Study Protocol C1-002

24/10/2022

Version 2.0

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DOCUMENT HISTORY

Version	Date	Description
V1.0	01/09/2022	**Final submission to EMA**
V2.0	24/10/2022	**Update incorporating EMA feedback after approval**

Study Title	Drug utilisation of valproate-containing medicinal products in women of childbearing potential
Protocol version identifier	v2.0
Date of last version of protocol	Version 1 01/09/2022, Version 2: 24/10/2022
EU PAS register number	Study not registered
Active substance	**Drug of interest** N03AG01 Valproic acid N03AG01 Sodium valproate N03AG01 Magnesium valproate N03AG01 Valproate semisodium N03AG02 Valpromide **Alternative treatments** N03AF01 Carbamazepine N03AA02 Phenobarbital N03AB02 Phenytoin N03AA03 Primidone N05BA09 Clobazam N03AE01 Clonazepam N03AF04 Eslicarbazepine acetate N03AX09 Lamotrigine N03AF02 Oxcarbazepine N03AX22 Perampanel N03AF03 Rufinamide N03AX11 Topiramate N03AX15 Zonisamide N03AX23 Brivaracetam N03AD01 Ethosuximide N03AX12 Gabapentin N03AX18 Lacosamide N03AX14 Levetiracetam N03AX16 Pregabalin N03AG06 Tiagabine N03AG04 Vigabatrin N05AN01 Lithium N05AH04 Quetiapine N05AH03 Olanzapine N03AX09 Lamotrigine C07AA05 Propranolol C07AB02 Metoprolol C07AB03 Atenolol C07AA12 Nadolol

	C07AA06 Timolol C07AB07 Bisprolol N03AX11 Topiramate N06AA09 Amitriptyline N07CA03 Flunarizine N02CX01 Pizotifen N02CX02 Clonidine
Medicinal product	N/A
Research question and objectives	Study Objectives: 1. To characterise the prevalence and incidence of use of valproate, valproate containing medicines, and alternative antiepileptic therapies among women aged 12 to 55 years of age, stratified by calendar year and age 2. To characterise the use of valproic acid or valproate containing medicines among women aged 12 to 55 years of age, stratified by indication, calendar year and age
Country(-ies) of study	The Netherlands, Spain, Belgium, Germany, Finland and United Kingdom
Author	Dr. Annika Jödicke Dr. Albert Prats-Uribe

LIST OF ABBREVIATIONS

Acronyms/terms	Description
CDM	Common Data Model
CPRD GOLD	Clinical Practice Research Datalink GOLD
DA	Disease Analyzer
DARWIN EU	Data Analysis and Real World Interrogation Network
DUS	Drug Utilization Study
EHR	Electronic Health Records
EMA	European Medicines Agency
GP	General Practitioner
HDSF	Auria Clinical Informatics at Turku University Hospital, Hospital District of Southwest Finland
IPCI	Integrated Primary Care Information Project
LPD	Longitudinal Patient Database
OMOP	Observational Medical Outcomes Partnership
PCT	Primary Care Teams
PRAC	Pharmacovigilance Risk Assessment Committee
RMM	Risk minimisation measures
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
VPA	Valproic acid/valorpate-containing medicine

1. TITLE

Drug utilisation of valproate-containing medicinal products in women of childbearing potential

2. RESPONSIBLE PARTIES – STUDY TEAM

Study team Role	Names	Organisation
Principal Investigators	Dr. Annika Jödicke Dr. Albert Prats-Uribe	University of Oxford
Data Scientists	Dr. Martí Català Sabaté Dr. Edward Burn	University of Oxford
Epidemiologists	Dr. Albert Prats-Uribe Dr. Annika Jödicke	University of Oxford
Clinical Domain Experts	Prof. Daniel Prieto-Alhambra Ass. Prof. Katia Verhamme	University of Oxford Erasmus MC
Statistician	Dr. Maria de Ridder	Erasmus MC
Data Manager		
Data Analyst		

3. ABSTRACT (STAND ALONE SUMMARY OF THE STUDY PROTOCOL)

Title

Drug utilisation of valproate-containing medicinal products in women of childbearing potential.

Rationale and Background

Vaproic acid/valproate-containing medicine (VPA) are first-line treatment for generalised tonic-clonic seizures (epilepsy) and adjunctive therapies in other types of seizures. They are also used as second-line treatments or adjuncts for the treatment of bipolar disorder, and for migraine prevention. Valproic acid is a teratogen, with prenatal exposure carrying a substantial risk of neurodevelopmental impairment and congenital malformations in the child. Therefore, its use in women of childbearing age is restricted to prevent valproate exposure during conception and pregnancy.

The European Medicines Agency (EMA) has issued risk minimisation measures in 2014 and 2018 including a compulsory pregnancy prevention program. Timely information on the use of VPA in young women across Europe is important.

Research question and Objectives

The objectives of this study are

1. To estimate the population-level use (incidence rate and prevalence) of VPA in women between 12 and 55 years of age
2. To characterise patient-level VPA use in women between 12 and 55 years of age initiating treatment with VPA.

Research Methods

Study design

- Population level cohort study (Objective 1, Population-level VPA utilisation)
- New user cohort study (Objective 2, Patient-level VPA utilisation)

Population

Population-level utilisation of VPA and alternative treatments: All women aged between 12 years and ≤55 years between 01/01/2010 and 31/12/2021 (or latest date available), with at least 365 days of prior history before the day they become eligible for study inclusion. For incidence, anyone with prior use of VPA will be excluded from the analysis.

Patient-level VPA utilisation: New users of VPA in the period between 01/01/2010 and 31/12/2021 (or latest date available), with at least 365 days of visibility prior to the date of their first VPA prescription, and no used VPA in the previous 365 days.

Variables

Drug of interest: Valproic acid, Sodium valproate, Magnesium valproate, Valproate semisodium and Valpromide

Alternative treatments: Carbamazepine, Phenobarbital, Phenytoin, Primidone, Clobazam, Clonazepam, Eslicarbazepine acetate, Lamotrigine, Oxcarbazepine, Perampanel, Rufinamide, Topiramate, Zonisamide, Brivaracetam, Ethosuximide, Gabapentin, Lacosamide, Levetiracetam, Pregabalin, Tiagabine, Vigabatrin, Lithium, Quetiapine, Olanzapine, Lamotrigine, Propranolol, Metoprolol, Atenolol, Nadolol, Timolol, Bisprolol, Topiramate, Amitriptyline, Flunarizine, Pizotifen, Clonidine

Data sources

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium), Belgium
4. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
5. Auria Clinical Informatics at Turku University Hospital, Hospital District of Southwest Finland (HDSF), Finland
6. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom

Sample size

No sample size has been calculated.

Data analyses

For all analyses a minimum cell count of 5 will be used when reporting results, with any smaller counts obscured.

Population-level VPA utilisation: Annual period prevalence of VPA use and alternative treatments will be estimated, as will annual incidence rates per 100,000 person years.

Patient-level VPA utilisation: Large-scale patient-level characterisation will be conducted. Index date will be the date of the first VPA prescription for each person. Medical History will be assessed for anytime - 366 days before index date, for 365 to 31 days before index date, for 30 to 1 day before index date, and at index date.

Medication use will be reported for 365 to 31 days before index date , for 30 to 1 day before index date, and at index date. Frequency of indication, namely epilepsy, bipolar disorder and migraine at index date will be assessed. Initial dose/strength and treatment duration will be estimated and the minimum, p25, median, p75, and maximum will be provided.

4. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
Version 2	24/10/2022	8.2	Update	Updated information on Databases

5. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE
Draft Study Protocol	23/08/2022
Final Study Protocol	01/09/2022
Creation of Analytical code	
Execution of Analytical Code on the data	
Interim Study Report (if applicable)	
Draft Study Report	
Final Study Report	

6. RATIONALE AND BACKGROUND

Valproic acid/valproate salts are gamma-amino butyric acid (GABA) agonists, which have been used as a potent anti-epileptic agent since the mid-1960s[1 2]. Valproic acid/valproate-containing medicines (VPA) are currently recommended as first-line treatment for generalised tonic-clonic seizures, and as an adjunctive therapy for other types of seizures. In the late 2000s, their indication was extended to include treatment of manic episodes in bipolar disorder, and in some countries, they are also used for migraine prevention[1 3].

VPA are serious (dose-dependent) teratogens, with prenatal exposure carrying a substantially increased risk of neurodevelopmental impairment and congenital malformations in the child[4-8]. Therefore, their use during pregnancy is contraindicated with few exceptions, and pregnancy prevention measures were implemented for young women to reduce the risk of VPA exposed pregnancies.

In 2014, the European Medicines Agency (EMA) reinforced warnings on VPA use among women of childbearing age, stating that VPA and its derivatives should not be prescribed, except in case of intolerance or ineffectiveness of alternatives[9]. Subsequently, several studies assessed the incidence of VPA use among young women with epilepsy following the issue of risk minimization measures (RMM): While prevalence of VPA use in women of childbearing age decreased in France, there were still young women being started on VPA[9]. A multinational, European study assessing the effectiveness of the RMM measures in France, Germany, Spain, Sweden and UK using routinely-collected outpatient data, reports an increase in the proportion of VPA initiated as second-line therapy in incident users in Sweden and UK[10], while it remained unchanged in Germany and Spain[11] and decreased in France[12]. These results suggested that the effectiveness of the RMM on VPA use was limited. However, the incidence rate of VPA exposed pregnancies in Spain and UK was successfully reduced[10 11]. In Ireland, no changes in monthly prevalence in VPA use was seen among women aged 16–44 years before and after the RMM implementation, but a significant decreasing trend of use in younger women aged 16-24 was reported[13].

In 2018, again, EMA's Pharmacovigilance Risk Assessment Committee (PRAC) issued new restrictions on the use of valproate-containing medication and presented a new pregnancy prevention program to minimise valproate exposure during pregnancy and conception[5]: PRAC emphasised that valproate must not be used in pregnancy for bipolar disorder and migraine. While it should also be avoided in epilepsy, valproate may be the most effective medication for some people with specific epilepsies[4]. Hence, for some women it may not be possible to stop valproate and they may need to continue treatment under specialist care during pregnancy to avoid uncontrolled seizures. For female patients in child-bearing age, valproate must not be used unless the conditions of the new pregnancy prevention programme are met, which includes effective contraception, pregnancy tests, counselling patients about the risk of valproate treatment, annual treatment review by a specialist and completing a risk acknowledgement form[5]. Surveys among neurologists in Sweden and Norway, however, revealed limited implementation and use of the new pregnancy prevention program, with 44% having prescribed VPA to women of childbearing age in the last 2019/2020 years, with only a small minority using patient information brochures or the risk acknowledgement form[14]. A similar survey among Italian experts in epilepsy showed that while people were aware of the new recommendation and VPA was less prescribed for first-line treatments, 64% reported to have difficulties to implement the recommendations for their female patients[15].

Little information is currently available on the prevalence and incidence of VPA use across Europe in women of childbearing-age before and after the new RMM recommendation in 2018. A recent study observed no declining trend of incidence after the 2018 intervention compared to the time prior[16]. Additionally, more insight into the characteristics of recent new users including their indication for treatment is needed. The EMA therefore requested a combined population-level and patient-level VPA utilisation study through the DARWIN EU initiative.

7. RESEARCH QUESTION AND OBJECTIVES

This study will address the following objectives:

1. To characterise the prevalence and incidence of use of VPA and alternative antiepileptic therapies among women aged 12 to 55 years of age. Analyses will be stratified by calendar year and age.
2. To characterise the use of VPA among women aged 12 to 55 years of age. Analyses will be stratified by indication (i.e. epilepsy, bipolar disorder and migraine prevention), calendar year and age.

Table 1: Primary research question and objective

Objectives:	(1) To characterise the prevalence and incidence of use of VPA and alternative antiepileptic therapies among women aged 12 to 55 years of age. (2) To characterise the use of VPA among women aged 12 to 55 years of age.
Hypothesis:	NA
Population *(mention key inclusion-exclusion criteria):*	All women present in the databases and aged between ≥12 years and ≤55 years on 1st of January of each year in the period 2010-2022 (or

	the latest available), with at least 365 days of data availability before the day they become eligible for study inclusion.
Exposure:	VPA
Comparator:	Alternative antiepileptic therapies
Outcome:	NA
Time *(when follow up begins and ends):*	Follow-up will start on a pre-specified calendar time point e.g. 1st of January for each calendar year between 2010-2022 for the calculation of annual incidence/prevalence rates. End of follow-up will be defined as the earliest of loss to follow-up, end of data availablility, or death
Setting:	Electronic Health Care Record Databases across Europe namely IPCI, SIDIAP, IQVIA LPD Belgium, IQVIA DA Germany, HDSF and CPRD GOLD
Main measure of effect:	Incidence and Prevalence, Patient-level drug utilisation

8. RESEARCH METHODS

8.1 Study type and Study Design

Retrospective cohort studies will be conducted using routinely-collected health data from 6 databases. The study will comprise two consecutive parts:

1. A population-based cohort study will be conducted to address objective 1, assessing the prevalence and incidence of VPA and alternative treatments.
2. A new drug user cohort will be used to characterise patient-level VPA utilisation.

Table 2. Description of Potential Study Types and Related Study Designs

STUDY TYPE	STUDY DESIGN	STUDY CLASSIFICATION
Population Level DUS	Population Level Cohort	Off the shelf (C1)
Patient Level DUS	New drug/s user cohort	Off the shelf (C1)

8.2 Study Setting and Data Sources

This study will be conducted using routinely collected data from 6 databases in 6 European countries (5 EU countries and United Kingdom). All databases were previously mapped to the OMOP CDM .

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain

3. IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium), Belgium
4. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
5. Auria Clinical Informatics at Turku University Hospital, Hospital District of Southwest Finland (HDSF), Finland
6. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom

Detailed information on data source is described in **Table 3**.

Table 3. Description of the selected Data Sources.

Country	Name of Database	Justification for Inclusion	Health Care setting (e.g. primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of active subjects	Data lock for the last update
NL	IPCI	Database covers primary care setting where valproate prescriptions are issued.	Primary care	EHR	1.39M	1/1/2022
ES	SIDIAP		Primary care	EHR	5.8 million	To be confirmed
BE	IQVIA LPD Belgium		outpatient specialist care	EHR	435,200	To be confirmed
DE	IQVIA DA Germany		outpatient specialist care	EHR	8.5 million	To be confirmed
FI	HDSF	Database covers specialist care setting where valproate prescriptions are issued.	in-and outpatient specialist care	EHR	765,000	To be confirmed
UK	CPRD GOLD	Database covers primary care setting where valproate prescriptions are issued.	Primary care	EHR	3 million	To be confirmed

NL = The Netherlands, ES = Spain, BE = Belgium, DE = Germany, FI = Finland, UK = United Kingdom, IPCI = Integrated Primary Care Information Project; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, LPD = Longitudinal Patient Database, DA = Disease Analyzer, HDSF = Auria Clinical Informatics at Turku University Hospital, Hospital District of Southwest Finland , CPRD GOLD = Clinical Practice Research Datalink GOLD, EHR = Electronic Heath record. Exposure is based on prescription data.

Integrated Primary Care Information Project (IPCI), The Netherlands (Erasmus)

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands.[17] The selection of 374 GP practices is representative of the entire country. The database contains records from 2.8 million patients out of a Dutch population of 17M starting in 1996[17]. The median follow-up is 4.7 years. The observation period for a patient is determined by the date of registration at the GP and the date of leave/death. The observation period start date is refined by many quality indicators, e.g. exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. Drugs are captured as prescription records with product, quantity, dosing directions, strength and indication. Drugs not prescribed in the GP setting might be underreported. Indications are available as diagnoses by the GPs and, indirectly, from secondary care providers but the latter might not be complete. Approval needs to be obtained for each study from the Governance Board[17].

Information System for Research in Primary Care (SIDIAP), Spain (IDIAP Jordi Gol)

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of GPs, nurses and non-clinical staff[18]. The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 10 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee.

Longitudinal Patient Database (LPD) Belgium, Belgium (IQVIA)

LPD Belgium is a computerised network of GPs who contribute to a centralised database of anonymised data of patients with ambulatory visits. Currently, around 300 GPs from 234 practices are contributing to the database covering 1.1M patients from a total of 11.5M Belgians (10.0%). The database covers time from 2005 through the present. Observation time is defined by the first and last consultation dates. Drug information is derived from GP prescriptions. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is necessary for drug utilisation studies.

Disease Analyser (DA) Germany, Germany (IQVIA)

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings[19]. Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patient visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to 28.8% General, 13.4% Orthopaedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynaecology, 6.2% various Neurology and Psychiatry 7.0% Paediatric, 4.6% Urology, 3.7% Cardiology, 3.5% Gastroenterology, 1.5% Pulmonary and 0.7% Rheumatology practices. Drugs are recorded as prescriptions of marketed products. No registration or approval is required for drug utilisation studies.

Auria Clinical Informatics at Turku University Hospital, Hospital District of Southwest Finland (HDSF)

The data covers the patient register at the Hospital District of Southwest Finland (HDSF), containing Turku University Hospital, which is one of the five university hospitals in Finland. It covers the public specialist health care and most emergency health care in the area of Southwest Finland (Varsinais-Suomi) for all demographic groups (765K persons). The data is utilized for scientific research from the data lake in the HDSF under the Finnish legislation (The Act on Secondary Use of Health and Social Data). The most relevant data domains are patients, visits, inpatient episodes, diagnoses, laboratory results, procedures, medication, pathology, radiology, radiotherapy and chemotherapy.

Clinical Practice Research Datalink GOLD, United Kingdom (University of Oxford)

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (https://cprd.com). CPRD GOLD[20] comprises computerized records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients (predominantly from Scotland (52% of practices) and Wales (28% of practices). The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases. Quality checks on patient and practice level are applied during the initial processing. Data are available for 20 million patients, including 3.2 million currently registered patients. Access to CPRD GOLD data requires approval via the Research Data Governance Process.

8.3 Study Period

The study period will start on 1st January 2010 until the latest data available as provided in Table 2.

8.4 Follow-up

8.4.1 Population-level Utilisation of VPA and alternative treatments

Both incidence and prevalence require an appropriate denominator population and their contributed observation time to first be identified. Study participants in the denominator population will begin contributing person time on the respective date of the latest of the following: 1) study start date (1st January 2010), 2) date at which they have a year of prior history recorded, 3) date at which they reach a minimum age (12 years old for the overall population or the lower age limit of a strata when stratifying by age). Participants will stop contributing person time at the earliest date of the following: 1) study end date (end of available data in each of the data sources), 2) date at which their observation period ends, 3) the last day in which they have the maximum age (55 years old for the overall population or the upper age limit of a strata when stratifying by age).

An example of entry and exit into the denominator population is shown in **Figure 1**. In this example person ID 1 and 3 enter the study on the day they reach the minimum age and exits at the study end date. Person ID 2 enters the study on the study start date and exits at the maximum age. Person ID 4 enters the study on the day they reach the minimum age and leaves when they exit the database (the end of their observation period). Person ID 5 enters the study on the day they have sufficient prior history and exits at the study end date. Lastly, person ID 6 has two observation periods in the database. For the first they enter and contribute

time until their exit, for the second they start contributing time again once they have sufficient prior history and exit at the maximum age.

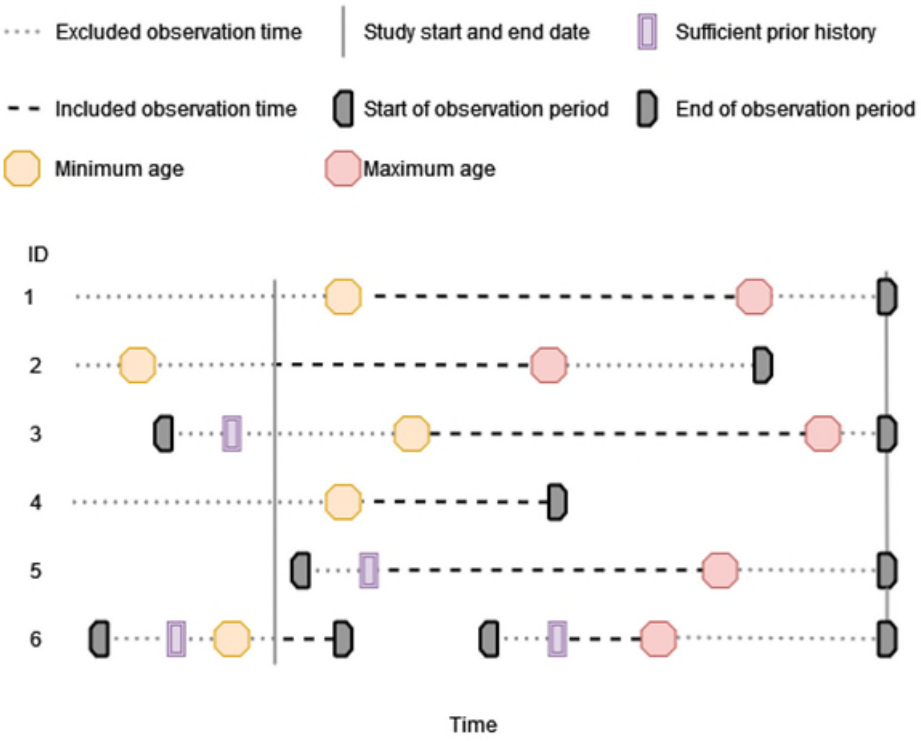


Figure 1. Included observation time for the denominator population

8.4.2 Patient-level Utilisation of VPA

Participants will be followed up from the day of therapy initiation, i.e. the date of the first prescription of valproic acid/valproate-containing medication (index date), until the earliest of loss to follow-up, end of data availablility, death, or end of continuous exposure.

8.5 Study Population with inclusion and exclusion criteria

8.5.1 Population-level Utilisation of VPA and alternative treatments

The study cohort will comprise all women aged between ≥12 years and ≤55 years on 1st of January of each year in the period 2010-2022 (or the latest available), with at least 365 days of data availability before the day they become eligible for study inclusion.

Additional eligibility criteria will be applied for the calculation of incidence rates: The observation time of users of the drug of interest is excluded during use and 365 days afterwards. For this study, incident VPA

users will not be excluded if they had alternative anti-epileptic treatments in the past and start VPA as second-line therapy of add-on.

8.5.2 Patient-level Utilisation of VPA

New users of VPA in the period between 01/01/2010 and 31/12/2021 (or latest date available), with at least 365 days of visibility prior to the date of their first VPA prescription, and not used VPA in the previous 365 days.

Table 4. Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
all women aged between ≥12 years and ≤55 years on 1st of January of each year in the period 2010-2022 (or the latest available)	See under inclusion criterion	After	N/A	Primary care and combination of primary and secondary care for IQVIA Germany and Finland (HDSF)	N/A	N/A	All women within the selected databases	N/A	N/A
Prior database history of 1 year	Study participants will be required to have a year of prior history observed before contributing observation time	After	1 year	Primary care and combination of primary and secondary care for IQVIA Germany and Finland (HDSF)	N/A	N/A	All women within the selected databases	N/A	N/A

* After as first possible study entry date is selected and then it is checked whether patient has one year of database history. In a sensitivity analysis, this rule will be removed. In another sensitivity analysis, required history will be increased to 3 years.

8.6 Variables

8.6.1. Exposure/s

8.6.1.1 Primary exposure of interest:

ATC	Name
N03AG01	valproic acid, sodium valproate, magnesium valproate, valproate semisodium
N03AG02	valpromide

8.6.1.2 Secondary drugs of interest, i.e. alternative treatments for the same indications (Population-level Utilisation study only)

Therapeutic drug class: N03A

1) Other anti-epileptic drugs:

ATC	Name
N03AF01	Carbamazepine
N03AA02	Phenobarbital
N03AB02	Phenytoin
N03AA03	Primidone
N05BA09	Clobazam
N03AE01	Clonazepam
N03AF04	Eslicarbazepine acetate
N03AX09	Lamotrigine
N03AF02	Oxcarbazepine
N03AX22	Perampanel
N03AF03	Rufinamide
N03AX11	Topiramate
N03AX15	Zonisamide
N03AX23	Brivaracetam
N03AD01	Ethosuximide
N03AX12	Gabapentin
N03AX18	Lacosamide
N03AX14	Levetiracetam
N03AX16	Pregabalin
N03AG06	Tiagabine
N03AG04	Vigabatrin

2) Other drugs for bipolar disorder treatment (maintenance):

ATC	Name
N05AN01	Lithium
N05AH04	Quetiapine
N05AH03	Olanzapine
N03AX09	Lamotrigine

3) Alternatives for migraine prophylaxis:

ATC	Name
C07AA05	Propranolol
C07AB02	Metoprolol
C07AB03	Atenolol
C07AA12	Nadolol
C07AA06	Timolol
C07AB07	Bisoprolol
N03AX11	Topiramate
N06AA09	Amitriptyline
N07CA03	Flunarizine
N02CX01	Pizotifen
N02CX02	Clonidine

Table 5. Exposure details

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting	Code Type	Diagnosis position	Applied to study populations :	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
VPA	Preliminary code lists provided in Appendix 1	365days for new users	Calendar year	Primary and secondary care	RxNorm	N/A	Women aged 12-55 in the respective databases	Previous VPA use	N/A	N/A
Alternative treatments for epilepsy, bipolar disorder and migraine prevention		365days for new users	Calendar year	Primary and secondary care	RxNorm	N/A	Women aged 12-55 in the respective databases	Previous use of the same ingredient	N/A	N/A

8.6.2. Outcome/s

N/A

8.6.3. Other covariates, including confounders, effect modifiers and other variables (where relevant)

8.6.3.1 Covariates for stratification in population-level drug utilisation study:

- Age: 5-year age bands will be used: 12-14, 15-19, 20-24, … , 50-54, 55.
- Calendar year

8.6.3.2 Covariates for patient-level drug utilisation study:

- Age: 5-year age bands will be used: 12-14, 15-19, 20-24, … , 50-54, 55.
- The following conditions will be of interest (indication):
    - Epilepsy
    - Bipolar disorder
    - Migraine (indication: migraine prevention)
- Co-morbidities and co-medication for large-scale patient characterisation

Table 6. Operational definition of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Indication of Use	Check for conditions of interest related to use of VPA (epilepsy, bipolar disorder, migraine, "other"*)	Counts	At index date and in a window of 7, 30 days and anytime as sensitivity analysis	Primary care and combination of primary and secondary care for IQVIA Germany and Finland (HDSF)	SNOMED	N/A	Women aged 12-55 in the respective databases	N/A	N/A
Comorbidity (see 8.8.4)	Large-scale patient-level characterisation with regard to underlying comorbidity	Counts	At index date (ID), for 30 to 1 day before ID, for 365 to 31 days before ID and at any time before ID	Primary care and combination of primary and secondary care for IQVIA Germany and Finland (HDSF)	SNOMED	N/A	N/A	N/A	N/A
Concomitant medication (see 8.8.4)	Large-scale patient-level characterisation with regard to use	Counts	At index date (ID), for 30 to 1 day before ID and for 365 to	Primary care and combination of primary and	RxNorm	N/A	N/A	N/A	N/A

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
	of concomitant drugs		31 days before ID	secondary care for IQVIA Germany and Finland (HDSF)					

*If none of the specific indications was recorded during the assessment window, but there was a record for any other conditions the person will be included to the “other” indication group.

8.7 Study size

No sample size has been calculated. Prevalence and Incidence of VPA use among the study population will be estimated as part of Objective 1.

8.8 Analysis

This section describes the details of the analysis approach and rationale for the choice of analysis, with reference to the D1.3.8.1 Draft Catalogue of Data Analysis which describes the type of analysis in function of the study type.

Table 7. Description of Study Types and Type of analysis

STUDY TYPE	STUDY CLASSIFICATION	TYPE OF ANALYSIS
Population Level DUS	Off-the-shelf (C1)	• Population-based incidence rates • Population-based prevalence
Patient Level DUS	Off-the-shelf (C1)	• Characterisation of patient-level features for new VPA users • Frequency and % of indication/s • Estimation of minimum, p25, median, p75, and maximum initially prescribed or dispensed dose/strength of VPA • Estimation of minimum, p25, median, p75, and maximum treatment duration VPA

8.8.1 Federated Network Analyses

Analyses will be conducted separately for each database. Before study initiation, test runs of the analytics are performed on a subset of the data sources or on a simulated set of patients and quality control checks are performed. Once all the tests are passed, the final package is released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally execute the analytics against the OMOP-CDM in R Studio and review and approve the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple execution iterations are performed, and additional fine tuning of the code base is needed. A service desk will be available during the study execution for support.

The study results of all data sources are checked after which they are made available to the team in the Digital Research Environment and the Dissemination Phase can start. All results are locked and timestamped for reproducibility and transparency.

8.8.2 Patient privacy protection

Cell suppression will be applied as required by databases to protect people's privacy. Cell counts < 5 will be clouded.

8.8.3 Statistical model specification and assumptions of the analytical approach considered

R-packages

We will use the R package "DrugUtilizationCharacteristics" for the patient-level drug utilisation analyses including patient-level characterisation, and "IncidencePrevalence" package for the population-level estimation of drug utilisation.

Drug exposure calculations

Drug eras will be defined as follows: Exposure starts at date of the first prescription, e.g. the index date the person entered the cohort. For each prescription, the estimated duration of use is retrieved from the drug exposure table in the CDM. Subsequent prescriptions will be combined into continuous exposed episodes (drug eras) using the following specifications.

Two drug eras will be merged into one continuous drug era if the distance in days between end of the first era and start of the second era is ≤ 30 days. The time between the two joined eras will be considered as exposed by the first era as show in in **Figure 2**.

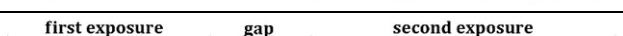
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

Figure 2. Gap era joint mode

If two eras overlap, the overlap time will be considered exposed by the first era (**Figure 3**). No time will be added at the end of the combined drug era to account for the overlap.

Overlap mode	Schematics	Dose overlap
"first"		d_1
"second"		d_2
"both"		$d_1 + d_2$
"maximum"		$\max(d_1, d_2)$

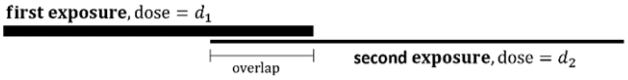


Figure 3. Gap era overlap mode

If two eras start at the same date, the overlapping period will be considered exposed by both. We will not consider repetitive exposure.

New user cohorts

New users will be selected based on their first prescription of the respective drug of interest after the start of the study and/or in a pre-defined time window. For each patient, at least 365 days of data visibility will be required prior to that prescription. New users will be required to not have been exposed to the drug of interest for at least 365 days prior the current prescription. If the index day does not fulfil the exposure washout criteria the whole exposure is eliminated.

8.8.4 Methods to derive parameters of interest

Calendar time

Calendar time will be based on the calendar year of the index prescription.

Age

Age at index date will be calculated using January 1st of the year of birth as proxy for the actual birthday. The following age groups will be used for stratification: 12-14, 15-19, 20-24, 25-29,30-34, 35-39, 40-44, 45-49, 50-54, 55.

Indication

Indication will be determined based on recordings of 3 pre-defined conditions, namely epilepsy, bipolar disorder and migraine, at the date of the first prescription of the respective drug (index date)[primary definition] or during assessment windows [sensitivity analyses]. If none of the specific indications was recorded on index date or during the assessment window, but there was a record for any other conditions, the person will be considered having an "other" indication.

Characterisation of patient-level features

Large-scale patient-level characterisation will be conducted. Co-variates will be extracted for the following time intervals: Concepts in the "condition" domain will be assessed for anytime - 366 days before index date, for 365 to 31 days before index date, for 30 to 1 day before index date, and at index date. Concepts in the

"drug" domain will be reported for 365 to 31 days before index date, for 30 to 1 day before index date, and at index date.

Co-variates to be presented in a summary baseline characteristics table will be pre-defined in addition:

Medical History: *Asthma, COPD, Chronic Liver disease, Crohn's Disease, Diabetes mellitus, GERD, GI-Bleeding, HIV, Hyperlipidemia, Hypertension, Obesity, Osteoarthritis, Pneumonia, Psoriasis, Renal impairment, Ulcerative Collitis, Urinary Tract infection, Viral Hepatitis, Visual system disorder [General] -- Schizophrenia, Dementia, Parkinson, Depressive disorder, Anxiety, ADHS [Neurology] --- Cancer, conditions related to Infertility (if available) [specific]*

Medication use: *Agents acting on the renin-angiotensin system, Antibacterials for systemic use, Antidepressants, Antiepileptics, Antiinflammatory and antirheumatic products, Antineoplastic agents, Antipsoriatics, Antithrombotic agents, Beta blocking agents, Calcium channel blockers, Diuretics, Drugs for acid related disorders, Drugs for obstructive airway diseases, Drugs used in diabetes, Immunosuppressants, Lipid modifying agents, Opioids, Psycholeptics, Psychostimulants, agents used for adhd and nootropics [General] -- contraceptives [contraceptives]*

8.8.5 Methods planned to obtain point estimates with confidence intervals of measures of occurrence

Population-level drug utilisation study

Prevalence and incidence calculations will be conducted separately for VPA and each alternative treatment.

Prevalence calculations

Prevalence will be calculated as annual period prevalence which summarises the total number of individuals who use the drug of interest during a given year divided by the population at risk of getting exposed during that year. Therefore, period prevalence gives the proportion of individuals exposed at any time during a specified interval. An illustration of the calculation of period prevalence is shown below in **Figure 4**. Between time t+2 and t+3, two of the five study participants are VPA users giving a prevalence of 40%. Meanwhile, for the period t to t+1 all five also have some observation time during the year with one of the five study participants VPA users giving a prevalence of 20%.

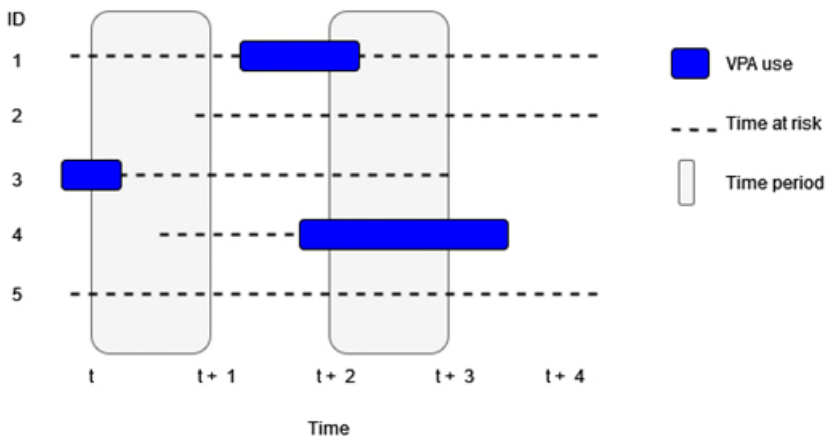


Figure 4. Period prevalence example for VPA use

Incidence calculations

Annual incidence rates for VPA and alternative treatments will be calculated as the of number of **new users** per 100,000 person-years of the population at risk of getting exposed during the period for each calendar year. Any study participants with use of the medication of interest prior to the date at which they would have otherwise satisfied the criteria to enter the denominator population (as described above) will be excluded. Those study participants who enter the denominator population will then contribute time at risk up their first prescription (e.g. VPA use) during the study period. Or if they do not have a drug exposure, they will contribute time at risk up as described above in section 8.4.1 (study end, end of observation period, or the last day of maximum age).

An illustration of the calculation of incidence of VPA use is shown below in **Figure 5**. Patient ID 1 and 4 contribute time at risk up to the point at which they become incident users of VPA. Patient ID 2 and 5 are not seen to use VPA and so contribute time at risk but no incident outcomes. Meanwhile, patient ID 3 is excluded from the analysis as they are seen to have had the outcome before the study start date.

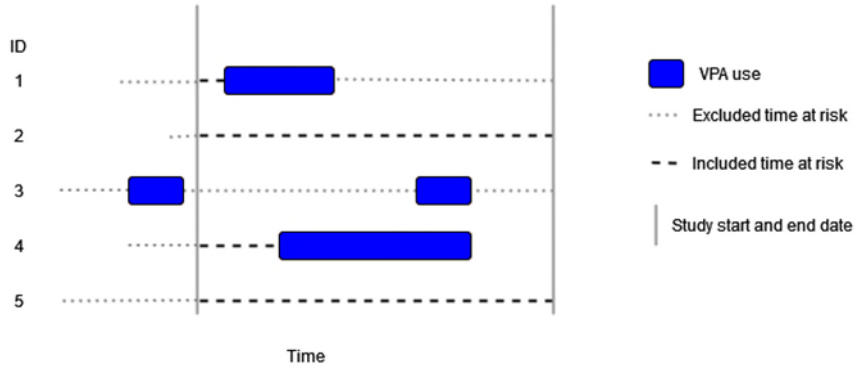


Figure 5. Incidence example for VPA use

Patient-level drug utilisation study

New drug user patient-level characteristics on/before index date

For each concept extracted before/at index date, the number of persons (N, %) with a record within the pre-specified time windows will be provided.

Indication

The number of persons (N, %) with a record of the respective indication (specific: epilepsy, bipolar disorder, migraine prevention; "other") will be provided. If a person has a record of more than one specific indication, that person will be included in both specific indication groups separately.

Initially prescribed or dispensed dose/strength

For each prescription at index date, the prescribed dose/strength will be retrieved from the drug_exposure and drug_strength tables, where the amount quantity and units are available.

The quality of recording of drug dose and drug strengths might be of varying quality for different (unmapped) databases. Therefore, data quality checks will be conducted to evaluate the quality of the recording of units, dosage and strength (OMOP drug_exposure and drug_strength tables) for VPA in the databases this study will be conducted in.

From this, the initial dose/strength in the cohort will be characterised by the minimum dose/strength, p25, median, p75, and maximum dose/strength.

Note: VPA is typically used in different doses for different indications: While dose recommendations might vary between countries, valproate for epilepsy in adults is typically initiated with 600 mg daily in 2–4 divided doses. For treatment of manic episodes associated with bipolar disorder the initial dose of valproic acid is 750 mg daily given in 2–3 divided doses. For migraine, prophylaxis is initiated at 250 mg twice daily in adults (https://bnf.nice.org.uk/drugs/valproic-acid/).

Therefore, in databases where no dosage information is available but only the strength of the product (e.g. CPRD), strength will not display the actual dose taken by the person.

Treatment duration

Treatment duration will be calculated as the duration of the first continuous exposure episode. Estimations of treatment duration will be summarized providing the minimum, p25, median, p75, and maximum treatment duration. For databases, where duration cannot be calculated due to e.g. missing information on quantity or dosing, treatment duration will not be provided.

8.8.6 Methods to control for potential sources of bias

NA

8.8.7 Methods to deal with missing data

For the drug utilisation studies we assume that the absence of a prescription records means that the person did not receive the respective drug. For indications, we assume that the missingness of a record of the respective condition means that that condition was not the indication for the drug prescription.

8.8.8 Presentation of results

The following tables will be provided for the overall cohort of new drug users and for each stratification level:

Population-level drug utilisation study

- Table providing the number of participants, the total number of drug users in each source population during the study period overall and stratified by age
- Figures and tables providing the incidence rates of VPA over time (annually) overall and stratified by age
- Figures and tables providing the incidence rates of alternative treatments over time (annually) overall and stratified by age
- Figures and tables period prevalence of VPA use over calendar time (annually) overall and stratified by age
- Figures and tables period prevalence of use of alternative treatments (annually) overall and stratified by age

Patient-level drug utilisation study

- Table of baseline characteristics of new drug user/s at the time of therapy initiation, including pre-specified indication/s overall and stratified by age
- Table of descriptive measures of initial dose/strength, indication and treatment duration overall and stratified by ageLarge-scale characterisation table with all extracted co-variates. *This table will only be available in a web-application and not be included in the study report.*

8.8.9 Description of sensitivity analyses

- Population-level drug utilisation analyses will be stratified for indication for VPA, and incidence and prevalence of alternative treatments will be conducted in a subgroup of patients with the respective indication.
- Indication of Bipolar disorder: a broad definition (Bipolar disorder incl. unspecified, depressive and manic episodes) and a narrow definition, including only manic episodes, will be used
- Indication gap: In addition to indication recorded at the index date, indication will also be assessed in the 7 days, 30 days and anytime before index date.

8.9 Evidence synthesis

Results from analyses described in section 8.8 will be presented separately for each database and no pooling of results will be conducted.

9. DATA MANAGEMENT

9.1 Data management

All databases will have been mapped to the OMOP common data model. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org

This analytic code for this study will be written in R. Each data partner will execute the study code against their database containing patient-level data and will then return the results set which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

9.2 Data storage and protection

For this study, participants from various EU member states will process personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results.

The output files are stored in the DARWIN Remote Research Environment. These output files do not contain any data that allow identification of subjects included in the study. The RRE implements further security measures in order to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

10. QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it is expected that data partners will have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

When defining drug cohorts, non-systemic products will be excluded from the list of included codes summarised on the ingredient level. A pharmacist will review the codes for VPA and alternative treatments.

When defining cohorts for indications, a systematic search of possible codes for inclusion will be identified using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). This software allows

the user to define a search strategy and using this will then query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, the CohortDiagnostics R package (https://github.com/OHDSI/CohortDiagnostics) will be run if needed to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error.

The study code will be based on two R packages currently being developed to (1) estimate Incidence and Prevalence and (2) characterise drug utilisation using the OMOP common data model. These packages will include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

11. LIMITATIONS OF THE RESEARCH METHODS

The study will be informed by routinely collected health care data and so data quality issues must be considered. In particular, a recording of a prescription or dispensation does not mean that the patient actually took the drug. In addition, assumptions around the duration of drug use will be unavoidable. In databases where no dosage information is available but only the strength of the product (e.g. CPRD), strength will not display the actual dose taken by the person.

In addition, the recording of events used for patient characterisation and identification of the (potential) indication may vary across databases and recording of indication may be incomplete.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

In agreement with the new guideline on good pharmacovigilance practice (EMA/873138/2011), there will be no requirement for expedited reporting of adverse drug reactions as only secondary data will be used in this study.

13. GOVERNANCE BOARD ASPECTS

SIDIAP, IPCI, CPRD and HDSF will require ethical approvals to perform this study. IQVIA Belgium and IQVIA DA Germany will not require any further specific approvals to undertake this study.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

14.1 Study Report

A PDF report including an executive summary, and the specified tables and/or figures will be submitted to EMA by the DARWIN EU CC upon completion of the study.

An interactive dashboard incorporating all the results (tables and figures) will be provided alongside the pdf report. The full set of underlying aggregated data used in the dashboard will also be made available if requested.

15. OTHER ASPECTS

NA

16. REFERENCES

1. European Medicines Agency. Valproate 19/12/2009 [Available from: https://www.ema.europa.eu/en/medicines/human/referrals/valproate accessed 05/08/2022.
2. Angus-Leppan H, Liu RSN. Weighing the risks of valproate in women who could become pregnant. *BMJ* 2018;361:k1596. doi: 10.1136/bmj.k1596 [published Online First: 2018/04/20]
3. Vatzaki E, Straus S, Dogne JM, et al. Latest clinical recommendations on valproate use for migraine prophylaxis in women of childbearing age: overview from European Medicines Agency and European Headache Federation. *J Headache Pain* 2018;19(1):68. doi: 10.1186/s10194-018-0898-3 [published Online First: 2018/08/16]
4. Bromley R, Weston J, Adab N, et al. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. *Cochrane Database Syst Rev* 2014(10):CD010236. doi: 10.1002/14651858.CD010236.pub2 [published Online First: 2014/10/31]
5. European Medicines Agency. PRAC recommends new measures to avoid valproate exposure in pregnancy 09/02/2018 [Available from: https://www.ema.europa.eu/en/documents/press-release/prac-recommends-new-measures-avoid-valproate-exposure-pregnancy_en.pdf accessed 04/08/2022.
6. Christensen J, Gronborg TK, Sorensen MJ, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 2013;309(16):1696-703. doi: 10.1001/jama.2013.2270 [published Online First: 2013/04/25]
7. Meador K, Reynolds MW, Crean S, et al. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Res* 2008;81(1):1-13. doi: 10.1016/j.eplepsyres.2008.04.022 [published Online First: 2008/06/21]
8. Tanoshima M, Kobayashi T, Tanoshima R, et al. Risks of congenital malformations in offspring exposed to valproic acid in utero: A systematic review and cumulative meta-analysis. *Clin Pharmacol Ther* 2015;98(4):417-41. doi: 10.1002/cpt.158 [published Online First: 2015/06/06]
9. Degremont A, Polard E, Kerbrat S, et al. Impact of recommendations on sodium valproate prescription among women with epilepsy: An interrupted time-series study. *Epilepsy Behav* 2021;125:108449. doi: 10.1016/j.yebeh.2021.108449 [published Online First: 2021/11/29]
10. Ehlken B, Nishikawa C, Kaplan S, et al. Effectiveness of risk minimization measures for valproate: a drug utilization study based on implementation of a risk minimization programme in Europe, analysis of data from the UK. *Curr Med Res Opin* 2022;38(3):461-68. doi: 10.1080/03007995.2021.1997286 [published Online First: 2021/12/22]
11. Ehlken B, Stevanovic I, Kaplan S, et al. Effectiveness of risk minimisation measures for valproate: a drug utilisation study in Europe, analysis of data from Spain. *Rev Neurol* 2021;73(11):373-82. doi: 10.33588/rn.7311.2021247 [published Online First: 2021/11/27]
12. Toussi M, Shlaen M, Coste F, et al. Effectiveness of risk minimisation measures for valproate: A drug utilisation study in Europe. *Pharmacoepidemiol Drug Saf* 2021;30(3):292-303. doi: 10.1002/pds.5166 [published Online First: 2020/10/28]
13. Hughes JE, Buckley N, Looney Y, et al. Valproate utilisation trends among women of childbearing potential in Ireland between 2014 and 2019: A drug utilisation study using interrupted time series.

Pharmacoepidemiol Drug Saf 2022;31(6):661-69. doi: 10.1002/pds.5427 [published Online First: 2022/03/15]

14. Zelano J, Sveberg L, Tauboll E, et al. Valproate Restrictions in Sweden and Norway: Online survey suggests implementation deficit. *Acta Neurol Scand* 2022;145(5):551-56. doi: 10.1111/ane.13581 [published Online First: 2022/01/08]
15. Giuliano L, La Neve A, Galimberti CA, et al. Valproate and female patients: Prescribing attitudes of Italian epileptologists. *Epilepsy Behav* 2019;97:182-86. doi: 10.1016/j.yebeh.2019.05.024 [published Online First: 2019/06/30]
16. Klungel O, Sturkenboom M, Abtahi S. Impact of EU label changes and revised pregnancy prevention programme for medicinal products containing valproate: utilisation and prescribing trends 2022 [Available from: https://zenodo.org/record/7074588#.YylkVcmbvcs accessed 13/10/2022.
17. Vlug A, van der Lei J, Mosseveld B, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods of information in medicine* 1999;38:339-44.
18. Garcia-Gil Mdel M, Hermosilla E, Prieto-Alhambra D, et al. Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). *Informatics in primary care* 2011;19(3):135-45.
19. Rathmann W, Bongaerts B, Carius H, et al. Basic characteristics and representativeness of the German Disease Analyzer database. *Int J Clin Pharmacol Ther* 2018;56(10):459-66.
20. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;44(3):827-36. doi: 10.1093/ije/dyv098 [published Online First: 2015/06/08]

17. ANNEXES

Appendix I: Lists with concept definitions

Prescriptions will be identified based on the relevant ingredient. Non-systemic products will be excluded from the code list.

Primary exposure of interest

ATC	**Name**	**conceptID** ingredient
N03AG01	valproic acid, sodium valproate, magnesium valproate, valproate semisodium	745466*

N03AG02	valpromide	36878958

*Products containing calcium valproate will be excluded

Secondary drugs of interest, i.e. alternative treatments for the same indications

Therapeutic drug class: N03A

4) Alternatives for epilepsy treatment:

ATC	Name	conceptID ingredient
N03AF01	Carbamazepine	740275
N03AA02	Phenobarbital	734275
N03AB02	Phenytoin	740910
N03AA03	Primidone	751347
N05BA09	Clobazam	19050832
N03AE01	Clonazepam	798874
N03AF04	Eslicarbazepine acetate	44507780
N03AX09	Lamotrigine	705103
N03AF02	Oxcarbazepine	718122
N03AX22	Perampanel	42904177
N03AF03	Rufinamide	19006586
N03AX11	Topiramate	742267
N03AX15	Zonisamide	744798
N03AX23	Brivaracetam	35604901
N03AD01	Ethosuximide	750119
N03AX12	Gabapentin	797399
N03AX18	Lacosamide	19087394
N03AX14	Levetiracetam	711584
N03AX16	Pregabalin	734354
N03AG06	Tiagabine	715458
N03AG04	Vigabatrin	19020002

5) Alternatives for bipolar disorder treatment (maintenance):

ATC	Name	conceptID ingredient
N05AN01	Lithium	19124477
N05AH04	Quetiapine	766814
N05AH03	Olanzapine	785788
N03AX09	Lamotrigine	705103

6) Alternatives for migraine prophylaxis:

ATC	Name	conceptID ingredient
C07AA05	*Propranolol*	1353766
C07AB02	Metoprolol	1307046
C07AB03	Atenolol	1314002
C07AA12	Nadolol	1313200

C07AA06 C07AB07	Timolol Bisprolol	902427 1338005
N03AX11	Topiramate	742267
N06AA09	Amitriptyline	710062
N07CA03	Flunarizine	19055183
N02CX01	Pizotifen	19047076
N02CX02	Clonidine	1398937

Appendix II: ENCePP checklist for study protocols

Study title:
Drug utilisation of valproate-containing medicinal products in women of childbearing potential

EU PAS Register® number: N/A
Study reference number (if applicable): N/A

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for 1.1.1 Start of data collection[2]			X	5

1.1.2 End of data collection[3]			X	
1.1.3 Progress report(s)			X	
1.1.4 Interim report(s)	X			
1.1.5 Registration in the EU PAS Register®			X	
1.1.6 Final report of study results.	X			

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	X			6, 7
2.1.2 The objective(s) of the study?	X			
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	X			
2.1.4 Which hypothesis(-es) is (are) to be tested?			X	
2.1.5 If applicable, that there is no *a priori* hypothesis?			X	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	X			8.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	X			8.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	X			8.8
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))			X	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)			X	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	X			8.2/8.5
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	X			8.5

	4.2.2 Age and sex 4.2.3 Country of origin 4.2.4 Disease/indication 4.2.5 Duration of follow-up	X X X X			
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	X			8.5

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	X			8.6
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)		X		
5.3	Is exposure categorised according to time windows?	X			8.5
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	X			8.8
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?			X	
5.6	Is (are) (an) appropriate comparator(s) identified?	X			8.6

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?			X	
6.2	Does the protocol describe how the outcomes are defined and measured?			X	
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)			X	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)			X	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)			X	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)			X	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)			X	

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	X			8.8

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	X			8.6
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)			X	
9.1.3 Covariates and other characteristics?	X			8.6
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	X			8.6
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)			X	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	X			8.6
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	X			8.6
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))			X	
9.3.3 Covariates and other characteristics?	X			8.6
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)			X	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	X			8.8
10.2 Is study size and/or statistical precision estimated?			X	
10.3 Are descriptive analyses included?	X			8.8
10.4 Are stratified analyses included?	X			8.8
10.5 Does the plan describe methods for analytic control of confounding?			X	
10.6 Does the plan describe methods for analytic control of outcome misclassification?			X	
10.7 Does the plan describe methods for handling missing data?			X	
10.8 Are relevant sensitivity analyses described?	X			8.8

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	X			9.2
11.2 Are methods of quality assurance described?	X			10
11.3 Is there a system in place for independent review of study results?			X	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of: 12.1.1 Selection bias? 12.1.2 Information bias? 12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).			 X X X	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	X			8.2

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	X			13

13.2 Has any outcome of an ethical review procedure been addressed?			X	
13.3 Have data protection requirements been described?	X			9.2

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	X			4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	X			14
15.2 Are plans described for disseminating study results externally, including publication?	X			14

Comments:

Name of the main author of the protocol: Annika Jödicke

Date: 24/10/2022

Signature: A. Jödicke