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

Last updated: 22/01/2025

Study Finalised

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) investige 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

Finalised

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

Florent Richy

Primary lead investigator

Study timelines

Date when funding contract was signed

Actual: 09/10/2018

Study start date

Planned: 01/09/2020

Actual: 21/10/2020

Data analysis start date

Planned: 01/09/2020

Date of interim report, if expected

Planned: 13/08/2021

Actual: 22/11/2021

Date of final study report

Planned: 28/02/2023

Actual: 28/03/2023

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

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/A-31/1454

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:

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

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

SODIUM VALPROATE

VALPROATE MAGNESIUM

VALPROATE SEMISODIUM

Anatomical Therapeutic Chemical (ATC) code

(N03A) ANTIEPILEPTICS

ANTIEPILEPTICS

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)

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.

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)

Norwegian Health Registers

Data source(s), other

Swedish National Registries, Danish National Registries

Data sources (types)

Administrative healthcare records (e.g., claims)

Drug dispensing/prescription data

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