

# Risk of Skin Cancer and Lymphoma in Users of Topical Tacrolimus, Pimecrolimus, and Corticosteroids (JOELLE)

**First published:** 25/07/2013

**Last updated:** 17/06/2024

Study

Finalised

## Administrative details

### EU PAS number

EUPAS4357

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### Study ID

46412

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### DARWIN EU® study

No

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### Study countries

☐ Denmark

☐ Netherlands

☐ Sweden

☐ United Kingdom

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## Study description

Protopic JOint European Longitudinal Lymphoma and skin cancer Evaluation (JOELLE) Study is a European, multinational cohort study to assess the risk of skin cancer and lymphoma in the pediatric and adult population treated with topical tacrolimus, pimecrolimus, and corticosteroids and in the not-treated population. The study design is a cohort study in populations from four automated health databases: the PHARMO Record Linkage System in the Netherlands, Clinical Practice Research Datalink (CPRD), in the UK, the Danish National Health Database (through research center Southern Denmark University) in Denmark, and the Swedish National Health Databases (through research center Karolinska Institutet) in Sweden. The study will be coordinated by RTI Health Solutions in Spain and the United States. The study endpoints are nonmelanoma skin cancer, malignant melanoma, Hodgkin lymphoma, non-Hodgkin lymphoma, and cutaneous T cell lymphoma. Exposure propensity scores will be used to frequency match users of tacrolimus and users of pimecrolimus with users topical corticosteroids. The not-treated cohort will be individually matched to the corticosteroids cohort identified for comparison with users of tacrolimus. The study cohorts will be followed from the start date for the first occurrence of any one of the study endpoints. A minimum lag time of 6 months will be assumed between the start of exposure and the occurrence of the study endpoints. Person-years of follow-up will be classified according to ever use, single use, and switching/multiple use of tacrolimus and pimecrolimus and to cumulative dose and duration of exposure. The main exposure of interest will be the cumulative dose of topical tacrolimus and pimecrolimus. Stratified analysis and Mantel-Haenszel methods will be used to estimate crude and adjusted incidence rate ratios for each study endpoint and exposure category comparing users of tacrolimus and users of pimecrolimus with users of corticosteroids.

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## Study status

Finalised

## Research institutions and networks

## Institutions

### RTI Health Solutions (RTI-HS)

- ☐ France
- ☐ Spain
- ☐ Sweden
- ☐ United Kingdom
- ☐ United Kingdom (Northern Ireland)
- ☐ United States

**First published:** 21/04/2010

**Last updated:** 13/03/2025

**Institution**

**Not-for-profit**

**ENCePP partner**

### Clinical Practice Research Datalink (CPRD)

- ☐ United Kingdom

**First published:** 15/03/2010

**Last updated:** 17/01/2025

**Institution**

**Laboratory/Research/Testing facility**

**ENCePP partner**

### The PHARMO Institute for Drug Outcomes Research (PHARMO Institute)

- ☐ Netherlands

**First published:** 07/01/2022

**Last updated:** 24/07/2024

**Institution**

Laboratory/Research/Testing facility

ENCePP partner

## Centre for Pharmacoepidemiology, Karolinska Institutet (CPE-KI)

☐ Sweden

**First published:** 24/03/2010

**Last updated:** 23/04/2024

**Institution**

Educational Institution

Laboratory/Research/Testing facility

Not-for-profit

ENCePP partner

## Pharmacoepi center, University of Southern Denmark

☐ Denmark

**First published:** 22/04/2010

**Last updated:** 27/07/2023

**Institution**

Educational Institution

ENCePP partner

## Contact details

**Study institution contact**

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Study contact

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**Primary lead investigator**

Jordi Castellsague

Primary lead investigator

## Study timelines

**Date when funding contract was signed**

Planned: 01/01/2013

Actual: 04/01/2013

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**Study start date**

Planned: 31/12/2012

Actual: 01/03/2013

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**Data analysis start date**

Planned: 01/04/2013

Actual: 02/09/2013

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**Date of final study report**

Planned: 31/12/2015

Actual: 30/11/2015

## Sources of funding

- Pharmaceutical company and other private sector

## More details on funding

Astellas Pharma Europe B.V.

## Study protocol

[Protopic JOELLE Protocol V04 2013\\_04\\_10\\_2\\_redacted.pdf](#)(1.33 MB)

[Protopic JOELLE Protocol V4.3\\_2014-06-06\\_Ammendment.pdf](#)(1.19 MB)

## Regulatory

### **Was the study required by a regulatory body?**

Yes

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### **Is the study required by a Risk Management Plan (RMP)?**

EU RMP category 3 (required)

## Methodological aspects

### Study type

### Study type list

### **Study topic:**

Disease /health condition

Human medicinal product

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**Study type:**

Non-interventional study

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**Scope of the study:**

Drug utilisation

Safety study (incl. comparative)

**Data collection methods:**

Secondary use of data

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**Main study objective:**

To estimate the incidence rate ratios of skin cancer and lymphoma in the pediatric and adult populations for new users of topical tacrolimus and topical pimecrolimus compared with users of moderate- to high-potency topical corticosteroids diagnosed with atopic dermatitis.

## Study Design

**Non-interventional study design**

Cohort

## Study drug and medical condition

**Name of medicine, other**

Topical tacrolimus

Topical pimecrolimus

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**Anatomical Therapeutic Chemical (ATC) code**

(D11AH01) tacrolimus

tacrolimus

(D11AH02) pimecrolimus

pimecrolimus

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**Medical condition to be studied**

Malignant melanoma

Hodgkin's disease

Non-Hodgkin's lymphoma

Neoplasm skin

## Population studied

**Short description of the study population**

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

**Eligibility Criteria**

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

Because the study is focused on incident cases of skin cancer and lymphoma, patients with a history of any of these conditions any time before the start date



(date of cohort entry) will be excluded from the study population.

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### **Age groups**

Preterm newborn infants (0 – 27 days)

Term newborn infants (0 – 27 days)

Infants and toddlers (28 days – 23 months)

Children (2 to < 12 years)

Adolescents (12 to < 18 years)

Adults (18 to < 46 years)

Adults (46 to < 65 years)

Adults (65 to < 75 years)

Adults (75 to < 85 years)

Adults (85 years and over)

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### **Estimated number of subjects**

195931

## **Study design details**

### **Outcomes**

Skin Malignancies: Malignant melanoma, Nonmelanoma skin cancer,

Lymphomas: Cutaneous T cell lymphomas (CTCL), Hodgkin lymphomas (HL),

Non-Hodgkin lymphomas

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### **Data analysis plan**

Incidence rates of each study malignancy will be estimated in users of topical tacrolimus, topical pimecrolimus, moderate- to high-potency topical corticosteroids, and in the general population. Incidence rate ratios and 95% CIs will be estimated comparing the rates between users of topical tacrolimus and topical pimecrolimus and users of moderate- to high-potency corticosteroids,

and between users of moderate- to high-potency corticosteroids and the general population. Propensity scores will be used to match the study cohorts. Each research center will produce stratified data that will be analysed by the coordination center using standard stratified methods. The effect of cumulative dose and duration of use of topical tacrolimus and topical pimecrolimus will be estimated.

## Documents

### Study publications

[Risk of lymphoma risk in users of topical tacrolimus, pimecrolimus, and cortico...](#)

[Use of Topical Tacrolimus and Topical Pimecrolimus in Four European Countries: ...](#)

[A cohort study on the risk of lymphoma and skin cancer in users of topical tacr...](#)

[Probabilistic bias analysis for unmeasured confounders in a study of users of t...](#)

[Risk of skin cancer in users of topical tacrolimus, pimecrolimus, and corticost...](#)

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## Data management

## Data sources

### Data source(s)

Clinical Practice Research Datalink

Odense Pharmacoepidemiological Database

PHARMO Data Network

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## **Data sources (types)**

Administrative healthcare records (e.g., claims)

Disease registry

Drug dispensing/prescription data

Electronic healthcare records (EHR)

## Use of a Common Data Model (CDM)

### **CDM mapping**

No

## Data quality specifications

### **Check conformance**

Unknown

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### **Check completeness**

Unknown

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### **Check stability**

Unknown

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### **Check logical consistency**

Unknown

## Data characterisation

### **Data characterisation conducted**

No