

Incidence rates and IRRs were estimated for cutaneous and non-cutaneous lymphomas separately with data from NL-PHARMO and Sweden. Data from UK-CPRD and Denmark could not be segregated by the cutaneous or non-cutaneous origin of the lymphoma other than CTCLs. Estimates of the IRRs were greater for cutaneous lymphoma (Table 50) than for non-cutaneous lymphomas (Table 51).

Table 50. Sensitivity Analysis. Cutaneous Lymphoma: Pooled Crude Incidence Rates and Adjusted Incidence Rate Ratios in Users of Topical Tacrolimus and Pimecrolimus Compared With Users of Topical Corticosteroids—Adults

			Incidence Rate Per 1,000 Person-years						Incidence Rate Ratio					
			Crude			Standardised[a]			Crude			Adjusted[b]		
Exposure Category	Number of Cases	Person-years	IR	L95%	U95%	IR	L95%	U95%	IRR	L95%	U95%	IRR	L95%	U95%
Tacrolimus														
Corticosteroids[c]	168	1,136,964	0.148	0.126	0.172	0.141	0.119	0.163	1.00	(reference)		1.00	(reference)	
Single use	50	332,039	0.151	0.112	0.199	0.150	0.109	0.192	1.02	0.73	1.41	1.06	0.78	1.46
Pimecrolimus														
Corticosteroids[d]	30	283,717	0.106	0.071	0.151	0.108	0.069	0.146	1.00	(reference)		1.00	(reference)	
Single use	11	67,034	0.164	0.082	0.294	0.164	0.067	0.261	1.55	0.70	3.19	1.56	0.78	3.09

IR = incidence rate; IRR = incidence rate ratio; L95% = lower boundary of the 95% confidence interval; NL PHARMO = PHARMO Database Network (the Netherlands); U95% = upper boundary of the 95% confidence interval; UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

Note: Incidence rates are per 1,000 person-years. Pooled results are from NL-PHARMO and Sweden; Denmark and UK-CPRD data are not included.

[a] Tacrolimus section of the table is standardised to the tacrolimus person-time by decile and sex; similarly, pimecrolimus section is standardised to pimecrolimus person-time distribution.

[b] Mantel-Haenszel with strata formed by the cross-classification of the following variables: propensity score decile, sex, and prescriber type.

[c] Comparative cohort of users of moderate- to high-potency topical corticosteroids for topical tacrolimus.

[d] Comparative cohort of users of moderate- to high-potency topical corticosteroids for topical pimecrolimus.

Table 51. Sensitivity Analysis. Non-cutaneous Lymphoma: Pooled Crude Incidence Rates and Adjusted Incidence Rate Ratios in Users of Topical Tacrolimus and Pimecrolimus Compared With Users of Topical Corticosteroids—Adults

			Incidence Rate Per 1,000 Person-years						Incidence Rate Ratio					
			Crude			Standardised[a]			Crude			Adjusted[b]		
Exposure Category	Number of Cases	Person-years	IR	L95%	U95%	IR	L95%	U95%	IRR	L95%	U95%	IRR	L95%	U95%
Tacrolimus														
Corticosteroids[c]	226	1,136,964	0.199	0.174	0.226	0.200	0.172	0.227	1.00	(reference)		1.00	(reference)	
Single use	51	332,039	0.154	0.114	0.202	0.155	0.113	0.198	0.77	0.56	1.05	0.77	0.56	1.04
Pimecrolimus														
Corticosteroids[d]	63	283,717	0.222	0.171	0.284	0.220	0.166	0.275	1.00	(reference)		1.00	(reference)	
Single use	13	67,034	0.194	0.103	0.332	0.191	0.087	0.295	0.87	0.44	1.60	0.89	0.49	1.62

IR = incidence rate; IRR = incidence rate ratio; L95% = lower boundary of the 95% confidence interval; NL PHARMO = PHARMO Database Network (the Netherlands); U95% = upper boundary of the 95% confidence interval; UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

Note: Incidence rates are per 1,000 person-years. Pooled results are from NL-PHARMO and Sweden; Denmark and UK-CPRD data are not included.

[a] Tacrolimus section of the table is standardised to the tacrolimus person-time by decile and sex; similarly, pimecrolimus section is standardised to pimecrolimus person-time distribution.

[b] Mantel-Haenszel with strata formed by the cross-classification of the following variables: propensity score decile, sex, and prescriber type.

[c] Comparative cohort of users of moderate- to high-potency topical corticosteroids for topical tacrolimus.

[d] Comparative cohort of users of moderate- to high-potency topical corticosteroids for topical pimecrolimus.

10.5.9 Analyses of Malignant Melanoma, NMSC, and CTCL in Children Aged 2 to Less Than 16 Years

In this age range, no cases of malignant melanoma or NMSC were identified, but a single case of CTCL occurred.

10.5.10 Case Validation of Cutaneous Lymphomas to Minimise Protopathic Bias

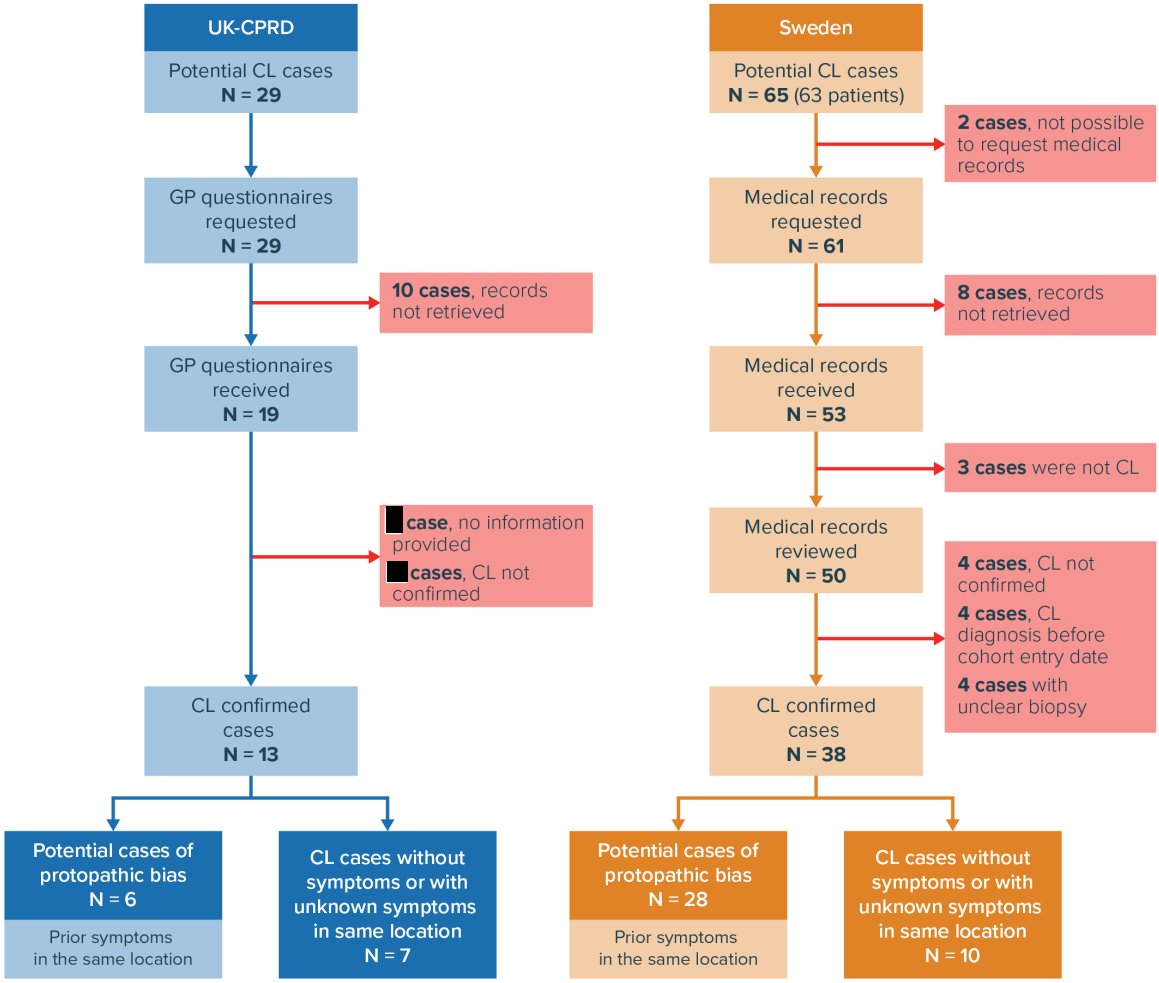
To evaluate the potential for protopathic bias we assessed whether treatment with the study medications may have been initiated for symptoms or signs that were diagnosed as atopic dermatitis (or another benign skin condition) but may also have been compatible with early manifestations of cutaneous lymphoma. We approached this by acquiring further information on the medical history of cutaneous lymphoma cases.

In total, 29 (UK-CPRD) and 70 (Sweden) potential cutaneous lymphoma cases were identified and included in the analysis to minimise protopathic bias.

In UK-CPRD, GP questionnaires were sent for all 29 potential cutaneous lymphoma events identified, and 19 were returned. One did not provide additional information. The diagnosis of cutaneous lymphoma was confirmed in 13 cases. Among these, in [redacted] cases the date of cutaneous lymphoma diagnosis identified by the case screening algorithm was changed by the GP to an earlier date (yet still occurring during patient follow-up). [redacted] cases had a history of signs or symptoms of a previously diagnosed skin condition in the same location as the cutaneous lymphoma and [redacted] did not. For the remaining six cases, the GP did not provide enough information in response to the questionnaire to assess whether there was a possibility of protopathic bias or not (Figure 25).

In Sweden, medical records were sought for 65 potential cutaneous lymphoma events identified in 63 patients. In 2 patients, the information could not be requested (private clinics or no information about the clinic). Among the remaining 61 patients, 53 medical records were retrieved; however, 3 patients were then excluded from the study due to a history of a non-cutaneous lymphoma diagnosis prior to cohort entry. Therefore, in total, 50 medical records were reviewed. The diagnosis of cutaneous lymphoma was confirmed in 38 cases. Among these, 28 cases had a history of signs or symptoms of a previously diagnosed skin condition in the same location as the cutaneous lymphoma. The remaining 10 cases had no previous history of a treated skin condition in the same location as the cutaneous lymphoma or not enough information was available to make a determination (Figure 25).

Figure 25. Validation Results in Sweden and UK-CPRD Databases



CL = cutaneous lymphoma; UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

For the protopathic bias sensitivity analyses of the association of topical tacrolimus or pimecrolimus with cutaneous lymphoma (compared with topical corticosteroids), we restricted the analyses to cases with unknown or no evidence of protopathic bias. In other words, these analyses included cases without documented evidence of symptoms or signs of a previous skin condition in the same location as the subsequently diagnosed cutaneous lymphoma, but cases with such evidence were excluded. These analyses also included cases not received and cases where the information provided was unclear, but excluded cases occurring in the first 6 months of follow-up. The IRRs in these analyses were not closer to the null value than the main analyses. Results are shown in Table 52 (Sweden) and Table 53 (UK-CPRD).

Table 52. Sensitivity Analysis. Cutaneous T-Cell Lymphoma, Crude and Adjusted Incidence Rates and Incidence Rate Ratios, Excluding Cases With Suspicion of Protopathic Bias: Sweden—Adults

	Original Incidence Rate Ratio						Incidence Rate Ratio From Sensitivity Analysis					
				Adjusted[a]						Adjusted[a]		
Exposure Category	Number of Cases	Person-years	IR	IRR	L95%	U95%	Number of Cases[b]	Person-years	IR	IRR	L95%	U95%
Tacrolimus[c]												
Corticosteroids[d]	30	752,796	0.04	1.00	(reference)		11	752,893	0.015	1.00	(reference)	
Single use	14	211,909	0.066	1.66	0.81	3.22	8	211,934	0.038	2.68	1.09	6.60
Pimecrolimus[c]												
Corticosteroids[e]	1	90,046	0.011	1.00	(reference)		0	90,048	0.000	1.00	(reference)	
Single use	0	20,798	0	1.090	0.120	9.820	0	20,798	0.000	N/E	N/E	N/E

IR = incidence rate; IRR = incidence rate ratio; L95% = lower boundary of the 95% confidence interval; U95% = upper boundary of the 95% confidence interval.

Note: Incidence rates are per 1,000 person-years.

[a] Mantel-Haenszel analysis with strata formed by the cross-classification of the following variables: propensity score decile, sex, and prescriber type.

[b] Cases included in the analysis were 10 cases for which relevant medical records could not be requested or were not received and 10 cases that either had no previous history of a treated skin condition or did not provide enough information. One of these cases occurred within the first 6 months after the cohort entry date and was excluded from the sensitivity analyses.

[c] Tacrolimus section of the table is standardised to the tacrolimus person-time by decile and sex; similarly, pimecrolimus section is standardised to pimecrolimus person-time distribution.

[d] Comparative cohort of users of moderate- to high-potency topical corticosteroids for topical tacrolimus.

[e] Comparative cohort of users of moderate- to high-potency topical corticosteroids for topical pimecrolimus.

Table 53. Sensitivity Analysis. Cutaneous T-Cell Lymphoma, Crude and Adjusted Incidence Rates and Incidence Rate Ratios, Excluding Cases With Suspicion of Protopathic Bias: UK-CPRD—Adults

	Original Incidence Rate Ratio						Incidence Rate Ratio From Sensitivity Analysis					
				Adjusted[a]						Adjusted[a]		
Exposure Category	Number of Cases	Person-years	IR	IRR	L95%	U95%	Number of Cases	Person-years	IR	IRR	L95%	U95%
Tacrolimus[b]												
Corticosteroids[c]	16	207,173	0.077	1.00	(reference)		14	207,175	0.068	1.00	(reference)	
Single use	13	51,814	0.251	3.27	1.56	6.83	12	51,821	0.232	3.44	1.58	7.45
Pimecrolimus												
Corticosteroids[d]	[redacted]	[redacted]	0.04	1.00	(reference)		[redacted]	[redacted]	0,020	1.00	(reference)	
Single use	[redacted]	[redacted]	0.043	1.09	0.12	9.82	[redacted]	[redacted]	0.043	2.18	0.20	24.32

IR = incidence rate; IRR = incidence rate ratio; L95% = lower boundary of the 95% confidence interval; U95% = upper boundary of the 95% confidence interval; UK-CPRD = Clinical Practice Research Datalink (United Kingdom).

Note: Incidence rates are per 1,000 person-years.

[a] Mantel-Haenszel with strata formed by the cross-classification of the following variables: propensity score decile and sex.

[b] Tacrolimus section of the table is standardised to the tacrolimus person-time by decile and sex; similarly, pimecrolimus section is standardised to pimecrolimus person-time distribution.

[c] Comparative cohort of users of moderate- to high-potency topical corticosteroids for topical tacrolimus.

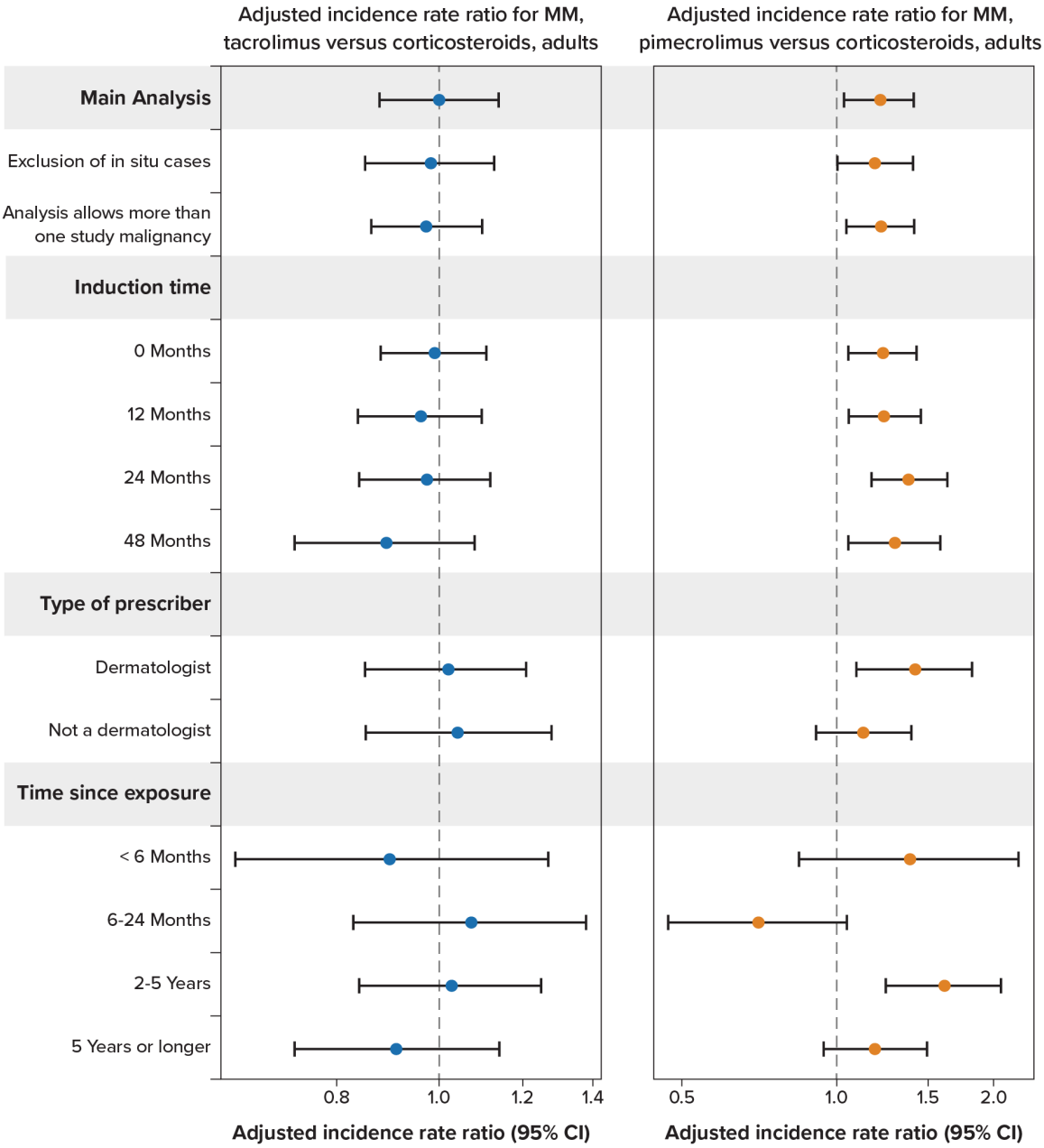
[d] Comparative cohort of users of moderate- to high-potency topical corticosteroids for topical pimecrolimus.

[e] UK-CPRD counts below 5 will need to be redacted if shared outside of the regulatory environment.

10.5.11 Summary of Sensitivity Analysis

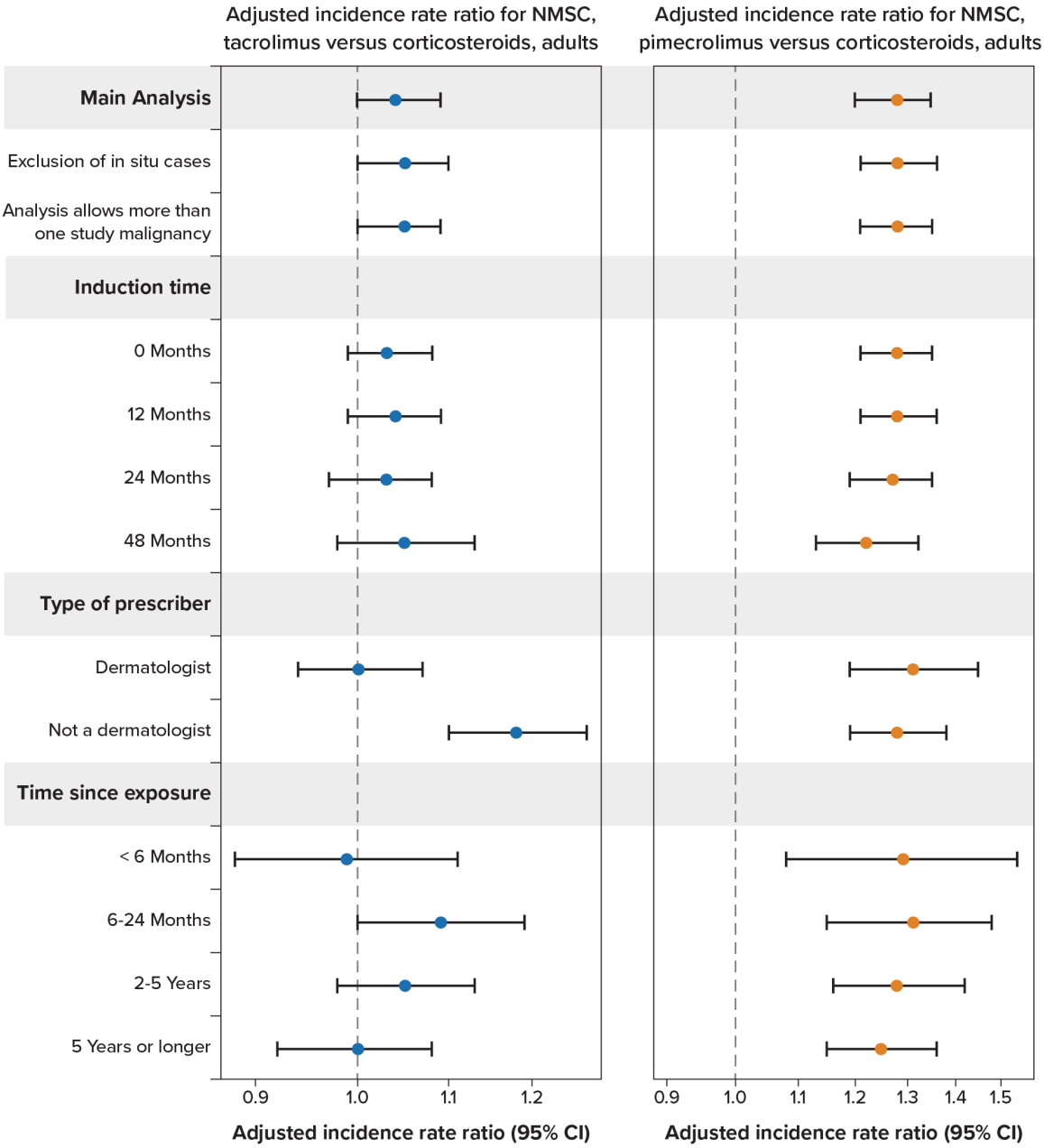
The sensitivity analyses are summarised in Figure 26 through Figure 28.

Figure 26. Adjusted Incidence Rate Ratios, Topical Calcineurin Inhibitors Versus Topical Corticosteroids, Malignant Melanoma



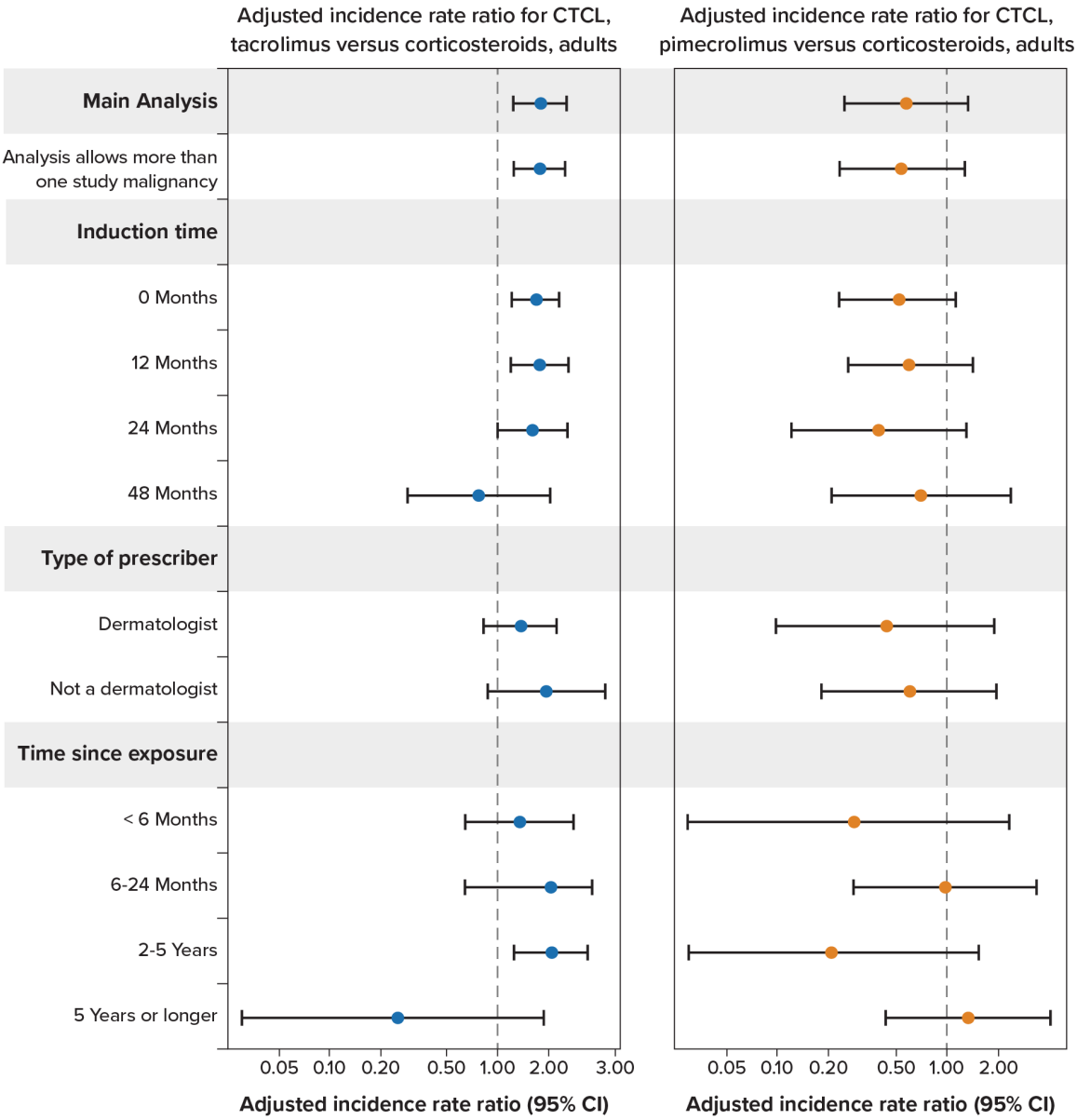
CI = confidence interval; MM = malignant melanoma.

Figure 27. Adjusted Incidence Rate Ratios, Topical Calcineurin Inhibitors Versus Topical Corticosteroids, NMSC



CI = confidence interval; NMSC = non-melanoma skin cancer.

Figure 28. Adjusted Incidence Rate Ratios, Topical Calcineurin Inhibitors Versus Topical Corticosteroids, CTCL



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

10.6 Adverse Events/Adverse Reactions

Given the information in the four data sources available for this study, other than the outcome variables, collection of information about adverse events in relation to the study medications was not possible. Based on current guidelines from ISPE[18] and the EMA,[42] non-interventional studies such as the JOELLE study, conducted using electronic claims and health care records, do not require reporting of suspected adverse events/reactions.

11 Discussion

11.1 Key Results

11.1.1 Participants

The study included 32,605 children (aged < 18 years) and 126,908 adults (aged ≥ 18 years) initiating treatment with topical tacrolimus and 27,961 children and 61,841 adults initiating treatment with topical pimecrolimus. The untreated cohort comprised 361,584 children and 1,291,042 adults matched on age and sex to users of topical corticosteroids included in the comparative cohort for topical tacrolimus.

Denmark and Sweden contributed the largest number and proportion of users of topical tacrolimus: together, they contributed 72.1% of all children and 73.5% of all adults. Denmark contributed the largest number and proportion of users of topical pimecrolimus: 72.8% of children and 69.6% of adults.

Among users of topical tacrolimus, the median follow-up period ranged from 4.0 years in UK-CPRD to 6.8 years in NL-PHARMO in children and from 3.7 years in UK-CPRD to 6.1 years in NL-PHARMO in adults. An estimate of the overall median was 5.7 years in children and 5.0 years in adults.

Among users of topical pimecrolimus, the median follow-up ranged from 5.5 years in the UK-CPRD and Sweden to 9.8 years in Denmark in children and from 4.7 years in UK-CPRD to 7.0 years in Denmark in adults. An estimate of the overall median was 8.9 years in children and 6.5 years in adults. JOELLE study extension phase follow-up was longer than the follow-up in any other study of TCIs and malignancies. Among children, the proportion of users with a duration of follow-up at least 10 years was 45.1% in Denmark, 34.1% in NL-PHARMO, and 25.3% in UK-CPRD. The overall percentage of children with a duration of follow-up of 10 years or longer was estimated to be 31.9%. Among adults, the proportion of users with a duration of follow-up of at least 10 years was 29.6% in Denmark, 26.5% in NL-PHARMO and 18.4% in UK-CPRD. In Sweden, the study period started on 1-Jan-2006,

and the proportion of users with at least 10 years of follow-up was less than 5%. The overall percentage of adults with a duration of follow-up of 10 years or longer was estimated at 19.4%.

Among children treated with topical tacrolimus, the median number of prescriptions was one prescription in Denmark and Sweden and two prescriptions in UK-CPRD and NL-PHARMO. The mean number of grams of active substance was 0.11 grams in UK-CPRD, 0.10 grams in Denmark, 0.09 grams in NL-PHARMO, and 0.05 grams in Sweden. Note that one tube of 30 grams at 0.03% contains 0.09 grams of tacrolimus.

Among adults treated with topical tacrolimus, the median number of prescriptions was one prescription in all the study populations. The mean number of grams of active substance was 0.12 grams in UK-CPRD, 0.10 grams in Demark, 0.11 grams in NL-PHARMO, and 0.07 grams in Sweden.

Because the sites of medical services providing study data vary among the data sources (i.e., hospital discharge and hospital outpatient clinic diagnoses in Denmark and Sweden, hospital discharge diagnoses in NL-PHARMO, and primary care diagnoses in UK-CPRD), the information about atopic dermatitis diagnoses and severity of atopic dermatitis may have differed among the data sources, and this may account for some of the differences observed in the baseline characteristics of the TCI and topical corticosteroids cohorts among the data sources. The difference in the percentage of patients in the different topical tacrolimus and pimecrolimus cohorts **without** a recorded diagnosis of atopic dermatis is noteworthy, around 1% in UK-CPRD, 48%-78% in Sweden, 90%-95% in Denmark, and greater than 99% NL-PHARMO. In UK-CPRD, a main reason for the shorter follow-up observed may be that patients switch between practices. In addition, in UK-CPRD, due to the switch to a new software provider, at least 50% of the practices were lost between 2011-2015, which might also partially account for why there is a relatively shorter duration of follow-up in this population.

11.1.2 Topical Tacrolimus Compared With Topical Corticosteroids

Among children treated with topical tacrolimus, the number of malignant melanoma and NMSC events was very low. For the skin cancer outcome, there appears to be no association between tacrolimus use and skin cancer in children across all study populations. The increased incidence of lymphomas in children with single use of tacrolimus relative to topical corticosteroid use varied by type of lymphoma: the pooled adjusted IRRs were 2.19 (95% CI, 0.81-5.97) for non-Hodgkin lymphoma other than CTCL, 2.37 (95% CI, 0.99-5.68) for Hodgkin lymphoma, and 7.77 (95% CI, 0.50-121.45) for CTCL. The IRR for each type of lymphoma was based on a small number of events and was elevated for low cumulative

doses, but not for medium and high cumulative doses for Hodgkin lymphoma, and not for medium doses for non-Hodgkin lymphoma. Associations with low cumulative dose are sometimes seen in cases of protopathic bias. In Hodgkin lymphoma, the long follow-up in the low cumulative dose category and the lack of outcomes in medium- and high-dose categories could be compatible with a null dose-response effect. For any lymphomas, the incidence was 2.5-fold higher in single users of topical tacrolimus than in users of topical corticosteroids (IRR, 2.49; 95% CI, 1.32-4.70).

In adults, compared with topical corticosteroids, users of topical tacrolimus had a slightly increased risk of NMSC, but the IRRs for non-Hodgkin lymphoma and Hodgkin lymphoma were lower than 1. For adults, in specific subpopulations, the incidence of non-Hodgkin lymphoma, Hodgkin lymphoma, and CTCL was elevated, especially in the tacrolimus cohort in UK-CPRD where the median follow-up was shorter. The adjusted IRR of CTCL for single use of tacrolimus was 1.80 (95% CI, 1.25-2.58). There was a dose-response relationship of increased incidence of CTCL with increasing dose and increasing duration of tacrolimus use. Adjusted IRRs for single use of tacrolimus were 0.81 (95% CI, 0.45-1.47) for a cumulative dose of 0.05 gram or less, 2.11 (95% CI, 1.13-3.95) for a cumulative dose from 0.05 to 0.10 gram, and 5.25 (95% CI, 3.21-8.56) for a cumulative dose greater than 0.10 gram. Note that one tube of 30 grams at 0.03% contains 0.09 grams of tacrolimus, and one tube of 30 grams at 0.1% contains 0.3 grams of tacrolimus.

11.1.3 Topical Pimecrolimus Compared With Topical Corticosteroids

Among children treated with topical pimecrolimus, there were few events of interest. There appears to be no association between pimecrolimus and any of the study outcomes in children across the study populations.

Among adults, the adjusted IRR of malignant melanoma for single use of pimecrolimus was 1.21 (95% CI, 1.03-1.41). The adjusted IRRs were higher in the highest category of cumulative dose, and the adjusted IRR for single use with a cumulative dose greater than 1 gram was 1.59 (95% CI, 1.14-2.22).

In adults, the adjusted IRR of non-melanoma skin cancer for single use of pimecrolimus was 1.27 (95% CI, 1.20-1.35). Crude and adjusted IRRs were higher in the highest category of cumulative dose. The adjusted IRR for single use with a cumulative dose greater than 1 gram was 1.43 (95% CI, 1.26-1.62). In adults, the IRRs for non-Hodgkin lymphoma (excluding CTCL), Hodgkin lymphoma, and CTCL for users of topical pimecrolimus compared with topical corticosteroids were lower than 1.

11.1.4 Topical Corticosteroids Compared With the Untreated Population

In adults, for skin malignancies, the IRR for use of topical corticosteroids compared with non-use of any study medication were elevated in all study populations except in Denmark. For lymphoma and its subtypes, the IRRs for use of topical corticosteroids compared with non-use of any study medication were elevated in all study populations. In the pooled analysis, except for malignant melanoma, all other outcomes were elevated among users of topical corticosteroids compared with non-users of any study medication. The IRRs were moderately increased except for CTCL, where the calculated IRR was greater than 5.

11.1.5 Sensitivity Analysis

Results from sensitivity analyses were generally consistent with those from the main analysis.

When analysing long-term follow-up, for topical tacrolimus, the IRR of CTCL for time since exposure > 5 years was 0.25 (95% CI, 0.03-1.87). In addition, in the analysis by induction time, the IRR of CTCL excluding the first 48 months of follow-up was 0.77 (95% CI, 0.29-2.04), suggesting that the risk is confined to the first 4 years after start of the medication. However, for topical pimecrolimus, the IRRs were similar in the various time periods analysed, except for malignant melanoma, where the IRRs fluctuated with no clear trend.

For the protopathic bias sensitivity analyses of the association of topical tacrolimus or pimecrolimus with cutaneous lymphoma (compared with topical corticosteroids), we restricted the analyses to cases with unknown or no evidence of protopathic bias. In other words, these analyses included cases without documented evidence of symptoms or signs of a previous skin condition in the same location as the subsequently diagnosed cutaneous lymphoma. The IRRs in these analyses were not closer to the null value than the main analyses, as would have been expected if protopathic bias contributed to the observed associations

11.2 Limitations

11.2.1 New Users of Topical Pimecrolimus and Topical Tacrolimus Versus New and Prevalent Users of Topical Corticosteroids

A key limitation of this study is that new users of topical tacrolimus and new users of topical pimecrolimus were each compared with a cohort of users of topical corticosteroids, which included both *new and prevalent* users of topical corticosteroids. The rationale for not limiting the topical corticosteroids users to the new users was that new users of topical corticosteroids would represent patients early in the course of atopic dermatitis and therefore would not capture the therapeutic decision requirements for the tacrolimus and pimecrolimus

label. The inclusion of prevalent users in the corticosteroids cohort in this study introduces several sources of bias, including the underascertainment of study outcome events that may have occurred early in therapy, the inability to control for factors along the causal pathway of the study outcomes that may have been influenced by the use of topical corticosteroids, and exclusion (depletion) of patients from the corticosteroids cohort who may have been inherently more susceptible to the study outcomes.

The new-user design for topical tacrolimus and pimecrolimus (1) allowed evaluation of potential effects of exposure to drugs that incorporated a specific time interval between the start of exposure and the onset of disease; (2) prevented potential survival bias secondary to the inclusion of prevalent users who were "survivors" of earlier periods of treatment; and (3) allowed a more accurate estimation of propensity scores and control of confounding by indication, as covariates were measured at the initiation of therapy and were not affected by the exposure itself.

In addition, because the prescription register in Sweden is available only since July 2005, in this data source, the eligibility criterion of 12 months of continuous enrolment resulted in the exclusion of patients receiving a prescription for topical tacrolimus or topical pimecrolimus between 1-Jul-2005 and 1-Jul-2006. Users of topical tacrolimus or topical pimecrolimus entering the study cohort might have been past users of these medications because topical tacrolimus was approved in 2002 and topical pimecrolimus in 2003.

11.2.2 Confounding by Indication

Topical tacrolimus is approved for the treatment of moderate to severe atopic dermatitis, and topical pimecrolimus is approved for the treatment of mild to moderate atopic dermatitis. Atopic dermatitis and severity of atopic dermatitis have been associated with an increased risk of lymphoma. In a review of published observational studies, the RR for all lymphoma in populations with atopic dermatitis ranged from 0.7 to 1.8,[5] and in a recent meta-analysis, the RR was 1.43 (95% CI, 1.12-1.81) in cohort studies (n = 4) and 1.18 (95% CI, 0.94-1.47) in case-control studies (n = 18).[43] For severity of atopic dermatitis, the RR for all lymphoma in patients with severe atopic dermatitis compared with patients with non-severe atopic dermatitis ranged from 2.0 to 3.7.[5] In studies by Arellano and colleagues, the OR for all lymphoma among patients with severe atopic dermatitis compared with patients with non-severe atopic dermatitis was 2.4 (95% CI, 1.5-3.8) in one study[7] and 3.72 (95% CI, 1.40-9.87) in the other study.[14]

In the topical corticosteroids comparison groups, the indications are likely to be diverse, and the occurrence and severity of atopic dermatitis is likely to be lower than in the TCI cohorts. This means that a higher proportion of patients receiving TCI would have atopic dermatitis,

and more severe atopic dermatitis, than the patients receiving topical corticosteroids. Driven by approved indications, if atopic dermatitis is associated with higher cancer risk, baseline high-risk patients would be present to a greater degree in the topical pimecrolimus cohort, and even greater in the tacrolimus cohort. In the present study, there was a clear variation in the incidence rate of CTCL in the different comparator groups, being lowest for the untreated cohort at 0.7 cases per 100,000 person-years (95% CI, 0.5-0.9), followed by the patients exposed to topical corticosteroids matched to patients exposed to topical pimecrolimus on baseline characteristics, 2.9 cases per 100,000 person-years (95% CI, 2.1-3.9). The highest incidence rate occurred for the patients exposed to topical corticosteroids and matched to patients exposed to topical tacrolimus, 4 cases per 100,000 person-years (95% CI, 3.2-5.0), suggesting that some of these characteristics shared with the tacrolimus cohort and with the pimecrolimus cohort have an effect on the incidence of CTCL.

Inability to adequately control for atopic dermatitis and severity of atopic dermatitis can result in confounding by indication and overestimation of effect estimates for medications indicated for more severe atopic dermatitis. Atopic dermatitis is managed mainly in the primary health care setting by GPs; more severe cases are expected to be managed by dermatologists. In this study, we underestimated the prevalence of atopic dermatitis and severity of atopic dermatitis as diagnosis information was based on hospital discharge and hospital outpatient clinic diagnoses in Denmark and Sweden and on hospital discharge diagnoses in NL-PHARMO. This could artificially increase our effect estimates, particularly for topical tacrolimus, as it is indicated for moderate to severe atopic dermatitis. We attempted to control for severity of atopic dermatitis in Denmark, NL-PHARMO, and Sweden by using information on type of prescriber of the first prescription (dermatologist or non-dermatologist). For topical tacrolimus, no differences were observed for malignant melanoma; for NMSC, the IRR if the prescriber was a dermatologist, 1.00 (95% CI, 0.94-1.07), was lower than if the prescriber was not a dermatologist, IRR, 1.18 (95% CI, 1.10-1.27). For CTCL, the IRR was lower if the prescriber was a dermatologist, IRR, 1.36 (95% CI, 0.82-2.25).

For topical pimecrolimus, for melanoma, the IRR was greater if the first prescriber was a dermatologist, IRR 1.41 (95% CI, 1.09-1.82); for NMSC and CTCL, results were similar for both categories of prescribers.

Nevertheless, type of prescriber is not a direct measure of severity of atopic dermatitis, and the lack of more accurate measures of the severity of atopic dermatitis (e.g., clinical assessment) could result in residual confounding and overestimation of the effect of TCIs, increasing the observed impact of topical tacrolimus.

11.2.3 Protopathic Bias (Reverse Causation)

Cutaneous T-cell lymphoma can manifest as a benign-appearing skin lesion that may progress slowly in several years or decades before it is diagnosed.[44] Signs and symptoms of CTCL can be misdiagnosed and treated as atopic dermatitis or another skin condition for 6 months to more than 10 years before the correct diagnosis is made.[35,36] Cutaneous involvement of other forms of lymphoma (e.g., itching) could also be misdiagnosed and treated as atopic dermatitis. If the signs and symptoms of misdiagnosed CTCL or other lymphomas are the reason for initiating topical treatment, this could result in protopathic bias and an increased observed association between topical treatment and CTCL or other types of lymphoma. This is supported by the findings of a study by Hui and colleagues[8] who in 4 of 16 patients with atopic dermatitis found evidence of suspected CTCL recorded in the medical records before the initiation of treatment with topical tacrolimus or topical pimecrolimus.

We attempted to control for protopathic bias using lag-time analysis and by estimating IRRs by time since the start of exposure. In the main analysis, we used a lag time of 6 months.

Results of lag-time analysis for topical tacrolimus and pimecrolimus in children were inconclusive as the number of events was too small to report the data.

In adults, for the analysis of tacrolimus and CTCL, the exclusion of the first 4 years after study entry reduced the IRR from 1.80 (95% CI, 1.25-2.58) to 0.77 (95% CI, 0.29-2.04), which could indicate protopathic bias. The time periods since the start of exposure analysed were 6 months, > 6 months to 2 years, > 2 to 5 years, and > 5 years.

The results of the analyses by time since the first exposure to tacrolimus, which were performed to further evaluate protopathic bias, suggest (as does the previous sensitivity analysis) that the risk is confined to the first years after start of the medication, either because the induction time is between 6 months and 2-3 years or because that is the period needed to wash out the protopathic bias effect.

To further evaluate the potential for protopathic bias, we assessed whether treatment with the study medications may have been initiated for symptoms or signs that were diagnosed as atopic dermatitis (or another benign skin condition) but may also have been compatible with early manifestations of cutaneous lymphoma. We approached this by acquiring further information on the medical history of cutaneous lymphoma cases in UK-CPRD and Sweden. We then restricted the comparative analyses to cases with unknown or no evidence of protopathic bias. In other words, these analyses were of cases without documented evidence of symptoms or signs of a previous skin condition in the same location as the subsequently diagnosed cutaneous lymphoma; cases with such evidence and those for which the

information was uncertain were excluded. The IRRs in these analyses were not closer to the null value than the main analyses, as would have been expected if protopathic bias contributed to the observed associations.

In summary, the results of different analyses addressing protopathic bias are inconclusive.

11.2.4 Surveillance Bias

Severity of atopic dermatitis is associated with frequent health care monitoring and referrals to dermatologists. On the other hand, while topical tacrolimus and topical pimecrolimus are mainly prescribed for atopic dermatitis, topical corticosteroids may be prescribed for a wide range of skin conditions that may require less frequent monitoring of patients. Imbalance in the intensity of health care monitoring may introduce surveillance bias. Increased monitoring of patients could result in an early detection of lymphomas, particularly those with cutaneous expression, and of early-stage skin tumours. We attempted to control for surveillance bias by including several measures of health care utilisation in the estimation of propensity scores. Information on stage of malignant melanoma either was not available or was “unknown,” therefore, the analysis by stage of malignant melanoma was not performed.

11.2.5 Residual Confounding

Residual confounding cannot be ruled out of our study. Cohorts of topical tacrolimus and of topical pimecrolimus comprised new users. Cohorts of topical corticosteroids were not restricted to new users, and although previous exposure to topical corticosteroids was included in the propensity score models, some residual confounding could remain. Similarly, we could not measure severity of atopic dermatitis, so we used a proxy that may not have eliminated confounding. In the comparison of topical corticosteroids with the untreated population, the methods for control of confounding adjusted for fewer variables than in the comparisons of TCIs with topical corticosteroids. Although untreated patients were individually matched to users of topical corticosteroids on age, sex, geographic region, and year of start date, there were major differences in the baseline characteristics of the two cohorts. In general, compared with untreated patients, users of topical corticosteroids had a higher baseline prevalence of disease such as atopic dermatitis and psoriasis and use of immunosuppressive drugs. A potential association of these risk factors with the incidence of lymphoma and/or with increased health care monitoring could have contributed to the observed association.

11.2.6 Study Size

This is the largest study evaluating the association of TCIs with skin cancer and lymphomas. After trimming, the study included 32,605 children and 126,908 adults initiating treatment

with topical tacrolimus matched, respectively, to 117,592 children and 452,996 adults treated with topical corticosteroids; 27,961 children and 61,841 adults initiating treatment with topical pimecrolimus matched, respectively, to 111,024 children and 244,572 adults treated with topical corticosteroids. Compared with JOELLE Phase I, the final cohort numbers represent increases of 39% and 48% new users of tacrolimus and 15% and 39% new users of pimecrolimus, for children and adults, respectively. The untreated cohort comprised 361,585 children and 1,291,042 adults.

A limitation of the study is related to rare outcomes in targeted populations. The low precision of the estimated measures of effect in children is due to the rarity of the events studied. Although this is the largest observational study on the use of topical tacrolimus and pimecrolimus to date, the study size was not sufficient to estimate precise measures of association for the very rare study endpoints.

11.2.7 Heterogeneity

Heterogeneity of the data available across countries also needs to be considered. Sweden and Denmark provide similar types of data, some of which are also available for NL-PHARMO and UK-CPRD. However, there are important variations, especially in the availability of information on primary care diagnoses and prescriptions dispensed in secondary care and in the coverage of cancer registries across study countries.

Incidence rates of lymphomas in users of topical corticosteroids were similar among the study populations and were lower in Sweden and higher in UK-CPRD than rates among users of tacrolimus in the rest of the populations. The high incidence of lymphoma in the tacrolimus cohort in the UK-CPRD population is noteworthy. The incidence rate ratios of non-Hodgkin lymphoma (except CTCL), Hodgkin lymphoma, and CTCL for users of topical tacrolimus compared with users of topical corticosteroids were elevated in the UK-CPRD, where follow-up was shortest among the study populations. For this JOELLE study extension phase, information on type of prescriber was available in the study populations of Denmark, NL-PHARMO, and Sweden. Adjustment for this variable was not possible in UK-CPRD, and the IRR was unadjusted for the effect of type of prescriber in UK-CPRD. UK-CPRD researchers investigated the possibility of using referrals to dermatology around the time of first prescription as a proxy for first prescriber. Although it was possible to identify referrals in some patient records, UK-CPRD researchers determined that the evidence was not strong enough to stratify data in the analysis. However, since the number of study patients from UK-CPRD was smaller than the number from the other data sources, the effect of not being able to adjust for type of provider in the UK-CPRD data is likely to have had only a limited effect on the overall results.

In this study, the incidence of each study outcome among untreated patients in Denmark was higher than among untreated patients in the rest of the study data sources.

11.2.8 Ratio of BCC to SCC

The results combining data from Denmark, NL-PHARMO, and Sweden for SCC versus BCC are the opposite of what would be expected based on the stronger relationship of SCC with immunosuppression than exists for BCC. The adjusted IRRs for both study medications were higher for BCC than for SCC. The overall ratio of BCC to SCC of the skin was 2.1 to 1 for the tacrolimus cohort (single use) and for the corticosteroids matched cohort. The overall BCC-to-SCC ratio was 3.9 to 1 for the pimecrolimus cohort (single use) and 3.2 to 1 for the corticosteroids matched cohort. These results suggest that systemic immunosuppression may not be a cause, or at least may not be the only cause, of the observed associations between exposure to the study drugs and the risk of NMSC in this study.

11.2.9 Patterns of Use of Topical Tacrolimus and Topical Pimecrolimus

Among children treated with topical tacrolimus, the median number of prescriptions was 1 prescription in Denmark and Sweden and 2 prescriptions in UK-CPRD and NL-PHARMO. Among adults treated with topical tacrolimus, the median number of prescriptions was 1 prescription in all the study populations. The median number of prescriptions for topical pimecrolimus was 1 for both children and adults in all databases, This means that half of the exposed population has received one prescription or dispensing. Furthermore, use is often “as needed”; therefore, we cannot determine whether patients actually used the medication, on which location, and to what extent.

Cumulative dose and duration of use for these treatments are highly correlated, as shown in the results.

11.3 Interpretation

Concern about a potential increase in risk of cancer, particularly for lymphoma and skin cancer, from the use of topical tacrolimus and topical pimecrolimus emerged from the increased risk observed with the systemic use of tacrolimus in organ transplantation in animal studies and in a small number of case reports. Administration of systemic tacrolimus at sustained high concentrations over a period of many years in transplant patients alongside other immunosuppressant drugs has been associated with an increased rate of lymphomas, non-melanoma skin cancer, and melanomas in sun-exposed skin areas.[45,46,47,48] The intensity of immunosuppression (i.e., number and dose of immunosuppressive agents used) and consequent decreased ability of the immune system to control Epstein-Barr virus infection

were found to be relevant factors in the increased risk of lymphomas after transplantation.[49] Although the dosage used in topical administration of TCIs is well below the dosage used in systemic indications, the hypothetical mechanisms through which TCIs could increase the risk of cancer in patients with atopic dermatitis, mediated by the development of local immunosuppression at the application site and/or systemic immunosuppression due to systemic absorption. However, reductions in systemic immune response related to the topical application of calcineurin inhibitors has not been demonstrated.[50] Absorption of TCIs assessed in children and adults with moderate to severe atopic dermatitis has been found to be low; pharmacokinetic studies have shown that the highest blood concentrations (2.39 ng/mL) following topical administration of tacrolimus detected in adults with moderate to severe atopic dermatitis are well below the target concentrations (5 ng/mL to 20 ng/mL) for immunosuppression in transplant patients.[51] In a study conducted in children, the average maximum blood concentration after topical application of tacrolimus was 3% of that found in children receiving oral tacrolimus for liver transplant.[52] Similar findings have been reported for topical pimecrolimus in adults and children.[53]

The dose-response relationship for cumulative dose of topical tacrolimus and the increased incidence of cutaneous T-cell lymphoma found in tacrolimus-exposed adults in this study could be compatible with a causal effect. However, the use of higher cumulative dose can be related to increased severity and/or duration of atopic dermatitis, with the dose-response relationship arising from residual confounding by indication. The IRR for CTCL was higher in UK-CPRD than in the other study populations, perhaps because UK-CPRD was the population where the analysis could not account for confounding by severity of atopic dermatitis. The observed IRR could be explained by confounding by severity or because UK-CPRD was the population with shortest follow-up and the risk for CTCL associated with tacrolimus was circumscribed to the first 4 years after new use of TCIs.

As reflected in their different approved indications (moderate to severe atopic dermatitis for topical tacrolimus; mild to moderate atopic dermatitis for topical pimecrolimus) and formulation strengths, topical tacrolimus has been shown to be a more potent calcineurin inhibitor than topical pimecrolimus.[50] In our study, effect estimates for lymphoma were in general higher for topical tacrolimus than for topical pimecrolimus, and effect estimates for skin cancer were higher for topical pimecrolimus than for topical tacrolimus. However, the IRRs for topical tacrolimus and topical pimecrolimus are not directly comparable because the reference groups are different. In our study, with malignant melanoma as the only exception, incidence rates of outcomes for users of topical corticosteroids were greater than incidence rates for untreated patients. The incidence rate of CTCL in corticosteroid-exposed patients matched to topical tacrolimus patients was greater than that in corticosteroid-exposed patients

matched to topical pimecrolimus patients and that in the untreated cohort, suggesting that some of the characteristics present in the tacrolimus cohort and in the pimecrolimus cohort have an effect on the incidence of CTCL.

The results of our study are in line with prior studies and could be compatible with an effect of topical tacrolimus on the incidence of lymphoma in children and CTCL in adults and with an effect of topical pimecrolimus on skin cancers. However, as in previously published studies, alternative possible explanations remain, including protopathic bias, surveillance bias, and especially confounding by indication. The low incidence of lymphoma and cutaneous T-cell lymphoma found in this study indicate that the public health impact of the excess risk of exposure to topical tacrolimus and topical pimecrolimus, if causal, would be low. This is reflected in the incidence rate difference of CTCL for topical tacrolimus compared with topical corticosteroids in adults in Sweden, calculated as 2.6 per 100,000 person-years, which was reduced to 2.3 per 100,000 person-years in the sensitivity excluding cases susceptible to protopathic bias. However, we cannot ensure that the excluded cases are not related to the exposure. Excluding cases susceptible to protopathic bias reduced the incidence rate of CTCL in Sweden from 6.6 per 100,000 person-years to 3.8 per 100,000 person-years.

Although the cohorts were re-created for this JOELLE study extension phase, a large portion of patients in JOELLE Phase I were also included in the JOELLE study extension phase. Results from the JOELLE study extension phase are thus similar to those from JOELLE Phase I, but add a longer follow-up to the existing knowledge. JOELLE study extension phase follow-up was longer than in any other study of TCIs and malignancies, with more than 20% of the study population followed for more than 10 years. In the sensitivity analyses performed by time since exposure to the study medications, IRRs for periods of 5 years or longer after first exposure to topical tacrolimus or topical pimecrolimus were not increased compared to the main analyses. When analysing the risk of malignancies associated with long-term follow-up, no evidence of increased risk can be seen.

11.3.1 Comparison of Results With Those From Published Studies

Results from our study are in line with those from most published studies.[7,8,9,11] In a cohort study conducted in the US, in patients diagnosed with atopic dermatitis, the risk of T-cell lymphoma (primarily cutaneous T-cell lymphoma) in patients treated with topical tacrolimus was 3 times higher than in untreated patients. A more moderate increase of about 86% has been observed for patients treated with topical pimecrolimus compared with untreated patients.[8] Among the limitations of this study, we need to consider protopathic bias and confounding by indication as the reported hazard ratio was adjusted for age and sex only.

In another cohort study, also conducted in the US, the incidence rate of cutaneous forms of lymphoma was higher in new users of topical tacrolimus (IRR, 2.53; 95% CI, 0.51-12.6), topical pimecrolimus (IRR, 1.49; 95% CI, 0.36-6.24), and topical corticosteroids (IRR, 1.27; 95% CI, 0.37-4.37) than in patients with untreated atopic dermatitis.[9] The incidence rates of any type of lymphoma were also higher in patients treated with these medications than in patients from the general population. In that study, the incidence of any lymphoma in new users of topical pimecrolimus was 16% higher than in new users of moderate- to high-potency corticosteroids and 15% higher than in new users of topical tacrolimus. However, no association was found for the cutaneous forms of lymphoma for these two comparisons.[9]

Data from the Pediatric Eczema Elective Registry in the US, a longitudinal cohort study of children with a history of atopic dermatitis treated at least 6 weeks with topical pimecrolimus, showed a standardised IRR of 2.9 (95% CI, 0.7-11.7) for lymphoma compared with the age-standardised incidence rates from the SEER programme of the US National Cancer Institute.[11]

Arellano et al.[7] published results from a nested case-control study in a cohort of patients with atopic dermatitis in the US PharMetrics database with data through early 2004. The OR was reported to be less than 1.0 but was based on cases not validated through medical chart reviews. Arana et al.[10,12] extended the study in PharMetrics until March 2009. The adjusted OR for overall lymphoma associated with pimecrolimus was 0.76 (95% CI, 0.54-1.08), and for tacrolimus was 1.24 (95% CI, 0.80-1.91). Pimecrolimus was not associated with any specific type of lymphoma, whereas tacrolimus was associated with T-cell lymphoma (OR, 4.95; 95% CI, 1.86-13.19); however, as stated in a 2011 briefing document to the US Food and Drug Administration, “causality is difficult to determine in light of the potential study biases (e.g., misclassification of lymphoma, protopathic bias, and confounding by indication).”[6]

In JOELLE Phase I, with data from 2002 through 2011, the IRR of topical tacrolimus versus topical corticosteroids for lymphoma was 3.74 (95% CI, 1.00-14.06) in children and 1.27 (95% CI, 0.94-1.71) in adults. For specific types of lymphoma, the highest IRRs were 3.17 (95% CI, 0.58-17.23) for Hodgkin lymphoma in children and 1.76 (95% CI, 0.81-3.79) for CTCL in adults. For pimecrolimus versus topical corticosteroids, the highest IRR was 1.31 (95% CI, 0.33-5.14) for CTCL in adults.[16]

11.4 Generalisability

Generalisations from the findings of this study depend on the nature of the finding.[54,55] Findings that relate to drug utilisation and patient characterisation apply to the specific

patient population in each country. Findings related to the risk of events among patients using topical tacrolimus and topical pimecrolimus should be generalisable to patients in countries with similar health care systems and ethnic origin, using these medications, apart from the effect of any as-yet-unidentified biological mediators. For Denmark and Sweden, information on dispensed medications was obtained from national registers covering all Danish and Swedish users of these medications during the study period. Data from the PHARMO Database Network in the Netherlands and the CPRD in the United Kingdom have been shown to be representative of the general populations of these countries.[56,57] The results that relate to outcome validation in the CPRD should be generalisable to database or medical record systems using data collection and data linkage approaches similar to those used in the CPRD.

12 Other Information

None

13 Conclusion

To date, this is the largest study and the one with the longest follow-up evaluating the risk of skin cancer and lymphoma in users of topical tacrolimus and topical pimecrolimus, although half of them received only one prescription/dispensing.

We found an approximately 2-fold increase of the incidence rate of lymphoma in children treated with topical tacrolimus compared with children treated with moderate- to high-potency topical corticosteroids, and a moderate increase in the incidence rate of CTCL in adults treated with topical tacrolimus. In children, the IRR for these types of lymphoma are based on a low number of events and are elevated for low cumulative doses, but not for medium and high cumulative doses. In adults, for topical tacrolimus and CTCL there was a dose-response relationship with increasing dose, and the sensitivity analyses for protopathic bias did not rule out the estimated effect. For skin cancer, we found associations for malignant melanoma and non-melanoma skin cancer in adults treated with topical pimecrolimus.

The excess risk of CTCL (per 100,000 person-years of follow-up) associated with the use of topical tacrolimus versus the use of moderate- to high-potency topical corticosteroids in adults was 3 cases of CTCL (95% CI, 1 to 6). The public health impact associated with such excess risk, if causal, would be low.

The results of this study are in line with prior studies and could be consistent with an increased risk with topical tacrolimus of CTCL in adults or of any lymphoma in children and an increased risk with topical pimecrolimus of skin cancer in adults. However, as in previous studies, the interpretation of these findings is complicated by alternative explanations, mainly confounding by indication, protopathic bias, and surveillance bias, which cannot be ruled out.

In the JOELLE study extension phase, follow-up was longer than in any other study of its kind. The evaluation of a longer latency period for the development of skin cancers and lymphomas in the sensitivity analyses performed by time since exposure to the study medications did not show evidence of malignancies associated with new use of topical tacrolimus or pimecrolimus with long-term follow-up.

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Appendices

Annex 1. List of Stand-Alone Documents

None.

Annex 2. Tables of Results by Study Population

List of Tables

Analysis Table 19b. Distribution of Follow-up Duration, by Final Study Cohorts: Adults

Analysis Table 6. New Users by Formulation

Annex 2 Table 1. Number of New Users Included in the Study Cohorts by Formulation at the Start Date, UK-CPRD

Formulation At Start Date[a]	New Users At The Start Date			
	Children < 18 years		Adults ≥ 18 years	
	n	%	n	%
Tacrolimus	3,895	100.0	12,705	100.0
Strength				
0.03%	1,532	39.3	9,366	73.7
0.10%	2,363	60.7	3,339	26.3
Quantity				
10 grams	0	0.0	0	0.0
30 grams	2,541	65.2	8,753	68.9
60 grams	1,332	34.2	3,870	30.5
Other	0	0.0	0	0.0
Unknown	22	0.6	82	0.6
Pimecrolimus	2,752	100.0	5,124	100.0
Quantity/Strength				
5 grams - 1%	0	0.0	0	0.0
15 grams - 1%	[redacted]	[redacted]	[redacted]	[redacted]
30 grams - 1%	2,025	73.6	3,912	76.3
60 grams - 1%	458	16.6	793	15.5
100 grams - 1%	233	8.5	379	7.4
Other - 1%	0	0.0	0	0.0
Unknown - 1%	35	1.3	37	0.7

[a] Users who receive two strengths or quantities on the start date are reported according to the maximum strength/quantity of the two.

[b] UK-CPRD counts below 5 will need to be redacted if shared outside of the regulatory environment.

Annex 2 Table 2. Number of New Users Included in the Study Cohorts by Formulation at the Start Date, Denmark

Formulation At Start Date[a]	New Users At The Start Date			
	Children < 18 years		Adults ≥ 18 years	
	n	%	n	%
Tacrolimus	11,417	100.0	40,710	100.0
Strength				
0.03%	5,047	44.2	6,091	15.0
0.10%	6,370	55.8	34,619	85.0
Quantity				
10 grams	4,007	35.1	18,195	44.7
30 grams	6,907	60.5	20,599	50.6
60 grams	503	4.4	1,916	4.7
Other	0	0.0	0	0.0
Pimecrolimus	20,343	100.0	43,042	100.0
Quantity/Strength				
5 grams - 1%	0	0.0	0	0.0
15 grams - 1%	11,110	54.6	24,740	57.5
30 grams - 1%	8,855	43.5	17,888	41.6
60 grams - 1%	299	1.5	344	0.8
100 grams - 1%	79	0.4	70	0.2
Other - 1%	0	0.0	0	0.0

[a] Users who receive two strengths or quantities on the start date are reported according to the maximum strength/quantity of the two.

Annex 2 Table 3. Number of New Users Included in the Study Cohorts by Formulation at the Start Date, NL-PHARMO

Formulation at Start Date[a]	New Users At The Start Date			
	Children < 18 years		Adults ≥ 18 years	
	n	%	n	%
Tacrolimus	5,197	100	21,037	100
Strength				
0.03%	3,443	66	4,109	20
0.10%	1,754	34	16,928	80
Quantity				
10 grams	0	0	0	0
30 grams	4,271	82	17,055	81
60 grams	819	16	3,559	17
Other	107	2	423	2
Pimecrolimus	3,189	100	8,506	100
Quantity/Strength				
5 grams - 1%	0	0	0	0
15 grams - 1%	0	0	0	0
30 grams - 1%	2,939	92	7,973	94
60 grams - 1%	215	7	454	5
100 grams - 1%	0	0	0	0
Other - 1%	35	1	79	1

[a] Users who receive two strengths or quantities on the start date are reported according to the maximum strength/quantity of the two.

Annex 2 Table 4. Number of New Users Included in the Study Cohorts by Formulation at the Start Date, Sweden

Formulation At Start Date[a]	New Users At The Start Date			
	Children < 18 years		Adults ≥ 18 years	
	n	%	n	%
Tacrolimus	12,096	100.0	52,456	100.0
Strength				
0.03%	7,460	61.7	6,075	11.6
0.10%	4,636	38.3	46,381	88.4
Quantity				
10 grams	2,844	23.5	14,171	27.0
30 grams	7,758	64.1	30,017	57.2
60 grams	1,494	12.4	8,264	15.8
Other	0	0.0	4	0.0
Pimecrolimus	1,677	100.0	5,169	100.0
Quantity/Strength				
5 grams - 1%	0	0.0	0	0.0
15 grams - 1%	764	45.6	2,392	46.3
30 grams - 1%	704	42.0	2,221	43.0
60 grams - 1%	209	12.5	555	10.7
100 grams - 1%	0	0.0	1	0.0
Other - 1%	0	0.0	0	0.0

[a] Users who receive two strengths or quantities on the start date are reported according to the maximum strength/quantity of the two.

Analysis Table 11a. Drug Utilization Patterns During Follow up, Children

Annex 2 Table 5. Utilization Patterns of Users of Topical Tacrolimus, Topical Pimecrolimus and Topical Corticosteroids During Follow-up[a], UK-CPRD: Children

Variable	Topical Tacrolimus	Topical Pimecrolimus	Topical Corticosteroids Plain	Topical Corticosteroids Combined
Number of users, n	3,895	2,752	14,599	10,200
Number of prescriptions per patient				
Mean (standard deviation)	4.03 (6.80)	2.76 (4.89)	8.91 (13.90)	3.82 (6.17)
20th Percentile	1	1	2	1
40th Percentile	1	1	3	2
50th Percentile	2	1	4	2
60th Percentile	2	2	6	3
80th Percentile	5	3	12	5
Number of grams of active substance per patient				
Mean (standard deviation)	0.11 (0.35)	1.25 (3.56)	NA	NA
20th Percentile	0.01	0.30	NA	NA
40th Percentile	0.03	0.30	NA	NA
50th Percentile	0.03	0.60	NA	NA
60th Percentile	0.04	0.60	NA	NA
80th Percentile	0.11	1.20	NA	NA
Duration of use (days)				
Mean (standard deviation)	190.39 (272.56)	155.32 (211.62)	NA	NA
20th Percentile	60	70	NA	NA
40th Percentile	60	70	NA	NA
50th Percentile	85	70	NA	NA
60th Percentile	120	77	NA	NA
80th Percentile	240	181	NA	NA

NA = not applicable

[a] Follow-up for the tacrolimus cohort stopped at the first use of pimecrolimus; follow-up for pimecrolimus stopped at the first use of tacrolimus. For the corticosteroids cohort, follow-up stopped at the first use of tacrolimus or pimecrolimus. Also, for any cohort, follow-up stopped at the first study outcome.

Annex 2 Table 6. Utilization Patterns of Users of Topical Tacrolimus, Topical Pimecrolimus and Topical Corticosteroids During Follow-up[a], Denmark: Children

Variable	Topical Tacrolimus	Topical Pimecrolimus	Topical Corticosteroids Plain	Topical Corticosteroids Combined
Number of users, n	11,417	20,343	106,111	48,019
Number of prescriptions per patient				
Mean (standard deviation)	2.8 (4.8)	2.6 (3.8)	4.8 (8.4)	2.4 (3.7)
20th Percentile	1	1	1	1
40th Percentile	1	1	2	1
50th Percentile	1	1	2	1
60th Percentile	2	2	3	2
80th Percentile	3	3	6	3
Number of grams of active substance per patient				
Mean (standard deviation)	0.1 (0.3)	0.8 (2.3)	NA	NA
20th Percentile	0.009	0.15	NA	NA
40th Percentile	0.018	0.3	NA	NA
50th Percentile	0.03	0.3	NA	NA
60th Percentile	0.03	0.3	NA	NA
80th Percentile	0.069	0.9	NA	NA
Duration of use (days)				
Mean (standard deviation)	169.6 (285.5)	185.1 (267.2)	NA	NA
20th Percentile	60	70	NA	NA
40th Percentile	60	70	NA	NA
50th Percentile	60	70	NA	NA
60th Percentile	120	140	NA	NA
80th Percentile	180	210	NA	NA

NA = not applicable

[a] Follow-up for the tacrolimus cohort stopped at the first use of pimecrolimus; follow-up for pimecrolimus stopped at the first use of tacrolimus. For the corticosteroids cohort, follow-up stopped at the first use of tacrolimus or pimecrolimus. Also, for any cohort, follow-up stopped at the first study outcome.

Annex 2 Table 7. Utilization Patterns of Users of Topical Tacrolimus, Topical Pimecrolimus and Topical Corticosteroids During Follow-up[a], NL-PHARMO: Children

Variable	Topical Tacrolimus	Topical Pimecrolimus	Topical Corticosteroids Plain	Topical Corticosteroids Combined
Number of users, n	5,197	3,189	21,665	4,527
Number of prescriptions per patient				
Mean (standard deviation)	3.2 (4.7)	2.4 (3.4)	5.4 (7.5)	2.1 (2.7)
20th Percentile	1	1	1	1
40th Percentile	1	1	2	1
50th Percentile	2	1	3	1
60th Percentile	2	2	4	2
80th Percentile	4	3	7	3
Number of grams of active substance per patient				
Mean (standard deviation)	0.09 (0.36)	0.91 (1.94)	NA	NA
20th Percentile	0.01	0.3	NA	NA
40th Percentile	0.02	0.3	NA	NA
50th Percentile	0.03	0.3	NA	NA
60th Percentile	0.04	0.6	NA	NA
80th Percentile	0.09	0.9	NA	NA
Duration of use (days)				
Mean (standard deviation)	163.9 (212.7)	145.9 (171.0)	NA	NA
20th Percentile	60	70	NA	NA
40th Percentile	60	70	NA	NA
50th Percentile	75	70	NA	NA
60th Percentile	120	92	NA	NA
80th Percentile	211	194	NA	NA

NA = not applicable

[a] Follow-up for the tacrolimus cohort stopped at the first use of pimecrolimus; follow-up for pimecrolimus stopped at the first use of tacrolimus. For the corticosteroids cohort, follow-up stopped at the first use of tacrolimus or pimecrolimus. Also, for any cohort, follow-up stopped at the first study outcome.

Annex 2 Table 8. Utilization Patterns of Users of Topical Tacrolimus, Topical Pimecrolimus and Topical Corticosteroids During Follow-up[a], Sweden: Children

Variable	Topical Tacrolimus	Topical Pimecrolimus	Topical Corticosteroids Plain	Topical Corticosteroids Combined
Number of users, n	12,096	1,677	58,203	9,802
Number of prescriptions per patient				
Mean (standard deviation)	2.26 (2.76)	1.83 (2.28)	4.47 (6.73)	1.97 (2.31)
20th Percentile	1	1	1	1
40th Percentile	1	1	2	1
50th Percentile	1	1	2	1
60th Percentile	2	1	3	1
80th Percentile	3	2	6	2
Number of grams of active substance per patient	0.05 (0.10)	0.57 (1.06)	NA	NA
Mean (standard deviation)				
20th Percentile	0.01	0.15	NA	NA
40th Percentile	0.01	0.3	NA	NA
50th Percentile	0.02	0.3	NA	NA
60th Percentile	0.03	0.3	NA	NA
80th Percentile	0.06	0.6	NA	NA
Duration of use (days)				
Mean (standard deviation)	139.1 (151.7)	122.8 (128.3)	NA	NA
20th Percentile	60	70	NA	NA
40th Percentile	60	70	NA	NA
50th Percentile	60	70	NA	NA
60th Percentile	120	70	NA	NA
80th Percentile	180	140	NA	NA

NA = not applicable

[a] Follow-up for the tacrolimus cohort stopped at the first use of pimecrolimus; follow-up for pimecrolimus stopped at the first use of tacrolimus. For the corticosteroids cohort, follow-up stopped at the first use of tacrolimus or pimecrolimus. Also, for any cohort, follow-up stopped at the first study outcome.

Analysis Table 11b. Drug Utilization Patterns During Follow up, Adults

Annex 2 Table 9. Utilization Patterns of Users of Topical Tacrolimus, Topical Pimecrolimus and Topical Corticosteroids During Follow-up[a], UK-CPRD: Adults

Variable	Topical Tacrolimus	Topical Pimecrolimus	Topical Corticosteroids Plain	Topical Corticosteroids Combined
Number of users, n	12,705	5,124	47,534	32,581
Number of prescriptions per patient				
Mean (standard deviation)	3.04 (6.38)	2.21 (4.05)	7.62 (13.64)	4.92 (9.49)
20th Percentile	1	1	2	1
40th Percentile	1	1	3	2
50th Percentile	1	1	4	2
60th Percentile	2	1	5	3
80th Percentile	3	2	9	6
Number of grams of active substance per patient				
Mean (standard deviation)	0.12 (0.49)	0.96 (2.98)	NA	NA
20th Percentile	0.02	0.30	NA	NA
40th Percentile	0.03	0.30	NA	NA
50th Percentile	0.03	0.30	NA	NA
60th Percentile	0.06	0.60	NA	NA
80th Percentile	0.12	0.90	NA	NA
Duration of use (days)				
Mean (standard deviation)	149.80 (246.65)	132.35 (197.67)	NA	NA
20th Percentile	60	70	NA	NA
40th Percentile	60	70	NA	NA
50th Percentile	60	70	NA	NA
60th Percentile	74	70	NA	NA
80th Percentile	177.5	140	NA	NA

NA = not applicable

[a] Follow-up for the tacrolimus cohort stopped at the first use of pimecrolimus; follow-up for pimecrolimus stopped at the first use of tacrolimus. For the corticosteroids cohort, follow-up stopped at the first use of tacrolimus or pimecrolimus. Also, for any cohort, follow-up stopped at the first study outcome.

Annex 2 Table 10. Utilization Patterns of Users of Topical Tacrolimus, Topical Pimecrolimus and Topical Corticosteroids During Follow-up[a], Denmark: Adults

Variable	Topical Tacrolimus	Topical Pimecrolimus	Topical Corticosteroids Plain	Topical Corticosteroids Combined
Number of users, n	40,710	43,042	278,224	119,408
Number of prescriptions per patient				
Mean (standard deviation)	2.5 (4.2)	2.4 (4.0)	5.2 (9.1)	2.8 (4.5)
20th Percentile	1	1	1	1
40th Percentile	1	1	2	1
50th Percentile	1	1	3	1
60th Percentile	2	1	3	2
80th Percentile	3	3	7	3
Number of grams of active substance per patient				
Mean (standard deviation)	0.1 (0.3)	0.7 (2.0)	NA	NA
20th Percentile	0.01	0.15	NA	NA
40th Percentile	0.03	0.3	NA	NA
50th Percentile	0.03	0.3	NA	NA
60th Percentile	0.03	0.3	NA	NA
80th Percentile	0.06	0.6	NA	NA
Duration of use (days)				
Mean (standard deviation)	147.9 (254.8)	165.1 (280.8)	NA	NA
20th Percentile	60	70	NA	NA
40th Percentile	60	70	NA	NA
50th Percentile	60	70	NA	NA
60th Percentile	120	70	NA	NA
80th Percentile	180	210	NA	NA

NA = not applicable

[a] Follow-up for the tacrolimus cohort stopped at the first use of pimecrolimus; follow-up for pimecrolimus stopped at the first use of tacrolimus. For the corticosteroids cohort, follow-up stopped at the first use of tacrolimus or pimecrolimus. Also, for any cohort, follow-up stopped at the first study outcome.

Annex 2 Table 11. Utilization Patterns of Users of Topical Tacrolimus, Topical Pimecrolimus and Topical Corticosteroids During Follow-up[a], NL-PHARMO: Adults

Variable	Topical Tacrolimus	Topical Pimecrolimus	Topical Corticosteroids Plain	Topical Corticosteroids Combined
Number of users, n	21,037	8,506	83,266	21,829
Number of prescriptions per patient				
Mean (standard deviation)	2.7 (4.5)	2.2 (3.8)	5.5 (7.6)	2.8 (3.8)
20th Percentile	1	1	1	1
40th Percentile	1	1	2	1
50th Percentile	1	1	3	2
60th Percentile	2	1	4	2
80th Percentile	3	3	7	4
Number of grams of active substance per patient				
Mean (standard deviation)	0.11 (0.64)	0.83 (2.29)	NA	NA
20th Percentile	0.03	0.3	NA	NA
40th Percentile	0.03	0.3	NA	NA
50th Percentile	0.04	0.3	NA	NA
60th Percentile	0.06	0.6	NA	NA
80th Percentile	0.12	0.9	NA	NA
Duration of use (days)				
Mean (standard deviation)	136.9 (195.0)	139.6 (193.3)	NA	NA
20th Percentile	60	70	NA	NA
40th Percentile	60	70	NA	NA
50th Percentile	60	70	NA	NA
60th Percentile	98	70	NA	NA
80th Percentile	180	140	NA	NA

NA = not applicable

[a] Follow-up for the tacrolimus cohort stopped at the first use of pimecrolimus; follow-up for pimecrolimus stopped at the first use of tacrolimus. For the corticosteroids cohort, follow-up stopped at the first use of tacrolimus or pimecrolimus. Also, for any cohort, follow-up stopped at the first study outcome.

Annex 2 Table 12. Utilization Patterns of Users of Topical Tacrolimus, Topical Pimecrolimus and Topical Corticosteroids During Follow-up[a], Sweden: Adults

Variable	Topical Tacrolimus	Topical Pimecrolimus	Topical Corticosteroids Plain	Topical Corticosteroids Combined
Number of users, n	52,456	5,169	233,370	52,542
Number of prescriptions per patient				
Mean (standard deviation)	2.26 (2.97)	2.00 (2.63)	4.93 (7.54)	2.63 (3.73)
20th Percentile	1	1	1	1
40th Percentile	1	1	2	1
50th Percentile	1	1	3	1
60th Percentile	2	1	3	2
80th Percentile	3	2	7	3
Number of grams of active substance per patient	0.07 (0.14)	0.59 (1.07)	NA	NA
Mean (standard deviation)				
20th Percentile	0.01	0.15	NA	NA
40th Percentile	0.03	0.3	NA	NA
50th Percentile	0.03	0.3	NA	NA
60th Percentile	0.05	0.3	NA	NA
80th Percentile	0.09	0.6	NA	NA
Duration of use (days)				
Mean (standard deviation)	139.0 (159.2)	140.75 (175.45)	NA	NA
20th Percentile	60	70	NA	NA
40th Percentile	60	70	NA	NA
50th Percentile	60	70	NA	NA
60th Percentile	120	70	NA	NA
80th Percentile	180	140	NA	NA

NA = not applicable

[a] Follow-up for the tacrolimus cohort stopped at the first use of pimecrolimus; follow-up for pimecrolimus stopped at the first use of tacrolimus. For the corticosteroids cohort, follow-up stopped at the first use of tacrolimus or pimecrolimus. Also, for any cohort, follow-up stopped at the first study outcome.

Analysis Table 12. New Users Switching Between Topical Tacrolimus and Pimecrolimus During Follow up: Children and Adults

Annex 2 Table 13. Topical Tacrolimus and Topical Pimecrolimus: Number of Users Switching Between Tacrolimus and Pimecrolimus During Follow-up[a], by Strength at the Start Date: UK-CPRD

	Children			Adults		
Formulation At The Start Date	New Users At The Start Date N	Users Switching Between Tacrolimus and Pimecrolimus During Follow-up[a] n	%	New Users At The Start Date N	Users Switching Between Tacrolimus and Pimecrolimus During Follow-up[a] n	%
Tacrolimus	3,895	268	6.9	12,705	549	4.3
Strength						
0.03%	2,739	184	6.7	4,163	192	4.6
0.10%	1,237	93	7.5	8,827	391	4.4
Pimecrolimus						
Strength 1%	2,752	340	12.4	5,124	571	11.1

[a] Follow-up stopped at first study outcome.

Annex 2 Table 14. Topical Tacrolimus and Topical Pimecrolimus: Number of Users Switching Between Tacrolimus and Pimecrolimus During Follow-up[a], by Strength at the Start Date: Denmark

	Children			Adults		
Formulation At The Start Date	New Users At The Start Date N	Users Switching Between Tacrolimus and Pimecrolimus During Follow-up[a] n	%	New Users At The Start Date N	Users Switching Between Tacrolimus and Pimecrolimus During Follow-up[a] n	%
Tacrolimus	11,417	1,211	10.6	40,710	3,104	7.6
Strength						
0.03%	5,068	499	9.9	6,162	425	6.9
0.10%	6,349	712	11.2	34,548	2,679	7.8
Pimecrolimus						
Strength 1%	20,343	3,199	15.7	43,042	5,752	13.4

[a] Follow-up stopped at first study outcome.

Annex 2 Table 15. Topical Tacrolimus and Topical Pimecrolimus: Number of Users Switching Between Tacrolimus and Pimecrolimus During Follow-up[a], by Strength at the Start Date: NL-PHARMO

	Children			Adults		
Formulation At The Start Date	New Users At The Start Date	Users Switching Between Tacrolimus and Pimecrolimus During Follow-up[a]		New Users At The Start Date	Users Switching Between Tacrolimus and Pimecrolimus During Follow-up[a]	
	N	n	%	N	n	%
Tacrolimus	5,197	396	7.6	21,037	1,137	5.4
Strength						
0.03%	3,443	243	7.1	4,109	227	5.5
0.10%	1,754	153	8.7	16,928	910	5.4
Pimecrolimus						
Strength 1%	3,189	377	11.8	8,506	913	10.7

[a] Follow-up stopped at first study outcome.

Annex 2 Table 16. Topical Tacrolimus and Topical Pimecrolimus: Number of Users Switching Between Tacrolimus and Pimecrolimus During Follow-up[a], by Strength at the Start Date: Sweden

	Children			Adults		
Formulation At The Start Date	New Users At The Start Date	Users Switching Between Tacrolimus and Pimecrolimus During Follow-up[a]		New Users At The Start Date	Users Switching Between Tacrolimus and Pimecrolimus During Follow-up[a]	
	N	n	%	N	n	%
Tacrolimus	12,096	277	2.3	52,456	977	1.9
Strength						
0.03%	7,465	151	2.0	6,079	93	1.5
0.10%	4,631	126	2.7	46,377	884	1.9
Pimecrolimus						
Strength 1%	1,677	241	14.4	5,169	734	14.2

[a] Follow-up stopped at first study outcome.

Analysis Table 13a. Number of Prescriptions Before and After First Switch Between Topical Tacrolimus and Pimecrolimus, by Formulation: Children

Annex 2 Table 17. Number of Prescriptions Before and After First Switch Between Tacrolimus and Pimecrolimus, by Formulation at the Start Date, UK-CPRD: Children

Formulation At The Start Date	New Users Switching During Follow-up[a]	Number of Prescriptions Before and After Switching Between Tacrolimus and Pimecrolimus			
		Before Switching		After Switching	
		Topical Tacrolimus	Topical Pimecrolimus	Topical Tacrolimus	Topical Pimecrolimus
	n	n	n	n	n
Tacrolimus	305	1,129	NA	1,038	872
Strength					
0.03%	197	795	NA	713	625
0.10%	108	334	NA	325	247
Pimecrolimus					
Strength 1%	369	NA	982	1,967	434

Annex 2 Table 18. Number of Prescriptions Before and After First Switch Between Tacrolimus and Pimecrolimus, by Formulation at the Start Date, Denmark: Children

Formulation At The Start Date	New Users Switching During Follow-up[a]	Number of Prescriptions Before and After Switching Between Tacrolimus and Pimecrolimus			
		Before Switching		After Switching	
		Topical Tacrolimus	Topical Pimecrolimus	Topical Tacrolimus	Topical Pimecrolimus
	n	n	n	n	n
Tacrolimus	1,211	3,144	NA	1,992	2,958
Strength					
0.03%	499	1,042	NA	808	1,164
0.10%	712	2,102	NA	1,184	1,794
Pimecrolimus					
Strength 1%	3,199	NA	8,982	12,137	3,089

Annex 2 Table 19. Number of Prescriptions Before and After First Switch Between Tacrolimus and Pimecrolimus, by Formulation at the Start Date, NL-PHARMO: Children

Formulation At The Start Date	New Users Switching During Follow-up[a]	Number of Prescriptions Before and After Switching Between Tacrolimus and Pimecrolimus			
		Before Switching		After Switching	
		Topical Tacrolimus	Topical Pimecrolimus	Topical Tacrolimus	Topical Pimecrolimus
	n	n	n	n	n
Tacrolimus	396	1,307	NA	614	1,244
Strength					
0.03%	243	787	NA	357	698
0.10%	153	520	NA	257	546
Pimecrolimus					
Strength 1%	377	NA	916	1,398	242

Annex 2 Table 20. Number of Prescriptions Before and After First Switch Between Tacrolimus and Pimecrolimus, by Formulation at the Start Date, Sweden: Children

Formulation At The Start Date	New Users Switching During Follow-up[a]	Number of Prescriptions Before and After Switching Between Tacrolimus and Pimecrolimus			
		Before Switching		After Switching	
		Topical Tacrolimus	Topical Pimecrolimus	Topical Tacrolimus	Topical Pimecrolimus
	n	n	n	n	n
Tacrolimus	277	692	NA	255	330
Strength					
0.03%	151	344	NA	118	158
0.10%	126	348	NA	137	172
Pimecrolimus					
Strength 1%	241	NA	494	470	66

Analysis Table 13b. Number of Prescriptions Before and After First Switch Between Topical Tacrolimus and Pimecrolimus, by Formulation: Adults

Annex 2 Table 21. Number of Prescriptions Before and After First Switch Between Tacrolimus and Pimecrolimus, by Formulation at the Start Date, UK-CPRD: Adults

Formulation At The Start Date	New Users Switching During Follow-up[a]	Number of Prescriptions Before and After Switching Between Tacrolimus and Pimecrolimus			
		Before Switching		After Switching	
		Topical Tacrolimus	Topical Pimecrolimus	Topical Tacrolimus	Topical Pimecrolimus
	n	n	n	n	n
Tacrolimus	652	1,796	NA	1,344	1,593
Strength					
0.03%	238	713	NA	466	517
0.10%	414	1,083	NA	878	1,076
Pimecrolimus					
Strength 1%	644	NA	1,272	1,987	778

Annex 2 Table 22. Number of Prescriptions Before and After First Switch Between Tacrolimus and Pimecrolimus, by Formulation at the Start Date, Denmark: Adults

Formulation At The Start Date	New Users Switching During Follow-up[a]	Number of Prescriptions Before and After Switching Between Tacrolimus and Pimecrolimus			
		Before Switching		After Switching	
		Topical Tacrolimus	Topical Pimecrolimus	Topical Tacrolimus	Topical Pimecrolimus
	n	n	n	n	n
Tacrolimus	3,104	6,757	NA	3,797	7,428
Strength					
0.03%	425	846	NA	428	1,070
0.10%	2,679	5,911	NA	3,369	6,358
Pimecrolimus					
Strength 1%	5,752	NA	12,305	17,061	4,840

Annex 2 Table 23. Number of Prescriptions Before and After First Switch Between Tacrolimus and Pimecrolimus, by Formulation at the Start Date, NL-PHARMO: Adults

Formulation At The Start Date	New Users Switching During Follow-up[a]	Number of Prescriptions Before and After Switching Between Tacrolimus and Pimecrolimus			
		Before Switching		After Switching	
		Topical Tacrolimus	Topical Pimecrolimus	Topical Tacrolimus	Topical Pimecrolimus
	n	n	n	n	n
Tacrolimus	1,137	2,694	NA	1,522	3,067
Strength					
0.03%	227	587	NA	356	580
0.10%	910	2,107	NA	1,166	2,487
Pimecrolimus					
Strength 1%	913	NA	1,655	2,697	638

Annex 2 Table 24. Number of Prescriptions Before and After First Switch Between Tacrolimus and Pimecrolimus, by Formulation at the Start Date, Sweden: Adults

Formulation At The Start Date	New Users Switching During Follow-up[a]	Number of Prescriptions Before and After Switching Between Tacrolimus and Pimecrolimus			
		Before Switching		After Switching	
		Topical Tacrolimus	Topical Pimecrolimus	Topical Tacrolimus	Topical Pimecrolimus
	n	n	n	n	n
Tacrolimus	977	2,226	NA	1,051	1,124
Strength					
0.03%	93	177	NA	51	88
0.10%	884	2,049	NA	1,000	1,036
Pimecrolimus					
Strength 1%	734	NA	1,497	1,185	325

Analysis Table 18. Distribution of Prescriptions of Index Drug During Follow Up: Children and Adults

Annex 2 Table 25. Distribution of Number of Prescriptions/Dispensings of Index Drug During Follow-up, by Final Study Cohorts: UK-CPRD

Number of Prescriptions or Dispensings of Index Drug[a] During Follow-up[b]	Children Cohorts				Adult Cohorts			
	Tacrolimus Cohort		Pimecrolimus Cohort		Tacrolimus Cohort		Pimecrolimus Cohort	
	n	%	n	%	n	%	n	%
1	1,591	57.8	3,500	68.3	1,794	46.1	7,345	57.8
2	433	15.7	748	14.6	635	16.3	2,108	16.6
3	187	6.8	263	5.1	346	8.9	931	7.3
4	137	5.0	152	3.0	231	5.9	501	3.9
5	101	3.7	84	1.6	162	4.2	353	2.8
6	51	1.9	74	1.4	114	2.9	241	1.9
7	47	1.7	42	0.8	91	2.3	186	1.5
8	29	1.1	39	0.8	65	1.7	139	1.1
9	22	0.8	27	0.5	55	1.4	117	0.9
≥ 10	154	5.6	195	3.8	402	10.3	784	6.2

[a] For Tacrolimus cohort this is tacrolimus, for pimecrolimus cohort this is pimecrolimus.

[b] Follow-up period is from index date until loss to follow-up, first study cancer event, or end of study period.

Annex 2 Table 26. Distribution of Number of Prescriptions/Dispensings of Index Drug During Follow-up, by Final Study Cohorts: Denmark

Number of Prescriptions or Dispensings of Index Drug[a] During Follow-up[b]	Children Cohorts				Adult Cohorts			
	Tacrolimus Cohort		Pimecrolimus Cohort		Tacrolimus Cohort		Pimecrolimus Cohort	
	n	%	n	%	n	%	n	%
1	6,139	53.8	11,289	55.5	23,746	58.3	26,996	62.7
2	2,107	18.5	3,565	17.5	7,419	18.2	7,032	16.3
3	1,064	9.3	1,665	8.2	3,358	8.2	2,968	6.9
4	538	4.7	1,060	5.2	1,803	4.4	1,761	4.1
5	370	3.2	666	3.3	1,116	2.7	1,020	2.4
6	257	2.3	467	2.3	754	1.9	701	1.6
7	184	1.6	375	1.8	521	1.3	515	1.2
8	135	1.2	232	1.1	386	0.9	380	0.9
9	101	0.9	175	0.9	270	0.7	263	0.6
≥ 10	522	4.6	849	4.2	1,337	3.3	1,406	3.3

[a] For Tacrolimus cohort this is tacrolimus, for pimecrolimus cohort this is pimecrolimus.

[b] Follow-up period is from index date until loss to follow-up, first study cancer event, or end of study period.

Annex 2 Table 27. Distribution of Number of Prescriptions/Dispensings of Index Drug During Follow-up, by Final Study Cohorts: NL-PHARMO

Number of Prescriptions or Dispensings of Index Drug[a] During Follow-up[b]	Children Cohorts				Adult Cohorts			
	Tacrolimus Cohort		Pimecrolimus Cohort		Tacrolimus Cohort		Pimecrolimus Cohort	
	n	%	n	%	n	%	n	%
1	2,518	48.5	1,862	58.4	11,570	55.0	5,344	62.8
2	979	18.8	558	17.5	4,002	19.0	1,445	17.0
3	502	9.7	268	8.4	1,872	8.9	678	8.0
4	313	6.0	147	4.6	1,027	4.9	321	3.8
5	186	3.6	99	3.1	646	3.1	183	2.2
6	146	2.8	57	1.8	423	2.0	119	1.4
7	112	2.2	44	1.4	305	1.4	83	1.0
8	70	1.3	33	1.0	220	1.0	57	0.7
9	57	1.1	25	0.8	151	0.7	48	0.6
≥ 10	314	6.0	96	3.0	821	3.9	228	2.7

[a] For Tacrolimus cohort this is tacrolimus, for pimecrolimus cohort this is pimecrolimus.

[b] Follow-up period is from index date until loss to follow-up, first study cancer event, or end of study period.

Annex 2 Table 28. Distribution of Number of Prescriptions/Dispensings of Index Drug During Follow-up, by Final Study Cohorts: Sweden

Number of Prescriptions or Dispensings of Index Drug[a] During Follow-up[b]	Children Cohorts				Adult Cohorts			
	Tacrolimus Cohort		Pimecrolimus Cohort		Tacrolimus Cohort		Pimecrolimus Cohort	
	n	%	n	%	n	%	n	%
1	6,745	55.8	1,106	66.0	29,442	56.1	3,308	64.0
2	2,351	19.4	292	17.4	10,262	19.6	903	17.5
3	1,128	9.3	105	6.3	4,686	8.9	345	6.7
4	622	5.1	64	3.8	2,713	5.2	204	3.9
5	356	2.9	32	1.9	1,538	2.9	106	2.1
6	241	2.0	25	1.5	1,000	1.9	68	1.3
7	145	1.2	11	0.7	734	1.4	42	0.8
8	108	0.9	13	0.8	470	0.9	47	0.9
9	80	0.7	4	0.2	347	0.7	21	0.4
≥ 10	320	2.6	25	1.5	1,264	2.4	125	2.4

[a] For Tacrolimus cohort this is tacrolimus, for pimecrolimus cohort this is pimecrolimus.

[b] Follow-up period is from index date until loss to follow-up, first study cancer event, or end of study period.

Analysis Table 19a. Distribution of Follow-up Duration, by Final Study Cohorts: Children

Annex 2 Table 29. Distribution of Follow-up Duration, by Final Study Cohorts, UK-CPRD: Children

Duration of Follow-up[a] (Years)	Tacrolimus and Comparator Cohort				Pimecrolimus and Comparator Cohort					
	Tacrolimus		Corticosteroid		Pimecrolimus		Corticosteroid		Untreated	
	n	%	n	%	n	%	n	%	n	%
≤ 1	524	13.5	2,483	16.3	304	11.0	1,347	12.2	11,629	19.1
>1 to ≤ 2	520	13.4	2,033	13.3	264	9.6	1,145	10.4	9,173	15.0
>2 to ≤ 3	465	11.9	1,705	11.2	233	8.5	1,002	9.1	7,586	12.4
>3 to ≤ 4	365	9.4	1,453	9.5	221	8.0	918	8.3	6,143	10.1
>4 to ≤ 5	309	7.9	1,242	8.1	183	6.6	715	6.5	4,998	8.2
>5 to ≤ 6	299	7.7	1,078	7.1	182	6.6	730	6.6	4,295	7.0
>6 to ≤ 7	243	6.2	905	5.9	181	6.6	683	6.2	3,383	5.5
>7 to ≤ 8	220	5.6	829	5.4	171	6.2	661	6.0	2,959	4.9
>8 to ≤ 9	158	4.1	654	4.3	123	4.5	579	5.3	2,300	3.8
>9 to ≤ 10	153	3.9	582	3.8	170	6.2	593	5.4	2,002	3.3
>10 to ≤ 11	175	4.5	640	4.2	183	6.6	780	7.1	1,985	3.3
>11 to ≤ 12	194	5.0	711	4.7	218	7.9	856	7.8	1,924	3.2
>12 to ≤ 13	122	3.1	457	3.0	206	7.5	632	5.7	1,351	2.2
>13 to ≤ 14	99	2.5	321	2.1	113	4.1	366	3.3	862	1.4
>14	49	1.3	160	1.0	0	0.0	[redacted]	[redacted]	411	0.7

[a] Follow-up period is from start date until loss to follow-up, first study cancer event, or end of study period.

Annex 2 Table 30. Distribution of Follow-up Duration, by Final Study Cohorts, Denmark: Children

Duration of Follow-up[a] (Years)	Tacrolimus and Comparator Cohort				Pimecrolimus and Comparator Cohort					
	Tacrolimus		Corticosteroid		Pimecrolimus		Corticosteroid		Untreated	
	n	%	n	%	n	%	n	%	n	%
≤ 1	43	0.4	2,088	4.8	118	0.6	4,353	5.4	12,965	8.2
>1 to ≤ 2	995	8.7	4,020	9.2	1,213	6.0	6,126	7.5	19,626	12.4
>2 to ≤ 3	880	7.7	3,436	7.9	1,027	5.0	5,000	6.2	16,008	10.1
>3 to ≤ 4	838	7.3	3,264	7.5	1,137	5.6	4,881	6.0	14,242	9.0
>4 to ≤ 5	1,049	9.2	3,612	8.3	1,111	5.5	4,790	5.9	13,937	8.8
>5 to ≤ 6	1,211	10.6	4,132	9.5	1,166	5.7	4,845	6.0	14,301	9.0
>6 to ≤ 7	1,258	11.0	4,159	9.5	1,293	6.4	5,179	6.4	13,570	8.6
>7 to ≤ 8	1,198	10.5	3,901	8.9	1,129	5.5	4,677	5.8	12,173	7.7
>8 to ≤ 9	742	6.5	2,893	6.6	1,028	5.1	4,842	6.0	8,861	5.6
>9 to ≤ 10	465	4.1	1,915	4.4	1,183	5.8	4,752	5.9	5,912	3.7
>10 to ≤ 11	453	4.0	1,863	4.3	1,191	5.9	4,866	6.0	5,346	3.4
>11 to ≤ 12	547	4.8	2,123	4.9	1,785	8.8	6,339	7.8	5,652	3.6
>12 to ≤ 13	770	6.7	2,790	6.4	2,643	13.0	7,701	9.5	6,871	4.3
>13 to ≤ 14	557	4.9	2,149	4.9	2,793	13.7	8,072	9.9	5,147	3.3
>14	411	3.6	1,328	3.0	1,526	7.5	4,717	5.8	3,478	2.2

[a] Follow-up period is from start date until loss to follow-up, first study cancer event, or end of study period.

Annex 2 Table 31. Distribution of Follow-up Duration, by Final Study Cohorts, NL-PHARMO: Children

Duration of Follow-up[a] (Years)	Tacrolimus and Comparator Cohort				Pimecrolimus and Comparator Cohort					
	Tacrolimus		Corticosteroid		Pimecrolimus		Corticosteroid		Untreated	
	n	%	n	%	n	%	n	%	n	%
≤ 1	66	1.3	775	5.2	61	1.9	568	4.7	2,598	4.4
>1 to ≤ 2	366	7.0	1,250	8.4	238	7.5	977	8.0	5,148	8.8
>2 to ≤ 3	446	8.6	1,459	9.8	260	8.2	1,113	9.1	6,193	10.6
>3 to ≤ 4	431	8.3	1,275	8.6	246	7.7	1,021	8.4	5,517	9.4
>4 to ≤ 5	435	8.4	1,238	8.3	219	6.9	875	7.2	5,093	8.7
>5 to ≤ 6	467	9.0	1,226	8.2	242	7.6	839	6.9	4,996	8.6
>6 to ≤ 7	487	9.4	1,360	9.1	221	6.9	824	6.8	5,352	9.2
>7 to ≤ 8	468	9.0	1,105	7.4	192	6.0	703	5.8	4,344	7.4
>8 to ≤ 9	458	8.8	1,145	7.7	225	7.1	808	6.6	4,200	7.2
>9 to ≤ 10	400	7.7	948	6.4	241	7.6	847	7.0	3,547	6.1
>10 to ≤ 11	359	6.9	856	5.7	213	6.7	736	6.0	3,234	5.5
>11 to ≤ 12	213	4.1	587	3.9	158	5.0	596	4.9	2,162	3.7
>12 to ≤ 13	119	2.3	406	2.7	195	6.1	636	5.2	1,493	2.6
>13 to ≤ 14	199	3.8	539	3.6	345	10.8	1,133	9.3	1,840	3.1
>14	283	5.4	735	4.9	133	4.2	492	4.0	2,707	4.6

[a] Follow-up period is from start date until loss to follow-up, first study cancer event, or end of study period.

Annex 2 Table 32. Distribution of Follow-up Duration, by Final Study Cohorts, Sweden: Children

Duration of Follow-up[a] (Years)	Tacrolimus and Comparator Cohort				Pimecrolimus and Comparator Cohort					
	Tacrolimus		Corticosteroid		Pimecrolimus		Corticosteroid		Untreated	
	n	%	n	%	n	%	n	%	n	%
≤ 1	29	0.2	1,245	2.8	3	0.2	151	2.3	2,463	2.9
>1 to ≤ 2	1,608	13.3	5,978	13.7	220	13.1	937	14.0	12,431	14.8
>2 to ≤ 3	1,447	12.0	5,292	12.1	210	12.5	887	13.2	10,730	12.8
>3 to ≤ 4	1,592	13.2	5,570	12.7	182	10.9	718	10.7	11,093	13.2
>4 to ≤ 5	1,622	13.4	5,452	12.5	143	8.5	569	8.5	10,485	12.5
>5 to ≤ 6	1,703	14.1	5,683	13.0	161	9.6	598	8.9	10,672	12.7
>6 to ≤ 7	1,505	12.4	5,169	11.8	193	11.5	698	10.4	9,541	11.3
>7 to ≤ 8	1,273	10.5	4,646	10.6	215	12.8	822	12.3	8,276	9.8
>8 to ≤ 9	967	8.0	3,518	8.0	230	13.7	867	12.9	6,141	7.3
>9 to ≤ 10	350	2.9	1,209	2.8	120	7.2	461	6.9	2,238	2.7

[a] Follow-up period is from start date until loss to follow-up, first study cancer event, or end of study period.

Analysis Table 19b. Distribution of Follow-up Duration, by Final Study Cohorts: Adults

Annex 2 Table 33. Distribution of Follow-up Duration, by Final Study Cohorts, UK-CPRD: Adults

Duration of Follow-up[a] (Years)	Tacrolimus and Comparator Cohort				Pimecrolimus and Comparator Cohort					
	Tacrolimus		Corticosteroid		Pimecrolimus		Corticosteroid		Untreated	
	n	%	n	%	n	%	n	%	n	%
≤ 1	1,943	15.3	8,915	17.5	659	12.9	2,680	13.1	43,568	21.5
>1 to ≤ 2	1,815	14.3	7,286	14.3	609	11.9	2,387	11.6	34,193	16.9
>2 to ≤ 3	1,496	11.8	5,921	11.7	547	10.7	2,154	10.5	26,198	12.9
>3 to ≤ 4	1,235	9.7	5,043	9.9	451	8.8	1,924	9.4	21,106	10.4
>4 to ≤ 5	1,143	9.0	4,356	8.6	418	8.2	1,675	8.2	17,555	8.7
>5 to ≤ 6	922	7.3	3,693	7.3	347	6.8	1,455	7.1	13,702	6.8
>6 to ≤ 7	802	6.3	3,116	6.1	335	6.5	1,385	6.8	11,007	5.4
>7 to ≤ 8	703	5.5	2,758	5.4	326	6.4	1,175	5.7	9,302	4.6
>8 to ≤ 9	566	4.5	2,106	4.1	224	4.4	1,052	5.1	6,492	3.2
>9 to ≤ 10	530	4.2	1,954	3.8	251	4.9	1,108	5.4	5,638	2.8
>10 to ≤ 11	492	3.9	1,783	3.5	272	5.3	1,094	5.3	4,790	2.4
>11 to ≤ 12	482	3.8	1,766	3.5	322	6.3	1,174	5.7	4,205	2.1
>12 to ≤ 13	312	2.5	1,170	2.3	240	4.7	837	4.1	2,621	1.3
>13 to ≤ 14	210	1.7	711	1.4	123	2.4	394	1.9	1,567	0.8
>14	54	0.4	244	0.5	0	0.0	[redacted]	[redacted]	515	0.3

[a] Follow-up period is from start date until loss to follow-up, first study cancer event, or end of study period.

Annex 2 Table 34. Distribution of Follow-up Duration, by Final Study Cohorts, Denmark: Adults

Duration of Follow-up[a] (Years)	Tacrolimus and Comparator Cohort				Pimecrolimus and Comparator Cohort					
	Tacrolimus		Corticosteroid		Pimecrolimus		Corticosteroid		Untreated	
	n	%	n	%	n	%	n	%	n	%
≤ 1	690	1.7	6,592	4.4	688	1.6	6,680	3.9	53,217	11.0
>1 to ≤ 2	4,634	11.4	17,632	11.8	3,760	8.7	15,671	9.2	73,128	15.1
>2 to ≤ 3	4,529	11.1	16,547	11.1	3,807	8.8	15,135	8.9	61,272	12.6
>3 to ≤ 4	4,069	10.0	15,041	10.1	3,603	8.4	14,065	8.3	50,377	10.4
>4 to ≤ 5	4,090	10.0	14,744	9.9	3,236	7.5	12,825	7.6	45,683	9.4
>5 to ≤ 6	4,264	10.5	14,996	10.0	3,281	7.6	12,786	7.5	42,823	8.8
>6 to ≤ 7	3,880	9.5	13,736	9.2	3,089	7.2	12,087	7.1	37,143	7.7
>7 to ≤ 8	3,529	8.7	12,689	8.5	3,020	7.0	11,785	7.0	33,034	6.8
>8 to ≤ 9	2,408	5.9	8,953	6.0	2,346	5.5	9,324	5.5	22,544	4.7
>9 to ≤ 10	1,572	3.9	5,820	3.9	2,452	5.7	9,529	5.6	14,632	3.0
>10 to ≤ 11	1,296	3.2	4,492	3.0	2,469	5.7	9,573	5.6	11,202	2.3
>11 to ≤ 12	1,555	3.8	5,410	3.6	2,875	6.7	10,707	6.3	12,324	2.5
>12 to ≤ 13	1,923	4.7	6,297	4.2	3,787	8.8	13,511	8.0	13,823	2.9
>13 to ≤ 14	1,579	3.9	4,565	3.1	3,374	7.8	11,730	6.9	9,639	2.0
>14	692	1.7	1,728	1.2	1,255	2.9	4,151	2.4	3,948	0.8

[a] Follow-up period is from start date until loss to follow-up, first study cancer event, or end of study period.

Annex 2 Table 35. Distribution of Follow-up Duration, by Final Study Cohorts, NL-PHARMO: Adults

Duration of Follow-up[a] (Years)	Tacrolimus and Comparator Cohort				Pimecrolimus and Comparator Cohort					
	Tacrolimus		Corticosteroid		Pimecrolimus		Corticosteroid		Untreated	
	n	%	n	%	n	%	n	%	n	%
≤ 1	584	2.8	3,239	4.8	273	3.2	1,607	4.7	16,847	6.4
>1 to ≤ 2	1,990	9.5	6,908	10.3	830	9.8	3,286	9.7	30,296	11.5
>2 to ≤ 3	2,099	10.0	6,926	10.3	824	9.7	3,600	10.6	29,790	11.3
>3 to ≤ 4	1,975	9.4	6,603	9.8	833	9.8	3,366	9.9	27,447	10.4
>4 to ≤ 5	1,887	9.0	6,025	9.0	751	8.8	3,129	9.2	23,987	9.1
>5 to ≤ 6	1,843	8.8	5,750	8.5	718	8.4	2,874	8.5	22,563	8.5
>6 to ≤ 7	1,853	8.8	5,739	8.5	707	8.3	2,751	8.1	21,397	8.1
>7 to ≤ 8	1,723	8.2	5,179	7.7	590	6.9	2,397	7.1	19,207	7.3
>8 to ≤ 9	1,637	7.8	4,625	6.9	585	6.9	2,203	6.5	16,766	6.3
>9 to ≤ 10	1,200	5.7	3,770	5.6	522	6.1	1,995	5.9	13,126	5.0
>10 to ≤ 11	1,047	5.0	3,176	4.7	503	5.9	1,828	5.4	11,100	4.2
>11 to ≤ 12	819	3.9	2,580	3.8	422	5.0	1,391	4.1	8,781	3.3
>12 to ≤ 13	773	3.7	2,177	3.2	449	5.3	1,549	4.6	7,356	2.8
>13 to ≤ 14	947	4.5	2,611	3.9	439	5.2	1,491	4.4	8,669	3.3
>14	660	3.1	1,985	2.9	60	0.7	374	1.1	7,046	2.7

[a] Follow-up period is from start date until loss to follow-up, first study cancer event, or end of study period.

Annex 2 Table 36. Distribution of Follow-up Duration, by Final Study Cohorts, Sweden: Adults

Duration of Follow-up[a] (Years)	Tacrolimus and Comparator Cohort				Pimecrolimus and Comparator Cohort					
	Tacrolimus		Corticosteroid		Pimecrolimus		Corticosteroid		Untreated	
	n	%	n	%	n	%	n	%	n	%
≤ 1	880	1.7	7,531	4.1	70	1.4	838	4.1	16,870	5.0
>1 to ≤ 2	7,561	14.4	26,361	14.2	675	13.1	2,844	13.8	53,001	15.6
>2 to ≤ 3	7,397	14.1	25,611	13.8	705	13.6	2,774	13.4	49,565	14.6
>3 to ≤ 4	7,112	13.6	24,256	13.1	632	12.2	2,378	11.5	45,908	13.5
>4 to ≤ 5	6,879	13.1	22,925	12.3	523	10.1	2,078	10.1	41,859	12.3
>5 to ≤ 6	6,827	13.0	22,706	12.2	581	11.2	2,209	10.7	39,910	11.8
>6 to ≤ 7	6,031	11.5	21,111	11.4	558	10.8	2,245	10.9	35,621	10.5
>7 to ≤ 8	4,780	9.1	17,298	9.3	548	10.6	2,068	10.0	28,389	8.4
>8 to ≤ 9	3,722	7.1	13,690	7.4	577	11.2	2,178	10.5	21,657	6.4
>9 to ≤ 10	1,267	2.4	4,150	2.2	300	5.8	1,064	5.1	6,636	2.0

[a] Follow-up period is from start date until loss to follow-up, first study cancer event, or end of study period.

Annex 3. Characteristics of the Study Cohorts at the Cohort Entry Date

List of Tables

Annex 3 Table 1. Description of Demographic Characteristics of Tacrolimus Study Cohort at Cohort Entry Date, by Study Population—Children

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Tacrolimus (N = 3,895)		Corticosteroids (N = 15,253)		Tacrolimus (N = 11,417)		Corticosteroids (N = 43,673)		Tacrolimus (N = 5,197)		Corticosteroids (N = 14,904)		Tacrolimus (N = 12,096)		Corticosteroids (N = 43,762)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Demographics																
Age (years)																
0-1	266	6.8	1,181	7.7	1,670	14.6	7,019	16.1	90	1.7	514	3.4	707	5.8	2,924	6.7
2-4	972	25.0	3,732	24.5	2,726	23.9	9,853	22.6	1,144	22.0	3,112	20.9	2,216	18.3	8,271	18.9
5-9	1,038	26.6	4,144	27.2	2,304	20.2	8,755	20.0	1,392	26.8	3,867	25.9	3,078	25.4	11,270	25.8
10-14	959	24.6	3,713	24.3	2,554	22.4	9,862	22.6	1,386	26.7	4,039	27.1	3,277	27.1	11,492	26.3
15-17	660	16.9	2,483	16.3	2,163	18.9	8,184	18.7	1,185	22.8	3,372	22.6	2,818	23.3	9,805	22.4
Sex, female	2,013	51.7	7,818	51.3	5,996	52.5	22,850	52.3	2,773	53.4	7,802	52.3	6,650	55.0	23,429	53.5
Duration of follow-up (years)																
≤ 1	1,044	26.8	4,516	29.6	1,039	9.1	6,110	14.0	432	8.3	2,025	13.6	1,637	13.5	7,223	16.5
2-4	1,139	29.2	4,400	28.8	2,775	24.3	10,320	23.6	1,313	25.3	3,977	26.7	4,661	38.5	16,314	37.3
5+	1,712	44.0	6,337	41.5	7,603	66.6	27,243	62.4	3,452	66.4	8,902	59.7	5,798	47.9	20,225	46.2
Medical history[a]																
Diseases interacting with the immune system	1,455	37.4	5,563	36.5	1,195	10.5	4,286	9.8	174	3.3	496	3.3	3,072	25.4	11,016	25.2
Psoriasis	162	4.2	558	3.7	49	0.4	123	0.3	3	0.1	2	0.0	423	3.5	1,353	3.1
Epstein-Barr virus infection	14	0.4	54	0.4	16	0.1	46	0.1	93	1.8	251	1.7	27	0.2	73	0.2
Rheumatoid arthritis	0	0.0	n < 5		n < 5	n < 5	10	0.0	1	0.0	4	0.0	3	0.0	8	0.0
Systemic lupus erythematosus	n < 5		n < 5		n < 5	n < 5	8	0.0	0	0.0	1	0.0	9	0.1	26	0.1
Sjögren’s syndrome	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.0	3	0.0
Celiac sprue	7	0.2	25	0.2	13	0.1	49	0.1	2	0.0	12	0.1	130	1.1	429	1.0
Asthma	1,049	26.9	4,214	27.6	1,041	9.1	3,814	8.7	72	1.4	225	1.5	2,158	17.8	8,012	18.3

Annex 3 Table 1. Description of Demographic Characteristics of Tacrolimus Study Cohort at Cohort Entry Date, by Study Population—Children

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Tacrolimus (N = 3,895)		Corticosteroids (N = 15,253)		Tacrolimus (N = 11,417)		Corticosteroids (N = 43,673)		Tacrolimus (N = 5,197)		Corticosteroids (N = 14,904)		Tacrolimus (N = 12,096)		Corticosteroids (N = 43,762)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Allergic rhinitis	585	15.0	2,005	13.1	195	1.7	592	1.4	4	0.1	10	0.1	1,127	9.3	4,182	9.6
Disease of the immune system	9	0.2	26	0.2	19	0.2	86	0.2	2	0.0	5	0.0	62	0.5	213	0.5
Skin diseases	1,572	40.4	5,272	34.6	388	3.4	1,178	2.7	48	0.9	117	0.8	1,930	16.0	6,138	14.0
Chronic diseases	252	6.5	1,099	7.2	637	5.6	2,343	5.4	64	1.2	244	1.6	829	6.9	2,743	6.3
Malignancy other than study outcomes	n < 5		12	0.1	10	0.1	33	0.1	4	0.1	20	0.1	5	0.0	52	0.1
Renal failure	n < 5		19	0.1	n < 5	n < 5	11	0.0	0	0.0	4	0.0	9	0.1	36	0.1
Liver diseases	n < 5		16	0.1	6	0.1	28	0.1	1	0.0	4	0.0	15	0.1	51	0.1
Ischemic heart disease	n < 5		0	0.0	n < 5	n < 5	n < 5	n < 5	0	0.0	0	0.0	3	0.0	9	0.0
Hypertensive disease	7	0.2	17	0.1	7	0.1	24	0.1	2	0.0	8	0.1	12	0.1	40	0.1
Heart failure	0	0.0	6	0.0	5	0.0	18	0.0	0	0.0	0	0.0	8	0.1	24	0.1
Other cardiovascular diseases	41	1.1	170	1.1	54	0.5	194	0.4	8	0.2	24	0.2	108	0.9	344	0.8
Cerebrovascular diseases	n < 5		13	0.1	7	0.1	39	0.1	1	0.0	4	0.0	10	0.1	39	0.1
Diabetes mellitus	21	0.5	85	0.6	27	0.2	172	0.4	7	0.1	25	0.2	73	0.6	235	0.5
Respiratory diseases	n < 5		20	0.1	127	1.1	476	1.1	10	0.2	31	0.2	37	0.3	134	0.3
Musculoskeletal and connective disease	184	4.7	807	5.3	411	3.6	1,463	3.3	31	0.6	136	0.9	596	4.9	1,905	4.4
Organ transplantation	n < 5		16	0.1	7	0.1	26	0.1	2	0.0	5	0.0	21	0.2	65	0.1
HIV infection or AIDS	0	0.0	n < 5		n < 5	n < 5	5	0.0	0	0	1	0.0	1	0.0	2	0.0

Annex 3 Table 1. Description of Demographic Characteristics of Tacrolimus Study Cohort at Cohort Entry Date, by Study Population—Children

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Tacrolimus (N = 3,895)		Corticosteroids (N = 15,253)		Tacrolimus (N = 11,417)		Corticosteroids (N = 43,673)		Tacrolimus (N = 5,197)		Corticosteroids (N = 14,904)		Tacrolimus (N = 12,096)		Corticosteroids (N = 43,762)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Prior use of medications[b]																
Immunosuppressant and cytostatics	796	20.4	2,431	15.9	286	2.5	877	2.0	223	4.3	611	4.1	1,052	8.7	2,988	6.8
Systemic corticosteroids	751	19.3	2,285	15.0	140	1.2	385	0.9	193	3.7	521	3.5	944	7.8	2,663	6.1
Systemic tacrolimus	n < 5		n < 5	0.1	0	0.0	0	0.0	1	0.0	2	0.0	2	0.0	17	0.0
Immunosuppres-sants[c]	22	0.6	52	0.3	0	0.0	0	0.0	16	0.3	45	0.3	92	0.8	241	0.6
Systemic antivirals	56	1.4	171	1.1	151	1.3	508	1.2	22	0.4	71	0.5	101	0.8	283	0.6
Antineoplastic agents[d]	n < 5		7	0.0	0	0.0	0	0.0	5	0.1	17	0.1	9	0.1	28	0.1
Immunostimulants	0	0.0	0	0.0	0	0.0	0	0.0	1	0.0	5	0.0	1	0.0	3	0.0
Antipsoriatics topical	184	4.7	590	3.9	162	1.4	473	1.1	172	3.3	442	3.0	135	1.1	419	1.0
Antipsoriatics systemic	0	0.0	0	0.0	0	0.0	0	0.0	1	0.0	6	0.0	1	0.0	7	0.0
Other dermatological agents	3,895	100.0	12,632	82.8	4,043	35.4	14,951	34.2	5,197	100.0	11,090	74.4	6,484	53.6	20,251	46.3
Other medications	1,093	28.1	4,158	27.3	2,911	25.5	10,349	23.7	1,219	23.5	3,647	24.5	2,891	23.9	10,477	23.9
Cardiovascular system drugs	247	6.3	472	3.1	150	1.3	510	1.2	217	4.2	610	4.1	438	3.6	1,121	2.6
Anti-inflammatory agents	305	7.8	1,358	8.9	342	3.0	1,395	3.2	198	3.8	655	4.4	362	3.0	1,294	3.0
Other antirheumatic agents	0	0.0	0	0.0	0	0.0	0	0.0	1	0.0	0	0.0	0	0.0	0	0.0
Hormone-replacement therapy	n < 5		5	0.0	5	0.0	18	0.0	7	0.1	22	0.1	4	0.0	15	0.0
Lipid-modifying agents	0	0.0	7	0.0	n < 5	n < 5	9	0.0	4	0.1	6	0.0	0	0.0	0	0.0

Annex 3 Table 1. Description of Demographic Characteristics of Tacrolimus Study Cohort at Cohort Entry Date, by Study Population—Children

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Tacrolimus (N = 3,895)		Corticosteroids (N = 15,253)		Tacrolimus (N = 11,417)		Corticosteroids (N = 43,673)		Tacrolimus (N = 5,197)		Corticosteroids (N = 14,904)		Tacrolimus (N = 12,096)		Corticosteroids (N = 43,762)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Insulins	11	0.3	38	0.2	26	0.2	170	0.4	6	0.1	28	0.2	61	0.5	211	0.5
Oral antidiabetics	n < 5		5	0.0	n < 5	n < 5	n < 5	n < 5	5	0.1	10	0.1	3	0.0	9	0.0
Antiepileptics	10	0.3	80	0.5	49	0.4	202	0.5	17	0.3	51	0.3	60	0.5	333	0.8
Drugs for asthma and COPD	669	17.2	2,693	17.7	2,175	19.1	7,743	17.7	795	15.3	2,345	15.7	2,183	18.0	8,136	18.6
Inhaled corticosteroids	668	17.2	2,687	17.6	1,171	10.3	4,288	9.8	455	8.8	1,333	8.9	1,155	9.5	4,316	9.9
Utilization of health care resources[b]																
General practitioner visits																
0	193	5.0	1,295	8.5	NA		NA		NA		NA		4,182	34.6	12,711	29.0
1	277	7.1	1,849	12.1	NA		NA		NA		NA		3,082	25.5	11,347	25.9
2-3	746	19.2	3,725	24.4	NA		NA		NA		NA		3,313	27.4	14,373	32.8
4+	2,679	68.8	8,384	55.0	NA		NA		NA		NA		1,519	12.6	5,331	12.2
Dermatologist visits																
0	3,324	85.3	13,178	86.4	NA		NA		NA		NA		8,836	73.0	34,259	78.3
1	400	10.3	1,491	9.8	NA		NA		NA		NA		1,987	16.4	7,182	16.4
2-3	141	3.6	500	3.3	NA		NA		NA		NA		980	8.1	1,957	4.5
4+	30	0.8	84	0.6	NA		NA		NA		NA		293	2.4	364	0.8
Paediatrician visits																
0	3,553	91.2	13,970	91.6	NA		NA		NA		NA		7,898	65.3	28,229	64.5
1	206	5.3	734	4.8	NA		NA		NA		NA		1,883	15.6	7,074	16.2
2-3	102	2.6	402	2.6	NA		NA		NA		NA		1,455	12.0	5,400	12.3
4+	34	0.9	147	1.0	NA		NA		NA		NA		860	7.1	3,059	7.0

Annex 3 Table 1. Description of Demographic Characteristics of Tacrolimus Study Cohort at Cohort Entry Date, by Study Population—Children

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Tacrolimus (N = 3,895)		Corticosteroids (N = 15,253)		Tacrolimus (N = 11,417)		Corticosteroids (N = 43,673)		Tacrolimus (N = 5,197)		Corticosteroids (N = 14,904)		Tacrolimus (N = 12,096)		Corticosteroids (N = 43,762)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Emergency department visits																
0	3,440	88.3	13,496	88.5	9,756	85.5	37,264	85.3	NA		NA		NA		NA	
1	331	8.5	1,309	8.6	1,341	11.7	5,079	11.6	NA		NA		NA		NA	
2-3	106	2.7	390	2.6	296	2.6	1,240	2.8	NA		NA		NA		NA	
4+	18	0.5	58	0.4	24	0.2	90	0.2	NA		NA		NA		NA	
Outpatient hospital visits																
0	2,681	68.8	10,945	71.8	NA		NA		NA		NA		3,392	28.0	11,703	26.7
1	622	16.0	2,184	14.3	NA		NA		NA		NA		3,233	26.7	13,713	31.3
2-3	412	10.6	1,455	9.5	NA		NA		NA		NA		3,077	25.4	11,036	25.2
4+	180	4.6	669	4.4	NA		NA		NA		NA		2,394	19.8	7,310	16.7
Hospitalisations																
0	3,586	92.1	14,271	93.6	9,563	83.8	36,503	83.6	4,885	94.0	14,466	97.1	11,459	94.7	41,214	94.2
1	218	5.6	716	4.7	1,273	11.2	4,961	11.4	230	4.4	347	2.3	497	4.1	1,950	4.5
2-3	73	1.9	219	1.4	479	4.2	1,821	4.2	63	1.2	70	0.5	113	0.9	439	1.0
4+	18	0.5	47	0.3	102	0.9	388	0.9	19	0.4	21	0.1	27	0.2	159	0.4
Prescriptions																
0	0	0.0	0	0.0	179	1.6	2,761	6.3	0	0.0	0	0.0	1,412	11.7	3,561	8.1
1	76	2.0	435	2.9	3,336	29.2	13,455	30.8	0	0.0	0	0.0	1,155	9.5	5,499	12.6
2-4	363	9.3	3,167	20.8	5,281	46.3	18,743	42.9	1,067	20.5	3,315	22.2	3,236	26.8	15,940	36.4
5-9	640	16.4	4,561	29.9	1,906	16.7	6,466	14.8	1,578	30.4	4,689	31.5	3,198	26.4	11,755	26.9
10+	2,816	72.3	7,090	46.5	715	6.3	2,248	5.1	2,552	49.1	6,900	46.3	3,095	25.6	7,007	16.0

Annex 3 Table 1. Description of Demographic Characteristics of Tacrolimus Study Cohort at Cohort Entry Date, by Study Population—Children

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Tacrolimus (N = 3,895)		Corticosteroids (N = 15,253)		Tacrolimus (N = 11,417)		Corticosteroids (N = 43,673)		Tacrolimus (N = 5,197)		Corticosteroids (N = 14,904)		Tacrolimus (N = 12,096)		Corticosteroids (N = 43,762)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Type of prescriber of first prescription[e]																
Dermatologist	NA	NA	NA	NA	4,450	39.0	12,608	28.9	2,641	50.8	5,123	34.4	6,295	52.0	20,503	46.9
Paediatrician	NA	NA	NA	NA	581	5.1	550	1.3	151	2.9	294	2.0	3,026	25.0	8,227	18.8
General practitioner	NA	NA	NA	NA	2,186	19.1	17,818	40.8	1,341	25.8	8,877	59.6	2,148	17.8	12,328	28.2
Other	NA	NA	NA	NA	4,200	36.8	12,697	29.1	1,064	20.5	610	4.1	623	5.2	2,697	6.2
Unknown	NA	NA	NA	NA	0	0.0	0	0.0	0	0%	0	0%	4	0.0	7	0.0
Prior use of topical corticosteroids plain[b,e]																
0	907	23.3	2,144	14.1	3,714	32.5	11,435	26.2	1,391	26.8	141	0.9	5,507	45.5	15,576	35.6
1	642	16.5	5,720	37.5	3,961	34.7	27,292	62.5	1,421	27.3	369	2.5	2,669	22.1	18,353	41.9
2-3	899	23.1	5,427	35.6	2,677	23.4	4,342	9.9	1,452	27.9	12,751	85.6	2,429	20.1	7,693	17.6
4+	1,447	37.2	1,962	12.9	1,065	9.3	604	1.4	933	18.0	1,643	11.0	1,491	12.3	2,140	4.9
Prior use of topical corticosteroids combined[b,e]																
0	2,353	60.4	9,399	61.6	8,327	72.9	32,483	74.4	4,551	87.6	12,715	85.3	10,883	90.0	40,590	92.8
1	751	19.3	3,777	24.8	2,111	18.5	10,158	23.3	493	9.5	1,574	10.6	937	7.7	2,512	5.7
2-3	499	12.8	1,796	11.8	762	6.7	902	2.1	137	2.6	561	3.8	215	1.8	596	1.4
4+	292	7.5	281	1.8	217	1.9	130	0.3	16	0.3	54	0.4	61	0.5	64	0.1

UK-CPRD = Clinical Practice Research Datalink; HIV = human immunodeficiency virus; NA = not applicable; NL-PHARMO = PHARMO Database Network (the Netherlands).

Note: The matching ratio is not exactly 4:1 in some databases because in few strata of twentiles of propensity scores this ratio could not be attained.

Note: Data counts between 1-4 are reported as n <5 to comply with data protection rules.

Note: Sweden did not have information about the actual number of visits; therefore, a proxy was used based on the number of unique prescriptions made by GPs from the prescriber drug register.

[a] At any time before the start date.

[b] Within 12 months before the start date.

[c] "Immunosuppressants" category includes azathioprine (ATC code: L04AX01), methotrexate (ATC codes: L01BA01, L04AX03), cyclosporin (ATC code: L04AD01), and other immunosuppressants excluding systemic tacrolimus (ATC codes: L04AA, L04AB, L04AC, L04AX02, L04AX04)

[d] "Antineoplastic agents" category includes antineoplastic agents, except methotrexate (ATC codes: L01A, L01BA03-L01BA05, L01BB, L01BC, L01C, L01D, L01X)

[e] Variable not evaluated in the estimation of exposure propensity scores.

Annex 3 Table 2. Description of Demographic Characteristics of Tacrolimus Study Cohort at Cohort Entry Date, by Study Population—Adults

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Tacrolimus (N = 12,705)		Corticosteroids (N = 50,822)		Tacrolimus (N = 40,710)		Corticosteroids (N = 149,242)		Tacrolimus (N = 21,037)		Corticosteroids (N = 67,293)		Tacrolimus (N = 52,456)		Corticosteroids (N = 185,639)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Age (years)																
18-24	1,357	10.7	5,621	11.1	4,662	11.5	16,077	10.8	2,323	11.0	7,284	10.8	6,226	11.9	20,467	11.0
25-34	2,134	16.8	8,686	17.1	6,738	16.6	24,096	16.1	2,959	14.1	8,926	13.3	8,428	16.1	27,532	14.8
35-44	2,370	18.7	9,385	18.5	7,411	18.2	26,776	17.9	3,830	18.2	11,867	17.6	9,148	17.4	30,805	16.6
45-54	2,361	18.6	9,497	18.7	7,238	17.8	27,033	18.1	4,159	19.8	12,896	19.2	9,395	17.9	33,332	18.0
55-64	2,081	16.4	8,040	15.8	7,108	17.5	26,687	17.9	3,772	17.9	12,193	18.1	9,432	18.0	35,675	19.2
65-74	1,482	11.7	5,922	11.7	5,099	12.5	19,632	13.2	2,533	12.0	8,565	12.7	6,556	12.5	25,074	13.5
75-84	762	6.0	3,021	5.9	1,970	4.8	7,248	4.9	1,164	5.5	4,456	6.6	2,633	5.0	10,282	5.5
85+	158	1.2	650	1.3	484	1.2	1,693	1.1	297	1.4	1,106	1.6	638	1.2	2,472	1.3
Sex, female	7,654	60.2	30,412	59.8	24,368	59.9	88,909	59.6	13,252	63.0	41,948	62.3	32,181	61.3	111,883	60.3
Duration of follow-up (years)																
≤ 1	3,758	29.6	16,201	31.9	5,325	13.1	24,236	16.2	2,575	12.2	10,150	15.1	8,441	16.1	33,892	18.3
2-4	3,874	30.5	15,320	30.1	12,701	31.2	46,379	31.1	5,963	28.3	19,578	29.1	21,388	40.8	72,792	39.2
5+	5,073	39.9	19,301	38.0	22,684	55.7	78,627	52.7	12,499	59.4	37,565	55.8	22,627	43.1	78,955	42.5
Medical history[a]																
Diseases interacting with the immune system	6,604	52.0	24,046	47.3	4,013	9.9	13,750	9.2	364	1.7	1,133	1.7	10,153	19.4	35,346	19.0
Psoriasis	2,235	17.6	6,661	13.1	723	1.8	2,378	1.6	77	0.4	201	0.3	4,791	9.1	16,701	9.0
Epstein-Barr virus infection	222	1.7	889	1.7	40	0.1	113	0.1	87	0.4	281	0.4	135	0.3	434	0.2
Rheumatoid arthritis	193	1.5	890	1.8	392	1.0	1,434	1.0	65	0.3	207	0.3	563	1.1	2,722	1.5
Systemic lupus erythematosus	189	1.5	517	1.0	206	0.5	625	0.4	16	0.1	44	0.1	387	0.7	1,211	0.7
Sjögren’s syndrome	42	0.3	133	0.3	109	0.3	347	0.2	6	0.0	22	0.0	266	0.5	913	0.5
Celiac sprue	72	0.6	261	0.5	75	0.2	264	0.2	8	0.0	21	0.0	329	0.6	1,118	0.6

Annex 3 Table 2. Description of Demographic Characteristics of Tacrolimus Study Cohort at Cohort Entry Date, by Study Population—Adults

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Tacrolimus (N = 12,705)		Corticosteroids (N = 50,822)		Tacrolimus (N = 40,710)		Corticosteroids (N = 149,242)		Tacrolimus (N = 21,037)		Corticosteroids (N = 67,293)		Tacrolimus (N = 52,456)		Corticosteroids (N = 185,639)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Asthma	3,163	24.9	13,163	25.9	2,050	5.0	7,113	4.8	107	0.5	345	0.5	2,892	5.5	10,022	5.4
Allergic rhinitis	2,407	18.9	8,615	17.0	903	2.2	2,889	1.9	3	0.0	9	0.0	2,174	4.1	7,156	3.9
Disease of the immune system	93	0.7	359	0.7	179	0.4	641	0.4	10	0.0	30	0.0	336	0.6	1,140	0.6
Skin diseases	7,463	58.7	24,780	48.8	3,457	8.5	10,559	7.1	304	1.4	981	1.5	14,495	27.6	44,393	23.9
Chronic diseases	6,312	49.7	26,389	51.9	13,980	34.3	51,681	34.6	3,324	15.8	12,787	19.0	17,672	33.7	66,378	35.8
Malignancy other than study outcomes	569	4.5	2,297	4.5	1,422	3.5	5,437	3.6	518	2.5	1,838	2.7	2,182	4.2	8,768	4.7
Renal failure	603	4.7	2,358	4.6	225	0.6	849	0.6	105	0.5	359	0.5	391	0.7	1,950	1.1
Liver diseases	197	1.6	929	1.8	349	0.9	1,257	0.8	88	0.4	345	0.5	441	0.8	1,681	0.9
Ischemic heart disease	696	5.5	3,002	5.9	2,138	5.3	8,146	5.5	643	3.1	2,294	3.4	2,185	4.2	8,407	4.5
Hypertensive disease	2,487	19.6	11,099	21.8	3,372	8.3	12,981	8.7	387	1.8	1,398	2.1	5,113	9.7	20,975	11.3
Heart failure	154	1.2	639	1.3	501	1.2	1,888	1.3	135	0.6	515	0.8	726	1.4	2,858	1.5
Other cardiovascular diseases	1,192	9.4	5,194	10.2	3,018	7.4	11,241	7.5	664	3.2	2,417	3.6	3,953	7.5	15,541	8.4
Cerebrovascular diseases	348	2.7	1,618	3.2	1,099	2.7	4,192	2.8	235	1.1	844	1.3	1,213	2.3	4,691	2.5
Diabetes mellitus	915	7.2	4,279	8.4	1,452	3.6	5,638	3.8	326	1.5	1,111	1.7	2,082	4.0	8,156	4.4
Respiratory diseases	423	3.3	1,731	3.4	1,151	2.8	4,285	2.9	182	0.9	704	1.0	1,083	2.1	4,126	2.2
Musculoskeletal and connective diseases	4,191	33.0	17,323	34.1	7,664	18.8	27,298	18.3	1,577	7.5	6,202	9.2	9,946	19.0	36,105	19.4
Organ transplantation	32	0.3	91	0.2	59	0.1	209	0.1	29	0.1	101	0.2	257	0.5	800	0.4
HIV infection or AIDS	8	0.1	30	0.1	51	0.1	128	0.1	3	0.0	11	0.0	36	0.1	140	0.1

Annex 3 Table 2. Description of Demographic Characteristics of Tacrolimus Study Cohort at Cohort Entry Date, by Study Population—Adults

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Tacrolimus (N = 12,705)		Corticosteroids (N = 50,822)		Tacrolimus (N = 40,710)		Corticosteroids (N = 149,242)		Tacrolimus (N = 21,037)		Corticosteroids (N = 67,293)		Tacrolimus (N = 52,456)		Corticosteroids (N = 185,639)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Prior use of medications[b]																
Immunosuppressants and cytostatics	4,652	36.6	14,137	27.8	4,886	12.0	17,841	12.0	3,060	14.5	9,374	13.9	9,451	18.0	29,759	16.0
Systemic corticosteroids	4,352	34.3	13,050	25.7	3,477	8.5	12,638	8.5	2,453	11.7	7,645	11.4	7,059	13.5	22,216	12.0
Systemic tacrolimus	11	0.1	32	0.1	0	0.0	0	0.0	13	0.1	36	0.1	52	0.1	187	0.1
Immunosuppressants[c]	367	2.9	1,173	2.3	0	0.0	0	0.0	509	2.4	1,326	2.0	1,692	3.2	5,659	3.0
Systemic antivirals	298	2.3	1,118	2.2	1,570	3.9	5,743	3.8	286	1.4	813	1.2	1,934	3.7	5,669	3.1
Antineoplastic agents[d]	43	0.3	147	0.3	0	0.0	0	0.0	124	0.6	443	0.7	97	0.2	361	0.2
Immunostimulants	0	0.0	<5		0	0.0	0	0.0	16	0.1	57	0.1	106	0.2	396	0.2
Antipsoriatics topical	1,604	12.6	5,261	10.4	1,541	3.8	5,111	3.4	1,245	5.9	3,081	4.6	2,341	4.5	8,400	4.5
Antipsoriatics systemic	5	0.0	5	0.0	136	0.3	402	0.3	132	0.6	327	0.5	199	0.4	598	0.3
Other dermatological agents	12,705	100	33,272	65.5	15,987	39.3	49,311	33.0	21,037	100.0	41,634	61.9	24,987	47.6	88,393	47.6
Other medications	6,671	52.5	28,446	56.0	23,374	57.4	86,710	58.1	11,406	54.2	39,363	58.5	26,147	49.8	98,711	53.2
Cardiovascular system drugs	3,502	27.6	15,431	30.4	12,487	30.7	46,514	31.2	5,823	27.7	19,599	29.1	13,049	24.9	52,301	28.2
Anti-inflammatory agents	2,389	18.8	10,797	21.2	9,500	23.3	38,262	25.6	4,951	23.5	18,870	28.0	10,572	20.2	39,669	21.4
Other antirheumatic agents	7	0.1	26	0.1	n < 5	n < 5	18	0.0	3	0.0	11	0.0	5	0.0	24	0.0
Hormone-replacement therapy	694	5.5	2,661	5.2	3,580	8.8	13,072	8.8	608	2.9	2,082	3.1	5,312	10.1	19,005	10.2
Lipid-modifying agents	1,823	14.3	7,879	15.5	4,853	11.9	18,637	12.5	2,785	13.2	9,496	14.1	5,243	10.0	20,236	10.9
Insulins	183	1.4	778	1.5	665	1.6	2,608	1.7	421	2.0	1,674	2.5	1,084	2.1	4,040	2.2
Oral antidiabetics	464	3.7	2,249	4.4	1,329	3.3	5,147	3.4	973	4.6	3,399	5.1	1,585	3.0	6,979	3.8
Antiepileptics	510	4.0	2,469	4.9	1,385	3.4	5,156	3.5	551	2.6	1,916	2.8	1,578	3.0	7,010	3.8

Annex 3 Table 2. Description of Demographic Characteristics of Tacrolimus Study Cohort at Cohort Entry Date, by Study Population—Adults

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Tacrolimus (N = 12,705)		Corticosteroids (N = 50,822)		Tacrolimus (N = 40,710)		Corticosteroids (N = 149,242)		Tacrolimus (N = 21,037)		Corticosteroids (N = 67,293)		Tacrolimus (N = 52,456)		Corticosteroids (N = 185,639)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Drugs for asthma and COPD	1,564	12.3	6,585	13.0	4,332	10.6	15,937	10.7	2,771	13.2	9,310	13.8	5,869	11.2	20,914	11.3
Inhaled corticosteroids	1,532	12.1	6,447	12.7	1,853	4.6	6,169	4.1	987	4.7	3,189	4.7	2,404	4.6	8,648	4.7
Utilization of health care resources[b]																
General practitioner visits																
0	558	4.4	2,623	5.2	NA		NA		NA		NA		13,973	26.6	41,443	22.3
1	713	5.6	3,801	7.5	NA		NA		NA		NA		10,508	20.0	36,194	19.5
2-3	1,939	15.3	8,633	17.0	NA		NA		NA		NA		14,084	26.8	55,326	29.8
4+	9,495	74.7	35,765	70.4	NA		NA		NA		NA		13,891	26.5	52,676	28.4
Dermatologist visits																
0	10,459	82.3	41,941	82.5	NA		NA		NA		NA		34,815	66.4	125,107	67.4
1	1,004	7.9	5,402	10.6	NA		NA		NA		NA		9,618	18.3	40,231	21.7
2-3	885	7.0	2,854	5.6	NA		NA		NA		NA		5,623	10.7	16,264	8.8
4+	357	2.8	625	1.2	NA		NA		NA		NA		2,400	4.6	4,037	2.2
Paediatrician visits																
0	12,697	99.9	NR	99.9	NA		NA		NA		NA		52,251	99.6	184,942	99.6
1	[redacted]	[redacted]	NR	0.1	NA		NA		NA		NA		101	0.2	357	0.2
2-3	n < 5		NR	0.0	NA		NA		NA		NA		59	0.1	194	0.1
4+	0	0.0	NR	0.0	NA		NA		NA		NA		45	0.1	146	0.1
Emergency department visits																
0	11,658	91.8	46,619	91.7	36,247	89.0	132,710	88.9	NA		NA		NA		NA	
1	792	6.2	3,160	6.2	3,646	9.0	13,506	9.0	NA		NA		NA		NA	
2-3	224	1.8	890	1.8	722	1.8	2,683	1.8	NA		NA		NA		NA	
4+	31	0.2	153	0.3	95	0.2	343	0.2	NA		NA		NA		NA	

Annex 3 Table 2. Description of Demographic Characteristics of Tacrolimus Study Cohort at Cohort Entry Date, by Study Population—Adults

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Tacrolimus (N = 12,705)		Corticosteroids (N = 50,822)		Tacrolimus (N = 40,710)		Corticosteroids (N = 149,242)		Tacrolimus (N = 21,037)		Corticosteroids (N = 67,293)		Tacrolimus (N = 52,456)		Corticosteroids (N = 185,639)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Outpatient hospital visits																
0	8,206	64.6	31,481	61.9	NA		NA		NA		NA		13,758	26.2	44,800	24.1
1	1,577	12.4	7,181	14.1	NA		NA		NA		NA		12,346	23.5	48,076	25.9
2-3	1,507	11.9	6,665	13.1	NA		NA		NA		NA		12,826	24.5	47,716	25.7
4+	1,415	11.1	5,495	10.8	NA		NA		NA		NA		13,526	25.8	45,047	24.3
Hospitalisations																
0	11,457	90.2	45,771	90.1	35,116	86.3	128,865	86.3	18,902	89.9	64,114	95.3	47,199	90.0	162,455	87.5
1	876	6.9	3,368	6.6	3,756	9.2	13,452	9.0	1,388	6.6	2,166	3.2	3,682	7.0	15,718	8.5
2-3	299	2.4	1,369	2.7	1,437	3.5	5,410	3.6	530	2.5	771	1.1	1,200	2.3	5,604	3.0
4+	73	0.6	314	0.6	401	1.0	1,515	1.0	217	1.0	242	0.4	375	0.7	1,862	1.0
Prescriptions																
0	0	0.0	0	0.0	164	0.4	388	0.3	0	0.0	0	0.0	3,806	7.3	3,678	2.0
1	242	1.9	1,036	2.0	6,214	15.3	24,078	16.1	0	0.0	0	0.0	2,960	5.6	11,154	6.0
2-4	1,194	9.4	7,230	14.2	13,125	32.2	46,928	31.4	2,242	10.7	7,321	10.9	9,054	17.3	37,910	20.4
5-9	2,084	16.4	10,426	20.5	11,165	27.4	40,224	27.0	4,079	19.4	13,302	19.8	11,033	21.0	42,199	22.7
10+	9,185	72.3	32,130	63.2	10,042	24.7	37,624	25.2	14,716	70.0	46,670	69.4	25,603	48.8	90,698	48.9
Type of prescriber of first prescription[e]																
Dermatologist	NA	NA	NA	NA	17,231	42.3	58,395	39.1	11,210	53.3	29,644	44.1	37,511	71.5	125,428	67.6
Paediatrician	NA	NA	NA	NA	na	na	na	na	15	0.1	16	0.0	304	0.6	426	0.2
General practitioner	NA	NA	NA	NA	6,655	16.3	50,076	33.6	5,211	24.8	35,114	52.2	9,695	18.5	43,137	23.2
Other	NA	NA	NA	NA	16,777	41.2	40,751	27.3	4,601	21.9	2,519	3.7	4,924	9.4	16,631	9.0
Unknown	NA	NA	NA	NA	n < 5	n < 5	n < 5	n < 5	0	0%	0	0%	22	0.0	17	0.0

Annex 3 Table 2. Description of Demographic Characteristics of Tacrolimus Study Cohort at Cohort Entry Date, by Study Population—Adults

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Tacrolimus (N = 12,705)		Corticosteroids (N = 50,822)		Tacrolimus (N = 40,710)		Corticosteroids (N = 149,242)		Tacrolimus (N = 21,037)		Corticosteroids (N = 67,293)		Tacrolimus (N = 52,456)		Corticosteroids (N = 185,639)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Prior use of topical corticosteroids plain[b,e]																
0	4,173	32.8	9,253	18.2	17,922	44.0	34,284	23.0	6,007	28.6	1,369	2.0	27,271	52.0	40,957	22.1
1	2,784	21.9	17,851	35.1	11,832	29.1	107,038	71.7	5,568	26.5	2,345	3.5	11,156	21.3	105,558	56.9
2-3	2,757	21.7	21,380	42.1	7,562	18.6	7,193	4.8	5,574	26.5	60,808	90.4	8,963	17.1	30,769	16.6
4+	2,991	23.5	2,338	4.6	3,394	8.3	727	0.5	3,888	18.5	2,771	4.1	5,066	9.7	8,355	4.5
Prior use of topical corticosteroids combined[b,e]																
0	8,486	66.8	30,831	60.7	31,931	78.4	113,006	75.7	17,513	83.2	54,414	80.9	47,215	90.0	164,068	88.4
1	2,103	16.6	10,892	21.4	5,971	14.7	34,806	23.3	2,369	11.3	8,110	12.1	3,600	6.9	16,990	9.2
2-3	1,316	10.4	8,364	16.5	2,193	5.4	1,257	0.8	949	4.5	4,163	6.2	1,276	2.4	3,893	2.1
4+	800	6.3	735	1.4	615	1.5	173	0.1	206	1.0	606	0.9	365	0.7%	688	0.4

UK-CPRD = Clinical Practice Research Datalink; HIV = human immunodeficiency virus; NA = not applicable; na = not available; NR = not reported; NL-PHARMO = PHARMO Database Network (the Netherlands).

Note: The matching ratio is not exactly 4:1 in some databases because in few strata of twentiles of propensity scores this ratio could not be attained.

Note: Data counts between 1-4 are reported as n < 5 to comply with data protection rules.

Note: Sweden did not have information about the actual number of visits; therefore, a proxy was used based on the number of unique prescriptions made by GPs from the prescriber drug register.

[a] At any time before the start date.

[b] Within 12 months before the start date.

[c] "Immunosuppressants" category includes azathioprine (ATC code: L04AX01), methotrexate (ATC codes: L01BA01, L04AX03), cyclosporin (ATC code: L04AD01), and other immunosuppressants excluding systemic tacrolimus (ATC codes: L04AA, L04AB, L04AC, L04AX02, L04AX04)

[d] "Antineoplastic agents" category includes antineoplastic agents, except methotrexate (ATC codes: L01A, L01BA03-L01BA05, L01BB, L01BC, L01C, L01D, L01X)

[e] Variable not evaluated in the estimation of exposure propensity scores.

Annex 3 Table 3. Description of Demographic Characteristics of Pimecrolimus Study Cohort at Cohort Entry Date, by Study Population—Children

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Pimecrolimus (N = 2,752)		Corticosteroids (N = 11,008)		Pimecrolimus (N = 20,343)		Corticosteroids (N = 81,140)		Pimecrolimus (N = 3,189)		Corticosteroids (N = 12,168)		Pimecrolimus (N = 1,677)		Corticosteroids (N = 6,708)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Age (years)																
0-1	379	13.8	1,450	13.2	6,022	29.6	21,953	27.1	258	8.1	1,049	8.6	173	10.3	696	10.4
2-4	824	29.9	3,356	30.5	5,422	26.7	19,512	24.0	932	29.2	3,488	28.7	368	21.9	1,504	22.4
5-9	692	25.1	2,821	25.6	3,128	15.4	12,921	15.9	759	23.8	2,966	24.4	420	25.0	1,691	25.2
10-14	528	19.2	2,068	18.8	3,230	15.9	14,332	17.7	681	21.4	2,623	21.6	407	24.3	1,600	23.9
15-17	329	12.0	1,313	11.9	2,541	12.5	12,422	15.3	559	17.5	2,042	16.8	309	18.4	1,217	18.1
Sex, female	1,439	52.3	5,781	52.5	10,647	52.3	41,769	51.5	1,756	55.1	6,546	53.8	942	56.2	3,782	56.4
Duration of follow-up (years)																
≤ 1	568	20.6	2,491	22.6	1,331	6.5	10,483	12.9	299	9.4	1,545	12.7	223	13.3	1,088	16.2
2-4	637	23.1	2,635	23.9	3,282	16.1	14,692	18.1	726	22.8	3,011	24.7	535	31.9	2,174	32.4
5+	1,547	56.2	5,881	53.4	15,730	77.3	55,965	69.0	2,164	67.9	7,612	62.6	919	54.8	3,446	51.4
Medical history[a]																
Diseases interacting with the immune system	865	31.4	3,364	30.6	1,883	9.3	7,313	9.0	83	2.6	327	2.7	431	25.7	1,691	25.2
Psoriasis	50	1.8	327	3.0	39	0.2	178	0.2	0	0.0	5	0.0	24	1.4	148	2.2
Epstein-Barr virus infection	n < 5		24	0.2	14	0.1	70	0.1	49	1.5	189	1.6	4	0.2	14	0.2
Rheumatoid arthritis	n < 5		n<5		6	0.0	23	0.0	0	0.0	4	0.0	0	0.0	1	0.0
Systemic lupus erythematosus	0	0.0	n < 5		n < 5	n < 5	10	0.0	0	0.0	1	0.0	1	0.1	2	0.0
Sjögren's syndrome	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Celiac sprue	6	0.2	22	0.2	29	0.1	93	0.1	3	0.1	16	0.1	21	1.3	72	1.1
Asthma	623	22.6	2,544	23.1	1,704	8.4	6,626	8.2	31	1.0	114	0.9	325	19.4	1,285	19.2
Allergic rhinitis	369	13.4	1,158	10.5	293	1.4	909	1.1	0	0.0	5	0.0	158	9.4	620	9.2
Disease of the immune system	n < 5		9	0.1	32	0.2	143	0.2	0	0.0	3	0.0	11	0.7	34	0.5

Annex 3 Table 3. Description of Demographic Characteristics of Pimecrolimus Study Cohort at Cohort Entry Date, by Study Population—Children

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Pimecrolimus (N = 2,752)		Corticosteroids (N = 11,008)		Pimecrolimus (N = 20,343)		Corticosteroids (N = 81,140)		Pimecrolimus (N = 3,189)		Corticosteroids (N = 12,168)		Pimecrolimus (N = 1,677)		Corticosteroids (N = 6,708)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Skin diseases	935	34.0	3,462	31.4	484	2.4	1,589	2.0	23	0.7	76	0.6	265	15.8	924	13.8
Chronic diseases	157	5.7	634	5.8	777	3.8	3,517	4.3	41	1.3	167	1.4	93	5.5	375	5.6
Malignancy other than study outcomes	n < 5		10	0.1	24	0.1	96	0.1	3	0.1	8	0.1	0	0.0	5	0.1
Renal failure	n < 5		10	0.1	n < 5	n < 5	27	0.0	0	0.0	9	0.1	1	0.1	3	0.0
Liver diseases	n < 5		n < 5		11	0.1	48	0.1	1	0.0	3	0.0	0	0.0	9	0.1
Ischemic heart disease	n < 5		n < 5		n < 5	n < 5	16	0.0	0	0.0	0	0.0	0	0.0	3	0.0
Hypertensive disease	0	0.0	8	0.1	8	0.0	36	0.0	1	0.0	5	0.0	1	0.1	6	0.1
Heart failure	0	0.0	n < 5		10	0.0	33	0.0	1	0.0	4	0.0	2	0.1	6	0.1
Other cardiovascular diseases	28	1.0	101	0.9	63	0.3	268	0.3	4	0.1	21	0.2	16	1.0	65	1.0
Cerebrovascular diseases	n < 5		n < 5		11	0.1	50	0.1	1	0.0	4	0.0	0	0.0	9	0.1
Diabetes mellitus	8	0.3	25	0.2	27	0.1	207	0.3	8	0.3	19	0.2	7	0.4	27	0.4
Respiratory diseases	7	0.3	16	0.1	191	0.9	784	1.0	7	0.2	18	0.1	3	0.2	8	0.1
Musculoskeletal and connective diseases	109	4.0	496	4.5	462	2.3	2,131	2.6	16	0.5	83	0.7	68	4.1	258	3.8
Organ transplantation	n < 5		n < 5		6	0.0	36	0.0	0	0.0	0	0.0	2	0.1	5	0.1
HIV infection or AIDS	0	0.0	n < 5		0	0.0	n < 5	n < 5	0	0	1	0.0	0	0.0	0	0.0
Prior use of medications[b]																
Immunosuppressants and cytostatics	429	15.6	1,325	12.0	369	1.8	1,413	1.7	107	3.4	391	3.2	134	8.0	439	6.5
Systemic corticosteroids	417	15.2	1,280	11.6	138	0.7	541	0.7	90	2.8	344	2.8	126	7.5	399	5.9
Systemic tacrolimus	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.0	1	0.1	5	0.1
Immunosuppressants[c]	n < 5		13	0.1	0	0.0	0	0.0	7	0.2	25	0.2	6	0.4	33	0.5
Systemic antivirals	16	0.6	55	0.5	236	1.2	890	1.1	8	0.3	29	0.2	6	0.4	33	0.5
Antineoplastic agents[d]	0	0.0	n < 5		0	0.0	0	0.0	5	0.2	13	0.1	0	0.0	4	0.1

Annex 3 Table 3. Description of Demographic Characteristics of Pimecrolimus Study Cohort at Cohort Entry Date, by Study Population—Children

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Pimecrolimus (N = 2,752)		Corticosteroids (N = 11,008)		Pimecrolimus (N = 20,343)		Corticosteroids (N = 81,140)		Pimecrolimus (N = 3,189)		Corticosteroids (N = 12,168)		Pimecrolimus (N = 1,677)		Corticosteroids (N = 6,708)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Immunostimulants	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.0	0	0.0	0	0.0
Antipsoriatics topical	75	2.7	326	3.0	208	1.0	681	0.8	101	3.2	380	3.1	11	0.7	42	0.6
Antipsoriatics systemic	0	0.0	0	0.0	n < 5		n < 5		0	0.0	2	0.0	0	0.0	0	0.0
Other dermatological agents	2,752	100.0	9,138	83.0	7,612	37.4	25,235	31.1	3,189	100.0	9,033	74.2	889	53.0	3,128	46.6
Other medications	650	23.6	2,619	23.8	5,995	29.5	21,762	26.8	708	22.2	2,850	23.4	400	23.9	1,667	24.9
Cardiovascular system drugs	123	4.5	304	2.8	225	1.1	872	1.1	146	4.6	555	4.6	63	3.8	162	2.4
Anti-inflammatory agents	213	7.7	923	8.4	384	1.9	2,114	2.6	86	2.7	414	3.4	40	2.4	194	2.9
Other antirheumatic agents	0	0.0	n < 5		0	0.0	0	0.0					0	0.0	0	0.0
Hormone-replacement therapy	0	0.0	11	0.1	n < 5	n < 5	22	0.0	2	0.1	9	0.1	1	0.1	7	0.1
Lipid-modifying agents	n < 5		n < 5		n < 5	n < 5	11	0.0	1	0.0	2	0.0	0	0.0	2	0.0
Insulins	n < 5		5	0.0	27	0.1	192	0.2	8	0.3	21	0.2	4	0.2	23	0.3
Oral antidiabetics	0	0.0	n < 5		n < 5	n < 5	7	0.0	1	0.0	1	0.0	0	0.0	2	0.0
Antiepileptics	14	0.5	45	0.4	83	0.4	368	0.5	7	0.2	36	0.3	7	0.4	46	0.7
Drugs for asthma and COPD	383	13.9	1,593	14.5	4,928	24.2	17,538	21.6	476	14.9	1,855	15.2	331	19.7	1,318	19.6
Inhaled corticosteroids	383	13.9	1,593	14.5	2,503	12.3	8,603	10.6	256	8.0	998	8.2	172	10.3	773	11.5

Annex 3 Table 3. Description of Demographic Characteristics of Pimecrolimus Study Cohort at Cohort Entry Date, by Study Population—Children

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Pimecrolimus (N = 2,752)		Corticosteroids (N = 11,008)		Pimecrolimus (N = 20,343)		Corticosteroids (N = 81,140)		Pimecrolimus (N = 3,189)		Corticosteroids (N = 12,168)		Pimecrolimus (N = 1,677)		Corticosteroids (N = 6,708)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Utilization of health care resources[b]																
General practitioner visits																
0	139	5.1	827	7.5	NA		NA		NA		NA		625	37.3	1,947	29.0
1	231	8.4	1,288	11.7	NA		NA		NA		NA		467	27.8	1,716	25.6
2-3	569	20.7	2,657	24.1	NA		NA		NA		NA		422	25.2	2,241	33.4
4+	1,813	65.9	6,236	56.6	NA		NA		NA		NA		163	9.7	804	12.0
Dermatologist visits																
0	2,454	89.2	9,890	89.8	NA		NA		NA		NA		1,329	79.2	5,560	82.9
1	201	7.3	751	6.8	NA		NA		NA		NA		230	13.7	863	12.9
2-3	87	3.2	331	3.0	NA		NA		NA		NA		93	5.5	246	3.7
4+	10	0.4	36	0.3	NA		NA		NA		NA		25	1.5	39	0.6
Paediatrician visits																
0	2,543	92.4	10,228	92.9	NA		NA		NA		NA		1,070	63.8	4,259	63.5
1	119	4.3	434	3.9	NA		NA		NA		NA		229	13.7	974	14.5
2-3	70	2.5	269	2.4	NA		NA		NA		NA		222	13.2	890	13.3
4+	20	0.7	77	0.7	NA		NA		NA		NA		156	9.3	585	8.7
Emergency department visits																
0	2,465	89.6	9,938	90.3	17,397	85.5	69,105	85.2	NA		NA		NA		NA	
1	203	7.4	736	6.7	2,365	11.6	9,607	11.8	NA		NA		NA		NA	
2-3	[redacted]	[redacted]	309	2.8	536	2.6	2,233	2.8	NA		NA		NA		NA	
4+	n < 5		25	0.2	45	0.2	195	0.2	NA		NA		NA		NA	

Annex 3 Table 3. Description of Demographic Characteristics of Pimecrolimus Study Cohort at Cohort Entry Date, by Study Population—Children

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Pimecrolimus (N = 2,752)		Corticosteroids (N = 11,008)		Pimecrolimus (N = 20,343)		Corticosteroids (N = 81,140)		Pimecrolimus (N = 3,189)		Corticosteroids (N = 12,168)		Pimecrolimus (N = 1,677)		Corticosteroids (N = 6,708)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Outpatient hospital visits																
0	2,065	75.0	8,399	76.3	NA		NA		NA		NA		591	35.2	2,047	30.5
1	351	12.8	1,327	12.1	NA		NA		NA		NA		370	22.1	1,882	28.1
2-3	231	8.4	909	8.3	NA		NA		NA		NA		396	23.6	1,626	24.2
4+	105	3.8	373	3.4	NA		NA		NA		NA		320	19.1	1,153	17.2
Hospitalisations																
0	2,579	93.7	10,374	94.2	15,703	77.2	64,196	79.1	3,016	94.6	11,829	97.2	1,578	94.1	6,282	93.6
1	128	4.7	454	4.1	3,261	16.0	12,002	14.8	129	4.0	265	2.2	78	4.7	337	5.0
2-3	37	1.3	149	1.4	1,150	5.7	4,034	5.0	39	1.2	59	0.5	14	0.8	64	1.0
4+	8	0.3	31	0.3	229	1.1	908	1.1	5	0.2	15	0.1	7	0.4	25	0.4
Prescriptions																
0	0	0.0	0	0.0	151	0.7	2,663	3.3	0	0.0	0	0.0	206	12.3	530	7.9
1	64	2.3	302	2.7	6,650	32.7	28,586	35.2	0	0.0	0	0.0	194	11.6	863	12.9
2-4	368	13.4	2,287	20.8	9,117	44.8	34,902	43.0	785	24.6	2,963	24.4	459	27.4	2,473	36.9
5-9	595	21.6	3,417	31.0	3,339	16.4	11,563	14.3	952	29.9	3,824	31.4	430	25.6	1,768	26.4
10+	1,725	62.7	5,002	45.4	1,086	5.3	3,426	4.2	1,452	45.5	5,381	44.2	388	23.1	1,074	16.0
Type of prescriber of first prescription[e]																
Dermatologist	NA	NA	NA	NA	4,588	22.6	14,617	18.0	1,235	38.7	4,571	37.6	610	36.4	2,452	36.6
Paediatrician	NA	NA	NA	NA	628	3.1	956	1.2	66	2.1	250	2.1	471	28.1	1,584	23.6
General practitioner	NA	NA	NA	NA	6,807	33.5	36,152	44.6	1,437	45.1	6,911	56.8	355	21.2	2,157	32.2
Other	NA	NA	NA	NA	8,320	40.9	29,415	36.3	451	14.1	436	3.6	240	14.3	514	7.7
Unknown	NA	NA	NA	NA	0	0.0	0	0.0	0	0%	0	0%	1	0.1	1	0.0

Annex 3 Table 3. Description of Demographic Characteristics of Pimecrolimus Study Cohort at Cohort Entry Date, by Study Population—Children

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Pimecrolimus (N = 2,752)		Corticosteroids (N = 11,008)		Pimecrolimus (N = 20,343)		Corticosteroids (N = 81,140)		Pimecrolimus (N = 3,189)		Corticosteroids (N = 12,168)		Pimecrolimus (N = 1,677)		Corticosteroids (N = 6,708)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Prior use of topical corticosteroids plain[b,e]																
0	851	30.9	1,644	14.9	7,587	37.3	19,470	24.0	997	31.3	102	0.8	854	50.9	2,343	34.9
1	548	19.9	4,101	37.3	7,230	35.5	51,040	62.9	884	27.7	269	2.2	357	21.3	1,671	24.9
2-3	595	21.6	3,907	35.5	4,046	19.9	9,087	11.2	853	26.7	10,330	84.9	310	18.5	1,928	28.7
4+	758	27.5	1,356	12.3	1,480	7.3	1,543	1.9	455	14.3	1,467	12.1	156	9.3	766	11.4
Prior use of topical corticosteroids combined[b,e]																
0	1,752	63.7	6,561	59.6	15,263	75.0	59,581	73.4	2,795	87.6	10,389	85.4	1,521	90.7	6,260	93.3
1	526	19.1	2,803	25.5	3,660	18.0	19,503	24.0	304	9.5	1,288	10.6	131	7.8	180	2.7
2-3	318	11.6	1,474	13.4	1,175	5.8	1,808	2.2	76	2.4	454	3.7	18	1.1	245	3.7
4+	156	5.7	170	1.5	245	1.2	248	0.3	14	0.4	37	0.3	7	0.4	23	0.3

UK-CPRD = Clinical Practice Research Datalink; HIV = human immunodeficiency virus; NA = not applicable; NL-PHARMO = PHARMO Database Network (the Netherlands).

Note: The matching ratio is not exactly 4:1 in some databases because in few strata of twentiles of propensity scores this ratio could not be attained.

Note: Data counts between 1-4 are reported as n <5 to comply with data protection rules.

Note: Sweden did not have information about the actual number of visits; therefore, a proxy was used based on the number of unique prescriptions made by GPs from the prescriber drug register.

[a] At any time before the start date.

[b] Within 12 months before the start date.

[c] "Immunosuppressants" category includes azathioprine (ATC code: L04AX01), methotrexate (ATC codes: L01BA01, L04AX03), cyclosporin (ATC code: L04AD01), and other immunosuppressants excluding systemic tacrolimus (ATC codes: L04AA, L04AB, L04AC, L04AX02, L04AX04)

[d] "Antineoplastic agents" category includes antineoplastic agents, except methotrexate (ATC codes: L01A, L01BA03-L01BA05, L01BB, L01BC, L01C, L01D, L01X)

[e] Variable not evaluated in the estimation of exposure propensity scores.

Annex 3 Table 4. Description of Demographic Characteristics of Pimecrolimus Study Cohort at Cohort Entry Date, by Study Population—Adults

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Pimecrolimus (N = 5,124)		Corticosteroids (N = 20,496)		Pimecrolimus (N = 43,042)		Corticosteroids (N = 169,559)		Pimecrolimus (N = 8,506)		Corticosteroids (N = 33,841)		Pimecrolimus (N = 5,169)		Corticosteroids (N = 20,676)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Age (years)																
18-24	574	11.2	2,393	11.7	5,403	12.6	20,334	12.0	930	10.9	3,799	11.2	620	12.0	2,449	11.8
25-34	913	17.8	3,710	18.1	8,350	19.4	32,010	18.9	1,151	13.5	4,457	13.2	863	16.7	3,403	16.5
35-44	1,022	19.9	4,067	19.8	8,622	20.0	34,292	20.2	1,610	18.9	6,469	19.1	954	18.5	3,777	18.3
45-54	925	18.1	3,641	17.8	7,518	17.5	30,359	17.9	1,737	20.4	6,977	20.6	963	18.6	3,888	18.8
55-64	783	15.3	3,113	15.2	6,648	15.4	27,081	16.0	1,503	17.7	5,981	17.7	881	17.0	3,620	17.5
65-74	618	12.1	2,341	11.4	4,476	10.4	17,732	10.5	1,002	11.8	3,860	11.4	579	11.2	2,350	11.4
75-84	244	4.8	1,053	5.1	1,655	3.8	6,342	3.7	450	5.3	1,798	5.3	279	5.4	1,038	5.0
85+	45	0.9	178	0.9	370	0.9	1,409	0.8	123	1.4	500	1.5	30	0.6	151	0.7
Sex, female	3,295	64.3	12,944	63.2	27,720	64.4	109,234	64.4	5,556	65.3	22,130	65.4	3,148	60.9	12,600	60.9
Duration of follow-up (years)																
≤ 1	1,268	24.7	5,067	24.7	4,450	10.3	22,364	13.2	1,103	13	4,897	14.5	745	14.4	3,682	17.8
2-4	1,416	27.6	5,753	28.1	10,653	24.8	42,070	24.8	2,411	28.3	10,105	29.9	1,860	36.0	7,230	35.0
5+	2,440	47.6	9,676	47.2	27,939	64.9	105,125	62.0	4,992	58.7	18,839	55.7	2,564	49.6	9,764	47.2
Medical history[a]																
Diseases interacting with the immune system	2,373	46.3	9,368	45.7	3,739	8.7	13,480	8.0	130	1.5	499	1.5	843	16.3	4,005	19.4
Psoriasis	592	11.6	2,453	12.0	559	1.3	2,028	1.2	17	0.2	64	0.2	304	5.9	1,922	9.3
Epstein-Barr virus infection	89	1.7	382	1.9	34	0.1	136	0.1	36	0.4	143	0.4	14	0.3	49	0.2
Rheumatoid arthritis	64	1.2	278	1.4	335	0.8	1,305	0.8	22	0.3	78	0.2	44	0.9	266	1.3
Systemic lupus erythematosus	43	0.8	100	0.5	116	0.3	423	0.2	4	0.0	19	0.1	32	0.6	118	0.6
Sjögren’s syndrome	12	0.2	40	0.2	95	0.2	344	0.2	2	0.0	7	0.0	25	0.5	86	0.4
Celiac sprue	25	0.5	98	0.5	78	0.2	282	0.2	4	0.0	15	0.0	29	0.6	154	0.7

Annex 3 Table 4. Description of Demographic Characteristics of Pimecrolimus Study Cohort at Cohort Entry Date, by Study Population—Adults

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Pimecrolimus (N = 5,124)		Corticosteroids (N = 20,496)		Pimecrolimus (N = 43,042)		Corticosteroids (N = 169,559)		Pimecrolimus (N = 8,506)		Corticosteroids (N = 33,841)		Pimecrolimus (N = 5,169)		Corticosteroids (N = 20,676)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Asthma	1,259	24.6	5,213	25.4	1,996	4.6	7,260	4.3	41	0.5	151	0.4	297	5.7	1,132	5.5
Allergic rhinitis	1,006	19.6	3,437	16.8	965	2.2	3,141	1.9	2	0.0	10	0.0	257	5.0	877	4.2
Disease of the immune system	26	0.5	113	0.6	162	0.4	616	0.4	5	0.1	23	0.1	26	0.5	94	0.5
Skin diseases	2,813	54.9	9,648	47.1	2,439	5.7	7,984	4.7	110	1.3	446	1.3	1,256	24.3	4,754	23.0
Chronic diseases	2,369	46.2	10,197	49.8	12,742	29.6	49,841	29.4	1,358	16.0	6,047	17.9	1,647	31.9	6,690	32.4
Malignancy other than study outcomes	186	3.6	769	3.8	1,362	3.2	5,132	3.0	253	3.0	1,014	3.0	186	3.6	869	4.2
Renal failure	131	2.6	697	3.4	172	0.4	631	0.4	36	0.4	138	0.4	37	0.7	170	0.8
Liver diseases	68	1.3	344	1.7	304	0.7	1,208	0.7	36	0.4	121	0.4	38	0.7	133	0.6
Ischemic heart disease	222	4.3	1,040	5.1	1,777	4.1	6,963	4.1	245	2.9	971	2.9	197	3.8	821	4.0
Hypertensive disease	926	18.1	4,191	20.4	2,845	6.6	11,270	6.6	163	1.9	652	1.9	476	9.2	1,981	9.6
Heart failure	40	0.8	177	0.9	332	0.8	1,245	0.7	36	0.4	139	0.4	61	1.2	250	1.2
Other cardiovascular diseases	438	8.5	1,848	9.0	2,501	5.8	9,740	5.7	252	3.0	1,032	3.0	378	7.3	1,526	7.4
Cerebrovascular diseases	97	1.9	555	2.7	957	2.2	3,627	2.1	114	1.3	427	1.3	100	1.9	413	2.0
Diabetes mellitus	306	6.0	1,474	7.2	1,043	2.4	4,657	2.7	117	1.4	453	1.3	159	3.1	697	3.4
Respiratory diseases	129	2.5	555	2.7	917	2.1	3,721	2.2	85	1.0	356	1.1	75	1.5	287	1.4
Musculoskeletal and connective diseases	1,534	29.9	6,636	32.4	7,064	16.4	26,725	15.8	650	7.6	2,976	8.8	932	18.0	3,663	17.7
Organ transplantation	7	0.1	25	0.1	60	0.1	222	0.1	7	0.1	30	0.1	18	0.3	70	0.3
HIV infection or AIDS	n < 5		12	0.1	45	0.1	135	0.1	1	0.0	7	0.0	1	0.0	4	0.0
Prior use of medications[b]																
Immunosuppressants and cytostatics	1,596	31.1	5,257	25.6	4,562	10.6	17,625	10.4	1,081	12.7	4,198	12.4	872	16.9	3,170	15.3

Annex 3 Table 4. Description of Demographic Characteristics of Pimecrolimus Study Cohort at Cohort Entry Date, by Study Population—Adults

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Pimecrolimus (N = 5,124)		Corticosteroids (N = 20,496)		Pimecrolimus (N = 43,042)		Corticosteroids (N = 169,559)		Pimecrolimus (N = 8,506)		Corticosteroids (N = 33,841)		Pimecrolimus (N = 5,169)		Corticosteroids (N = 20,676)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Systemic corticosteroids	1,493	29.1	4,848	23.7	2,981	6.9	11,621	6.9	842	9.9	3,277	9.7	618	12.0	2,401	11.6
Systemic tacrolimus	n < 5		19	0.1	0	0.0	0	0.0	2	0.0	4	0.0	4	0.1	17	0.1
Immunosuppressants[c]	77	1.5	272	1.3	0	0.0	0	0.0	150	1.8	579	1.7	127	2.5	492	2.4
Systemic antivirals	105	2.0	445	2.2	1,739	4.0	6,491	3.8	108	1.3	410	1.2	226	4.4	632	3.1
Antineoplastic agents[d]	13	0.3	60	0.3	0	0.0	0	0.0	78	0.9	285	0.8	15	0.3	71	0.3
Immunostimulants	0	0.0	0	0.0	0	0.0	0	0.0	3	0.0	5	0.0	13	0.3	62	0.3
Antipsoriatics topical	404	7.9	1,829	8.9	1,364	3.2	5,121	3.0	358	4.2	1,460	4.3	226	4.4	959	4.6
Antipsoriatics systemic	0	0.0	n < 5		70	0.2	286	0.2	34	0.4	128	0.4	16	0.3	54	0.3
Other dermatological agents	5,124	100.0	12,756	62.2	19,150	44.5	54,186	32.0	8,506	100.0	20,662	61.1	2,573	49.8	9,916	48.0%
Other medications	2,572	50.2	11,128	54.3	23,939	55.6	94,584	55.8	4,499	52.9	18,841	55.7	2,529	48.9	10,541	51.0%
Cardiovascular system drugs	1,309	25.5	5,885	28.7	11,822	27.5	46,698	27.5	2,249	26.4	8,963	26.5	1,243	24.0	5,220	25.2
Anti-inflammatory agents	914	17.8	4,400	21.5	10,221	23.7	43,907	25.9	1,933	22.7	9,348	27.6	1,050	20.3	4,421	21.4
Other antirheumatic agents	n < 5		n < 5		n < 5	n < 5	7	0.0	0	0.0	1	0.0	2	0.0	3	0.0
Hormone-replacement therapy	305	6.0	1,091	5.3	3,992	9.3	15,823	9.3	204	2.4	899	2.7	512	9.9	2,034	9.8
Lipid-modifying agents	577	11.3	2,761	13.5	4,022	9.3	16,044	9.5	1,005	11.8	4,004	11.8	501	9.7	2,082	10.1
Insulins	57	1.1	217	1.1	426	1.0	2,337	1.4	142	1.7	704	2.1	55	1.1	236	1.1
Oral antidiabetics	142	2.8	796	3.9	953	2.2	3,640	2.1	339	4.0	1,383	4.1	135	2.6	647	3.1
Antiepileptics	183	3.6	814	4.0	1,343	3.1	5,352	3.2	215	2.5	865	2.6	121	2.3	702	3.4
Drugs for asthma and COPD	631	12.3	2,636	12.9	4,321	10.0	17,178	10.1	1,091	12.8	4,395	13.0	589	11.4	2,289	11.1
Inhaled corticosteroids	625	12.2	2,612	12.7	2,037	4.7	7,141	4.2	364	4.3	1,465	4.3	248	4.8	957	4.6

Annex 3 Table 4. Description of Demographic Characteristics of Pimecrolimus Study Cohort at Cohort Entry Date, by Study Population—Adults

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Pimecrolimus (N = 5,124)		Corticosteroids (N = 20,496)		Pimecrolimus (N = 43,042)		Corticosteroids (N = 169,559)		Pimecrolimus (N = 8,506)		Corticosteroids (N = 33,841)		Pimecrolimus (N = 5,169)		Corticosteroids (N = 20,676)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Utilization of health care resources[b]																
General practitioner visits																
0	214	4.2	1,033	5.0	NA		NA		NA		NA		1,538	29.8	4,853	23.5
1	333	6.5	1,594	7.8	NA		NA		NA		NA		1,048	20.3	4,105	19.9
2-3	846	16.5	3,635	17.7	NA		NA		NA		NA		1,373	26.6	6,133	29.7
4+	3,731	72.8	14,234	69.4	NA		NA		NA		NA		1,210	23.4	5,585	27.0
Dermatologist visits																
0	4,513	88.1	18,049	88.1	NA		NA		NA		NA		3,871	74.9	14,073	68.1
1	301	5.9	1,484	7.2	NA		NA		NA		NA		757	14.6	4,305	20.8
2-3	220	4.3	809	3.9	NA		NA		NA		NA		395	7.6	1,838	8.9
4+	90	1.8	154	0.8	NA		NA		NA		NA		146	2.8	460	2.2
Paediatrician visits																
0	5,119	99.9	20,478	99.9	NA		NA		NA		NA		5,144	99.5	20,574	99.5
1	5	0.1	11	0.1	NA		NA		NA		NA		13	0.3	55	0.3
2-3	0	0.0	7	0.0	NA		NA		NA		NA		7	0.1	23	0.1
4+	0	0.0	0	0.0	NA		NA		NA		NA		5	0.1	24	0.1
Emergency department visits																
0	4,775	93.2	19,001	92.7	38,276	88.9	150,687	88.9	NA		NA		NA		NA	
1	277	5.4	1,140	5.6	3,920	9.1	15,565	9.2	NA		NA		NA		NA	
2-3	66	1.3	321	1.6	762	1.8	2,974	1.8	NA		NA		NA		NA	
4+	6	0.1	34	0.2	84	0.2	333	0.2	NA		NA		NA		NA	

Annex 3 Table 4. Description of Demographic Characteristics of Pimecrolimus Study Cohort at Cohort Entry Date, by Study Population—Adults

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Pimecrolimus (N = 5,124)		Corticosteroids (N = 20,496)		Pimecrolimus (N = 43,042)		Corticosteroids (N = 169,559)		Pimecrolimus (N = 8,506)		Corticosteroids (N = 33,841)		Pimecrolimus (N = 5,169)		Corticosteroids (N = 20,676)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Outpatient hospital visits																
0	3,601	70.3	13,934	68.0	NA		NA		NA		NA		1,902	36.8	5,123	24.8
1	583	11.4	2,630	12.8	NA		NA		NA		NA		1,083	21.0	5,586	27.0
2-3	505	9.9	2,257	11.0	NA		NA		NA		NA		1,093	21.1	5,210	25.2
4+	435	8.5	1,675	8.2	NA		NA		NA		NA		1,091	21.1	4,757	23.0
Hospitalisations																
0	4,743	92.6	18,734	91.4	37,569	87.3	148,143	87.4	7,748	91.1	32,464	95.9	4,695	90.8	18,332	88.7
1	246	4.8	1,221	6.0	3,888	9.0	15,123	8.9	482	5.7	941	2.8	360	7.0	1,605	7.8
2-3	103	2.0	450	2.2	1,263	2.9	4,997	2.9	189	2.2	331	1.0	94	1.8	562	2.7
4+	32	0.6	91	0.4	322	0.7	1,296	0.8	87	1.0	105	0.3	20	0.4	177	0.9
Prescriptions																
0	0	0.0	0	0.0	n < 5	n < 5	143	0.1	0	0.0	0	0.0	339	6.6	425	2.1
1	116	2.3	436	2.1	7,144	16.6	28,759	17.0	0	0.0	0	0.0	309	6.0	1,296	6.3
2-4	588	11.5	3,121	15.2	14,437	33.5	56,883	33.5	1,000	11.8	3,916	11.6	942	18.2	4,377	21.2
5-9	998	19.5	4,493	21.9	12,449	28.9	48,301	28.5	1,928	22.7	7,591	22.4	1,104	21.4	4,757	23.0
10+	3,422	66.8	12,445	60.7	.	.	35,473	20.9	5,578	65.6	22,334	66.0	2,475	47.9	9,821	47.5
Type of prescriber of first prescription[e]																
Dermatologist	NA		NA		14,525	33.7	54,519	32.2	3,805	44.7	15,522	45.9	3,487	67.5	14,035	67.9
Paediatrician	NA		NA		NA	NA	21	0.0	3	0.0	6	0.0	52	1.0	71	0.3
General practitioner	NA		NA		10,594	24.6	60,052	35.4	3,098	36.4	17,126	50.6	1,096	21.2	4,683	22.6
Other	NA		NA		17,889	41.6	54,967	32.4	1,600	18.8	1,187	3.5	528	10.2	1,886	9.1
Unknown	NA		NA		n < 5	n < 5	0	0.0	0	0%	0	0%	6	0.1	1	0.0

Annex 3 Table 4. Description of Demographic Characteristics of Pimecrolimus Study Cohort at Cohort Entry Date, by Study Population—Adults

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Pimecrolimus (N = 5,124)		Corticosteroids (N = 20,496)		Pimecrolimus (N = 43,042)		Corticosteroids (N = 169,559)		Pimecrolimus (N = 8,506)		Corticosteroids (N = 33,841)		Pimecrolimus (N = 5,169)		Corticosteroids (N = 20,676)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Prior use of topical corticosteroids plain[b,e]																
0	2,179	42.5	3,818	18.6	22,684	52.7	38,863	22.9	3,029	35.6	690	2.0	2,870	55.5	4,598	22.2
1	1,176	23.0	7,444	36.3	11,843	27.5	120,969	71.3	2,511	29.5	1,263	3.7	1,082	20.9	5,524	26.7
2-3	937	18.3	8,461	41.3	6,223	14.5	8,653	5.1	1,955	23.0	30,728	90.8	789	15.3	8,058	39.0
4+	832	16.2	773	3.8	2,292	5.3	1,074	0.6	1,011	11.9	1,160	3.4	428	8.3	2,496	12.1
Prior use of topical corticosteroids combined[b,e]																
0	3,726	72.7	12,543	61.2	35,823	83.2	126,951	74.9	7,138	83.9	27,272	80.6	4,676	90.5	18,130	87.7
1	763	14.9	4,426	21.6	5,195	12.1	40,769	24.0	947	11.1	4,238	12.5	354	6.8	888	4.3
2-3	426	8.3	3,322	16.2	1,662	3.9	1,633	1.0	357	4.2	2,086	6.2	104	2.0	1,446	7.0
4+	209	4.1	205	1.0	362	0.8	206	0.1	64	0.8	245	0.7	35	0.7	212	1.0

UK-CPRD = Clinical Practice Research Datalink; HIV = human immunodeficiency virus; NA = not applicable; NL-PHARMO = PHARMO Database Network (the Netherlands).

Note: The matching ratio is not exactly 4:1 in some databases because in few strata of twentiles of propensity scores this ratio could not be attained.

Note: Data counts between 1-4 are reported as n <5 to comply with data protection rules.

Note: Sweden did not have information about the actual number of visits; therefore, a proxy was used based on the number of unique prescriptions made by GPs from the prescriber drug register.

[a] At any time before the start date.

[b] Within 12 months before the start date.

[c] "Immunosuppressants" category includes azathioprine (ATC code: L04AX01), methotrexate (ATC codes: L01BA01, L04AX03), cyclosporin (ATC code: L04AD01), and other immunosuppressants excluding systemic tacrolimus (ATC codes: L04AA, L04AB, L04AC, L04AX02, L04AX04)

[d] "Antineoplastic agents" category includes antineoplastic agents, except methotrexate (ATC codes: L01A, L01BA03-L01BA05, L01BB, L01BC, L01C, L01D, L01X)

[e] Variable not evaluated in the estimation of exposure propensity scores.

Annex 3 Table 5. Description of Demographic Characteristics of the Untreated Study Cohort at Cohort Entry Date, by Study Population—Children

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Untreated Cohort (N = 61,001)		Corticosteroids (N = 15,253)		Untreated Cohort (N = 158,089)		Corticosteroids (N = 43,673)		Untreated Cohort (N = 58,424)		Corticosteroids (N = 14,904)		Untreated Cohort (N = 84,070)		Corticosteroids (N = 43,762)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Age (years)																
0-1	4,989	8.2	1,181	7.7	27,262	17.2	7,019	16.1	1,696	2.9	514	3.4	6,176	7.3	2,924	6.7
2-4	14,644	24.0	3,732	24.5	35,218	22.3	9,853	22.6	12,344	21.1	3,112	20.9	15,303	18.2	8,271	18.9
5-9	16,580	27.2	4,144	27.2	33,247	21.0	8,755	20.0	15,223	26.1	3,867	25.9	21,769	25.9	11,270	25.8
10-14	14,864	24.4	3,713	24.3	35,344	22.4	9,862	22.6	15,914	27.2	4,039	27.1	22,290	26.5	11,492	26.3
15-17	9,924	16.3	2,483	16.3	27,018	17.1	8,184	18.7	13,247	22.7	3,372	22.6	18,532	22.0	9,805	22.4
Sex, female	31,271	51.3	7,818	51.3	84,070	53.2	22,850	52.3	30,615	52.4	7,802	52.3	44,953	53.5	23,429	53.5
Duration of follow-up (years)																
≤ 1	20,802	34.1	4,516	29.6	32,605	20.6	6,110	14.0	7,746	13.3	2,025	13.6	14,894	17.7	7,223	16.5
2-4	18,727	30.7	4,400	28.8	44,215	28.0	10,320	23.6	16,824	28.8	3,977	26.7	32,308	38.4	16,314	37.3
5+	21,472	35.2	6,337	41.5	81,269	51.4	27,243	62.4	33,854	57.9	8,902	59.7	36,868	43.9	20,225	46.2
Medical history[a]																
Diseases interacting with the immune system	10,470	17.2	5,563	36.5	8,838	5.6	4,286	9.8	1,105	1.9	496	3.3	8,403	10.0	11,016	25.2
Psoriasis	196	0.3	558	3.7	55	0.0	123	0.3	1	0.0	2	0.0	103	0.1	1,353	3.1
Epstein-Barr virus infection	146	0.2	54	0.4	116	0.1	46	0.1	728	1.2	251	1.7	102	0.1	73	0.2
Rheumatoid arthritis	18	0.0	n < 5		38	0.0	10	0.0	5	0.0	4	0.0	14	0.0	8	0.0
Systemic lupus erythematosus	[redacted]	0.0	n < 5		5	0.0	8	0.0	2	0.0	1	0.0	4	0.0	26	0.1
Sjögren's syndrome	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	3	0.0	3	0.0
Celiac sprue	68	0.1	25	0.2	116	0.1	49	0.1	20	0.0	12	0.1	525	0.6	429	1.0
Asthma	7,472	12.2	4,214	27.6	8,103	5.1	3,814	8.7	349	0.6	225	1.5	6,777	8.1	8,012	18.3
Allergic rhinitis	4,009	6.6	2,005	13.1	757	0.5	592	1.4	9	0.0	10	0.1	1,904	2.3	4,182	9.6
Disease of the immune system	29	0.0	26	0.2	197	0.1	86	0.2	19	0.0	5	0.0	119	0.1	213	0.5

Annex 3 Table 5. Description of Demographic Characteristics of the Untreated Study Cohort at Cohort Entry Date, by Study Population—Children

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Untreated Cohort (N = 61,001)		Corticosteroids (N = 15,253)		Untreated Cohort (N = 158,089)		Corticosteroids (N = 43,673)		Untreated Cohort (N = 58,424)		Corticosteroids (N = 14,904)		Untreated Cohort (N = 84,070)		Corticosteroids (N = 43,762)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Skin diseases	11,162	18.3	5,272	34.6	1,516	1.0	1,178	2.7	190	0.3	117	0.8	3,346	4.0	6,138	14.0
Chronic diseases	3,356	5.5	1,099	7.2	6,278	4.0	2,343	5.4	530	0.9	244	1.6	3,774	4.5	2,743	6.3
Malignancy other than study outcomes	66	0.1	12	0.1	142	0.1	33	0.1	56	0.1	20	0.1	56	0.1	52	0.1
Renal failure	34	0.1	19	0.1	45	0.0	11	0.0	14	0.0	4	0.0	44	0.1	36	0.1
Liver diseases	27	0.0	16	0.1	57	0.0	28	0.1	15	0.0	4	0.0	58	0.1	51	0.1
Ischemic heart disease	9	0.0	0	0.0	19	0.0	n < 5	n < 5	0	0.0	0	0.0	10	0.0	9	0.0
Hypertensive disease	30	0.0	17	0.1	64	0.0	24	0.1	22	0.0	8	0.1	42	0.0	40	0.1
Heart failure	16	0.0	6	0.0	50	0.0	18	0.0	8	0.0	0	0.0	27	0.0	24	0.1
Other cardiovascular diseases	490	0.8	170	1.1	525	0.3	194	0.4	52	0.1	24	0.2	428	0.5	344	0.8
Cerebrovascular diseases	44	0.1	13	0.1	90	0.1	39	0.1	12	0.0	4	0.0	47	0.1	39	0.1
Diabetes mellitus	218	0.4	85	0.6	269	0.2	172	0.4	60	0.1	25	0.2	312	0.4	235	0.5
Respiratory diseases	35	0.1	20	0.1	1,133	0.7	476	1.1	53	0.1	31	0.2	195	0.2	134	0.3
Musculoskeletal and connective diseases	2,551	4.2	807	5.3	4,123	2.6	1,463	3.3	259	0.4	136	0.9	2,682	3.2	1,905	4.4
Organ transplantation	9	0.0	16	0.1	29	0.0	26	0.1	11	0.0	5	0.0	24	0.0	65	0.1
HIV infection or AIDS	n<5	0.0	n < 5		16	0.0	5	0.0	0	0	1	0.0	8	0.0	2	0.0
Prior use of medications[b]																
Immunosuppressants and cytostatics	4,299	7.0	2,431	15.9	1,196	0.8	877	2.0	391	0.7	611	4.1	1,553	1.8	2,988	6.8
Systemic corticosteroids	4,094	6.7	2,285	15.0	323	0.2	385	0.9	307	0.5	521	3.5	1,297	1.5	2,663	6.1
Systemic tacrolimus	[redacted]	0.0	[redacted]	0.0	0	0.0	0	0.0	3	0.0	2	0.0	11	0.0	17	0.0

[redacted]

Annex 3 Table 5. Description of Demographic Characteristics of the Untreated Study Cohort at Cohort Entry Date, by Study Population—Children

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Untreated Cohort (N = 61,001)		Corticosteroids (N = 15,253)		Untreated Cohort (N = 158,089)		Corticosteroids (N = 43,673)		Untreated Cohort (N = 58,424)		Corticosteroids (N = 14,904)		Untreated Cohort (N = 84,070)		Corticosteroids (N = 43,762)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Immunosuppressants[c]	38	0.1	52	0.3	0	0.0	0	0.0	34	0.1	45	0.3	111	0.1	241	0.6
Systemic antivirals	210	0.3	171	1.1	882	0.6	508	1.2	49	0.1	71	0.5	211	0.3	283	0.6
Antineoplastic agents[d]	11	0.0	7	0.0	0	0.0	0	0.0	15	0.0	17	0.1	9	0.0	28	0.1
Immunostimulants	0	0.0	0	0.0	0	0.0	0	0.0	2	0.0	5	0.0	2	0.0	3	0.0
Antipsoriatics topical	590	3.9	590	3.9	112	0.1	473	1.1	39	0.1	442	3.0	9	0.0	419	1.0
Antipsoriatics systemic	0	0.0	0	0.0	0	0.0	0	0.0	-	-	6	0.0	0	0.0	7	0.0
Other dermatological agents	11,866	19.5	12,632	82.8	16,276	10.3	14,951	34.2	7,953	13.6	11,090	74.4	4,437	5.3	20,251	46.3
Other medications	7,950	13.0	4,158	27.3	21,999	13.9	10,349	23.7	5,774	9.9	3,647	24.5	9,572	11.4	10,477	23.9
Cardiovascular system drugs	651	1.1	472	3.1	829	0.5	510	1.2	492	0.8	610	4.1	586	0.7	1,121	2.6
Anti-inflammatory agents	4,029	6.6	1,358	8.9	2,978	1.9	1,395	3.2	1,417	2.4	655	4.4	1,647	2.0	1,294	3.0
Other antirheumatic agents	0	0.0	0	0.0	0	0.0	0	0.0			0	0.0	2	0.0	0	0.0
Hormone-replacement therapy	7	0.0	5	0.0	35	0.0	18	0.0	25	0.0	22	0.1	21	0.0	15	0.0
Lipid-modifying agents	7	0.0	7	0.0	8	0.0	9	0.0	14	0.0	6	0.0	8	0.0	0	0.0
Insulins	105	0.2	38	0.2	245	0.2	170	0.4	84	0.1	28	0.2	281	0.3	211	0.5
Oral antidiabetics	7	0.0	5	0.0	14	0.0	n < 5	n < 5	5	0.0	10	0.1	15	0.0	9	0.0
Antiepileptics	221	0.4	80	0.5	494	0.3	202	0.5	177	0.3	51	0.3	364	0.4	333	0.8
Drugs for asthma and COPD	3,495	5.7	2,693	17.7	16,395	10.4	7,743	17.7	3,411	5.8	2,345	15.7	6,745	8.0	8,136	18.6
Inhaled corticosteroids	3,494	5.7	2,687	17.6	7,314	4.6	4,288	9.8	1,889	3.2	1,333	8.9	3,053	3.6	4,316	9.9

Annex 3 Table 5. Description of Demographic Characteristics of the Untreated Study Cohort at Cohort Entry Date, by Study Population—Children

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Untreated Cohort (N = 61,001)		Corticosteroids (N = 15,253)		Untreated Cohort (N = 158,089)		Corticosteroids (N = 43,673)		Untreated Cohort (N = 58,424)		Corticosteroids (N = 14,904)		Untreated Cohort (N = 84,070)		Corticosteroids (N = 43,762)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Utilization of health care resources[b]																
General practitioner visits																
0	16,537	27.1	1,295	8.5	NA		NA		NA		NA		58,571	69.7	12,711	29.0
1	11,676	19.1	1,849	12.1	NA		NA		NA		NA		15,778	18.8	11,347	25.9
2-3	15,111	24.8	3,725	24.4	NA		NA		NA		NA		8,158	9.7	14,373	32.8
4+	17,677	29.0	8,384	55.0	NA		NA		NA		NA		1,563	1.9	5,331	12.2
Dermatologist visits																
0	60,699	99.5	13,178	86.4	NA		NA		NA		NA		83,191	99.0	34,259	78.3
1	200	0.3	1,491	9.8	NA		NA		NA		NA		675	0.8	7,182	16.4
2-3	79	0.1	500	3.3	NA		NA		NA		NA		164	0.2	1,957	4.5
4+	23	0.0	84	0.6	NA		NA		NA		NA		40	0.0	364	0.8
Paediatrician visits																
0	58,201	95.4	13,970	91.6	NA		NA		NA		NA		69,850	83.1	28,229	64.5
1	1,701	2.8	734	4.8	NA		NA		NA		NA		7,773	9.2	7,074	16.2
2-3	870	1.4	402	2.6	NA		NA		NA		NA		4,459	5.3	5,400	12.3
4+	229	0.4	147	1.0	NA		NA		NA		NA		1,988	2.4	3,059	7.0
Emergency department visits																
0	55,393	90.8	13,496	88.5	137,251	86.8	37,264	85.3	NA		NA		NA		NA	
1	4,301	7.1	1,309	8.6	16,912	10.7	5,079	11.6	NA		NA		NA		NA	
2-3	1,164	1.9	390	2.6	3,663	2.3	1,240	2.8	NA		NA		NA		NA	
4+	143	0.2	58	0.4	263	0.2	90	0.2	NA		NA		NA		NA	

Annex 3 Table 5. Description of Demographic Characteristics of the Untreated Study Cohort at Cohort Entry Date, by Study Population—Children

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Untreated Cohort (N = 61,001)		Corticosteroids (N = 15,253)		Untreated Cohort (N = 158,089)		Corticosteroids (N = 43,673)		Untreated Cohort (N = 58,424)		Corticosteroids (N = 14,904)		Untreated Cohort (N = 84,070)		Corticosteroids (N = 43,762)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Outpatient hospital visits																
0	52,501	86.1	10,945	71.8	NA		NA		NA		NA		57,093	67.9	11,703	26.7
1	4,856	8.0	2,184	14.3	NA		NA		NA		NA		13,273	15.8	13,713	31.3
2-3	2,629	4.3	1,455	9.5	NA		NA		NA		NA		9,128	10.9	11,036	25.2
4+	1,015	1.7	669	4.4	NA		NA		NA		NA		4,576	5.4	7,310	16.7
Hospitalisations																
0	58,307	95.6	14,271	93.6	136,226	86.2	36,503	83.6	55,396	94.8	14,466	97.1	81,141	96.5	41,214	94.2
1	2,048	3.4	716	4.7	16,468	10.4	4,961	11.4	2,437	4.2	347	2.3	2,447	2.9	1,950	4.5
2-3	570	0.9	219	1.4	4,550	2.9	1,821	4.2	513	0.9	70	0.5	406	0.5	439	1.0
4+	76	0.1	47	0.3	845	0.5	388	0.9	78	0.1	21	0.1	76	0.1	159	0.4
Prescriptions																
0	24,247	39.7	0	0.0	115,722	73.2	2,761	6.3	29,807	51.0	0	0.0	44,708	53.2	3,561	8.1
1	9,475	15.5	435	2.9	20,812	13.2	13,455	30.8	8,532	14.6	0	0.0	13,871	16.5	5,499	12.6
2-4	14,597	23.9	3,167	20.8	14,727	9.3	18,743	42.9	12,095	20.7	3,315	22.2	16,818	20.0	15,940	36.4
5-9	7,655	12.5	4,561	29.9	5,503	3.5	6,466	14.8	5,414	9.3	4,689	31.5	6,176	7.3	11,755	26.9
10+	5,027	8.2	7,090	46.5	1,325	0.8	2,248	5.1	2,576	4.4	6,900	46.3	2,497	3.0	7,007	16.0

COPD = chronic obstructive pulmonary disease; UK-CPRD = Clinical Practice Research Datalink; HIV = human immunodeficiency virus; NA = not applicable; NL-PHARMO = PHARMO Database Network (the Netherlands).

Note: Data counts between 1-4 are reported as n <5 to comply with data protection rules.

Note: Sweden did not have information about the actual number of visits; therefore, a proxy was used based on the number of unique prescriptions made by GPs from the prescriber drug register.

[a] At any time before the start date.

[b] Within 12 months before the start date.

[c] "Immunosuppressants" category includes azathioprine (ATC code: L04AX01), methotrexate (ATC codes: L01BA01, L04AX03), cyclosporin (ATC code: L04AD01), and other immunosuppressants excluding systemic tacrolimus (ATC codes: L04AA, L04AB, L04AC, L04AX02, L04AX04)

[d] "Antineoplastic agents" category includes antineoplastic agents, except methotrexate (ATC codes: L01A, L01BA03-L01BA05, L01BB, L01BC, L01C, L01D, L01X)

Annex 3 Table 6. Description of Demographic Characteristics of the Untreated Study Cohort at Cohort Entry Date, by Study Population—Adults

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Untreated Cohort (N = 202,459)		Corticosteroids (N = 50,822)		Untreated Cohort (N = 484,789)		Corticosteroids (N = 149,242)		Untreated Cohort (N = 264,378)		Corticosteroids (N = 67,293)		Untreated Cohort (N = 339,416)		Corticosteroids (N = 185,639)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Age (years)																
18-24	22,462	11.1	5,621	11.1	53,517	11.0	16,077	10.8	28,578	10.8	7,284	10.8	39,469	11.6	20,467	11.0
25-34	34,731	17.2	8,686	17.1	89,239	18.4	24,096	16.1	35,278	13.3	8,926	13.3	52,231	15.4	27,532	14.8
35-44	37,525	18.5	9,385	18.5	96,851	20.0	26,776	17.9	46,879	17.7	11,867	17.6	58,651	17.3	30,805	16.6
45-54	37,974	18.8	9,497	18.7	88,860	18.3	27,033	18.1	50,791	19.2	12,896	19.2	62,368	18.4	33,332	18.0
55-64	32,146	15.9	8,040	15.8	79,838	16.5	26,687	17.9	47,828	18.1	12,193	18.1	64,673	19.1	35,675	19.2
65-74	23,633	11.7	5,922	11.7	53,821	11.1	19,632	13.2	33,424	12.6	8,565	12.7	42,897	12.6	25,074	13.5
75-84	11,859	5.9	3,021	5.9	18,628	3.8	7,248	4.9	17,371	6.6	4,456	6.6	16,000	4.7	10,282	5.5
85+	2,129	1.1	650	1.3	4,035	0.8	1,693	1.1	4,229	1.6	1,106	1.6	3,127	0.9	2,472	1.3
Sex, female	121,208	59.9	30,412	59.8	288,207	59.4	88,909	59.6	164,703	62.3	41,948	62.3	203,537	60.0	111,883	60.3
Duration of follow-up (years)																
≤ 1	77,761	38.4	16,201	31.9	126,416	26.1	24,236	16.2	47,144	17.8	10,150	15.1	69,871	20.6	33,892	18.3
2-4	64,870	32.0	15,320	30.1	157,441	32.5	46,379	31.1	81,322	30.8	19,578	29.1	137,332	40.5	72,792	39.2
5+	59,828	29.6	19,301	38.0	200,932	41.4	78,627	52.7	135,912	51.4	37,565	55.8	132,213	39.0	78,955	42.5
Medical history[a]																
Diseases interacting with the immune system	48,985	24.2	24,046	47.3	23,913	4.9	13,750	9.2	2,005	0.8	1,133	1.7	22,602	6.7	35,346	19.0
Psoriasis	3,897	1.9	6,661	13.1	1,787	0.4	2,378	1.6	103	0.0	201	0.3	2,509	0.7	16,701	9.0
Epstein-Barr virus infection	2,999	1.5	889	1.7	320	0.1	113	0.1	646	0.2	281	0.4	655	0.2	434	0.2
Rheumatoid arthritis	1,902	0.9	890	1.8	3,408	0.7	1,434	1.0	511	0.2	207	0.3	3,024	0.9	2,722	1.5
Systemic lupus erythematosus	233	0.1	517	1.0	481	0.1	625	0.4	47	0.0	44	0.1	414	0.1	1,211	0.7

Annex 3 Table 6. Description of Demographic Characteristics of the Untreated Study Cohort at Cohort Entry Date, by Study Population—Adults

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Untreated Cohort (N = 202,459)		Corticosteroids (N = 50,822)		Untreated Cohort (N = 484,789)		Corticosteroids (N = 149,242)		Untreated Cohort (N = 264,378)		Corticosteroids (N = 67,293)		Untreated Cohort (N = 339,416)		Corticosteroids (N = 185,639)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sjögren's syndrome	164	0.1	133	0.3	456	0.1	347	0.2	33	0.0	22	0.0	627	0.2	913	0.5
Celiac sprue	596	0.3	261	0.5	412	0.1	264	0.2	42	0.0	21	0.0	1,187	0.3	1,118	0.6
Asthma	26,682	13.2	13,163	25.9	13,806	2.8	7,113	4.8	570	0.2	345	0.5	9,869	2.9	10,022	5.4
Allergic rhinitis	21,268	10.5	8,615	17.0	4,643	1.0	2,889	1.9	24	0.0	9	0.0	6,646	2.0	7,156	3.9
Disease of the immune system	570	0.3	359	0.7	1,299	0.3	641	0.4	64	0.0	30	0.0	974	0.3	1,140	0.6
Skin diseases	44,488	22.0	24,780	48.8	10,697	2.2	10,559	7.1	1,804	0.7	981	1.5	21,824	6.4	44,393	23.9
Chronic diseases	86,299	42.6	26,389	51.9	133,713	27.6	51,681	34.6	34,128	12.9	12,787	19.0	93,945	27.7	66,378	35.8
Malignancy other than study outcomes	7,859	3.9	2,297	4.5	15,500	3.2	5,437	3.6	6,297	2.4	1,838	2.7	10,693	3.2	8,768	4.7
Renal failure	7,110	3.5	2,358	4.6	2,145	0.4	849	0.6	960	0.4	359	0.5	1,981	0.6	1,950	1.1
Liver diseases	2,342	1.2	929	1.8	3,286	0.7	1,257	0.8	870	0.3	345	0.5	2,086	0.6	1,681	0.9
Ischemic heart disease	8,892	4.4	3,002	5.9	18,989	3.9	8,146	5.5	6,581	2.5	2,294	3.4	12,748	3.8	8,407	4.5
Hypertensive disease	35,560	17.6	11,099	21.8	30,541	6.3	12,981	8.7	3,661	1.4	1,398	2.1	28,658	8.4	20,975	11.3
Heart failure	1,950	1.0	639	1.3	4,558	0.9	1,888	1.3	1,514	0.6	515	0.8	4,775	1.4	2,858	1.5
Other cardiovascular diseases	14,992	7.4	5,194	10.2	26,823	5.5	11,241	7.5	6,984	2.6	2,417	3.6	20,967	6.2	15,541	8.4
Cerebrovascular diseases	5,025	2.5	1,618	3.2	10,801	2.2	4,192	2.8	3,023	1.1	844	1.3	7,676	2.3	4,691	2.5
Diabetes mellitus	12,730	6.3	4,279	8.4	13,703	2.8	5,638	3.8	3,182	1.2	1,111	1.7	12,304	3.6	8,156	4.4
Respiratory diseases	4,771	2.4	1,731	3.4	10,001	2.1	4,285	2.9	2,074	0.8	704	1.0	5,305	1.6	4,126	2.2

Annex 3 Table 6. Description of Demographic Characteristics of the Untreated Study Cohort at Cohort Entry Date, by Study Population—Adults

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Untreated Cohort (N = 202,459)		Corticosteroids (N = 50,822)		Untreated Cohort (N = 484,789)		Corticosteroids (N = 149,242)		Untreated Cohort (N = 264,378)		Corticosteroids (N = 67,293)		Untreated Cohort (N = 339,416)		Corticosteroids (N = 185,639)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Musculoskeletal and connective diseases	52,246	25.8	17,323	34.1	69,396	14.3	27,298	18.3	14,648	5.5	6,202	9.2	47,458	14.0	36,105	19.4
Organ transplantation	196	0.1	91	0.2	591	0.1	209	0.1	211	0.1	101	0.2	587	0.2	800	0.4
HIV infection or AIDS	115	0.1	30	0.1	403	0.1	128	0.1	15	0.0	11	0.0	220	0.1	140	0.1
Prior use of medications[b]																
Immunosuppressants and cytostatics	30,532	15.1	14,137	27.8	24,562	5.1	17,841	12.0	10,827	4.1	9,374	13.9	20,772	6.1	29,759	16.0
Systemic corticosteroids	28,842	14.2	13,050	25.7	16,279	3.4	12,638	8.5	8,685	3.3	7,645	11.4	14,402	4.2	22,216	12.0
Systemic tacrolimus	54	0.0	32	0.1	0	0.0	0	0.0	50	0.0	36	0.1	155	0.0	187	0.1
Immunosuppressants[c]	1,280	0.6	1,173	2.3	0	0.0	0	0.0	1,403	0.5	1,326	2.0	3,660	1.1	5,659	3.0
Systemic antivirals	1,610	0.8	1,118	2.2	8,750	1.8	5,743	3.8	971	0.4	813	1.2	4,859	1.4	5,669	3.1
Antineoplastic agents[d]	205	0.1	147	0.3	0	0.0	0	0.0	508	0.2	443	0.7	269	0.1	361	0.2
Immunostimulants	5	0.0	n<5		0	0.0	0	0.0	84	0.0	57	0.1	498	0.1	396	0.2
Antipsoriatics topical	553	0.3	5,261	10.4	1,988	0.4	5,111	3.4	500	0.2	3,081	4.6	733	0.2	8,400	4.5
Antipsoriatics systemic	n < 5		5	0.0	66	0.0	402	0.3	34	0.0	327	0.5	18	0.0	598	0.3
Other dermatological agents	20,722	10.2	33,272	65.5	45,587	9.4	49,311	33.0	23,628	8.9	41,634	61.9	20,708	6.1	88,393	47.6

Annex 3 Table 6. Description of Demographic Characteristics of the Untreated Study Cohort at Cohort Entry Date, by Study Population—Adults

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Untreated Cohort (N = 202,459)		Corticosteroids (N = 50,822)		Untreated Cohort (N = 484,789)		Corticosteroids (N = 149,242)		Untreated Cohort (N = 264,378)		Corticosteroids (N = 67,293)		Untreated Cohort (N = 339,416)		Corticosteroids (N = 185,639)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Other medications	79,698	39.4	28,446	56.0	206,489	42.6	86,710	58.1	87,400	33.1	39,363	58.5	133,289	39.3	98,711	53.2
Cardiovascular system drugs	44,529	22.0	15,431	30.4	107,266	22.1	46,514	31.2	45,015	17.0	19,599	29.1	70,955	20.9	52,301	28.2
Anti-inflammatory agents	28,886	14.3	10,797	21.2	89,677	18.5	38,262	25.6	39,005	14.8	18,870	28.0	49,576	14.6	39,669	21.4
Other antirheumatic agents	45	0.0	26	0.1	29	0.0	18	0.0	9	0.0	11	0.0	20	0.0	24	0.0
Hormone-replacement therapy	6,318	3.1	2,661	5.2	23,485	4.8	13,072	8.8	2,877	1.1	2,082	3.1	19,094	5.6	19,005	10.2
Lipid-modifying agents	24,692	12.2	7,879	15.5	46,016	9.5	18,637	12.5	23,940	9.1	9,496	14.1	31,230	9.2	20,236	10.9
Insulins	2,089	1.0	778	1.5	6,108	1.3	2,608	1.7	3,439	1.3	1,674	2.5	6,631	2.0	4,040	2.2
Oral antidiabetics	6,551	3.2	2,249	4.4	13,674	2.8	5,147	3.4	8,938	3.4	3,399	5.1	10,341	3.0	6,979	3.8
Antiepileptics	5,362	2.6	2,469	4.9	11,779	2.4	5,156	3.5	3,885	1.5	1,916	2.8	7,201	2.1	7,010	3.8
Drugs of asthma and COPD	11,091	5.5	6,585	13.0	30,684	6.3	15,937	10.7	15,439	5.8	9,310	13.8	21,332	6.3	20,914	11.3
Inhaled corticosteroids	10,853	5.4	6,447	12.7	11,623	2.4	6,169	4.1	5,033	1.9	3,189	4.7	9,068	2.7	8,648	4.7
Utilization of health care resources[b]																
General practitioner visits																
0	46,242	22.8	2,623	5.2	NA		NA		NA		NA		177,548	52.3	41,443	22.3
1	25,474	12.6	3,801	7.5	NA		NA		NA		NA		65,960	19.4	36,194	19.5
2-3	40,026	19.8	8,633	17.0	NA		NA		NA		NA		57,948	17.1	55,326	29.8
4+	90,717	44.8	35,765	70.4	NA		NA		NA		NA		37,960	11.2	52,676	28.4

Annex 3 Table 6. Description of Demographic Characteristics of the Untreated Study Cohort at Cohort Entry Date, by Study Population—Adults

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Untreated Cohort (N = 202,459)		Corticosteroids (N = 50,822)		Untreated Cohort (N = 484,789)		Corticosteroids (N = 149,242)		Untreated Cohort (N = 264,378)		Corticosteroids (N = 67,293)		Untreated Cohort (N = 339,416)		Corticosteroids (N = 185,639)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Dermatologist visits																
0	200,726	99.1	41,941	82.5	NA		NA		NA		NA		331,952	97.8	125,107	67.4
1	1,182	0.6	5,402	10.6	NA		NA		NA		NA		5,755	1.7	40,231	21.7
2-3	457	0.2	2,854	5.6	NA		NA		NA		NA		1,513	0.4	16,264	8.8
4+	94	0.0	625	1.2	NA		NA		NA		NA		196	0.1	4,037	2.2
Paediatrician visits																
0	202,361	100.0		99.9	NA		NA		NA		NA		338,525	99.7	184,942	99.6
1	82	0.0		0.1	NA		NA		NA		NA		482	0.1	357	0.2
2-3	[redacted]	[redacted]		0.0	NA		NA		NA		NA		267	0.1	194	0.1
4+	N<5			0.0	NA		NA		NA		NA		142	0.0	146	0.1
Emergency department visits																
0	189,583	93.6	46,619	91.7	435,805	89.9	132,710	88.9	NA		NA		NA		NA	
1	9,956	4.9	3,160	6.2	40,014	8.3	13,506	9.0	NA		NA		NA		NA	
2-3	2,553	1.3	890	1.8	8,122	1.7	2,683	1.8	NA		NA		NA		NA	
4+	367	0.2	153	0.3	848	0.2	343	0.2	NA		NA		NA		NA	
Outpatient hospital visits																
0	160,131	79.1	31,481	61.9	NA		NA		NA		NA		207,396	61.1	44,800	24.1
1	18,897	9.3	7,181	14.1	NA		NA		NA		NA		54,646	16.1	48,076	25.9
2-3	14,591	7.2	6,665	13.1	NA		NA		NA		NA		44,710	13.2	47,716	25.7
4+	8,840	4.4	5,495	10.8	NA		NA		NA		NA		32,664	9.6	45,047	24.3

Annex 3 Table 6. Description of Demographic Characteristics of the Untreated Study Cohort at Cohort Entry Date, by Study Population—Adults

	UK-CPRD				Denmark				NL-PHARMO				Sweden			
	Untreated Cohort (N = 202,459)		Corticosteroids (N = 50,822)		Untreated Cohort (N = 484,789)		Corticosteroids (N = 149,242)		Untreated Cohort (N = 264,378)		Corticosteroids (N = 67,293)		Untreated Cohort (N = 339,416)		Corticosteroids (N = 185,639)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Hospitalisations																
0	189,692	93.7	45,771	90.1	428,401	88.4	128,865	86.3	240,053	90.8	64,114	95.3	309,126	91.1	162,455	87.5
1	9,036	4.5	3,368	6.6	38,925	8.0	13,452	9.0	16,576	6.3	2,166	3.2	22,098	6.5	15,718	8.5
2-3	3,144	1.6	1,369	2.7	13,588	2.8	5,410	3.6	6,017	2.3	771	1.1	6,451	1.9	5,604	3.0
4+	587	0.3	314	0.6	3,875	0.8	1,515	1.0	1,732	0.7	242	0.4	1,741	0.5	1,862	1.0
Prescriptions																
0	58,188	28.7	0	0.0	209,654	43.2	388	0.3	114,413	43.3	0	0.0	102,523	30.2	3,678	2.0
1	17,617	8.7	1,036	2.0	57,422	11.8	24,078	16.1	17,842	6.7	0	0.0	34,454	10.2	11,154	6.0
2-4	32,232	15.9	7,230	14.2	87,329	18.0	46,928	31.4	38,525	14.6	7,321	10.9	64,221	18.9	37,910	20.4
5-9	25,359	12.5	10,426	20.5	68,912	14.2	40,224	27.0	32,003	12.1	13,302	19.8	50,942	15.0	42,199	22.7
10+	69,062	34.1	32,130	63.2	61,472	12.7	37,624	25.2	61,595	23.3	46,670	69.4	87,276	25.7	90,698	48.9

UK-CPRD = Clinical Practice Research Datalink; HIV = human immunodeficiency virus; NA = not applicable; NL-PHARMO = PHARMO Database Network (the Netherlands).

Note: Data counts between 1-4 are reported as n <5 to comply with data protection rules.

Note: Sweden did not have information about the actual number of visits; therefore, a proxy was used based on the number of unique prescriptions made by GPs from the prescriber drug register.

[a] At any time before the start date.

[b] Within 12 months before the start date.

[c] "Immunosuppressants" category includes azathioprine (ATC code: L04AX01), methotrexate (ATC codes: L01BA01, L04AX03), cyclosporin (ATC code: L04AD01), and other immunosuppressants excluding systemic tacrolimus (ATC codes: L04AA, L04AB, L04AC, L04AX02, L04AX04)

[d] "Antineoplastic agents" category includes antineoplastic agents, except methotrexate (ATC codes: L01A, L01BA03-L01BA05, L01BB, L01BC, L01C, L01D, L01X)

Annex 4. Patient Characteristics Comparing Patients Included in the Final Cohort at the Start Date After Trimming and Frequency Matching and Patients Excluded in the Trimming Process

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Annex 4 Table 1. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Continuous Variables, UK-CPRD, Children

	Topical Tacrolimus						Topical Pimecrolimus					
	Final Cohort After Trimming and Matching (N=3,895)			Subjects Excluded During the Trimming and Matching Process (N=1,052)			Final Cohort After Trimming and Matching (N=2,752)			Subjects Excluded During the Trimming and Matching Process (N=301)		
Variable	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**
Age (years)	8.2	4.9	7.8	2.2	3.3	1.3	7.0	4.8	5.9	2.2	3.3	1.3
Duration of follow-up (years)	5.0	3.9	4.0	5.3	3.6	4.9	6.0	4.1	5.5	5.3	3.6	4.9
Duration of medical history up to the start date (years)	6.4	4.1	5.5	2.0	2.7	1.3	5.3	3.8	4.2	2.0	2.7	1.3
Time since first diagnoses of atopic dermatitis (years)[a]	3.3	3.8	1.8	0.7	1.7	0.2	2.6	3.4	1.2	0.7	1.7	0.2
Time since first prescription for topical corticosteroids (years)[b]	3.7	4.1	2.1	0.9	2.0	0.3	3.1	3.7	1.6	0.9	2.0	0.3

SD = standard deviation

[a] Patients with no record of diagnosis of atopic dermatitis are excluded from this calculation

[b] Patients with no record of topical corticosteroid prescription are excluded from this calculation

Annex 4 Table 2. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Continuous Variables, UK-CPRD, Adults

	Topical Tacrolimus						Topical Pimecrolimus					
	Final Cohort After Trimming and Matching (N=12,705)			Subjects Excluded During the Trimming and Matching Process (N=3,040)			Final Cohort After Trimming and Matching (N=5,124)			Subjects Excluded During the Trimming and Matching Process (N=608)		
Variable	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**
Age (years)	47.3	17.9	46.4	67.6	18.9	72.0	46.1	17.7	44.6	67.6	18.9	72.0
Duration of follow-up (years)	4.6	3.6	3.6	6.5	4.7	5.7	5.4	3.9	4.6	6.5	4.7	5.7
Duration of medical history up to the start date (years)	11.9	6.1	11.8	8.5	5.3	7.9	10.9	6.0	10.7	8.5	5.3	7.9
Time since first diagnoses of atopic dermatitis (years)[a]	5.7	9.3	0.9	4.3	8.3	1.1	5.0	8.6	0.5	4.3	8.3	1.1
Time since first prescription for topical corticosteroids (years)[b]	5.6	6.4	2.7	5.6	5.0	4.4	5.2	6.0	2.5	5.6	5.0	4.4

SD = standard deviation

[a] Patients with no record of diagnosis of atopic dermatitis are excluded from this calculation

[b] Patients with no record of topical corticosteroid prescription are excluded from this calculation

Continuous Variables, Denmark

Annex 4 Table 3. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Continuous Variables, Denmark, Children

	Topical Tacrolimus						Topical Pimecrolimus					
	Final Cohort After Trimming and Matching (N=11,417)			Subjects Excluded During the Trimming and Matching Process (N=4,412)			Final Cohort After Trimming and Matching (N=20,343)			Subjects Excluded During the Trimming and Matching Process (N=9,110)		
Variable	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**
Age (years)	7.9	5.6	7.0	8.4	5.2	9.0	5.9	5.6	3.0	5.7	5.3	4.0
Duration of follow-up (years)	7.0	3.7	6.6	6.0	3.3	5.6	9.0	4.1	9.8	8.9	4.2	9.6
Duration of medical history up to the start date (years)	8.2	5.6	7.3	8.6	5.2	8.5	6.2	5.5	3.7	6.1	5.2	4.2
Time since first diagnoses of atopic dermatitis (years)[a]	4.2	4.4	2.4	4.4	4.0	2.8	3.6	3.9	2.0	5.3	4.6	4.4
Time since first prescription for topical corticosteroids (years)[b]	4.6	4.4	3.1	6.0	4.2	5.2	3.5	3.9	1.9	5.4	3.7	4.7

SD = standard deviation

[a] Patients with no record of diagnosis of atopic dermatitis are excluded from this calculation

[b] Patients with no record of topical corticosteroid prescription are excluded from this calculation

Annex 4 Table 4. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Continuous Variables, Denmark, Adults

	Topical Tacrolimus						Topical Pimecrolimus					
	Final Cohort After Trimming and Matching (N=40,710)			Subjects Excluded During the Trimming and Matching Process (N=10,399)			Final Cohort After Trimming and Matching (N=43,042)			Subjects Excluded During the Trimming and Matching Process (N=10,652)		
Variable	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**
Age (years)	47.1	17.4	47.0	42.7	14.8	41.0	45.0	16.9	43.0	40.8	14.6	39.0
Duration of follow-up (years)	6.1	3.6	5.5	5.2	3.3	4.7	7.3	4.1	7.0	6.6	4.1	5.8
Duration of medical history up to the start date (years)	28.9	8.5	31.3	28.3	9.4	31.7	27.7	8.2	28.7	26.9	9.1	28.2
Time since first diagnoses of atopic dermatitis (years)[a]	5.5	5.4	3.9	7.5	6.3	6.2	6.9	5.7	6.0	5.8	4.9	4.8
Time since first prescription for topical corticosteroids (years)[b]	9.5	5.6	9.6	10.8	5.5	11.3	8.8	5.3	8.6	9.9	5.2	9.5

SD = standard deviation

[a] Patients with no record of diagnosis of atopic dermatitis are excluded from this calculation

[b] Patients with no record of topical corticosteroid prescription are excluded from this calculation

Continuous Variables, NL-PHARMO

Annex 4 Table 5. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Continuous Variables, NL-PHARMO, Children

	Topical Tacrolimus						Topical Pimecrolimus					
	Final Cohort After Trimming and Matching (N=5,197)			Subjects Excluded During the Trimming and Matching Process (N=1,463)			Final Cohort After Trimming and Matching (N=3,189)			Subjects Excluded During the Trimming and Matching Process (N=673)		
Variable	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**
Age (years)	9.4	5.0	9.0	9.4	5.0	9.0	7.9	5.4	7.0	6.5	5.0	4.0
Duration of follow-up (years)	7.1	3.8	6.8	6.8	3.2	6.7	7.7	4.1	7.6	9.0	4.3	9.6
Duration of medical history up to the start date (years)	5.6	3.6	4.9	5.9	3.6	5.2	4.9	3.5	3.9	4.0	2.8	3.2
Time since first diagnoses of atopic dermatitis (years)[a]	3.1	3.3	2.1	2.2	3.0	1.2	4.1	2.8	3.9	1.2	1.0	1.1
Time since first prescription for topical corticosteroids (years)[b]	3.3	3.5	2.4	3.7	3.7	2.8	2.7	3.5	1.9	2.0	3.0	1.7

SD = standard deviation

[a] Patients with no record of diagnosis of atopic dermatitis are excluded from this calculation

[b] Patients with no record of topical corticosteroid prescription are excluded from this calculation

Annex 4 Table 6. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Continuous Variables, NL-PHARMO, Adults

	Topical Tacrolimus						Topical Pimecrolimus					
	Final Cohort After Trimming and Matching (N=21,037)			Subjects Excluded During the Trimming and Matching Process (N=7,247)			Final Cohort After Trimming and Matching (N=8,506)			Subjects Excluded During the Trimming and Matching Process (N=2,941)		
Variable	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**
Age (years)	48.0	17.4	48.0	43.9	17.7	43.0	47.9	17.2	48.0	43.2	16.2	42.0
Duration of follow-up (years)	6.5	3.8	6.1	6.3	3.5	5.9	6.5	3.8	6.0	6.3	3.8	5.6
Duration of medical history up to the start date (years)	7.4	4.3	6.7	7.9	4.3	7.2	7.5	4.2	7.1	8.2	4.2	7.7
Time since first diagnoses of atopic dermatitis (years)[a]	3.7	3.3	3.2	1.6	2.0	1.0	3.0	3.7	1.6	4.3	5.0	2.9
Time since first prescription for topical corticosteroids (years)[b]	4.3	4.3	3.5	4.9	4.2	4.2	4.2	4.3	3.3	4.8	4.5	4.4

SD = standard deviation

[a] Patients with no record of diagnosis of atopic dermatitis are excluded from this calculation

[b] Patients with no record of topical corticosteroid prescription are excluded from this calculation

Continuous Variables, Sweden

Annex 4 Table 7. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Continuous Variables, Sweden, Children

	Topical Tacrolimus						Topical Pimecrolimus					
	Final Cohort After Trimming and Matching (N=12,096)			Subjects Excluded During the Trimming and Matching Process (N=1,254)			Final Cohort After Trimming and Matching (N=1,677)			Subjects Excluded During the Trimming and Matching Process (N=123)		
Variable	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**
Age (years)	9.4	5.2	10.0	11.0	4.9	12.0	8.3	5.4	8.0	7.4	5.4	7.0
Duration of follow-up (years)	4.9	2.3	4.9	4.6	2.3	4.6	5.4	2.6	5.5	3.9	2.7	2.4
Duration of medical history up to the start date (years)	9.6	5.3	9.6	11.1	5.1	12.0	8.6	5.4	8.1	7.8	5.4	6.3
Time since first diagnoses of atopic dermatitis (years)[a]	3.0	3.3	1.7	4.1	3.7	3.2	2.7	3.1	1.4	3.4	3.5	2.1
Time since first prescription for topical corticosteroids (years)[b]	2.6	2.2	2.0	3.2	2.5	2.7	2.2	2.1	1.5	2.4	2.6	1.4

SD = standard deviation

[a] Patients with no record of diagnosis of atopic dermatitis are excluded from this calculation

[b] Patients with no record of topical corticosteroid prescription are excluded from this calculation

Annex 4 Table 8. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Continuous Variables, Sweden, Adults

	Topical Tacrolimus						Topical Pimecrolimus					
	Final Cohort After Trimming and Matching (N=52,456)			Subjects Excluded During the Trimming and Matching Process (N=5,663)			Final Cohort After Trimming and Matching (N=5,169)			Subjects Excluded During the Trimming and Matching Process (N=507)		
Variable	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**
Age (years)	47.3	17.5	47.0	37.6	16.0	35.0	46.5	17.2	46.0	38.9	16.6	37.0
Duration of follow-up (years)	4.6	2.3	4.5	3.4	2.2	2.8	5.0	2.5	4.9	2.7	1.9	2.1
Duration of medical history up to the start date (years)	22.5	5.0	23.4	22.2	5.8	23.8	21.8	5.3	22.7	22.9	5.8	25.3
Time since first diagnoses of atopic dermatitis (years)[a]	3.7	4.3	2.0	4.3	5.2	2.3	3.8	4.7	2.0	3.9	5.0	1.2
Time since first prescription for topical corticosteroids (years)[b]	3.2	2.5	2.8	3.9	2.8	3.8	2.9	2.4	2.3	3.9	2.9	3.6

SD = standard deviation

[a] Patients with no record of diagnosis of atopic dermatitis are excluded from this calculation
[b] Patients with no record of topical corticosteroid prescription are excluded from this calculation

Categorical Variables, UK-CPRD

Annex 4 Table 9. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, UK-CPRD, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=3,895)		Subjects Excluded During the Trimming and Matching Process (N=1,052)		Final Cohort After Trimming and Matching (N=2,752)		Subjects Excluded During the Trimming and Matching Process (N=301)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Demographics								
Age								
0-1	266	6.8	58	5.5	379	13.8	30	10.0
2-4	972	25.0	303	28.8	824	29.9	136	45.2
5-9	1,038	26.6	339	32.2	692	25.1	67	22.3
10-14	959	24.6	191	18.2	528	19.2	44	14.6
15-17	660	16.9	161	15.3	329	12.0	24	8.0
Sex female	2,013	51.7	517	49.1	1,439	52.3	159	52.8
Calendar year								
2002	177	4.5	21	2.0	0	0.0	0	0.0
2003	271	7.0	25	2.4	312	11.3	[redacted]	[redacted]
2004	267	6.9	24	2.3	454	16.5	27	9.0
2005	350	9.0	29	2.8	441	16.0	22	7.3
2006	210	5.4	25	2.4	270	9.8	18	6.0
2007	178	4.6	28	2.7	130	4.7	[redacted]	[redacted]
2008	219	5.6	45	4.3	131	4.8	18	6.0
2009	264	6.8	80	7.6	153	5.6	25	8.3
2010	257	6.6	84	8.0	136	4.9	36	12.0
2011	294	7.5	101	9.6	127	4.6	19	6.3
2012	303	7.8	113	10.7	138	5.0	26	8.6
2013	290	7.4	120	11.4	154	5.6	29	9.6
2014	310	8.0	116	11.0	139	5.1	34	11.3
2015	273	7.0	122	11.6	97	3.5	20	6.6
2016	232	6.0	119	11.3	70	2.5	10	3.3
Primary care center/region								
North East	43	1.1	12	1.1	12	0.4	7	2.3
North West	426	10.9	148	14.1	322	11.7	43	14.3
Yorkshire & The Humber	91	2.3	8	0.8	122	4.4	[redacted]	[redacted]
East Midlands	74	1.9	17	1.6	83	3.0		
West Midlands	270	6.9	64	6.1	260	9.4	22	7.3
East of England	277	7.1	77	7.3	209	7.6	12	4.0
South West	261	6.7	68	6.5	124	4.5	13	4.3

Annex 4 Table 9. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, UK-CPRD, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=3,895)		Subjects Excluded During the Trimming and Matching Process (N=1,052)		Final Cohort After Trimming and Matching (N=2,752)		Subjects Excluded During the Trimming and Matching Process (N=301)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
South Central	358	9.2	121	11.5	233	8.5	18	6.0
London	564	14.5	200	19.0	352	12.8	50	16.6
South East Coast	323	8.3	109	10.4	259	9.4	19	6.3
Northern Ireland	359	9.2	109	10.4	153	5.6	35	11.6
Scotland	470	12.1	25	2.4	201	7.3	14	4.7
Wales	379	9.7	94	8.9	422	15.3	57	18.9
Duration of follow-up (years)								
≤1	1,044	26.8	414	39.4	568	20.6	76	25.2
2-4	1,139	29.2	326	31.0	637	23.1	94	31.2
5+	1,712	44.0	312	29.7	1,547	56.2	131	43.5
Duration of medical history up to the start date (years)								
≤1	366	9.4	73	6.9	484	17.6	38	12.6
2-4	1,292	33.2	332	31.6	1,073	39.0	145	48.2
5+	2,237	57.4	647	61.5	1,195	43.4	118	39.2
Body mass index								
20-25	41	1.1	16	1.5	18	0.7	0	0.0
<20	68	1.7	19	1.8	24	0.9	[redacted]	[redacted]
>25	32	0.8	11	1.0	15	0.5		
Unknown	3,754	96.4	1,006	95.6	2,695	97.9	299	99.3
Current smoker								
Yes	96	2.5	21	2.0	70	2.5	[redacted]	[redacted]
Unknown	2,949	75.7	799	76.0	2,274	82.6	249	82.7
Index of multiple socio-economic deprivations UK-CPRD								
1st quintile (least deprived)	717	18.4	175	16.6	556	20.2	57	18.9
2nd quintile	606	15.6	165	15.7	416	15.1	48	15.9
3rd quintile	840	21.6	230	21.9	585	21.3	57	18.9
4th quintile	759	19.5	208	19.8	553	20.1	63	20.9
5th quintile	973	25.0	274	26.0	642	23.3	76	25.2

Annex 4 Table 9. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, UK-CPRD, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=3,895)		Subjects Excluded During the Trimming and Matching Process (N=1,052)		Final Cohort After Trimming and Matching (N=2,752)		Subjects Excluded During the Trimming and Matching Process (N=301)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Type of prescriber of first prescription								
Dermatologist	NA		NA		NA		NA	
Paediatrician	NA		NA		NA		NA	
General practitioner	NA		NA		NA		NA	
Other	NA		NA		NA		NA	
Unknown	NA		NA		NA		NA	
Atopic dermatitis								
Diagnosis at any time before start date								
Any diagnosis	NA		NA		NA		NA	
General practitioner	NA		NA		NA		NA	
Paediatrician	NA		NA		NA		NA	
Dermatologist	NA		NA		NA		NA	
Hospital outpatient visit	NA		NA		NA		NA	
Primary or secondary hospital discharge diagnosis	NA		NA		NA		NA	
Other specialties	NA		NA		NA		NA	
Time since first diagnosis of atopic dermatitis (years)								
≤1	1,002	25.7	202	19.2	988	35.9	87	28.9
2-4	873	22.4	282	26.8	562	20.4	97	32.2
5-9	655	16.8	192	18.3	314	11.4	39	13.0
10-15	294	7.5	73	6.9	135	4.9	[redacted]	[redacted]
15+	52	1.3	23	2.2	16	0.6		
Not applicable[a]	1,019	26.2	280	26.6	737	26.8	60	19.9
Time since first prescription for topical corticosteroids								
≤1	1,113	28.6	285	27.1	948	34.4	104	34.6
2-4	1,089	28.0	341	32.4	712	25.9	116	38.5
5-9	846	21.7	240	22.8	467	17.0	47	15.6
10-15	500	12.8	103	9.8	269	9.8	21	7.0
15+	101	2.6	25	2.4	43	1.6	5	1.7
Not applicable[b]	246	6.3	58	5.5	313	11.4	8	2.7

Annex 4 Table 9. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, UK-CPRD, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=3,895)		Subjects Excluded During the Trimming and Matching Process (N=1,052)		Final Cohort After Trimming and Matching (N=2,752)		Subjects Excluded During the Trimming and Matching Process (N=301)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Medical history								
Diseases interacting with the immune system	1,455	37.4	474	45.1	865	31.4	99	32.9
Psoriasis	162	4.2	87	8.3	50	1.8	6	2.0
Epstein-Barr virus infection	14	0.4	5	0.5	[redacted]	[redacted]	[redacted]	[redacted]
Rheumatoid arthritis	0	0.0	[redacted]	[redacted]	[redacted]	[redacted]	0	0.0
Systemic lupus erythematosus	[redacted]	[redacted]	[redacted]	[redacted]	0	0.0	0	0.0
Sjögren's syndrome	0	0.0	0	0.0	0	0.0	0	0.0
Celiac sprue	7	0.2	[redacted]	[redacted]	6	0.2	0	0.0
Asthma	1,049	26.9	337	32.0	623	22.6	78	25.9
Allergic rhinitis	585	15.0	151	14.4	369	13.4	33	11.0
Disease of the immune system	9	0.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin diseases (excluding atopic dermatitis, eczema and psoriasis)	1,572	40.4	529	50.3	935	34.0	143	47.5
Inflammatory skin disease	1,426	36.6	436	41.4	896	32.6	124	41.2
Sun burn	11	0.3	[redacted]	[redacted]	5	0.2	[redacted]	[redacted]
Other skin diseases	199	5.1	147	14.0	61	2.2	27	9.0
Chronic diseases	252	6.5	75	7.1	157	5.7	25	8.3
Malignancy excluding skin cancer and lymphoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0.0
Renal failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0.0
Chronic liver diseases and hepatic failure	[redacted]	[redacted]	0	0.0	[redacted]	[redacted]	[redacted]	[redacted]
Ischemic heart disease	[redacted]	[redacted]	0	0.0	[redacted]	[redacted]	0	0.0
Hypertensive disease	7	0.2	[redacted]	[redacted]	0	0.0	0	0.0
Heart failure	0	0.0	[redacted]	[redacted]	0	0.0	0	0.0
Other cardiovascular diseases	41	1.1	9	0.9	28	1.0	6	2.0
Cerebrovascular diseases	[redacted]	[redacted]	0	0.0	[redacted]	[redacted]	0	0.0
Diabetes mellitus	21	0.5	18	1.7	8	0.3	[redacted]	[redacted]
COPD, emphysema, respiratory insufficiency	[redacted]	[redacted]	[redacted]	[redacted]	7	0.3	0	0.0
Musculoskeletal system and connective disease (excluding rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome)	184	4.7	44	4.2	109	4.0	17	5.6

Annex 4 Table 9. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, UK-CPRD, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=3,895)		Subjects Excluded During the Trimming and Matching Process (N=1,052)		Final Cohort After Trimming and Matching (N=2,752)		Subjects Excluded During the Trimming and Matching Process (N=301)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Organ transplantation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	0.0
HIV infection or AIDs	0	0.0	0	0.0	0	0.0	[redacted]	[redacted]
Use of medications								
Topical corticosteroids plain								
Any potency								
0	907	23.3	181	17.2	851	30.9	41	13.6
1	642	16.5	156	14.8	548	19.9	34	11.3
2-3	899	23.1	193	18.3	595	21.6	66	21.9
4+	1,447	37.2	522	49.6	758	27.5	160	53.2
Weak potency								
0	1,943	49.9	502	47.7	1,331	48.4	110	36.5
1	797	20.5	183	17.4	611	22.2	64	21.3
2-3	648	16.6	193	18.3	474	17.2	69	22.9
4+	507	13.0	174	16.5	336	12.2	58	19.3
Moderately potent								
0	2,290	58.8	552	52.5	1,920	69.8	123	40.9
1	690	17.7	171	16.3	403	14.6	53	17.6
2-3	517	13.3	189	18.0	257	9.3	69	22.9
4+	398	10.2	140	13.3	172	6.3	56	18.6
Potent								
0	2,273	58.4	487	46.3	2,000	72.7	157	52.2
1	727	18.7	216	20.5	387	14.1	60	19.9
2-3	539	13.8	165	15.7	206	7.5	46	15.3
4+	356	9.1	184	17.5	159	5.8	38	12.6
Very potent								
0	3,689	94.7	971	92.3	2,679	97.3	292	97.0
1	144	3.7	62	5.9	59	2.1	6	2.0
2-3	54	1.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4+	8	0.2						

[redacted]

Annex 4 Table 9. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, UK-CPRD, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=3,895)		Subjects Excluded During the Trimming and Matching Process (N=1,052)		Final Cohort After Trimming and Matching (N=2,752)		Subjects Excluded During the Trimming and Matching Process (N=301)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Topical corticosteroids combined								
Any potency								
0	2,353	60.4	616	58.6	1,752	63.7	152	50.5
1	751	19.3	176	16.7	526	19.1	68	22.6
2-3	499	12.8	152	14.4	318	11.6	47	15.6
4+	292	7.5	108	10.3	156	5.7	34	11.3
Weak potency								
0	3,040	78.0	813	77.3	2,050	74.5	210	69.8
1	527	13.5	154	14.6	463	16.8	53	17.6
2-3	229	5.9	58	5.5	172	6.3	31	10.3
4+	99	2.5	27	2.6	67	2.4	7	2.3
Moderately potent								
0	3,670	94.2	961	91.3	2,642	96.0	276	91.7
1	140	3.6	64	6.1	78	2.8	17	5.6
2-3	66	1.7	18	1.7	[redacted]	[redacted]	[redacted]	[redacted]
4+	19	0.5	9	0.9				
Potent								
0	3,066	78.7	803	76.3	2,348	85.3	221	73.4
1	466	12.0	113	10.7	244	8.9	43	14.3
2-3	258	6.6	89	8.5	109	4.0	23	7.6
4+	105	2.7	47	4.5	51	1.9	14	4.7
Very potent								
0	3,879	99.6	1,049	99.7	2,743	99.7	[redacted]	[redacted]
1	9	0.2	[redacted]	[redacted]	7	0.3		
2-3	[redacted]	[redacted]			[redacted]	[redacted]	0	0.0
4+			0	0.0			0	0.0
Immunosuppressants, immunostimulants, and cytostatics	796	20.4	265	25.2	429	15.6	69	22.9
Systemic corticosteroids	751	19.3	241	22.9	417	15.2	64	21.3
Systemic tacrolimus	[redacted]	[redacted]	0	0.0	0	0.0	0	0.0
Azathioprine	13	0.3	5	0.5	[redacted]	[redacted]	0	0.0
Methotrexate	[redacted]	[redacted]	[redacted]	[redacted]			0	0.0
Cyclosporin	5	0.1	7	0.7	0	0.0	[redacted]	[redacted]

[redacted]

Annex 4 Table 9. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, UK-CPRD, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=3,895)		Subjects Excluded During the Trimming and Matching Process (N=1,052)		Final Cohort After Trimming and Matching (N=2,752)		Subjects Excluded During the Trimming and Matching Process (N=301)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Other antineoplastic agents except methotrexate	[redacted]	[redacted]	[redacted]	[redacted]	0	0.0	0	0.0
Other immunosuppressants except systemic tacrolimus	[redacted]	[redacted]	0	0.0	0	0.0	0	0.0
Systemic antivirals	56	1.4	30	2.9	16	0.6	6	2.0
Immunostimulants	0	0.0	0	0.0	0	0.0	0	0.0
Antipsoriatics topical	184	4.7	91	8.7	75	2.7	9	3.0
Tars	115	3.0	56	5.3	50	1.8	6	2.0
Antracen derivatives	7	0.2	6	0.6	0	0.0	0	0.0
Psoralens topical	0	0.0	0	0.0	0	0.0	0	0.0
Other antipsoriatics topical	105	2.7	54	5.1	29	1.1	[redacted]	[redacted]
Antipsoriatics systemic	0	0.0	0	0.0	0	0.0		
Psoralens systemic	0	0.0	0	0.0	0	0.0	0	0.0
Retinoids	0	0.0	0	0.0	0	0.0	[redacted]	[redacted]
Other antipsoriatics systemic	0	0.0	0	0.0	0	0.0	0	0.0
Other dermatological agents	3,895	100.0	1,052	100.0	2,752	100.0	301	100.0
Topical salicylic acid preparations	11	0.3	18	1.7	6	0.2	10	3.3
Other dermatological agents	3,895	100.0	1,052	100.0	2,752	100.0	301	100.0
Other medications	1,093	28.1	341	32.4	650	23.6	96	31.9
Cardiovascular system drugs	247	6.3	81	7.7	123	4.5	21	7.0
Anti-inflammatory and anti-rheumatic agents, nonsteroidal	305	7.8	76	7.2	213	7.7	27	9.0
Other antirheumatic agents	0	0.0	0	0.0	0	0.0	0	0.0
Hormone-replacement therapy	[redacted]	[redacted]	0	0.0	0	0.0	0	0.0
Lipid-modifying agents	0	0.0	[redacted]	[redacted]	[redacted]	[redacted]	0	0.0
Insulins	11	0.3	8	0.8			0	0.0
Oral antidiabetics	[redacted]	[redacted]	[redacted]	[redacted]	0	0.0	0	0.0
Antiepileptics	10	0.3			14	0.5	0	0.0
Drugs for asthma and COPD excluding inhaled corticosteroids	669	17.2	226	21.5	383	13.9	60	19.9
Inhaled corticosteroids	668	17.2	224	21.3	383	13.9	60	19.9

Annex 4 Table 9. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, UK-CPRD, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=3,895)		Subjects Excluded During the Trimming and Matching Process (N=1,052)		Final Cohort After Trimming and Matching (N=2,752)		Subjects Excluded During the Trimming and Matching Process (N=301)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Utilization of health care resources in the year before the start date								
General practitioner visits								
0	193	5.0	30	2.9	139	5.1	9	3.0
1	277	7.1	49	4.7	231	8.4	7	2.3
2-3	746	19.2	176	16.7	569	20.7	46	15.3
4+	2,679	68.8	797	75.8	1,813	65.9	239	79.4
Dermatologist visits								
0	3,324	85.3	57	5.4	2,454	89.2	43	14.3
1	400	10.3	334	31.7	201	7.3	80	26.6
2-3	141	3.6	433	41.2	87	3.2	106	35.2
4+	30	0.8	228	21.7	10	0.4	72	23.9
Paediatrician visits								
0	3,553	91.2	806	76.6	2,543	92.4	229	76.1
1	206	5.3	151	14.4	119	4.3	38	12.6
2-3	102	2.6	65	6.2	70	2.5	25	8.3
4+	34	0.9	30	2.9	20	0.7	9	3.0
Emergency department visits								
0	3,440	88.3	865	82.2	2,465	89.6	244	81.1
1	331	8.5	131	12.5	203	7.4	36	12.0
2-3	106	2.7	49	4.7	[redacted]	[redacted]	[redacted]	[redacted]
4+	18	0.5	7	0.7				
Outpatient hospital visits								
0	2,681	68.8	49	4.7	2,065	75.0	38	12.6
1	622	16.0	228	21.7	351	12.8	52	17.3
2-3	412	10.6	393	37.4	231	8.4	106	35.2
4+	180	4.6	382	36.3	105	3.8	105	34.9
Hospitalisations								
0	3,586	92.1	929	88.3	2,579	93.7	263	87.4
1	218	5.6	93	8.8	128	4.7	31	10.3
2-3	73	1.9	[redacted]	[redacted]	37	1.3	[redacted]	[redacted]
4+	18	0.5			8	0.3		

[redacted]

Annex 4 Table 9. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, UK-CPRD, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=3,895)		Subjects Excluded During the Trimming and Matching Process (N=1,052)		Final Cohort After Trimming and Matching (N=2,752)		Subjects Excluded During the Trimming and Matching Process (N=301)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Prescriptions								
0	0	0.0	0	0.0	0	0.0	[redacted]	[redacted]
1	76	2.0	18	1.7	64	2.3		
2-3	363	9.3	65	6.2	368	13.4	12	4.0
5-9	640	16.4	128	12.2	595	21.6	30	10.0
10+	2,816	72.3	841	79.9	1,725	62.7	256	85.0

NA = not available
[a] Not applicable, no record of diagnosis of atopic dermatitis.
[b] Not applicable, no record of topical corticosteroid prescription.

Annex 4 Table 10. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, UK-CPRD, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=12,705)		Subjects Excluded During the Trimming and Matching Process (N=3,040)		Final Cohort After Trimming and Matching (N=5,124)		Subjects Excluded During the Trimming and Matching Process (N=608)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Demographics								
Age								
18-24	1,357	10.7	382	12.6	574	11.2	107	17.6
25-34	2,134	16.8	600	19.7	913	17.8	128	21.1
35-44	2,370	18.7	655	21.5	1,022	19.9	138	22.7
45-54	2,361	18.6	644	21.2	925	18.1	96	15.8
55-64	2,081	16.4	415	13.7	783	15.3	64	10.5
65-74	1,482	11.7	230	7.6	618	12.1	20	3.3
75-84	762	6.0	82	2.7	244	4.8	35	5.8
85+	158	1.2	32	1.1	45	0.9	20	3.3
Sex female	7,654	60.2	1,902	62.6	3,295	64.3	417	68.6
Calendar year								
2002	236	1.9	119	3.9	0	0.0	0	0.0
2003	672	5.3	29	1.0	394	7.7	21	3.5
2004	818	6.4	56	1.8	642	12.5	26	4.3
2005	952	7.5	74	2.4	696	13.6	41	6.7
2006	810	6.4	47	1.5	449	8.8	35	5.8
2007	773	6.1	63	2.1	319	6.2	46	7.6
2008	767	6.0	89	2.9	298	5.8	34	5.6
2009	943	7.4	146	4.8	313	6.1	63	10.4
2010	915	7.2	214	7.0	324	6.3	39	6.4
2011	977	7.7	224	7.4	296	5.8	48	7.9
2012	1,074	8.5	346	11.4	321	6.3	50	8.2
2013	982	7.7	353	11.6	329	6.4	69	11.3
2014	960	7.6	444	14.6	313	6.1	68	11.2
2015	993	7.8	443	14.6	252	4.9	34	5.6
2016	833	6.6	393	12.9	178	3.5	34	5.6
Primary care center/region								
North East	117	0.9	19	0.6	45	0.9	[redacted]	[redacted]
North West	1,332	10.5	468	15.4	622	12.1	140	23.0
Yorkshire & The Humber	275	2.2	22	0.7	164	3.2	[redacted]	[redacted]
East Midlands	233	1.8	23	0.8	135	2.6	12	2.0
West Midlands	852	6.7	191	6.3	491	9.6	47	7.7
East of England	722	5.7	152	5.0	352	6.9	25	4.1

Annex 4 Table 10. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, UK-CPRD, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=12,705)		Subjects Excluded During the Trimming and Matching Process (N=3,040)		Final Cohort After Trimming and Matching (N=5,124)		Subjects Excluded During the Trimming and Matching Process (N=608)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
South West	1,056	8.3	192	6.3	256	5.0	16	2.6
South Central	1,080	8.5	244	8.0	424	8.3	24	3.9
London	1,238	9.7	487	16.0	546	10.7	69	11.3
South East Coast	1,042	8.2	278	9.1	460	9.0	49	8.1
Northern Ireland	1,348	10.6	488	16.1	368	7.2	76	12.5
Scotland	2,064	16.2	168	5.5	485	9.5	13	2.1
Wales	1,346	10.6	308	10.1	776	15.1	125	20.6
Duration of follow-up (years)								
≤1	3,758	29.6	1,319	43.4	1,268	24.7	176	28.9
2-4	3,874	30.5	1,051	34.6	1,416	27.6	224	36.8
5+	5,073	39.9	670	22.0	2,440	47.6	208	34.2
Duration of medical history up to the start date (years)								
≤1	367	2.9	37	1.2	210	4.1	10	1.6
2-4	1,458	11.5	177	5.8	912	17.8	52	8.6
5+	10,880	85.6	2,826	93.0	4,002	78.1	546	89.8
Body mass index								
20-25	753	5.9	197	6.5	365	7.1	44	7.2
<20	5,050	39.7	1,195	39.3	2,206	43.1	258	42.4
>25	5,143	40.5	1,312	43.2	1,862	36.3	220	36.2
Unknown	1,759	13.8	336	11.1	691	13.5	86	14.1
Current smoker								
Yes	3,424	27.0	740	24.3	1,397	27.3	148	24.3
Unknown	353	2.8	54	1.8	172	3.4	14	2.3
Index of multiple socio-economic deprivations UK-CPRD								
1st quintile (least deprived)	2,515	19.8	541	17.8	1,036	20.2	142	23.4
2nd quintile	1,836	14.5	521	17.1	827	16.1	99	16.3
3rd quintile	2,880	22.7	679	22.3	1,181	23.0	139	22.9
4th quintile	2,402	18.9	558	18.4	961	18.8	105	17.3
5th quintile	3,072	24.2	741	24.4	1,119	21.8	123	20.2

Annex 4 Table 10. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, UK-CPRD, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=12,705)		Subjects Excluded During the Trimming and Matching Process (N=3,040)		Final Cohort After Trimming and Matching (N=5,124)		Subjects Excluded During the Trimming and Matching Process (N=608)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Type of prescriber of first prescription								
Dermatologist	NA		NA		NA		NA	
Paediatrician	NA		NA		NA		NA	
General practitioner	NA		NA		NA		NA	
Other	NA		NA		NA		NA	
Unknown	NA		NA		NA		NA	
Atopic dermatitis								
Diagnosis at any time before start date								
Any diagnosis	NA		NA		NA		NA	
General practitioner	NA		NA		NA		NA	
Paediatrician	NA		NA		NA		NA	
Dermatologist	NA		NA		NA		NA	
Hospital outpatient visit	NA		NA		NA		NA	
Primary or secondary hospital discharge diagnosis	NA		NA		NA		NA	
Other specialties	NA		NA		NA		NA	
Time since first diagnosis of atopic dermatitis (years)[a]								
≤1	1,664	13.1	356	11.7	865	16.9	92	15.1
2-4	878	6.9	223	7.3	355	6.9	41	6.7
5-9	941	7.4	298	9.8	356	6.9	59	9.7
10-15	465	3.7	196	6.4	173	3.4	35	5.8
15+	1,009	7.9	293	9.6	369	7.2	68	11.2
Not applicable[a]	7,748	61.0	1,674	55.1	3,006	58.7	313	51.5
Time since first prescription for topical corticosteroids[a]								
≤1	2,731	21.5	568	18.7	1,101	21.5	113	18.6
2-4	2,215	17.4	497	16.3	879	17.2	101	16.6
5-9	2,650	20.9	627	20.6	1,026	20.0	117	19.2
10-15	2,073	16.3	521	17.1	792	15.5	102	16.8
15+	1,919	15.1	689	22.7	583	11.4	134	22.0
Not applicable[b]	1,117	8.8	138	4.5	743	14.5	41	6.7

Annex 4 Table 10. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, UK-CPRD, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=12,705)		Subjects Excluded During the Trimming and Matching Process (N=3,040)		Final Cohort After Trimming and Matching (N=5,124)		Subjects Excluded During the Trimming and Matching Process (N=608)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Medical history								
Diseases interacting with the immune system	6,604	52.0	2,042	67.2	2,373	46.3	397	65.3
Psoriasis	2,235	17.6	723	23.8	592	11.6	134	22.0
Epstein-Barr virus infection	222	1.7	67	2.2	89	1.7	17	2.8
Rheumatoid arthritis	193	1.5	54	1.8	64	1.2	5	0.8
Systemic lupus erythematosus	189	1.5	178	5.9	43	0.8	12	2.0
Sjögren's syndrome	42	0.3	18	0.6	12	0.2	[redacted]	[redacted]
Celiac sprue	72	0.6	26	0.9	25	0.5		
Asthma	3,163	24.9	1,076	35.4	1,259	24.6	227	37.3
Allergic rhinitis	2,407	18.9	764	25.1	1,006	19.6	155	25.5
Disease of the immune system	93	0.7	53	1.7	26	0.5	6	1.0
Skin diseases (excluding atopic dermatitis, eczema and psoriasis)	7,463	58.7	2,020	66.4	2,813	54.9	387	63.7
Inflammatory skin disease	6,537	51.5	1,764	58.0	2,556	49.9	347	57.1
Sun burn	78	0.6	22	0.7	24	0.5	10	1.6
Other skin diseases	2,062	16.2	636	20.9	699	13.6	111	18.3
Chronic diseases	6,312	49.7	1,533	50.4	2,369	46.2	261	42.9
Malignancy excluding skin cancer and lymphoma	569	4.5	109	3.6	186	3.6	29	4.8
Renal failure	603	4.7	122	4.0	131	2.6	32	5.3
Chronic liver diseases and hepatic failure	197	1.6	70	2.3	68	1.3	10	1.6
Ischemic heart disease	696	5.5	121	4.0	222	4.3	32	5.3
Hypertensive disease	2,487	19.6	552	18.2	926	18.1	93	15.3
Heart failure	154	1.2	32	1.1	40	0.8	14	2.3
Other cardiovascular diseases	1,192	9.4	325	10.7	438	8.5	64	10.5
Cerebrovascular diseases	348	2.7	70	2.3	97	1.9	20	3.3
Diabetes mellitus	915	7.2	239	7.9	306	6.0	33	5.4
COPD, emphysema, respiratory insufficiency	423	3.3	91	3.0	129	2.5	23	3.8
Musculoskeletal system and connective disease (excluding rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome)	4,191	33.0	1,057	34.8	1,534	29.9	167	27.5

Annex 4 Table 10. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, UK-CPRD, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=12,705)		Subjects Excluded During the Trimming and Matching Process (N=3,040)		Final Cohort After Trimming and Matching (N=5,124)		Subjects Excluded During the Trimming and Matching Process (N=608)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Organ transplantation	32	0.3	8	0.3	7	0.1	[redacted]	[redacted]
HIV infection or AIDs	8	0.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use of medications								
Topical corticosteroids plain								
Any potency								
0	4,173	32.8	760	25.0	2,179	42.5	179	29.4
1	2,784	21.9	626	20.6	1,176	23.0	132	21.7
2-3	2,757	21.7	736	24.2	937	18.3	137	22.5
4+	2,991	23.5	918	30.2	832	16.2	160	26.3
Weak potency								
0	9,864	77.6	2,329	76.6	3,839	74.9	446	73.4
1	1,764	13.9	388	12.8	810	15.8	90	14.8
2-3	712	5.6	215	7.1	330	6.4	51	8.4
4+	365	2.9	108	3.6	145	2.8	21	3.5
Moderately potent								
0	9,862	77.6	2,177	71.6	4,168	81.3	418	68.8
1	1,630	12.8	481	15.8	596	11.6	103	16.9
2-3	776	6.1	231	7.6	247	4.8	61	10.0
4+	437	3.4	151	5.0	113	2.2	26	4.3
Potent								
0	7,202	56.7	1,464	48.2	3,402	66.4	343	56.4
1	2,440	19.2	669	22.0	847	16.5	122	20.1
2-3	1,688	13.3	496	16.3	496	9.7	75	12.3
4+	1,375	10.8	411	13.5	379	7.4	68	11.2
Very potent								
0	10,285	81.0	2,240	73.7	4,629	90.3	522	85.9
1	1,398	11.0	457	15.0	313	6.1	51	8.4
2-3	669	5.3	229	7.5	129	2.5	24	3.9
4+	353	2.8	114	3.8	53	1.0	11	1.8

Annex 4 Table 10. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, UK-CPRD, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=12,705)		Subjects Excluded During the Trimming and Matching Process (N=3,040)		Final Cohort After Trimming and Matching (N=5,124)		Subjects Excluded During the Trimming and Matching Process (N=608)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Topical corticosteroids combined								
Any potency								
0	8,486	66.8	1,854	61.0	3,726	72.7	389	64.0
1	2,103	16.6	520	17.1	763	14.9	103	16.9
2-3	1,316	10.4	390	12.8	426	8.3	64	10.5
4+	800	6.3	276	9.1	209	4.1	52	8.6
Weak potency								
0	11,489	90.4	2,714	89.3	4,596	89.7	521	85.7
1	900	7.1	248	8.2	405	7.9	65	10.7
2-3	247	1.9	59	1.9	97	1.9	17	2.8
4+	69	0.5	19	0.6	26	0.5	5	0.8
Moderately potent								
0	11,862	93.4	2,811	92.5	4,857	94.8	574	94.4
1	603	4.7	155	5.1	181	3.5	18	3.0
2-3	171	1.3	59	1.9	68	1.3	11	1.8
4+	69	0.5	15	0.5	18	0.4	5	0.8
Potent								
0	9,819	77.3	2,171	71.4	4,284	83.6	466	76.6
1	1,493	11.8	387	12.7	479	9.3	66	10.9
2-3	921	7.2	290	9.5	242	4.7	40	6.6
4+	472	3.7	192	6.3	119	2.3	36	5.9
Very potent								
0	12,469	98.1	2,994	98.5	5,071	99.0	602	99.0
1	131	1.0	30	1.0	36	0.7	[redacted]	[redacted]
2-3	75	0.6	11	0.4	12	0.2		
4+	30	0.2	5	0.2	5	0.1		
Immunosuppressants, immunostimulants, and cytostatics	4,652	36.6	1,450	47.7	1,596	31.1	251	41.3
Systemic corticosteroids	4,352	34.3	1,300	42.8	1,493	29.1	211	34.7
Systemic tacrolimus	11	0.1	0	0.0	[redacted]	[redacted]	[redacted]	[redacted]
Azathioprine	112	0.9	87	2.9	27	0.5	14	2.3
Methotrexate	145	1.1	104	3.4	34	0.7	7	1.2
Cyclosporin	71	0.6	105	3.5	9	0.2	22	3.6

Annex 4 Table 10. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, UK-CPRD, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=12,705)		Subjects Excluded During the Trimming and Matching Process (N=3,040)		Final Cohort After Trimming and Matching (N=5,124)		Subjects Excluded During the Trimming and Matching Process (N=608)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Other antineoplastic agents except methotrexate	43	0.3	7	0.2	13	0.3	[redacted]	[redacted]
Other immunosuppressants except systemic tacrolimus	39	0.3	30	1.0	7	0.1	[redacted]	[redacted]
Systemic antivirals	298	2.3	109	3.6	105	2.0	29	4.8
Immunostimulants	0	0.0	0	0.0	0	0.0	0	0.0
Antipsoriatics topical	1,604	12.6	602	19.8	404	7.9	107	17.6
Tars	497	3.9	274	9.0	134	2.6	52	8.6
Antracen derivatives	51	0.4	41	1.3	12	0.2	13	2.1
Psoralens topical	0	0.0	0	0.0	0	0.0	0	0.0
Other antipsoriatics topical	1,366	10.8	495	16.3	328	6.4	88	14.5
Antipsoriatics systemic	5	0.0	12	0.4	0	0.0	[redacted]	[redacted]
Psoralens systemic	0	0.0	0	0.0	0	0.0	0	0.0
Retinoids	[redacted]	[redacted]	12	0.4	0	0.0	[redacted]	[redacted]
Other antipsoriatics systemic	[redacted]	[redacted]	0	0.0	0	0.0	0	0.0
Other dermatological agents	12,705	100.0	3,040	100.0	5,124	100.0	608	100.0
Topical salicylic acid preparations	34	0.3	19	0.6	6	0.1	0	0.0
Other dermatological agents	12,705	100.0	3,040	100.0	5,124	100.0	608	100.0
Other medications	6,671	52.5	1,638	53.9	2,572	50.2	312	51.3
Cardiovascular system drugs	3,502	27.6	802	26.4	1,309	25.5	156	25.7
Anti-inflammatory and anti-rheumatic agents, nonsteroidal	2,389	18.8	556	18.3	914	17.8	112	18.4
Other antirheumatic agents	7	0.1	[redacted]	[redacted]	[redacted]	[redacted]	0	0.0
Hormone-replacement therapy	694	5.5	161	5.3	305	6.0	27	4.4
Lipid-modifying agents	1,823	14.3	368	12.1	577	11.3	66	10.9
Insulins	183	1.4	51	1.7	57	1.1	5	0.8
Oral antidiabetics	464	3.7	105	3.5	142	2.8	14	2.3
Antiepileptics	510	4.0	152	5.0	183	3.6	22	3.6
Drugs for asthma and COPD excluding inhaled corticosteroids	1,564	12.3	494	16.3	631	12.3	101	16.6
Inhaled corticosteroids	1,532	12.1	478	15.7	625	12.2	98	16.1

Annex 4 Table 10. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, UK-CPRD, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=12,705)		Subjects Excluded During the Trimming and Matching Process (N=3,040)		Final Cohort After Trimming and Matching (N=5,124)		Subjects Excluded During the Trimming and Matching Process (N=608)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Utilization of health care resources in the year before the start date								
General practitioner visits								
0	558	4.4	56	1.8	214	4.2	14	2.3
1	713	5.6	124	4.1	333	6.5	20	3.3
2-3	1,939	15.3	386	12.7	846	16.5	91	15.0
4+	9,495	74.7	2,474	81.4	3,731	72.8	483	79.4
Dermatologist visits								
0	10,459	82.3	206	6.8	4,513	88.1	62	10.2
1	1,004	7.9	1,353	44.5	301	5.9	305	50.2
2-3	885	7.0	990	32.6	220	4.3	164	27.0
4+	357	2.8	491	16.2	90	1.8	77	12.7
Paediatrician visits								
0	12,697	99.9	3,037	99.9	5,119	99.9	606	99.7
1	7	0.1	[redacted]	[redacted]	5	0.1	[redacted]	[redacted]
2-3	[redacted]	[redacted]			0	0.0		
4+			0	0.0	0	0.0	0	0.0
Emergency department visits								
0	11,658	91.8	2,697	88.7	4,775	93.2	534	87.8
1	792	6.2	254	8.4	277	5.4	51	8.4
2-3	224	1.8	77	2.5	66	1.3	[redacted]	[redacted]
4+	31	0.2	12	0.4	6	0.1		
Outpatient hospital visits								
0	8,206	64.6	171	5.6	3,601	70.3	39	6.4
1	1,577	12.4	829	27.3	583	11.4	197	32.4
2-3	1,507	11.9	947	31.2	505	9.9	192	31.6
4+	1,415	11.1	1,093	36.0	435	8.5	180	29.6
Hospitalisations								
0	11,457	90.2	2,575	84.7	4,743	92.6	557	91.6
1	876	6.9	312	10.3	246	4.8	35	5.8
2-3	299	2.4	117	3.8	103	2.0	10	1.6
4+	73	0.6	36	1.2	32	0.6	6	1.0

Annex 4 Table 10. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, UK-CPRD, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=12,705)		Subjects Excluded During the Trimming and Matching Process (N=3,040)		Final Cohort After Trimming and Matching (N=5,124)		Subjects Excluded During the Trimming and Matching Process (N=608)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Prescriptions								
0	0	0.0	0	0.0	0	0.0	0	0.0
1	242	1.9	23	0.8	116	2.3	9	1.5
2-3	1,194	9.4	172	5.7	588	11.5	40	6.6
5-9	2,084	16.4	427	14.0	998	19.5	90	14.8
10+	9,185	72.3	2,418	79.5	3,422	66.8	469	77.1

NA = not available

[a] Not applicable, no record of diagnosis of atopic dermatitis.

[b] Not applicable, no record of topical corticosteroid prescription.

Categorical Variables, Denmark

Annex 4 Table 11. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Denmark, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=11,417)		Subjects Excluded During the Trimming and Matching Process (N=4,412)		Final Cohort After Trimming and Matching (N=20,343)		Subjects Excluded During the Trimming and Matching Process (N=9,110)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Demographics								
Age								
0-1	1,670	14.6	470	10.7	6,022	29.6	2,784	30.6
2-4	2,726	23.9	847	19.2	5,422	26.7	1,972	21.6
5-9	2,304	20.2	1,125	25.5	3,128	15.4	1,784	19.6
10-14	2,554	22.4	1,322	30.0	3,230	15.9	1,884	20.7
15-17	2,163	18.9	648	14.7	2,541	12.5	686	7.5
Sex female	5,996	52.5	2,431	55.1	10,647	52.3	4,947	54.3
Calendar year								
2002	438	3.8	46	1.0	1,620	8.0	585	6.4
2003	616	5.4	145	3.3	2,987	14.7	1,343	14.7
2004	823	7.2	178	4.0	2,746	13.5	1,290	14.2
2005	575	5.0	172	3.9	1,857	9.1	845	9.3
2006	459	4.0	130	2.9	1,221	6.0	508	5.6
2007	467	4.1	131	3.0	1,169	5.7	481	5.3
2008	747	6.5	227	5.1	1,033	5.1	495	5.4
2009	1,207	10.6	465	10.5	1,121	5.5	538	5.9
2010	1,259	11.0	529	12.0	1,245	6.1	600	6.6
2011	1,188	10.4	631	14.3	1,137	5.6	471	5.2
2012	1,038	9.1	451	10.2	1,068	5.2	449	4.9
2013	805	7.1	404	9.2	1,067	5.2	550	6.0
2014	843	7.4	434	9.8	962	4.7	489	5.4
2015	952	8.3	469	10.6	1,110	5.5	466	5.1
Duration of follow-up (years)								
≤1	1,039	9.1	509	11.5	1,331	6.5	583	6.4
2-4	2,775	24.3	1,321	29.9	3,282	16.1	1,560	17.1
5+	7,603	66.6	2,582	58.5	15,730	77.3	6,967	76.5
Duration of medical history up to the start date (years)								
≤1	1,739	15.2	505	11.4	6,136	30.2	2,832	31.1
2-4	2,807	24.6	885	20.1	5,473	26.9	2,029	22.3
5+	6,871	60.2	3,022	68.5	8,734	42.9	4,249	46.6

Annex 4 Table 11. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Denmark, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=11,417)		Subjects Excluded During the Trimming and Matching Process (N=4,412)		Final Cohort After Trimming and Matching (N=20,343)		Subjects Excluded During the Trimming and Matching Process (N=9,110)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Type of prescriber of first prescription								
Dermatologist	4,450	39.0	1,918	43.5	4,588	22.6	1,331	14.6
Paediatrician	581	5.1	109	2.5	628	3.1	134	1.5
General practitioner	2,186	19.1	1,102	25.0	6,807	33.5	4,081	44.8
Other	4,200	36.8	NA		8,320	40.9	NA	
Unknown	0	0.0	NA		0	0.0	NA	
Other/Unknown	NA		1,283	29.1	NA		3,564	39.1
Atopic dermatitis								
Diagnosis at any time before start date								
Any diagnosis	NA		NA		NA		NA	
General practitioner	NA		NA		NA		NA	
Paediatrician	NA		NA		NA		NA	
Dermatologist	NA		NA		NA		NA	
Hospital outpatient visit	NA		NA		NA		NA	
Primary or secondary hospital discharge diagnosis	NA		NA		NA		NA	
Other specialties	NA		NA		NA		NA	
Time since first diagnosis of atopic dermatitis (years)								
≤1	593	46.1	102	41.1	850	49.8	143	33.5
2-4	274	21.3	53	21.4	357	20.9	90	21.1
5-9	248	19.3	66	26.6	349	20.4	110	25.8
10-15	141	11.0	NR	NR	137	8.0	74	17.3
15+	30	2.3	n < 5	NR	15	0.9	10	2.3
Not applicable[a]	10,131	88.7	4,164	94.4	18,635	91.6	8,683	95.3
Time since first prescription for topical corticosteroids (years)								
≤1	4,032	41.4	573	21.6	7,790	51.1	774	20.9
2-4	2,014	20.7	705	26.6	3,088	20.3	1,171	31.7
5-9	2,227	22.9	824	31.1	3,015	19.8	1,244	33.6
10-15	1,281	13.2	499	18.8	1,166	7.7	466	12.6
15+	181	1.9	48	1.8	181	1.2	44	1.2
Not applicable[b]	1,682	14.7	1,763	40.0	5,103	25.1	5,411	59.4

Annex 4 Table 11. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Denmark, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=11,417)		Subjects Excluded During the Trimming and Matching Process (N=4,412)		Final Cohort After Trimming and Matching (N=20,343)		Subjects Excluded During the Trimming and Matching Process (N=9,110)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Medical history								
Diseases interacting with the immune system	1,195	10.5	304	6.9	1,883	9.3	377	4.1
Psoriasis	49	0.4	22	0.5	39	0.2	6	0.1
Epstein-Barr virus infection	16	0.1	5	0.1	14	0.1	n < 5	NR
Rheumatoid arthritis	n < 5	NR	0	0.0	6	0.0	n < 5	NR
Systemic lupus erythematosus	n < 5	NR	n < 5	NR	n < 5	NR	0	0.0
Sjögren's syndrome	0	0.0	0	0.0	0	0.0	0	0.0
Celiac sprue	13	0.1	n < 5	NR	29	0.1	7	0.1
Asthma	1,041	9.1	249	5.6	1,704	8.4	329	3.6
Allergic rhinitis	195	1.7	35	0.8	293	1.4	54	0.6
Disease of the immune system	19	0.2	9	0.2	32	0.2	9	0.1
Skin diseases (excluding atopic dermatitis, eczema and psoriasis)	388	3.4	187	4.2	484	2.4	129	1.4
Inflammatory skin disease	347	3.0	121	2.7	465	2.3	123	1.4
Sun burn	n < 5	NR	0	0.0	n < 5	NR	0	0.0
Other skin diseases	42	0.4	73	1.7	21	0.1	8	0.1
Chronic diseases	637	5.6	189	4.3	777	3.8	250	2.7
Malignancy excluding skin cancer and lymphoma	10	0.1	n < 5	NR	24	0.1	n < 5	NR
Renal failure	n < 5	NR	0	0.0	n < 5	NR	n < 5	NR
Chronic liver diseases and hepatic failure	6	0.1	n < 5	NR	11	0.1	0	0.0
Ischemic heart disease	n < 5	NR	0	0.0	n < 5	NR	n < 5	NR
Hypertensive disease	7	0.1	n < 5	NR	8	0.0	5	0.1
Heart failure	5	0.0	n < 5	NR	10	0.0	n < 5	NR
Other cardiovascular diseases	54	0.5	16	0.4	63	0.3	NR	NR
Cerebrovascular diseases	7	0.1	n < 5	NR	11	0.1	n < 5	NR
Diabetes mellitus	27	0.2	NR	NR	27	0.1	n < 5	NR
COPD, emphysema, respiratory insufficiency	127	1.1	27	0.6	191	0.9	47	0.5
Musculoskeletal system and connective disease (excluding rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome)	411	3.6	131	3.0	462	2.3	162	1.8

Annex 4 Table 11. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Denmark, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=11,417)		Subjects Excluded During the Trimming and Matching Process (N=4,412)		Final Cohort After Trimming and Matching (N=20,343)		Subjects Excluded During the Trimming and Matching Process (N=9,110)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Organ transplantation	7	0.1	n < 5	NR	6	0.0	0	0.0
HIV infection or AIDs	n < 5	NR	0	0.0	0	0.0	n < 5	NR
Use of medications								
Topical corticosteroids plain								
Any potency								
0	3,714	32.5	3,765	85.3	7,587	37.3	8,735	95.9
1	3,961	34.7	187	4.2	7,230	35.5	195	2.1
2-3	2,677	23.4	237	5.4	4,046	19.9	109	1.2
4+	1,065	9.3	223	5.1	1,480	7.3	71	0.8
Weak potency								
0	9,518	83.4	4,237	96.0	16,070	79.0	8,995	98.7
1	1,484	13.0	120	2.7	3,223	15.8	75	0.8
2-3	331	2.9	45	1.0	868	4.3	27	0.3
4+	84	0.7	10	0.2	182	0.9	13	0.1
Moderately potent								
0	6,393	56.0	3,950	89.5	11,930	58.6	8,856	97.2
1	3,293	28.8	201	4.6	5,804	28.5	156	1.7
2-3	1,324	11.6	176	4.0	2,036	10.0	62	0.7
4+	407	3.6	85	1.9	573	2.8	36	0.4
Potent								
0	8,517	74.6	4,109	93.1	17,149	84.3	8,996	98.7
1	1,986	17.4	162	3.7	2,262	11.1	89	1.0
2-3	727	6.4	98	2.2	738	3.6	17	0.2
4+	187	1.6	43	1.0	194	1.0	8	0.1
Very potent								
0	10,951	95.9	4,346	98.5	20,011	98.4	9,103	99.9
1	350	3.1	33	0.7	267	1.3	NR	NR
2-3	95	0.8	21	0.5	52	0.3	n < 5	NR
4+	21	0.2	12	0.3	13	0.1	0	0.0

Annex 4 Table 11. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Denmark, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=11,417)		Subjects Excluded During the Trimming and Matching Process (N=4,412)		Final Cohort After Trimming and Matching (N=20,343)		Subjects Excluded During the Trimming and Matching Process (N=9,110)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Topical corticosteroids combined								
Any potency								
0	8,327	72.9	4,081	92.5	15,263	75.0	8,926	98.0
1	2,111	18.5	171	3.9	3,660	18.0	113	1.2
2-3	762	6.7	112	2.5	1,175	5.8	48	0.5
4+	217	1.9	48	1.1	245	1.2	23	0.3
Weak potency								
0	10,560	92.5	4,330	98.1	18,392	90.4	9,040	99.2
1	737	6.5	64	1.5	1,648	8.1	46	0.5
2-3	104	0.9	NR	NR	277	1.4	16	0.2
4+	16	0.1	n < 5	NR	26	0.1	8	0.1
Moderately potent								
0	10,953	95.9	4,370	99.0	19,254	94.6	9,041	99.2
1	347	3.0	31	0.7	861	4.2	42	0.5
2-3	88	0.8	NR	NR	195	1.0	20	0.2
4+	29	0.3	n < 5	NR	33	0.2	7	0.1
Potent								
0	9,260	81.1	4,144	93.9	17,653	86.8	9,033	99.2
1	1,564	13.7	149	3.4	2,105	10.3	61	0.7
2-3	464	4.1	84	1.9	476	2.3	NR	NR
4+	129	1.1	35	0.8	109	0.5	n < 5	NR
Very potent								
0	11,417	100.0	4,412	100.0	20,343	100.0	9,110	100.0
1	0	0.0	0	0.0	0	0.0	0	0.0
2-3	0	0.0	0	0.0	0	0.0	0	0.0
4+	0	0.0	0	0.0	0	0.0	0	0.0
Immunosuppressants, immunostimulants, and cytostatics	286	2.5	49	1.1	369	1.8	15	0.2
Systemic corticosteroids	140	1.2	30	0.7	138	0.7	6	0.1
Systemic tacrolimus	0	0.0	0	0.0	0	0.0	0	0.0
Azathioprine	0	0.0	0	0.0	0	0.0	0	0.0
Methotrexate	0	0.0	0	0.0	0	0.0	0	0.0
Cyclosporin	0	0.0	0	0.0	0	0.0	0	0.0
Other antineoplastic agents except methotrexate	0	0.0	0	0.0	0	0.0	0	0.0

Annex 4 Table 11. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Denmark, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=11,417)		Subjects Excluded During the Trimming and Matching Process (N=4,412)		Final Cohort After Trimming and Matching (N=20,343)		Subjects Excluded During the Trimming and Matching Process (N=9,110)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Other immunosuppressants except systemic tacrolimus	0	0.0	0	0.0	0	0.0	0	0.0
Systemic antivirals	151	1.3	19	0.4	236	1.2	9	0.1
Immunostimulants	0	0.0	0	0.0	0	0.0	0	0.0
Antipsoriatics topical	162	1.4	48	1.1	208	1.0	31	0.3
Tars	44	0.4	8	0.2	105	0.5	31	0.3
Antracen derivatives	0	0.0	0	0.0	0	0.0	0	0.0
Psoralens topical	0	0.0	0	0.0	0	0.0	0	0.0
Other antipsoriatics topical	118	1.0	41	0.9	104	0.5	0	0.0
Antipsoriatics systemic	0	0.0	0	0.0	n < 5	NR	0	0.0
Psoralens systemic	0	0.0	0	0.0	0	0.0	0	0.0
Retinoids	0	0.0	0	0.0	n < 5	NR	0	0.0
Other antipsoriatics systemic	0	0.0	0	0.0	0	0.0	0	0.0
Other dermatological agents	4,043	35.4	386	8.7	7,612	37.4	219	2.4
Topical salicylic acid preparations	n < 5	NR	0	0.0	5	0.0	n < 5	NR
Other dermatological agents	NR	NR	386	8.7	7,610	37.4	NR	NR
Other medications	2,911	25.5	281	6.4	5,995	29.5	198	2.2
Cardiovascular system drugs	150	1.3	19	0.4	225	1.1	10	0.1
Anti-inflammatory and anti-rheumatic agents, nonsteroidal	342	3.0	27	0.6	384	1.9	11	0.1
Other antirheumatic agents	0	0.0	0	0.0	0	0.0	0	0.0
Hormone-replacement therapy	5	0.0	n < 5	NR	n < 5	NR	n < 5	NR
Lipid-modifying agents	n < 5	NR	0	0.0	n < 5	NR	n < 5	NR
Insulins	26	0.2	8	0.2	27	0.1	n < 5	NR
Oral antidiabetics	n < 5	NR	n < 5	NR	n < 5	NR	0	0.0
Antiepileptics	49	0.4	n < 5	NR	83	0.4	n < 5	NR
Drugs for asthma and COPD excluding inhaled corticosteroids	2,175	19.1	219	5.0	4,928	24.2	170	1.9
Inhaled corticosteroids	1,171	10.3	143	3.2	2,503	12.3	104	1.1

Annex 4 Table 11. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Denmark, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=11,417)		Subjects Excluded During the Trimming and Matching Process (N=4,412)		Final Cohort After Trimming and Matching (N=20,343)		Subjects Excluded During the Trimming and Matching Process (N=9,110)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Utilization of health care resources in the year before the start date								
General practitioner visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	
Dermatologist visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	
Paediatrician visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	
Emergency department visits								
0	9,756	85.5	3,846	87.2	17,397	85.5	8,010	87.9
1	1,341	11.7	466	10.6	2,365	11.6	929	10.2
2-3	296	2.6	93	2.1	536	2.6	163	1.8
4+	24	0.2	7	0.2	45	0.2	8	0.1
Outpatient hospital visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	
Hospitalisations								
0	9,563	83.8	3,878	87.9	15,703	77.2	6,845	75.1
1	1,273	11.2	406	9.2	3,261	16.0	1,781	19.5
2-3	479	4.2	106	2.4	1,150	5.7	432	4.7
4+	102	0.9	22	0.5	229	1.1	52	0.6

Annex 4 Table 11. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Denmark, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=11,417)		Subjects Excluded During the Trimming and Matching Process (N=4,412)		Final Cohort After Trimming and Matching (N=20,343)		Subjects Excluded During the Trimming and Matching Process (N=9,110)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Prescriptions								
0	179	1.6	3,587	81.3	151	0.7	8,588	94.3
1	3,336	29.2	89	2.0	6,650	32.7	131	1.4
2-3	5,281	46.3	137	3.1	9,117	44.8	166	1.8
5-9	1,906	16.7	379	8.6	3,339	16.4	126	1.4
10+	715	6.3	220	5.0	1,086	5.3	99	1.1

NA = not available; NR = not reportable.

[a] Not applicable, no record of diagnosis of atopic dermatitis

[b] Not applicable, no record of topical corticosteroid prescription

Note: Some cells contain “NR” to prevent calculation of the values in other cells that have cell counts less than 5 (i.e., cells containing “n < 5”).

Annex 4 Table 12. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Denmark, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=40,710)		Subjects Excluded During the Trimming and Matching Process (N=10,399)		Final Cohort After Trimming and Matching (N=43,042)		Subjects Excluded During the Trimming and Matching Process (N=10,652)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Demographics								
Age								
18-24	4,662	11.5	1,107	10.6	5,403	12.6	1,214	11.4
25-34	6,738	16.6	2,280	21.9	8,350	19.4	2,762	25.9
35-44	7,411	18.2	2,704	26.0	8,622	20.0	3,151	29.6
45-54	7,238	17.8	2,074	19.9	7,518	17.5	1,773	16.6
55-64	7,108	17.5	1,326	12.8	6,648	15.4	975	9.2
65-74	5,099	12.5	646	6.2	4,476	10.4	438	4.1
75-84	1,970	4.8	196	1.9	1,655	3.8	215	2.0
85+	484	1.2	66	0.6	370	0.9	124	1.2
Sex female	24,368	59.9	5,863	56.4	27,720	64.4	6,496	61.0
Calendar year								
2002	822	2.0	288	2.8	1,436	3.3	515	4.8
2003	1,918	4.7	206	2.0	4,090	9.5	692	6.5
2004	2,327	5.7	307	3.0	4,504	10.5	863	8.1
2005	1,790	4.4	244	2.3	3,276	7.6	619	5.8
2006	1,422	3.5	206	2.0	2,701	6.3	537	5.0
2007	1,696	4.2	215	2.1	2,566	6.0	431	4.0
2008	2,618	6.4	398	3.8	2,374	5.5	464	4.4
2009	3,779	9.3	766	7.4	3,085	7.2	661	6.2
2010	4,061	10.0	1,028	9.9	3,051	7.1	766	7.2
2011	4,278	10.5	1,388	13.3	3,124	7.3	850	8.0
2012	3,986	9.8	1,270	12.2	3,040	7.1	716	6.7
2013	3,792	9.3	1,123	10.8	3,246	7.5	1,163	10.9
2014	4,136	10.2	1,387	13.3	3,356	7.8	1,199	11.3
2015	4,085	10.0	1,573	15.1	3,193	7.4	1,176	11.0
Duration of follow-up (years)								
≤1	5,325	13.1	1,770	17.0	4,450	10.3	1,430	13.4
2-4	12,701	31.2	3,875	37.3	10,653	24.8	3,249	30.5
5+	22,684	55.7	4,754	45.7	27,939	64.9	5,973	56.1

Annex 4 Table 12. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Denmark, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=40,710)		Subjects Excluded During the Trimming and Matching Process (N=10,399)		Final Cohort After Trimming and Matching (N=43,042)		Subjects Excluded During the Trimming and Matching Process (N=10,652)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Duration of medical history up to the start date (years)								
≤1	305	0.7	113	1.1	355	0.8	131	1.2
2-4	806	2.0	289	2.8	903	2.1	299	2.8
5+	39,599	97.3	9,997	96.1	41,784	97.1	10,222	96.0
Type of prescriber of first prescription								
Dermatologist	17,231	42.3	6,286	60.4	14,525	33.7	4,566	42.9
Paediatrician	NR	NR	6	0.1	NR	NR	7	0.1
General practitioner	6,655	16.3	1,526	14.7	10,594	24.6	2,725	25.6
Other	16,777	41.2		NA	17,889	41.6		NA
Unknown	n < 5	NR		NA	n < 5	NR		NA
Other/Unknown		NA	2,581	24.8		NA	3,354	31.5
Atopic dermatitis								
Diagnosis at any time before start date								
Any diagnosis		NA		NA		NA		NA
General practitioner		NA		NA		NA		NA
Paediatrician		NA		NA		NA		NA
Dermatologist		NA		NA		NA		NA
Hospital outpatient visit		NA		NA		NA		NA
Primary or secondary hospital discharge diagnosis		NA		NA		NA		NA
Other specialties		NA		NA		NA		NA
Time since first diagnosis of atopic dermatitis (years)								
≤1	880	38.7	181	30.0	457	27.1	94	28.0
2-4	387	17.0	84	14.0	279	16.6	82	24.0
5-9	519	22.9	121	20.0	469	27.9	99	29.0
10-15	333	14.7	119	20.0	285	16.9	37	11.0
15+	152	6.7	92	15.0	194	11.5	24	7.0
Not applicable[a]	38,439	94.4	9,802	94.0	41,358	96.1	10,316	97.0

Annex 4 Table 12. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Denmark, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=40,710)		Subjects Excluded During the Trimming and Matching Process (N=10,399)		Final Cohort After Trimming and Matching (N=43,042)		Subjects Excluded During the Trimming and Matching Process (N=10,652)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Time since first prescription for topical corticosteroids (years)								
≤1	5,128	13.9	673	8.0	4,907	13.3	512	7.0
2-4	3,918	10.6	917	11.0	4,521	12.3	1,021	13.0
5-9	10,259	27.8	2,044	24.0	12,820	34.8	2,534	33.0
10-15	10,648	28.8	2,424	29.0	8,927	24.2	1,978	26.0
15+	6,988	18.9	2,313	28.0	5,661	15.4	1,571	21.0
Not applicable[b]	3,769	9.3	2,028	20.0	6,206	14.4	3,036	29.0
Medical history								
Diseases interacting with the immune system	4,013	9.9	1,475	14.0	3,739	8.7	807	8.0
Psoriasis	723	1.8	396	4.0	559	1.3	109	1.0
Epstein-Barr virus infection	40	0.1	15	0.0	34	0.1	9	0.0
Rheumatoid arthritis	392	1.0	80	1.0	335	0.8	44	0.0
Systemic lupus erythematosus	206	0.5	146	1.0	116	0.3	29	0.0
Sjögren's syndrome	109	0.3	42	0.0	95	0.2	14	0.0
Celiac sprue	75	0.2	19	0.0	78	0.2	22	0.0
Asthma	2,050	5.0	654	6.0	1,996	4.6	399	4.0
Allergic rhinitis	903	2.2	386	4.0	965	2.2	291	3.0
Disease of the immune system	179	0.4	61	1.0	162	0.4	28	0.0
Skin diseases (excluding atopic dermatitis, eczema and psoriasis)	3,457	8.5	1,714	16.0	2,439	5.7	620	6.0
Inflammatory skin disease	2,988	7.3	1,514	15.0	2,142	5.0	563	5.0
Sun burn	9	0.0	n < 5	NR	7	0.0	n < 5	NR
Other skin diseases	574	1.4	264	3.0	368	0.9	65	1.0
Chronic diseases	13,980	34.3	2,605	25.0	12,742	29.6	1,901	18.0
Malignancy excluding skin cancer and lymphoma	1,422	3.5	276	3.0	1,362	3.2	191	2.0
Renal failure	225	0.6	30	0.0	172	0.4	25	0.0
Chronic liver diseases and hepatic failure	349	0.9	56	1.0	304	0.7	37	0.0
Ischemic heart disease	2,138	5.3	254	2.0	1,777	4.1	162	2.0
Hypertensive disease	3,372	8.3	312	3.0	2,845	6.6	176	2.0
Heart failure	501	1.2	51	0.0	332	0.8	62	1.0
Other cardiovascular diseases	3,018	7.4	460	4.0	2,501	5.8	351	3.0

Annex 4 Table 12. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Denmark, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=40,710)		Subjects Excluded During the Trimming and Matching Process (N=10,399)		Final Cohort After Trimming and Matching (N=43,042)		Subjects Excluded During the Trimming and Matching Process (N=10,652)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Cerebrovascular diseases	1,099	2.7	143	1.0	957	2.2	114	1.0
Diabetes mellitus	1,452	3.6	148	1.0	1,043	2.4	78	1.0
COPD, emphysema, respiratory insufficiency	1,151	2.8	163	2.0	917	2.1	106	1.0
Musculoskeletal system and connective disease (excluding rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome)	7,664	18.8	1,667	16.0	7,064	16.4	1,221	11.0
Organ transplantation	59	0.1	9	0.0	60	0.1	7	0.0
HIV infection or AIDs	51	0.1	10	0.0	45	0.1	n < 5	NR
Use of medications								
Topical corticosteroids plain								
Any potency								
0	17,922	44.0	7,627	73.0	22,684	52.7	9,138	86.0
1	11,832	29.1	1,141	11.0	11,843	27.5	791	7.0
2-3	7,562	18.6	976	9.0	6,223	14.5	487	5.0
4+	3,394	8.3	655	6.0	2,292	5.3	236	2.0
Weak potency								
0	38,170	93.8	10,111	97.0	39,095	90.8	10,355	97.0
1	2,173	5.3	239	2.0	3,501	8.1	268	3.0
2-3	312	0.8	NR	NR	394	0.9	NR	NR
4+	55	0.1	n < 5	NR	52	0.1	n < 5	NR
Moderately potent								
0	32,086	78.8	9,255	89.0	33,363	77.5	9,892	93.0
1	6,430	15.8	787	8.0	7,425	17.3	592	6.0
2-3	1,732	4.3	280	3.0	1,817	4.2	135	1.0
4+	462	1.1	77	1.0	437	1.0	33	0.0
Potent								
0	28,239	69.4	8,730	84.0	33,715	78.3	9,871	93.0
1	7,718	19.0	927	9.0	6,154	14.3	469	4.0
2-3	3,430	8.4	482	5.0	2,319	5.4	218	2.0
4+	1,323	3.2	260	3.0	854	2.0	94	1.0

Annex 4 Table 12. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Denmark, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=40,710)		Subjects Excluded During the Trimming and Matching Process (N=10,399)		Final Cohort After Trimming and Matching (N=43,042)		Subjects Excluded During the Trimming and Matching Process (N=10,652)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Very potent								
0	34,294	84.2	9,471	91.0	39,991	92.9	10,423	98.0
1	4,163	10.2	549	5.0	2,086	4.8	148	1.0
2-3	1,638	4.0	254	2.0	728	1.7	56	1.0
4+	615	1.5	125	1.0	237	0.6	25	0.0
Topical corticosteroids combined								
Any potency								
0	31,931	78.4	9,329	90.0	35,823	83.2	10,181	96.0
1	5,971	14.7	677	7.0	5,195	12.1	340	3.0
2-3	2,193	5.4	312	3.0	1,662	3.9	98	1.0
4+	615	1.5	81	1.0	362	0.8	33	0.0
Weak potency								
0	39,569	97.2	10,269	99.0	41,589	96.6	10,560	99.0
1	1,002	2.5	117	1.0	1,273	3.0	81	1.0
2-3	122	0.3	NR	NR	155	0.4	NR	NR
4+	17	0.0	n < 5	NR	25	0.1	n < 5	NR
Moderately potent								
0	39,361	96.7	10,334	99.0	41,332	96.0	10,590	99.0
1	1,004	2.5	41	0.0	1,324	3.1	38	0.0
2-3	283	0.7	NR	NR	327	0.8	17	0.0
4+	62	0.2	n < 5	NR	59	0.1	7	0.0
Potent								
0	33,794	83.0	9,465	91.0	38,397	89.2	10,301	97.0
1	4,802	11.8	598	6.0	3,439	8.0	263	2.0
2-3	1,663	4.1	269	3.0	987	2.3	67	1.0
4+	451	1.1	67	1.0	219	0.5	21	0.0
Very potent								
0	40,710	100.0	10,399	100.0	43,042	100.0	10,652	100.0
1	0	0.0	0	0.0	0	0.0	0	0.0
2-3	0	0.0	0	0.0	0	0.0	0	0.0
4+	0	0.0	0	0.0	0	0.0	0	0.0

Annex 4 Table 12. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Denmark, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=40,710)		Subjects Excluded During the Trimming and Matching Process (N=10,399)		Final Cohort After Trimming and Matching (N=43,042)		Subjects Excluded During the Trimming and Matching Process (N=10,652)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Immunosuppressants, immunostimulants, and cytostatics	4,886	12.0	1,054	10.0	4,562	10.6	559	5.0
Systemic corticosteroids	3,477	8.5	698	7.0	2,981	6.9	221	2.0
Systemic tacrolimus	0	0.0	0	0.0	0	0.0	0	0.0
Azathioprine	0	0.0	0	0.0	0	0.0	0	0.0
Methotrexate	0	0.0	0	0.0	0	0.0	0	0.0
Cyclosporin	0	0.0	0	0.0	0	0.0	0	0.0
Other antineoplastic agents except methotrexate	0	0.0	0	0.0	0	0.0	0	0.0
Other immunosuppressants except systemic tacrolimus	0	0.0	0	0.0	0	0.0	0	0.0
Systemic antivirals	1,570	3.9	405	4.0	1,739	4.0	350	3.0
Immunostimulants	0	0.0	0	0.0	0	0.0	0	0.0
Antipsoriatics topical	1,541	3.8	736	7.0	1,364	3.2	263	2.0
Tars	137	0.3	42	0.0	123	0.3	42	0.0
Antracen derivatives	n < 5	NR	0	0.0	n < 5	NR	0	0.0
Psoralens topical	0	0.0	0	0.0	0	0.0	0	0.0
Other antipsoriatics topical	1,417	3.5	696	7.0	1,250	2.9	234	2.0
Antipsoriatics systemic	136	0.3	140	1.0	70	0.2	11	0.0
Psoralens systemic	29	0.1	n < 5	NR	13	0.0	n < 5	NR
Retinoids	109	0.3	NR	NR	57	0.1	NR	NR
Other antipsoriatics systemic	0	0.0	0	0.0	0	0.0	0	0.0
Other dermatological agents	15,987	39.3	1,796	17.0	19,150	44.5	1,398	13.0
Topical salicylic acid preparations	45	0.1	n < 5	NR	26	0.1	n < 5	NR
Other dermatological agents	15,962	39.2	NR	NR	19,142	44.5	NR	NR
Other medications	23,374	57.4	2,405	23.0	23,939	55.6	1,450	14.0
Cardiovascular system drugs	12,487	30.7	1,033	10.0	11,822	27.5	559	5.0
Anti-inflammatory and anti-rheumatic agents, nonsteroidal	9,500	23.3	973	9.0	10,221	23.7	621	6.0
Other antirheumatic agents	n < 5	NR	n < 5	NR	n < 5	NR	0	0.0
Hormone-replacement therapy	3,580	8.8	416	4.0	3,992	9.3	187	2.0
Lipid-modifying agents	4,853	11.9	360	3.0	4,022	9.3	128	1.0
Insulins	665	1.6	78	1.0	426	1.0	24	0.0
Oral antidiabetics	1,329	3.3	85	1.0	953	2.2	56	1.0

Annex 4 Table 12. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Denmark, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=40,710)		Subjects Excluded During the Trimming and Matching Process (N=10,399)		Final Cohort After Trimming and Matching (N=43,042)		Subjects Excluded During the Trimming and Matching Process (N=10,652)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Antiepileptics	1,385	3.4	132	1.0	1,343	3.1	84	1.0
Drugs for asthma and COPD excluding inhaled corticosteroids	4,332	10.6	694	7.0	4,321	10.0	421	4.0
Inhaled corticosteroids	1,853	4.6	282	3.0	2,037	4.7	197	2.0
Utilization of health care resources in the year before the start date								
General practitioner visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	
Dermatologist visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	
Paediatrician visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	
Emergency department visits								
0	36,247	89.0	9,500	91.0	38,276	88.9	9,678	91.0
1	3,646	9.0	750	7.0	3,920	9.1	825	8.0
2-3	722	1.8	138	1.0	762	1.8	137	1.0
4+	95	0.2	11	0.0	84	0.2	12	0.0
Outpatient hospital visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	

Annex 4 Table 12. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Denmark, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=40,710)		Subjects Excluded During the Trimming and Matching Process (N=10,399)		Final Cohort After Trimming and Matching (N=43,042)		Subjects Excluded During the Trimming and Matching Process (N=10,652)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Hospitalisations								
0	35,116	86.3	9,398	90.0	37,569	87.3	9,736	91.0
1	3,756	9.2	705	7.0	3,888	9.0	642	6.0
2-3	1,437	3.5	223	2.0	1,263	2.9	210	2.0
4+	401	1.0	73	1.0	322	0.7	64	1.0
Prescriptions								
0	164	0.4	6,256	60.0	n < 5	NR	7,919	74.0
1	6,214	15.3	208	2.0	7,144	16.6	100	1.0
2-3	13,125	32.2	874	8.0	14,437	33.5	702	7.0
5-9	11,165	27.4	1,511	15.0	12,449	28.9	1,233	12.0
10+	10,042	24.7	1,550	15.0	NR	NR	698	7.0

NA = not available; NR = not reportable.

[a] Not applicable, no record of diagnosis of atopic dermatitis

[b] Not applicable, no record of topical corticosteroid prescription

Note: Some cells contain “NR” to prevent calculation of the values in other cells that have cell counts less than 5 (i.e., cells containing “n < 5”).

Categorical Variables, NL-PHARMO

Annex 4 Table 13. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, NL-PHARMO, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=5,197)		Subjects Excluded During the Trimming and Matching Process (N=1,463)		Final Cohort After Trimming and Matching (N=3,189)		Subjects Excluded During the Trimming and Matching Process (N=673)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Demographics								
Age								
0-1	90	1.7	54	3.7	258	8.1	57	8.5
2-4	1,144	22.0	269	18.4	932	29.2	280	41.6
5-9	1,392	26.8	412	28.2	759	23.8	155	23.0
10-14	1,386	26.7	412	28.2	681	21.4	106	15.8
15-17	1,185	22.8	316	21.6	559	17.5	75	11.1
Sex female	2,773	53.4	803	54.9	1,756	55.1	333	49.5
Calendar year								
2002	27	0.5	11	0.8			0	0.0
2003	341	6.6	51	3.5	176	5.5	53	7.9
2004	268	5.2	57	3.9	444	13.9	248	36.8
2005	159	3.1	28	1.9	234	7.3	40	5.9
2006	235	4.5	32	2.2	188	5.9	27	4.0
2007	399	7.7	69	4.7	251	7.9	46	6.8
2008	414	8.0	92	6.3	248	7.8	41	6.1
2009	476	9.2	196	13.4	226	7.1	49	7.3
2010	463	8.9	190	13.0	186	5.8	33	4.9
2011	483	9.3	209	14.3	203	6.4	18	2.7
2012	466	9.0	157	10.7	209	6.6	24	3.6
2013	386	7.4	131	9.0	198	6.2	27	4.0
2014	390	7.5	116	7.9	224	7.0	22	3.3
2015	386	7.4	91	6.2	219	6.9	25	3.7
2016	304	5.8	33	2.3	183	5.7	20	3.0
Primary care center/region								
Drenthe	32	0.6	13	0.9	17	0.5	1	0.1
Flevoland	622	12.0	241	16.5	491	15.4	145	21.5
Friesland	42	0.8	4	0.3	43	1.3	16	2.4
Gelderland	276	5.3	44	3.0	209	6.6	28	4.2
Groningen	20	0.4	3	0.2	9	0.3	1	0.1
Limburg	389	7.5	94	6.4	337	10.6	60	8.9
Noord-Brabant	1,206	23.2	189	12.9	743	23.3	140	20.8

Annex 4 Table 13. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, NL-PHARMO, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=5,197)		Subjects Excluded During the Trimming and Matching Process (N=1,463)		Final Cohort After Trimming and Matching (N=3,189)		Subjects Excluded During the Trimming and Matching Process (N=673)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Noord-Holland	978	18.8	442	30.2	412	12.9	91	13.5
Overijssel	226	4.3	40	2.7	151	4.7	56	8.3
Utrecht	158	3.0	43	2.9	81	2.5	14	2.1
Zeeland	88	1.7	29	2.0	79	2.5	29	4.3
Zuid-Holland	1,160	22.3	321	21.9	617	19.3	92	13.7
Duration of follow-up (years)								
≤1	432	8.3	63	4.3	299	9.4	48	7.1
2-4	1,313	25.3	375	25.6	726	22.8	115	17.1
5+	3,452	66.4	1,025	70.1	2,164	67.9	510	75.8
Duration of medical history up to the start date (years)								
≤1	743	14.3	191	13.1	767	24.1	205	30.5
2-4	1,889	36.3	499	34.1	1,107	34.7	245	36.4
5+	2,565	49.4	773	52.8	1,315	41.2	223	33.1
Socioeconomic index NL-PHARMO								
Low	1,600	30.8	385	26.3	1,010	31.7	208	30.9
Middle	1,636	31.5	410	28.0	1,014	31.8	197	29.3
High	1,954	37.6	666	45.5	1,162	36.4	268	39.8
Unknown	7	0.1	2	0.1	3	0.1	0	0.0
Type of prescriber of first prescription								
Dermatologist	2,641	50.8	1,155	78.9	1,235	38.7	393	58.4
Paediatrician	151	2.9	29	2.0	66	2.1	11	1.6
General practitioner	1,341	25.8	182	12.4	1,437	45.1	237	35.2
Other	1,064	20.5	97	6.6	451	14.1	32	4.8
Unknown	0	0.0	0	0.0	0	0.0	0	0.0
Atopic dermatitis								
Diagnosis at any time before start date								
Any diagnosis	NA		NA		NA		NA	
General practitioner	NA		NA		NA		NA	
Paediatrician	NA		NA		NA		NA	
Dermatologist	NA		NA		NA		NA	
Hospital outpatient visit	NA		NA		NA		NA	
Primary or secondary hospital discharge diagnosis	NA		NA		NA		NA	

Annex 4 Table 13. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, NL-PHARMO, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=5,197)		Subjects Excluded During the Trimming and Matching Process (N=1,463)		Final Cohort After Trimming and Matching (N=3,189)		Subjects Excluded During the Trimming and Matching Process (N=673)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Other specialties	NA		NA		NA		NA	
Time since first diagnosis of atopic dermatitis (years)								
≤1	23	0.4	36	2.5	5	0.2	16	2.4
2-4	14	0.3	12	0.8	10	0.3	3	0.4
5-9	8	0.2	6	0.4	7	0.2	.	.
10-15	2	0.0	2	0.1	1	0.0	.	.
15+	1	0.0	1,407	96.2	.	.	654	97.2
Not applicablea	5,149.00	99.10	525.00	35.90	3,166.00	99.30	339.00	50.40
Time since first prescription for topical corticosteroids (years)								
≤1	2,210	42.5	426	29.1	1,559	48.9	175	26.0
2-4	1,481	28.5	318	21.7	799	25.1	76	11.3
5-9	983	18.9	93	6.4	523	16.4	8	1.2
10-15	249	4.8	8	0.5	123	3.9	1	0.1
15+	26	0.5	93	6.4	6	0.2	74	11.0
Not applicable[a]	248	4.8	93	6.4	179	5.6	74	11.0
Medical history								
Diseases interacting with the immune system	174	3.3	110	7.5	83	2.6	42	6.2
Psoriasis	3	0.1	0	0.0	0	0.0	2	0.3
Epstein-Barr virus infection	93	1.8	39	2.7	49	1.5	25	3.7
Rheumatoid arthritis	1	0.0	0	0.0	0	0.0	0	0.0
Systemic lupus erythematosus	0	0.0	0	0.0	0	0.0	0	0.0
Sjögren’s syndrome	0	0.0	0	0.0	0	0.0	0	0.0
Celiac sprue	2	0.0	3	0.2	3	0.1	2	0.3
Asthma	72	1.4	66	4.5	31	1.0	15	2.2
Allergic rhinitis	4	0.1	3	0.2	0	0.0	0	0.0
Disease of the immune system	2	0.0	5	0.3	0	0.0	0	0.0
Skin diseases (excluding atopic dermatitis, eczema and psoriasis)	48	0.9	31	2.1	23	0.7	14	2.1
Inflammatory skin disease	31	0.6	22	1.5	18	0.6	13	1.9
Sun burn	0	0.0	0	0.0	0	0.0	0	0.0
Other skin diseases	17	0.3	9	0.6	6	0.2	1	0.1

Annex 4 Table 13. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, NL-PHARMO, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=5,197)		Subjects Excluded During the Trimming and Matching Process (N=1,463)		Final Cohort After Trimming and Matching (N=3,189)		Subjects Excluded During the Trimming and Matching Process (N=673)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Chronic diseases	64	1.2	39	2.7	41	1.3	14	2.1
Malignancy excluding skin cancer and lymphoma	4	0.1	1	0.1	3	0.1	0	0.0
Renal failure	0	0.0	2	0.1	0	0.0	0	0.0
Chronic liver diseases and hepatic failure	1	0.0	1	0.1	1	0.0	1	0.1
Ischemic heart disease	0	0.0	0	0.0	0	0.0	0	0.0
Hypertensive disease	2	0.0	0	0.0	1	0.0	1	0.1
Heart failure	0	0.0	1	0.1	1	0.0	1	0.1
Other cardiovascular diseases	8	0.2	3	0.2	4	0.1	1	0.1
Cerebrovascular diseases	1	0.0	1	0.1	1	0.0	0	0.0
Diabetes mellitus	7	0.1	4	0.3	8	0.3	2	0.3
COPD, emphysema, respiratory insufficiency	10	0.2	13	0.9	7	0.2	2	0.3
Musculoskeletal system and connective disease (excluding rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome)	31	0.6	15	1.0	16	0.5	6	0.9
Organ transplantation	2	0.0	4	0.3	0	0.0	1	0.1
HIV infection or AIDs	0	0.0	0	0.0	0	0.0	0	0.0
Use of medications								
Topical corticosteroids plain								
Any potency								
0	1,391	26.8	401	27.4	997	31.3	288	42.8
1	1,421	27.3	240	16.4	884	27.7	116	17.2
2-3	1,452	27.9	405	27.7	853	26.7	145	21.5
4+	933	18.0	417	28.5	455	14.3	124	18.4
Weak potency								
0	3,631	69.9	1,056	72.2	2,098	65.8	481	71.5
1	1,064	20.5	255	17.4	740	23.2	124	18.4
2-3	408	7.9	120	8.2	294	9.2	50	7.4
4+	94	1.8	32	2.2	57	1.8	18	2.7

Annex 4 Table 13. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, NL-PHARMO, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=5,197)		Subjects Excluded During the Trimming and Matching Process (N=1,463)		Final Cohort After Trimming and Matching (N=3,189)		Subjects Excluded During the Trimming and Matching Process (N=673)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Moderately potent								
0	3,215	61.9	826	56.5	2,061	64.6	470	69.8
1	1,107	21.3	273	18.7	671	21.0	97	14.4
2-3	617	11.9	244	16.7	344	10.8	70	10.4
4+	258	5.0	120	8.2	113	3.5	36	5.3
Potent								
0	3,331	64.1	800	54.7	2,260	70.9	489	72.7
1	1,032	19.9	314	21.5	544	17.1	89	13.2
2-3	574	11.0	218	14.9	268	8.4	58	8.6
4+	260	5.0	131	9.0	117	3.7	37	5.5
Very potent								
0	4,952	95.3	1,387	94.8	3,088	96.8	661	98.2
1	173	3.3	58	4.0	86	2.7	9	1.3
2-3	62	1.2	13	0.9	11	0.3	3	0.4
4+	10	0.2	5	0.3	4	0.1	0	0.0
Topical corticosteroids combined								
Any potency								
0	4,551	87.6	1,273	87.0	2,795	87.6	603	89.6
1	493	9.5	136	9.3	304	9.5	53	7.9
2-3	137	2.6	42	2.9	76	2.4	13	1.9
4+	16	0.3	12	0.8	14	0.4	4	0.6
Weak potency								
0	4,616	88.8	1,300	88.9	2,822	88.5	607	90.2
1	448	8.6	123	8.4	290	9.1	49	7.3
2-3	120	2.3	33	2.3	65	2.0	13	1.9
4+	13	0.3	7	0.5	12	0.4	4	0.6
Moderately potent								
0	5,137	98.8	1,443	98.6	3,162	99.2	671	99.7
1	48	0.9	11	0.8	18	0.6	2	0.3
2-3	11	0.2	7	0.5	8	0.3	0	0.0
4+	1	0.0	2	0.1	1	0.0	0	0.0

Annex 4 Table 13. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, NL-PHARMO, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=5,197)		Subjects Excluded During the Trimming and Matching Process (N=1,463)		Final Cohort After Trimming and Matching (N=3,189)		Subjects Excluded During the Trimming and Matching Process (N=673)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Potent								
0	5,182	99.7	1,449	99.0	3,181	99.7	671	99.7
1	10	0.2	10	0.7	8	0.3	2	0.3
2-3	5	0.1	4	0.3	0	0.0	0	0.0
4+	0	0.0	0	0.0	0	0.0	0	0.0
Very potent								
0	5,197	100.0	1,463	100.0	3,189	100.0	673	100.0
1	0	0.0	0	0.0	0	0.0	0	0.0
2-3	0	0.0	0	0.0	0	0.0	0	0.0
4+	0	0.0	0	0.0	0	0.0	0	0.0
Immunosuppressants, immunostimulants, and cytostatics	223	4.3	138	9.4	107	3.4	28	4.2
Systemic corticosteroids	193	3.7	119	8.1	90	2.8	24	3.6
Systemic tacrolimus	1	0.0	1	0.1	0	0.0	1	0.1
Azathioprine	5	0.1	3	0.2	2	0.1	1	0.1
Methotrexate	5	0.1	1	0.1	1	0.0	0	0.0
Cyclosporin	1	0.0	8	0.5	2	0.1	1	0.1
Other antineoplastic agents except methotrexate	5	0.1	3	0.2	5	0.2	0	0.0
Other immunosuppressants except systemic tacrolimus	5	0.1	5	0.3	2	0.1	1	0.1
Systemic antivirals	22	0.4	12	0.8	8	0.3	4	0.6
Immunostimulants	1	0.0	0	0.0	0	0.0	0	0.0
Antipsoriatics topical	172	3.3	161	11.0	101	3.2	35	5.2
Tars	119	2.3	142	9.7	73	2.3	31	4.6
Antracen derivatives	6	0.1	2	0.1	1	0.0	0	0.0
Psoralens topical	0	0.0	0	0.0	0	0.0	0	0.0
Other antipsoriatics topical	50	1.0	22	1.5	27	0.8	4	0.6
Antipsoriatics systemic	1	0.0	0	0.0	0	0.0	1	0.1
Psoralens systemic	0	0.0	0	0.0	0	0.0	0	0.0
Retinoids	1	0.0	0	0.0	0	0.0	0	0.0
Other antipsoriatics systemic	0	0.0	0	0.0	0	0.0	1	0.1

Annex 4 Table 13. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, NL-PHARMO, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=5,197)		Subjects Excluded During the Trimming and Matching Process (N=1,463)		Final Cohort After Trimming and Matching (N=3,189)		Subjects Excluded During the Trimming and Matching Process (N=673)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Other dermatological agents	5,197	100.0	1,463	100.0	3,189	100.0	673	100.0
Topical salicylic acid preparations	6	0.1	1	0.1	2	0.1	0	0.0
Other dermatological agents	5,197	100.0	1,463	100.0	3,189	100.0	673	100.0
Other medications	1,219	23.5	474	32.4	708	22.2	193	28.7
Cardiovascular system drugs	217	4.2	83	5.7	146	4.6	51	7.6
Anti-inflammatory and anti-rheumatic agents, nonsteroidal	198	3.8	64	4.4	86	2.7	19	2.8
Other antirheumatic agents	1	0.0	0	0.0			0	0.0
Hormone-replacement therapy	7	0.1	7	0.5	2	0.1	0	0.0
Lipid-modifying agents	4	0.1	0	0.0	1	0.0	1	0.1
Insulins	6	0.1	4	0.3	8	0.3	2	0.3
Oral antidiabetics	5	0.1	0	0.0	1	0.0	0	0.0
Antiepileptics	17	0.3	6	0.4	7	0.2	6	0.9
Drugs for asthma and COPD excluding inhaled corticosteroids	795	15.3	345	23.6	476	14.9	128	19.0
Inhaled corticosteroids	455	8.8	206	14.1	256	8.0	88	13.1
Utilization of health care resources in the year before the start date								
General practitioner visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	
Dermatologist visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	
Paediatrician visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	

Annex 4 Table 13. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, NL-PHARMO, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=5,197)		Subjects Excluded During the Trimming and Matching Process (N=1,463)		Final Cohort After Trimming and Matching (N=3,189)		Subjects Excluded During the Trimming and Matching Process (N=673)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Emergency department visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	
Outpatient hospital visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	
Hospitalisations								
0	4,885	94.0	927	63.4	3,016	94.6	358	53.2
1	230	4.4	379	25.9	129	4.0	234	34.8
2-3	63	1.2	116	7.9	39	1.2	64	9.5
4+	19	0.4	41	2.8	5	0.2	17	2.5
Prescriptions								
0	0	0.0	0	0.0	0	0.0	0	0.0
1	0	0.0	230	15.7	0	0.0	152	22.6
2-3	1,067	20.5	56	3.8	785	24.6	64	9.5
5-9	1,578	30.4	86	5.9	952	29.9	120	17.8
10+	2,552	49.1	1,091	74.6	1,452	45.5	337	50.1

NA = not available

[a] Not applicable, no record of topical corticosteroid prescription

Annex 4 Table 14. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, NL-PHARMO, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=21,037)		Subjects Excluded During the Trimming and Matching Process (N=7,247)		Final Cohort After Trimming and Matching (N=8,506)		Subjects Excluded During the Trimming and Matching Process (N=2,941)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Demographics								
Age								
18-24	2,323	11.0	1,328	18.3	930	10.9	477	16.2
25-34	2,959	14.1	1,165	16.1	1,151	13.5	481	16.4
35-44	3,830	18.2	1,412	19.5	1,610	18.9	696	23.7
45-54	4,159	19.8	1,355	18.7	1,737	20.4	602	20.5
55-64	3,772	17.9	951	13.1	1,503	17.7	352	12.0
65-74	2,533	12.0	576	7.9	1,002	11.8	216	7.3
75-84	1,164	5.5	392	5.4	450	5.3	92	3.1
85+	297	1.4	68	0.9	123	1.4	25	0.9
Sex female	13,252	63.0	5,151	71.1	5,556	65.3	2,327	79.1
Calendar year								
2002	28	0.1	49	0.7	0	0.0	0	0.0
2003	1,098	5.2	367	5.1	103	1.2	128	4.4
2004	1,408	6.7	367	5.1	662	7.8	142	4.8
2005	1,016	4.8	244	3.4	603	7.1	284	9.7
2006	1,042	5.0	239	3.3	539	6.3	112	3.8
2007	1,238	5.9	259	3.6	634	7.5	159	5.4
2008	1,368	6.5	345	4.8	599	7.0	152	5.2
2009	1,798	8.5	568	7.8	631	7.4	193	6.6
2010	1,823	8.7	743	10.3	620	7.3	215	7.3
2011	1,859	8.8	938	12.9	692	8.1	208	7.1
2012	1,788	8.5	851	11.7	663	7.8	286	9.7
2013	1,699	8.1	678	9.4	690	8.1	320	10.9
2014	1,689	8.0	651	9.0	734	8.6	278	9.5
2015	1,690	8.0	477	6.6	723	8.5	261	8.9
2016	1,493	7.1	471	6.5	613	7.2	203	6.9
Primary care center/region								
Drenthe	126	0.6	38	0.5	58	0.7	11	0.4
Flevoland	1,751	8.3	767	10.6	809	9.5	483	16.4
Friesland	188	0.9	42	0.6	119	1.4	102	3.5
Gelderland	1,245	5.9	300	4.1	716	8.4	206	7.0
Groningen	104	0.5	33	0.5	45	0.5	15	0.5
Limburg	2,073	9.9	575	7.9	1,025	12.1	494	16.8

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	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=21,037)		Subjects Excluded During the Trimming and Matching Process (N=7,247)		Final Cohort After Trimming and Matching (N=8,506)		Subjects Excluded During the Trimming and Matching Process (N=2,941)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Noord-Brabant	5,619	26.7	1,695	23.4	2,017	23.7	449	15.3
Noord-Holland	3,788	18.0	1,758	24.3	1,269	14.9	380	12.9
Overijssel	1,045	5.0	287	4.0	373	4.4	94	3.2
Utrecht	546	2.6	142	2.0	271	3.2	131	4.5
Zeeland	311	1.5	72	1.0	141	1.7	63	2.1
Zuid-Holland	4,241	20.2	1,538	21.2	1,663	19.6	513	17.4
Duration of follow-up (years)								
≤1	2,575	12.2	728	10.0	1,103	13.0	325	11.1
2-4	5,963	28.3	2,098	28.9	2,411	28.3	984	33.5
5+	12,499	59.4	4,421	61.0	4,992	58.7	1,632	55.5
Duration of medical history up to the start date (years)								
≤1	1,952	9.3	436	6.0	762	9.0	157	5.3
2-4	4,753	22.6	1,554	21.4	1,833	21.5	482	16.4
5+	14,332	68.1	5,257	72.5	5,911	69.5	2,302	78.3
Socioeconomic index NL-PHARMO								
Low	7,066	33.6	2,146	29.6	2,970	34.9	1,028	35.0
Middle	7,060	33.6	2,373	32.7	2,787	32.8	912	31.0
High	6,880	32.7	2,718	37.5	2,734	32.1	986	33.5
Unknown	31	0.1	10	0.1	15	0.2	15	0.5
Type of prescriber of first prescription								
Dermatologist	11,210	53.3	6,383	88.1	3,805	44.7	2,319	78.9
Paediatrician	15	0.1	0	0.0	3	0.0	1	0.0
General practitioner	5,211	24.8	538	7.4	3,098	36.4	440	15.0
Other	4,601	21.9	326	4.5	1,600	18.8	181	6.2
Unknown	0	0.0	0	0.0	0	0.0	0	0.0
Atopic dermatitis								
Diagnosis at any time before start date								
Any diagnosis	NA		NA		NA		NA	
General practitioner	NA		NA		NA		NA	
Paediatrician	NA		NA		NA		NA	
Dermatologist	NA		NA		NA		NA	
Hospital outpatient visit	NA		NA		NA		NA	

Annex 4 Table 14. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, NL-PHARMO, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=21,037)		Subjects Excluded During the Trimming and Matching Process (N=7,247)		Final Cohort After Trimming and Matching (N=8,506)		Subjects Excluded During the Trimming and Matching Process (N=2,941)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Primary or secondary hospital discharge diagnosis	NA		NA		NA		NA	
Other specialties	NA		NA		NA		NA	
Time since first diagnosis of atopic dermatitis (years)								
≤1	40	0.2	131	1.8	10	0.1	12	0.4
2-4	39	0.2	31	0.4	4	0.0	6	0.2
5-9	28	0.1	9	0.1	3	0.0	3	0.1
10-15	3	0.0	2	0.0	.	.	2	0.1
15+	1	0.0	.	.	1	0.0	2	0.1
Not applicable[a]	20,926	99.5	7,074	97.6	8,488	99.8	2,916	99.1
Time since first prescription for topical corticosteroids (years)								
≤1	7,332	34.9	2,019	27.9	3,077	36.2	863	29.3
2-4	5,088	24.2	1,872	25.8	1,847	21.7	670	22.8
5-9	5,257	25.0	2,019	27.9	2,132	25.1	855	29.1
10-15	1,806	8.6	775	10.7	683	8.0	284	9.7
15+	426	2.0	146	2.0	154	1.8	79	2.7
Not applicable[b]	1,128	5.4	416	5.7	613	7.2	190	6.5
Medical history								
Diseases interacting with the immune system	364	1.7	254	3.5	130	1.5	64	2.2
Psoriasis	77	0.4	73	1.0	17	0.2	8	0.3
Epstein-Barr virus infection	87	0.4	44	0.6	36	0.4	17	0.6
Rheumatoid arthritis	65	0.3	34	0.5	22	0.3	13	0.4
Systemic lupus erythematosus	16	0.1	20	0.3	4	0.0	3	0.1
Sjögren's syndrome	6	0.0	2	0.0	2	0.0	0	0.0
Celiac sprue	8	0.0	8	0.1	4	0.0	2	0.1
Asthma	107	0.5	76	1.0	41	0.5	20	0.7
Allergic rhinitis	3	0.0	2	0.0	2	0.0	2	0.1
Disease of the immune system	10	0.0	6	0.1	5	0.1	0	0.0
Skin diseases (excluding atopic dermatitis, eczema and psoriasis)	304	1.4	192	2.6	110	1.3	50	1.7
Inflammatory skin disease	84	0.4	70	1.0	21	0.2	8	0.3
Sun burn	0	0.0	0	0.0	0	0.0	0	0.0

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	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=21,037)		Subjects Excluded During the Trimming and Matching Process (N=7,247)		Final Cohort After Trimming and Matching (N=8,506)		Subjects Excluded During the Trimming and Matching Process (N=2,941)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Other skin diseases	228	1.1	131	1.8	90	1.1	42	1.4
Chronic diseases	3,324	15.8	1,655	22.8	1,358	16.0	624	21.2
Malignancy excluding skin cancer and lymphoma	518	2.5	258	3.6	253	3.0	107	3.6
Renal failure	105	0.5	61	0.8	36	0.4	7	0.2
Chronic liver diseases and hepatic failure	88	0.4	51	0.7	36	0.4	11	0.4
Ischemic heart disease	643	3.1	253	3.5	245	2.9	96	3.3
Hypertensive disease	387	1.8	178	2.5	163	1.9	60	2.0
Heart failure	135	0.6	65	0.9	36	0.4	16	0.5
Other cardiovascular diseases	664	3.2	286	3.9	252	3.0	95	3.2
Cerebrovascular diseases	235	1.1	130	1.8	114	1.3	47	1.6
Diabetes mellitus	326	1.5	144	2.0	117	1.4	49	1.7
COPD, emphysema, respiratory insufficiency	182	0.9	99	1.4	85	1.0	26	0.9
Musculoskeletal system and connective disease (excluding rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome)	1,577	7.5	911	12.6	650	7.6	323	11.0
Organ transplantation	29	0.1	19	0.3	7	0.1	4	0.1
HIV infection or AIDs	3	0.0	1	0.0	1	0.0	2	0.1
Use of medications								
Topical corticosteroids plain								
Any potency								
0	6,007	28.6	1,862	25.7	3,029	35.6	978	33.3
1	5,568	26.5	1,422	19.6	2,511	29.5	711	24.2
2-3	5,574	26.5	2,045	28.2	1,955	23.0	784	26.7
4+	3,888	18.5	1,918	26.5	1,011	11.9	468	15.9
Weak potency								
0	17,508	83.2	5,986	82.6	6,654	78.2	2,254	76.6
1	2,796	13.3	955	13.2	1,512	17.8	542	18.4
2-3	647	3.1	255	3.5	310	3.6	125	4.3
4+	86	0.4	51	0.7	30	0.4	20	0.7

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	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=21,037)		Subjects Excluded During the Trimming and Matching Process (N=7,247)		Final Cohort After Trimming and Matching (N=8,506)		Subjects Excluded During the Trimming and Matching Process (N=2,941)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Moderately potent								
0	14,307	68.0	4,596	63.4	5,948	69.9	1,934	65.8
1	4,090	19.4	1,442	19.9	1,628	19.1	609	20.7
2-3	1,962	9.3	880	12.1	727	8.5	312	10.6
4+	678	3.2	329	4.5	203	2.4	86	2.9
Potent								
0	12,504	59.4	3,782	52.2	5,919	69.6	1,921	65.3
1	4,467	21.2	1,546	21.3	1,533	18.0	531	18.1
2-3	2,751	13.1	1,222	16.9	759	8.9	340	11.6
4+	1,315	6.3	697	9.6	295	3.5	149	5.1
Very potent								
0	16,972	80.7	5,666	78.2	7,657	90.0	2,613	88.8
1	2,357	11.2	836	11.5	553	6.5	194	6.6
2-3	1,241	5.9	521	7.2	219	2.6	94	3.2
4+	467	2.2	224	3.1	77	0.9	40	1.4
Topical corticosteroids combined								
Any potency								
0	17,513	83.2	6,008	82.9	7,138	83.9	2,436	82.8
1	2,369	11.3	797	11.0	947	11.1	346	11.8
2-3	949	4.5	351	4.8	357	4.2	127	4.3
4+	206	1.0	91	1.3	64	0.8	32	1.1
Weak potency								
0	18,247	86.7	6,308	87.0	7,341	86.3	2,507	85.2
1	1,980	9.4	652	9.0	834	9.8	304	10.3
2-3	684	3.3	228	3.1	285	3.4	107	3.6
4+	126	0.6	59	0.8	46	0.5	23	0.8
Moderately potent								
0	20,765	98.7	7,131	98.4	8,382	98.5	2,895	98.4
1	194	0.9	85	1.2	94	1.1	37	1.3
2-3	60	0.3	24	0.3	27	0.3	7	0.2
4+	18	0.1	7	0.1	3	0.0	2	0.1

Annex 4 Table 14. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, NL-PHARMO, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=21,037)		Subjects Excluded During the Trimming and Matching Process (N=7,247)		Final Cohort After Trimming and Matching (N=8,506)		Subjects Excluded During the Trimming and Matching Process (N=2,941)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Potent								
0	20,431	97.1	6,994	96.5	8,379	98.5	2,899	98.6
1	411	2.0	160	2.2	94	1.1	29	1.0
2-3	159	0.8	78	1.1	25	0.3	9	0.3
4+	36	0.2	15	0.2	8	0.1	4	0.1
Very potent								
0	21,009	99.9	7,237	99.9	8,502	100.0	2,938	99.9
1	18	0.1	6	0.1	1	0.0	3	0.1
2-3	8	0.0	4	0.1	3	0.0	0	0.0
4+	2	0.0	0	0.0	0	0.0	0	0.0
Immunosuppressants, immunostimulants, and cytostatics	3,060	14.5	1,590	21.9	1,081	12.7	419	14.2
Systemic corticosteroids	2,453	11.7	1,310	18.1	842	9.9	311	10.6
Systemic tacrolimus	13	0.1	15	0.2	2	0.0	0	0.0
Azathioprine	93	0.4	61	0.8	33	0.4	22	0.7
Methotrexate	195	0.9	92	1.3	64	0.8	33	1.1
Cyclosporin	50	0.2	119	1.6	16	0.2	17	0.6
Other antineoplastic agents except methotrexate	124	0.6	41	0.6	78	0.9	24	0.8
Other immunosuppressants except systemic tacrolimus	171	0.8	140	1.9	37	0.4	17	0.6
Systemic antivirals	286	1.4	123	1.7	108	1.3	54	1.8
Immunostimulants	16	0.1	8	0.1	3	0.0	0	0.0
Antipsoriatics topical	1,245	5.9	812	11.2	358	4.2	186	6.3
Tars	213	1.0	428	5.9	67	0.8	51	1.7
Antracen derivatives	11	0.1	12	0.2	3	0.0	6	0.2
Psoralens topical	0	0.0	0	0.0	0	0.0	0	0.0
Other antipsoriatics topical	1,046	5.0	422	5.8	298	3.5	136	4.6
Antipsoriatics systemic	132	0.6	95	1.3	34	0.4	10	0.3
Psoralens systemic	9	0.0	4	0.1	2	0.0	2	0.1
Retinoids	104	0.5	85	1.2	26	0.3	5	0.2
Other antipsoriatics systemic	20	0.1	7	0.1	6	0.1	3	0.1

Annex 4 Table 14. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, NL-PHARMO, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=21,037)		Subjects Excluded During the Trimming and Matching Process (N=7,247)		Final Cohort After Trimming and Matching (N=8,506)		Subjects Excluded During the Trimming and Matching Process (N=2,941)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Other dermatological agents	21,037	100.0	7,247	100.0	8,506	100.0	2,941	100.0
Topical salicylic acid preparations	26	0.1	19	0.3	3	0.0	2	0.1
Other dermatological agents	21,037	100.0	7,247	100.0	8,506	100.0	2,941	100.0
Other medications	11,406	54.2	3,834	52.9	4,499	52.9	1,493	50.8
Cardiovascular system drugs	5,823	27.7	1,603	22.1	2,249	26.4	621	21.1
Anti-inflammatory and anti-rheumatic agents, nonsteroidal	4,951	23.5	1,837	25.3	1,933	22.7	772	26.2
Other antirheumatic agents	3	0.0	1	0.0	0	0.0	0	0.0
Hormone-replacement therapy	608	2.9	231	3.2	204	2.4	83	2.8
Lipid-modifying agents	2,785	13.2	716	9.9	1,005	11.8	267	9.1
Insulins	421	2.0	136	1.9	142	1.7	41	1.4
Oral antidiabetics	973	4.6	253	3.5	339	4.0	74	2.5
Antiepileptics	551	2.6	190	2.6	215	2.5	62	2.1
Drugs for asthma and COPD excluding inhaled corticosteroids	2,771	13.2	1,275	17.6	1,091	12.8	438	14.9
Inhaled corticosteroids	987	4.7	396	5.5	364	4.3	149	5.1
Utilization of health care resources in the year before the start date								
General practitioner visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	
Dermatologist visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	
Paediatrician visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	

Annex 4 Table 14. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, NL-PHARMO, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=21,037)		Subjects Excluded During the Trimming and Matching Process (N=7,247)		Final Cohort After Trimming and Matching (N=8,506)		Subjects Excluded During the Trimming and Matching Process (N=2,941)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Emergency department visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	
Outpatient hospital visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	
Hospitalisations								
0	18,902	89.9	3,785	52.2	7,748	91.1	1,546	52.6
1	1,388	6.6	2,128	29.4	482	5.7	941	32.0
2-3	530	2.5	918	12.7	189	2.2	350	11.9
4+	217	1.0	416	5.7	87	1.0	104	3.5
Prescriptions								
0	0	0.0	0	0.0	0	0.0	0	0.0
1	0	0.0	540	7.5	0	0.0	217	7.4
2-3	2,242	10.7	217	3.0	1,000	11.8	140	4.8
5-9	4,079	19.4	436	6.0	1,928	22.7	343	11.7
10+	14,716	70.0	6,054	83.5	5,578	65.6	2,241	76.2

NA = not available

[a] Not applicable, no record of diagnosis of atopic dermatitis

[b] Not applicable, no record of topical corticosteroid prescription

Categorical Variables, Sweden

Annex 4 Table 15. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Sweden, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=12,096)		Subjects Excluded During the Trimming and Matching Process (N=1,254)		Final Cohort After Trimming and Matching (N=1,677)		Subjects Excluded During the Trimming and Matching Process (N=123)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Demographics								
Age								
0-1	707	5.8	63	5.0	173	10.3	15	12.2
2-4	2,216	18.3	92	7.3	368	21.9	40	32.5
5-9	3,078	25.4	280	22.3	420	25.0	27	22.0
10-14	3,277	27.1	416	33.2	407	24.3	21	17.1
15-17	2,818	23.3	403	32.1	309	18.4	20	16.3
Sex female	6,650	55.0	774	61.7	942	56.2	81	65.9
Calendar year	0	0.0	0	0.0	0	0.0	0	0.0
2006	365	3.0	74	5.9	128	7.6	6	4.9
2007	993	8.2	59	4.7	238	14.2	9	7.3
2008	1,292	10.7	88	7.0	221	13.2	12	9.8
2009	1,531	12.7	122	9.7	194	11.6	6	4.9
2010	1,716	14.2	214	17.1	156	9.3	7	5.7
2011	1,621	13.4	186	14.8	143	8.5	6	4.9
2012	1,577	13.0	156	12.4	178	10.6	3	2.4
2013	1,428	11.8	148	11.8	204	12.2	31	25.2
2014	1,573	13.0	207	16.5	215	12.8	43	35.0
Primary care center/region								
Uppsala	2,237	18.5	183	14.6	245	14.6	16	13.0
Stockholm	3,551	29.4	404	32.2	394	23.5	12	9.8
South-West	1,017	8.4	67	5.3	160	9.5	8	6.5
North	445	3.7	49	3.9	128	7.6	4	3.3
South	2,520	20.8	199	15.9	477	28.4	81	65.9
West	2,326	19.2	352	28.1	273	16.3	2	1.6
Duration of follow-up (years)								
≤1	1,637	13.5%	213	17.0%	223	13.3%	43	35.0%
2-4	4,661	38.5%	491	39.2%	535	31.9%	40	32.5%
5+	5,798	47.9%	550	43.9%	919	54.8%	40	32.5%

Annex 4 Table 15. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Sweden, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=12,096)		Subjects Excluded During the Trimming and Matching Process (N=1,254)		Final Cohort After Trimming and Matching (N=1,677)		Subjects Excluded During the Trimming and Matching Process (N=123)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Duration of medical history up to the start date (years)								
≤1	787	6.5%	79	6.3%	181	10.8%	15	12.2%
2-4	2,378	19.7%	119	9.5%	386	23.0%	40	32.5%
5+	8,931	73.8%	1,056	84.2%	1,110	66.2%	68	55.3%
Type of prescriber of first prescription								
Dermatologist	6,295	52.0	1,119	89.2	610	36.4	104	84.6
Paediatrician	3,026	25.0	81	6.5	471	28.1	9	7.3
General practitioner	2,148	17.8	34	2.7	355	21.2	3	2.4
Other	623	5.2	20	1.6	240	14.3	7	5.7
Unknown	4	0.0	0	0.0	1	0.1	0	0.0
Atopic dermatitis								
Diagnosis at any time before start date								
Any diagnosis	6,268	51.8	558	44.5	729	43.5	62	50.4
General practitioner	NA		NA		NA		NA	
Paediatrician	1,790	14.8	119	9.5	305	18.2	13	10.6
Dermatologist	4,097	33.9	407	32.5	364	21.7	45	36.6
Hospital outpatient visit	6,248	51.7	558	44.5	727	43.4	62	50.4
Primary or secondary hospital discharge diagnosis	204	1.7	21	1.7	30	1.8	0	0.0
Other specialties	385	3.2	32	2.6	60	3.6	4	3.3
Time since first diagnosis of atopic dermatitis (years)								
≤1	3,794	31.4%	255	20.3%	440	26.2%	33	26.8%
2-4	1,161	9.6%	104	8.3%	142	8.5%	9	7.3%
5-9	1,069	8.8%	156	12.4%	125	7.5%	18	14.6%
10-15	234	1.9%	42	3.3%	21	1.3%	2	1.6%
15+	10	0.1%	1	0.1%	1	0.1%	0	0.0%
Not applicable[a]	5,828	48.2%	696	55.5%	948	56.5%	61	49.6%

Annex 4 Table 15. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Sweden, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=12,096)		Subjects Excluded During the Trimming and Matching Process (N=1,254)		Final Cohort After Trimming and Matching (N=1,677)		Subjects Excluded During the Trimming and Matching Process (N=123)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Time since first prescription for topical corticosteroids (years)								
≤1	4,419	36.5%	329	26.2%	646	38.5%	55	44.7%
2-4	3,018	25.0%	264	21.1%	313	18.7%	20	16.3%
5-9	1,461	12.1%	203	16.2%	150	8.9%	17	13.8%
10-15	0	0.0%	0	0.0%	0	0.0%	0	0.0%
15+	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Not applicable[b]	3,198	26.4%	458	36.5%	568	33.9%	31	25.2%
Medical history								
Diseases interacting with the immune system	3,072	25.4	458	36.5	431	25.7	48	39.0
Psoriasis	423	3.5	40	3.2	24	1.4	2	1.6
Epstein-Barr virus infection	27	0.2	8	0.6	4	0.2	2	1.6
Rheumatoid arthritis	3	0.0	1	0.1	0	0.0	0	0.0
Systemic lupus erythematosus	9	0.1	9	0.7	1	0.1	1	0.8
Sjögren’s syndrome	1	0.0	1	0.1	0	0.0	0	0.0
Celiac sprue	130	1.1	24	1.9	21	1.3	3	2.4
Asthma	2,158	17.8	315	25.1	325	19.4	34	27.6
Allergic rhinitis	1,127	9.3	281	22.4	158	9.4	24	19.5
Disease of the immune system	62	0.5	15	1.2	11	0.7	3	2.4
Skin diseases (excluding atopic dermatitis, eczema and psoriasis)	1,930	16.0	743	59.3	265	15.8	45	36.6
Inflammatory skin disease	1,799	14.9	199	15.9	245	14.6	29	23.6
Sun burn	0	0.0	0	0.0	0	0.0	0	0.0
Other skin diseases	152	1.3	620	49.4	25	1.5	18	14.6
Chronic diseases	829	6.9	111	8.9	93	5.5	9	7.3
Malignancy excluding skin cancer and lymphoma	5	0.0	0	0.0	0	0.0	0	0.0
Renal failure	9	0.1	2	0.2	1	0.1	1	0.8
Chronic liver diseases and hepatic failure	15	0.1	1	0.1	0	0.0	2	1.6
Ischemic heart disease	3	0.0	0	0.0	0	0.0	0	0.0
Hypertensive disease	12	0.1	1	0.1	1	0.1	0	0.0
Heart failure	8	0.1	0	0.0	2	0.1	0	0.0
Other cardiovascular diseases	108	0.9	22	1.8	16	1.0	0	0.0

Annex 4 Table 15. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Sweden, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=12,096)		Subjects Excluded During the Trimming and Matching Process (N=1,254)		Final Cohort After Trimming and Matching (N=1,677)		Subjects Excluded During the Trimming and Matching Process (N=123)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Cerebrovascular diseases	10	0.1	3	0.2	0	0.0	1	0.8
Diabetes mellitus	73	0.6	10	0.8	7	0.4	1	0.8
COPD, emphysema, respiratory insufficiency	37	0.3	6	0.5	3	0.2	0	0.0
Musculoskeletal system and connective disease (excluding rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome)	596	4.9	69	5.5	68	4.1	5	4.1
Organ transplantation	21	0.2	10	0.8	2	0.1	0	0.0
HIV infection or AIDs	1	0.0	0	0.0	0	0.0	0	0.0
Use of medications								
Topical corticosteroids plain								
Any potency								
0	5,507	45.5	702	56.0	854	50.9	63	51.2
1	2,669	22.1	244	19.5	357	21.3	26	21.1
2-3	2,429	20.1	188	15.0	310	18.5	23	18.7
4+	1,491	12.3	120	9.6	156	9.3	11	8.9
Weak potency								
0	9,247	76.4	1,035	82.5	1,326	79.1	99	80.5
1	1,813	15.0	137	10.9	231	13.8	16	13.0
2-3	733	6.1	62	4.9	81	4.8	6	4.9
4+	303	2.5	20	1.6	39	2.3	2	1.6
Moderately potent								
0	8,590	71.0	992	79.1	1,233	73.5	86	69.9
1	2,161	17.9	162	12.9	283	16.9	24	19.5
2-3	1,005	8.3	76	6.1	122	7.3	9	7.3
4+	340	2.8	24	1.9	39	2.3	4	3.3
Potent								
0	8,641	71.4	954	76.1	1,283	76.5	96	78.0
1	2,106	17.4	187	14.9	264	15.7	15	12.2
2-3	1,022	8.4	82	6.5	101	6.0	10	8.1
4+	327	2.7	31	2.5	29	1.7	2	1.6

Annex 4 Table 15. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Sweden, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=12,096)		Subjects Excluded During the Trimming and Matching Process (N=1,254)		Final Cohort After Trimming and Matching (N=1,677)		Subjects Excluded During the Trimming and Matching Process (N=123)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Very potent								
0	11,841	97.9	1,213	96.7	1,660	99.0	122	99.2
1	201	1.7	29	2.3	14	0.8	0	0.0
2-3	41	0.3	9	0.7	3	0.2	1	0.8
4+	13	0.1	3	0.2	0	0.0	0	0.0
Topical corticosteroids combined								
Any potency								
0	10,883	90.0	1,154	92.0	1,521	90.7	101	82.1
1	937	7.7	72	5.7	131	7.8	18	14.6
2-3	215	1.8	22	1.8	18	1.1	4	3.3
4+	61	0.5	6	0.5	7	0.4	0	0.0
Weak potency								
0	11,601	95.9	1,225	97.7	1,595	95.1	110	89.4
1	429	3.5	23	1.8	78	4.7	12	9.8
2-3	57	0.5	5	0.4	4	0.2	1	0.8
4+	9	0.1	1	0.1	0	0.0	0	0.0
Moderately potent								
0	12,012	99.3	1,250	99.7	1,657	98.8	123	100.0
1	64	0.5	2	0.2	18	1.1	0	0.0
2-3	16	0.1	2	0.2	2	0.1	0	0.0
4+	4	0.0	0	0.0	0	0.0	0	0.0
Potent								
0	11,382	94.1	1,182	94.3	1,612	96.1	112	91.1
1	528	4.4	52	4.1	48	2.9	9	7.3
2-3	142	1.2	15	1.2	11	0.7	2	1.6
4+	44	0.4	5	0.4	6	0.4	0	0.0
Very potent								
0	12,096	100.0	1,254	100.0	1,677	100.0	123	100.0
1	0	0.0	0	0.0	0	0.0	0	0.0
2-3	0	0.0	0	0.0	0	0.0	0	0.0
4+	0	0.0	0	0.0	0	0.0	0	0.0

Annex 4 Table 15. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Sweden, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=12,096)		Subjects Excluded During the Trimming and Matching Process (N=1,254)		Final Cohort After Trimming and Matching (N=1,677)		Subjects Excluded During the Trimming and Matching Process (N=123)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Immunosuppressants, immunostimulants, and cytostatics	1,052	8.7	150	12.0	134	8.0	10	8.1
Systemic corticosteroids	944	7.8	133	10.6	126	7.5	8	6.5
Systemic tacrolimus	2	0.0	2	0.2	1	0.1	0	0.0
Azathioprine	26	0.2	9	0.7	1	0.1	2	1.6
Methotrexate	31	0.3	5	0.4	2	0.1	1	0.8
Cyclosporin	13	0.1	6	0.5	0	0.0	2	1.6
Other antineoplastic agents except methotrexate	9	0.1	1	0.1	0	0.0	1	0.8
Other immunosuppressants except systemic tacrolimus	22	0.2	10	0.8	3	0.2	0	0.0
Systemic antivirals	101	0.8	14	1.1	6	0.4	0	0.0
Immunostimulants	1	0.0	0	0.0	0	0.0	0	0.0
Antipsoriatics topical	135	1.1	22	1.8	11	0.7	1	0.8
Tars	13	0.1	4	0.3	1	0.1	1	0.8
Antracen derivatives	0	0.0	0	0.0	0	0.0	0	0.0
Psoralens topical	0	0.0	0	0.0	0	0.0	0	0.0
Other antipsoriatics topical	123	1.0	19	1.5	10	0.6	0	0.0
Antipsoriatics systemic	1	0.0	6	0.5	0	0.0	0	0.0
Psoralens systemic	0	0.0	1	0.1	0	0.0	0	0.0
Retinoids	1	0.0	5	0.4	0	0.0	0	0.0
Other antipsoriatics systemic	0	0.0	0	0.0	0	0.0	0	0.0
Other dermatological agents	6,484	53.6	587	46.8	889	53.0	69	56.1
Topical salicylic acid preparations	167	1.4	21	1.7	17	1.0	1	0.8
Other dermatological agents	6,484	53.6	587	46.8	889	53.0	69	56.1
Other medications	2,891	23.9	393	31.3	400	23.9	35	28.5
Cardiovascular system drugs	438	3.6	65	5.2	63	3.8	4	3.3
Anti-inflammatory and anti-rheumatic agents, nonsteroidal	362	3.0	53	4.2	40	2.4	0	0.0
Other antirheumatic agents	0	0.0	0	0.0	0	0.0	0	0.0
Hormone-replacement therapy	4	0.0	0	0.0	1	0.1	0	0.0
Lipid-modifying agents	0	0.0	0	0.0	0	0.0	1	0.8
Insulins	61	0.5	10	0.8	4	0.2	2	1.6
Oral antidiabetics	3	0.0	2	0.2	0	0.0	0	0.0

Annex 4 Table 15. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Sweden, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=12,096)		Subjects Excluded During the Trimming and Matching Process (N=1,254)		Final Cohort After Trimming and Matching (N=1,677)		Subjects Excluded During the Trimming and Matching Process (N=123)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Antiepileptics	60	0.5	5	0.4	7	0.4	2	1.6
Drugs for asthma and COPD excluding inhaled corticosteroids	2,183	18.0	317	25.3	331	19.7	29	23.6
Inhaled corticosteroids	1,155	9.5	152	12.1	172	10.3	14	11.4
Utilization of health care resources in the year before the start date								
General practitioner visits								
0	4,182	34.6	525	41.9	625	37.3	41	33.3
1	3,082	25.5	327	26.1	467	27.8	38	30.9
2-3	3,313	27.4	289	23.0	422	25.2	30	24.4
4+	1,519	12.6	113	9.0	163	9.7	14	11.4
Dermatologist visits								
0	8,836	73.0	519	41.4	1,329	79.2	70	56.9
1	1,987	16.4	519	41.4	230	13.7	30	24.4
2-3	980	8.1	171	13.6	93	5.5	18	14.6
4+	293	2.4	45	3.6	25	1.5	5	4.1
Paediatrician visits								
0	7,898	65.3	808	64.4	1,070	63.8	70	56.9
1	1,883	15.6	175	14.0	229	13.7	19	15.4
2-3	1,455	12.0	166	13.2	222	13.2	14	11.4
4+	860	7.1	105	8.4	156	9.3	20	16.3
Emergency department visits								
0	NA		NA		NA		NA	
1	NA		NA		NA		NA	
2-3	NA		NA		NA		NA	
4+	NA		NA		NA		NA	
Outpatient hospital visits								
0	3,392	28.0	148	11.8	591	35.2	24	19.5
1	3,233	26.7	405	32.3	370	22.1	26	21.1
2-3	3,077	25.4	385	30.7	396	23.6	36	29.3
4+	2,394	19.8	316	25.2	320	19.1	37	30.1

Annex 4 Table 15. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Sweden, Children

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=12,096)		Subjects Excluded During the Trimming and Matching Process (N=1,254)		Final Cohort After Trimming and Matching (N=1,677)		Subjects Excluded During the Trimming and Matching Process (N=123)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Hospitalisations								
0	11,459	94.7	1,189	94.8	1,578	94.1	113	91.9
1	497	4.1	48	3.8	78	4.7	9	7.3
2-3	113	0.9	12	1.0	14	0.8	0	0.0
4+	27	0.2	5	0.4	7	0.4	1	0.8
Prescriptions								
0	1,412	11.7	210	16.7	206	12.3	13	10.6
1	1,155	9.5	139	11.1	194	11.6	14	11.4
2-3	3,236	26.8	296	23.6	459	27.4	32	26.0
5-9	3,198	26.4	291	23.2	430	25.6	26	21.1
10+	3,095	25.6	318	25.4	388	23.1	38	30.9

NA = not available

[a] Not applicable, no record of diagnosis of atopic dermatitis

[b] Not applicable, no record of topical corticosteroid prescription

Annex 4 Table 16. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Sweden, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=52,456)		Subjects Excluded During the Trimming and Matching Process (N=5,663)		Final Cohort After Trimming and Matching (N=5,169)		Subjects Excluded During the Trimming and Matching Process (N=507)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Demographics								
Age								
18-24	6,226	11.9	1,429	25.2	620	12.0	102	20.1
25-34	8,428	16.1	1,398	24.7	863	16.7	111	21.9
35-44	9,148	17.4	1,351	23.9	954	18.5	195	38.5
45-54	9,395	17.9	706	12.5	963	18.6	38	7.5
55-64	9,432	18.0	375	6.6	881	17.0	12	2.4
65-74	6,556	12.5	185	3.3	579	11.2	18	3.6
75-84	2,633	5.0	140	2.5	279	5.4	11	2.2
85+	638	1.2	79	1.4	30	0.6	20	3.9
Sex female	32,181	61.3	4,409	77.9	3,148	60.9	379	74.8
Calendar year								
2006	1,433	2.7	270	4.8	342	6.6	26	5.1
2007	4,124	7.9	206	3.6	635	12.3	9	1.8
2008	5,167	9.9	85	1.5	575	11.1	10	2.0
2009	6,466	12.3	254	4.5	591	11.4	17	3.4
2010	7,089	13.5	533	9.4	599	11.6	16	3.2
2011	6,968	13.3	913	16.1	500	9.7	8	1.6
2012	7,042	13.4	594	10.5	617	11.9	43	8.5
2013	7,100	13.5	827	14.6	680	13.2	166	32.7
2014	7,067	13.5	1,981	35.0	630	12.2	212	41.8
Primary care center/region								
Uppsala	10,209	19.5	856	15.1	752	14.5	8	1.6
Stockholm	14,931	28.5	2,779	49.1	1,569	30.4	285	56.2
South-West	4,994	9.5	316	5.6	334	6.5	13	2.6
North	1,806	3.4	125	2.2	308	6.0	15	3.0
South	10,970	20.9	715	12.6	1,324	25.6	166	32.7
West	9,546	18.2	872	15.4	882	17.1	20	3.9
Duration of follow-up (years)								
≤1	8,441	16.1%	2,098	37.0%	745	14.4%	228	45.0%
2-4	21,388	40.8%	2,363	41.7%	1,860	36.0%	221	43.6%
5+	22,627	43.1%	1,202	21.2%	2,564	49.6%	58	11.4%

Annex 4 Table 16. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Sweden, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=52,456)		Subjects Excluded During the Trimming and Matching Process (N=5,663)		Final Cohort After Trimming and Matching (N=5,169)		Subjects Excluded During the Trimming and Matching Process (N=507)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Duration of medical history up to the start date (years)								
≤1	325	0.6%	42	0.7%	44	0.9%	4	0.8%
2-4	889	1.7%	147	2.6%	112	2.2%	11	2.2%
5+	51,242	97.7%	5,474	96.7%	5,013	97.0%	492	97.0%
Type of prescriber of first prescription								
Dermatologist	37,511	71.5	5,087	89.8	3,487	67.5	450	88.8
Paediatrician	304	0.6	11	0.2	52	1.0	1	0.2
General practitioner	9,695	18.5	342	6.0	1,096	21.2	45	8.9
Other	4,924	9.4	223	3.9	528	10.2	11	2.2
Unknown	22	0.0	0	0.0	6	0.1	0	0.0
Atopic dermatitis								
Diagnosis at any time before start date								
Any diagnosis	16,937	32.3	2,526	44.6	1,103	21.3	184	36.3
General practitioner	NA		NA		NA		NA	
Paediatrician	204	0.4	60	1.1	26	0.5	5	1.0
Dermatologist	15,042	28.7	2,288	40.4	975	18.9	171	33.7
Hospital outpatient visit	16,776	32.0	2,507	44.3	1,088	21.0	183	36.1
Primary or secondary hospital discharge diagnosis	813	1.5	129	2.3	66	1.3	6	1.2
Other specialties	1,702	3.2	178	3.1	105	2.0	8	1.6
Time since first diagnosis of atopic dermatitis (years)								
≤1	10,080	19.2%	1,484	26.2%	625	12.1%	115	22.7%
2-4	2,688	5.1%	337	6.0%	170	3.3%	19	3.7%
5-9	3,064	5.8%	421	7.4%	216	4.2%	32	6.3%
10-15	766	1.5%	213	3.8%	56	1.1%	12	2.4%
15+	339	0.6%	71	1.3%	36	0.7%	6	1.2%
Not applicable[a]	35,519	67.7%	3,137	55.4%	4,066	78.7%	323	63.7%

Annex 4 Table 16. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Sweden, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=52,456)		Subjects Excluded During the Trimming and Matching Process (N=5,663)		Final Cohort After Trimming and Matching (N=5,169)		Subjects Excluded During the Trimming and Matching Process (N=507)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Time since first prescription for topical corticosteroids (years)								
≤1	14,770	28.2%	1,344	23.7%	1,562	30.2%	122	24.1%
2-4	13,262	25.3%	1,210	21.4%	1,130	21.9%	97	19.1%
5-9	9,542	18.2%	1,541	27.2%	740	14.3%	130	25.6%
10-15	0	0.0%	0	0.0%	0	0.0%	0	0.0%
15+	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Not applicable[b]	14,882	28.4%	1,568	27.7%	1,737	33.6%	158	31.2%
Medical history								
Diseases interacting with the immune system	10,153	19.4	2,513	44.4	843	16.3	144	28.4
Psoriasis	4,791	9.1	452	8.0	304	5.9	26	5.1
Epstein-Barr virus infection	135	0.3	37	0.7	14	0.3	5	1.0
Rheumatoid arthritis	563	1.1	79	1.4	44	0.9	3	0.6
Systemic lupus erythematosus	387	0.7	324	5.7	32	0.6	3	0.6
Sjögren’s syndrome	266	0.5	81	1.4	25	0.5	4	0.8
Celiac sprue	329	0.6	97	1.7	29	0.6	5	1.0
Asthma	2,892	5.5	1,056	18.6	297	5.7	61	12.0
Allergic rhinitis	2,174	4.1	1,380	24.4	257	5.0	86	17.0
Disease of the immune system	336	0.6	72	1.3	26	0.5	1	0.2
Skin diseases (excluding atopic dermatitis, eczema and psoriasis)	14,495	27.6	2,690	47.5	1,256	24.3	168	33.1
Inflammatory skin disease	11,209	21.4	1,318	23.3	985	19.1	129	25.4
Sun burn	0	0.0	0	0.0	0	0.0	0	0.0
Other skin diseases	4,890	9.3	1,790	31.6	443	8.6	70	13.8
Chronic diseases	17,672	33.7	1,647	29.1	1,647	31.9	121	23.9
Malignancy excluding skin cancer and lymphoma	2,182	4.2	114	2.0	186	3.6	14	2.8
Renal failure	391	0.7	34	0.6	37	0.7	6	1.2
Chronic liver diseases and hepatic failure	441	0.8	25	0.4	38	0.7	2	0.4
Ischemic heart disease	2,185	4.2	163	2.9	197	3.8	13	2.6
Hypertensive disease	5,113	9.7	319	5.6	476	9.2	28	5.5
Heart failure	726	1.4	63	1.1	61	1.2	11	2.2
Other cardiovascular diseases	3,953	7.5	356	6.3	378	7.3	37	7.3

Annex 4 Table 16. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Sweden, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=52,456)		Subjects Excluded During the Trimming and Matching Process (N=5,663)		Final Cohort After Trimming and Matching (N=5,169)		Subjects Excluded During the Trimming and Matching Process (N=507)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Cerebrovascular diseases	1,213	2.3	96	1.7	100	1.9	12	2.4
Diabetes mellitus	2,082	4.0	130	2.3	159	3.1	18	3.6
COPD, emphysema, respiratory insufficiency	1,083	2.1	98	1.7	75	1.5	7	1.4
Musculoskeletal system and connective disease (excluding rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome)	9,946	19.0	1,102	19.5	932	18.0	76	15.0
Organ transplantation	257	0.5	51	0.9	18	0.3	1	0.2
HIV infection or AIDs	36	0.1	0	0.0	1	0.0	0	0.0
Use of medications								
Topical corticosteroids plain								
Any potency								
0	27,271	52.0	2,903	51.3	2,870	55.5	296	58.4
1	11,156	21.3	1,219	21.5	1,082	20.9	113	22.3
2-3	8,963	17.1	960	17.0	789	15.3	67	13.2
4+	5,066	9.7	581	10.3	428	8.3	31	6.1
Weak potency								
0	47,610	90.8	4,989	88.1	4,704	91.0	463	91.3
1	3,681	7.0	497	8.8	353	6.8	40	7.9
2-3	916	1.7	143	2.5	90	1.7	3	0.6
4+	249	0.5	34	0.6	22	0.4	1	0.2
Moderately potent								
0	44,156	84.2	4,709	83.2	4,368	84.5	421	83.0
1	5,806	11.1	686	12.1	577	11.2	63	12.4
2-3	2,017	3.8	211	3.7	167	3.2	20	3.9
4+	477	0.9	57	1.0	57	1.1	3	0.6
Potent								
0	36,146	68.9	3,851	68.0	3,671	71.0	376	74.2
1	9,015	17.2	1,027	18.1	879	17.0	88	17.4
2-3	5,037	9.6	528	9.3	437	8.5	28	5.5
4+	2,258	4.3	257	4.5	182	3.5	15	3.0

Annex 4 Table 16. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Sweden, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=52,456)		Subjects Excluded During the Trimming and Matching Process (N=5,663)		Final Cohort After Trimming and Matching (N=5,169)		Subjects Excluded During the Trimming and Matching Process (N=507)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Very potent								
0	46,748	89.1	5,166	91.2	4,833	93.5	492	97.0
1	3,227	6.2	295	5.2	229	4.4	12	2.4
2-3	1,785	3.4	154	2.7	107	2.1	3	0.6
4+	696	1.3	48	0.8	0	0.0	0	0.0
Topical corticosteroids combined								
Any potency								
0	47,215	90.0	5,132	90.6	4,676	90.5	477	94.1
1	3,600	6.9	386	6.8	354	6.8	21	4.1
2-3	1,276	2.4	109	1.9	104	2.0	6	1.2
4+	365	0.7	36	0.6	35	0.7	3	0.6
Weak potency								
0	51,309	97.8	5,545	97.9	5,017	97.1	495	97.6
1	929	1.8	103	1.8	123	2.4	10	2.0
2-3	176	0.3	13	0.2	21	0.4	1	0.2
4+	42	0.1	2	0.0	8	0.2	1	0.2
Moderately potent								
0	52,089	99.3	5,637	99.5	5,121	99.1	507	100.0
1	260	0.5	18	0.3	33	0.6	0	0.0
2-3	85	0.2	5	0.1	13	0.3	0	0.0
4+	22	0.0	3	0.1	2	0.0	0	0.0
Potent								
0	48,542	92.5	5,263	92.9	4,858	94.0	488	96.3
1	2,623	5.0	280	4.9	217	4.2	12	2.4
2-3	998	1.9	90	1.6	69	1.3	5	1.0
4+	293	0.6	30	0.5	25	0.5	2	0.4
Very potent								
0	52,456	100.0	5,663	100.0	5,169	100.0	507	100.0
1	0	0.0	0	0.0	0	0.0	0	0.0
2-3	0	0.0	0	0.0	0	0.0	0	0.0
4+	0	0.0	0	0.0	0	0.0	0	0.0

Annex 4 Table 16. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Sweden, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=52,456)		Subjects Excluded During the Trimming and Matching Process (N=5,663)		Final Cohort After Trimming and Matching (N=5,169)		Subjects Excluded During the Trimming and Matching Process (N=507)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Immunosuppressants, immunostimulants, and cytostatics	9,451	18.0	1,406	24.8	872	16.9	74	14.6
Systemic corticosteroids	7,059	13.5	1,018	18.0	618	12.0	50	9.9
Systemic tacrolimus	52	0.1	3	0.1	4	0.1	0	0.0
Azathioprine	235	0.4	62	1.1	23	0.4	3	0.6
Methotrexate	833	1.6	185	3.3	57	1.1	0	0.0
Cyclosporin	182	0.3	99	1.7	17	0.3	0	0.0
Other antineoplastic agents except methotrexate	97	0.2	4	0.1	15	0.3	4	0.8
Other immunosuppressants except systemic tacrolimus	442	0.8	56	1.0	30	0.6	2	0.4
Systemic antivirals	1,934	3.7	312	5.5	226	4.4	25	4.9
Immunostimulants	106	0.2	2	0.0	13	0.3	0	0.0
Antipsoriatics topical	2,341	4.5	172	3.0	226	4.4	10	2.0
Tars	111	0.2	25	0.4	14	0.3	3	0.6
Antracen derivatives	4	0.0	0	0.0	2	0.0	0	0.0
Psoralens topical	0	0.0	0	0.0	0	0.0	0	0.0
Other antipsoriatics topical	2,238	4.3	148	2.6	212	4.1	8	1.6
Antipsoriatics systemic	199	0.4	120	2.1	16	0.3	1	0.2
Psoralens systemic	31	0.1	30	0.5	0	0.0	0	0.0
Retinoids	169	0.3	93	1.6	16	0.3	1	0.2
Other antipsoriatics systemic	0	0.0	0	0.0	0	0.0	0	0.0
Other dermatological agents	24,987	47.6	2,805	49.5	2,573	49.8	258	50.9
Topical salicylic acid preparations	893	1.7	81	1.4	68	1.3	5	1.0
Other dermatological agents	24,987	47.6	2,805	49.5	2,573	49.8	258	50.9
Other medications	26,147	49.8	2,712	47.9	2,529	48.9	196	38.7
Cardiovascular system drugs	13,049	24.9	920	16.2	1,243	24.0	82	16.2
Anti-inflammatory and anti-rheumatic agents, nonsteroidal	10,572	20.2	1,086	19.2	1,050	20.3	73	14.4
Other antirheumatic agents	5	0.0	0	0.0	2	0.0	0	0.0
Hormone-replacement therapy	5,312	10.1	445	7.9	512	9.9	25	4.9
Lipid-modifying agents	5,243	10.0	227	4.0	501	9.7	29	5.7
Insulins	1,084	2.1	68	1.2	55	1.1	11	2.2
Oral antidiabetics	1,585	3.0	86	1.5	135	2.6	15	3.0

Annex 4 Table 16. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Sweden, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=52,456)		Subjects Excluded During the Trimming and Matching Process (N=5,663)		Final Cohort After Trimming and Matching (N=5,169)		Subjects Excluded During the Trimming and Matching Process (N=507)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Antiepileptics	1,578	3.0	169	3.0	121	2.3	15	3.0
Drugs for asthma and COPD excluding inhaled corticosteroids	5,869	11.2	1,140	20.1	589	11.4	64	12.6
Inhaled corticosteroids	2,404	4.6	463	8.2	248	4.8	32	6.3
Utilization of health care resources in the year before the start date								
General practitioner visits								
0	13,973	26.6	1,518	26.8	1,538	29.8	131	25.8
1	10,508	20.0	1,193	21.1	1,048	20.3	105	20.7
2-3	14,084	26.8	1,518	26.8	1,373	26.6	151	29.8
4+	13,891	26.5	1,434	25.3	1,210	23.4	120	23.7
Dermatologist visits								
0	34,815	66.4	2,720	48.0	3,871	74.9	278	54.8
1	9,618	18.3	1,691	29.9	757	14.6	152	30.0
2-3	5,623	10.7	853	15.1	395	7.6	65	12.8
4+	2,400	4.6	399	7.0	146	2.8	12	2.4
Paediatrician visits								
0	52,251	99.6	5,599	98.9	5,144	99.5	502	99.0
1	101	0.2	32	0.6	13	0.3	2	0.4
2-3	59	0.1	26	0.5	7	0.1	0	0.0
4+	45	0.1	6	0.1	5	0.1	3	0.6
Emergency department visits								
0		NA		NA		NA		NA
1		NA		NA		NA		NA
2-3		NA		NA		NA		NA
4+		NA		NA		NA		NA
Outpatient hospital visits								
0	13,758	26.2	681	12.0	1,902	36.8	101	19.9
1	12,346	23.5	1,372	24.2	1,083	21.0	128	25.2
2-3	12,826	24.5	1,608	28.4	1,093	21.1	139	27.4
4+	13,526	25.8	2,002	35.4	1,091	21.1	139	27.4

Annex 4 Table 16. Comparison of Users Included in the Final Cohort at the Start Date After Trimming and Frequency Matching, and Patients Excluded in the Trimming Process; Categorical Variables, Sweden, Adults

	Topical Tacrolimus				Topical Pimecrolimus			
	Final Cohort After Trimming and Matching (N=52,456)		Subjects Excluded During the Trimming and Matching Process (N=5,663)		Final Cohort After Trimming and Matching (N=5,169)		Subjects Excluded During the Trimming and Matching Process (N=507)	
Type of Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Hospitalisations								
0	47,199	90.0	5,070	89.5	4,695	90.8	434	85.6
1	3,682	7.0	419	7.4	360	7.0	55	10.8
2-3	1,200	2.3	126	2.2	94	1.8	14	2.8
4+	375	0.7	48	0.8	20	0.4	4	0.8
Prescriptions								
0	3,806	7.3	330	5.8	339	6.6	29	5.7
1	2,960	5.6	282	5.0	309	6.0	28	5.5
2-3	9,054	17.3	964	17.0	942	18.2	91	17.9
5-9	11,033	21.0	1,293	22.8	1,104	21.4	144	28.4
10+	25,603	48.8	2,794	49.3	2,475	47.9	215	42.4

NA = not available

[a] Not applicable, no record of diagnosis of atopic dermatitis

[b] Not applicable, no record of topical corticosteroid prescription

Annex 5. Validation Results

List of Tables

Annex 5 Table 1. Positive Predictive Values of All Diagnosis Codes and Subsets of Codes for Adjudicated Cases of Study Outcomes, UK-CPRD, Adults

Codes or Subset of Codes	Number of Potential Cases Identified by Algorithm and Reviewed	Number Confirmed[a]	Positive Predictive Value (95% CI)
Malignant melanoma, including in situ carcinomas			
All read codes	118	97	82.2 (74.1 - 88.6)
Diagnosis codes	55	50	90.9 (80.0 - 97.0)
Morphology codes	63	47	74.6 (62.1 - 84.7)
ICD-10 codes	42	40	95.2 (83.8 - 99.4)
Non-melanoma skin cancer (NMSC) including in situ carcinomas			
All read codes	439	397	90.4 (87.3 - 93.0)
Diagnosis codes	409	370	90.5 (87.2 - 93.1)
Morphology codes	30	27	90.0 (73.5 - 97.9)
ICD-10 codes	38	32	84.2 (68.7-94.0)
Cutaneous T-cell lymphomas (CTCL)			
All read codes	31	22	71.0 (52.0-85.8)
Diagnosis codes	[redacted]	[redacted]	72.0 (50.6 - 87.9)
Morphology codes	[redacted]	[redacted]	33.3 (4.3 - 77.7)
ICD-10 codes	[redacted]	[redacted]	23.1 (5.0-53.8)
Hodgkin lymphomas			
All read codes	0		
Diagnosis codes	0		
Morphology codes	0		
ICD-10 codes	12	11	91.7 (61.5 - 99.8)
Non-Hodgkin lymphomas, excluding CTCL			
All read codes	8	7	87.5 (47.3-99.7)
Diagnosis codes	[redacted]	[redacted]	80.0 (28.4 - 99.5)
Morphology codes	[redacted]	[redacted]	100.0 (29.2 - 100.0)
ICD-10 codes	14	10	71.4 (41.9 - 91.6)

[a] Required the cancer to be the same type of cancer initially identified by the algorithm.

[b] UK-CPRD counts below 5 will need to be redacted if shared outside of the regulatory environment.

Annex 5 Table 2. Case Validation Disposition; NL-PHARMO, Adults

Type of Malignancy	Definite Correct Diagnosis %	(Possible) Incorrect Diagnosis %	Possible Correct, But Uncertain[a] %
Malignant melanoma	87	0	13
Basal cell carcinoma	100	0	0
Squamous cell carcinoma	100	0	0
Non-Hodgkin lymphoma	76	6	18
Hodgkin lymphoma	83	11	6
Cutaneous T-cell lymphoma	50	24	26

[a] A definite diagnosis could not be made based on the free-text pathology excerpts.