Characterization of neurodevelopmental disorders in children exposed or unexposed in utero to valproate and/or other antiepileptic drugs with long-term follow-up: retrospective study of multiple European data sources (AVALON)

First published: 23/02/2023 Last updated: 02/07/2024





## Administrative details

#### **PURI**

https://redirect.ema.europa.eu/resource/105976

#### **EU PAS number**

EUPAS103711

### Study ID

105976

#### **DARWIN EU® study**

No

#### Study countries

Denmark

Finland

France

Italy

Netherlands

Norway

Sweden

**United Kingdom** 

### Study description

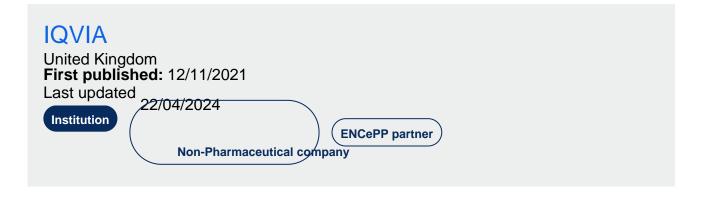
This is a population-based retrospective cohort study conducted using secondary data from multiple databases with mother-to-child linkage from recording longitudinal medical data including registries within Norway, Sweden, Finland, Denmark, the Netherlands, England, Wales, France and Italy. It aims at comparing the risk of Neurodevelopmental Disorders (NDD) up to 17 years of age in children exposed in utero to valproate (VPA) and in those with in utero exposure to other AEDs. A further aim is to investigate incidence and characteristics of minor congenital malformations (mCMs) in children exposed to valproate in utero. NDD will be defined as a composite outcome and separately by NDD sub-types (ASD, ADHD, ID, CD, DPD, MD)). Primary objective will consider VPA/other AEDs in monotherapy while secondary objective will evaluate exposure in polytherapy. In exploratory objectives, NDD risk, disease course and clinical pathway in children exposed in utero to VPA (mono and polytherapy) will be compared with those with exposure to each one of 13 AEDs and with no exposure to AEDs. Finally, exploratory objectives will also address the risk of minor congenital malformations in children exposed in utero to VPA.

### Study status

Planned

## Research institution and networks

## Institutions



## Contact details

Study institution contact Florent Richy Study contact

PAS\_registrations@iqvia.com
Primary lead investigator
Florent Richy

# Study timelines

### Date when funding contract was signed

Planned: 09/10/2018

### Study start date

Planned: 01/08/2023

### **Date of final study report**

Planned: 01/08/2026

# 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/0094

# Methodological aspects

Study type list

#### Study type:

Non-interventional study

### Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

#### Main study objective:

Investigate the risk and the course of NDD (including ASD and ADHD), in infants, children and adolescents exposed in utero to valproate and other antiepileptic drugs, with a long-term follow-up from birth (until maximum 17 years. And to investigate the incidence and characteristics of mCM in children exposed to valproate in utero.

# Study Design

### Non-interventional study design

Cohort

# Study drug and medical condition

### **Anatomical Therapeutic Chemical (ATC) code**

(N03AG01) valproic acid (N03AG02) valpromide

#### Medical condition to be studied

Neurodevelopmental disorder Multiple congenital abnormalities

## Population studied

#### Age groups

Term newborn infants (0 – 27 days)
Infants and toddlers (28 days – 23 months)
Children (2 to < 12 years)
Adolescents (12 to < 18 years)

### Special population of interest

Pregnant women

#### **Estimated number of subjects**

15138

# Study design details

#### **Outcomes**

NDD as a composite outcome, defined as at least one diagnosis of NDD during the follow-up within any of the NDD categories, the date associated to the event will be the date of the first NDD diagnosis after birth. All NDD sub-types (ASD, ADHD, ID, CD, DPD, MD), defined as at least one diagnosis of each sub-type, the date associated to the event will be when the NDD subtype diagnosis after birth. NDD characteristics (severity, attending specialized school, receiving special needs support at school, education level, treatments received) and characteristics of NDD course (changes in NDD pharmacotherapeutic treatments, healthcare resources consumption) and disease pathway (time-interval between consecutive NDD-related events). Minor congenital malformations

#### Data analysis plan

Descriptive and comparative analysis will be performed according to the study objectives. Categorical variables will be presented as counts (n), proportions (%) with confidence interval where relevant. Continuous variables will be presented as means with standard deviation and as medians with interquartile range, where appropriate. Incidence rates and cumulative incidence of the main outcomes will be estimated. Hazard ratios from a Cox proportional hazards regression model (with propensity score weighting) will be calculated to estimate the effect of exposure in utero to valproate vs comparator drugs on NDD composite – all types and NDD sub-types. Summary statistics for time-to-event outcomes will be estimated using the Kaplan-Meier estimator. The results related to the primary outcomes and incidence of mCM will be meta-analysed across all eligible databases. Different sensitivity analysis will be performed to test the robustness of the results obtained in the main analysis.

## Data management

## Data sources

Data source(s)
SAIL Databank
Hospital Episode Statistics
Clinical Practice Research Datalink

PHARMO Data Network

Danish registries (access/analysis)

#### Data source(s), other

Norwegian national registries Norway, Swedish national health and socioeconomic registries Sweden, Finnish national health and socioeconomic registries Finland, Système national des données de santé, SNDS France, Lazio administrative databases Italy

### Data sources (types)

Administrative data (e.g. claims)
Disease registry
Drug dispensing/prescription data
Other

## Data sources (types), other

Medical Birth Registers

# 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