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

First published: 16/01/2018

Last updated: 17/06/2024

Study Finalised

Administrative details

PURI

https://redirect.ema.europa.eu/resource/46397

EU PAS number

EUPAS21769

Study ID

46397

DARWIN EU® study

No

Study countries

- [ ] Denmark
- [ ] Netherlands
- [ ] Sweden
- [ ] United Kingdom

Study description

The Protopic JOint European Longitudinal Lymphoma and skin cancer Evaluation (JOELLE) Study is a European, multinational cohort study to assess the risk of skin cancer and lymphoma in the pediatric and adult population treated with topical tacrolimus, pimecrolimus, and corticosteroids and in the untreated population.The primary objective of the study is to estimate the incidence rate ratios of skin cancer and lymphoma in the pediatric and adult populations for new users of topical tacrolimus and topical pimecrolimus compared with users of moderate- to high-potency topical corticosteroids. Secondary objectives of the study are (1) to estimate the incidence rate ratios of skin cancer and lymphoma in users of moderate- to high-potency topical corticosteroids compared with persons not treated with topical tacrolimus, pimecrolimus, or corticosteroids and (2) to describe the patterns of use and the characteristics of users of topical tacrolimus, pimecrolimus, and corticosteroids.Phase I of the study (EUPAS4357), involving the period 2002-2011, has been completed and the report was submitted to the EMA in December 2015. In the JOELLE Extension, the study has been extended for 4 additional years (2012-2015) in order to increase the number of exposed patients and the length of follow-up. Data beyond 2015 may be available in some databases and will be included in the analysis.

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

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Primary lead investigator

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Study timelines

Date when funding contract was signed

Planned: 01/10/2017

Actual: 28/09/2017

Study start date

Planned: 15/11/2017

Actual: 27/10/2017

Date of final study report

Planned: 30/09/2019

Actual: 20/09/2019

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

LEO Pharma A/S

Study protocol

Protopic JOELLE Protocol Final 30Jun2017_Redacted.pdf(5.81 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 use of data

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

PROTOPIC

Name of medicine, other

Elidel

Topical tacrolimus

Topical pimecrolimus

Anatomical Therapeutic Chemical (ATC) code

(D11AH01) tacrolimus

tacrolimus

(D11AH02) pimecrolimus

pimecrolimus

Medical condition to be studied

Malignant melanoma

Neoplasm skin

Hodgkin's disease nodular sclerosis

Hodgkin's disease lymphocyte predominance type stage unspecified

Hodgkin's disease lymphocyte depletion type stage unspecified

Non-Hodgkin's lymphoma stage I

Non-Hodgkin's lymphoma stage II

Non-Hodgkin's lymphoma stage III

Non-Hodgkin's lymphoma stage IV

Population studied

Short description of the study population

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

Network in the Netherlands, the Danish health databases, the Swedish health databases, and the Clinical Practice Research Datalink (CPRD) in the UK. The study population is all individuals of any age registered in the study databases from the date topical tacrolimus became available in each country through 31 December 2014 (period of inclusion), and who have at least 12 months of continuous enrollment in the study databases, except for children 0 to 12 months of age. Because the study is focused on incident cases of skin cancer and lymphoma, patients with a history of any of these conditions any time before the start date (date of cohort entry) will be excluded from the study population. The study will include four primary cohorts identified from all eligible individuals in the study population who are prescribed topical tacrolimus, topical pimecrolimus, or moderate- to high-potency topical corticosteroids during the study period, and one secondary cohort of untreated patients.

Age groups

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

250000

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 results

JOELLE Final Report_Final-20Sep2019_Abstract_Redacted.pdf(45.18 KB)

Study report

JOELLE Final Report_Final V1-2_5Mar2020_Signed_Redacted.pdf(7.1 MB)

JOELLE StudyReport_ LIST OF ERRATA.pdf(66.59 KB)

Study, other information

Annex5_DoIForm_Additional_Feb2019.pdf(494.76 KB)

Annex5_DoIForm_Additional_Mar2019.pdf(25.3 KB)

Study publications

Long-term risk of skin cancer and lymphoma in users of topical tacrolimus and p…

To what extent are topical tacrolimus or pimecrolimus associated with increased…

Case validation of cutaneous lymphoma to minimize protopathic bias

Data management

ENCePP Seal

This study has been awarded the ENCePP seal

Conflicts of interest of investigators

Annex5_DoIForm_ALL.pdf(2.7 MB)

Composition of steering group and observers

JOELLE_NoSteeringGroup.pdf(6.47 KB)

Signed code of conduct

2018-0047_Declaration_EUPAS21769.pdf(417.42 KB)

Signed code of conduct checklist

2018-0047-Checklist CoC_EUPAS21769.pdf(806.87 KB)

Signed checklist for study protocols

2018-0047_Checklist for Study Protocols_EUPAS21769.pdf(1.46 MB)

Data sources

Data source(s)

Clinical Practice Research Datalink (CPRD) GOLD

PHARMO Data Network

Odense Pharmacoepidemiological Database

Data source(s), other

Swedish National Health Databases, Sweden

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

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No