

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

PURI

<https://redirect.ema.europa.eu/resource/46412>

EU PAS number

EUPAS4357

Study ID

46412

DARWIN EU® study

No

Study countries

Denmark

Netherlands

Sweden

United Kingdom

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.

Study status

Finalised

Research institution 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

19/02/2024

Institution

Not-for-profit

ENCePP partner

Clinical Practice Research Datalink (CPRD)

United Kingdom
First published: 15/03/2010
Last updated

02/07/2019

Institution

Laboratory/Research/Testing facility

ENCePP partner

The PHARMO Institute for Drug Outcomes Research (PHARMO Institute)

Netherlands
First published: 07/01/2022
Last updated

10/01/2022

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

Jordi Castellsague

Study contact

castellsague@rti.org

Primary lead investigator

Jordi Castellsague

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned:

01/01/2013

Actual:

04/01/2013

Study start date

Planned:

31/12/2012

Actual:

01/03/2013

Data analysis start date

Planned:

01/04/2013

Actual:

02/09/2013

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

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

Study type:

Non-interventional study

Scope of the study:

Drug utilisation
Safety study (incl. comparative)

Data collection methods:

Secondary data collection

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

Anatomical Therapeutic Chemical (ATC) code

(D11AH01) tacrolimus

(D11AH02) pimecrolimus

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.

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)

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

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...](#)

Data management

Data sources

Data source(s)

Clinical Practice Research Datalink
Odense Pharmacoepidemiological Database
PHARMO Data Network

Data sources (types)

Administrative data (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

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No