PaTernal exposure to vAlproate, further iNvestiGation on the risk of NeuroDevelopmental Disorders (NDD) and Major Congenital Malformation (MCM) in Offspring: A Non-Interventional Post-Authorization Safety Study (TANGO)

First published: 17/09/2025

Last updated: 26/09/2025

Study Planned

Administrative details

EU PAS number

EUPAS1000000707

Study ID

1000000707

DARWIN EU® study

No

Study countries

- [ ] Denmark
- [ ] Finland
- [ ] Germany
- [ ] Norway
- [ ] Sweden

Study description

As part of the 2018 EU-referral, a previous PASS(EUPAS34201) was conducted to evaluate the association between paternal exposure to valproate and the risk of neurodevelopmental disorders (NDD), as well as congenital malformation (CM) in offspring.

Regarding NDD, the results suggested a possible increased risk in children born to fathers taking valproate in the 3 months prior to conception (spermatogenic window) in comparison to lamotrigine or levetiracetam (in monotherapy). The risk in children born to fathers exposed outside of the spermatogenic window wasn’t investigated. Regarding CM, this study did not identify a higher risk in offspring.

That first study had limitations, including differences between the groups in the conditions for which the medicines were used and in follow-up times. PRAC could therefore not establish whether the increased occurrence of these disorders was due to valproate use. In addition, the study was not large enough to assess the NDD subtypes.

On January 2024, PRAC requested to conduct a new PASS to further investigate the association between paternal exposure to valproate and the risk of NDD, as well as CM in offspring, and provided methodological recommendations to control biases and limitations.

The TANGO study has been set up to further investigate the association between paternal exposure to valproate and (1)the risk of NDD in offspring and (2)the risk of major CM in live and non-live born offspring, considering different paternal exposure windows and other relevant factors such as valproate

indication, type of epilepsy, characteristics of the follow-up and outcome occurrence.

This study will be a multi-country, real-world, population-based cohort study using routinely collected data from registries and databases in where the family linkage (father-mother-child) is available: Denmark, Finland, Germany, Norway and Sweden, and will use all the data available to date in each country, allowing at least 1 year pre-inclusion period.

Study status

Planned

Research institutions and networks

Institutions

Leibniz Institute for Prevention Research and Epidemiology - BIPS

☐ Germany

First published: 29/03/2010

Last updated: 30/03/2026

Institution | Not-for-profit | 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

Aarhus University & Aarhus University Hospital DEPARTMENT OF CLINICAL EPIDEMIOLOGY

Denmark

First published: 20/07/2021

Last updated: 02/04/2024

Institution | Educational Institution | 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

Department of Chronic Diseases, Pharmacoepidemiologic Research Group, Norwegian Institute of Public Health (NIPH)

Norway

First published: 29/04/2010

Last updated: 06/05/2024

Institution | Laboratory/Research/Testing facility | Other | ENCePP partner

Bordeaux PharmacoEpi, University of Bordeaux

France

First published: 07/02/2023

Last updated: 08/12/2025

Institution | Educational Institution | Hospital/Clinic/Other health care facility | Not-for-profit | ENCePP partner

Sanofi

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Networks

The SIGMA Consortium (SIGMA)

- [ ] Denmark
- [ ] European Union
- [ ] France
- [ ] Germany
- [ ] Italy
- [ ] Netherlands
- [ ] Norway
- [ ] Spain
- [ ] Sweden
- [ ] United Kingdom

First published: 10/02/2013

Last updated: 19/01/2026

Network **ENCePP partner**

Contact details

Study institution contact

Patrick Blin patrick.blin@u-bordeaux.fr

Study contact

patrick.blin@u-bordeaux.fr

Primary lead investigator

Laure Carcaillon-Bentata 0000-0003-1556-8590

Primary lead investigator

ORCID number:

0000-0003-1556-8590

Study timelines

Date when funding contract was signed
Planned: 08/01/2025

Study start date
Planned: 30/09/2026

Data analysis start date
Planned: 01/07/2027

Date of final study report
Planned: 30/03/2028

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

A Consortium of Marketing Authorization Holders for valproate and related substances

Regulatory

Was the study required by a regulatory body?

Yes

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

EU RMP category 1 (imposed as condition of marketing authorisation)

Regulatory procedure number

EMEA/H/N/PSP/J/0108

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 will be a multi-country, real-world, population-based cohort study using routinely collected data from registries and databases in Denmark, Finland, Germany, Norway and Sweden.
The study will use all the data available to date in each country, allowing at least 1 year pre-inclusion period.

Main study objective:
The primary objective is to estimate and compare the risk of NDD (as composite, all subtypes combined and by subtype) in offspring paternally exposed to valproate as monotherapy in the 3 months prior to conception (‘current users’) compared to offspring paternally exposed to lamotrigine/ levetiracetam as composite monotherapy in the same exposure window (‘current users’).
In the valproate exposed group, only monotherapy will be considered.
In the active comparator group, fathers exposed to lamotrigine monotherapy or levetiracetam monotherapy (‘composite monotherapy’) will be considered as the reference.

Study Design

Non-interventional study design
Cohort

Study drug and medical condition

Medicinal product name, other
Valproate and related substances: valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpromide, valproate bismuth, calcium

valproate, valproate magnesium.

Comparators: lamotrigine/levetiracetam.

Anatomical Therapeutic Chemical (ATC) code

(N03AG01) valproic acid

valproic acid

(N03AG02) valpromide

valpromide

(N03AX09) lamotrigine

lamotrigine

(N03AX14) levetiracetam

levetiracetam

Medical condition to be studied

Neurodevelopmental disorder

Congenital anomaly in offspring

Population studied

Short description of the study population

Inclusion criteria of the family units (i.e. family triads offspring-mother-father): Pregnancies will be included if they meet all the following inclusion criteria: singleton pregnancies, with pregnancy outcome occurring during the study period with mothers' continuous records in the database for ≥12 months prior to the date of their last menstrual period plus 2 weeks (LMP2) and with linkage to father within the study time period; fathers with continuous records in the database for ≥12 months prior to the LMP2 date of the linked mother, and treated with at least one anti-seizure medication (ASM) (valproate or lamotrigine or levetiracetam) from 12 months prior to LMP2 date, and up to 12

months after LMP2 date (this inclusion criteria will be modified for secondary outcomes and/or sensitivity analyses).

Exclusion criteria of the family units :
Family units will be excluded if any of the following criteria are met: pregnancies associated with in vitro fertilization (IVF), offspring being adopted, offspring with genetic disorder, offspring born to mother with a diagnosis of epilepsy or bipolar disorder (BD) prior to conception and/or during pregnancy, offspring born to mother treated with ASMs prior to conception and/or during pregnancy, offspring born to fathers who switch to, from or between ASMs during the window of interest, offspring born to mothers with infections resulting in major malformation and parents with CM related to chromosomal disorders.

Cohorts of offspring :
Two different cohorts will be derived:
- one cohort for NDD (primary outcome),
- one cohort for MCM (secondary outcome) excluding mothers exposed to teratogenic drugs during pregnancy and fathers exposed to teratogenic drugs during spermatogenesis.
The inclusion date (index date) will be the offspring birth date for the NDD cohort and the conception date for the MCM cohort. Offspring will be followed from index date up to 12 years of age for NDD, from index date to the first year of age for MCM.

Each individual offspring (live born or non-live birth for MCM) will be considered as the unit for analysis. If the father or mother has more than one offspring during the study period, the families can be included as many times as the number of considered offspring if the family unit is eligible for that

pregnancy/child as long as inclusion/exclusion criteria are met. All variables collected for fathers and mothers will be re-calculated for each included pregnancy/offspring.

Age groups

- **In utero**
- **Paediatric Population (< 18 years)**
  - Neonate
    - 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)
- **Adult and elderly population (≥18 years)**
  - Adults (18 to < 65 years)
    - Adults (18 to < 46 years)
    - Adults (46 to < 65 years)
  - Elderly (≥ 65 years)
    - Adults (65 to < 75 years)
    - Adults (75 to < 85 years)
    - Adults (85 years and over)

Special population of interest

Other

Special population of interest, other

Family unit (i.e. family triad offspring-mother-father)

Study design details

Setting

Large longitudinal patient-level registries with family linkage (father-mother-child) were selected for this study, representing five European countries: Denmark, Finland, Germany, Norway and Sweden.

Main characteristics of the chosen databases:

- Father infant linkage available for all databases
- High rate of linkage for live birth outcomes in most databases (>90%)
- High rate of father infant linkage with non-live birth outcomes expected
- Number of live births captured per year: between 40,000 and 100,000 in Danish, Finnish, Norwegian and Swedish National registries, and between 115,000 and 210,000 in the German database (GePaRD).
- Valuable information on key variables including on pregnancy characteristics, identification of siblings and birth sex; data on parents' epilepsy and bipolar disorder diagnoses, study medication and indication;
- ASM exposure window classification possible;
- Valuable information on NDD (all data sources are exhaustive) and MCM.

Comparators

-The risk of NDD in offspring paternally exposed to valproate as monotherapy will be estimated and compared to offspring paternally exposed to lamotrigine/ levetiracetam as composite monotherapy in the same exposure window.

In addition to 'current users', two other exposure windows will be considered: 'former users' defined as fathers exposed up to 3 months prior to conception, but not during the 3 months prior conception (i.e. prior to spermatogenesis but not during), and 'later users' defined as fathers not exposed before conception, but exposed after.

-The risk of NDD in offspring paternally exposed to valproate as monotherapy will be estimated and compared to offspring paternally exposed to valproate as monotherapy between the different exposure windows.

-The risk of MCM in live born offspring paternally exposed to valproate as monotherapy in current users will be estimated and compared in live born offspring paternally exposed to lamotrigine/levetiracetam in current users.
-Only in the group of offspring paternally exposed to valproate: the risk of MCM in live and non-live born i) in ‘former users’ vs ‘later users’, and ii) in ‘current users’ vs ‘later users’ will be estimated and compared.

Outcomes

NDD outcomes:
- at least one code (ICD-10) of NDD (composite outcome),

NDD by subtype outcomes:
- at least one code per NDD subtype (possible diagnosis), or
- at least 2 codes of any subtype (co-occurence), or
- at least 2 codes within the same NDD subtype (confirmation), or
- at least 2 codes within the same subtype with ADHD specificity, 1 ADHD ICD code and at least 1 ADHD medication or no ADHD code but at least 2 ADHD medications,

from offspring birth date to the occurrence of the outcome

MCM outcome: at least one ICD-10 code of MCM recorded from live birth (or from conception) to 1 year of age (excluding MCM associated with maternal infections)

Data analysis plan

The following analyses will be performed:
Descriptive analysis: Description of the study population, offspring outcomes and follow-up will be conducted, by data source, for each exposure group and each exposure window.
Crude analyses of primary (NDD) and secondary (MCM) outcomes will be

conducted.
In addition, adjusted comparative analyses and risk estimate will be conducted using propensity score methods:
-Selection of variables for propensity score (PS): each covariate will be assessed regarding its association with the outcome, and with the exposure. PS will be estimated using two different approaches: 1) Common PS models (same PS in all the countries for the main analysis) and 2) Database-driven PS models (PS specific to each country in a sensitivity analysis, to rule out residual confounding due to covariates not initially anticipated a priori).
-Risk of NDD estimation
-Risk of MCM estimation
Controlling for confounding: Models listed above will be performed on the whole population in each data source. To further assess confounding and robustness, results will also be stratified if numbers allow it, by:
· Indication for treatment,
· Sub-type of epilepsy,
· Calendar year of birth in suitable categories (e.g. 2 or 3 years).
· The risk factors parental NDD/MCM.
Landmark methods will be used to analyze such a long follow-up period, by choosing specific time points based on clinical relevance for diagnosis of NDD.
Sensitivity analyses: Multiple sensitivity analyses will be conducted to assess residual confounding and/or the robustness of the main analyses results
Meta-analysis: All comparative analyses will be considered for pooling to achieve a more precise estimate of the observed effect size and identify any potential country-specific patterns in the data

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)

German Pharmacoepidemiological Research Database

Lääketoimitukset (Kanta - Reseptikeskus)

The Norwegian Prescribed Drug Registry

Swedish Cause of Death Register

Sweden National Prescribed Drugs Register / Läkemedelsregistret

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Data source(s), other

- DENMARK: Danish Civil Registration System, National Prescription Registry, National Patient Registry, Cause of death register, Medical Birth Registry, The IVF Register, The Danish Psychiatric Central Research Register, Danish National Hospital Medication Register,
- FINLAND: Population register, Care register for Health care, Prescription register, Kanta electronic prescriptions, Special Reimbursement Register, Causes of Death register, medical births register, Register of Medical abortions, Register of Congenital malformations,
- NORWAY: Population Registry, Norwegian Prescribed Drug Registry, Norwegian Patient Registry, Medical Birth Registry of Norway, Cause of Death Registry, National Education Database,
- SWEDEN : Multigenerational register, Cause of death register, National prescription registry, National patient registry, medical birth registry, Population Register.

Data sources (types)

Administrative healthcare records (e.g., claims)

Birth registry

Congenital anomaly registry

Death registry

Drug prescriptions

Population registry

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

Unknown