Characterization of neurodevelopmental disorders in children exposed 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: 22/01/2025

Study Ongoing

Administrative details

EU PAS number

EUPAS103711

Study ID

105976

DARWIN EU® study

No

Study countries

- [ ] Denmark
- [ ] Finland
- [ ] France
- [ ] 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 and France.
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

Ongoing

Research institutions 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

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Study contact

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Primary lead investigator

Mickael Arnaud

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 09/10/2018

Study start date

Planned: 31/01/2025

Actual: 27/11/2024

Date of final study report
Planned: 30/09/2028

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/0094

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

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

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

VALPROIC ACID

VALPROMIDE

Anatomical Therapeutic Chemical (ATC) code

(N03AG01) valproic acid

valproic acid

(N03AG02) valpromide

valpromide

Medical condition to be studied

Neurodevelopmental disorder

Multiple congenital abnormalities

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)

Adolescents (12 to < 18 years)

Special population of interest

Pregnant women

Estimated number of subjects

18253

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

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)

Hospital Episode Statistics

Clinical Practice Research Datalink

PHARMO Data Network

Danish registries (access/analysis)

Norwegian Health Registers

Système National des Données de Santé (French national health system main database)

Data source(s), other

Swedish national health and socioeconomic registries (Sweden)

Finnish national health and socioeconomic registries (Finland)

Data sources (types)

Administrative healthcare records (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