# 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)

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**Last updated:** 02/07/2024

Study | Planned

## 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

### IQVIA
United Kingdom
**First published:** 12/11/2021
Last updated
22/04/2024
Institution
Non-Pharmaceutical company
ENCePP partner

# Contact details

**Study institution contact**
Florent Richy
Study contact
PAS_registrations@iqvia.com
**Primary lead investigator**
Florent Richy

Primary lead investigator

# 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

## 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