Non-Interventional retrospective longitudinal study in the United Kingdom and France to investigate the therapeutic strategies after discontinuation of valproate and related substances in clinical practice (VALSE study - VALNAC09344)

First published: 30/09/2020
Last updated: 05/07/2024

Study | Finalised

Administrative details

PURI
https://redirect.ema.europa.eu/resource/48865

EU PAS number
EUPAS37438

Study ID
48865

DARWIN EU® study
No

Study countries
France
United Kingdom

Study description
In Europe, valproate and related substances have been licensed to treat epilepsy and bipolar disorder. Following the identification of an increased risk of malformations and neurodevelopmental disorders in children exposed to valproate in utero, in 2018 the Pharmacovigilance Risk Assessment Committee (PRAC) recommended restrictions on the

use of valproate for the treatment of woman of child-bearing potential (WCBP) and pregnant woman. Recommendations on switching or discontinuation of valproate remained poorly defined. The PRAC requested the consortium of Marketed Authorization Holders to conduct an observational study aimed to evaluate and identify the best practices for switching of valproate in clinical practice. The primary study objective is (i) to determine the clusters of patients that are the most likely to reflect a success in epilepsy/ bipolar disorder management after valproate discontinuation based on: (i) the description of the overall treatment patterns in the year following valproate discontinuation, (ii) the categorization of patients according to their treatment patterns (clusters), and (iii) the description of patients' and treatment characteristics at baseline, and clinical relapse occurrence, pregnancy occurrence, and other healthcare resources in the follow-up period in each of these clusters. The secondary study objective is to identify the baseline factors (e.g., patients', Epilepsy/BD treatments, disease characteristics) associated with the potential successful / unsuccessful clusters. The objectives will be split for each indication of valproate (epilepsy or bipolar disorder). This is a cohort study conducted with secondary data from the UK electronic medical records database (Clinical Practice Research Datalink) and the French claims database (Système National des Données de Santé) which will include women aged 13 to 49 years, who have discontinued valproate from 2014 to 2017 and followed for 1 year.

Study status
Finalised

Research institution and networks

Institutions

Bordeaux PharmacoEpi, University of Bordeaux

France
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Last updated
08/02/2023

Institution
Educational Institution
Hospital/Clinic/Other health care facility
Not-for-profit
ENCePP partner

Sanofi Winthrop Industrie, France

Contact details

Study institution contact
Laure Carcaillon-Bentata
Study contact

plateforme.bpe@u-bordeaux.fr
Primary lead investigator
Laure Carcaillon-Bentata
Primary lead investigator

Study timelines

Date when funding contract was signed
Actual:
08/04/2019

Study start date
Planned:
01/01/2021
Actual:
29/03/2021

Data analysis start date
Planned:
01/01/2021
Actual:
29/03/2021

Date of interim report, if expected
Planned:
31/01/2023
Actual:
14/12/2022

Date of final study report
Planned:
31/07/2023
Actual:
05/07/2023

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

VALSE_Protocol v8.0_08NOV2022-clean.pdf(2.15 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:
Disease /health condition
Human medicinal product

Study type:
Non-interventional study

Scope of the study:
Disease epidemiology
Drug utilisation

Effectiveness study (incl. comparative)

Data collection methods:
Secondary data collection

Main study objective:
To determine clusters of patients that are the most likely to reflect a success in epilepsy/ BD management after VPA discontinuation For each cluster, success will be defined based on the absence of VPA reintroduction in the follow-up period, and contextualised according to several parameters (clinical relapse, number of hospitalizations, polypharmacy) and discussed with a Scientific Committee.

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
Epilepsy
Bipolar disorder

Population studied

Short description of the study population
The study population comprised of patients aged 13-49 years old diagnosed with epilepsy or bipolar disorder who had discontinued valproate and related substances from 2014 to 2017 identified through UK the electronic medical records database (Clinical Practice Research Datalink) and the French nationwide claims (Système National des Données de Santé).

Age groups
Adolescents (12 to < 18 years)
Adults (18 to < 46 years)
Adults (46 to < 65 years)

Special population of interest
Other
Pregnant women

Special population of interest, other
Patients with epilepsy and bipolar disorders

Estimated number of subjects
384

Study design details

Outcomes
Description of all situations of therapeutic management after discontinuation observed in clinical practice: clusters defined by an unsupervised clustering method. The clusters and their characteristics will be reviewed by a Scientific Committee to determine which, in their experience, are likely to reflect successful management of epilepsy/BD after VPA discontinuation. Secondary outcomes: first occurrence of VPA reintroduction, occurrence of clinical relapse, occurrence of pregnancy. Other outcomes will be also considered (hospitalisation and discharge diagnoses, emergency room visits, diagnoses…). Modelling analyses to identify factors associated with clusters will be conditioned by the size of the clusters and the number of candidate covariates.

Data analysis plan
The following analyses will be performed separately for each database: - Description of women's recruitment, women's characteristics, treatment patterns of valproate, - Identification and characterisation of the different clusters identified in each database (if available) during follow-up, and based on unsupervised machine learning methods (clustering analysis) - Description of secondary outcomes - Identification of covariates associated with the most relevant clusters performed using a multivariable multinomial logistic regression model, with dependent variable having several possible categories (cluster 1, cluster 2, … cluster n). Modelling analyses are exploratory conditioned by the size of the clusters and the number of candidate covariates, with at least 10-15 patients expected per covariate modality).

Documents

Study results
PASS VALSE_Abstract Final report-V1.0-v20230630-clean.pdf(273.15 KB)

Data management

Data sources

Data source(s)
Clinical Practice Research Datalink
Système National des Données de Santé (French national health system main database)

Data sources (types)
Administrative data (e.g. claims)
Drug dispensing/prescription data
Electronic healthcare records (EHR)

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