POST-AUTHORISATION SAFETY STUDY (PASS) PROTOCOL

TITLE: Surveys among Health Care Professionals and Patients to assess their knowledge and behaviour with respect to the new (2018) Risk Minimization Measures for valproate use in Europe.

COMPOUND: Valproate and related substances

STUDY NUMBER: VALNAC09348 (SANOFI internal referencing system)

POST-AUTHORISATION SAFETY STUDY (PASS) PROTOCOL

PASS INFORMATION

TITLE	Surveys among Health Care Professionals and Patients to assess their knowledge and behaviour with respect to the new (2018) Risk Minimization Measures for valproate use in Europe
PROTOCOL VERSION IDENTIFIER	Version 6.0
DATE OF LAST VERSION OF PROTOCOL	November 4th, 2020
EU PAS REGISTER NUMBER	EUPAS34465 registerd since 28th April 2020
ACTIVE SUBSTANCE	Valproate and related substances: • ATC code: N03AG01 • ATC code: N03AG02
MEDICINAL PRODUCT(S)	Valproate and related substances*: • magnesium valproate • sodium valproate • valproic acid • valproate semisodium • valpromide *All substances will be summarized 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 HOLDER(S) (MAH)	The joint initiative involves several companies via a consortium APOTEX EUROPE B.V.; ARISTO PHARMA GMBH; ARROW GENERIQUES; BETAPHARM ARZNEIMITTEL GMBH; BIOGARAN; BIOMO PHARMA GMBH; CONSILIENT HEALTH LIMITED, CRESCENT PHARMA, DESITIN ARZNEIMITTEL GMBH; GENERIS FARMACEUTICA S.A.; G.L. PHARMA GMBH; HEXAL AG; LUPIN HEALTHCARE (UK) LTD; MYLAN SAS; NEURAXPHARM ARZNEIMITTEL GMBH; ORION CORPORATION; PHARMASWISS CESKA REPUBLIKA S.R.O.; SANOFI R&D; STADA ARZNEIMITTEL AG; TECNIFAR S.A.; TEVA PHARMACEUTICALS EUROPE; WOCKHARDT UK LIMITED.
JOINT PASS	Yes

RESEARCH QUESTION AND OBJECTIVES	Research question: What is the impact of the implementation of the new (2018) Risk Minimisation Measures (RMMs) and Pregnancy Prevention Programme (PPP) on the knowledge and behaviour of Health Care Professionals (HCPs) who prescribe or dispense valproate and of patients treated with valproate in Europe? Objectives for survey among HCPs: • To assess HCPs awareness related to both receipt and reading of the new (2018) RMMs including direct healthcare professional communication (DHPC) and educational materials (EMs) for valproate-containing medicines. • To assess HCPs knowledge with respect to the new (2018) RMMs including measures of PPP, prescribing/dispensing conditions and risks associated with exposure to valproate-containing medicines during pregnancy. • To assess HCPs behaviour with respect to the new (2018) RMMs regarding the measures of the PPP. Objectives for survey among Patients: • To assess the awareness of women of child bearing potential (WCBP) treated with valproate-containing medicines related to both receipt and reading of the new (2018) RMMs including the educational materials provided by the HCPs. • To assess the knowledge of WCBP treated with valproate-containing medicines with regards to risks associated with use of valproate-containing medicines during pregnancy and measures to avoid exposed pregnancies. • To assess the behaviour of WCBP treated with valproate-containing medicines with respect to the new (2018) RMMs including measures of the PPP.
COUNTRY(-IES) OF STUDY	France, United Kingdom, Sweden, Poland, Germany and Spain
AUTHORS	Sara Miranda, PharmD, IQVIA Real World Insights Massoud Toussi, MD, MSc, PhD, IQVIA Real World Evidence Solutions On behalf of IQVIA and the consortium

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	This section provides contact details of the companies involved in the consortium (All MAHs contact details are provided in Annex 4). APOTEX EUROPE B.V.; ARISTO PHARMA GMBH; ARROW GENERIQUES; BETAPHARM ARZNEIMITTEL GMBH; BIOGARAN; BIOMO PHARMA GMBH; CONSILIENT HEALTH LIMITED, CRESCENT PHARMA, DESITIN ARZNEIMITTEL GMBH; GENERIS FARMACEUTICA S.A.; G.L. PHARMA GMBH; HEXAL AG; LUPIN HEALTHCARE (UK) LTD; MYLAN SAS; NEURAXPHARM ARZNEIMITTEL GMBH; ORION CORPORATION; PHARMASWISS CESKA REPUBLIKA S.R.O.; SANOFI R&D; STADA ARZNEIMITTEL AG; TECNIFAR S.A.; TEVA PHARMACEUTICALS EUROPE; WOCKHARDT UK LIMITED
MAH contact person (on behalf of MAHs)	Amélie Prieur, Deputy QPPV SANOFI R&D 1 Avenue Pierre Brossolette 91385 Chilly-Mazarin France

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

1. TABLE OF CONTENTS

List of Tables

2. LIST OF ABBREVIATIONS

AE	Adverse event
ANSM	Agence nationale de sécurité du médicament et des produits de santé
CI	Confidence interval
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures – Human
DHPC	Direct Healthcare Professional communication
DUS	drug utilisation study
EDC	Electronic data capture
EC	Ethics committee
EM	Educational Materials
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EphMRA	European Pharmaceutical Marketing Research Association
EU	European Union
EuC	European Commission
GP	General Practitioner
GVP	Good Pharmacovigilance Practice
HCP	Healthcare Professional
IRB	institutional review board
MAH	marketing authorisation holder
PPP	Pregnancy Prevention Program
PRAC	Pharmacovigilance Risk Assessment Committee
PV	Pharmacovigilance
RMM	Risk Minimization Measure
SAP	Statistical analysis plan
SmPC	Summary of product characteristics
SOP	Standard operating procedure
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
WCBP	Women of Child Bearing 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 WORLD PUBLICATIONS LTD,** a company registered under the laws of England and Wales, company registration number 01124807 Address: 210 Pentonville Road, London, N1 9JY, United Kingdom Contact: Mathieu Rosé Phone: +33 (0)1 7320 4064
Principal Investigator	Massoud Toussi, MD, (Principal Investigator) Medical Director, Lead Pharmacoepidemiology and Drug Safety, IQVIA
IQVIA project team	• Scientific oversight: Massoud Toussi, MD, (Principal Physician) Medical Director, Lead Pharmacoepidemiology and Drug Safety • Project Manager: Mathieu Rosé, MSc, Pharmacoepidemiology and Drug Safety • Field Work Coordination: Urszula Blak, MSc, Consultant, Primary Intelligence • Medical writing: Sara Miranda, PharmD, Senior Medical Writer / Senior Pharmacoepidemiologist, Real World Insights • Biostatistical Oversight: NN

4. ABSTRACT

Full Study Title: Surveys among Health Care Professionals and Patients to assess their knowledge and behaviour with respect to the new (2018) Risk Minimization Measures for valproate use in Europe.

Protocol version 6.0 dated November 4th, 2020

Rationale and background:

Valproate and related substances (sodium valproate, valproic acid, valproate semisodium, valpromide, and valproate magnesium) have been licensed since 1967 to treat epilepsy and since 1995 to treat bipolar disorders 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, women of child bearing potential (WCBP) and pregnant women, due to the risk of malformations and developmental disorders in babies exposed to valproate in utero. The review confirmed the already known teratogenic risks associated with the use of valproate in pregnant women. Available data showed an increased incidence of minor and major malformations in children born to mothers treated with valproate and related substances during pregnancy. Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems. For the epilepsy and manic episodes in bipolar disorder indications, the PRAC concluded that in view of the risks associated with use during pregnancy, valproate and related substances should not be used in female children, women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated.

Measures taken following the 2014 Article 31 referral included restrictions on the use of valproate containing substances. Restrictions were applied to the label and risk minimization measures (RMMs), such as educational materials for physicians and patients, were implemented (EMA, 2014).

The results of various utilization 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.

The French National Agency for Medicines and Health Products Safety (ANSM) 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 RMMs in the current levels of exposure to valproate during pregnancy and their impact on benefit-risk balance. 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. The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed the PRAC recommendation on 21 March 2018 and an EC decision was adopted on 31 May 2018

The PRAC requested MAHs to conduct surveys among healthcare professionals (HCPs) and patients to assess the effectiveness of the new risk minimization measures, imposed as two conditions to the marketing authorisation (cf extract of PRAC assessment report below):

"The MAHs are requested to conduct a survey among HCPs (including prescribers, gynaecologists and pharmacists) to assess their knowledge and behaviour with regard to the pregnancy Prevention Program as well as their receipt/use of the Direct Healthcare Professional communication (DHPC) and educational materials (EMs). In addition, the MAHs should perform a survey among patients to assess knowledge of the patients with regards to the PPP as well as receipt/use of educational materials."

Research question and objectives:

Research question:

What is the impact of the implementation of the new (2018) RMMs and PPP on the knowledge and behaviour of HCPs who prescribe or dispense valproate and of patients treated with valproate in Europe?

Objectives for survey among HCPs:

- To assess HCPs awareness related to both receipt and reading of the new (2018) RMMs including DHPC and EMs for valproate-containing medicines.
- To assess HCPs knowledge with respect to the new (2018) RMMs including measures of PPP, prescribing/dispensing conditions and risks associated with exposure to valproate-containing medicines during pregnancy.
- To assess HCPs behaviour with respect to the new (2018) RMMs regarding the measures of the PPP.

Objectives for survey among Patients:

- To assess the awareness of WCBP treated with valproate-containing medicines related to both receipt and reading of the new (2018) RMMs including the educational materials provided bythe HCPs.
- To assess the knowledge of WCBP treated with valproate-containing medicines with regards to risks associated with use of valproate-containing medicines during pregnancy and measures to avoid exposed pregnancies.
- To assess the behaviour of WCBP treated with valproate-containing medicines with respect to the new (2018) RMMs including measures of the PPP.

Study design:

This is a cross-sectional, multinational and non-interventional survey including multiple healthcare professionals (including prescribing physicians, gynaecologists and pharmacists) and patients (including WCBP treated with valproate and related substances, either for epilepsy or bipolar disorders). The prescribers, gynaecologists and patients' surveys are planned to be conducted in six European countries (France, UK, Sweden, Poland, Germany and Spain) whereas, pharmacists' survey is planned to be conducted in five European countries (UK, Sweden, Poland, Germany and Spain).

The HCPs' surveys will be conducted first. This will be followed by the patients' survey. Patients will be recruited through three different pathways in all but one country (Spain); by HCPs who participated in the physicians' survey, HCPs who did not participate in the physicians' survey and by a consumers panel. In Spain, patients will be recruited by a consumers panel only.

HCPs population:

- General Practitioners (GPs), neurologists (including paediatric neurologists), paediatricians and psychiatrists who have prescribed valproate to female patients at least once in the six months prior to participation in the survey
- Gynaecologists who have seen patients treated with valproate at least once in the six months prior to participation in the survey
- Pharmacists who have dispensed valproate to female patients at least once in the six months prior to participation in the survey

Patient population:

- Female patients of childbearing age (i.e., 13 to 49 years of age) and being treated with valproate-containing medicines at the time of the survey

Variables:

<u>Collected through HCPs surveys</u>

<u>Prescribing physicians/ Gynaecologists/ Pharmacists</u>

- Variables related to HCPs participation:
    - Response rate
    - Refusal rate

- Variables related to HCPs practice information:
    - Demographic information (country, age, gender)
    - HCP primary specialty (GP/ psychiatrist/ neurologist/ gynaecologist or pharmacist)
    - Duration of practice in primary specialty
    - Practice setting
        - office and/or hospital-based
        - urban or rural area
    - Prescribing/Dispensing volume (number of WCBP treated/ dispensed valproate, average per month in the 6 months prior to participation in the survey, proportion of children patients) [GP/ psychiatrist/ neurologist, or pharmacist]

Prescribing physicians

- Variables related to the HCPs awareness on the DHPC and educational materials recently approved for valproate-containing medicines:
    - Receipt and reading of DHPC (Yes/No/ I do not remember tick boxes)
    - Receipt and reading of educational materials (HCPs guide, patient guide, patient card and annual risk acknowledgement forms)

- Variables related to the knowledge of the risks associated with valproate exposure during pregnancy and the recently approved restrictions of use in WCBP and during pregnancy:
    - Prescribing conditions of valproate (True/False/ I don't know tick boxes)
    - Congenital malformations and neurodevelopmental disorders associated with valproate use during pregnancy (True/False/ I don't know tick boxes)
    - PPP measures (True/False/ I don't know tick boxes)

- Variables related to the HCPs behaviour regarding the measures of the PPP:
    - Version of HCP guide used (original or downloaded)
    - Use of the annual risk acknowledgment form; ensuring patients' knowledge on the risks of valproate use and on PPP measures, including counselling patients for effective contraception throughout the treatment (tick boxes listing various actions with the annual risk acknowledgement form)
    - Dissemination of the patient's guide to women of childbearing potential (Yes/No tick boxes)
    - Advice on contraceptive methods to patients
    - Management of information about contraception methods (tick boxes with various options of counselling)
    - Pregnancy tests to be conducted before treatment initiation, and also during the treatment with valproate (tick boxes with frequency of pregnancy testing)
    - Conditions of use of valproate (tick boxes with clinical cases consistent or inconsistent with the recommended conditions of use)
    - Counselling patients when they are planning for pregnancy (tick boxes with answers that are either consistent or inconsistent with the PPP)
    - Counselling patients in case of unplanned pregnancy or pregnancy suspicion (tick boxes with answers that are either consistent or inconsistent with the PPP and reference to get a specialized teratology/prenatal advice)
    - Annual review of treatment by a specialist (tick boxes with frequency of follow-up visits)

Gynaecologists

- Variables related to the HCPs awareness on the DHPC and educational materials targeted to gynaecologists:
    - Receipt and reading of DHPC (Yes/No/I do not remember tick boxes)
    - Receipt and reading of HCP guide (Yes/No/I do not remember tick boxes)
    - Awareness about the existence of a patient card (Yes/No tick boxes)

- Variables related to the knowledge of the risks associated with valproate exposure during pregnancy and the recently approved restrictions of use in WCBP and during pregnancy:
    - Prescribing conditions of valproate (True/False/I don't know tick boxes)
    - Risks of congenital malformations and neurodevelopmental disorders associated with valproate use during pregnancy (True/False/I don't know tick boxes)
    - PPP measures (True/False/I don't know tick boxes)
    - Methods of effective contraception (tick boxes listing various contraceptive methods)

- Variables related to the HCPs behaviour regarding the measures of the PPP:
    - Version of HCP guide used (original or downloaded)
    - Counselling patients when they are planning for pregnancy (tick boxes with answers that are either consistent or inconsistent with the PPP)
    - Counselling patients in case of unplanned pregnancy or pregnancy suspicion (tick boxes with answers that are either consistent or inconsistent with the PPP and reference to get a specialized teratology/prenatal advice)
    - Counselling patients for effective contraception throughout the treatment (tick boxes with answers that are either consistent or inconsistent with the PPP)

<u>Pharmacists</u>

- Variables related to the HCPs awareness on the DHPC and educational materials:
    - Receipt and reading of DHPC (Yes/No/I do not remember tick boxes)
    - Receipt and reading of the patients' cards (Yes/No/I do not remember tick boxes)
    - Receipt and reading of HCP guide (Yes/No/I do not remember tick boxes)
    - Version of HCP guide used (original or downloaded)

- Variables related to the knowledge of the risks associated with valproate exposure during pregnancy and the recently approved restrictions of use in WCBP and during pregnancy:
    - Prescribing conditions of valproate (True/False/I don't know tick boxes)
    - Risks of congenital malformations and neurodevelopmental disorders associated with valproate use during pregnancy (True/False/I don't know tick boxes)
    - PPP measures (True/False/I don't know tick boxes)

- Variables related to the HCPs behaviour regarding the measures of the PPP:
    - Distribution and discussion around Patient Card during dispensing
    - Counselling patients when they are planning for pregnancy (tick boxes with answers that are either consistent or inconsistent with the PPP)
    - Counselling patients in case of unplanned pregnancy or pregnancy suspicion (tick boxes with answers that are either consistent or inconsistent with the PPP and reference to get a specialized teratology/prenatal advice)

Collected through the patients survey

- Variables related to patients treated with valproate:
  - Patient age
  - Length of valproate treatment
  - Education level
  - Parity and pregnancy history, current pregnancy, desire for pregnancy
- Variables related to the patients' awareness of the Educational materials
  - Receipt of EMs containing information on the risks of valproate use from the HCPs (patient guide, patient card and annual risk acknowledgement form)
  - Patient's preference for finding more information related to valproate treatment
  - Reading of the content of EMs
- Variables related to the patients' knowledge of the risks of valproate use and measures to avoid pregnancies exposed to valproate:
  - Conditions of use of valproate (True/False/I don't know tick boxes)
  - Risks of congenital malformations and neurodevelopmental disorders (True/False/I don't know tick boxes)
  - Measures needed during valproate treatment (True/False/I don't know tick boxes)
- Variables related to the patients' behaviour to the RMMs
  - Pregnancy testing before treatment with valproate (Yes/No/I do not remember tick boxes)
  - Type of pregnancy test usually done (tick boxes listing urinary test and/or blood test)
  - Use of contraceptive methods used during treatment with valproate (Yes/no tick boxes
  - Types of contraceptive methods used during treatment with valproate (tick boxes listing various types of contraceptive methods)
  - (if applicable) Reason(s) for not using contraception during treatment with valproate (tick boxes listing various possible reasons)
  - Receipt of information on the methods for effective contraception (Yes/No/I do not remember tick boxes)
  - Actions to be taken in case the patient plans to become pregnant (Yes/No)
  - Actions to be taken in case of unplanned pregnancy or pregnancy suspicion (Yes/No)
  - Frequency of visits to different HCPs (tick boxes with frequency of follow-up visits by HCP)

Data Sources:

The study is a survey using primary data collection conducted through HCP *(*including prescribing physicians, gynaecologists and pharmacists) and patient questionnaires administered by web. Paper-version of the questionnaire will be offered to Patients only. The prescribers, gynaecologists and patients' surveys are planned to be conducted in six European countries (*France, UK, Sweden, Poland, Germany and Spain*) whereas, pharmacists' survey is planned to be conducted in five European countries (*UK, Sweden, Poland, Germany and Spain*).

Study size:

A sample size of 1328 completed questionnaires from physicians who have prescribed valproate at least once in the six months prior to participation in the survey, is envisaged. Also, the survey will target 215 completed questionnaires from gynaecologists, having seen patients treated with valproate in the six months prior to participation in the survey.

A sample size of 384 completed questionnaires from pharmacists who have dispensed valproate at least once in the six months prior to participation in the survey, is envisaged.

A sample size of 768 completed questionnaires from patients treated with valproate at the time of survey participation, is envisaged.

Data analysis:

The statistical analysis will be conducted using the SAS® softwareV9.4 or above on Windows™ (SAS Institute, North Carolina, USA).

All the analyses will be descriptive. Continuous variables will be described by their mean, standard deviation, and median, first quantile (Q1), third quantile (Q3), minimum and maximum. Categorical variables will be described as total number and relative percentage per category.

Analysis for the survey will be performed for patients and HCPs (prescribers, gynaecologists and pharmacists) separately for the endpoints described below, and will include the total number of patients and HCPs with valid responses to all relevant questions and the percentage of patients and HCPs with a positive response for the endpoints:

- Awareness will be assessed through the percentage of patients and HCPs who received and read the EMs
- A knowledge score will be created to summarize all responses at individual patient and HCP level. An individual patient/HCP score is calculated as the proportion of correct responses among all questions related to knowledge.
- A behaviour score will be created to summarize all responses at individual patient and HCP level. An individual patient/HCP score is calculated as the proportion of correct responses among all questions related to behaviour.

The statistical results of the included European countries will be presented overall and then at country level. The analysis of the Patients' and HCPs' surveys will then be broken down by subpopulation of interest, i.e. according to therapeutic indication (epilepsy / bipolar disorders).

Finally, the following additional sub-group analysis are planned:

- by age group (under 18 / adults) for Patient survey
- by medical specialty (GPs, specialists managing epilepsy (neurologists or paediatricians), psychiatrists, gynaecologists) for the Physicians' Survey
- by receipt/non-receipt of the educational materials

Among pharmacists, no other sub-group analysis is planned beyond country-level.

Milestones:

Initial protocol submission: 30 November 2018

Registration in the EU PAS register: 28 April 2020

Start of data collection for HCP: 10 July 2020

Start of data collection for patients: 05 August 2020

End of data collection for HCP: 05 October 2020

End of data collection for patients: as soon as the targeted sample size is reached, anticipated to be in Q1 2021

Final report including HCP and Patients' results: 16 August 2021

5. AMENDMENTS AND UPDATES

Substantial protocol amendments will be submitted to the Institutional Review Board (IRB)/Ethics Committee (EC) and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes that involve logistical or administrative aspects only (e.g. change in contact information).

Number	Date	Section of the Protocol	Amendment or update	Reason
1	23/06/2020	9.2.4 and 9.5.2	Update: Patients enrolment in Spain limited to 25 patients recruited by Consumers Panel only	Regulatory requirements in Spain
		9.7.2	Update on the "period between implementation of the aRMM and administration of the survey (<6 months, 6-12 months, more than 12 months)"	Period between of implementation of the aRMM and administration of the survey exceeding 12 months
2	07/10/ 2020	6.	Milestones	Extension of the data collection period for patients due to slow increase in the recruitment of patients completing the survey
3	04/11/ 2020	6.	Milestones	PRAC requested to submit HCP and Patient reports at the same time for parallel assessment. The extended submission due date for both reports is 16 August 2021

6. MILESTONES

The planned dates for key study milestones are:

Milestone	Planned date
Initial protocol submission	30 November 2018
Start of data collection for HCP	10 July 2020
Start of data collection for patients	05 August 2020
End of data collection for HCP	05 October 2020
End of data collection for patients	As soon as the targeted sample size is reached, anticipated to be in Q1 2021
Registration in the EU PAS register	28 April 2020
Final report including HCP and Patients' results	16 August 2021

The table below summarizes per country the time schedule of distribution of DHPC and EM in the study countries.

Table 1 Time schedule of distribution of DHPC and EM in the study countries

	France	UK	Sweden	Poland	Germany	Spain
Completion date for distribution of DHPC completion	July 2018	September 2018	October 2018	November 2018	November 2018	July 2018 (to HCPs via the Societies)
Completion date for EM (HCP Guide, Patient Guide, Patient Card, Annual Risk Acknowledgment form)	October 2018	September 2018	October 2018	December 2018	November 2018	July 2018* and September 2018**

*to HCPs via the Societies ; ** Patient Card by post to pharmacists

7. RATIONALE AND BACKGROUND

7.1 Background

Valproate and related substances are licensed since 1967 to treat epilepsy and since 1995 to treat bipolar disorders in Europe. In some European Union (EU) countries, valproate is also indicated in prophylaxis of migraine attacks.

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, women of child bearing potential (WCBP) and pregnant women. The review confirmed the already known teratogenic risks associated with the use of valproate in pregnant women. Data derived from a meta-analysis had shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% confidence intervals: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established. The incidence of risk appears also to be higher with valproate than with other antiepileptics (EMA, 2014).

Available data showed an increased incidence of minor and major malformations in children born to mothers treated with valproate and related substances during pregnancy. The most common types of malformations included neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems (EMA, 2014).

Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded (EMA, 2014).

Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems. Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ. Available data showed that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population. Limited data suggested that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD) (EMA, 2014).

For the epilepsy and manic episodes in bipolar disorder indications, the PRAC concluded that in view of the risks associated with use during pregnancy, valproate and related substances should not be used in female children, women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated. The PRAC noted that in some Member States valproate is authorized for the prevention of migraine attacks. In view of the risks of valproate use during pregnancy and the available therapeutic alternatives for the treatment of acute migraine attacks, the PRAC concluded that in prophylaxis of migraine attacks valproate should be contraindicated in pregnancy or in women of childbearing potential who are not using effective methods of contraception. Pregnancy must be excluded before start of treatment with valproate. A survey was conducted in 2016 through a web questionnaire among prescribers of valproate over 5 European countries, sponsored by a valproate companies consortium. This survey found that

the majority of participating physicians were knowledgeable about the indication and the safety aspects of prescribing and using valproate, particularly those who acknowledged receipt of precedent versions of DHPC and Educational materials (EMs): 95.5% of physicians only prescribed valproate for epilepsy and bipolar disorder in women if other treatments were ineffective or not tolerated, 92.1% of physicians always informed patients about the risks of taking the drug during pregnancy before prescribing valproate and/or related substances to a female of childbearing potential, and 94.4% of the physicians advised the patient about using effective contraception during the treatment before prescribing valproate and/or related substances to a woman of childbearing potential.

However, the results of various utilization 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. Notably, a survey conducted on two samples of over 200 pharmacies in metropolitan France, successively in 2016 and 2017. Overall, the level of compliance with prescribing and dispensing conditions was very insufficient, even though it has progressed since 2016. In fact, compliance rates found in this pharmacy survey were of the order of 31% in 2016 and 47% in 2017. The risk acknowledgment form was only presented for 50% of dispensations in 2017 (33% in 2016).

In this context, in March 2017, French Health authorities triggered a referral under Article 31 of Directive 2001/83/EC and requested the PRAC to assess the impact of risk minimization measures (RMMs) for the current levels of exposure to valproate during pregnancy 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 PPP and revised educational measures. The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed the PRAC recommendation on 21 March 2018 and an EC decision was adopted on 31 May 2018.

Specifically the PRAC recommendations are:

- Where licensed for migraine or bipolar disorder:
  - *In pregnancy*: valproate must not be used.
  - *In female patients from the time they become able to have children*: valproate must not be used unless the conditions of a new PPP (see below) are met.
- For epilepsy:
  - *In pregnancy*: valproate must not be used. However it is recognized that for some women with epilepsy it may not be possible to stop valproate and they may have to continue treatment (with appropriate specialist care) in pregnancy.
  - *In female patients from the time they become able to have children*: valproate must not be used unless the conditions of the new PPP are met.

Additional measures have been taken to ensure increased awareness, knowledge and adherence of HCPs and patients to the new (2018) RMMs with respect to PPP. The additional RMMs (aRMMs) distributed to HCPs included DHPC and EMs recently approved for valproate-containing medicines including HCP brochure, patient guide, patient card and annual risk acknowledgement form. The aRMMs distributed to WCBP who are

being treated with valproate-containing medicines included receipt of EMs from the HCPs such as patient guide, patient card and annual risk acknowledgement form.

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. In anticipation of time needed to have this outer package changes fully implemented, the Patient Card will be provided by the pharmacist, separately.

The PRAC has also recommended that the outer packaging of all valproate medicines should include a visual warning about the risks in pregnancy. In addition to boxed text, this may include a symbol/pictogram, with the details to be approved by national competent authorities.

Based on 8 February 2018 EMA/67672/2018 the main points of the PPP for valproate and related substances include:

- *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
- explaining the need for effective contraception throughout treatment,
- carrying out *reviews of treatment* by a specialist 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.
- an update of *educational materials* (HCPs and Patient Guides, Annual Risk Acknowledgement Form) and introduction of a patient card attached to the packaging with the aim to fully inform patients and healthcare professionals of the risks to the unborn child when exposed in utero to valproate:

The PPP addresses the issues of effective contraceptive use, pregnancy testing and planning, annual visit of the treatment.

7.2 Rationale

Following CMDh endorsement of PRAC recommendations, the companies that market valproate must carry out further studies to characterize the nature and extent of the risks posed by valproate and monitor ongoing valproate use and the long-term effects of affected pregnancies. Among these, the PRAC requested MAHs to conduct surveys among HCPs and patients to assess the effectiveness of the new RMMs imposed as two conditions to the marketing authorisation:

The MAHs of medicinal products with substances related to valproate shall perform a survey among HCP to assess knowledge of HCP and behaviour with regard to PPP as well as receipt/use of DHPC and educational materials. Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC : The final study report shall be submitted to the PRAC:	Within 6 months of the Commission decision. Within 12 months after endorsement of the study protocol.
The MAHs of medicinal products with substances related to valproate shall perform a survey among patients to assess knowledge of the patients with regards to PPP as well as receipt/use of educational materials. Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC : The final study report shall be submitted to the PRAC:	Within 6 months of the Commission decision. Within 12 months after endorsement of the study protocol.

As per PRAC assessment report, the studies should aim to "assess HCPs and patients' knowledge and behaviour with regard to the PPP as well as their receipt/use of DHPC and educational materials".

A single study was designed to assess the effectiveness of RMMs among HCPs and patients due to alignment of objectives.

This joint post-authorisation safety study (PASS) survey will be conducted according to the Guideline on good pharmacovigilance practices (GVP) – Module VIII (Rev 3) dated 9 October 2017 (EMA/813938/2011 Rev 3).

8. RESEARCH QUESTION AND OBJECTIVES

Research question:

What is the impact of the implementation of the new (2018) RMMs and PPP on the knowledge and behaviour of HCPs who prescribe or dispense valproate and of patients treated with valproate in Europe?

Objectives for survey among HCPs:

- To assess HCPs awareness related to both receipt and reading of the new (2018) RMMs including DHPC and EMs for valproate-containing medicines.

- To assess HCPs knowledge with respect to the new (2018) RMMs including measures of PPP, prescribing/dispensing conditions and risks associated with exposure to valproate-containing medicines during pregnancy.
- To assess HCPs behaviour with respect to the new (2018) RMMs regarding the measures of the PPP.

Objectives for survey among Patients:

- To assess the awareness of WCBP treated with valproate-containing medicines related to both receipt and reading of the new (2018) RMMs including the educational materials provided by the HCPs.
- To assess the knowledge of WCBP treated with valproate-containing medicines with regards to risks associated with use of valproate-containing medicines during pregnancy and measures to avoid exposed pregnancies.
- To assess the behaviour of WCBP treated with valproate-containing medicines with respect to the new (2018) RMMs including measures of the PPP.

9. RESEARCH METHODS

9.1 Study design

This is a cross-sectional, multinational and non-interventional survey conducted among healthcare professionals (including prescribing physicians, gynaecologists and pharmacists) and patients (including WCBP treated with valproate and related substances, either for epilepsy or bipolar disorders). The physicians and patients' surveys are planned to be conducted in six European countries (France, UK, Sweden, Poland, Germany and Spain) whereas, pharmacists' survey is planned to be conducted in five European countries (UK, Sweden, Poland, Germany and Spain). The pharmacists' survey will not be deployed in France, where specific annual surveys have been performed at Agence nationale de sécurité du médicament et des produits de santé (ANSM) request. However, the study results will be put in perspective with those published from these annual pharmacists' surveys conducted in France. There will not be any statistical comparison.

The HCPs' surveys will be conducted first. This will be followed by the patients' survey. Patients will be recruited through three different pathways in all but one country (Spain); by HCPs who participated in the physicians' survey, by HCPs who did not participate in the physicians' survey and by a consumers panel. In Spain, patients will be recruited by a consumers panel only.

9.1.1 Data collection

The data collection period for the physicians (prescribers and gynaecologists), pharmacists and patients' surveys will take about six months of fieldwork. In case a higher number of participants need to be included, the fieldwork will be extended accordingly. The fieldwork in each country will only start after the educational materials (EM) containing the RMMs have been distributed in each country to enable the assessment of EM effectiveness. Generally, a six to twelve-month period is considered after the distribution of the EM to allow for full implementation of the RMMs. Accordingly, the survey start date will begin approximately eighteen to twenty-four months after the date of distribution of the EM in the

individual countries listed for evaluation within this protocol. This date may vary by country, based on the date of EM approval by the local Health Authority. Data will be collected from HCPs from an online questionnaire, patients will get the additional option to answer on paper.

To ensure that the invitation and survey are comprehensible, all outreach will be conducted in the local language of each country.

Due to regulatory constraints, the survey for HCPs and patients will be conducted separately. In fact, if the survey for HCPs and patients are conducted at the same time, the submission of the names of HCPs to the EC becomes a requirement in some countries. In this case, the HCPs shall be contacted before the survey to give consent for the submission of their names to the EC. This process would bias the survey as they would know upfront about the survey in which they would participate later. In order to avoid this information bias, we will first conduct the survey among HCPs. In this step, prescribing physicians will also be invited to recruit patients for the next step. IRB/EC submissions for the patient survey will be conducted and prescribing physicians will enrol patients for participation in the survey.

9.1.2 Approaches for increasing response rates

In order to increase the response rate among HCPs, a compensation fee will be proposed to HCPs for their participation in the survey, as a financial incentive-based approach has been shown to improve HCP response rates (VanGeest et al. 2007).

9.2 Setting

The HCPs (including prescribing physicians, gynaecologists and pharmacists) and patients' survey (including WCBP treated with valproate and related substances, either for epilepsy or bipolar disorders) will be conducted via a web questionnaire. The prescribers, gynaecologists and patients' surveys are planned to be conducted in six European countries (France, UK, Sweden, Poland, Germany and Spain) whereas, pharmacists' survey is planned to be conducted in five European countries (UK, Sweden, Poland, Germany and Spain). Paper-version of the questionnaire will be offered to Patients only.

These countries have been selected considering the following items:
- representativeness in term of target population size
- representativeness in term of European region
- representativeness in term of regulatory feasibility

The table below summarizes per country the proportion of sales of valproate and related substances in Europe:

Table 2 Proportion of sales of valproate and related substances in Europe

Country	% sales
France	16,1%
UK	15,8%
Germany	15,0%
Italy	13,6%

Country	% sales
Spain	7,9%
Russia	6,5%
Poland	6,3%
Netherlands	2,4%
Turkey	2,2%
Portugal	1,9%
Belgium	1,6%
Finland	1,3%
Romania	1,3%
Switzerland	1,1%
Czech	1,0%
Greece	0,8%
Sweden	0,8%
Ireland	0,8%
Norway	0,7%
Austria	0,6%
Bulgaria	0,6%
Slovakia	0,5%
Croatia	0,4%
Hungary	0,4%
Lithuania	0,3%
Slovenia	0,1%
Latvia	0,1%
Estonia	0,1%
Luxembourg	0,05%

Indeed, valproate use is variable across countries, higher in France (16.1%), UK (15.8%), intermediate in Spain (7.9%) or Poland (6.3%) and low in Sweden (0.8%). Variation in countries' population size is also to be considered. Finally, sample selection must reflect different EU regions (Western, Eastern, Northern and Southern regions). In each country, eligible HCPs will be identified according to their specialty as specified in IQVIA ***OneKey*** database. HCPs at both office-based practices and hospitals will be included in the study.

Patients will be recruited by prescribing physicians that participate in the HCP survey, and who agree to distribute the patient questionnaires or by a consumer's panel. Pharmacists will be selected through a randomized sampling plan according to the vendor (Sermo) panel, including retail and hospital pharmacies.

The three tables below summarize the percentage of valproate prescriptions covered by various medical specialties between October 2017 to September 2018 in France, Germany and Spain.

Table 3 France: valproate and related substances in Europe

France :valproate prescriptions from October 2017 to September 2018	
Prescribers	**% sales**
GPs	61.7%
Psychiatrists	34.8%

France :valproate prescriptions from October 2017 to September 2018	
Prescribers	**% sales**
Neurologists	2.6%
Cardiologists, Enterologists, Paediatricians, Endocrinologists	less than 1% (by specialty)

Table 4 Germany: valproate and related substances in Europe

Germany : valproate prescriptions from October 2017 to September 2018	
Prescribers	**% sales**
Psychiatrists and Neurologists*	52.2%
GPs	43.5%
Paediatricians	3.8%
Rheumatologists, Gastroenterologists, Cardiologists, Urologists, Ear/ Nose/Throat specialists	less than 1% (by specialty)
Gynaecologists	0.06%

*In Germany, prescriptions of valproate of psychiatrists and neurologists are grouped in the same category and the details between both are not available.

Table 5: Spain: valproate and related substances in Europe

Spain : valproate prescriptions from October 2017 to September 2018	
Prescribers	**% sales**
Psychiatrists	49.7%
GPs	29.2%
Neurologists	14.6%
Paediatricians	4.2%
Internists, surgeons, Endocrinologists, Nephrologists, Cardiologists Rheumatologists, Urologists	less than 1% (by specialty)

Study period

Study started on 10 July 2020 and will be completed as soon as the targeted sample size of patients is reached, anticipated to be Q1 2021.

9.2.1 Inclusion criteria

The survey will be conducted among HCPs and patients meeting the following inclusion criteria:

Prescribers of valproate

GPs, neurologists (including pediatric neurologists), paediatricians and psychiatrists who prescribed valproate containing medicines to female patients of childbearing potential in the last 6 months.

Gynaecologists

Gynaecologists who have had a consultation with at least one female patient of childbearing potential treated with valproate containing medicines in the last 6 months.

Pharmacists

Pharmacists who have dispensed valproate containing medicines to female patients of childbearing potential in the last 6 months. The survey will enrol only those pharmacists who have dispensed the drug in a pre-specified period of last six months.

Patients

- Female patients of childbearing age (i.e., 13 to 49 years of age) and being treated with valproate-containing medicines at the time of the survey
- Who consent to participate in this self-administered survey (for patients between 13 to 17 years of age, the survey shall be filled out by their parent, guardian or caregiver).

9.2.2 Exclusion criteria

- HCPs or patients who may have conflicts of interest with the survey (i.e. patients employed by regulatory bodies or pharmaceutical companies).
- HCPs or patients (with a relative) involved in valproate-related lawsuits or associations for victims of valproate syndrome.

9.2.3 Subpopulations of interest

Sub-groups analysis will be conducted according to the indication for use of valproate:

- Epilepsy
- Bipolar disorders

For the Patients' survey, the variable "therapeutic indication" will be collected at individual level and will be used for subpopulation classification. Patients who report both indications will be treated as a third sub-group.

However, for the Physicians' survey, assumptions are deemed necessary for the classification of a prescriber according to therapeutic disease, since the summary of product characteristics (SmPC) and the RMMs are different between epilepsy and bipolar disorders (indication). The following key hypothesis will be employed for determining what therapeutic indication is expected to be more frequently found among the patients treated with valproate for each participant prescriber (further specifications will be provided later in the SAP):

- Neurologists are more likely to treat patients with Epilepsy.
- Psychiatrists are more likely to treat patients with Bipolar disorders.
- However, as GPs and Gynaecologists can follow patient with epilepsy or bipolar disorder, it would be difficult to allocate their responses to one therapeutic indication over another. Thus, an exploratory sub-group analysis, according to main therapeutic indication managed, will only be possible among those GPs that report treating mostly one of the two indications (assessed via Prescribing physician's questionnaire question D9).

9.2.4 Study enrolment

The following groups will be considered as the target population:

- All physicians in the study countries who are:
  - Main prescribers of valproate (GPs, psychiatrists, neurologists, paediatricians) or
  - Gynaecologists seeing patients who are treated with valproate. Despite the fact that gynaecologists in the UK may not be involved in managing contraception, they will be targeted in the UK as they may provide additional information on use of valproate in pregnant women or women planning pregnancy.
- All pharmacists in the study countries that are eligible to dispense valproate. The pharmacists' survey will not be deployed in France, where specific annual surveys have been performed at ANSM request.

The targeted HCPs will be randomly selected and enrolled on an ongoing basis until the study size is reached (Kish 1965). Random selection of physicians and pharmacists is performed to minimize selection bias.

Physicians

Physicians who consent to participate in these types of surveys will be first contacted by email, then by phone if they do not respond to the email. Their recruitment will be done as follows:

- Physicians will be invited to participate in the survey via email. The email invitations will contain the link to the web questionnaire. In the phone invitation, the survey background and objectives, the contact information for questions, and the proposed compensation will be explained to the Physicians at this step. Compensation will be compliant with relevant guidelines of each country and will compensate the actual effort and time needed to fill up the questionnaire.
- If the questionnaire is not completed, the Physicians will be sent a reminder by email one week after the start of the survey.
- If the target is not achieved, a second reminder by phone will be conducted circa 1.5 weeks after the start of the survey.
- If the questionnaire is still not completed, a third reminder will be sent to the Physicians by email approximately three weeks after the start of the survey.

A Physician will be considered unreachable if he/she has been contacted between three to five times without answer.

If necessary, i.e. if the target number of responders is still not reached, recruitment will continue to achieve the targeted study sample size.

For each physician selected, the number of times the physician was contacted, as well as the date and time when he/she completed the web questionnaire, will be recorded. The recruitment in each stratum (physician specialty/country) will be stopped when the target number is reached (See Section 9.5.2 Physician survey for details). If the list of physicians

is exhausted in any particular stratum, recruitment in this stratum will be prematurely ended, and a strategy will be determined to adjust the sample size with associated weighting.

The number of physicians that are eligible for inclusion in the study and the survey response rate will be monitored regularly.

Pharmacists

Pharmacists will be recruited by IQVIA's trusted and assessed vendor – Sermo, from the vendor representative panel. As in the Physicians' surveys, Pharmacists will be first contacted by email, then by phone if they do not respond to the email. Their recruitment will be done as follows:

- The sampling of pharmacists will follow a randomized sampling method which ensures the representativeness of the population being reached in order to limit selection bias which is commonly found in opportunistic selection method. However, only pharmacists who consent will participate, which brings some degree of selection bias that cannot be ruled out.
- Sermo team randomly contact pharmacists by e-mails or phone calls when needed, according to their sub-groups (See Section 9.5.2 Pharmacist survey for details). Survey background and objectives, the contact information for questions, and the proposed compensation will be explained at this stage.
- If they agree to participate in the survey, they will receive a link to access the survey and the instructions for web questionnaire completion.
- If the questionnaire is not completed in the IQVIA Primary Intelligence EDC system, the pharmacists will be sent a reminder by email one week after the start of the survey. Another reminder will be conducted by phone 1.5 week after the start of the survey.
- Sermo telephone team can call the pharmacists if they see that they get stuck during the course of completing the survey, or if they stop for any reason – they might provide technical help or other advice. These interactions cannot be scripted.
- A screening log is maintained to follow-up the inclusion of pharmacists in the survey over time.

A pharmacist will be considered unreachable if he/she has been contacted between three and five times without any answer being received.

If necessary, i.e. if the target number of responders is still not reached, recruitment will continue to achieve the targeted study sample size.

The number of pharmacists that are eligible for inclusion in the study and the survey response rate will be monitored regularly.

Patients

Patients in France, UK, Sweden, Poland and Germany will be recruited through three different pathways

- by HCPs who participated in the physicians' survey,

- by HCPs who did not participate in the physicians' survey
- by consumer's panels

In Spain, patients will be recruited by the consumer's panel only.

Recruitment by HCPs who participated in the the physicians' survey:

For patient questionnaires, each prescribing physician who has agreed to recruit patients will systematically distribute a kit containing a simplified guide for taking the web survey to eligible patients (that fit inclusion criteria) and the paper questionnaire so the patient can choose the most convenient option to complete the survey. A minimum of sixteen kits will be distributed per prescribing physician. To limit selection bias, HCP will be requested to select the last 16 patients to whom they have prescribed valproate.

Patient anonymity will be maintained throughout the study. When material for the web survey/paper questionnaire is given to a patient, the unique number for the patient survey is registered by the prescribing physician on the web survey. However, no log would be kept at the prescribing physician level which would provide linkage between material for the web survey distributed to the patients and patient identity. When a patient fills in the survey on the internet or sends it via post, the unique number for the patient survey will ensure that no more than sixteen patient questionnaires originate from the same practice.

Patient recruitment is competitive. The incentive for patient recruitment, which entails asking the patient to participate and forward the survey, will be small.

Selection bias is reduced through the systematic recruitment of patients by each prescribing physician and competitive selection, which does not guarantee that the whole physician's sample of selected patients will be finally included in the analysis sample of patients' surveyed. Furthermore, as there will be no information linking the patients' identities with the recruiting prescribing physician, there would be no incentive for prescribing physician to recruit their best patients.

Recruitment by HCPs who did not participate in the physicians' survey:

Patients will be recruited using the same methods, as used by the HCPs who participated in the prescribers' survey.

HCPs who have not participated to the physicians' survey will be contacted and asked a few screening questions in order to confirm their eligibility to participate in the survey and help with patients' recruitment. Each physician who has agreed to recruit patients will systematically distribute a kit containing a simplified guide for taking the web survey to eligible patients (that fit inclusion criteria) and the paper questionnaire so the patient can choose the most convenient option to complete the survey. A minimum of sixteen kits will be distributed per prescribing physician. To limit selection bias, HCP will be requested tp select the last 16 patients to whom they have prescribed valproate.

Patient anonymity will be maintained throughout the study. When material for the web survey/paper questionnaire is given to a patient, the unique number for the patient survey is registered by the prescribing physician on the web survey. However, no log would be kept at the prescribing physician level which would provide linkage between material for the web survey distributed to the patients and patient identity. When a patient fills in the survey on the internet or sends it via post, the unique number for the patient survey will ensure that no more than sixteen patient questionnaires originate from the same practice.

Recruitment from the consumers panels:

Patients will be recruited by IQVIA's trusted and assessed vendor – Glocal Mind, from the vendor panel.

Panelists enrolled to Glocal Mind are recruited by using various methods including web-banners, website referrals, pay-per-click, natural search optimization, affiliate marketing, email, and online public relations activities.

Potential panelists are also recruited through innovative approach "river samples" - It consists of recruiting individuals in real- time from a network of websites with which they have developed referral relationships. This methodology taps into many potential survey takers online who are willing to participate in surveys, but may not necessarily want to join a market research panel. Potential survey respondents are then asked a series of demographic (and attitudinal) questions. They are then directed to available surveys for which they might qualify.

Patients will be contacted by email. Their recruitment will be done as follows:

- The survey invite will be sent to profiled panel members (e.g. gender, age) via the e-mail they provided when registering. Only patients who consent will participate, which brings some degree of selection bias that cannot be ruled out.
- Survey background and objectives, the contact information for questions, the proposed compensation and the instruction for web questionnaire completion will be explained at the initial stage.
- If the questionnaire is not completed in the IQVIA Primary Intelligence EDC system, the patients will be sent a reminder by email one week after the start of the survey. Another reminder will follow 1.5 week after the start of the survey.
- In case of any technical problems with a completion of the survey or additional questions, respondents will contact Glocal Mind and they will provide IQVIA's team with an anonymous question and a request for help. IQVIA will not be in direct contact with respondents.
- A screening log is maintained to follow-up the inclusion of patients in the survey over time.

For all of the three recruitment pathways, data collection data management and quality control will follow the same process and manage by IQVIA as described in the paragraph 9.6 and 9.8.

The fieldwork will be controlled to ensure than the boundary of 50 % of the total number of patients surveyed is not exceeded for each of the three recruitment pathways in order to ensure a consistent sample for all the recruitment pathways.

9.3 Variables

9.3.1 Outcome definition and measures

9.3.1.1 Variables collected through the HCPs' surveys

The following variables are collected through the HCPs' surveys:

<u>Prescribing physicians/Gynaecologists/Pharmacists</u>

- Variables related to HCPs participation:
  - Response rate
  - Refusal rate

- Variables related to HCPs practice information:
  - Demographic information (country, age, gender)
  - HCP primary specialty (GP/ psychiatrist/ neurologist, with an additional paediatric specialty/ paediatrician/ gynaecologist or pharmacist)
  - Duration of practice in primary specialty
  - Practice setting
    - office and/or hospital-based
    - urban or rural area
  - Prescribing/Dispensing volume (number of WCBP treated/ dispensed with valproate, average per month in the 6 months prior to participation in the survey, proportion of children patients) [GP/ psychiatrist/ neurologist/paediatrician, or pharmacist]

<u>Prescribing physicians</u>

- Variables related to the HCPs awareness on the DHPC and educational materials:
  - Receipt and reading of DHPC (Yes/No/I do not remember tick boxes)
  - Receipt and reading of educational materials (HCPs guide, patient guide, patient card and annual risk acknowledgement forms) (Yes/No/I do not remember tick boxes)

- Variables related to the knowledge of the risks associated with valproate exposure during pregnancy and the recently approved restrictions of use in WCBP and during pregnancy:
  - Prescribing conditions of valproate (True/False/I don't know tick boxes)
  - Congenital malformations and neurodevelopmental disorders associated with valproate use during pregnancy (True/False/I don't know tick boxes)
  - PPP measures (True/False/I don't know tick boxes)

- Variables related to the HCPs behaviour regarding the measures of the PPP:
    - Version of HCP guide used (original or downloaded)
    - Use of the annual risk acknowledgement form; ensuring patients' knowledge on the risks of valproate use and on PPP measures, including counselling patients for effective contraception throughout the treatment (tick boxes with answers that are either consistent or inconsistent with the PPP)
    - Dissemination of the patient's guide to women of childbearing potential (tick boxes with answers that are either consistent or inconsistent with the PPP)
    - Advice on contraceptive methods to patients
    - Management of information about contraception methods (tick boxes with various HCPs)
    - Pregnancy tests to be conducted before treatment initiation, and also during the treatment with valproate (tick boxes with answers that are either consistent or inconsistent with the PPP)
    - Conditions of use of valproate (tick boxes with clinical cases consistent or inconsistent with the recommended conditions of use)
    - Counselling patients when they are planning for pregnancy (tick boxes with answers that are either consistent or inconsistent with the PPP)
    - Counselling patients in case of unplanned pregnancy or pregnancy suspicion (tick boxes with answers that are either consistent or inconsistent with the PPP and reference to get a specialized teratology/prenatal advice)
    - Annual review of treatment by a specialist (tick boxes with answers that are either consistent or inconsistent with the PPP)

<u>Gynaecologists</u>

- Variables related to the HCPs awareness on the DHPC and educational materials targeted to gynaecologists:
    - Receipt and reading of DHPC (Yes/No/I do not remember tick boxes)
    - Receipt and reading of HCP guide (Yes/No/I do not remember tick boxes)
    - Awareness about the existence of a patient card (Yes/No tick boxes)

- Variables related to the knowledge of the risks associated with valproate exposure during pregnancy and the recently approved restrictions of use in WCBP and during pregnancy:
    - Prescribing conditions of valproate (True/False/I don't know tick boxes)
    - Risks of congenital malformations and neurodevelopmental disorders associated with valproate use during pregnancy (True/False/I don't know tick boxes)
    - PPP measures (True/False/I don't know tick boxes)
    - Methods of effective contraception (tick boxes listing various contraceptive methods)

- Variables related to the HCPs behaviour regarding the measures of the PPP:
    - Version of HCP guide used (original or downloaded)
    - ECounselling patients when they are planning for pregnancy (tick boxes with answers that are either consistent or inconsistent with the PPP)

- Counselling patients in case of unplanned pregnancy or pregnancy suspicion (tick boxes with answers that are either consistent or inconsistent with the PPP)
- Counselling patients for effective contraception throughout the treatment (tick boxes with answers that are either consistent or inconsistent with the PPP and reference to get a specialized teratology/prenatal advice)

Pharmacists

- Variables related to the HCPs awareness on the DHPC and educational materials:
  - Receipt and reading of DHPC (Yes/No/I do not remember tick boxes)
  - Receipt and reading of the patients' cards (Yes/No/I do not remember tick boxes)
  - Receipt and reading of HCP guide (Yes/No/I do not remember tick boxes)
  - Version of HCP guide used (original or downloaded)

- Variables related to the knowledge of the risks associated with valproate exposure during pregnancy and the recently approved restrictions of use in WCBP and during pregnancy:
  - Prescribing conditions of valproate (True/False/I don't know tick boxes)
  - Risks of congenital malformations and neurodevelopmental disorders associated with valproate use during pregnancy (True/False/I don't know tick boxes)
  - PPP measures (True/False/I don't know tick boxes)

- Variables related to the HCPs behaviour regarding the measures of the PPP:
  - Distribution and discussion around Patient Card during dispensing
  - Counselling patients when they are planning for pregnancy (tick boxes with answers that are either consistent or inconsistent with the PPP)
  - Counselling patients in case of unplanned pregnancy or pregnancy suspicion (tick boxes with answers that are either consistent or inconsistent with the PPP and reference to get a specialized teratology/prenatal advice)

9.3.1.2 Variables collected through the patient survey

The following variables are collected through the patient survey:

- Variables related to the patients treated with valproate:
  - Patient age
  - Length of valproate treatment
  - Education level
  - Parity, pregnancy history, current pregnancy, desire for pregnancy

- Variables related to the patients' awareness of the educational materials
  - Receipt of EMs containing information on the risks of valproate use from the HCPs (patient guide, patient card and annual risk acknowledgement form)
  - Patient's preference for finding more information related to valproate treatment
  - Reading of the content of EMs

- Variables related to the patients' knowledge of the risks of valproate use and measures to avoid pregnancies exposed to valproate:
    - Conditions of use of valproate (True/False/I don't know tick boxes)
    - Risks of congenital malformations and neurodevelopmental disorders (True/False/I don't know tick boxes)
    - Measures needed during valproate treatment (True/False/I don't know tick boxes)

- Variables related to the patients' behaviour to the RMMs
    - Pregnancy testing before treatment with valproate (Yes/No/ I do not remember tick boxes)
    - Type of pregnancy test usually done (tick boxes listing urinary and/or blood test)
    - Use of contraceptive methods used during treatment with valproate (Yes/No tick boxes)
    - Types of contraceptive methods used during treatment with valproate (tick boxes listing various types of contraceptive methods)
    - (if applicable) Reason(s) for not using contraception during treatment with valproate (tick boxes listing various possible reasons)
    - Receipt of information on the methods for effective contraception (Yes/No/I do not remember tick boxes)
    - Actions to be taken in case the patient plans to become pregnant (Yes/No)
    - Actions to be taken in case of unplanned pregnancy or pregnancy suspicion (Yes/No)
    - Frequency of visits to different HCPs (tick boxes with various frequency of follow-up visits)

9.4 Data sources

The survey is a primary data collection conducted through:

- Physicians and Pharmacists questionnaires administered by web
- Patient questionnaire administered by web or self-report paper questionnaire

Physicians recruitment

Physicians will be identified randomly from ***OneKey*** lists (IQVIA) which is representative of the target population in all of countries and specialties. In case the number of Physicians are limited in a country, an invitation will be sent to all of them. The table below provides figures on the universe of OneKey physicians, that will be used for sampling:

Table 6: number of HCPs in OneKey database

One Key physicians uiniverse					
Country	Type of phycisians				
	GPs	**Neurologist (N) / pediatric neurologists (PN)**	**Psychiatrist**	**Gynaecologists**	**Paediatricians**
France	87,694	3,073 (N)	12,885	8,100	8,210
UK	52,953	1,700 (N)	5,482	3,529*	5,357
Sweden	7,267	565 (N)+ 70 (PN)	1,721	1,529*	1,325
Poland	25,158	3,737 (N)+ 208 (PN)	3,543	6,900*	10,999
Germany	46,417	15,301 (N) +502 (PN)	13,587	18,037*	13,248
Spain	16,753	2,895	6,603	8,629*	14,126

* includes obstetrician and gynaecologists

Pharmacists recruitment

Pharmacists will be identified according to panel of subcontractor Sermo representative following a randomized sampling plan for the whole pharmacist population for each country, which includes approximately:

- Sweden: 1,440 retail pharmacists (no hospital pharmacists)
- Poland: 13,500 retail pharmacists and 870 hospital pharmacists
- UK: 11,000 retail pharmacists and 7,000 hospital pharmacists
- Germany: 60,736 retail pharmacists and 2,212 hospital pharmacists
- Spain: 62,148 retail pharmacists and 2,119 hospital pharmacists

Patient recruitment

Patients in France, UK, Sweden, Poland and Germany will be recruited through three different pathways

- by HCPs who participated in the physicians' survey,
- by HCPs who did not participate in the physicians' survey
- by consumer's panels

In Spain, patients will be recruited by the consumer's panel only.

The table below provides figures on the consumers panel, that will be used for sampling:

Table 7 consumer panels: number of women aged 18-54 years

Consumers panels: Number of women aged 18-54 years	
Country	**n**
France	284,882
UK	268,400
Sweden	82,732
Poland	123,648
Germany	189,980
Spain	181,608

Limitations: women age < 18 years are not included in the consumers panel

9.5 Study sample size

9.5.1 Sample size calculation

The sample size formula, based on the normal approximation to the binomial distribution, for calculating the number of subjects required for a proportion is the following:

$$n = \frac{P \cdot (1-P) \cdot \left(Z_{1-\alpha/2}\right)^2}{e^2},$$

Where P is the expected proportion, e is one half the desired width of the confidence interval, and Z1–α/2 is the standard normal Z value corresponding to a cumulative probability of 1 – α/2 (e.g., if α = .05 then Z = 1.96). The following table provides the margin of error for 95% CI based on various sample sizes and proportions of interest.

Table 8 margin of error for 95% CI based on various sample sizes and proportions of interest

Margin of error for 95%CI (absolute precision)				
Proportion	**5%**	**4%**	**3%**	**2%**
10%	139	216	384	864
30%	323	504	896	2,017
50%	384	600	1,067	2,401
70%	323	504	896	2,017
90%	139	216	384	864

The proportions of interest (p) here are the proportions of HCPs and patients aware, knowledgeable and adherent to the PPP and RMMs.

As the proportion of interest (p) is not known for each objective in advance, we consider it to be 50% (maximum uncertainty). Such a hypothesis yields the most conservative i.e. the largest sample size.

Considering the expected minimum level of precision for the three-surveys population is 5%, the minimum required sample size would be 384 for a proportion of 50% and precision levels of 5% for each survey (physicians, pharmacist and patient survey).

Specific sample size requirement for physicians' survey:

The level of precision in the sub-population of the physician survey corresponds to both valproate indication, epilepsy and bipolar disorder, which have to be considered as sub-groups of interest of the survey. With a sample of only 384 physicians, based on the assumption than the expected number of physician by indication was 50%, the estimations among each group of 192 physicians by indication would have precision levels > 7%.

To enhance the level of precision by indication, the target will be boosted up to 1543 physicians to be surveyed:

- 529 GPs, enabling precision levels ≤5% around estimations.
- 385 psychiatrists and 414 specialists managing epilepsy (including a minimum of 340 neurologists and pediactric neurologists), enabling precision levels of ≤ 5% around estimations.
- 215 gynaecologists, enabling precision levels ≤7% around estimations.

Specific sample size requirement for patients' survey:

Based on the same rational as for the physician survey, the sample of patients has to be augmented to enhance precision of the subpopulation corresponding to both valproate indications. To enhance the level of precision by indication, 768 patients will be surveyed corresponding approximately to 384 patients by indication, enabling a precision of 5.0% for a proportion of 50%.

9.5.2 Sampling plan

Physician survey

For each selected country, the sample survey will include physicians identified and recruited from *OneKey* lists. A screening question will check whether the physician has prescribed valproate (or has seen patients treated with valproate, for gynaecologists) within the last six months and therefore can be considered for the survey.

Considering 80-90% of all questions will be provided with an answer, approximately 1715-1930 physicians shall be surveyed to obtain a sample of 1543 physicians. Ideally the sample of 1543 physicians should be proportionally split between the selected countries based on the number of physicians in each country and then further split among physicians based on their real proportion in each country.

However, due to the expected variance of the number of physicians in the six countries such a distribution is not feasible as it might yield a too small number of interviews in smaller countries. We propose a pragmatic split to allocate a sufficient size to the less represented strata of the sample. We will weigh the results back according to the real proportion of physicians from OneKey lists to allow the representativeness of the overall sample (see sample adjustment below).

As per sample size defined above and the number of selected countries, physicians can be stratified per country and per specialty according to the following table:

Table 9: sample size of the physicians' survey

Physicians' survey	**Sample size**				
Country	**GPs**	**Specialists managing epilepsy***	**Psychiatrists**	**Gynaecologists**	**Total**
France	150	70	90	40	350
UK	90	70	85	40	285
Sweden	35	34	30	15	114
Poland	50	65	40	20	175
Germany	112	85	85	50	332
Spain	92	90	55	50	287
Total	529	414	385	215	1543

* *including neurologists, pediatric neurologists and paediatricians*

The specialists managing epilepsy will be composed mainly of neurologists and pediatric neurologists with a desired sample of 384 as well as a desired sample of 30 paediatricians. The reason is that among all patients with epilepsy, based on valproate sales, the paediatric group represents about less than 5%. A minimum of 340 neurologists and pediatric neurologists will be considered as acceptable sample size for this specialty.

The recruitment will continue until the target number of physicians will be included in each strata (country*specialty) defined in the table above. Once a strata is completed, the recruitment is stopped in this strata in order to ensure the completion of the others and avoiding a competitive fieldwork with a potential unbalancing sizes between the strata.

In case the list of physicians in any particular stratum is exhausted, the recruitment will be prioritized within the strata of HCP type (HCPs survey) over the recruitment by country.

Pharmacist survey:

Ideally the sample of 384 pharmacists should be proportionally split between the selected countries based on the number of pharmacists in each country. The potential responders will be randomly selected. Recruitment will continue until a sufficient number of pharmacists have been enrolled.

However, due to the expected variance of the number of pharmacist in targeted countries such a distribution is not feasible as it might yield a too small number of interviews in smaller countries. We propose a pragmatic split to allocate a sufficient size to the less represented strata of the sample. We will weigh the results back according to the real proportion of pharmacists from Sermo lists to allow the representativeness of the overall sample (see sample adjustment below).

Table 10: sample size of the pharmacists' survey

Pharmacists' survey	
Country	**Total**
UK	88
Sweden	48
Poland	80
Germany	80
Spain	88
Total	**384**

We are expecting a proportion of 25% of hospital pharmacists and 75% of retail pharmacist in Poland, Germany and Spain. Hospital pharmacists' survey is not possible in UK and Sweden (100% of retail pharmacist).

Patient survey

Patients will be recruited through three different pathways; by HCPs who participated in the physicians' survey, HCPs who did not participate in the physicians' survey and by IQVIA's trusted and assessed vendor – Glocal Mind, from the vendor panel.

Among the 1254 prescribing physicians who contribute to the prescribing physicians survey and the HCPs who did not participate in the physicians' survey, we will expect 188 HCPs to participate in the patient survey including 7 patients each on average. Considering that about 80-90% of all questionnaires will be fully completed, approximately 745 patients will be surveyed by the intermediate of the HCPs recruitment. We will weigh the results back according to the real proportion of prescribers from OneKey lists to allow the representativeness of the overall sample (see section Sampling adjustment below).

The potential responders will be randomly selected. Recruitment will continue until a sufficient number of patients have been included to allow for sub-group analyses i.e. according to therapeutic indication (epilepsy/ bipolar disorders) and, by age group (under 18/ adults). The stratified analyses per receipt/non-receipt of the materials will also be conducted. The patient recruitment will stop once the target sample size is achieved.

Aditionally, around 215 patients will be surveyed by the intermediate of the external panel considering that same level expected of fully completed questionnaires expect (about 80-90%). Recruitment will continue until a sufficient number of patients have been included to allow for sub-group analyses i.e. according to therapeutic indication (epilepsy/ bipolar disorders). The patient recruitment will stop once the target sample size is achieved. Patient age < 18 years are not included in the Glocal Mind panel.

Based on the above assumptions, the hypothetical distribution of patients per country would be the following:

Table 11: sample size of patients' survey

Patients' survey			
Country	**Number of patients recruited via prescribing physicians** (of the prescribers' survey or other prescribers)	**Number of patients recruited via external panel**	**Total**
France	166	39	205
UK	166	30	196
Sweden	85	14	99
Poland	105	30	135
Germany	75	33	108
Spain	0*	25	25
Total	**597**	**171**	**768**
**In Spain, no patient will be recruited by prescribing physicians.*			

The fieldwork will be controlled to ensure than the boundary of 50 % of the total number of patients surveyed is not exceeded for each of the three recruitment pathways in order to ensure a consistent sample for all the recruitment pathways.

The recruitment of patients via prescribing physicians will continue until the target number of patients will be included in each country defined in the table above. Once a country is completed, the recruitment is stopped in this country in order to ensure the completion of the others and avoid a competitive fieldwork with a potential unbalance between the countries.
But, in case of unbalance between both indications, the recruitment will be prioritized for complete the indication with the smaller size, to ensure a size of around 384 patients for epilepsy and for bilopar disorder.

9.5.3 Sampling adjustment

HCP survey
Since the relative weight of each country and each category of HCPs in the final sample may be different from its real proportion, the extrapolation of the raw survey results to the overall target population would be more relevant after adjustment. The survey results will be weighted to reflect the real proportion of the countries and the real proportion of each specialty in order to allow the extension of the survey results to the overall target population. Both unweighted and weighted results will be reported.

A weight variable will be applied to each statistical unit (i.e., the HCPs) during the results calculation in order to correct any over- or under-sampling that may have occurred for a country or specialty. This weight variable will indicate how many unit(s) of the population

of interest an observation will count in a statistical procedure. Its value will change per country and per specialty. The weights will be normalised to obtain their sum equal to the sample size.

Patient survey

Of note, the level of contribution of HCPs and patients is not known in advance and will depend on the volume of valproate prescribed in the target countries as well as the survey response rate and participation rate. For patients. the uncertainty on the sample distribution is even higher, as it depends on the number of patients which can be recruited by prescribers' physicians. In any case, the sample will be weighted based on the expected number of patients in each of the participating countries. Given that we cannot perform direct patient follow-up, increasing patient response rates will be through the HCPs. Alternatively, we can consider this sample as it is without performing an adjustment.

9.6 Data management

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

Collected data will be entered and stored in a central database specific to the survey.

A study database will be created by merging the databases of each country together. The study database will be locked once validated.

9.6.1 Data entry/electronic data capture

The survey data will be collected using a secure online electronic data capture (EDC) survey system. The proposed data entry system has been tested and is secure for receiving and storing survey data. A web-based data repository will be used to warehouse survey data and other relevant program information. This platform ensures compliance with all relevant regulatory guidelines and is already used in several PRAC-approved surveys.

All data will be performed via single data entry, directly done by the respondent. Only patients will have the option to complete the survey on paper. The paper questionnaires will be entered to the database by IQVIA Data Collection specialists, using the IQVIA EDC data system.

9.6.2 File retention and archiving

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 IRB/EC and governmental approval/notification (if required) and study reports.

Records and documents pertaining to the conduct of this study will be retained at least 15 years after completion of the study. The length of storage can be extended based on MAH-specific SOPs or storage requirements of relevant national or local health authorities to meet the requirement for document retention, 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's Standards and will transfer the documentation to the MAHs for long term archiving.

9.7 Data analyses

The statistical analyses will be described and further detailed into a Statistical Analysis Plan (SAP). The described analysis below might be revised, and adjustments might occur. The final SAP version will include (empty) table shells to be populated for the clinical study report.

9.7.1 General considerations

The statistical analysis will be conducted using the SAS® softwareV9.4 or above on Windows™ (SAS Institute, North Carolina, USA).

All the analyses will be descriptive.

Continuous variables will be described by their mean, standard deviation, and median, first quantile (Q1), third quantile (Q3), minimum and maximum.

Categorical variables will be described as the total number and relative percentage per category.

In case of multiple-choice questions, the frequency of each option provided by the physicians will be reported in the statistical results.

The CIs of 95% will be evaluated, when relevant.

The proportions of correct and appropriate answers to selected questions asked in the questionnaire will be expressed among HCPs and patients who provided answers to those questions (the missing data will not be counted as a denominator in proportions).

9.7.2 Planned analyses

The statistical results of the included European countries will be presented overall and then by country level.

Then, the analysis of the Patients and HCPs' surveys will be broken down by subpopulation of interest, i.e. according to therapeutic indication (epilepsy / bipolar disorders).

Finally, the following additional sub-group analysis are planned:

- by age group (under 18 / adults and age category <13 years, 13 - 18 years, 18-24 years, 25-34 years, 35-44 years, 45-49 years, ≥ 50 years) for Patients' survey.
- by medical specialty: GPs, neurologists (including pediatric neurologists), paediatricians, psychiatrists, gynaecologists for Physicians' Survey.
- by receipt/non-receipt of the educational materials.

Among pharmacists, no other sub-group analysis is planned, beyond country-level but the study results will be put in perspective with those published from these annual pharmacists' surveys conducted in France in the discussion part of the study report.

In a first step, calculations will be performed on raw data for the overall sample. No projection factor will be applied to generalize the results to the entire HCP population. As a consequence, the line "Overall - unweighted results" will show only the results observed on the overall sample and will not reflect the countries 'entire population habits since this sample is not proportional to the size of the lists in each country.

In a second step, the results will be weighted according to the real proportion of HCPs in each country in order to accurately reflect the population that the survey seeks to measure.

9.7.2.1 Analysis of participation rate

The following different cases will be distinguished:

- HCPs or patients who did not participate (R): HCPs or patients who did not respond or that explicitly indicated their refusal to participate
- HCPs or patients with partially-answered questionnaires (P): HCPs or patients who clicked on the link provided in the invitation email, and who began answering the questionnaire but never submitted it
- HCPs or patients with completed questionnaire (C): HCPs or patients who completed the entire questionnaire
- Contacted HCPs or patients: HCPs who were reached by phone or who received a web link to the online survey via email OR patients who received a web link to the online survey via email = C+P+R
- HCPs or patients who agreed to participate: HCPs or patients willing to participate in the survey (e.g.by clicking on the link provided in the invitation email) = P+C

The HCPs and patients participation in the survey will be examined as follows (adapted from The American Association for Public Opinion Research. 2016. Standard Definitions: Final Dispositions of Case Codes and Outcome Rates for Surveys. 9th edition. AAPOR)

- Response rate $= \frac{C}{C+P+R}$
- Refusal rate $= \frac{R}{C+P+R}$

The participation rates will be presented by country and by physicians specialty.

9.7.2.2 Questionnaire analysis

The general statistical considerations described in section 9.7.1 will be applied as stated. The web questionnaire will be programmed to prevent the opportunity for participants to skip any questions. Consequently, no missing values are expected, and thus, the need for replacement or imputation of missing data is not anticipated (Sterne et al. 2009). 95% CIs will be evaluated for all endpoint variables.
NB: An unlikely exception is that in the event a paper-based questionnaires is administered in place of a web-based questionnaire that is not accessible, missing values may be expected. If applicable, missing values per question will be presented as numbers (and percentages) but missing values will not be imputed.

Analysis for the survey will be performed for patients and HCPs (prescribers, gynaecologists and pharmacists) separately for the endpoints below described:

- **Awareness** will be assessed through the percentage of patients and HCPs who received and read the EMs
- A **knowledge** score will be created to summarise all responses at individual patient and HCP level. An individual patient/HCP score is calculated as the proportion of correct responses among all questions related to knowledge.
- A **behaviour** score will be created to summarise all responses at individual patient and HCP level. An individual patient/HCP score is calculated as the proportion of correct responses among all questions related to behaviour.

The number and relative percentage of HCPs/patients who have provided correct answer to each of the questions and then number and relative percentage of HCPs/patients with correct responses to 70%, 80%, 90% and 100% of all the questions will be described.

The number and relative percentage of HCPs/patients who have provided correct answer to each of the questions and then number and relative percentage of HCPs/patients with correct responses to 70%, 80%, 90% and 100% of all the questions will be described.

Assessment of success:

In each of the four surveys, the proportion of correct (in case of knowledge questions) or desirable (in case of awareness or behaviour questions) responses across all questions related to the evaluation of the objectives of the surveys will be considered to assess the success.

The questions considered as complementary will not be included in the assessment of success. The details of the assessment of the sucescs for each surveys and each objective is described in the annexe 2 (Table 12 for prescribing physician survey, Table 13 for gynaecologist survey, Table 14 for pharmacist survey and table 15 for patient survey).

Success at the HCP level will be defined for each objective based on the number of sub-questions related to that objective being answered correctly or desirable. It is proposed to set the threshold to at least 80% of sub-questions correctly answered..

Also, a threshold of 90% successful HCPs for each of the outcomes awareness, behaviour, and knowledge would be considered appropriate for assessing the effectiveness of RMM as successful. The overall effectiveness of the new aRMMS for HCPs will be considered satisfactory if the critical end goal is reached meaning the behaviour outcome and at least one of the two others outcomes evaluated (awareness and/ or knowledge) are above the threshold defined.
This threshold for success is partially based on results observed in the HCP survey conducted in 2016. However, it must be noted that the content of the RMM somewhat differed and some of the outcomes will consequently be new in the upcoming survey. Also, it is expected that the level of correct answers may vary by key risk message, HCP specialty, and country. A thorough analysis of results will be made and potentially lead to modifications to the educational materials and/or the dissemination mode, if needed, in order to achieve an optimal understanding of the risks and conditions for valproate use.

The results will be contextualized considering other available information, such as the results from a similar survey conducted among HCPs in 2016. when the following conditions are met:

- within the country where both surveys were performed
- within the same HCP sub-group where both surveys were performed
- the question refers to the same concept (eg receipt of materials, knowledge about a specific risk, etc) in both surveys.

For patients, Success will be defined for each objective based on the number of sub-questions related to that objective being answered correctly or desirable. It is proposed to set the threshold to at least 80% of sub-questions correctly answered.

Also, a threshold of 80% successful patients on each of the outcomes awareness, behaviour, and knowledge would be considered appropriate for assessing the effectiveness of RMM as successful. The overall effectiveness of the new aRMMS for patients will be considered satisfactory if the critical end goal is reached meaning the behaviour outcome and at least one of the two others outcomes evaluated (awareness and/ or knowledge) are above the threshold defined. The reasoning is that a patient may have acquired the necessary information via other means that the EM or may not have read properly the EMs but still behave as required after receiving advise from a HCP.
The selection of this threshold for success is not based on a priori knowledge or experience but has often been defined in similar studies (Mazzaglia 2017). Also, it is expected that the level of correct answers may vary by key risk message, indication, and country. A thorough analysis of results will be made and potentially lead to modifications to the educational materials and/or the dissemination mode, if needed, in order to achieve an optimal understanding of the risks and conditions for valproate use.

Profile of HCPs with incorrect answers

The profile of HCPs with incorrect answers to questions related to the three success factors will be described using all available and relevant HCPs characteristics collected in the survey (i.e., country, specialty, duration of practice, practice setting, prescribing/dispensing volume, age and gender).

Profile of patients with incorrect answers

The profile of patients with incorrect answers to questions related to the three success factors will be described using all available and relevant patient characteristics collected in the survey (i.e., country, age, indication).

9.7.3 Handling of missing data

The web questionnaire will be programmed in such a way that participants cannot skip questions. We thus do not expect missing values in submitted questionnaires, and neither replacement nor imputation of missing data is expected to be required. Missing values could exist for the paper version of questionnaire available for patients' survey. No imputation method is planned to replace these missing values.

9.8 Quality control

9.8.1 Data collection, validation and data quality control

Data will be collected using a web-administered questionnaire to physicians, pharmacists and patients. Patients will have an option to complete the questionnaire on paper. The survey will be conducted according to the SOPs of IQVIA Primary Intelligence and IQVIA Real World Evidence Solutions.

For web version of the questionnaires, data will be collected using an EDC system developed following a full validation process. A rigorous System Development Life Cycle that complies with IQVIA Primary Intelligence information technology SOPs is used for validation. The programmed survey will be tested and validated in accordance with IQVIA SOPs, which cover validation for all clinical and risk management-related applications. The internet-based repository will be used to store survey data and other relevant program information. Questions are programmed to ensure that they are asked in the appropriate sequence. Skip patterns are clearly indicated. Respondents cannot go back to a question once the question has been answered and they cannot skip ahead. Response options presented in a list are randomized to minimize positional bias. Programming will be reviewed by Quality Control and simulated users (User Testing) prior to implementation.

Collected data will be entered and stored in a database specific to the survey and the country. A study database will be created by merging of databases of each country. HCP identifying information will be stored separately from survey data.

Only the patients will be given the option to answer the questionnaire on paper. The paper version will be designed as a self-report questionnaire with the clear instructions for the respondents on how to proceed.

Data will be checked in terms of consistency before data analysis:

- Removal of duplicates (if required)
- Data labelling and data formatting
- Range and consistency checks for each variable to identify potential non-admissible values
- Cross-check the consistency of data for related variables (if feasible)
- Incomplete paper questionnaires will be removed from the analysis.

The study database will be locked once validated.

A data management plan that further describes data quality review, study compliance assessments, and risk management, will be generated.

9.8.2 Approaches for validating the questionnaires

The Physicians and Pharmacists questionnaires will be tested by two to three HCPs for clarity, consistency and the appropriateness of medical terms. Physician and pharmacist comments will be implemented in the final version. Likewise, the patient questionnaire will be tested by two to three non-medical IQVIA personnel per country for optimal readability by patients.

The translated versions of the questionnaire from English into local languages will be done using the back and forth method (from English into the local language and then from the local language into English) to ensure an accurate translation.

After the translations are completed and the EDC specification is finalized and tested – the soft launch procedure will be applied to gather the first 3 – 5 interviews per country and survey (Physicians/Pharmacists). The soft launch will allow to check if there are no issues with understanding the questionnaire and completing the survey.

Completion of the physicians, pharmacists and patient questionnaires is estimated to take approximately 15-20 minutes each.

9.8.3 Approaches for validating the results

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

1. Every effort will be undertaken to collect complete and valid data.

2. At the study database level, final data quality checks will be applied to count the number of inconsistent values and estimate the associated relative percentage.

3. At the statistical analysis level: all data management and statistical analysis programs 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, etc.

4. 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 take into account the reviewers' comments.

5. At the study level, all aspects of the study will be conducted according to the SOPs of IQVIA Real World Evidence Solutions and Primary Intelligence divisions. 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 survey results and report will be conducted by a person who was not in charge of their preparation.

9.8.4 Safeguards, security and traceability of contacts

Operators of the call center specialized in health surveys will be assigned to the project and trained on the survey methodology prior to fieldwork. The email contacts will be traced using the management software.

Participating HCPs/patients will access the website (https:// secured site) via a secure link. This link is unique to each HCP/patient.

The answers provided will be collected in an anonymous way. Only aggregated data and presented as a synthesis will be transmitted to the valproate consortium.

Data will be recorded in a central database and tracked using an audit trail. The system will enable retrieving all introduced data at any time and will include security elements to prevent anyone other than authorized staff from accessing data. Each user will have a specific profile which will limit his/her use of the database. A copy of the database and the application files will be made outside the server housing the web-based study. These copies for security purposes will be periodically made and stored outside this server.

9.9 Limitations of research methods

The described methods have the following limitations:

1. Bias

    a. HCP Survey:

    Selection bias:
    The potential for selection bias of HCPs participating in a survey is an inherent limitation to any study based on volunteer participation. For instance, it is possible that HCPs willing to participate in the study will have the highest awareness of risks associated with use of valproate, as well as of the PPP. In order to quantify any selection bias, the distribution of each stratification criterion of HCPs (country, specialty, and other demographic information collected) will be compared between participants and non-participants.
    Non-response bias may also be introduced into the study if targeted HCPs have activated filters in their mailbox that block spam and unsolicited emails. Having multiple email addresses could also affect responsiveness, especially if the one used for sending the invitation is not the HCPs primary address. HCPs who do not check their email frequently might not receive the invitation during the recruitment period. These are among the reasons why HCPs will also be contacted by phone.

    Bias in the questionnaires completion:
    Web surveys may promote information bias that may result from social desirability, which refers to the tendency of physicians to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or behaviour, e.g. HCPs can copy-paste or refer to information gathered online instead of giving their own opinions (Nederhof 1985).

Social desirability can affect the validity of survey research findings, but the use of pre-populated items in the questionnaire could/tends to reduce this bias (Nederhof 1985).
Recall biais may lead to an underestimation of the physicians recalling having received EM. In an attempt to comment about these differences in accuracy or completeness of the recollections retrieved when answering the survey, if any, we will provide updated information about the distribution of EMs in each participating country.

b. Patient survey:

Selection bias:
For the patients recruitment by HCPs (who participated or not participate in the physicians' survey), prescribing physicians who are aware of the educational materials and provided them to the patients/caregivers are more likely to participate in recruiting patients for the patient survey.

Prescribing physicians will consecutively solicit patients for participating in the survey. The recruitment of patients will occur in the defined study period and until the boundary of 16 patients per prescriber is reached. Although consecutive recruitment should minimize selection bias, HCP compliance to this approach cannot be verified. However, as there will be no information linking the identify of patient respondents with the recruiting prescribing physician, there is no incentive for prescribing physician to be selective in their recruitment (e.g. inviting their 'best' or most compliant patients to participate). The characteristics of the patients who do not fulfill eligibility criteria cannot be captured so it is not possible to know the extent of the selection bias.

For patient recruitment through Glocal Mind, from the vendor panel, only patient who consent to participate will be surveyed which means that selection bias cannot be ruled out.
The fieldwork will be controlled to ensure than the boundary of 50 % of the total number of patients surveyed is not exceeded for each of the three recruitment pathways in order to ensure a consistent sample for all the recruitment pathways and limits the impact of the different bias inherent to the recruitment methods.

Bias in the questionnaires completion:

- Social desirability:
  Theoretically, the social desirability bias may also arise when the patients are recruited by the same HCPs who have participated in the survey. There is also a potential for an HCP who participated in the survey to increase the awareness of his or her patients about the topics covered in the survey.
  However, due to the anonymity of the survey, competitive recruitment (HCP will not be certain if a patient questionnaire will ultimately be considered in the study), and that results of the patient survey will not be analysed per centre but as separate samples, this limitation is less likely to happen. As a result, we do not consider it necessary to distinguish between HCPs who participate in the survey from those who also recruit patients.

- For the sub population of patients between 13 to 17 years:
  This survey includes products that are prescribed to patients between 13 and 17 years of age. In such case, the questionnaire will be filled by the parent or the guardian, which may impact responses to questions related to contraceptives and pregnancies. In a sub-group analysis, the answers related to contraceptive and pregnancies will be described for the patients between 13 and 17 years old versus the adult patients.
  - Patients involved in valproate-related lawsuits or associations for victims of valproate syndrome were excluded but this information will rely on patient self-reported information and, due to data protection and patient anonymity, cannot be verified

2. Limits inherent to web surveys

   In such surveys, the generalization and external validity of the results is restricted to HCPs who have an active email address and are willing (and able) to answer a questionnaire online. These HCPs may not be fully representative of the whole targeted population (Wyatt 2000).

3. Generalization of the survey results to the overall target population with adjustment

   The raw survey results can only be generalised to the overall target population, if a sample adjustment is applied. For more transparency and accuracy, both unweighted (i.e. raw data) and weighted results will be presented in the report.

9.10 Other aspects

- The information contained in the ***OneKey*** list of each country is updated continuously with proactive updates. Quality controls are performed on ***OneKey*** content on a regular basis. ***OneKey*** is the most comprehensive list of HCPs in the world with very high coverage in most countries.

- The sampling of HCPs follows a randomized method which guarantees the representativeness of the contacted population in order to limit selection bias due to voluntary participation. Batches of HCPs will be contacted up to five times before moving forward to other HCPs in the lists.

- The questionnaire includes general questions followed by specific ones in order to limit a learning process during the survey. As the HCPs may understand the right answer in subsequent questions, it would not be possible to go back in the questionnaire and edit answers in former questions.

- The questionnaire is tested for its clarity. It is also checked whether there are questions which would suggest a specific answer for any reason for example social desirability. The translation of the questionnaire is tested before implementation.

- The access to the web questionnaire interface will be limited to the invited participants. Each participant will receive a unique link (URL) to the questionnaire and will only be allowed to participate only once.

10. PROTECTION OF HUMAN SUBJECTS

The survey is non-interventional and totally anonymous to the study sponsor. Data collected will remain absolutely confidential. Only aggregated data will be analyzed and communicated in a report. 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).

10.1 Information on survey participants and informed consent

HCPs and patients participating in the survey will be informed about the targets of the investigation, the nature of the transmitted data, the intended use of data, recipients of these data, and their right of access and rectification to their personal data, as well as their right of objection to use their data or to IQVIA keeping their data.

IQVIA will ensure that the national and European data protection and ethical requirements are met for the patients and HCPs. This will be done electronically.

10.2 Patient confidentiality

Patient recruitment by HCPs for the survey is through the delivery of the survey questionnaire. This does not involve a key coding.

The survey is non-interventional and totally anonymous to the valproate consortium. Data collected will remain absolutely confidential, and only aggregated data will be communicated and analyzed.

10.3 Independent ethics committee/institutional review board

10.3.1 Ethical principles, laws and regulations

The survey will follow the regulatory and ethical requirements of each country. The survey will comply with the module VIII of the good pharmacovigilance practices (GVP).

IQVIA will follow the European Pharmaceutical Marketing Research Association (EphMRA) code of conduct guidelines for all countries (EphMRA 2013).

HCPs, patients and caregivers participating in the study have also to consent for data collection and need to be informed about the purpose of the survey and their storage of data. IQVIA will make sure that the national and European data protection and ethical requirements are met for the patients and HCPs.

10.3.2 Financial disclosure

HCPs will be offered a compensation for the time spent participating in this survey (that they may refuse). The time to complete the survey is estimated to be ca. 15-20 minutes. In addition, the HCP will receive a small incentive for asking the patient if she wants to participate and distribute the patient kits.

The amount of this compensation will be in line with laws like the Sunshine Act, and determined according to the EphMRA recommendations and the Association of Opinion and Behaviour in health field research companies charter, which states:

"When it is necessary to compensate an HCP in return to the time spent during an interview or a group meeting, the compensation must not exceed the fees commonly taken by the HCP for his/her advice or consultation and must be proportional to the time provided. The compensations should be clearly stated prior to the HCPs participation in the survey. They must be declared to the tax authorities in accordance with applicable laws. "

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study is a survey to evaluate the effectiveness of Educational material implemented as RMM. This survey does not involve data collection on clinical endpoints on individual patients. Therefore, adverse events will not be systematically solicited. However, any safety information for an individual patient that is volunteered by a study participant during the course of this research must be reported as described below.

In addition, as per GVP Module VI, the safety observations made during the conduct of the study, if any, will be summarized in the final study report.

11.1 Safety instructions

All adverse events will be managed and reported in compliance with all applicable regulations.

11.1.1 Definitions of Adverse Event and Serious Adverse Event

An **Adverse Event** (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment [Dir 2001/20/EC Art 2(m)].

An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (see GVP Annex IV, ICH-E2D Guideline).

A **Serious Adverse Event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death or;
- Is life-threatening or; (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event.
- Suspected transmission of infectious agent; is any suspected transmission of an infectious agent via a medicinal product (e.g., product contamination).

11.1.2 Other

In addition, any information received during the context of this study that is suggestive of the following occurrences during the exposure to valproate, will also be promptly communicated to the relevant MAHs:

- Pregnancy
- Breastfeeding
- Abnormal laboratory findings
- Overdose, abuse, misuse, off-label use, medication error or occupational exposure
- Reports of lack of efficacy
- Product quality defects and falsified medicinal products
- Data related to a suspected transmission of an infectious agent via a medicinal product
- Drug interactions (including drug/drug, drug/food, drug/device and drug/alcohol)

11.1.3 Obligations regarding safety reporting

Any AE information received will be documented and reported following the European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practices Module VI – Management and Reporting of Adverse Reactions to Medicinal Products and in accordance with EMA regulations (Regulation 520/2012 on the performance of pharmacovigilance activities provided for in Regulation [EC] No 726/2004).

The survey does not include questions that could potentially identify a safety event and does not provide an opportunity (e.g. free text field) where study participants could provide information that may constitute a safety event. Further, routine communication with participants via email or phone with the IQVIA staff may not be expected during the conduct of the survey. However, it is possible that a study participant may provide information that could constitute a safety event (e.g. serious and non-serious AEs and/or scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure) to the IQVIA staff while in conversation about the survey for any reason (e.g. seeking information about the purpose of the survey).

Such information suggestive of adverse events or other reportable occurence as listed in 11.1.2 will be communicated to the MAH of the concerned brand (if brand is mentioned) or to all the MAHs for valproate in case the brand is unknown (adverse event Report Form signed and dated by IQVIA staff), within the timelines and as described in the application agreement between IQVIA and the MAHs. If information about the safety event is incomplete, the IQVIA staff should prompt the primary reporter, when possible, to obtain supplementary detailed information significant for the scientific evaluation of the case.

The MAH(s) will perform case assessment and reporting as per routine Pharmacovigilance practice. Follow-up information will be communicated in the same way and following the same timeline.

All staff involved in providing the Services of the study (including, but not limited to, employees, consultants, contractors and Subcontractors) will undergo pharmacovigilance training.

11.2 Obligations of MAHs

During the course of the study, the MAHs will report safety data to health authorities according to all applicable local and global regulations. In order to prevent duplicate or mutiple reporting to EU-Health Authorities, Sanofi only will report valproate cases with unknown brand to EU-Health Authorities,

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 Reporting

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 (ICMJE), updated April 2010.

All reporting will be consistent with the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) Initiative checklist for cohort studies (STROBE 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.

13. REFERENCES

Agyemang, E, Bailey L, Talbot J. Additional Risk Minimisation Measures for Medicinal Products in the European Union: A Review of the Implementation and Effectiveness of Measures in the United Kingdom by One Marketing Authorisation Holder. Pharmaceutical Medicine 20[1]7; 31:101-12.

von Elm E, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008 ; 61(4):344–9.

EphMRA. Code of conduct 2013. [En ligne] http://www.ephmra.org/Code-of-Conduct.

European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (Rev 3) [resource on the Internet]. 2017 [revision 13 October 2017; cited 05 September 2018]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf.

European Medicines Agency . Module VI - European Medicines Agency - Europa.eu. [Online] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500172402.pdf.

European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module XVI [Online] https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xvi-risk-minimisation-measures-selection-tools_en-3.pdf

IQVIA data privacy obligations. [Online] https://www.iqvia.com/about-us/privacy

Kellerman SE, Herold J. Physician response to surveys: A review of the literature. Am J Prev Med. 2001 Jan; 20(1):61-7.

Kish, L. (1965). Survey Sampling. New York: Wiley.

Nederhof, AJ. Methods of coping with social desirability bias: A review. European Journal of Social Psychology. 1985; 15(3):263–80.

Sterne JAC, White IR, Carlin JB, *et al*. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009; 338:b2393.

VanGeest, JB, Johnson TP, Welch, VL. Methodologies for improving response rates in surveys of HCPs: a systematic review. Eval Health Prof. 2007; Dec; 30 (4): 303 - 21.

Wyatt, JC. When to Use Web-based Surveys. J Am Med Inform Assoc JAMIA. 2000; 7(4):426–9.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

	Document reference number	Date	Title
1	VALNAC09348 Surveys Questionnaires	11/09/2019	Supportive documentation to the protocol : Survey among HCPs and patients to assess their knowledge and behaviour with respect to the new risk minimization measures for Valproate in Europe

ANNEX 2. ASSESSMENT OF SUCCESS

Table 12 Assessment of success – Prescribing physicians survey

Objectives	Variables	Questions	Is the question included in the assessment of success? (Yes/No)	Definition of correctlyanswered question	Assessment of success
Awareness (4 questions)	Reception of the DHPC	Q1 Have you received the DHPC relating to valproate and related substances since (date of installation of RMMs)?	YES	question correctly completed (1 sub-question)	A prescriber is successful for **awareness** when at least 8 of the 10 sub-questions regarding **awareness**, are correctly completed. Success for awereness if ≥ 90% of Prescribers are successful
	Reading of the DHPC	Q2 Have you read the DHPC relating to valproate since (date of installation of RMMs)?	YES	question correctly completed (1 sub-question)	
	Reception of educational materials (details)	Q3 Which of the following EM did you get (either from post, email, pharmaceutical company/ professional association/ health authority/ website, or from other channel)?	YES	question correctly completed (4 sub-questions)	
	Reading of educational materials	Q4 Which of the following EM relating to valproate have you read?	YES	question correctly completed (4 sub-questions)	
Knowledge (3 questions)	Prescribing conditions of valproate	Q6 According to your knowledge about the conditions of use of valproate, which of the following statements are true and which are false?	YES	question correctly completed (6 sub-questions)	A prescriber is successful for **knowledge** when at least 15 of the 18 sub-questions regarding knowledge are correctly completed. Success for knowledge if ≥ 90% of Prescribers are successful
	Risks of congenital malformations and neurodevelopmental disorders	Q7 According to your knowledge about the risks to the unborn child when exposed in utero to valproate, which of the following statements are true and which are false?	YES	question correctly completed (5 sub-questions)	
	PPP measures	Q8 According to your knowledge about the new PPP implemented for valproate, which of the following statements are true and which are false?	YES	question correctly completed (7 sub-questions)	
Behaviour (8 questions)	Distribution and discussion of EMs	Q5 In your daily practice, what version of the EM do you use?	NO, complementary information about mode of dissemination		A prescriber is successful for **behaviour** when at least 15 of the 18 sub-questions for GPs and 12 of the 15 sub-questions

		Q10. Do you provide patients with the patient guide?	YES	question correctly completed (1 sub-question)	for other prescribing physicians , regarding **behaviour** are correctly completed. Success for behaviour if ≥ 90% of Prescribers are successful
	Use of annual risk acknowledgement form; Ensuring patients' knowledge on the risks of valproate use and on PPP measures, including counselling patients for effective contraception throughout the treatment	Q9 Please answer to the following questions related to the annual risk acknowledgement form.	YES	question correctly completed (3 sub-questions)	
	Advice on contraceptive methods to patients	Q11 Do you advise your patient on the need to have an effective method of contraception when they are treated with valproate?	YES	question correctly completed (1 sub-question)	
	HCPs' management of contraception	Q12 Do you refer your patients treated with valproate to other healthcare professionnals so they get information on effective methods of contraception?	NO, complementary question about HCPs' management of contraception		
	Pregnancy tests before initiation of valproate	Q13 How often do you prescribe pregnancy tests to your patients treated with valproate?	YES	question correctly completed (1 sub-question)	
	Valproate conditions of use	Q14 Would you prescribe valproate in the following clinical situations?	YES	question correctly completed (4 sub-questions)	
	Counselling WCBP when planning for pregnancy (informing about the risks, referring to a specialist, advising to consult prescriber)	Q15 Please answer the following questions related to your usual behaviour when a patient treated with valproate plans to become pregnant.	YES	question correctly completed (4 sub-questions for GPs and 2 sub-questions for other prescribing physicians)	
	Counselling WCBP when unplanned pregnancy or pregnancy suspicion:	Q16 Please answer the following questions related to behaviour towards a patient treated with valproate in case of unplanned pegnancy or pregnancy suspicion.	YES	question correctly completed (3 sub-questions for GPs and 2 sub-questions for other prescribing physicians)	
	Annual review by a specialist	Q17 In general, how often do you schedule follow-up visits with WCBP who are being treated with valproate?	YES	question correctly completed (1 sub-question)	

Table 13: Assessment of success - Gynaecologist survey

Objectives	Variables	Questions	Is the question included in the assessment of success? (Yes/No)	Definition of correctly answered question	Assessment of success
Awareness (4 questions)	Reception of the DHPC	Q1 Have you received the DHPC relating to valproate since (date of installation of RMMs)?	YES	question correctly completed (1 sub-question)	A gynaecologist is successful for **awareness** when at least 3 of 4 sub-questions regarding **awareness** are correctly completed. Success for awereness if ≥ 90% of gynaecologists are successful
	Reading of the DHPC	Q2 Have you read the DHPC relating to valproate since (date of installation of RMMs)?	YES	question correctly completed (1 sub-question)	
	Reception of educational materials (details)	Q3 Did you get (either from post, email, pharmaceutical company/ professional association/ health authority/ website, or from other channel) the guide for Healthcare professionals	YES	question correctly completed (1 sub-question)	
	Reading of educational materials	Q4 Have you read the guide for Healthcare professionals?	YES	question correctly completed (1 sub-question)	
	Awareness about patient card	Q6 Are you aware of the existence of a patient card related to valproate?	NO, this question is complementary		
Knowledge (4 questions)	Prescribing conditions of valproate	Q7 According to your knowledge about the conditions of use of valproate, which of the following statements are true and which are false?	YES	question correctly completed (6 sub-questions)	A gynaecologist is successful for **knowledge** when at least 14 of 17 sub-questions regarding **knowledge** are correctly completed Success for knowledge if ≥ 90% of gynaecologists are successful
	Risks of congenital malformations and neurodevelopmental disorders	Q8 According to your knowledge about the risks to the unborn child when exposed in utero to valproate, which of the following statements are true and which are false?	YES	question correctly completed (5 sub-questions)	
	PPP measures	Q9 According to your knowledge about the new PPP implemented for valproate, which of the following statements are true and which are false?	YES	question correctly completed (6 sub-questions)	
	contraceptive methods	Q10 Which of the following contraceptive methods would you consider as effective for the prevention of pregnancies in women who are exposed to valproate in the list below?	NO, this question is complementary		
Behaviour (4 questions)	Distribution and discussion of EMs / Use of annual risk acknowledgement form	Q5 In your daily practice, what version of the guide for Healthcare professionals do you use?	NO, complementary information about mode of dissemination		A gynaecologist is successful for **behaviour** when at least 7 of 8 sub-questions regarding **behaviour** are correctly
	Counselling WCBP when planning for pregnancy (informing about the risks, referring to a specialist,	Q11 Please answer the following questions related to your usual behaviour when a patient treated with valproate plans to become pregnant	YES	question correctly completed (4 sub-questions)	

	advising to consult prescriber)				completed Success for behaviour if ≥ 90% of gynaecologists are successful
	Counselling WCBP when unplanned pregnancy or pregnancy suspicion:	Q12 Please answer the following questions related to behaviour towards a patient treated with valproate in case of unplanned pregnancy or pregnancy suspecion.	YES	question correctly completed (3 sub-questions)	
	Counselling patients for effective contraception throughout the treatment	Q13 Do you advise your patient on the need to have for an effective method of contraception when they are treated with valproate?	YES	question correctly completed (1 sub-question)	

Table 14 Assessment of success - Pharmacist survey

Objectives	Variables	Questions	Is the question included in the assessment of success? (Yes/No)	Definition of correctlyanswered question	Assessment of success
Awareness (8 questions)	Reception of the DHPC	Q1 Have you received the DHPC relating to valproate since (date of installation of RMMs)?	YES	question correctly completed (1 sub-question)	A pharmacist is successful for **awareness** when at least 5 of 6 sub-questions regarding **awareness** are correctly completed Success for knowledge if ≥ 90% pharmacists are successful
	Reading of the DHPC	Q2 Have you read the DHPC relating to valproate since (date of installation of RMMs)?	YES	question correctly completed (1 sub-question)	
	Reception of educational materials	Q3 Have you received the Patient Cards related to the valproate?	YES	question correctly completed (1 sub-question)	
	Reception of educational materials	Q5 In your opinion, how would you describe the quantity of Patients Cards received? (suggestion to remove this question)	NO, complementary information		
	Reception of educational materials	Q6. Did you get the HCP guide related to valproate (either from post, email, pharmaceutical company/ professional association/ health authority/ website, or other channel)?	YES	question correctly completed (1 sub-question)	
	Reception of educational materials	Q8.In your daily practice, what version of the guide for Healthcare professionals do you use?	NO, complementary information		
	Reading of educational materials	Q4 Have you read the Patient Cards relatied to the valproate and related substances?	YES	question correctly completed (1 sub-question)	
	Reading of educational materials	Q7. Did you read the HCP guide related to valproate?	YES	question correctly completed (1 sub-question)	
Knowledge (3 questions)	Prescribing conditions of valproate	Q9 According to your knowledge about the conditions of use of valproate, which of the following statements are true and which are false?	YES	question correctly completed (6 sub-questions)	A pharmacist is successful for **knowledge** when at least 13 of 16 sub-questions regarding **knowledge** are correctly completed Success for knowledge if ≥ 90% of pharmacists are successful
	Risks of congenital malformations and neurodevelopmental disorders	Q10 According to your knowledge about the risks to the unborn child when exposed in utero to valproate, which of the following statements are true and which are false?	YES	question correctly completed (5 sub-questions)	
	PPP measures	Q11 According to your knowledge about the new PPP implemented for valproate, which of the following statements are true and which are false?	YES	question correctly completed (5 sub-questions)	
Behaviour (3 questions)	Distribution and discussion around patient card during dispensing	Q12 Please answer the following questions related to your experience when dispensing valproate.	YES	question correctly completed (2 sub-questions)	A pharmacist is successful for **behaviour** when at least 8 of 9 sub-questions regarding

	Counselling WCBP when planning for pregnancy (informing about the risks, referring to a specialist, advising to consult prescriber)	Q13 Please answer the following questions related to your usual behaviour when a patient treated with valproateplans to become pregnant.	YES	question correctly completed (4 sub-questions)	**behaviour** are correctly completed. Success for behaviour if ≥ 90% of pharmacists are successful
	Counselling WCBP when unplanned pregnancy or pregnancy suspicion	Q14 Please answer the following questions related to behaviour towards a patient treated with valproate in case of unplanned pegnancy or pregnancy suspecion.	YES	question correctly completed (3 sub-questions)	

Table 15 Assessment of success - Patient survey

Objectives	Variables	Questions	Is the question included in the assessment of success? (Yes/No)	Definition of correctlyanswered question	Assessment of success
Awareness (5 questions)	Receipt of educational materials	Q1 Have you been provided with the following materials related to valproate and related substances?	YES	question correctly completed (3 sub-questions)	A patients is successful for **awareness** when at least 9 of 11 sub-questions regarding **awareness** are correctly completed Success for knowledge if ≥ 80% succesful patients
	Reading of educational materials	Q2 Did you read the Guide for patients?	YES	question correctly completed (1 sub-question)	
	Reading of educational materials	Q3 Please answer the following questions related to the Patient Card.	YES	question correctly completed (4 sub-questions)	
	Reading of educational materials	Q4 Please answer the following questions related to the annual risk acknowledgment form.	YES	question correctly completed (3 sub-questions)	
	Patient's preference for finfing more information related to valproate treatment	Q5 In order to find more information about your valproate treatment, did you ever? *Please select all that apply*.	Not included: complemetary information on the mode of information		
Knowledge (3 questions)	Conditions of use of valproate	Q6 According to your knowledge about the conditions of use of valproate, is the following statement true or false?	YES	question correctly completed (3 sub-questions)	A patient is successful for **knowledge** when at least 8 of 10 sub-questions regarding knowledge are correctly completed. Success for knowledge if ≥ 80% of succesful patients
	Risks of congenital malformations and neurodevelopmental disorders	Q7 According to your knowledge about the risks to the unborn child when exposed in utero to valproate, which of the following statements are true and which are false?	YES	question correctly completed (3 sub-questions)	
	PPP measures	Q8 According to your knowledge about the measures needed during valproate treatment, which of the following statements are true and which are false?	YES	question correctly completed (4 sub-questions)	
Behaviour (9 questions)	Pregnancy testing	Q9 Before starting valproate treatment, did you have a pregnancy test	YES	question correctly completed (1 sub-question)	A patients is successful for **behaviour** when at least 8 of 10 sub-questions regarding
	Pregnancy testing	Q10 In general, what kind of pregnancy tests do you have?	NO, complementary information		

	Use of contraceptive method	Q11 Are you using at least one form of contraception during treatement with valproate so far?	YES	question correctly completed (1 sub-question)	**behaviour** are correctly completed. Success for behaviour if ≥ 80% of succesful patients
	Types of contraceptive methods used during treatment with valproate	Q12 What form(s) of contraception do you use while being treated with valproate?	NO, complementary information to describe the patient's preferences		
	Reason for not using contraception (if applicable)	Q13 What was your reason for not using contraception?	NO, complementary information to describe the patient's preference		
	Counselling for effective contraception throughout the treatment	Q14 Were you provided with information on the methods for an effective contraception during a treatment by valproate?	YES	question correctly completed (1 sub-question)	
	Actions to be taken in case the patient plans pregnancy, knows she is pregnant, or suspects to be	Q15 If ever you plan to become pregnant while being treated with valproate, would you immediately stop your contraception.?	YES	question correctly completed (1 sub-question)	
		Q16 If ever you plan to become pregnant while being treated with valproate, would you immediately stop valproate?	YES	question correctly completed (1 sub-question)	
		Q17 If ever you plan to become pregnant while being treated with valproate, would you consult your physician about it during the next planned visit?	YES	question correctly completed (1 sub-question)	
	Actions to be taken in case of unplanned pregnancy or pregnancy suspicion	Q18 If you know you're pregnant, or you suspect to be, would you immediately stop valproate?	YES	question correctly completed (1 sub-question)	
		Q19 If you know you're pregnant, or you suspect to be, would you schedule an urgent appointment with your physician?	YES	question correctly completed (1 sub-question)	
	Frequency of visits to different HCPs	Q20 How often did you see the following HCPs in relation to your valproate treatment?	YES	question correctly completed (2 sub-questions)	

ANNEX 3. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 4)

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

Study title: Surveys among Health Care Professionals and Patients to assess their knowledge and behaviour with respect to the new (2018) Risk Minimization Measures for valproate use in Europe

EU PAS Register® number: not yet registered

Study reference number (if applicable): VALNAC09348 (Sanofi internal reference number)

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

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☐	☐	☐	9
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

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 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
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
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
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9
4.2.2 Age and sex	☒	☐	☐	9
4.2.3 Country of origin	☒	☐	☐	9
4.2.4 Disease/indication	☒	☐	☐	9
4.2.5 Duration of follow-up	☐	☐	☒	
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

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)	☐	☐	☒	
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?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
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?	☒	☐	☐	9
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9
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
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	
9.1.3 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)	☐	☒	☐	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	
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)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
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?	☒	☐	☐	
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
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?	☒	☐	☐	9.7.3
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)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	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)	☒	☐	☐	9.1

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?	☒	☐	☐	10.4
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☐	☐	☐	10.1

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: M Toussi

Date: 04/November/2020

Signature: _____

ANNEX 4. LIST AND CONTACT DETAILS OF REPRESENTED MAHS

List of represented MAHs contact details

MAH identified as contact for referral	Represented MAHs
APOTEX EUROPE B.V. Archimedesweg 2 2333 CN Leiden The Netherlands	APOTEX EUROPE B.V. Archimedesweg 2 2333 CN Leiden 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
BIOGARAN 15, Boulevard Charles de Gaulle 92707 Colombes Cedex France	BIOGARAN 15, Boulevard Charles de Gaulle 92707 Colombes Cedex France
BIOMO PHARMA GMBH Josef-Dietzgen-Str 3 53773 Hennef Germany	BIOMO PHARMA GMBH Josef-Dietzgen-Str 3 53773 Hennef Germany
CONSILIENT HEALTH LIMITED 5th Floor, Beaux Lane House, Mercer Street Lower, Dublin 2, Ireland	CONSILIENT HEALTH LIMITED 5th Floor, Beaux Lane House, Mercer Street Lower, Dublin 2, Ireland
CRESCENT PHARMA LIMITED 3 & 4 Quidhampton Business Units, Polhampton Lane, Overton, Hampshire RG25 3ED, United Kingdom	CRESCENT PHARMA LIMITED 3 & 4 Quidhampton Business Units, Polhampton Lane, Overton, Hampshire RG25 3ED, 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

G.L. PHARMA GMBH Schlossplatz 1 8502 Lannach Austria	Gerot PHARMAZEUTIKA GES.M.B.H. Arnethgasse 3 1160 Vienna Austria LANNACHER HEILMITTEL GES.M.B.H. Schlossplatz 1 8502 Lannach Austria
LUPIN HEALTHCARE (UK) LTD The Urban building 9 Albert street Slough SL12BE United Kingdom	LUPIN HEALTHCARE (UK) LTD The Urban building 9 Albert street Slough SL12BE United Kingdom
SANDOZ/HEXAL AG Industriestrasse 25 83607 Holzkirchen Germany	SANDOZ S.A.S. 49, avenue Georges Pompidou, 92300 Levallois-Perret, France 1 A PHARMA GMBH Keltenring 1 + 3 82041 Oberhaching Germany HEXAL AG Industriestrasse 25 83607 Holzkirchen Germany SANDOZ N.V. Telecom Gardens, Medialaan 40 1800 Vilvoorde Belgium SANDOZ GMBH Biochemiestrasse 10 6250 Kundl Austria SANDOZ A/S Edvard Thomsens Vej 14 2300 Copenhagen Denmark SANDOZ PHARMACEUTICALS D.D. Verovškova 57 1526 Ljubljana Slovenia SANDOZ S.P.A. Largo U. Boccioni, 1 21040 Origgio (VA) Italy SANDOZ B.V. Veluwezoom 22 1327 AH Almere The Netherlands

MYLAN EMEA SAS 117 allée des Parcs 69800 Saint Priest France	MYLAN BVBA/SPRL Terhulpsesteenweg 6A B-1560 Hoeilaart Belgium MYLAN DURA GMBH Wittichstr. 6 64295, Darmstadt Germany MYLAN SAS 117 allée des Parcs 69800 Saint Priest France GENERICS [UK] LIMITED Station Close EN6 1TL Potters Bar Hertfordshire United Kingdom
NEURAXPHARM ARZNEIMITTEL GMBH Elisabeth-Selbert-Str. 23 40764 Langenfeld Germany	NEURAXPHARM ARZNEIMITTEL GMBH Elisabeth-Selbert-Str. 23 40764 Langenfeld Germany
ORION CORPORATION, ORION PHARMA Orionintie 1, P.O.Box 65 FI-02101 Espoo Finland	ORION CORPORATION, ORION PHARMA Orionintie 1, P.O.Box 65 FI-02101 Espoo Finland
PHARMASWISS ČESKÁ REPUBLIKA S.R.O Jankovcova 1569/2c 170 00 Prague 7 Czech Republic	PHARMASWISS ČESKÁ REPUBLIKA S.R.O Jankovcova 1569/2c 170 00 Prague 7 Czech Republic
SANOFI AVENTIS R&D 1 Avenue Pierre Brossolette 91385 Chilly-Mazarin France	Sanofi-Aventis GmbH Austria Leonard-Bernstein-Strasse 10 Vienna 1220 Austria SANOFI BELGIUM Leonardo Da Vincilaan 19 1831 Diegem Belgium Sanofi Bulgaria EOOD 90 Tsarigradsko chaussee Blvd., Office building Capital Fort, section A, 10th floor, Sofia 1784, Bulgaria SANOFI-AVENTIS CROATIA D.O.O. Heinzelova 70 Zagreb 10 000 Croatia

	Sanofi-aventis Cyprus Ltd. Leoforos Athalassas 91, Office 301, Strovolos, 2012 Nicosia Ciprus SANOFI-AVENTIS, S.R.O. Evropská 846/176a 160 00 Prague 6 Czech Republic Sanofi A/S Lyngbyvej 2 2100 København Ø Denmark SANOFI-AVENTIS ESTONIA OÜ Pärnu mnt 139E/2 11317 Tallinn Estonia Sanofi Oy Revontulenkuja 1 02100 ESPOO Finland Sanofi-Aventis France 82, avenue Raspail 94250 Gentilly France SANOFI-AVENTIS DEUTSCHLAND GMBH Industriepark Höchst Gebäude K703 65926 Frankfurt am Main Germany Sanofi-Aventis A.E.B.E. 348, Syngrou Ave. - Building A Athens 17674 Greece SANOFI-AVENTIS ZRT. Tó u. 5. H-1045 Budapest Hungary Sanofi Aventis Ireland Ltd. T/A SANOFI 18 Riverwalk Citywest Business Campus Dublin 24 Ireland SANOFI-AVENTIS SPA Viale Luigi Bodio, 37/B 20158 Milano Italy Sanofi-aventis Latvia SIA

	33-8 Kr. Valdemara street Riga LV-1010 Latvia UAB „SANOFI-AVENTIS LIETUVA “ A. Juozapavičiaus g. 6/2 LT-09310 Vilnius Lithuania SANOFI-AVENTIS SP. Z O.O. 17 Bonifraterska Str. 00-203 Warsaw Poland SANOFI – PRODUTOS FARMACÊUTICOS, LDA. Empreendimento Lagoas Park Edifício 7, 3º Piso, 2740-244 Porto Salvo Portugal SANOFI-AVENTIS SLOVAKIA S R.O. Einsteinova 24 85101 Bratislava Slovak Republic SANOFI-AVENTIS D.O.O. Dunajska cesta 151 1000 Ljubljana Slovenia SANOFI AVENTIS, S.A. Josep Plá, 2 08019 Barcelona Spain Sanofi Lindhagensgatan 120 Stockholm 112 51 Sweden Sanofi-aventis Netherlands B.V. Paasheuvelweg 25 1105 BP Amsterdam The Netherlands AVENTIS PHARMA LIMITED 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT United Kingdom
STADA ARZNEIMITTEL AG Stadastraße 2-18 61118 Bad Vilbel Germany	EUROGENERICS N.V./S.A. Esplanade Heysel b 22 1020 Bruxelles Belgium

	EG LABO LABORATOIRES EUROGENERICS 12 rue Danjou "Le Quintet" - Bâtiment A 92517 Boulogne-Billancourt Cedex (Paris) France ALIUD PHARMA GMBH Gottlieb-Daimler-Straße 19 89150 Laichingen Germany STADAPHARM GMBH Stadastraße 2-18 61118 Bad Vilbel Germany EG S.p.A. Via Pavia, 6 20136 Milano Italy CENTRAFARM B.V. Nieuwe Donk 3 4879 Etten-Leur Netherlands
TECNIFAR S.A Rua Jose da Costa Pedreira, n° 11 B, Torre Sul 1750-130 Lisboa Portugal	TECNIFAR S.A Rua Jose da Costa Pedreira, n° 11 B, Torre Sul 1750-130 Lisboa Portugal
TEVA PHARMACEUTICALS EUROPE B.V. Piet Heinkade 107, P.O. Box 16416, 1001 RM Amsterdam The Netherlands	ABZ-PHARMA GMBH Graf-Arco-Str. 3 89079 Ulm Germany PHARMACHEMIE B.V. Swensweg 5, Box 552 2031 GA HAARLEM The Netherlands RATIOPHARM-COMERCIO E INDUSTRIA DE PRODUTOS FARMACEUTICOS LDA Lagoas Park 5-A, Piso 2, Porto Salvo 2740-245 Pt Portugal RATIOPHARM GMBH Graf-Arco-Str. 3 89079 Ulm Germany TEVA NEDERLAND B.V. Swensweg 5 2031 GA HAARLEM The Netherlands

WOCKHARDT UK LIMITED Ash Road North Wrexham Industrial Estate Wrexham LL13 9UF United Kingdom	WOCKHARDT UK LIMITED Ash Road North Wrexham Industrial Estate Wrexham LL13 9UF United Kingdom