POST-AUTHORISATION SAFETY STUDY (PASS) PROTOCOL

TITLE: A Drug Utilisation Study extension (DUS ext.) of valproate and related substances, in Europe, using databases.

COMPOUND: Valproate and related substances

STUDY NUMBER: VALNAC09343 (Sanofi internal referencing system)

Final **Total number of pages** **100**

PASS INFORMATION

TITLE	Drug Utilisation Study extension (DUS ext.) of valproate and related substances, in Europe, using databases.
PROTOCOL VERSION IDENTIFIER	Version 13.0
DATE OF LAST VERSION OF PROTOCOL	25 April 2025
EU PAS REGISTER NUMBER	EUPAS34519
ACTIVE SUBSTANCE	Valproate and related substances: ATC code: N03AG01 ATC code: N03AG02
MEDICINAL PRODUCTS	Valproate and related substances*: magnesium valproate sodium valproate valproic acid sodium valproate/ valproic acid valproate semi sodium valpromide *All substances will be summarised under the term ‘valproate’
PRODUCT REFERENCE	Information is detailed in the cover letter’s Annex 1
PROCEDURE NUMBER	EMEA/H/A-31/1454
MARKETING AUTHORISATION HOLDERS (MAHs)	The joint initiative involves several companies via a consortium: Aurobindo Pharma B.V., (Formerly Apotex Europe B.V.); Aristo Pharma GmbH; Arrow Generiques; Betapharm Arzneimittel GmbH; Consilient Health Limited; Crescent Pharma; Desitin Arzneimittel GmbH; Generis Farmacêutica S.A.; G.L. Pharma GmbH; Hexal AG; Lupin Healthcare (UK) Limited; Neuraxpharm Arzneimittel GmbH; Orion Corporation; SANOFI WINTHROP INDUSTRIE; Stada Arzneimittel Ag; Tecnifar S.A.; Teva Pharmaceuticals Europe B.V.; Viatris Healthcare (Formerly Mylan EMEA SAS); Wockhardt UK Limited. Contact details are detailed in Annex 4

JOINT PASS	Yes

RESEARCH QUESTION AND OBJECTIVES	The research question is, 'What is the impact of the implementation of the Risk Minimisation Measures and Pregnancy Prevention Programme (PPP) on the use of valproate in women of childbearing potential in Europe (WCBP)?'
	
	The aim of this study is to describe the prescribing practices before and after the dissemination of the new risk minimisation measures (RMM) (planned over Q2 2018 – Q4 2018, depending on approval by National Competent Authorities) in Europe and to assess the effectiveness of these measures.
	
	Primary objectives:
	• To describe and compare the prescribing practices in WCBP receiving valproate during the pre- and post-implementation periods with respect to elements of the PPP (where available in each of the data sources) separately:
	  ○ Use of contraceptives without interruption during treatment
	  ○ Laboratory pregnancy tests before treatment
	  ○ Treatment reviews by a specialist at least once per year (using a proxy of consultation by a specialist as a marker for treatment review)
	  ○ Specialty of prescribing physician at initiation
	• To describe and compare proportion of patients for which all elements of the PPP measurable with this DUS are fulfilled, during the pre- and post-implementation periods
	• To describe and compare the incidence of valproate exposed pregnancies, and characteristics of exposed pregnancies during the pre- and post-implementation period
	
	Secondary objective:
	• To describe and compare the following prescribing patterns in WCBP during the pre- and post-implementation periods, overall and in subgroups of patients:
	  ○ Demographic characteristics of WCBP prescribed or dispensed valproate in oral form
	  ○ Indication for use (epilepsy, bipolar disorder and other)
	  ○ Use of prior medication for valproate indications before valproate initiation

COUNTRY(-IES) OF STUDY	The study will be conducted in France, Germany, Netherlands, Spain, Sweden, and in the United Kingdom (UK)
AUTHOR	Mickael Arnaud, PhD (Principal Investigator) On behalf of IQVIA and the consortium

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	The joint initiative involves several companies via a consortium: Aurobindo Pharma B.V., (Formerly Apotex Europe B.V.); Aristo Pharma GmbH; Arrow Generiques; Betapharm Arzneimittel GmbH; Consilient Health Limited; Crescent Pharma; Desitin Arzneimittel GmbH; Generis Farmacêutica S.A.; G.L. Pharma GmbH; Hexal AG; Lupin Healthcare (UK) Limited; Neuraxpharm Arzneimittel GmbH; Orion Corporation; SANOFI WINTHROP INDUSTRIE; Stada Arzneimittel Ag; Tecnifar S.A.; Teva Pharmaceuticals Europe B.V.; Viatris Healthcare (Formerly Mylan EMEA SAS); Wockhardt UK Limited.
MAH contact person (on behalf of MAHs)	Leslie DONDEY-NOUVELDEPUTY QQPV SANOFI-AVENTIS R&D 82 Av, Raspail, 94250 Gentilly France

This protocol contains confidential information that should only be disclosed to those persons responsible for execution and organisation of the study and on condition that all such persons agree not to further disseminate it.

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2 LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
EBM	Einheitlicher Bewertungsmaßstab (outpatient reimbursement code)
CI	Confidence Interval
CIH	Catalan Institute of Health
CNIL	Commission Nationale de l'Informatique et des Libertés (French Data Protection Authority)
CPRD	Clinical Practice Research Datalink
CPT	Current Procedural Terminology
DHPC	Direct Healthcare Professional Communication
DRG	Diagnosis Related Groups
EBM	Einheitlicher Bewertungsmaßstab (out-patient reimbursement code)
EM	Educational Materials
EMA	European Medicines Agency
EMR	Electronic Medical Record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERB	Ethical Review Boards
EU	European Union
E-CAP	Estació Clínica de treball d'Atenció Primària (clinical work station of primary care)
GePaRD	German Pharmacoepidemiological Research Database
GKV	Gesetzliche Krankenversicherung (Statutory health insurance in Germany)
GVP	Good Pharmacovigilance Practice
GPP	Good Pharmacoepidemiology Practice
HCG	Human Chorionic Gonadotropin
HEOR	Health Economics and Outcomes Research
ICD-10	International Classification of Diseases, Tenth Revision
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICD-10-GM	International Classification of Diseases, Tenth Revision, German Modification
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	Institut Català de la Salut (Catalan Institute of Health)
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society of Pharmacoepidemiology

IQR	Interquartile range
ITS	Interrupted Time Series
IUD	Intra Uterine Device
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency
OPS	Operation and Procedure Code (Operationen- und Prozedurenschlüssel)
PAS	Post-Authorisation Study
PASS	Post-Authorisation Safety Study
PCT	Primary Care Teams
PDC	Proportion of Days Covered
PHARMO	Institute for Drug Outcomes Research (NL)
PPP	Pregnancy Prevention Programme
PRAC	Pharmacovigilance Risk Assessment Committee
PRN	Perinatal Registry
PZN	Pharmazentralnummer
RMM	Risk Minimisation Measures
SAP	Statistical Analysis Plan
SD	Standard Deviation
SIDIAP	Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària (the Information System for the Development of Primary Care Research in Catalonia)
SNIIRAM	Système National d'Information Inter-Régimes de l'Assurance Maladie
SNDS	Système National des Données de Santé
SOP	Standard Operating Procedure
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
UK	United Kingdom
WCBP	Women of Childbearing Potential

3 RESPONSIBLE PARTIES

Responsible Party	Name and Affiliation
Consortium	Valproate consortium of MAH (contact details for all MAHs are provided in Annex 4)
Sponsors	All MAHs involved in the valproate consortium
MAH responsible for submissions to HA	SANOFI
Contracting vendor	**IQVIA LTD,** a company registered under the laws of England and Wales, company registration number 01124807 Address: 210 Pentonville Road, London, N1 9JY, United Kingdom Phone: +46701427001 Contact: Antje Kretzschmar
Principal Investigator	Mickael Arnaud, PhD (Principal Investigator), IQVIA
IQVIA project team	Project Oversight: Antje Kretzschmar, PhD Lead Epidemiologist: Giorgi Tskhvarashvili, MSc Epidemiologist: Olga Rocha, PhD Biostatistical Oversight: Leyla Nunez, MSc Lead Biostatistician: Thomas Faux, MSc Lead Statistical Programmer: Alexandrina Lambova, MSc Global Project Manager: Vanessa Domingos, MSc Project Manager: Sanni Sihvonen, MSc

4 ABSTRACT

Full Study Title: Drug Utilisation Study extension (DUS ext.) of valproate and related substances, in Europe, using databases.

Protocol version 13.0 dated 25 April 2025

Rationale and background:

Valproate and related substances (sodium valproate, valproic acid, valproate semi sodium, valpromide, and valproate magnesium) have been licensed since 1967 to treat epilepsy and since 1995 to treat bipolar disorder in Europe.

In October 2014, the Pharmacovigilance Risk Assessment Committee (PRAC) concluded a review under Article 31 of Directive 2001/8/EC of all available data from published literature, spontaneous reports as well as the views of the relevant experts on the safety and efficacy of valproate and related substances in female children, in women of childbearing potential (WCBP) and pregnant women, due to the risk of malformations and developmental disorders in babies exposed to valproate in utero. Restrictions on the use of valproate containing substances were applied to the label and Risk Minimisation Measures (RMM) such as educational materials (EM) for physicians and patients were implemented.

The results of various utilisation studies in Europe showed that the pattern of use of valproate in WCBP had not changed significantly over 2014-2016 and indicated that valproate was still used by a considerable proportion of WCBP for both epilepsy and bipolar disorder indications.

France triggered on 08 March 2017 a second referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data and requested PRAC to assess the impact of the RMM in the current pregnancy exposure of the treatment with medicinal products containing substances related to valproate and their impact on the benefit-risk balance. On 08 February 2018, the PRAC issued a recommendation including revised prescribing conditions in the product information, a Pregnancy Prevention Programme (PPP) and revised educational measures. The Co-ordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh) endorsed the PRAC recommendation on 21 March 2018 and a European Commission (EC) decision was adopted on 31 May 2018.

PRAC requested the Marketing Authorisation Holders (MAHs) to continue the ongoing drug utilisation study conducted in France, Germany, Spain, Sweden and in the UK and to amend the study design to include the updated conditions of use for valproate and related substances. Databases capturing variables that would be used to assess the compliance to PPP were considered for the extension study including Système National des Données de Santé (SNDS) (France), GKV (Germany), the Information System for the Development of Primary Care Research in Catalonia (SIDIAP) (Spain), PHARMO database network and Perinatal Registry (PRN) (Netherlands), Clinical Practice Research Datalink (CPRD) linked to the Pregnancy Register (UK) and national registries (Sweden).

Research question and objectives:

The research question is, 'What is the impact of the implementation of the RMM and PPP on the use of valproate in WCBP in Europe?'

The aim of this study is to describe the prescribing practices before and after the dissemination of the new RMM (Q2 2018 – Q4 2018, depending on national competent authorities' approval) in Europe and to assess the effectiveness of these measures.

Primary objectives:

- To describe and compare the prescribing practices in WCBP receiving valproate during the pre- and post-implementation periods with respect to elements of the PPP (where available in each of the data sources) separately:
    - Use of contraceptives without interruption during treatment
    - Laboratory pregnancy tests before treatment
    - Treatment reviews by a specialist at least once per year (using a proxy of consultation by a specialist as a marker for treatment review)
    - Specialty of prescribing physician at initiation
- To describe and compare proportion of patients for which all elements of the PPP measurable with this DUS ext. are fulfilled, during the pre- and post-implementation periods
- To describe and compare the incidence of valproate exposed pregnancies, and characteristics of exposed pregnancies during the pre- and post-implementation period

Secondary objective:

- To describe and compare the following prescribing patterns in WCBP during the pre- and post-implementation periods, overall and in subgroups of patients:
    - Demographic characteristics of WCBP prescribed or dispensed valproate in oral form
    - Indication for use (epilepsy, bipolar disorder and other)
    - Use of prior medication for valproate indications before valproate initiation

Study design:

This is a non-interventional longitudinal retrospective cohort study of WCBP exposed to valproate, conducted with secondary data obtained from electronic medical records or administrative healthcare databases. The study design has been informed by logic models describing and defining the parameters to be measured in the study in the pre- and post-implementation periods.

A cohort of patients initiating valproate will be defined with a pre- and post-study design. This DUS ext. will cover the 36-month pre- and post-implementation periods related to the implementation of new (2018) RMM, and will be based on pre-existing databases recording prescriptions, patients' demographics and diagnosis, in the selected European countries (France, Germany, the Netherlands, Spain, Sweden and the UK).

Periods will be defined as follow:

Pre-implementation period (36-month duration): This period will capture 36 months before the end of the distribution of the EM. A transition period will be defined starting from PRAC recommendations announcement (February 2018) to the end of EMs distribution (6 to 11 months depending on the target country).

Post-implementation period (36-month duration): This period will capture the 36-month time starting after the end of the distribution of the EM approved by the respective national competent authorities. The start date varies by target country. These periods are country-specific because the dates of implementation of EM distribution vary by country.

Population:

The study population will include all WCBP prescribed valproate during the pre-defined periods identified from the healthcare databases selected. Users will be defined as:

- **Prevalent users** (includes recurrent and incident users): At least one valproate prescription issued (UK) or dispensed (all other countries) for patients with at least 12 months of history prior to index date.
    - **Recurrent users:** At least one valproate prescription issued (UK) or dispensed (all other countries) in the 12 months prior to the index date.
    - **Incident users**: No valproate prescription issued (UK) or dispensed (all other countries) in the database in the 12 months prior to the index date.
        - **First-ever user**s (*a sub-group of incident users)*: No valproate prescription issued (UK) or dispensed (all other countries) at any time in the database prior to the index date.

Among the study populations, sub-populations of interest will be:

- pregnant women
- valproate indication (epilepsy, bipolar disorder and other)

Inclusion criteria

- Female gender
- Age 13-49
- At least one prescription of valproate in the selected databases during the pre-defined periods

Exclusion criteria

- No exclusion criteria will be applied.

Variables:

The exposure is defined as one or more prescriptions or dispensations of valproate during one of the study periods. The following variables will be considered: patient age, use of medications for valproate indication in the 12 months before index date, prescriber specialty, as well as PPP-specific variables such as contraceptive use and - if available - pregnancy testing. In addition, information on exposed pregnancies and outcome (if available) will be provided.

Data Sources:

The following established longitudinal data sources will be utilised for data extraction:

France: SNDS
Germany: Statutory health insurance database in Germany (Gesetzliche Krankenversicherung) (GKV)
Netherlands: PHARMO database network (Out-Patient Pharmacy Database and Hospitalisation database) and Perinatal Registry (PRN)
Spain: SIDIAP, the Information System for the Development of Primary Care Research in Catalonia
Sweden: national drug-, patient-, and birth registers
UK: CPRD and CPRD Pregnancy Register

Study size:

All WCBP receiving valproate available in pre-defined periods of the selected databases will be included in the analysis.

The estimated number of WCBP receiving valproate according to an initial feasibility assessment in the selected databases was found to be 38,566 in France, 3,230 in Germany, 2,200 in the Netherlands, 2,754 in Spain, 5,739 in Sweden and 2,638 in the UK.

Data analysis:

Given the study objectives the analyses will be mainly descriptive and will be conducted by country and study time periods (both pre-implementation period and post-implementation period).

When applicable, quantitative variables will be statistically compared with a Student's t-test (parametric test) or Wilcoxon signed-rank sum test (non-parametric test, when necessary). Categorical variables will be statistically compared with a Pearson Chi^2 or with Fisher's exact test (if the expected frequency lower or equal to five for one or several cells). Each statistical test will be two tailed and will not be adjusted for multiple comparisons. As appropriate, 95% confidence intervals will also be calculated.

In addition, an interrupted time series (ITS) analysis will be considered in case the conditions for this analysis will be met. Results for key variables will be presented and visualised over time where patient numbers permit to provide insights on trends during the pre- and post-implementation periods.

Milestones

Protocol submission: December 2019

Registration in the EU Post-authorisation study (PAS) register: Planned, April 2020; actual, 28 April 2020

Anticipated start of data collection (extraction): Planned, August 2020; actual, August 2020

Anticipated end of data collection: Planned, August 2023; Actual October 2024

Interim report 1: Planned, February 2021; actual, 12 February 2021

Interim report 2: Planned, August 2021; actual, 13 August 2021

Interim report 3: Planned, February 2022; actual, 11 February 2022

Interim report 4: Planned, August 2022; actual, 21 September 2022

Final report: Planned, February 2024; Postponed to 22 July 2025

5 AMENDMENTS AND UPDATES

Version	Date	Summary of changes
Amendment 01 (Protocol Version 05)	10 February 2021	Updated German database from German Pharmacoepidemiological Research Database (GePaRD) to GKV (Statutory health insurance database in Germany or Gesetzliche Krankenversicherung). The following sections are updated: Section 2, 4, 5, 7, 9, 10, and 13
Amendment 02 (Protocol Version 06)	22 June 2021	Updated newly proposed alternative data sources in more detail in Section 9.4.2 In Table 1: Updated time periods for main period (data collection for main analysis) during pre-implementation period Updated post-implementation period (data collection) time period for Germany in Table 1 Updated footnote of Table 1 Updated Figure 2
Amendment 03 (Protocol Version 07)	17 September 2021	Updated wording in section 9.7.2.2 (user subgroups for evaluation of compliance to the Pregnancy Prevention Program)
Amendment 04 (Protocol Version 08)	26 January 2022	Figures 1-2, Table 1 and associated text in section 9.1 updated Information in Table 2 in section 9.4 corrected with regards to France, Spain and Sweden Sections 9.4.3 and 9.4.4 corrected with regards to description of the PHARMO Database Network and SIDIAP, respectively Link in section 9.4.5 updated Wording in section 9.7.2.2 further updated for clarity Section 9.9.2 updated with regards to statement on availability of data on induced abortions in Sweden and specialist visits in Spain, data lag times in the same countries, and handling of missing data on duration of contraceptives (all countries)

		Annex 1 and Annex 4 updated
Amendment 05 (Protocol Version 09)	27 May 2022	Section 9.1, Table 2 and Section 9.9.2 updated to align with the new reduced data lag in PRN in the Netherlands In Table 1, a typo in relation to the end of the pre-implementation main period corrected for Germany, the Netherlands, Spain and Sweden In Table 2, information on frequency of database updates per year added Figure 2 corrected in alignment with Table 1 for Germany Section 8 Secondary objective *"Use of prior medication for valproate indication"* has been updated to *"Use of prior medication for valproate indications before valproate initiation"* Section 9.3.4 (1) clarification of the variable medical history; (2) restriction of the medication use prior to valproate in the 12 months before index date to incident users and first ever users (since, for this population, medication history before index date is the medication history prior to valproate initiation); (3) valproate indication, add of use of valproate brand names in France to reclassify the patients in the unknown category; (4) Clarification of the prescriber specialty considered. Section 9.3.5 (1) clarification of the specialities of valproate prescribers at initiation; (2) correction on how contraceptives and pregnancy tests are captured in Spain Section 9.4.4 details added on drug prescriptions/dispensations in the Spanish data Section 9.5. Clarified Section 9.5.3 Study Sample Size updated, and estimated sample size of the Netherlands corrected in Table 5

		Section 9.7.2 Clarified Section 9.7.2.1 same updates as in Section 9.3.4 Sections 9.7.2.2 and 9.7.2.3 updated for clarity Section 9.7.4 (1) Sensitivity analysis excluding sterilised women prior to index date added; (2) Section updated for clarity Section 9.9.2 Alignment of information on the data lag in the PRN in the Netherlands and clarification on information on the specialty of physicians in referral letters in Spain
Amendment 06 (Protocol Version 10)	11 Oct 2022	Marketing authorization holders' list and responsible parties (Section 3) updated Section 4 (abstract) (1) statement on the length of the post-implementation period in pregnancy analyses added (2) non-rounded numbers provided for study sample size to match the numbers in section 9.5.3 (3) countries listed in alphabetical order as they are presented throughout the document Section 7.2 Rationale slightly amended for clarity Section 9.1 Study Design: (1) clarity provided on the length of the post-implementation period with distinction between analyses of prescription patterns and compliance to the PPP and pregnancy analyses (2) Clarity provided on analyses of post-implementation period for pregnancy (3) update of Table 1 and Figure 2 with this information

		Table 1 Time periods for the main (interim- and final) analyses, by country: (a) updates on study time periods planned for final analyses distinguishing between analyses related to prescribing practices and compliance to the PPP, and for analyses related to pregnancy. (b) Footnotes updated for clarity Figure 2 Time periods for primary and sensitivity analyses by report and country: (a) Germany and Sweden removed from IR4 as these countries were not included in the report. (b) additional information added to footnotes regarding the shortened length of the post-implementation period in analyses related to pregnancy. (4) unnecessary details on interim report plans and data lags removed Section 9.2 Text regarding databases used in DUS 1 and DUS ext. reformulated for clarity. Section 9.2.1 definition of user sub-groups removed from inclusion criteria so as not to repeat the information presented in section 9.3.2 Section 9.3.2 - subsection Definition of exposure during pregnancy reformulated for clarity Sections 9.3.3 - 9.3.4 sections revised for clarity

		Section 9.3.5 (1) specialities of valproate prescribers at initiation clarified and expanded to describe a new category “undefined specialty (hospital setting)” Section 9.3.6 (1) an overview on pregnancy identification is added Section 9.4, including Table 2, updated with regards to: (1) CPRD linkage to CPRD pregnancy register (2) pregnancy identification (all countries) (3) specialists’ visits in Spain (4) specialty of valproate prescribing physician (5) contraception in GKV Paragraph on the data lags in different countries moved from Section 9.9.2 Limitations of data sources to 9.4 Data Sources Sections 9.4.1 - 9.4.6: sections revised for clarity and details on pregnancy identification added Section 9.5 and subsections slightly updated for clarity Section 9.7.1: a description of the study periods and their durations was added Section 9.9.2: section updated with details related to contraceptives covered by insurance in Germany and information on specialist visits in Spain

Amendment 07 (version 11.0)	17 February 2023	Update the study milestones for a final report submission postponed to September 2024
Amendment 08 (version 12.0)	22 May 2023	Update the study milestones for a final report submission postponed to February 2025 to ensure a 36-month post-implementation period Remove all information regarding the proposed reduced post-implementation period for the pregnancy analysis
Amendment 09 (Version 13.0)	25 April 2025	Update of: • Document author name • List and contact details of represented MAHs • Responsibilities parties' names • Study milestones for a final report submission postponed to 22 July 2025

6 MILESTONES

The conditions to market authorisation stated in the PRAC assessment report define the following reporting requirement: The first interim report shall be submitted to the PRAC within 12 months after endorsement of the study protocol. Further interim reports, if any, should be submitted to the PRAC 6-monthly thereafter for the first 2 years and the final study report shall be submitted to the PRAC within 48 months after endorsement of the study protocol.

The planned dates for key study milestones are:

Milestone	**Planned date**	**Actual date**
Registration in the EU PAS register	April 2020	28 April 2020
Start of data collection (data extraction)	August 2020	August 2020
End of data collection (data extraction)	Estimated August 2023	October 2024
Interim report 1	February 2021 (within 12 months after endorsement of the study protocol)	12 February 2021
Interim report 2	August 2021 (within 6 months after 1st interim report submission to PRAC)	13 August 2021
Interim report 3	February 2022 (within 6 months after 2nd interim report submission to PRAC)	11 February 2022
Interim report 4	August 2022 (within 6 months after 3rd interim report submission to PRAC)	21 September 2022
Final report of study results	Estimated February 2024 (within 48 months after protocol endorsement by PRAC) Postponed to 22 July 2025	

7 RATIONALE AND BACKGROUND

7.1 Background

Valproate and related substances are licensed since 1967 to treat epilepsy and since 1995 to treat bipolar disorder in Europe. In some European Union (EU) countries, valproate is also indicated in prophylaxis of migraine attacks, indication which is supported by some but not all Marketing authorisation holders (MAHs).

In October 2014, the Pharmacovigilance Risk Assessment Committee (PRAC) concluded a review under Article 31 of Directive 2001/83/EC of all available data from published literature, spontaneous reports as well as the views of the relevant experts on the safety and efficacy of valproate and related substances in female children, in women of childbearing potential (WCBP) and pregnant women. Restrictions on the use of valproate containing substances were applied to the label.

The results of various utilisation studies in Europe showed that the pattern of use of valproate in WCBP had not changed significantly over 2014-2016 and indicated that valproate was still used by a considerable proportion of WCBP for both epilepsy and bipolar disorder indications. In March 2017, France triggered a referral under Article 31 of Directive 2001/83/EC and requested the PRAC to assess the impact of the risk minimisation measures (RMM) in the current pregnancy exposure of the treatment with medicinal products containing substances related to valproate and their impact on the benefit-risk balance.

Several consultations including a Public Hearing and two Scientific Advice Group meetings with Neurologists and Psychiatrists were held in September-October 2017. On 8 February 2018, the PRAC issued a recommendation including revised prescribing conditions in the product information, a Pregnancy Prevention Program (PPP) and revised educational measures.

Specifically, the contraindications as agreed by the European Commission's final decision and listed in Annex III (product information) are:

Treatment of epilepsy

- In pregnancy unless there is no suitable alternative treatment.
- In WCBP, unless the conditions of the PPP are fulfilled.

Treatment of bipolar disorder and prophylaxis of migraine attacks

- In pregnancy
- In WCBP, unless the conditions of the PPP are fulfilled.

The PRAC has also recommended that the outer packaging of all valproate medicines must include a visual warning about the risks in pregnancy and the need for effective contraception. In addition to boxed text, this may include a symbol/pictogram, with the details to be adapted at national level. A patient reminder card will also be attached to the outer package for pharmacists to discuss with the patient each time the medicine is dispensed.

Based on 8 February 2018 PRAC recommendation (EMA/67672/2018), the PPP for valproate and related substances includes:

- *Assessing patients* for the potential of becoming pregnant and involving the patient in evaluating her individual circumstances and supporting informed decision making.
- *Pregnancy tests* before and during the treatment, as needed.
- *Counselling* patients about the risks of valproate treatment and ensure timely discussions and switching to alternative treatment options prior to conception and before contraception is discontinued.
- Explaining the need for effective contraception, without interruption during the entire duration of the treatment with valproate.
- Carrying out *reviews of treatment* by a specialist experienced in the management of epilepsy, or bipolar disorders or migraine at least annually.
- Introduction of a new *risk acknowledgement form* that patients and prescribers will go through at each such review to confirm that appropriate advice has been given and understood.

The PPP addresses the issues of effective contraceptive use, pregnancy testing, and rigorous monitoring by the treating physician.

7.2 Rationale

Following the Co-ordination Group for Mutual Recognition and Decentralised Procedures-Human and European Commission's endorsement of PRAC recommendation, the companies that market valproate must carry out further studies to characterise the nature and extent of the risks posed by valproate and monitor ongoing valproate use and the long-term effects from affected pregnancies.

Particularly, the PRAC requested to conduct an initial drug utilisation study to assess the effectiveness of new RMM and to further characterise the prescribing patterns for valproate in clinical practice. The PRAC recommended the MAHs to continue the initial drug utilisation study (DUS 1) (final report was submitted in January 2019 with a data collection period ending in January 2018) and to amend the study design to include the updated conditions of use for valproate and related substances.

Since information about pregnancy and contraception was very limited in the data sources used for Germany, Spain and France with respect to pregnancy information in DUS 1, this study (DUS ext.) is amended to capture the updated conditions of use for valproate and related substances in different databases (i.e. Gesetzliche Krankenversicherung [GKV], Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària [SIDIAP] and Système National des Données de Santé [SNDS]). As recommended by the PRAC, an additional country has been added, the Netherlands, with Out-Patient Pharmacy Database and Hospitalisation database (PHARMO) and Perinatal Registry (PRN).

8 RESEARCH QUESTION AND OBJECTIVES

The overall research question is, ‘What is the impact of the implementation of the RMM and PPP on the use of valproate in WCBP in Europe?’

The aim of this study is to describe the prescribing practices before and after the dissemination of the new RMM (planned over Q2 2018 - Q4 2018, depending on approval by National Competent Authorities) and to assess the effectiveness of these measures.

The objectives of the DUS ext. are:

Primary objectives:

- To describe and compare the prescribing practices in WCBP receiving valproate during the pre- and post-implementation periods with respect to elements of the PPP (where available in each of the data sources) separately:
    - Use of contraceptives without interruption during treatment
    - Laboratory pregnancy tests before treatment
    - Treatment reviews by a specialist at least once per year (using a proxy of consultation by a specialist as a marker for treatment review)
    - Specialty of prescribing physician at initiation
- To describe and compare proportion of patients for which all elements of the PPP measurable with this DUS ext., are fulfilled, during the pre- and post-implementation periods
- To describe and compare the incidence of valproate exposed pregnancies, and characteristics of exposed pregnancies during the pre- and post-implementation periods

Secondary objective:

- To describe and compare the following prescribing patterns in WCBP during the pre- and post-implementation periods, overall and in subgroups of patients:
    - Demographic characteristics of WCBP prescribed or dispensed valproate in oral form
    - Indication for use (epilepsy, bipolar disorder and others)
    - Use of prior medication for valproate indications before valproate initiation

9 RESEARCH METHODS

9.1 Study Design

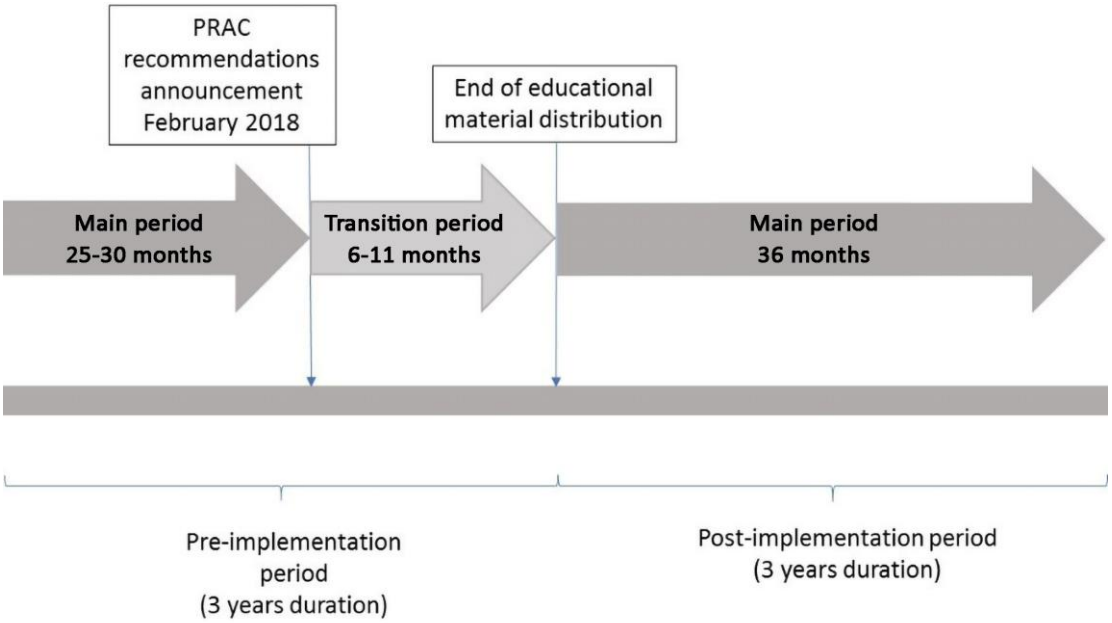
This is a non-interventional longitudinal retrospective cohort study of WCBP exposed to valproate, conducted with secondary data obtained from electronic medical records (EMRs) or administrative healthcare databases in 6 European countries (i.e. France, Germany, the Netherlands, Spain, Sweden, and the UK).

The study design has been informed by logic models describing and defining the parameters to be measured in the study in the pre- and post-implementation periods. A logic model is a graphic which represents the theory of how an intervention produces its outcomes. The periods are defined as (see Figure 1 and **Table 1**):

- **Pre-implementation period (36-month duration):** This period will capture 36 months before the end of the distribution of the Educational Materials (EM). This pre-implementation period will be considered as a baseline period and will be divided into two sub-periods in relation to the PRAC recommendation (February 2018):
    - **Main period (25-30 months' duration)**: Starting 36 months before the date of EMs distribution and ending at the date of PRAC recommendations announcement
    - **Transition period (6-11 months' duration):** Starting at the date of PRAC recommendations announcement and ending at the date of EM distribution.

  The purpose of the transition period is to define the time during which the different countries implemented the RMM (updated summary of product characteristics, patient leaflet and EM) following the PRAC recommendations in February 2018. For the purposes of the study design, this is included in the pre-implementation period in order to evaluate the impact of the implementation of the RMM once approved and distributed in each country.
- **Post-implementation period (36-month duration):** This period will capture the 36-month period starting at the end of the distribution of the EM approved by the respective national competent authorities. The start date will vary by target country.

Figure 1. Study periods



Abbreviations: PRAC: Pharmacovigilance Risk Assessment Committee

The final dates of the study periods depend on the final schedule of the implementation of the RMM in each country.

In total, four interim analyses and one final analysis are planned.

This study includes pregnancies that started during either of the study periods. Pregnancies are identified using country specific algorithms (described shortly in section 9.4) from events recorded during the pregnancy and/or after its completion (i.e., 9 months on average for live births) or by linkage to pregnancy registers. Thus, pregnancy identification requires either additional extraction of pregnancy data for running pregnancy identification algorithms (France, Germany and Spain) or a lag period to allow for pregnancies to be recorded in the respective pregnancy registers (the Netherlands, Sweden and the UK).

Details on study time periods planned for interim and final analyses as well as for single reports are presented in Table 1 and Figure 2 below.

Table 1. Time periods for the main (interim- and final) analyses, by country

	France	Germany	Netherlands	Spain	Sweden	UK
PRAC recommendations announcement on the prescribing practices	February 2018	February 2018	February 2018	February 2018	February 2018	February 2018
Distribution of DHPC/EM	July-October 2018	November 2018	December 2018	July 2018	September-October 2018	May-September 2018
Entire period (data collection)	01/11/2015-31/10/2021	01/12/2015-30/11/2021	01/01/2016-31/12/2021	01/08/2015-31/07/2021	01/11/2015-31/10/2021	01/10/2015-30/09/2021
Pre-implementation period (main + transition)	01/11/2015-31/10/2018 (36 months)	01/12/2015-30/11/2018 (36 months)	01/01/2016-31/12/2018 (36 months)	01/08/2015-31/07/2018 (36 months)	01/11/2015-31/10/2018 (36 months)	01/10/2015 – 30/09/2018 (36 months)
Pre-implementation main period (main analysis)	01/11/2015-31/01/2018 (27 months)	01/12/2015-31/01/2018 (26 months)	01/01/2016-31/01/2018 (25 months)	01/08/2015-31/01/2018 (30 months)	01/11/2015-31/01/2018 (27 months)	01/10/2015-31/01/2018 (28 months)
Pre-implementation transition period (sensitivity analysis)	01/02/2018-31/10/2018 (9 months)	01/02/2018-30/11/2018 (10 months)	01/02/2018-31/12/2018 (11 months)	01/02/2018-31/07/2018 (6 months)	01/02/2018-31/10/2018 (9 months)	01/02/2018-30/09/2018 (8 months)
Post-implementation period	01/11/2018-31/10/2021 (36 months)	01/12/2018-30/11/2021 (36 months)	01/01/2019-31/12/2021 (36 months)	01/08/2018-31/07/2021 (36 months)	01/11/2018-31/10/2021 (36 months)	01/10/2018-30/09/2021 (36 months)
Interim analysis 1 for Interim Report 1 (February 2021)	----	----	----	01/08/2015-31/07/2018	01/11/2015-31/10/2018	01/10/2015-30/09/2018
Interim analysis 2 for Interim Report 2 (August 2021)	----	----	----	----	----	01/10/2015-30/09/2019
Interim analysis 3 for Interim Report 3 (February 2022)	01/11/2015-31/10/2019	----	01/01/2016-31/12/2019	01/08/2015-31/07/2019	----	01/10/2015-30/06/2020
Interim analysis 4 for Interim Report 4 (August 2022)	----	----	----	----	----	01/10/2015-31/03/2021
Final analysis for Final Report (February 2025)*	01/11/2015-31/10/2021	01/12/2015-30/11/2021	01/01/2016-31/12/2021	01/08/2015-31/07/2021	01/11/2015-31/10/2021	01/10/2015-30/09/2021

* Pregnancies are identified in each database using on-going pregnancy information and/or pregnancy outcome. Therefore, the identification of all pregnancies which started during the study period would require observing a period of 3 months (Germany) or 10 months (all other countries) after the end of the post-implementation period.
Additional pregnancy data, beyond the entire study period, needs to be extracted in France (01/11/2021-30/11/2021) and in Spain (01/08/2021-30/11/2021) to allow the full pregnancy identification. While in France, the CNIL (Commission Nationale de l'Informatique et des Libertés) authorisation allows the use of data of the full year 2021, in Spain a submission of the PRAC-approved protocol to the ethics committee is required to allow the extraction of those data beyond the entire study period.
In the Netherlands, Sweden and the UK, pregnancy data are directly identified from the respective pregnancy registers (PRN in the Netherlands, MBR in Sweden and CPRD Pregnancy registry in the UK), and linked to the main data source in each country before data extraction. Hence, it is not needed to extract 10-month data beyond the study period for the pregnancy identification. However, data would only be available after those 10 extra months and according to the availability of data in each of the databases.
Abbreviations: CPRD: Clinical Practice Research Datalink, DHPC: Direct healthcare professional communication, EM: Educational materials, MBR: Medical Birth Registry, PRN: Perinatal Registry, UK: United Kingdom.

Figure 2. Time periods for primary and sensitivity analyses, by report and country

	Primary analysis		Sensitivity analysis
	Pre-implementation main period	Post-implementation period	Pre-implementation transition period*
Interim Report 1			
Spain	01/08/15-31/01/18 (30 months)		01/02/18-31/07/18 (6 months)
Sweden	01/11/15-31/01/18 (27 months)		01/02/18-31/10/18 (9 months)
UK	01/10/15-31/01/18 (28 months)		01/02/18-30/09/18 (8 months)
Interim Report 2			
UK	01/10/15-31/01/18 (28 months)	01/10/18-30/09/19 (12 months)	01/02/18-30/09/18 (8 months)
Interim Report 3			
France	01/11/15-31/01/18 (27 months)	01/11/18-31/10/19 (12 months)	01/02/18-31/10/18 (9 months)
Netherlands	01/01/16-31/01/18 (25 months)	01/01/19-31/12/19 (12 months)	01/02/18-31/12/18 (11 months)
Spain	01/08/15-31/01/18 (30 months)	01/08/18-31/07/19 (12 months)	01/02/18-31/07/18 (6 months)
UK	01/10/15-31/01/18 (28 months)	01/10/18-30/06/ (21 months)	01/02/18-30/09/18 (8 months)
Interim Report 4			
UK	01/10/15-31/01/18 (28 months)	01/10/18-31/03/21 (30 months)	01/02/18-30/09/18 (8 months)
Final report			
France	01/11/15-31/01/18 (27 months)	01/11/18-31/10/21 (36 months)	01/02/18-31/10/18 (9 months)
Germany	01/12/15-31/01/18 (26 months)	01/12/18-30/11/21 (36 months)	01/02/18-30/11/18 (10 months)
Netherlands	01/01/16-31/01/18 (25 months)	01/01/19-31/12/21 (36 months)	01/02/18-31/12/18 (11 months)
Spain	01/08/15-31/01/18 (30 months)	01/08/18-31/07/21 (36 months)	01/02/18-31/07/18 (6 months)
Sweden	01/11/15-31/01/18 (27 months)	01/11/18-31/10/21 (36 months)	01/02/18-31/10/18 (9 months)
UK	01/10/15-31/01/18 (28 months)	01/10/18-30/09/21 (36 months)	01/02/18-30/09/18 (8 months)

**Although the sensitivity analysis includes the pre-implementation main plus transition period, only the dates for the transition period are displayed here.*
Abbreviations: UK: United Kingdom

9.2 Setting

The selection of databases for the DUS ext. is based on the experience acquired during the currently running post-authorisation safety study (PASS) for valproate. The crucial point for the selection of data sources was a sufficient number of WCBP valproate users for the study and the provision of information on pregnancy.

Based on these criteria it was decided to keep databases used in the previous DUS 1 in the UK (CPRD) and in Sweden (National Health Registers) and to include the SNDS database in France, GKV in Germany and SIDIAP in Spain. In addition, PHARMO with data from the Netherlands will be included to increase coverage of the European territory. Countries for the DUS ext. were selected based on the following criteria:

- Countries in which the number of exposed patients was high based on market share
- Coverage of different regions in Europe
- Availability and accessibility of patient-level databases
- Availability of the information required to meet the study objectives (i.e., pregnancy, elements of the PPP)

9.2.1 Inclusion Criteria

The study population will include all WCBP receiving valproate prescriptions/dispensations during the pre-defined periods (pre- and post-implementation periods) in the selected databases of European target countries (France, Germany, the Netherlands, Spain, Sweden and the United Kingdom). Patients will be included in the respective study cohorts, if they have:

- Female gender,
- Age 13-49 years inclusive,
- At least one prescription/dispensation of valproate in the selected databases during the pre-defined periods.

9.2.2 Exclusion Criteria

- No exclusion criteria will be applied.

9.3 Variables

In order to meet the objectives of the DUS ext., the selection of variables was done with respect to the key elements requested by the PRAC as far as they are captured in established data sources.

9.3.1 Index Date

The index date will be defined as the date of first prescription issued (UK) or dispensed (other countries) for valproate within the study period.

9.3.2 Exposure Definition and Measures

<u>Definition of exposure:</u>

Exposure will be defined as one or more prescriptions of valproate (issued or dispensed) during one of the pre-defined study periods. Brand names and generics of all oral forms of valproate salts will be considered (sodium valproate, valproic acid, valproate semi sodium, valpromide, valproate magnesium) and summarised under the term 'valproate'.

Exposure will be described by prescription start, duration and (average) daily dose. It will be assumed that all prescriptions and their associated dates recorded in the databases reflect actual prescription fills and subjects will begin exposure at the index date.

The following variables will be extracted from the data sources:

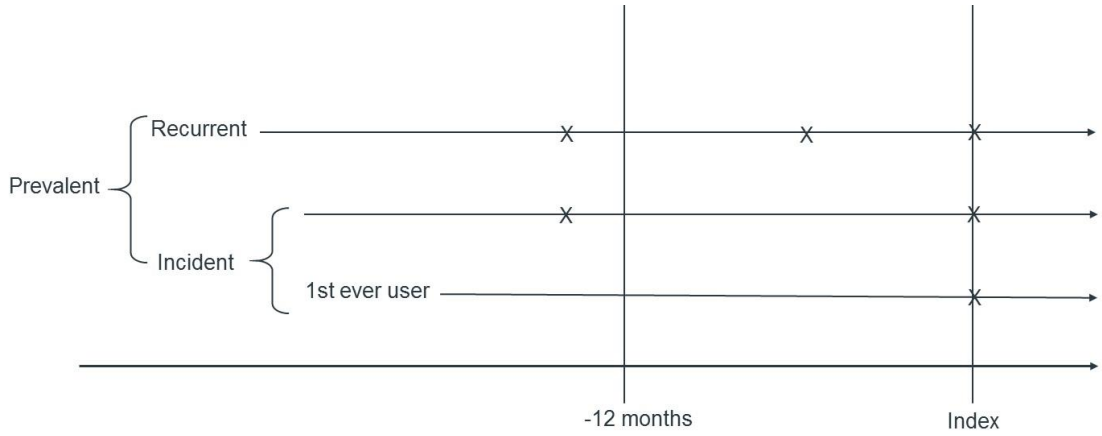
- Active substance
- Date of prescriptions issued (for CPRD in UK) or dispensed (other countries)
- Pack size or days' supply
- Strength
- Recommended dose (if available)

We will define the sub-groups of users as follows:

- **Prevalent users** (includes recurrent and incident users): At least one valproate prescription issued (UK) or dispensed (other countries) for patients with at least 12 months of history prior to index date.
    - **Recurrent users:** At least one valproate prescription issued (UK) or dispensed (other countries) in the 12 months prior to the index date.
    - **Incident users**: No valproate prescription issued (UK) or dispensed (other countries) in the database in the 12 months prior to the index date.
        - **First-ever user**s (a *sub-group of incident users):* No valproate prescription issued (UK) or dispensed (other countries) at any time in the database prior to the index date.

Patients with less than 12 months of history before index date will be described, but not included in the analysis.

Figure 3. Definitions for sub-groups of users



<u>Definition of exposure during pregnancy:</u>

Pregnant women exposed to valproate use will be presented as a pre-specified sub-group. In order to provide data that will be comparable to the ones provided in the literature [Blotière et al., 2018], we set the exposure window to be defined as 30 days before the estimated first day of pregnancy to the end of pregnancy. Valproate exposure will be stated in case of overlapping prescription/dispensation duration of valproate treatment with this exposure window. In order to cover all potential valproate treatments that would be ongoing at the start of the exposure window defined above, we will search for any prescription/dispensation in a look-back period up to 6 months before the estimated start of pregnancy.

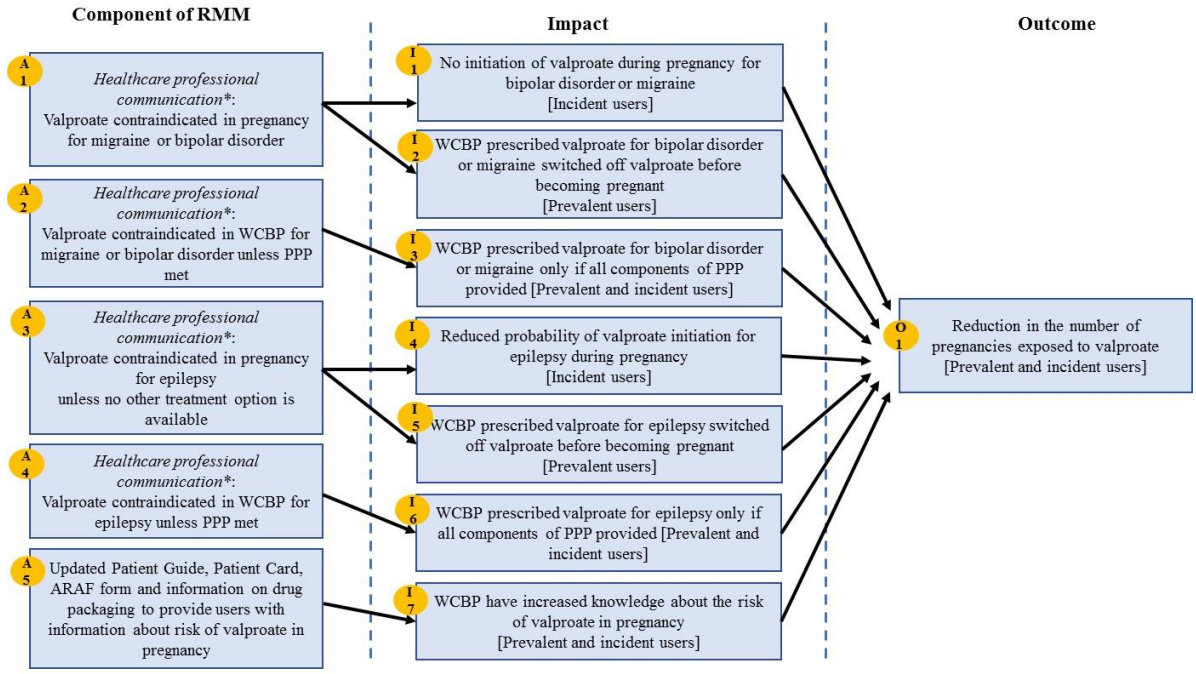
9.3.3 Assessment of the effectiveness of the RMM

Assessment of the effectiveness of the RMM will be evaluated according to the assumed programme logic (i.e., the hypothesised mechanisms of action) for the RMM and PPP. This logic is described as logic models [Moore et al., 2015] in Figure 4 (RMM) and Figure 5 (PPP), which lay out in graphical form the mechanisms by which the components of the RMM and PPP are hypothesised to lead to reduced numbers of pregnancies exposed to valproate.

Each of these logic models includes the components of the RMM (A1-A5) and PPP (a1-a7). These are linked to the hypothesised Impacts (I-7 and i-7), assuming that the RMM and PPP have their intended effects. In turn, these Impacts lead into the intended Outcome (O1; a reduction in the number of pregnancies exposed to valproate).

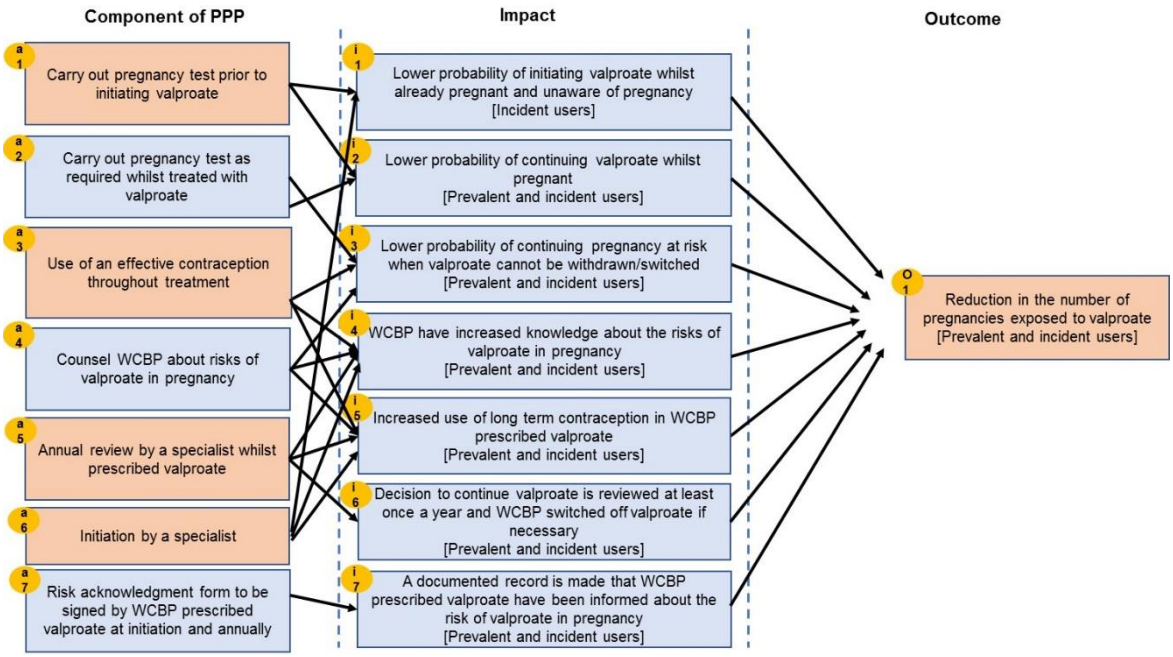
The aim of including the logic models is to make explicit the prior hypotheses about the intended mechanism of action of the RMM and PPP which have guided the design of the DUS ext. It is important to note that the models do not make any claims about the strength of association between each component in the model, or which components of the RMM and PPP are most important in reducing the number of pregnancies exposed to valproate. Similarly, the models are not intended to capture all the potential factors influencing causality in relation to the study question.

Figure 4. Logic model for the Risk Minimisation Measures



Abbreviations: ARAF, Annual Risk Acknowledgement Form; DHPC, Direct Healthcare Professional Communication; HCP, Healthcare Professional; PPP, Pregnancy Prevention Programme; RMM, Risk Minimisation Measures; WCBP, Women of Childbearing Potential

Figure 5. Logic model for the PPP



Abbreviations: PPP, Pregnancy prevention programme; WCBP, Women of childbearing potential

These logic models formally illustrate that:

- Not all the elements of the of the PPP (Impacts: i4, i7) and RMM (Impacts: I3, I6 and I7) can be evaluated in a database study using real world data
- Different elements of the RMM and PPP are relevant to different patient sub-groups (by indication, user type), and hence need to be evaluated in the appropriate sub-groups

However, components of the PPP (as per Primary Objective) that are measurable in DUS ext. (a1, a3, a5, a6) as well as the outcome of PPP (o1), denoted by orange squares in Figure 5, will be used in the assessment of the effectiveness of the RMM.

Hence, incidence rate of valproate exposed pregnancies as well as the proportion of patients for which all elements of the PPP measurable with this DUS ext. are fulfilled, will be used as main indicators to assess effectiveness of the RMM with this DUS ext., in line with the primary objective of DUS ext.

9.3.4 Demographics and prescribing practice

To describe the prescribing practices of valproate before and after the dissemination of RMM, the following variables will be considered (where available in the data sources):

- Patient demographics (age of included patients at the index date)
- Medical history with respect to diagnoses of epilepsy, bipolar disorder and other diagnoses (other psychiatric disorders and migraine) related to valproate indication coded by International Classification of Diseases, Tenth Revision (ICD-10) or

Read code in the UK (epilepsy, bipolar disorder and other, for code list please refer to Annex 3.2) up to 10 years before index date

- Indication for valproate prescription, determined based on:
    - Medical history: Diagnoses coded by ICD-10 or Read code in the UK (epilepsy, bipolar disorder and other, for code list please refer to Annex 3.2) at index date or, if unavailable, up to 10 years before index date
    - Medication history (incident users): use of medications related to valproate indication (epilepsy or bipolar disorder) in the 12 months prior to index date (for Anatomical Therapeutic Chemical [ATC] codes please refer to Annex 3.1)
    - Valproate product's brand-name at index date in France: considering that brand-names of valproate products in France are specifically labelled for either epilepsy or bipolar disorder
- Specialty of prescribing physicians (not available in CPRD for UK): Any Specialty (Neurologist, Psychiatrist, Paediatrician), General Practitioner, Other, Unspecified specialist (only available for France), Missing
- Laboratory pregnancy tests (based on availability in each data source) during valproate treatment
    - Prescription/dispensation of pregnancy tests (blood or urine) recorded in the databases (type, and date of prescription/dispensation)
    - Records (i.e., ICD-10 or Current Procedural Terminology [CPT] codes in Annex 3.5) which document the performance of a pregnancy test (date of test/record)

9.3.5 Compliance to the PPP in WCBP

Compliance to elements of the PPP will be evaluated using the following variables:

- Specialty of prescribing physician at initiation (for incident users) (not available in CPRD for UK)
    - Any Specialty (Neurologist, Psychiatrist, Paediatrician)
    - General Practitioner
    - Other: specialties other than neurology, psychiatry, paediatrics, and general practice
    - Undefined specialty (hospital setting): missing information on prescriber specialty, but the prescription originated from hospital settings (only available in France)
    - Missing: missing information on prescriber specialty, and either the prescription originated from non-hospital settings or the origin of the prescription is unknown
- Records of contraception or sterilisation in the medical history
    - Prescription/dispensation of contraceptives (other than Intra uterine device [IUD]) before and during valproate treatment
        - In all countries a look-back period of 12 months (for hormonal contraceptives for systemic use, hormonal patches and vaginal rings) to 3 years (for hormonal implants) before valproate prescription/dispensation will be used to research prescriptions issued

(Spain, UK) or dispensed (all other countries) of contraceptives (for ATC codes for hormonal contraception please refer to Annex 3.3)
    - Prescription of IUD
        - Date of prescription issued (Spain, UK) or dispensed (all other countries) will be searched up to 5 years before valproate prescription (UK)/dispensation (all other countries) as well as procedure for IUD implantation and removal (for ICD-10 codes for IUDs please refer to Annex 3.4)
    - Record for hysterectomy, surgical sterilisation or bilateral oophorectomy using a look-back period up to 10 years before index date (for ICD-10 codes for sterilisation please refer to Annex 3.4).

Concomitant use of contraception will be measured with respect to valproate exposure using an adaptation of the Proportion of Days Covered (PDC) methodology. This will take a person-time approach to estimate of the proportion (%) of days of valproate exposure where the patient was also covered by an effective form of contraception, adjusting for overlaps in prescription/dispensation of oral contraceptive. The PDC accounts for both adherence and persistence of effective contraceptive during the time period the patient is exposed to valproate.

The PDC with contraception will be calculated as a percentage, where the denominator is the number of days from the date of first valproate prescription in the study period until the date of discontinuation of valproate or end of follow-up (whichever occurs first). The numerator will be calculated as the number of days covered by a prescription for contraception. Prescriptions for oral contraceptives will be adjusted for overlaps in supply. Switching between contraceptives will be allowed as contributing to the days covered by effective contraception. The method for defining the time period covered by effective contraception will vary according to the type of contraceptive method.

- Laboratory pregnancy tests (based on availability in each data source) at initiation of valproate treatment (incident users)
    - Pregnancy tests (blood or urine) recorded in the databases (type, and date of test)
    - Records (i.e., ICD-10 or CPT codes in Annex 3.5) which document the performance of a pregnancy test (date of record)

  Prescription issued (UK, Spain) of a pregnancy test / procedure or ICD-10 code (all other countries) / laboratory result (Spain) signalling a pregnancy testing will be searched up to 1 month before and 1 month after the date of valproate prescription issued (UK)/dispensed (all other countries).
- Annual visits to a specialist within the specialty related to valproate indication (e.g., neurologist, psychiatrist, paediatrician).

9.3.6 Pregnancies

9.3.6.1 Pregnancy identification

The process to identify pregnancies varies across countries. Depending on algorithms used, pregnancies are identified through on-going pregnancy records and/or pregnancy outcome. In Germany, data from the first pregnancy trimester is used to identify pregnancies which started during the study period, while in other countries, pregnancy outcome is necessary for pregnancy identification. Therefore, a maximum of 10 months of extra data beyond the end of the study period is needed to identify each pregnancy starting within the study period (3 months for Germany and 10 months for other countries).

While in France, Germany and Spain, the algorithm for the pregnancy identification will be applied on data extracted from the respective country databases (SNDS in France, GKV in Germany and SIDIAP in Spain) needing data extraction beyond the study period, in the Netherlands, Sweden and the UK, information on pregnancies will be directly extracted from pregnancy registries (PRN in the Netherlands, MBR in Sweden and CPRD Pregnancy registry in the UK) and linked to the main data source in each country. However, those data will be fully available only after these 10 extra months beyond the study period and for all countries according to the lag time necessary for the data availability.

9.3.6.2 Pregnancy exposure and pregnancy outcomes

Exposure will be stated in case of overlapping prescription/dispensation duration of valproate treatment with the exposure window defined as follows: 30 days before the estimated first day of pregnancy to the end of pregnancy. In order to cover all potential valproate treatments that would be ongoing at the start of the exposure window defined above, we will search for any prescription/dispensation in a look-back period up to 6 months before the estimated start of pregnancy.

The following will be provided per country, per indication (epilepsy, bipolar disorder and others) and separately for the pre- and post-implementation period:

- Age at pregnancy start date
- Use of hormonal contraceptive or IUD before pregnancy
- Exposure to valproate in the period before (during the 30 days prior start of pregnancy), during (in days per trimester) and after pregnancy
- Start of valproate during pregnancy if any
- Discontinuation of valproate
    - before pregnancy
    - during pregnancy
    - alternative treatment used after valproate discontinuation
- Number of valproate prescriptions during pregnancy
- Average daily dose of valproate
- Visit to a specialist experienced in teratology/foetal abnormalities (gynaecologist, obstetrician, midwife) during pregnancy

- All the diagnoses and procedures, related to pregnancies and pregnancy outcomes (i.e., live birth, miscarriage, early termination, stillbirth, or recorded birth defect) will be searched in databases according to data availability. The relevant code lists are specified in Annex 3.6.

9.4 Data Sources

All information on exposure and outcomes will be derived from established secondary longitudinal data sources. The type of data may vary be country between claims, national registries, and EMR.

Data sources are considered for the DUS ext. based on enough patients on valproate and the availability of information relevant to describe the effectiveness of the updated PPP. Based on these criteria the following data sources will be considered (see Table 2 for more details):

- SNDS in France
- GKV in Germany
- PHARMO database network in the Netherlands and PRN
- SIDIAP in Spain
- National Health Registers in Sweden
- CPRD and CPRD Pregnancy Register in the UK

Note in relation to data lag time: The databases used for France, the Netherlands and Sweden are updated once a year. The annual update of the French claims database is available between July and September of the year adding data for an entire calendar year (2016 data was available in mid-July of 2017). Data in Spain requires 3 months to update. However, updated data is made available biannually (March and September) for the entire preceding year (The release of March 2022 would comprise data, including records of pregnancy outcome, up to 31 December 2021). Database updates for Germany (GKV) for year n is completed in year n + 16 months (16 months' lag). The Swedish National Patient Register annual update is completed in Q3 of the following year. There is also a possibility to receive monthly data earlier. However, monthly data are less quality-assured and, thus, more prone to changes and missingness. The Medical birth registry in Sweden update for year n is completed in December of year n+1. A similar situation is encountered for PHARMO PRN with an update for year n completed in year n + 16 months. Data in the UK is generally updated and made available every 3 months.

Table 2. Summary of various databases being considered for the DUS ext.

Country	**France**	**Germany**	**Netherlands**	**Spain**	**Sweden**	**UK**
Data source description						
Name and Type	***SNDS*** Claims database	***GKV*** Claims database	***PHARMO Database Network*** Out-patient Pharmacy Database, Hospitalisation Database and PRN	***SIDIAP*** EMR database	***National Health Registers*** National Drug-, Patient- and Birth registers	***CPRD*** GP's EMR database, Pregnancy Register
Overall representativeness	88% of French population	7% of the general Statutory health insurance population	25% of the general population	74% of Catalonian population	Complete coverage for Sweden	~6.9% of UK population
Size of the panel	All health insurance schemes in office-based care and hospitalisation	Statutory health insurance provider covering approx. 5 million statutory health insured people per year	4.2 million	About 5 million active people and about 7 million active, transferred and dead people	Specialist and hospital out- and in-patient care and all drugs dispensed for the Swedish population	11.3 million total, 4.4 million active
Data available since	2009	2008	1998	2005	2005 (1997)	1993
Data lag time (to access the last updated data)	9 months	~16 months	~12 months for pharmacy and hospital data, ~16 months for linkage with PRN	6 months	National Drug registry: 1 month National Medical Birth Registry: 12 months National Patient registry: 9-21 months	~1 month

Country	France	Germany	Netherlands	Spain	Sweden	UK
Data source description						
Frequency of database updates, per year	1	1	PHARMO (Out-patient Pharmacy Database): 1 PRN: 1	Generally: 2 Mother-baby linkage: 1	National Patient Register, Medical Birth Register: 1 National Drug Register: 12	Generally: continuously updated Pregnancy register: 4 (starting from May 2022)
Availability of parameters of interest						
Demographics (age)	Available	Available	Available	Available	Available	Available
Diagnosis	Available; ICD-10 codes	Available ICD-10-GM	Can be derived from surrounding diagnosis as well as proxy based on prescriber and medication history	Available; ICD-10-CM codes	Available; ICD-10 codes	Available; Read codes
Information on specialists' visits	Available	Available (date and doctors' specialty)	In- and out-patient visits and procedures (out-patients visits from 2016 onwards)	- Referrals from primary care - Visits to specialists working in primary care settings - Visits to secondary care specialists using e-CAP	Available	Referrals only

Country	France	Germany	Netherlands	Spain	Sweden	UK
Data source description						
Records of pregnancy tests	- Laboratory blood/urine tests performed - Not available: urinary test delivered in pharmacies or elsewhere	Only reimbursed tests are available via German out-patient reimbursement code, Einheitlicher Bewertungsmaßstab (EBM)	Only urinary tests delivered in pharmacy (reimbursed and not reimbursed)	Only urinary or blood tests performed	Only urinary or blood test performed	Only urinary or blood test prescribed by GPs
Record of contraception*	- Only reimbursed contraceptives - Sterilisation procedures are captured	- Only reimbursed contraceptives (limited to women aged <20 years, since 2019 women aged <22, and to women with specific medical conditions) Sterilisation procedures are captured	- All contraceptives dispensed (including non-reimbursed ones) - IUD are poorly captured - Sterilisation procedures are captured up to 2016	- Only contraceptives reimbursed and prescribed by primary care physicians - IUD are poorly captured - Sterilisation procedures are poorly captured	- All contraceptives prescribed (all are reimbursed in Sweden) - IUD are poorly captured - Sterilisation procedures are captured	- Only contraceptives prescribed by GPs or applied in the GP practice (e.g., IUD) - Sterilisation procedures are captured
Drug information for valproate (date of prescription, pack size, strength)	Available	Available	Available	Available	Available	Available

Country	France	Germany	Netherlands	Spain	Sweden	UK
Data source description						
Specialty of valproate prescribing physician	Available (specialty of the prescribing physician is directly associated to the dispensation)	Available (specialty of the prescribing physician is linked to each dispensation)	Available (specialty of the prescribing physician is directly associated to the dispensation)	Available (prescriber´s specialty for each dispensation derived from referral letters (if available) or the respective prescription (if available) issued by a physician of primary or of (scarcely) secondary care).	Available (specialty of the prescribing physician is linked to the drug dispensation)	Not available
Pregnancy record	Available	Available	Available	Available	Available	Available
Pregnancy outcomes	Available	Available	Available	Available	Available	Available

*Including:

- Oral hormonal contraception
- Copper based intrauterine device
- Hormone-based intrauterine device
- Hormone-based implants
- Vaginal ring
- Transdermal hormone patch
- Depot hormone-based injection
- Female sterilisation

Note: Other forms of contraception including barrier contraceptives, spermicides or sterilisation of male partner are not captured in any database.

Abbreviations: CPRD, Clinical Practice Research Datalink; e-CAP, Estació Clínica de treball d'Atenció Primària (clinical work station of primary care); EMR, Electronic Medical Record; GKV, Gesetzliche Krankenversicherung; ICD-10, International Classification of Diseases; Tenth Revision; ICD-10-CM/GM, International Classification of Diseases - Tenth Revision - Clinical

Modification/German Modification; GPs, General practitioners; IUD, Intra Uterine Device; PHARMO, Institute for Drug Outcomes Research; PRN, Perinatal Registry; SIDIAP, The Information System for the Development of Primary Care Research in Catalonia; SNDS, Système National des Données de Santé; UK, United Kingdom.

9.4.1 France - SNDS

The SNDS is a claims database, following the National Health Insurance expenses. The SNDS database is the largest and most comprehensive healthcare dataset available in Europe. It is a claims database covering all the Health Insurance schemes based on individuals' employment status in office-based care and hospitalisation and is individualised by beneficiary. The general health insurance plan covers employees in the industry, business, and service sectors; public service employees; and students, accounting for approximately 88% of the French population.

With this large sample size (57 million) of beneficiaries of the French General scheme, the SNDS provides a comprehensive and detailed health information, relevant and very useful for epidemiological and health economic studies [Tuppin et al., 2017]. The Real World Solutions department of IQVIA France has received the approval to conduct this study.

In 2018, an algorithm was published to identify pregnancy episodes in the French healthcare database [Blotière et al., 2018]. This algorithm is based on information recorded during pregnancy, including its outcome. To fully identify all pregnancies starting during the study period, extra data beyond its end is needed (up to 10 months to consider a possible period of hospitalization after delivery, as data on pregnancy outcomes might not get recorded until hospital discharge).

The data of medical services listed all the closing transactions related to the payment of services to the beneficiaries. These files include information related to the care recipient, the type of care giver, the type of care and the monetary flows induced. However, in these files of medical services, some health consumptions cannot be seen, such as consumptions not claimed for reimbursement, not reimbursable health services or self-medication.

The primary purpose of the SNDS is to determine the costs for all National Health Insurance System schemes in office-based care (Système National d'Information Inter-Régimes de l'Assurance Maladie [SNIIRAM]) and hospitalisation (Programme de medicalisation des systèmes d'information (PMSI) databases) and individualised by beneficiary. The SNIIRAM is linked to the PMSI. The PMSI is a comprehensive national database which classifies all hospital stays in all public and private healthcare institutions in France. PMSI access is managed by the Hospitalisation Information Technical Agency . PMSI data covers three different types of care centres:

- Acute care (Short duration stays) at hospital: the PMSI MCO (Médecine, chirurgie, obstétrique)
- Home hospitalisations stays: the PMSI HAD (Hospitalisation à domicile)
- Follow-up and rehabilitation care stays: the PMSI Hospitalisation à domicile SSR (Soins de suite ou de réadaptation)

In the PMSI, a unique identifier for each patient makes it possible to track the hospital course of patients over the years. PMSI data are updated once a year with the data from the full previous year.

Available data are:

- Demographic: age, gender, place of residence, and date of death at hospital
- Medical: diagnoses (main, related and associated), medical procedures performed (including surgeries), duration of stay, and month of hospital discharge
- Economic: fee schedule associated with each hospital stay, with additional costs for medicinal products and medical devices from the 'liste en sus', since 2009.

Diagnoses are coded in the database according to the ICD-10 and expensive drugs and devices with major benefits for patients are charged apart from the global stay's cost and are recorded in a specific list of drugs, the 'liste en sus'.

The SNIIRAM database has previously been used to evaluate the compliance with PPP recommendations in WCBP exposed to retinoids [Raguideau et al., 2015]. SNIIRAM has also been used for several other drug utilisation and safety studies, showing its validity for the evaluation of a wide range of populations and outcomes [Bouillon et al., 2018; Miranda et al., 2017; Weill et al., 2016] including studies on valproate utilisation and associated risks [ANSM, 2016, 2017].

9.4.2 Germany - GKV

Data in Germany is based on the Betriebskrankenkassen health insurances, which is part of the German GKV (Statutory Health Insurance) and is facilitated by Team Gesundheit. This data covers a total of ~5 million patients (~7% of all statutory insured patients) per year. The available datasets cover registration, out- and in-patient care, reimbursed drug prescriptions, sick leave and sick benefits, prescription of medical aids and other service (e.g., therapies). The data is updated with a lag of ~16 months.

Based on an overall-anonymised ID, data on patient-level can be analysed in all the datasets mentioned below. Also, the medical history of individuals can be examined longitudinally over several quarters or years. Patient-level data will be analysed within GKV and the German IQVIA team will only receive aggregated table outputs based on the statistical analysis plan (SAP) and the protocol.

The information on the following datasets is available:

- **Registration data**
  - Patient ID, year
  - Age, gender, and year of birth
  - Time insured: start date of the insurance policy (Number of days insured)
  - Employment status of the insured person (employed, family insured, retired etc.)
  - Start and end of employment
  - Regional distribution (places of residence) of the insured persons
- **Out-patient care**
  - Patient ID
  - Date of treatment
  - Code identifying the group of the physician in charge
  - ICD-10-GM diagnosis

- Additional information on ICD codes, such as ‘assured’, ‘exclusion of’, ‘status after’
- Operation and procedure code (OPS) code
- Reimbursement codes (Einheitlicher Bewertungsmaßstab [out-patient reimbursement code], billed Gebührenordnungsnummern according to EBM-Codes, [German system of medical remuneration for out-patient services]) and related costs

Outpatient care data are prepared quarterly. In exceptional cases, data analyses on a daily basis are possible.

- **In-patient care**
  - Patient ID
  - Date of hospitalisation and of discharge/total days of hospitalisation
  - Up to 30 OPS-codes per case
  - Medical department of the first diagnosis
  - Medical department of the involved hospital
  - First mandatory diagnosis (primary diagnosis, up to three available) and secondary diagnosis (up to 10 per main diagnosis, up to 30 in total, ICD-10-GM)
  - Cost of hospitalisation
  - Billed Diagnosis related groups (DRG) (German classification) and related costs
- **Drug prescriptions**
  - ATC Code of prescribed medications and related costs
  - PZN (Pharmazentralnummer) of prescribed medications
  - Usage of PZN offers to identify the content quantity of a prescribed medication package and information on substance concentrations (e.g., for calculation purposes of defined daily dose)
  - Prescription date (on a daily basis)
  - Specialty of the prescribing physician
  - Prescribed product (on Pharmazentralnummer, German National Drug Code [PZN]-level)
  - Prescribed amount, dosage
  - Receipt number
  - Receipt number links all medications prescribed at the same time.
- **Sick leave & sick benefits**
  - ICD-10-GM diagnoses
  - Duration of sickleave
  - Sum of sick benefits by sickleaves
- **Prescriptions of medical aids**
  - Identification code of medical aids and related costs
  - Date of prescription (on a daily basis)
  - Receipt number
- **Remedies**
- **Other benefits/miscellaneous**

- **Other services (among other things, remedies, cures and individual prevention courses)**
  - Type of service and related costs
  - Onset and end of services (on a daily basis)

The data does not contain information on the following entities:

- Lab values
- Outcomes
- Emergency department visits, physical/occupational therapy visits and ancillary care visits

Information on pregnancies is derived from EBM codes recorded in the database. The identification of a pregnancy is based on the first pregnancy related record (mainly during first pregnancy trimester). To fully identify all pregnancies starting during the study period, at least 3 months of extra data beyond its end is needed to allow all pregnancies identification.

GKV data was already used for scientific publications, including studies performed by IQVIA [Claessen et al., 2018; Clouth et al., 2018; Sittig et al., 2015].

9.4.3 Netherlands - PHARMO Network and PRN

The PHARMO Database Network is a dynamic cohort of participants that includes, among other information, drug-dispensing records from community pharmacies (Out-Patient Pharmacy Database) for more than four million individuals in the Netherlands (approximately 25% of the Dutch population) collected since 1991. The drug-dispensing data contain the following information per prescription: the ATC classification of the drug, dispensing date, regimen, quantity dispensed and estimated length of duration of use. Information on diagnoses (ICD-10) and in-patient procedures can be retrieved through a linkage to Hospitalisation database which covers 80% of the cohort of valproate users identified in Out-Patient Pharmacy Database. Pregnancies will be followed using a linkage between the PHARMO Database Network and the Netherlands PRN, which correspond to approximately 18% of all pregnancies included in the PRN. The PRN is a nationwide registry that contains linked and validated data from four databases: the national obstetric database for midwives (LVR-1), the national obstetric database for gynaecologists (LVR-2), the national obstetric database for general practitioners (LVR-h) and the national neonatal/paediatric database (LNR). The registry contains information about care before, during and after delivery as well as maternal and neonatal characteristics and outcome of 95% of 180 000 pregnancies annually in the Netherlands with a gestational age of at least 16 weeks. Pregnancies in the Netherlands are identified via their outcome. After the pregnancy outcome is recorded and PRN is updated, pregnancy related information becomes available.

The use of the PHARMO Network and Netherlands PRN for research on pregnancies has been reported in a few publications. Zomerdijk et al. studied exposure of pregnancies to potentially teratogenic drugs [Zomerdijk et al., 2015] and another study specifically measured isotretinoin exposure during pregnancy in Netherlands [Zomerdijk et al., 2014].

9.4.4 Spain – SIDIAP

The autonomous community of Catalonia has its own health system. Primary Care is organised in 370 Primary Care Teams (PCT), which consist of a variable number of GPs, nurses, paediatricians, gynaecologists, social workers, dentists and non-clinical support staff. Each resident of Catalonia is allocated a doctor and a nurse in a PCT. Annually, 76% of the population has at least one contact with the PCT.

The Catalan Institute of Health (CIH) (Institut Català de la Salut) is the main provider of health services in Catalonia. The CIH manages 279 PCT with a catchment of 5.564.292 people, approximately 74% of the Catalan population. SIDIAP is highly representative of the population of Catalonia in terms of geographical, age, and sex distributions [Bolíbar et al., 2012].

This database is supplied, among others, by information from the Primary Care EMRs (e-CAP) and from the Sexual and Reproductive Health Care Programme (ASSIR) of the CIH. The e-CAP system is mainly used by obstetricians, gynaecologists and midwives in primary care but also some specialists from secondary care facilities. The ASSIR records include data on pregnancy, delivery, and postpartum monitoring from women who attended the primary health care services of the ICS, accounting for 65.7% term pregnancies in Catalonia.

SIDIAP also includes comprehensive information on prescribed and dispensed medication. Prescribed medications are mainly captured from primary care, while dispensed drugs are captured through drug invoices from community pharmacies, which include prescriptions issued by specialists (general practitioners, neurologists, psychiatrists, paediatricians) from both primary and secondary care [Aliaga et al., 2019; Recalde et al., 2022].

Information on pregnancies is derived from the primary care and ASSIR records registered during pregnancy, including its outcome. To fully identify all pregnancies starting during the study period, extra data beyond its end is needed to allow all pregnancy related records to be analysed using the pregnancy identification algorithm (up to ten months considering nine months on average for live births plus a possible period of hospitalization after delivery, as data on pregnancy outcomes might not get recorded until hospital discharge).

9.4.5 Sweden - National Health Registers

Individual patient data is collected from both in- and out-patient hospital-based specialist care across all of Sweden. The National Patient Register dates back to 1964. From 1987 there is information on all completed in-patient admissions across the country. The collection of out-patient care data began in 2000. The register is updated annually and available from September/October the following year.

The available data in the National Patient Register include:

- Patient demographics (age, gender)

- Clinical information: diagnoses (ICD-10 code and associated position), DRG code, care setting (in-patient or out-patient), admission date and discharge date (for in-patient care), surgeries and procedure performed
- Hospital information: region, clinic, etc.

Information on patient anthropometrics (height, weight, etc.) and lifestyle (smoking, etc.) is not available through the National Patient Register, nor are laboratory and clinical measurements. In addition, information on drugs administered at the hospital is not available.

All medicines are prescribed electronically in Sweden. The National Prescription Register tracks the full details of all dispensed medications at individual patient-level in Sweden since July 1, 2005. Patients are followed longitudinally through their personal identification number, regardless of which pharmacy they visit. The National Drug Register is updated monthly and covers all sales from Swedish pharmacies.

The available data in the National Drug Register include:

- Patient demographics (age, gender, and residency)
- Prescription information (date of prescription, prescriber's specialty, WHO ATC code, and brand-name)
- Dispatch information (dispatch date, product number, total dose dispatched, number of packages dispatched, and drug cost)
- Product information (Package size, formulation, etc.)

Information on prescribed dose is only documented in free text format where available, and days' supply is not recorded.

The Medical Birth Register contains information about all pregnancies resulting in delivery in Sweden and is frequently used for quality improvement work and for research [Andersen et al., 2017; Nörby et al., 2017] including studies on valproate utilisation and associated risks [Wide et al., 2004]. The register contains detailed information about mothers and new-borns and is updated in the month following delivery. Information becomes then available in December of the following year. For more information about the register, please see https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/national-medical-birth-register/

9.4.6 UK - CPRD

The CPRD is an ongoing primary care database of anonymised medical records from general practitioners, with coverage of over 11.3 million patients from 674 practices in the UK. With 4.4 million active (alive, currently registered) patients meeting quality criteria, approximately 6.9% of the UK population are included and patients are broadly representative of the UK general population in terms of age, sex and ethnicity [Herrett et al., 2015]. General practitioners are the gatekeepers of primary care and specialist referrals in the UK. The CPRD primary care database is therefore a rich source of health data for research, including data on demographics, symptoms, tests, diagnoses, therapies, health-related behaviours and referrals to secondary care. For over half of patients, linkage with

datasets from secondary care, disease-specific cohorts and mortality records enhance the range of data available for research.

The CPRD GOLD is operated by the Medicines and Healthcare products Regulatory Agency (MHRA), containing coded longitudinal medical records from general practices and from hospital-based care (e.g., Hospital Episode Statistics).

The CPRD GOLD population closely matches the age and gender distribution of the UK population as a whole. Mean follow-up is 6.8 years (median 5.0 years). Recorded data include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes. Data are retrieved by means of the READ classification system [Chisholm, 1990].

The use of the CPRD GOLD database for research on pregnancies has previously been reported. Devine et al have developed an algorithm for identification of pregnancies [Devine et al., 2010]. Hardy et al have used CPRD GOLD records, for linking mother and baby automated records and to describe the frequency, type and pregnancy risk level of medications prescribed prior to and during early pregnancy [Hardy et al., 2006]. The CPRD GOLD database has been also assessed as an alternative for pregnancy registries to study drug exposure [Charlton et al., 2008], major congenital malformations [Charlton et al., 2010], and identification of potential teratogens [Charlton et al., 2011].

The CPRD GOLD Pregnancy Register contains a list of all pregnancy episodes recorded in CPRD GOLD. The Pregnancy Register is derived from the primary care data based on an algorithm developed for CPRD GOLD by CPRD and the London School of Hygiene and Tropical Medicine [Minassian et al., 2019]. Live births in the CPRD GOLD Pregnancy Register are linked to the CPRD GOLD Mother-Baby Link so that information on the resulting infants can be accessed.

9.5 Study Sample Size

9.5.1 Determination of sample size for descriptive analyses

The aim of this study is to describe the prescribing practices before and after the implementation of the new risk minimisation measures and to assess the effectiveness of these measures. Sample size for estimation of the main pre- and post- implementation periods will be considered independently. The final study sample size is driven by the patient numbers available in the data sources in the target countries.

The sample size calculation is a function of the precision (e) and of the confidence level (here assumed a 95%) in the estimation of proportions. As the expected proportion (p) is unknown, we considered it to be 50% (maximum uncertainty).

Calculation use the following formula (normal approximation):

$$n = \frac{p\,(1-p)}{e^2} \times\ \varepsilon_{\alpha}$$

With *n* sample size, *p* Proportion, ε_α=1.96 for 95% CI, *e* Precision.

Table **3** shows that assuming a proportion of 50%, 384 patients are needed to achieve a precision of 5%; assuming a proportion of 20%, 246 patients are needed to achieve a precision of 5%.

Table 3. Required number of patients by acceptable precision (e) and assuming a 95% confidence level and by proportions (normal approximation)

	Proportion (%)				
Precision	10%	20%	30%	40%	50%
± 2.0%	864	1537	2017	2305	2401
± 3.0%	384	683	896	1024	1067
± 4.0%	216	384	504	576	600
± 5.0%	139	246	323	369	384
± 6.0%	96	171	224	256	267
± 7.0%	71	125	165	188	196
± 10.0%	35	62	81	92	96

9.5.2 Determination of sample size for comparative analyses

In this section, we estimate the sample size necessary to detect a difference in the incidence rate of pregnancy among women on treatment with valproate between the pre-implementation and post-implementation periods. Additionally, we display the anticipated precision of that difference (the effect estimate). We focus on the incidence rate of pregnancy as it is the expected to be the most limiting outcome in the primary objective.

Sample size and precision estimates can be made by varying the estimated outcome parameters, i.e., the proportion of women prescribed continuous contraception while on valproate and the incidence rate of pregnancies while on valproate, and by varying the power and type I error probability. The type I error determines the rate at which, were the study to be repeated a large number of times using the same sample size, the study would find a difference to be not due to chance alone (significant) when in fact it is only due to chance. This is typically set at 5% and termed α. The power determines the likelihood of rejecting the null hypothesis that the observed difference is due to chance alone when it should be rejected. This is typically set at 80% and termed 1-β.

The precision represents the inverse of the variance or half the width of the CI. Given a fixed type I error and power, we estimate the likely sample size and precision by varying the outcome parameters around likely values.

In Table 4, based on previous studies with valproate (EU PAS Register Number: EUPAS9678), we estimate that the incidence of women who become pregnant while on treatment is around 0.01 per person-year (e.g., around 10 pregnancies in 1000 women observed on valproate for 1 year). Also based on previous studies, we estimate that the change in incidence between the pre-implementation period and the post-implementation period to be between 0.001 and 0.01 per person-year (e.g., for every 1000 women observed each year, less - between 1 and 10 women- would fall pregnant on valproate in the post-implementation by comparison to the pre-implementation period). The resulting required sample size per group, in person-years, appears on the right side of Table 4. The smaller the difference in incidence rate of pregnancy between pre-implementation and post-implementation periods, the larger the sample size required to detect a statistically significant effect estimate (i.e., p-value <0.05).

As there are three years planned for the pre- and post-implementation periods, the number of person-years of observation required is 3x the number of persons displayed. Finally, the precision estimates, or the likely width of the CIs around the estimates of the difference in incidence per year, appear in the last column of Table 4.

Table 4. Sample size and precision estimates for the incidence rate of women who become pregnant while on treatment with Valproate

Assumptions		Resulting estimates	
Reference incidence rate (per person-year)	**Estimated difference in incidence rate (per person-year)**	**Sample size per group (over each of the 3-years periods)**	**Precision (+/-)**
0.01	0.001	54365	0.0007
0.01	0.002	14231	0.0013
0.01	0.003	6609	0.0018
0.01	0.004	3877	0.0023
0.01	0.005	2584	0.0027
0.01	0.006	1865	0.0031
0.01	0.007	1422	0.0034
0.01	0.008	1129	0.0037
0.01	0.009	923	0.0039
0.01	0.010	773	0.0040

To interpret row 5 in the above Table 4, to observe a decrease of 5‰ in the incidence rates of pregnancy between the pre- and post-implementation period assuming a significance level of 5% and a power of 80%, a sample size of 2,584 WCBP is required to be included over the 3 years of each period (corresponding to 7,750 person-years). To observe a decrease of 10‰ in the incidence rates using the same assumptions, 773 WCBP will be required to be included over 3 years (or 2,319 person-years).

9.5.3 Sample Size for target countries

An overview of the sample size per country is displayed in the Table 5. The table provides the available number of WCBP (13 to 49 years of age) exposed to valproate.

Table 5. Estimation for female patients 13 to 49 years exposed to valproate (Periods: UK: August 2015 – July 2017; Sweden: August 2015 – December 2016; France: last trimester 2017; Germany: 2015 - 2018; Netherlands and Spain: 2018)

	WCBP patients with valproate prescription	
	All	**first-ever user***
Sweden[1]	5,739	1,243
UK[1]	2,638	326
France[2]	38,566	NA
Netherlands[3]	2,200	NA
Spain[4]	2,754	370
Germany[5]	3,230	NA

* corresponding to valproate users with no prior prescription for valproate within entire available medical history before the prescription index date during the defined period

[1] Estimation from Valproate DUS Third Interim Report (Periods: UK: August 2015 – July 2017, Sweden: August 2015 – December 2016)

[2] Estimation from: ANSM, Martin D. Valproate, Mesures de réduction du risque. 26 May 2018. (Number of prevalent valproate users in the last trimester 2017)

[3] Feasibility assessment – PHARMO. Number of female patients (age 13-49) with at least one valproate dispensation during 2018

[4] Feasibility assessment – SIDIAP. Number of female patients (age 13-49) with at least one valproate dispensation during 2018

[5] Feasibility assessment - GKV. Number of female patients (age 13-49) with at least one valproate dispensation in the period 2015-2018

Abbreviations: NA: not available, UK: United Kingdom, WCBP: Women of childbearing potential

All WCBP patients with valproate prescriptions available in the study population will be considered for the analysis. The number of first-ever users may be too low to conduct analyses for the UK and Spain in each report. However, the sufficient sample size for the analyses of the primary objective should be reached for the prevalent users.

In the event that the number of study participants is too low to yield statistically significant results, individual country results will be pooled. Pooling across countries will be considered for the primary outcome of incidence of valproate exposed pregnancies only and will only be carried out if necessary for sample size considerations and is subject to additional assumptions about the comparability of study data between countries. Where pooling is required, this will be done via meta-analysis of the summary estimates generated from the analysis of each country's data.

Descriptive analyses may be carried out regardless of sample size but is not likely to yield reliable information in very small numbers. The expected number of patients for each country (Table 5) will allow a precision in the estimates (assuming a proportion of 50%) ranging from 0.4% in France to 1.5% in the Netherlands.

9.6 Data Management

The DUS ext. will be conducted according to the Standard Operating Procedures (SOPs) of IQVIA's Primary Intelligence and IQVIA's Real World & Analytics Solutions.

The processes for database management differ by country. Generally, the data is stored at the database level and analysed locally. High data quality standards will be maintained, and processes and procedures utilised to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. SAS Software will be utilised for access to the raw data, to manage the analytic datasets and to conduct data analysis. If the study is conducted by a third party, the datasets and analytic programmes will be stored according to the vendor's procedures.

This study will follow relevant chapters of European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines for data management.

9.7 Data Analyses

9.7.1 General Considerations

Given the study objectives the analyses will be mainly descriptive and will be conducted by country, database, and study time periods (both pre-implementation periods and post-implementation period).

Results will be displayed by periods before and after the implementation of RMM, and by countries. The primary analysis will consider the pre-implementation main period and the post-implementation period while the sensitivity analysis will consider the pre-implementation main plus transition period and the post-implementation period.

The duration of the pre-implementation (main plus transition period) will be 36 months for all countries. The duration of the pre-implementation main period will vary between 25 and 30 months across the study countries.

The duration of the post-implementation period will be 36 months for all countries.

Statistical analyses will follow the tables shells validated by the MAHs consortium and will be displayed using tables, listings and/or graphs. The statistical analysis will be conducted using SAS 9.3 or above (or equivalent software). A detailed SAP will be prepared prior to data extraction.

The statistical results of all target countries will be presented in a single report.

9.7.2 Main analyses

The main analyses will describe and compare the prescribing practices in WCBP receiving valproate during the main pre- and the post-implementation periods with respect to key elements of the PPP; and will compare the incidence of valproate exposed pregnancies, and characteristics of exposed pregnancies during the same periods to meet the primary study objective. The analyses will be descriptive in nature.

Descriptive statistics will be provided for the patients, treatments and diagnosis characteristics.

Categorical variables will be presented as counts (n), proportions (%) and CIs when relevant. Continuous variables will be presented as means with SD and as medians with inter quartile range (IQR), when appropriate.

Categorical variables will be statistically compared with a Pearson Chi2 or with Fisher's exact test (if the expected frequency lower or equal to five for one or several cells). Continuous variables will be statistically compared with a Student's t-test (parametric test) or Wilcoxon signed-rank sum test (non-parametric test, when necessary). Each statistical test will be two tailed and will not be adjusted for multiple comparisons. As appropriate, 95% CIs will also be calculated.

In each study period, by country and by indication (epilepsy, bipolar disorder and others), the following analyses will be conducted, overall and in sub-groups of patients (incident and prevalent users).

Each analysis conducted in incident users will also be conducted in first ever users.

Patients with at least 12 months of available history in the databases will be considered in order to define the sub-group of valproate users.

9.7.2.1 Prescribing patterns

- Patients' demographics (age at index date)
- Medical history with respect to diagnoses of epilepsy, bipolar disorder and others in the 10 years prior to index date
- Medication history before valproate initiation (incident users): medications related to valproate indication (epilepsy, bipolar disorder) used in the 12 months prior to index date (valproate initiation for incident users)
- Valproate indication (epilepsy, bipolar disorder and others) based on diagnosis or medication history when diagnosis is missing. If a patient has several diagnoses, priority will be given to 1) epilepsy, 2) bipolar disorder and 3) others. If medical history and medication history are both missing, an unknown category will be considered. For France, valproate brand-names will be used to re-categorise women with an "unknown" category for valproate indication into epilepsy or bipolar disorder indication.
- Prescriber specialty (except for the UK as this information is unavailable in CPRD):
    - Any specialty (Neurologist, Psychiatrist, Paediatrician),
    - General Practitioner,
    - Others,
    - Unspecified specialist (only available for France),
    - Missing
- Frequency of pregnancy testing during valproate treatment

9.7.2.2 Compliance to the PPP

Change in absolute numbers and proportion of the following parameters will be compared between pre- and post-implementation main periods:

- Number and proportion of WCBP with annual visits to a specialist within indication (incident and/or recurrent patients)
- Number and proportion of WCBP initiated to valproate treatment by a specialist within indication (incident users).
- Number and proportion of WCBP (incident and/or recurrent patients) with either:
    - Medical history with respect to conditions / diagnoses allowing the assumption that a female patient in the age group 13 to 49 years is not of childbearing potential (such as records of sterilisation)
    - Concomitant use of contraceptive or IUD during valproate treatment

Concomitant use of contraception will be measured with respect to valproate exposure using an adaption of the PDC methodology. This will be used to quantify the extent of the overlap in contraception with respect to valproate exposure. This will take a person-time approach to estimate the proportion (%) of days of valproate exposure where the patient was also covered by an effective form of contraception, adjusting for overlaps in prescription/dispensation of oral contraceptive. The PDC accounts for both adherence and persistence of effective contraception during the time period the patient is exposed to valproate.

The PDC with contraception will be calculated as a percentage, where the denominator is the number of days from the date of first valproate prescription in the study period until the date of discontinuation of valproate or end of follow-up (whichever occurs first). The numerator will be calculated as the number of days of valproate exposure covered by a prescription for contraception. Prescriptions for oral contraceptives will be adjusted for overlaps in supply. Switching between contraceptives will be allowed as contributing to the days covered by effective contraception. The method for defining the time period covered by effective contraception will vary according to the type of contraceptive method.

The PDC with contraception will be described categorically: <80%, ≥80%, ≥95% (‘Complete coverage’). If the number of patients is at least 100, the PDC with contraception will also be described categorically as: <20%, 20-40%, 40-60%, 60-80%. The IQR and median proportions of the coverages for the pre-and post-implementation period will be reported.

Results will be displayed by age groups (13-18 years, 18-24 years, 25-34 years, 35-44 years, 45-49 years).

- Number and proportion of WCBP with a laboratory pregnancy test at treatment initiation (incident users)

- Number and proportion of WCBP fulfilling one, several or all elements of the PPP as applicable in each sub-population (incident and/or recurrent users)

9.7.2.3 Pregnancy

The following analyses will be performed:

- Number and proportion of pregnancies exposed to valproate and by trimester of exposure
- Exposure to valproate in the period before, during and after pregnancy (with daily dose of valproate, number of prescriptions, and cumulative dose)
    - Number of pregnancies with valproate started during pregnancy
    - Number of pregnancies with valproate discontinued before or during pregnancy and medications related to valproate indication used after valproate discontinuation
    - Number of exposed pregnancies with a visit to a teratology specialist after estimated date of pregnancy start
    - Number of exposed pregnancies with a visit to a specialist in the indication after estimated date of pregnancy start
    - Number of exposed pregnancies occurring while under concomitant use of contraceptive or IUD
- Incidence rates of pregnancies in female patients aged 13-49 years (using patient time within study)
- Information on pregnancy outcome (i.e., live birth, Miscarriage/early termination/stillbirth, recorded birth defect) will be provided when available in the databases

A pregnancy will be considered exposed if the duration of at least one valproate prescription/dispensation overlapped the period between 30 days before the estimated first day of pregnancy and the delivery/end of pregnancy.

In DUS 1, an overall number of 923 pregnancies including 451 exposed to valproate (48.9%) were observed in the entire pre-implementation period and 350 including 182 exposed to valproate (52.0%) in the entire post-implementation period. In Sweden and UK, countries with the most interpretable pregnancy data, the incidence rate of pregnancies exposed to valproate decreased from 0.0095 to 0.0080 per 12 person-months and from 0.0169 to 0.0109 per 12 person-months, respectively.

In the DUS ext., a reduction of pregnancies (number and/or rate) at least as important as the one observed in DUS 1 should be observed, as it is the ultimate goal of the new RMM.

Of note, even with effective RMM, some pregnancies could still be observed, particularly in the epilepsy indication, resulting from medical need or patient's choice despite information given to patients on the risks during pregnancy, and because patient's acknowledgement of risks cannot be documented in the DUS ext.

9.7.3 Secondary analyses

In order to provide insights on continuous trends of valproate use on a country-specific basis, especially after the implementation of RMM, results for key parameters will be presented on a quarterly basis where possible with respect to available patient numbers in all interim reports and the final report.

In addition, an interrupted time series (ITS) analysis using segmented regression analysis will be considered in the case the conditions for this analysis will be met in the interim and final reports [Wagner et al, 2002]. Using ITS analyses, data is evaluated at multiple time points before and after an intervention in order to detect whether or not an intervention had a significantly greater effect than any underlying trend. Regression analysis will be used to define the trends of the occurrence of pregnancies by indication of use, in pre- and post-implementation periods. Change in level and/or in slope will be compared between the two periods to provide insights into the impact of the implementation.

9.7.4 Sensitivity analysis

The main pre-implementation period (25-30 months) will be extended with the transition period (6-11 months) to enlarge study population in a sensitivity analysis for the primary objective.

A sensitivity analysis will also be conducted with regard to compliance with the PPP by calculating the percentage of incident users with a pregnancy test performed within a reduced time window [Raguideau et al., 2015]. Instead of a 2-month window around the index date used in main analyses, a more stringent window of 13 days (up to 10 days before the index date and 3 days after) will be used.

An additional sensitivity analysis will be performed with regards to compliance to the PPP by excluding women sterilised before index date.

9.7.5 Exploratory Analyses (If Applicable)

Not applicable

9.7.6 Handling of Missing Data

The number and type of missing values will be recorded and reported in the final study report. Statistical calculations (i.e., the denominator) will be adjusted accordingly for the analysis.

Information on recommended daily dose may be not available from all data sources. The proportion of missing values will be described. However, the degree of completeness varies between databases. The missing information will be highlighted.

9.8 Quality Control

The study will use existing databases, which are being used widely for research. The study will be executed in line with all applicable regulations and guidelines – such as best-practice guidelines applicable to non-interventional DUS, including but not limited to the

ENCePP Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols, and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE GPP) as well as the specific IQVIA SOPs. All study programmes, log files, and output files will be stored on the secure server. Where elements of the study are being conducted by a third party, the datasets and analytic programmes will be stored according to the vendor's procedures.

9.8.1 Approaches for Validating the Results

The quality control for validating the results will be conducted at three levels:

1) At the statistical analysis level: all data management and statistical analysis programmes developed and used in the analysis will be documented. All versions generated will be dated, kept with accompanying documentation and archived. The original database will be stored. A derived database will be created for the new versions of the data in order to include recoding and computing of new variables, especially stratification of continuous variables, combination of modalities for categorical variables, calculation of composite indicators, etc.
2) At the results level, a data review will be done to ensure data integrity. A statistical analysis report including all the results will be provided for review and discussion. The final statistical report will consider the reviewers' comments.
3) At the study level, all aspects of the study will be conducted according to the SOPs of IQVIA Real World & Analytics Solutions. The study documents have been approved by people competent in medical and safety areas of IQVIA. According to the SOPs, an independent review of the DUS results and report will be conducted by a person who was not in charge of their preparation.

9.8.2 Record Retention

The MAHs must maintain an adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, documentation of Institutional Review Board/Independent Ethics Committee (IRB/IEC) and governmental approval/notification (if required) and study reports.

Records and documents pertaining to the conduct of this study will be retained for at least 15 years after completion of the study. The length of storage can be extended based on MAH-specific SOPs or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

IQVIA will store study documentation on behalf of MAHs for 5 years, in accordance with IQVIA Standards and will transfer the documentation to the MAHs for long-term archiving.

9.9 Strengths and Limitations of Research Methods

9.9.1 Strengths

- The data sources have readily available data for the pre-implementation period of the RMM and future data for the post-implementation period will be collected routinely.
- The data sources contain a wealth of information on patients and allow for a more complete picture to be drawn of the patients.
- The results of the study are generalisable due to the comprehensive data collection and the setting in which the data is being collected.
- The data sources considered are routinely used for PASS requested by the European Medicines Agency (EMA) and the subject of many publications.

9.9.2 Limitations of data sources

- **Information on pregnancy, pregnancy termination and pregnancy outcomes**

The extent of available information on pregnancy, pregnancy termination and pregnancy outcomes may vary between databases and countries. In general, spontaneous abortions <14 weeks of gestation are rarely or not recorded in the databases.

In Sweden, the Medical Birth registry only includes pregnancies with a duration of ≥23 weeks, with both live and stillbirths available. Data on spontaneous abortions and ectopic pregnancies would be available from the National Patient Register, based on diagnosis codes, if a woman has been treated in hospital or out-patient clinic for these events. Data on induced abortions were treated anonymously (mother's personal ID not recorded) in Sweden before October 2016 and therefore not recorded in the National Patient Register. Abortion statistics based on anonymised data additionally show that medical abortions completed at home constituted 75% of the abortions performed before 9 weeks of gestation in 2017 and 83% in 2020 [Socialstyrelsen, 2021]. Consequently, data on induced abortions are not captured at all for the first 11 months of the pre-implementation period and likely incompletely captured for the remainder of the study period in the Swedish National Patient Register.

In France, spontaneous abortions under 22 weeks of gestation and some induced/ therapeutic abortions that are treated anonymously will be missing. There will also be an underestimation of neurodevelopmental disorders and minor birth defects such as ocular troubles that are not recorded reliably in the SNIIRAM. Based on the exhaustive French study performed on SNIIRAM [ANSM, 2017], a selection of 26 among the EUROCAT list of birth defects will be researched.

In the UK and in Spain, there is a potential for the incomplete ascertainment of elective terminations and spontaneous abortions. These procedures may occur at healthcare facilities other than the GP/primary care office, or may not be recorded in the medical record, either by omission or at the woman's request. Additionally, at the time of patient registration with the GP, information on pregnancies that occurred prior to the patient's registration is frequently incomplete.

In the Dutch databases, no information on spontaneous abortions that occurred until gestational age of 16 weeks nor information on elective termination of pregnancies, are captured.

In all German databases, in general, the outcome for the new-born cannot be determined because there is no linkage between information on pregnant women and their new-born babies. Therefore, the codes ICD-10 Q00-Q99 (Congenital malformations, deformations and chromosomal abnormalities) cannot be used for pregnancy outcome documentation. The ICD-10-GM codes O00-O99 and Z37 can only be used to express the pregnancy outcome for the mother.

- **Information on contraception**

An underestimation of contraceptive use and country-specific patterns will be taken into account as outlined in Table 2. In all databases, over the counter contraception (e.g., Condoms) that does not necessitate prescription will not be documented. In claim-based databases (SNDS and GKV) the limitation in contraceptive use assessment is related to the reimbursement policy of the country concerned, since they will record only reimbursed contraception. Reimbursement policy in the healthcare systems of the countries where the study will be conducted will be continuously reviewed for changes along the study period. In UK, where the study will be based on a GP-EMR database, not all patients will receive contraception through their GP and as the consequence these entries will be missed; therefore, information may not be available for all patients in CPRD. However, results from the third National Survey of Sexual Attitudes and Lifestyles indicate that most women use primary care practices alone or in combination with community clinic for contraceptive supply [French et al., 2018].

In France, IUDs and the first and second generation of hormonal contraceptives are reimbursed, the third and fourth generations, however, are not [ANSM, 2017]. Based on the results from a survey in 2016 [Agostini et al., 2018] and the reimbursement policies in France, it is expected that for over 50% of women in childbearing potential age records for contraceptives are captured in SNIIRAM [Agostini et al., 2018; Bezin et al., 2017]. Data from a large general practitioner EMR database (IQVIA longitudinal patient database) have shown that a small proportion of WCBP exposed to valproate receive a concomitant oral contraceptive that is not reimbursed (~18%).

In Sweden, the online database on prescriptions held by the National Board of Health and Welfare provides the following information on the annual prevalence of Swedish women aged 15-49 years who filled at least one prescription for hormonal contraceptives in 2012-2017: ATC G02B contraceptives for topical use: 4.3-5.4%; ATC G03A hormonal contraceptives for systemic use: 22.4-26.1% (reference: prescription registry).

In Spain, a study published in 2011 reported a prevalence of contraceptive use (including hormonal contraceptives, condoms, and IUDs) in sexually active adolescent to young women (ages 16-29) of approximately 86% [Carrasco-Garrido et al., 2011]. The most commonly used method of contraception was the condom followed by hormonal contraceptives. Most of the hormonal contraceptives are not funded by the national health system. As for IUDs, these devices can be prescribed and dispensed but there is no

reimbursement except for socioeconomic deprived women. Additionally, SIDIAP only captures contraceptives prescribed by primary care specialists. Hence, any form of contraception that is not reimbursed or prescribed by specialists not in a primary care practice will not be recorded in SIDIAP. Therefore, there will likely be an important underreporting of the use of contraceptives in Spain.

In PHARMO, all contraceptives dispensed (including non-reimbursed ones) are recorded. However, IUD use is likely to be underestimated as outlined in Table 2.

In Germany, contraception is only reimbursed for women aged <20, and since April 2019, for women aged <22. Prescription of contraception at the expense of an insurer is also possible in women 22 years and older if they have special medical conditions. These conditions, however, do not include epilepsy and bipolar disorder. Furthermore, reimbursement of contraceptives during treatment with teratogenic agents, such as valproate, although recommended by committed bodies, has not been legally enforced. Such limited access of German WCBP to reimbursed contraception significantly reduces the ability of GKV to capture contraceptive use in this population.

For all countries, when the durations of contraceptives are not specified from the prescriptions / dispensations, pre-specified default durations (90 days for hormonal injections [Jain et al., 2004], 28 days for combined and progesterone-only hormonal pills [Archer et al., 1997; VIDAL, 2021], 28 days for hormonal patches [European Medicines Agency, 2012] and vaginal rings [Organon Global, 2021b], 3 years for hormonal implants [Organon Global, 2021a] and 5 years for hormonal [U.S. Food and Drug Administration, 2014] and copper IUDs [Tayside Sexual & Reproductive Health Service, 2020]) will be used to impute the duration of contraception. Usage of default durations might not be optimal for estimating contraception coverage considering the variety of pharmaceutical forms and patients' therapeutic compliance.

- **Records of pregnancy tests**

Records of pregnancy tests will not be comprehensively captured in the databases and the extent may vary by country as outlined in Table 2. Pregnancy tests, as required by the PPP, may be conducted in a different setting depending on the local practice and policy. This may result in under-recording of pregnancy tests in EMR data sourced from primary care physicians (i.e., CPRD, SIDIAP). In Sweden, no lab test results are recorded in the registry data; the performance of pregnancy tests is only available when documented by ICD-10 codes like Z32 'Pregnancy examination and test'. Additionally, information on self-administered pregnancy tests at home is not captured in any database. For Germany, results of laboratory tests are not recorded in the database. As self-administered pregnancy test kits are available for purchase in Germany over the counter in drugstores and pharmacies, the tests recorded in the database might be underestimated.

- **Indication and visit to specialists**

In the CPRD, diagnosis information is available, but indication of prescription is not mandatory recorded. Therefore, diagnoses related to the indication of valproate will be checked at the date of valproate prescription or in the medical history of patients. In the

UK, referrals to specialists are only likely to be captured if the GP/primary care physician chooses to enter the information into the patient's computer record. Therefore, mention of a specialist visit may be under recorded in CPRD. However, in SIDIAP, referral letters include information on the specialty of the physician the patient is referred to. Also, some dispensations could be linked to their related prescription which contains information on the specialty of the prescriber. In addition, visits to paediatricians and gynaecologists within the primary care setting and visits to some specialists in secondary care facilities using the e-CAP system were directly captured in the database. In the German database, information regarding the prescribed medication and diagnosis codes are available; however, there is no direct link between indication and prescribed substance. Hence, information regarding valproate indication will be estimated based on the proximity of diagnoses related to the valproate indication to the date of prescriptions. Visits to specialists and their (reimbursed) prescriptions on patient level are fully covered in GKV.

- **Sample size**

This is a non-interventional observational study, and the study sample size cannot be modified. Precision estimates under various conditions for the primary objective have been detailed in Section 9.5. Statistical power is likely to be lower in Germany, the Netherlands, Spain, Sweden and the UK than in France due to lower sample size and hence lower numbers of events of interest.

Pooling of data across countries will be considered if necessary but this carries additional assumptions concerning the comparability of analyses across countries.

- **Generalisability**

The data sources are drawn from six high income European countries, all with universal healthcare systems. Most of these healthcare systems are funded primarily through general taxation. The extent of the funding and coverage by health care system varies in these countries and there may be differences in the details of healthcare organisation and clinical practice that will limit the generalisability of the findings to other EU countries. In addition, the process of implementation of RMM measures may vary from one country to another.

A companion survey study will be conducted simultaneously in seven countries. While the DUS ext. will reveal the level of implementation of the PPP by physicians, the survey will show the physician's and patient's level of understanding of the PPP. If both studies were to demonstrate similar levels of knowledge, understanding, and implementation/adherence, it could be argued that the two studies support each other's external validity. Furthermore, in countries where only one of the study types will be conducted (i.e., Poland), it can be inferred that the other would have produced similar patterns that if it had been conducted. Therefore, the survey can be regarded as supporting the extrapolation and generalisation of the results obtained from the DUS ext. to other European countries.

9.10 Other Aspects

9.10.1 Changes to the Protocol

The changes to the study protocol are detailed in Section 5.

9.10.2 Study Management

This study will be performed by IQVIA, with guidance, input, review and approval of the members of the MAH consortium for valproate, including development of materials, data management, analysis and reporting.

10 PROTECTION OF HUMAN SUBJECTS

This DUS ext. is non-interventional and analysis is based on secondary data use. No identifying data is collected in any of the planned approaches.

The study will be conducted in agreement with the regulation (EU) 2016/679 of the European Parliament on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation, GDPR).

Regulatory and ethical requirements will be followed in each country. The study will comply with the module VIII of the good pharmacovigilance practices (GVP).

Although EU Pharmacovigilance Directive (DIR 2010/84/EU) is a legal act, it does not carry the same binding force of a regulation; each Member State can determine how best to transpose the Directive into local legislation. As a result, the submission requirements for PASS vary throughout the EU, with some countries being more onerous than others. IQVIA includes experts dedicated to the review and advisement on the regulations and guidelines applicable to this study in the participating countries.

The study will be submitted to ethical review boards (ERB) for approval wherever required by local law. Regulatory authorities will be notified, and approval sought as required by local laws and regulations. Progress reports will be submitted to ERB and regulatory authorities as required by local laws and regulations.

10.1 Required submissions and approvals in the study target countries

The following submissions and approvals are required in the target countries:

In France, a study using SNDS data requires the following submission:

- Submission to an expert Committee on Public Interest which examines the public interest purpose
- The process takes over 8 months for approval

In Germany, a study using GKV data requires:

- Approval from GKV providers
- The process may take several weeks

In the Netherlands, a study using PHARMO data requires:

- Approval from a scientific committee
- The process takes 1-2 months

In Spain, the study requires:

- Approval from a scientific committee and from a clinical research ethics committee
- The process takes 1-3 months

In Sweden, the study requires two submissions/approvals:

- In order to gain access to the linked register, an approval from the local ethical review board is necessary, wherein the research project and ethical aspects should be explained in a formal application, with attached protocol. The ethics approval is dependent on the data being made publicly available in some form.
- A standard application will subsequently be submitted to the National Board of Health with the attached approval from the local ethical review board.
- The ethical approvals process takes approximately 10-11 weeks.

In the UK, all research involving data collected from National Health Service patients must be approved by a Research Ethics Committee.

- The CPRD GOLD has an ethical approval from a Multi-centre Research Ethics Committee for purely observational research (i.e. studies that do not include patient involvement). Under the terms of this ethics approval, studies using pre-collected, pseudonymised data must undergo scientific review to help ensure appropriate analysis and interpretation of the data. Conduct of the study will include, but will not be limited to, the following: CPRD GOLD's Independent Scientific Advisory Committee review and favourable opinion/approval of study protocol and any subsequent amendments.
- Ethics approval normally takes 4-8 weeks.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The DUS ext. is based on the secondary use of data. According to GVP module VIII the reporting of suspected adverse reactions in the form of individual case safety reports is not required for this kind of studies. With respect to the study objectives information on adverse events/adverse reactions will be not extracted from the databases and analysed in the context of this DUS. Information on pregnancies exposed to valproate will be provided in aggregated form in the final study report.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 Reporting

Interim reports and the final report will be communicated to the PRAC according to the timelines specified in Section 6.

In accordance with the 2010 EU pharmacovigilance legislation, the protocol of this study will be entered into the publicly available EU PAS register. Updates to the study protocol

in case of substantial amendments and the final study report will also be entered in the register.

12.2 Publications

Study findings will be published in a peer reviewed journal.

Any publication will be guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors, updated April 2010.

All reporting will be consistent with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) Initiative checklist for cohort studies [von Elm et al., 2008].

Still in line with the EMA guideline, and in order to allow competent authorities to review in advance the results and interpretations to be published, the MAHs should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within two weeks after first acceptance for publication.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

Study title: A Drug Utilisation Study extension (DUS ext.) of valproate and related substances, in Europe, using databases

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

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[4]	☒	☐	☐	6
1.1.2 End of data collection[5]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

[4] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[5] Date from which the analytical dataset is completely available.

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)	☒	☐	☐	7.2
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or sub-group to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☐	

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)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☒	☐	9.7
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))	☐	☒	☐	
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)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.4

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.1
	4.2.2 Age and sex	☒	☐	☐	9.2.1
	4.2.3 Country of origin	☒	☐	☐	9.1
	4.2.4 Disease/indication	☒	☐	☐	9.3.4
	4.2.5 Duration of follow-up	☒	☐	☐	9.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

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)	☒	☐	☐	9.3.2
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.3.2
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

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?	☒	☐	☐	8
6.2 Does the protocol describe how the outcomes are defined and measured?	☐	☐	☐	9.3
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)	☐	☒	☐	
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)	☐	☒	☐	

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)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

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)	☐	☐	☒	

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)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☐	☒	☐	
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)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Annex 3.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Annex 3.4
9.3.3 Covariates and other characteristics?	☒	☐	☐	Annex 3.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

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)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6 and 9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.6 and 9.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				9.9
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).	☐	☐	☒	
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)	☒	☐	☐	9.5

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?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	10

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?	☒	☐	☐	5

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)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Mickael Arnaud

Date: 25/April/2025

Signature _____

ANNEX 3. ADDITIONAL INFORMATION

Annex 3.1. Drug classes for treatment of bipolar disorder and epilepsy

Bipolar disorder

Drug class	Substance	ATC WHO code
Antidepressants*	Agomelatine	N06AX22
	Amitriptyline	N06AA09 N06CA01
	Bupropion	N06AX12 A08AA62
	Citalopram	N06AB04
	Clomipramine	N06AA04
	Doxepin	N06AA12
	Duloxetine	N06AX21
	Escitalopram	N06AB10
	Fluoxetine	N06AB03 N06CA03
	Imipramine	N06AA02
	Maprotiline	N06AA21
	Mianserin	N06AX03
	Mirtazapine	N06AX11
	Nortriptyline	N06AA10
	Paroxetine	N06AB05
	Reboxetine	N06AX18

Drug class	Substance	ATC WHO code
	Sertraline	N06AB06
	Tranylcypromine	N06AF04
	Trimipramine	N06AA06
	Venlafaxine	N06AX16
Mood stabilisers	Carbamazepine	N03AF01
	Lamotrigine	N03AX09
	Lithium	N05AN (N05AN01)
Typical neuroleptics	Haloperidol	N05AD01
Atypical neuroleptics	Amisulpride	N05AL05
	Aripiprazole	N05AX12
	Asenapine	N05AH05
	Clozapine	N05AH02
	Olanzapine	N05AH03
	Paliperidone	N05AX13
	Quetiapine	N05AH04
	Risperidone	N05AX08
	Ziprasidone	N05AE04

***Antidepressant are considered in this study because first episodes of depressions are often observed before the diagnosis of bipolar disorder is made**

Epilepsy

Drug class	Substance	ATC WHO code
Seizure control	Acetazolamide	S01EC01

Drug class	Substance	ATC WHO code
	Brivaracetam	N03AX23
	Bromide	M03AC06, M03AC08 M03AC09, N05CM11
	Carbamazepine	N03AF01
	Gabapentin	N03AX12
	Lacosamide	N03AX18
	Lamotrigine	N03AX09
	Levetiracetam	N03AX14
	Oxcarbazepine	N03AF02
	Phenobarbital	N03AA02
	Phenytoin	N03AB02 N03AB52
	Pregabalin	N03AX16
	Topiramate	N03AX11
	Zonisamide	N03AX15
	Clobazam	N05BA09
	Clonazepam	N03AE01
	Eslicarbazepine acetate	N03AF04
	Ethosuximide	N03AD01 N03AD51
	Felbamate	N03AX10
	Fosphenytoin	N03AB05
	Lorazepam	N05BA06, N05BA56

Drug class	Substance	ATC WHO code
	Mesuximide	N03AD03
	Midazolam	N05CD08
	Perampanel	N03AX22
	Primidone	N03AA03
	Retigabine	N03AX21
	Rufinamide	N03AF03
	Stiripentol	N03AX17
	Sultiame	N03AX03
	Tiagabine	N03AG06
	Vigabatrin	N03AG04

Annex 3.2. ICD-10 codes epilepsy, bipolar disorder and others

Category	ICD-10 code	Description
Epilepsy	G40	Epilepsy and recurrent seizures
	G41	
	R56	Convulsions, not elsewhere classified
Bipolar disorder	F31	Bipolar disorder
	F30*	Manic episode
	F32*	Major depressive disorder, single episode
	F33*	Major depressive disorder, recurrent
	F34*	Persistent mood [affective] disorder
	F39*	Unspecified mood [affective] disorder
Others		
Psychiatric disorders	F01-F99 Excluding F30-34, F39	Mental, Behavioural and Neurodevelopmental disorders
Migraine headache prophylaxis	G43 excluding G43.8	Migraine

***These codes in association with valproate are allocated to bipolar disorder**

Annex 3.3. Drug codes for hormonal contraceptives

ATC codes for hormonal contraceptives

G02B CONTRACEPTIVES FOR TOPICAL USE

G02BA Intrauterine contraceptives
G02BB Intravaginal contraceptives

G03A HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE

G03AA Progestogens and estrogens, fixed combinations
G03AB Progestogens and estrogens, sequential preparations
G03AC Progestogens
G03AD Emergency contraceptives

Annex 3.4. Codes for the identification of contraceptive management, pregnancy, outcome of delivery and sterilisation.

ICD-10 codes for the identification of contraceptive management, sterilisation and outcome of delivery.

Category	ICD-10 code	Description
Contraception		
IUD	T83.3	Mechanical complication of intrauterine contraceptive device
	Z30.1	Insertion of (intrauterine) contraceptive device
	Z30.5	Surveillance of (intrauterine) contraceptive device
	Z97.5	Presence of (intrauterine) contraceptive device
Other	Z30.0	General counselling and advice on contraception
	Z30.8	Other contraceptive management
	Z30.9	Contraceptive management, unspecified
	Z30.4	Surveillance of contraceptive drugs
Pregnancy		
	Z32.0	Pregnancy, not (yet) confirmed
	Z32.1	Pregnancy, confirmed
	Z33	Pregnant state, incidental
	Z34	Supervision of normal pregnancy
	Z35	Supervision of high-risk pregnancy
	Z36	Antenatal screening
	Z37	Outcome of delivery
	Z38	Liveborn infants according to place of birth
	Z39	Postpartum care and examination

Pregnancy and pregnancy outcomes	O00-O99	Pregnancy, childbirth and the puerperium
Certain conditions originating in the perinatal period	P00-P04	New-born affected by maternal factors and by complications of pregnancy, labour, and delivery
Sterilisation		
	Z30.2	Encounter for sterilisation
	Z90.7	Acquired absence of genital organ(s)
	E89.4	Postprocedural ovarian failure

Annex 3.5. Codes for the identification of pregnancy testing

Category	ICD-10 code	Description	CPT code	Description
Pregnancy examination and test (Z32)	Z32.0	Pregnancy, not (yet) confirmed		
	Z32.1	Pregnancy, confirmed		
			81025	Pregnancy test urine
			84703	Human chorionic gonadotropin (hCG),qualitative, blood
			84702	hCG, beta subunit, quantitative, blood

Annex 3.6. Codes for the identification of birth defects

	ICD-10-BPA
All anomalies*	Q-chapter, except Q90-Q99 section
*According to EUROCAT Guide 1.4 Chapter 3.3. https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/JRC-EUROCAT-Section-3.3-23-9-2020.pdf	

ANNEX 4. LIST AND CONTACT DETAILS OF REPRESENTED MAHS

List of represented MAHs contact details

MAH identified as contact for referral	Represented MAHs
AUROBINDO PHARMA B.V. (FORMERLY APOTEX EUROPE B.V.) Baarnsche Dijk 1, 3741 LN, Baarn, The Netherlands	AUROBINDO PHARMA B.V. (FORMERLY APOTEX EUROPE B.V.) Baarnsche Dijk 1, 3741 LN, Baarn, The Netherlands
ARISTO PHARMA GMBH Wallenroder Str. 8-10 D-13435 Berlin Germany	ARISTO PHARMA GMBH Wallenroder Str. 8-10 D-13435 Berlin Germany
ARROW GENERIQUES 26 Avenue Tony Garnier 69007 Lyon France	ARROW GENERIQUES 26 Avenue Tony Garnier 69007 Lyon France
BETAPHARM ARZNEIMITTEL GMBH Kobelweg 95 86156 Augsburg Germany	BETAPHARM ARZNEIMITTEL GMBH Kobelweg 95 86156 Augsburg Germany
CONSILIENT HEALTH LTD Floor 3, Block 3, Miesian Plaza, Dublin 2, D02 Y754, Ireland	CONSILIENT HEALTH LTD Floor 3, Block 3, Miesian Plaza, Dublin 2, D02 Y754, Ireland
CRESCENT PHARMA LTD Key House, Sarum Hill, Basingstoke, RG21 8SR United Kingdom	CRESCENT PHARMA LTD Key House, Sarum Hill, Basingstoke, RG21 8SR United Kingdom
DESITIN ARZNEIMITTEL GMBH Weg beim Jäger 214 22335 Hamburg Germany	DESITIN ARZNEIMITTEL GMBH Weg beim Jäger 214 22335 Hamburg Germany

GENERIS FARMACÊUTICA S.A. Rua João de Deus, 19 2700-487 Amadora Portugal	GENERIS FARMACÊUTICA S.A. Rua João de Deus, 19 2700-487 Amadora Portugal GENERICS [UK] LIMITED Station Close EN6 1TL Potters Bar Hertfordshire United Kingdom
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