TARGET-EU: Risk of adverse birth and neurodevelopmental outcomes in children born alive to fathers exposed to valproate versus levetiracetam for generalised epilepsy

First published: 11/05/2026

Last updated: 22/05/2026

Study Planned

Administrative details

EU PAS number

EUPAS1000000999

Study ID

1000000999

DARWIN EU® study

No

Study countries

Netherlands

Spain

Study description

Background:

Multiple studies have suggested that the intake of valproate for pregnant women during pregnancy has a negative effect on pregnancy outcomes. The evidence regarding the effect of paternal valproate exposure on offspring is much less clear, with multiple recent studies presenting contradictory results. Therefore, new evidence is needed for regulatory decision-making, particularly regarding how methodological aspects may affect study results.

Objectives:

The primary objective is to estimate the cumulative incidence of death, major congenital malformations, ADHD and autism in offspring born alive to fathers diagnosed with generalised epilepsy exposed to valproate compared to levetiracetam.

Methods:

We will conduct an observational cohort study following the target trial emulation approach in combination with the estimands framework using linked electronic health records from the Valencian Health Integrated Database (García-Sempere et al, 2020), a comprehensive database of longitudinal electronic health records of the Valencia region in Spain. Eligible individuals are males of reproductive age (≥ 18 years) diagnosed with generalised epilepsy exposed to valproate or levetiracetam. In the primary analysis, the hypothetical strategy is used for treatment switch and the treatment policy strategy is used for treatment discontinuation; a principal stratum strategy is used where the principal stratum consists of those who father live births. A Poisson regression is used to estimate relative risks, weighted by the propensity score. Because of challenges in uniquely defining time-zero, the sequential trial approach is also employed.

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

Health Services Research and Pharmacoepidemiology Unit (HSRP Unit) FISABIO

Spain

First published: 30/11/2023

Last updated: 30/11/2023

Institution | Other | 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

Teamit Institute

Spain

First published: 12/03/2024

Last updated: 12/03/2024

Institution | Other | ENCePP partner

Networks

Vaccine monitoring Collaboration for Europe (VAC4EU)

Belgium
Denmark
Finland
France
Germany
Italy
Netherlands
Norway
Spain
United Kingdom

First published: 22/09/2020

Last updated: 22/09/2020

Network | Outdated | ENCePP partner

EU Pharmacoepidemiology and Pharmacovigilance (PE&PV) Research Network

Netherlands

First published: 01/02/2024

Last updated: 24/09/2025

Network

Contact details

Study institution contact

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Primary lead investigator

Carlos González Poses

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 10/09/2024

Study start date

Planned: 09/03/2026

Data analysis start date
Planned: 16/03/2026

Date of final study report
Planned: 10/06/2026

Sources of funding

- EMA

Study protocol

Emulation_Protocol_CS7_REV6_clean.pdf (1019.19 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:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Main study objective:

To estimate the cumulative incidence of death, major congenital malformations, autism and ADHD in offspring born alive to fathers diagnosed with generalised epilepsy exposed to valproate compared to levetiracetam

Study Design

Non-interventional study design

Other

Non-interventional study design, other

Sequential trial design (combining multiple, partially overlapping, cohorts)

Study drug and medical condition

Study drug International non-proprietary name (INN) or common name

LEVETIRACETAM

VALPROIC ACID

Anatomical Therapeutic Chemical (ATC) code

(N03AG01) valproic acid

valproic acid

(N03AX14) levetiracetam

levetiracetam

Medical condition to be studied

Epilepsy

Additional medical condition(s)

Focus is on general epilepsy

Population studied

Short description of the study population

Study population includes males exposed to Valproate or Levetiracetam diagnosed with generalized epilepsy, with ages between 18 and 50, fertile, and no contraindications for any of the two drugs, during January 2010 and March 2016 in the region of Valencia, Spain, as captured in the Valencia Health System Integrated Database. It also includes their offspring and the mothers of their offspring (when a linkage between the three subjects is possible).

Age groups

- Adults (18 to < 65 years)
  - Adults (18 to < 46 years)
  - Adults (46 to < 65 years)

Special population of interest

Other

Special population of interest, other

Males diagnosed with generalized epilepsy and their offspring

Study design details

Setting

The study attempts to emulate a hypothetical target trial using routinely collected electronic health records in the region of Valencia, Spain, as recorded in the Valencia Health System Integrated Database in the periods 2010 to 2024. It uses primary care records, outpatient hospital records, pharmacy prescription and dispensing records, congenital anomaly registry records.

Comparators

In the study population that satisfies the inclusion and exclusion criteria, the comparators are 1) males exposed to Valproate, in any dose, formulation or regimen vs 2) males exposed to Levetiracetam, in any dose, formulation or regime. For both arms, concurrent use of any other antiseizure medication is not allowed. Because patients with generalized epilepsy are unlikely to go untreated, an active comparator allow us to reduce confounding by indication.

Outcomes

The primary endpoint is cumulative incidence by 8 years of age of a composite outcome of ADHD diagnosis, autism diagnosis, offspring death and offspring's congenital malformation. ADHD diagnosis and autism diagnosis were the initial endpoints of interest. However, offspring death and offspring's congenital malformation are part of the outcome because they are intercurrent events

dealt with the composite strategy.

Data analysis plan

The overall analysis tries to mimic the analysis reported in a hypothetical trial protocol, while dealing with electronic health records complications such as confounding.

For the primary estimand, the main estimand to support decision making, the cumulative incidence ratio will be estimated in the principal stratum of interest using a weighted Poisson regression model, using inverse probability of treament weights. To identify the principal stratum, we will assume that men who fathered a child in their assigned treatment would have also done so had they been assigned to the other treatment. Missing outcome and covariates data are imputed using Multiple Imputation algorithms. Treatment switch is handled via hypothetical strategy, meaning outcomes are set to missing after treatment switch. Sensitivity analyses will be performed to assess the robustness of the results to this and other assumptions made in the primary analysis.

The analysis for estimand 2 is kept the same with one difference: how the intercurrent event of treatment discontinuation is handled. In Estimand 1 this is dealt with via treatment policy. In Estimand 2, this is dealt with via hypothetical strategy 3 months before conception (which implies missing outcome data), and via treatment policy in the 3 months before conception (same as in estimand 1).
We refer to the protocol for details on the data analysis plan.

Summary results

Not yet available

Documents

Study, other information

CS7_Feasibility Assessment-2.pdf (311.49 KB)

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)

The Valencia Health System Integrated Database

Data sources (types)

Electronic healthcare records (EHR)

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 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. Briefly, VID was deemed feasible for the study question, with some limitations. The most important ones are the lack of some variables like intention to conceive, female partner-related selection criteria, and some outcomes (stillbirth and spontaneous abortion) which lead to changes in the protocol, such as adaptations of the research question and data analysis. Achieving sufficient sample size was flagged as a potential limitation.