TARGET-EU: Comparison of single-device vilanterol/fluticasone furoate with other single-device inhaled corticosteroid and long-acting beta agonist combinations in the risk of pneumonia in adolescents with asthma

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Study Planned

Administrative details

EU PAS number

EUPAS1000000989

Study ID

1000000989

DARWIN EU® study

No

Study countries

Belgium

Finland

Netherlands

United Kingdom

Study description

This case study is part of the broader TARGET EU project (EUPAS1000000539), which aims to advance the regulatory use of real-world data through the application of target trial emulation and estimand methodologies.

Background: Higher pneumonia rates for patients on vilanterol-fluticasone furoate (V+FF) treatment in comparison to inhaled corticosteroids (ICS) have been reported in trials on adolescent and asthma patients, but there are no estimates on pneumonia risk in adolescents with asthma. It is not known whether the V+FF combination pertains to higher pneumonia risk than other single device inhaled corticosteroid+long-acting beta adrenoceptor (LABA) agonist treatments.

Objective We evaluate the risk of pneumonia in V+FF initiators in comparison to other ICS+LABA single-device treatments in representative real-world settings among adolescents with asthma who are already on ICS treatment.

Methods: We will conduct an active comparator new-user cohort study using linked electronic health records from 2014 to 2023. The study is set primarily in primary care, drawing on longitudinal data from general practices with linkage to hospital data. Data are sourced from two European countries, the United Kingdom (Clinical Practice Research Datalink [CPRD]) and Finland (Finnish national registries), providing population-based and representative coverage of real-world clinical care. In the primary analysis we estimate HR of pneumonia for V+FF vs. other ICS+LABA combination in adolescent asthma patients who were on ICS treatment within the year preceding the initiation, alive and on treatment (i.e., before treatment discontinuation or switching to Other ICS+LABA combination), regardless of using other add-on or rescue

medications. Inverse probability of treatment weighted (IPTW) Cox regression is used to estimate treatment effects in the primary analysis. Supplemental analyses using an accelerated failure time model are conducted.

Study status

Planned

Research institutions and networks

Institutions

Electronic Health Records (EHR) Research Group, London School of Hygiene & Tropical Medicine (LSHTM)

United Kingdom

First published: 19/04/2010

Last updated: 30/10/2024

Institution **Educational Institution** **ENCePP partner**

Division of Pharmacoepidemiology & Clinical Pharmacology (PECP), Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University

Netherlands

First published: 01/03/2010

Last updated: 27/05/2026

Institution | Educational Institution | ENCePP partner

Real-World Evidence Team, University of Eastern Finland (RWE team)

Finland

First published: 20/12/2017

Last updated: 27/08/2024

Institution | Educational Institution | ENCePP partner

Clinical Pharmacology, Vall d'Hebron Institut de Recerca (VHIR)

Spain

First published: 18/05/2021

Last updated: 20/05/2021

Institution | Outdated | Hospital/Clinic/Other health care facility | ENCePP partner

University Medical Center Utrecht (UMCU)

Netherlands

First published: 24/11/2021

Last updated: 22/02/2024

Institution | Educational Institution | Hospital/Clinic/Other health care facility | ENCePP partner

Erasmus Medical Centre Rotterdam

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Teamit Institute

Spain

First published: 12/03/2024

Last updated: 12/03/2024

Institution | Other | ENCePP partner

Ghent University (Belgium)

Networks

Vaccine monitoring Collaboration for Europe (VAC4EU)

- Belgium
- Denmark
- Finland
- France
- Germany
- Italy
- Netherlands
- Norway
- Spain
- United Kingdom

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Network | Outdated | ENCePP partner

EU Pharmacoepidemiology and Pharmacovigilance (PE&PV) Research Network

- Netherlands

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Network

Contact details

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Study timelines

Date when funding contract was signed

Planned: 19/09/2024

Study start date

Planned: 09/03/2026

Date of final study report

Planned: 10/06/2026

Sources of funding

- EMA

Study protocol

Emulation_Protocol_CS5_REV5_clean.pdf (810.17 KB)

Regulatory

Was the study required by a regulatory body?

No

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

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

This study will emulate a hypothetical target trial using a retrospective, active-comparator, new-user cohort design based on routinely collected electronic health records.

Main study objective:

The main objective of this observational cohort study is to assess whether vilanterol+fluticasone increases the risk of pneumonia compared to other single-device inhaled corticosteroid+long-acting beta-2 adrenoceptor (ICS+LABA) combinations in adolescent patients with asthma already treated with ICS.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(R03AK10) vilanterol and fluticasone furoate

vilanterol and fluticasone furoate

Medical condition to be studied

Asthma

Population studied

Short description of the study population

This study is conducted using routinely collected electronic health records from 2014 to 2023. The study is set primarily in primary care, drawing on longitudinal data from general practices with linkage to hospital data. Data are sourced from two European countries, the United Kingdom (Clinical Practice Research Datalink [CPRD]) and Finland (Finnish national registries), providing population-based and representative coverage of real-world clinical care.

The study population will consist of adolescent asthma patients, age 12-17 who initiate vilanterol+fluticasone furoate treatment V+FF or other single-device inhaled corticosteroid+long-acting beta agonist treatment (ICS+LABA) and were on ICS treatment within the year preceding the initiation.

Age groups

- Adolescents (12 to < 18 years)

Special population of interest

Other

Special population of interest, other

Adolescents

Study design details

Setting

This study is conducted using routinely collected electronic health records from 2014 to 2023, reflecting the period of vilanterol-fluticasone furoate use in routine clinical practice. The study is set primarily in primary care, drawing on

longitudinal data from general practices with linkage to hospital data. Data are sourced from two European countries, the United Kingdom (Clinical Practice Research Datalink [CPRD]) and Finland, providing population-based and representative coverage of real-world clinical care.

Comparators

The use of an active comparator of other single-device inhaled corticosteroid+long-acting beta agonist treatmentns (ICS+SABA) combination treatments will allow us to compare initiators who are in need of a similar line of therapy and at a similar stage of asthma severity, reducing confounding by indication. Restriction to single-device treatment ensures similar compliance between the treatment groups.

Outcomes

Pneumonia is a severe infection, and its impact on patients with asthma can be particularly harmful due to underlying conditions. Pneumonia also increases the risk of asthma exacerbations in all age groups, and ICS increase the risk of pneumonia also in adolescents. Pneumonia has been included in the pre-specified adverse events in asthma RCTs, but there are no specific estimates on pneumonia risk in the adolescent population. Most pneumonia cases are treated in outpatient settings, therefore we include both in- and outpatient diagnoses as well as data from primary and secondary healthcare.

Data analysis plan

The analyses are conducted within a target trial emulation framework to estimate the effect of initiating vilanterol+fluticasone furoate treatment V+FF or other single-device inhaled corticosteroid+long-acting beta agonist (ICS+LABA) combination treatment on the risk of incident pneumonia.

For Estimand 1, the main estimand supporting decision making, the primary causal effect summary measure is the hazard ratio for time to incident pneumonia, estimated using an inverse probability of treatment weighted (IPTW) Cox proportional hazards model. The Cox model will be fitted separately within each data source (Finnish registers and CPRD), and the resulting hazard ratios will be combined using a random-effects meta-analysis; potential sources of heterogeneity will be described qualitatively, including structural differences (e.g., coding systems, population coverage) and measurement differences (e.g., recording practices) and their implications (e.g., residual confounding or misclassification).

Sensitivity analyses will assess robustness of the primary findings to key assumptions, including inverse probability of censoring weighting (IPCW), tipping point analysis, and probabilistic bias analysis for non-differential exposure misclassification.

Two supplemental estimands are also defined: Estimand 2, estimating treatment effects using restricted mean survival time (RMST) derived from an IPTW-weighted Weibull accelerated failure time (AFT) model and Estimand 3 (in Finnish data only), investigating time to first pneumonia diagnosis or pneumonia death with same statistical analysis methods as in Estimand 3. In addition, supplemental analyses (e.g., crude and IPTW-adjusted Kaplan–Meier curves, crude Cox models, event counts and incidence rates, propensity score and weight distributions, censoring and intercurrent event patterns, proportional hazards diagnostics and positivity checks) will be conducted to support interpretation of the main analysis.

Summary results

Not yet available

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s)

Clinical Practice Research Datalink

Terveydenhuollon hoitoilmoitusrekisteri (Finland Care Register for Health Care)

Data source(s), other

Finnish national registers (population information system, KANTA electronic dispensings, causes of death, special reimbursements, Care Register for Health Care)

Data sources (types)

Electronic healthcare records (EHR)

Population registry

Use of a Common Data Model (CDM)

CDM mapping

Yes

CDM Mappings

CDM name

ConcepTION CDM

CDM website

https://www.imi-conception.eu/

CDM release frequency

6 months

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Yes

Data characterisation moment

after data extraction

after extract-transform-load to a common data model

after creation of study variables

Data characterisation details

The feasibility assessment for this case study, detailed in the appendix of the study protocol, was conducted as part of the broader TARGET-EU feasibility assessment (EUPAS1000000791). Data source suitability was evaluated using a structured framework based on the EMA data quality framework, assessing system characteristics, data quality, and fitness for the research question. Finnish national registers and CPRD were selected as data sources for this study because they offer large, high-quality, population-based electronic health records with national coverage in Finland and the UK, respectively. Both sources provide the required data elements to operationalise the study design and have been used in regulatory studies and are known to support the emulation of clinical trial eligibility criteria and endpoints. Data extraction and feasibility assessments confirm that the study variables are available with sufficient completeness and temporal coverage to support the research objectives.

Data characterisation details

CS5_Feasibility Assessment.pdf

English (417.48 KB - PDF)

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