

A post-authorization safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorders as well as congenital abnormalities in offspring - a population-based retrospective study

**First published:** 30/04/2020

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Study

Ongoing

## Administrative details

### PURI

<https://redirect.ema.europa.eu/resource/50599>

### EU PAS number

EUPAS34201

### Study ID

50599

### DARWIN EU® study

No

### Study countries

Denmark

Norway

Sweden

## Study description

This population-based retrospective cohort study using secondary data from national registries within Norway, Denmark and Sweden aims to examine the association between paternal exposure to valproate at conception and the risk of Neurodevelopmental disorders (NDD), including Autism spectrum disorder (ASD), as well as Congenital Malformations (CM) in offspring. The primary objective is to investigate the risk of NDD, including ASD, in offspring paternally exposed to valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception. Secondary objectives are to 1) investigate the risk of CM in live and non-live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception, in Norway and Denmark, 2) describe the anti-epileptic drug (AED) exposure (posology and duration) data and health characteristics of male patients prescribed AEDs (including valproate and lamotrigine/levetiracetam) in treatment of epilepsy and other indications at the time of conception of their offspring, both for NDD and CM cohort, and 3) identify potentially important risk factors for outcomes of interest, in offspring paternally exposed to valproate (monotherapy) or lamotrigine or levetiracetam (composite monotherapy) at the time of conception, by examining AED exposure and health characteristics of the offspring and their mothers. Additional exploratory and sensitivity analyses apply (such as narrow case definition for primary outcome with a focus on ASD). Separate cohorts for analysis will be created where medical record linkage between offspring (<12 years), mother and father is available, the NDD cohort will consist of live births and the CM cohort will consist of live births, stillbirths and spontaneous abortions during gestation (2nd or 3rd trimester) for Norway and Denmark, and live births only for Sweden.

## Study status

Ongoing

## Research institution and networks

### Institutions

**IQVIA**

United Kingdom

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22/04/2024

Institution

Non-Pharmaceutical company

ENCePP partner

## Contact details

**Study institution contact**

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Study contact

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**Primary lead investigator**

Florent Richy

Primary lead investigator

## Study timelines

**Date when funding contract was signed**

Actual:

09/10/2018

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**Study start date**

Planned:

01/09/2020

Actual:

21/10/2020

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**Data analysis start date**

Planned:

01/09/2020

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**Date of interim report, if expected**

Planned:

13/08/2021

Actual:

22/11/2021

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**Date of final study report**

Planned:

28/02/2023

## Sources of funding

- Pharmaceutical company and other private sector

## More details on funding

A Consortium of Marketing Authorization Holders for valproate and related substances

## Study protocol

[Valproate\\_PASS\\_Protocol\\_V7.0.PDF](#)(4.09 MB)

## Regulatory

**Was the study required by a regulatory body?**

Yes

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

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

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**Regulatory procedure number**

EMA/H/A-31/1454

## Methodological aspects

### Study type

#### Study type list

**Study type:**

Non-interventional study

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**Scope of the study:**

Assessment of risk minimisation measure implementation or effectiveness

**Main study objective:**

To investigate the risk of NDD, including ASD, in offspring paternally exposed to valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception.

## Study Design

## Non-interventional study design

Cohort

# Study drug and medical condition

## Anatomical Therapeutic Chemical (ATC) code

(N03A) ANTIEPILEPTICS

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## Medical condition to be studied

Multiple congenital abnormalities

Neurodevelopmental disorder

Autism spectrum disorder

Bipolar disorder

Epilepsy

Migraine

Pregnancy

# Population studied

## 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)

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## Estimated number of subjects

4080

# Study design details

## Outcomes

The primary outcome of interest is NDD, including ASD in offspring up to twelve years of age based on ICD-10 diagnostic codes, as recorded in the National Patient Registries. The secondary outcome of interest is a composite of CM diagnosed in offspring up to twelve years of age, stillbirths and spontaneous abortions based on ICD-10 diagnostic codes, as recorded in the National Patient Registries and Medical Birth Registries.

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## Data analysis plan

For NDD and CM cohort by country, demographic and clinical characteristics of father at conception date, mother and offspring at delivery (index date) will be described overall and by paternal exposure group. Paternal AED exposure and maternal AED exposure will be characterised by cluster analysis. For NDD, risk and time to onset will be described overall and by paternal exposure group. A propensity-score (PS) matched Cox proportional

hazards regression model will estimate a hazard ratio (+95%CI) between offspring paternally exposed to valproate and offspring paternally exposed to lamotrigine/levetiracetam.

For CM, a PS-matched logistic regression model will estimate the odds ratio (+95%CI) of CM between offspring paternally exposed to valproate and offspring paternally exposed to lamotrigine/levetiracetam. Incidence % (+95%CI) will be calculated both for the composite CM endpoint and specific CM target body system organ groups (Norway/Denmark only). Data may be pooled via meta-analyse.

## Data management

### Data sources

#### Data source(s), other

Norwegian National Registries, Swedish National Registries, Danish National Registries

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#### Data sources (types)

[Administrative data \(e.g. claims\)](#)

[Drug dispensing/prescription data](#)

### Use of a Common Data Model (CDM)

#### CDM mapping

No

### Data quality specifications

#### Check conformance

Unknown

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#### Check completeness

Unknown

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#### Check stability

Unknown

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#### Check logical consistency

Unknown

### Data characterisation

**Data characterisation conducted**

No