NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	A Population-based Cohort Study of Pregabalin to Characterize Pregnancy Outcomes
Protocol number	A0081359
Protocol version identifier	1
Date of last version of protocol	Not applicable
EU Post Authorisation Study (PAS) register number	Study not yet registered
Active substance	Pregabalin (ATC N03AX16)
Medicinal product	Lyrica® (pregabalin) and Pregabalin Pfizer
Product reference	EMEA/H/C/000546 (Lyrica) EMEA/H/C/003880 (Pregabalin Pfizer)
Procedure number	EMEA/H/C/WS1364
Marketing Authorisation Holder (MAH)	Pfizer Limited
Joint PASS	No
Research question and objectives	The study objectives are to describe the use of pregabalin exposure in pregnancy and to estimate the risk of major congenital malformations, birth outcomes other than congenital malformations and neurodevelopmental outcomes with the use of pregabalin.

Countries of study	Denmark, Finland, Norway, Sweden
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
AED	Antiepileptic drug
ASD	Autism spectrum disorders
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CI	Confidence interval
CPE	Centre for Pharmacoepidemiology
DPP	Drugs and Pregnancy Project database
DUS	Drug utilisation study
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUROCAT	European Network of Congenital Anomaly Registers
GAD	General anxiety disorder
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practice
ICD-10	International Classification of Diseases, Tenth Revision
IEC	Independent Ethics Committee
IQR	Interquartile range
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
KI	Karolinska Institutet
LMP	Last Menstrual Period
MAH	Marketing Authorisation Holder
NI	Non-interventional
NOMESCO	Nordic Medico-Statistical Committee
NSAID	Non-steroidal anti-inflammatory drug
PAS	Post-Authorisation Study
PASS	Post-Authorisation Safety Study
PS	Propensity score
RCT	Randomised controlled trial
SD	Standard deviation
SGA	Small for gestational age
TIS	Teratology information services
US	United States

2. RESPONSIBLE PARTIES

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3. ABSTRACT

Protocol A0081359 Version 1.0 23 November 2018

Title: A Population-based Cohort Study of Pregabalin to Characterize Pregnancy Outcomes

Rationale and background: Pregabalin (Lyrica®, Pfizer Limited) was approved in July 2004 by the European Medicines Agency (EMA) for the treatment of peripheral neuropathic pain and as an adjunctive therapy for adult patients with partial onset seizures. Subsequently the marketing authorizations were expanded to include the additional indications of generalized anxiety disorder (GAD) in March 2006 and central neuropathic pain in September 2006.

A recent study using data from eight European Teratology Information Services (TIS), based on 164 pregabalin-exposed and 656 pregabalin-unexposed pregnancies, reported an increased risk in non-chromosomal major birth defects associated with first-trimester pregabalin exposure. A subsequent study based on 477 pregabalin-exposed pregnancies among Medicaid beneficiaries in the United States (US) did not confirm the increased risk. Pfizer is therefore conducting this study to address this issue.

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is a commitment to the EMA.

Research question and objectives:

The study objectives are to describe the use of pregabalin exposure in pregnancy and to estimate the risk of major congenital malformations, birth outcomes other than congenital malformations and neurodevelopmental outcomes with the use of pregabalin.

The primary objectives of the study are to:

- Describe use of pregabalin, lamotrigine, and duloxetine during pregnancy by
  - overall (as used in women for any therapeutic use),
  - trimester,
  - indication,
  - cumulative dose
  - calendar year of delivery,
  - as both overall and in the subcategory of monotherapy (no concomitant administration with other antiepileptic drugs AEDs);
- Describe the prevalence of major congenital malformations after first-trimester in-utero exposure to pregabalin (yes/no); after first-trimester exposure to lamotrigine, after first-trimester exposure to duloxetine and after first-trimester exposure to lamotrigine or duloxetine;
- Estimate the association between first-trimester exposure to pregabalin and prevalence of major congenital malformations, as compared with no exposure to

pregabalin; exposure to lamotrigine; exposure to duloxetine; and exposure to lamotrigine or duloxetine;
- Describe the prevalence of pre-specified birth outcomes other than major congenital malformations according to exposure (yes/no) to pregabalin any time during pregnancy, and after exposure to lamotrigine, exposure to duloxetine, and exposure to lamotrigine or duloxetine any time during pregnancy;
- Estimate the association between in utero exposure to pregabalin any time during pregnancy and the birth outcomes other than major congenital malformations, as compared with no exposure to pregabalin; exposure to lamotrigine; exposure to duloxetine; and exposure to lamotrigine or duloxetine.

The secondary objectives of the study are to:
- Estimate the incidence rates of pre-specified postnatal neurodevelopmental outcomes according to exposure (yes/no) to pregabalin any time during pregnancy, and after exposure to lamotrigine, exposure to duloxetine, and exposure to lamotrigine or duloxetine any time during pregnancy;
- Estimate the association between in utero exposure to pregabalin any time during pregnancy and the pre-specified postnatal neurodevelopmental outcomes, as compared with no exposure to pregabalin; exposure to lamotrigine; exposure to duloxetine; and exposure to lamotrigine or duloxetine.

Study design: This PASS is a population-based cohort study using administrative registries from four Nordic countries: Denmark, Finland, Norway, and Sweden.

Population: The study population consists of all pregnancies identified in the respective administrative registries from 1 January 2005 to 31 December 2015 in Denmark, Finland, and Norway and all pregnancies identified from 1 July 2006 to 31 December 2013 in Sweden.

Variables:
Exposure to medications under study is defined as follows:
Pregabalin exposure- At least one dispensing of pregabalin during pregnancy in the first trimester for the outcome of major congenital malformation and during any trimester for all remaining outcomes.

Comparator/reference groups:
Unexposed-This reference group consists of women who had no dispensing for pregabalin or other antiepileptic drugs (AEDs) including lamotrigine, and no dispensing for duloxetine during the first trimester for the outcome of major congenital malformations and during any trimester for all remaining outcomes.

Lamotrigine exposure- At least one dispensing of lamotrigine during the first trimester for the outcome of major congenital malformations and during any trimester for all remaining outcomes.

Duloxetine exposure- At least one dispensing of duloxetine during the first trimester for the outcome of major congenital malformations and during any trimester for all remaining outcomes.

Lamotrigine or duloxetine exposure. At least one dispensing of lamotrigine or duloxetine or both during the first trimester for the outcome of major congenital malformations and during any trimester for all remaining outcomes.

Primary Outcomes:
Birth outcomes

- Major congenital malformations, overall and specific types
- Stillbirth
- Low birth weight
- Small for gestational age among singletons
- Preterm birth
- Low Apgar score at 5 minutes
- Microcephaly

Secondary Outcomes:
Postnatal neurodevelopmental outcomes

- Attention deficit hyperactivity disorder (ADHD)
- Autism spectrum disorders (ASD)
- Learning disabilities (including mental retardation)

Covariates:
Characteristics of the study population will include perinatal covariates and covariates on the mother. Perinatal covariates include calendar year of delivery, maternal age at conception, parity, marital/cohabiting status, pregravid body mass index as recorded at the first antenatal visit, smoking during pregnancy as recorded at the first antenatal visit, multiple pregnancy, Caesarean delivery, and child's sex. Covariates on the mother will include indication for pregabalin use, morbidity, medication use, and indicators of health care utilisation.

Data source: Data will be linked from population-based administrative registries in Denmark, Finland, Norway, and Sweden.

Study size: The study size is estimated at greater than 2,000,000 pregnancies, including at least 1000 exposed to pregabalin in the first trimester.

Data analyses: For the outcome of major congenital malformations first-trimester exposure to pregabalin will be examined. For all remaining outcomes, any trimester exposure to pregabalin will be examined. Exposure periods for all comparators will be defined similar to pregabalin.

Primary analyses:

- Prevalence of pregabalin use in pregnancy will be described in terms of prevalence overall, by trimester, by indication, by calendar year of delivery, and as both overall and monotherapy.
- Distributions of the covariates in the study population will be tabulated according to pregabalin exposure categories.
- Distribution of maternal and offspring characteristics in the study population will be tabulated according to pregabalin and the active comparator categories.
- Crude prevalence of the major congenital malformations will be reported according to first-trimester exposure to pregabalin and the comparators. Crude prevalence of the other birth outcomes will be reported according to any trimester exposure to pregabalin and the comparators (unexposed, lamotrigine, duloxetine and lamotrigine or duloxetine. Lamotrigine and duloxetine chosen because they have indications similar to that of pregabalin [lamotrigine (epilepsy), duloxetine (GAD, neuropathic pain)]).
- Crude and propensity-score adjusted prevalence ratios will be estimated for the birth outcomes comparing pregnancies exposed to pregabalin during first trimester versus the four comparators.
    - Analyses will be conducted for all pregabalin exposed pregnancies, overall (i.e. all first trimester pregnancies irrespective of indication of use). Pregnancies ending in singleton/multiple live birth, stillbirth will be used.
    - Separate analyses will be conducted for pregabalin monotherapy.

Secondary analyses:
Will be similar to the primary analyses but with pre-specified postnatal neurodevelopmental outcomes.

Sensitivity analyses:
The analyses of major congenital malformations will be repeated with the inclusion of pregnancies ending in 2nd trimester therapeutic induced abortions (in all countries except Sweden).

Meta-analyses:
Country-specific crude and adjusted estimates of association will be combined in a meta-analysis.

Milestones: Pfizer will initiate the study upon endorsement of the protocol by the EMA. The earliest estimated timeline to submit the study report to the EMA is in the fourth quarter of 2019) (Q4 2019).

4. AMENDMENTS AND UPDATES

None

5. MILESTONES

Milestone	Planned Timeline	Planned date*
Draft protocol submission to the EMA		January 2018
Registration in the EU PAS register	Prior to start of data collection	30 November 2018
Start of data collection[†]	Within 1 month of protocol endorsement by the EMA	30 December 2018
End of data collection[‡]	Within 2 months of the start of data collection	28 February 2019
Final study report to the EMA	Within 7 months of the end of data collection	November 2019

EU: European Union; PAS: post-authorization study.

*Subject to change due to approval timelines and data queues at the government data custodians at each of the participating countries.

[†] For studies with secondary data collection, the start of data collection is defined as the planned date for starting data extraction for the purposes of the primary analysis.

[‡] For studies with secondary data collection, the end of data collection is defined as the planned date on which the analytical dataset will be first completely available; the analytic dataset is the minimum set of data required to perform the statistical analysis for the primary objective(s).

6. RATIONALE AND BACKGROUND

Pregabalin (Lyrica®, Pfizer Inc., New York, NY) was approved in July 2004 by the European Medicines Agency (EMA) for the treatment of peripheral neuropathic pain and as an adjunctive therapy for adult patients with partial onset seizures. Subsequently, the marketing authorizations were expanded to include generalized anxiety disorder (GAD), in March 2006 and central neuropathic pain, in September 2006. Per current European Union (EU) label, "Lyrica® should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus)."[1] In the general population (including men and women of all ages), pregabalin is mostly used for neuropathic pain (18-98%) and least used for epilepsy (4-6%).[2] Use of pregabalin in non-pregnant population, as assessed in a study in Sweden, is primarily for neuropathic pain (36%) and only 1.3% for epilepsy, with 40% of pregabalin initiators having no identifiable approved indication based on routine records.[3] Published data on the most common indication in pregnant women are unavailable at this time. A study based on two distinct United States (US) datasets reported an epilepsy indication frequency of 5.5% and 6.7% of pregabalin use in pregnant women.[4] In the feasibility assessment for this study, based on available Danish data, 21% of pregnancies exposed to pregabalin in the first trimester had a known indication identifiable by a hospital diagnosis in the previous year. Those included epilepsy (4% of those with identifiable indication), neuropathic pain (72% of those with identifiable indication), or GAD (24% of those with identifiable indication). Frequency distributions were similar for pregnancies exposed to pregabalin at any trimester (Table 1).

Evidence regarding pregabalin safety in pregnancy is limited. A recent study, using data from eight European Teratology Information Services (TIS), based on 164 pregabalin-exposed and 656 pregabalin-unexposed pregnancies, reported a 3-fold increased risk in non-chromosomal major birth defect associated with first-trimester pregabalin exposure.[5] Major limitations of the analysis include lack of data on specific malformations, potential selection and detection bias due to self-referral, low precision, and confounding by indication. A subsequent study based on 477 pregabalin-exposed pregnancies among Medicaid beneficiaries in the US did not confirm the increased risk. When all available evidence was combined, adjusted risk ratios for any major malformation were 1.3 for first-trimester exposure to pregabalin and 1.0 for pregabalin monotherapy exposure.[4] To extend the available evidence, safety of pregabalin use in pregnancy must be examined using outcomes other than malformations, including foetal growth indicators, and neurologic morbidity.

To reduce confounding by indication in observational study settings, risks in pregabalin-exposed pregnancies must, ideally, be compared among pregnancies with a given indication exposed and unexposed to pregabalin. Given that pregabalin has several indications and that administrative data available for this study have low sensitivity in identifying all pregnancies with relevant indications, in this study, pregnancies exposed to pregabalin will be compared with pregnancies exposed to medications with similar sets of indications. To the best of our knowledge, there is no single product with identical set indications as that of pregabalin. Nevertheless, the MAH identified lamotrigine and duloxetine as collectively suitable active comparators. In 2004-2010 lamotrigine was the most commonly used antiepileptic drug

(AED) in Europe, thus having an additional advantage of helping improve study precision.[6] In Europe, lamotrigine, alone or in combination with other AEDs, is indicated for treatment of epilepsy, partial and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut Syndrome in adults.[7] Lamotrigine is also indicated for treatment of bipolar disorder.[7] Lamotrigine has not been associated with an increased risk of congenital malformations.[8] In the feasibility assessment for this study, based on available Danish data, the following distribution of known pregabalin indications were identified for pregnancies exposed to lamotrigine in the first trimester: epilepsy (79% of those with identifiable indication), neuropathic pain (10% of those with identifiable indication), or GAD (10% of those with identifiable indication). Frequency distributions were similar for pregnancies exposed to lamotrigine at any trimester (Table 1). Duloxetine has been approved in the EU since 2004 for treatment of GAD, depressive disorder, major diabetic neuropathies and, since 2014, for treatment of neuralgia.[9] Available data, albeit sparse, do not suggest clinically important risk increase associated with duloxetine use in pregnancy.[10-12] In the feasibility assessment for this study, conducted using Danish data, the following pregabalin indication frequency estimates were reported for pregnancies exposed to duloxetine in the first trimester: epilepsy 7% (among those with identifiable indication); neuropathic pain 48% (among those with identifiable indication); GAD 45% (among those with identifiable indication) (Table 1).

Table 1. Pregabalin indication frequency proportions

	Source of data (N with recorded diagnosis)	Epilepsy (%)	Neuropathic pain (%)	GAD (%)
General population (United Kingdom)[2]	Pregabalin DUS (13,480)	4-6	18-98	7-28
Non-pregnancy population (Sweden)[3]	Pregabalin DUS (18,626)	1	36	4
Pregabalin (Denmark [A0081359]) (Feasibility assessment of this study)	First trimester (74)	4	72	24
	Anytime during pregnancy (117)	3	56	40
Lamotrigine (Denmark, [A0081359]) (Feasibility assessment of this study)	First trimester (675)	79	10	10
	Anytime during pregnancy (1164)	77	9	14
Duloxetine (Denmark, [A0081359]) (Feasibility assessment of this study)	First trimester (87)	7	48	45
	Anytime during pregnancy (179)	4	35	61

DUS, drug utilization study; GAD, generalised anxiety disorder.

This non-interventional study will evaluate the pattern of use and safety of pregabalin in pregnancy using data on all pregnancies identifiable from population-based registries in Denmark, Finland, Norway, and Sweden. The primary analyses will consist of a comparison of exposed vs unexposed to pregabalin during the relevant period of pregnancy. To control for confounding by indication,[13] in addition to assessing the risk of study outcomes according to exposure to pregabalin during pregnancy, the study outcomes will also be assessed in pregnancies exposed to agents with similar pregabalin indications – lamotrigine (epilepsy) and duloxetine (neuropathic pain, GAD).

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is a commitment to the EMA).

7. RESEARCH QUESTION AND OBJECTIVES

The study objectives are to describe the use of pregabalin exposure in pregnancy and to estimate the risk of major congenital malformations, birth outcomes other than congenital malformations and neurodevelopmental outcomes with the use of pregabalin. Association between pregabalin exposure and a given safety outcome will be assessed for pregabalin exposure during a relevant gestational period using, alternatively, unexposed subjects and subjects exposed to treatments with indications similar to those of pregabalin (active comparators); effect exposure to pregabalin monotherapy will be assessed in a sensitivity analysis.

The specific primary objectives of the study are to:

- Describe use of pregabalin, lamotrigine, and duloxetine during pregnancy overall, by trimester and by calendar year of delivery in pregnancies ending in live or stillbirths, as characterized by
  - Prevalence of use (proportion of pregnancies with 1 or more dispensing of a given drug),
  - Distribution of therapeutic indications among the exposed pregnancies (epilepsy, GAD, neuropathic pain),
  - Cumulative dose, based on dispensings count and amount dispensed in each;
- Describe the prevalence of (proportion of live or stillborn children with) major congenital malformations after first-trimester in-utero exposure to pregabalin (yes/no); after first-trimester exposure to lamotrigine, after first-trimester exposure to duloxetine, after first-trimester exposure to lamotrigine or duloxetine, in pregnancies ending in live or still birth; in live or stillborn children unexposed to antiepileptics in the first trimester; and in the total population of live or stillborn children;
- Estimate the association between first-trimester exposure to pregabalin and prevalence of major congenital malformations, as compared with no first-trimester exposure to pregabalin, with first-trimester exposure to lamotrigine, with first-trimester exposure to duloxetine, and first-trimester exposure to lamotrigine or duloxetine, in live or stillborn children;
- Describe the prevalence of birth outcomes other than major congenital malformations (listed in Section 8.3.2.1) according to exposure (yes/no) to pregabalin any time

during gestation, according to exposure to lamotrigine any time during gestation, according to any in utero exposure to duloxetine, according to any in utero exposure to lamotrigine or duloxetine, and in live or stillborn children unexposed in utero to antiepileptics;

- Estimate the association between any in utero exposure to pregabalin and the birth outcomes other than major congenital malformations, as compared with no exposure to pregabalin; any in utero exposure to lamotrigine; any in utero exposure to duloxetine; any in utero exposure to lamotrigine or duloxetine, and no in utero exposure to antiepileptics.
- Estimate, in a sensitivity analysis to evaluate potential impact of selection bias, association between first-trimester exposure to pregabalin and prevalence of major congenital malformations, as compared with no first-trimester exposure to pregabalin; first-trimester exposure to lamotrigine; first-trimester exposure to duloxetine; and first-trimester exposure to lamotrigine or duloxetine, in pregnancies ending in livebirth, stillbirth, or 2nd trimester induced abortion (in Denmark, Finland and Norway);

The specific secondary objectives of the study are to:

- Describe, in liveborn infants, the incidence rates (number of incident outcome events/postnatal person time) of pre-specified postnatal neurodevelopmental outcomes (listed in Section 8.3.2.2) according to exposure (yes/no) to pregabalin any time during pregnancy, after any in utero exposure to lamotrigine, after any in utero exposure to duloxetine, and after any in utero exposure to lamotrigine or duloxetine in pregnancies ending in live birth;
- Estimate, in liveborn infants, the association between in utero exposure to pregabalin and the pre-specified postnatal neurodevelopmental outcomes, as compared with no in utero exposure to pregabalin; any in utero exposure to lamotrigine any in utero exposure to duloxetine, and any in utero exposure to pregabalin or duloxetine.

The calculations of 'prevalence' and 'incidence rate' are further described in section 8.7.1 and section 8.7.2 respectively.

8. RESEARCH METHODS

8.1. Study design, study period, and follow-up

This PASS is a population-based cohort study based on routinely collected data from administrative and medical registers in four Nordic countries: Denmark, Finland, Norway, and Sweden and will include all identifiable pregnancies between 2005 and up to 2015, followed up to 2016 (with actual period varying slightly by country) Table 2. Each country has tax-supported universal health care; routine and prospectively collected data on outpatient dispensings, live and still births, hospital diagnoses, migrations and deaths; and individual-level data linkage including exact mother-child linkage (mother's personal identifier is a data field in the child's birth record).[14 15]

Because pregabalin is used to treat epilepsy, GAD and neuropathic pain, the comparators were chosen to represent the background occurrence of the outcomes, including occurrence in unexposed subjects and in subjects exposed to medications with indications similar to pregabalin (epilepsy, GAD, neuropathic pain) and are considered relatively safe for use in pregnancy, i.e., lamotrigine and/or duloxetine.

The outcomes ~~were~~ chosen are standard outcomes used to evaluate safety of medication exposure for the offspring and are the outcomes examined in previous studies[4-6,8,10,12] (birth outcomes) as well as postnatal outcomes.

Because confounding by indication or severity may persist even in contrasts against an active comparator, [13] the amount of confounding may be inferred indirectly by examining whether estimates of association differ depending on the nature of the comparator.

8.2. Setting

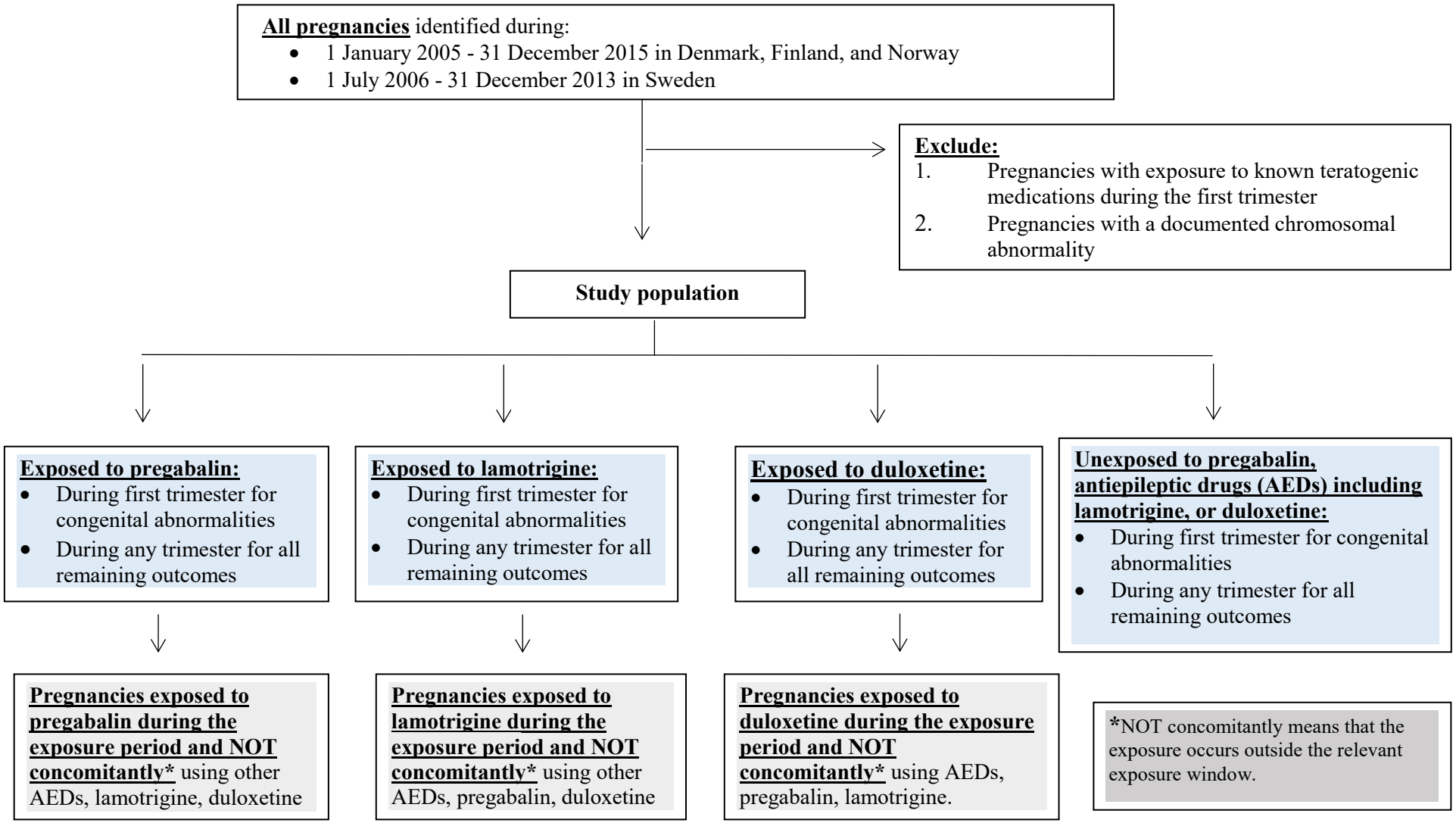
This study will be conducted using data from four Nordic countries: Denmark, Finland, Norway, and Sweden (listed alphabetically) in each country, all live births and stillbirths are recorded in the birth registries (in all countries from gestational week 22 from July 2008 onwards; in Sweden, from gestational week 28 until July 2008). During those periods there were approximately 580,000 – 730,000 live births in each of Denmark, Finland, and Norway, and 800,000 in Sweden.[16] The start of the study period in each country is selected to ensure availability of pregabalin and the candidate comparator on the market and availability of data on outpatient dispensings for at least 12 months before the end of the earliest identified pregnancy. For example, pregnancy ending at term with a live birth on 1 January 2005 in Denmark will have prescription history from 1 January 2004, thus covering the 9 months of gestation and 3 months preconception.

Population-based healthcare registries in Nordic countries are an optimal setting for examining safety of medicines in pregnancy. Their most important strengths are capture of all births and, in some cases, clinically relevant birth and postnatal outcomes; routine capture of dispensings of prescription medications to pregnant women; extensive information about maternal and offspring health outcomes; and exact linkage between the maternal and the offspring record. Thus, unlike studies based e.g., on data from TIS, there is no risk of bias by self-referral, recall, or access to health care. Dispensings of medicines represent a better proxy of actual drug intake than do issued prescriptions (primary compliance), reducing misclassification of the actual drug intake.

Study population

The study population consists of all pregnancies identified in the respective administrative registries from 1 January 2005 to 31 December 2015 in Denmark, Finland, and Norway and all pregnancies identified from 1 July 2006 to 31 December 2013 in Sweden, Figure 1 .

Figure 1. Study population flow diagram



All singleton and multiple gestations ending in live birth or stillbirth will be identified in each country's birth registry from 1 January 2005 to 31 December 2015 in Denmark, Finland, and Norway and pregnancies identified from 1 July 2006 to 31 December 2013 in Sweden. As all birth outcomes will have occurred as of the date of delivery, prevalence will be used as a measure of outcome occurrence.[14] However, to allow for delayed reporting/diagnosis, all congenital malformations diagnosis recorded until one year of age will be included, according to the standard procedure used by the European Network of Congenital Anomaly Registers (EUROCAT)[17] through the end of 2016 in Denmark, Finland and Norway and through the end of 2014 in Sweden. In addition, available information on pregnancies ending in 2nd trimester therapeutic induced abortions will be identified in Denmark, Finland and Norway.[18] Information on pregnancies ending in 2nd trimester therapeutic induced abortions is not available from Sweden. It will be especially important to identify pregnancy terminations due to malformations of the nervous system, as nearly half of the pregnancies affected by nervous system malformations may be terminated.[18]

For the birth outcomes, stillbirth prevalences at birth will be described and compared among the live and still born infants. For the birth outcomes other than congenital malformations or stillbirth, prevalences at birth will be described and compared.

For the postnatal neurodevelopmental outcomes, live-born offspring of all pregabalin-exposed and the comparator pregnancies will be followed from the date of birth until the earliest record of a given outcome of interest, emigration (except Sweden and Norway, where emigration data are unavailable), death, or end of study (31 December 2014 in Sweden; 31 December 2016 in the other countries); for this analysis children in Norway born before 2008 will be excluded as the Patient Registry of Norway was launched in 2008. Thus, for the neurodevelopmental postnatal outcomes, live-born children will be followed up to a minimum of 1 year and a maximum of 10 years postnatally in Denmark, Finland, and Norway and up to a maximum 8.5 years postnatally in Sweden (Figure 2).

8.2.1. Inclusion criteria

All pregnancies identified from 1 January 2005 through 31 December 2015 (both dates inclusive) in Denmark, Finland, and Norway and all pregnancies identified from 1 July 2006 through 31 December 2013 (both dates inclusive) in Sweden.

8.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Pregnancies with exposure to known teratogenic medications during the first trimester;

2. Pregnancies carrying a foetus with a chromosomal abnormality diagnosis.

8.3. Variables

8.3.1. Exposures

For the purposes of timing of exposure, trimesters of pregnancy will be defined as follows:

- First trimester: from the first day of the last menstrual period (LMP)-90 days to LMP+97 days (both dates inclusive);
- Second trimester: from LMP+98 days to LMP+202 days (both dates inclusive);
- Third trimester: from LMP+203 days (inclusive) until pregnancy end date (not included).

Exposure during the first trimester
Pregabalin exposure during the first trimester will be defined as at least one maternal dispensing of pregabalin during the first trimester. Pregabalin monotherapy in the first trimester will be defined as first-trimester exposure to pregabalin and no first-trimester dispensing for any other AED.

Comparators:
Unexposed to pregabalin during the first trimester comparator is defined as pregnancies without a dispensing for pregabalin or any other AED, including lamotrigine or duloxetine, during the first trimester.

Lamotrigine exposure in the first trimester is defined by at least one dispensing of lamotrigine during the first trimester. Lamotrigine monotherapy in the first trimester will be defined as first-trimester exposure to lamotrigine and no first-trimester dispensing for any other AED.

Duloxetine exposure in the first trimester is defined by at least one dispensing of duloxetine during the first trimester. Duloxetine monotherapy in the first trimester will be defined as first-trimester exposure to duloxetine and no first-trimester dispensing for any AED.

Lamotrigine or duloxetine exposure in the first trimester is defined by at least one dispensing of lamotrigine or duloxetine or both during the first trimester. Lamotrigine or duloxetine monotherapy in the first trimester will be defined as first-trimester dispensing of lamotrigine or duloxetine or both and no first-trimester dispensing for any other AED.

For analyses that use lamotrigine as the comparator, pregnancies exposed to both pregabalin and lamotrigine in the first trimester will be excluded. For analyses that use duloxetine as the comparator, pregnancies exposed to both pregabalin and duloxetine in the first trimester will be excluded.

Exposure any time during pregnancy
Pregabalin exposure any time during pregnancy is defined by at least one dispensing of pregabalin during any trimester. Pregabalin monotherapy any time during pregnancy will be defined as any-pregnancy exposure to pregabalin and no dispensing for any other AED during any trimester.

Comparators:
Unexposed to pregabalin during any trimester comparator is defined as pregnancies without dispensing for pregabalin or other AEDs including lamotrigine, or duloxetine during any trimester.

Lamotrigine exposure any time during pregnancy is defined by at least one dispensing of lamotrigine during any trimester. Lamotrigine monotherapy any time during pregnancy will be defined as any-pregnancy exposure to lamotrigine and no dispensing for any other AED during any trimester.

Duloxetine exposure any time during pregnancy is defined by at least one dispensing of duloxetine during any trimester. Duloxetine monotherapy any time during pregnancy will be defined as any-pregnancy exposure to duloxetine and no dispensing for any AED during any trimester.

Lamotrigine or duloxetine exposure any time during pregnancy defined by at least one dispensing of lamotrigine or duloxetine or both during any trimester. Lamotrigine or duloxetine monotherapy any time during pregnancy will be defined as any-pregnancy exposure to lamotrigine or duloxetine or both and no dispensing for any other AED during any trimester.

For analyses that use lamotrigine as the comparator pregnancies exposed to both pregabalin and lamotrigine in any trimester will be excluded. For analyses that use duloxetine as the comparator pregnancies exposed to both pregabalin and duloxetine in any trimester will be excluded.

In a sensitivity analysis, monotherapy with pregabalin, lamotrigine, and/or duloxetine will be defined by absence of other AED, selective serotonin reuptake inhibitors, or benzodiazepines.

8.3.2. Outcomes

This study will describe use and assess safety of pregabalin use during pregnancy based on a series or birth and postnatal outcomes. For each outcome defined below, the population (denominator), period of pregnancy identification, and follow-up for outcome assessment are described in Table 2.

Table 2. Types of pregnancies included in analysis of each outcome for the primary analyses, secondary analyses, and sensitivity analyses

Outcome	Study population and period of pregnancy identification				Follow-up for outcome assessment
	Denmark	Finland	Norway	Sweden	

Table 2. Types of pregnancies included in analysis of each outcome for the primary analyses, secondary analyses, and sensitivity analyses

Outcome		Study population and period of pregnancy identification				Follow-up for outcome assessment
		Denmark	Finland	Norway	Sweden	
Primary analyses	Major congenital malformations (overall and specific)	Pregnancies ending in singleton/multiple live birth, stillbirth, 1Jan2005 - 31Dec2015 inclusive			Pregnancies ending in singleton/multiple live birth or stillbirth 1Jul2006-31Dec2013 inclusive	Prevalence at birth with outcomes identified at birth, and until the first birthday (inclusive) through 2016 in Denmark, Finland and Norway and through 2014 in Sweden
	Stillbirth	Pregnancies ending in singleton/multiple live birth, stillbirth, 1Jan2005 - 31Dec2015 inclusive			Pregnancies ending in singleton/multiple live birth or stillbirth 1Jul2006-31Dec2013 inclusive	Prevalence at birth
	Low birth weight SGA[19] Preterm birth Low Apgar score at 5 minutes Microcephaly	Pregnancies ending in singleton/multiple live birth, 1Jan2005 - 31Dec2015 inclusive			Pregnancies ending in singleton/multiple live birth 1Jul2006-31Dec2013 inclusive	Prevalence at birth
Secondary analyses	Attention deficit hyperactivity disorder Autism spectrum disorders Learning disabilities (including mental retardation)	Pregnancies ending in singleton/multiple live birth, 1Jan2005 - 31Dec2015 inclusive		Pregnancies ending in singleton/multiple live birth, 1Jan2008 - 31Dec2015 inclusive	Pregnancies ending in singleton/multiple live birth 1Jul2006-31Dec2013 inclusive	Minimum 1 year postnatally. Maximum available postnatally, 31Dec 2016 Denmark, Finland, Norway; 31Dec 2014 Sweden.
Sensitivity analyses	Major congenital malformations (overall and specific) including malformations identified prenatally	Pregnancies ending in singleton/multiple live birth, stillbirth, 1Jan2005 - 31Dec2015 inclusive and pregnancies ending in therapeutic 2nd trimester induced abortion, 1Jan2005-31Dec2015 inclusive (Denmark, Norway) 31Dec2012 (Finland)			None	Prevalence at birth with outcomes identified prenatally, at birth, and until the first birthday (inclusive) through 2016 in Denmark and Norway and 31Dec2016 in Finland

SGA, Small for gestational age.
* The Patient Registry of Norway, the source of data for the postnatal outcomes, has existed from 2008.

8.3.2.1. Primary Outcomes (Birth outcomes)

- Major congenital malformations, any and specific, according to the European Network of Congenital Anomaly Registers (EUROCAT) classification[20]
- Stillbirth, as recorded in each country's birth registry
- Low birth weight (birth weight < 2500 g)
- Small for gestational age (SGA), defined, for singleton pregnancies, as a dichotomous variable (yes/no) of birth weight below 2 standard deviations (SDs) of sex- and gestational week specific distributions, using country-specific reference standard.[19,21] SGA non-singleton gestations will be defined if appropriate reference standard can be defined/identified; otherwise set to missing.
- Preterm birth, defined as gestational age <37 weeks
- Low Apgar score at 5 minutes, defined as a dichotomous variable (score 0-6 vs. score 7-10)
- Microcephaly, defined as a dichotomous variable (yes/no) of head circumference at birth (cm) smaller than 2 SD of sex- and gestational week specific distribution, using country-specific reference standard

8.3.2.2. Secondary Outcomes (Postnatal neurodevelopmental outcomes)

- Attention deficit hyperactivity disorder (ADHD) (identified via inpatient or outpatient hospital diagnosis or a medication proxy)
- Autism spectrum disorders (ASD) (identified via inpatient or outpatient hospital diagnosis)
- Learning disabilities (including mental retardation)(identified via inpatient or outpatient hospital diagnosis)

8.3.2.3. Sensitivity Analysis Outcomes (Major congenital malformations)

- Major congenital malformations identified at live or stillbirths or 2nd trimester abortions, any and specific as described above (Denmark, Finland, Norway)

8.3.2.4. Other Outcomes

- Major congenital malformations identified in the total study population of live or stillbirths, to provide context

8.3.3. Covariates and other population characteristic

Characteristics of the study population will include perinatal covariates and covariates of the mother. Perinatal covariates include calendar year of delivery, maternal age at conception, parity (number of live and still births prior to the on-study pregnancy); marital/cohabiting status; pregravid body mass index (BMI) as recorded at the first antenatal visit or via a hospital diagnosis of obesity; smoking during pregnancy as recorded at the first antenatal visit; single or multiple gestation; Caesarean delivery; and child's sex. Caesarean delivery and child's sex will be reported but will not be used for adjustment. Indication for pregabalin use in 12-months pre-LMP (epilepsy, neuropathic pain, GAD and related disorders) will be reported descriptively but will not be used for adjustment.

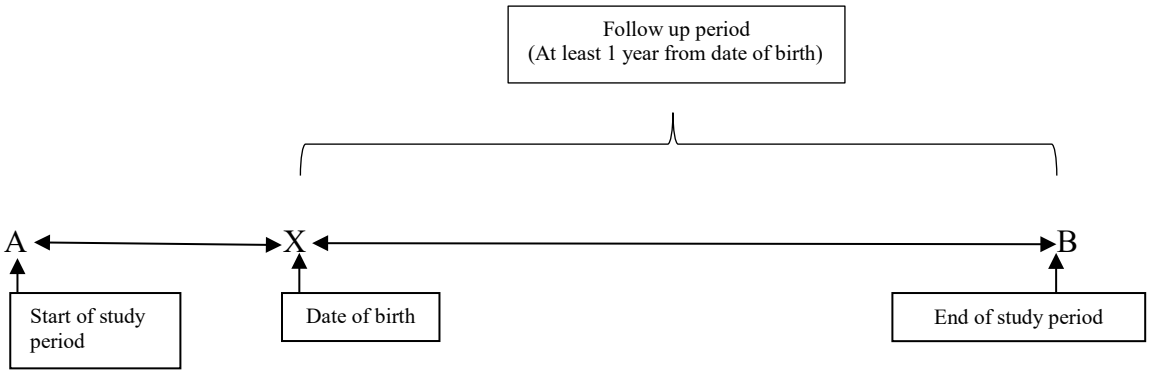
Covariates of the mother considered for adjustment (inclusion in propensity-score model) will include:

- calendar year of delivery;
- age in years at conception;
- marital/cohabiting status;
- smoking during pregnancy;
- Obesity (BMI =>30 kg/m^2) or a hospital diagnosis of obesity;
- Single or multiple gestation
- hospital-recorded morbidity based on inpatient and outpatient specialist care or proxy medication use in 12 months pre-LMP: migraine or other headache syndromes, other neurologic disorders, depression, bipolar disorder, alcohol abuse or dependence, drug abuse or dependence, hypertension, haematological diseases, diabetes, asthma, liver diseases, renal impairment, rheumatic diseases, obesity, disorders of female pelvic organs/genital tract, thyroid disorders, infections [infections will be assessed in 90 days pre-LMP]. In Finland, in addition to the hospital diagnoses, diagnoses from primary care are also available and will be used;
- indicators of maternal health care utilisation in the 12 months pre-LMP (number of inpatient and specialised outpatient encounters);
- for the outcome congenital malformations: maternal medication use each as a dichotomous variable, defined by at least one dispensing during the first trimester (AEDs, antidepressants, hypnotics, antipsychotics, analgesics, antihypertensives, non-steroidal anti-inflammatory drugs, drugs for peptic ulcer/gastroesophageal reflux, folic acid, drugs for in-vitro fertilization, thyroid hormones, systemic corticosteroids, and antiinfectives for systemic use);
- for the outcomes other than congenital malformations: maternal medication use each as a dichotomous variable, defined by at least one dispensing during any trimester (AEDs, antidepressants, hypnotics, antipsychotics, analgesics, antihypertensives, non-steroidal anti-inflammatory drugs, drugs for peptic ulcer/gastroesophageal reflux, folic acid, drugs for in-vitro fertilization, thyroid hormones, systemic corticosteroids, and antiinfectives for systemic use).

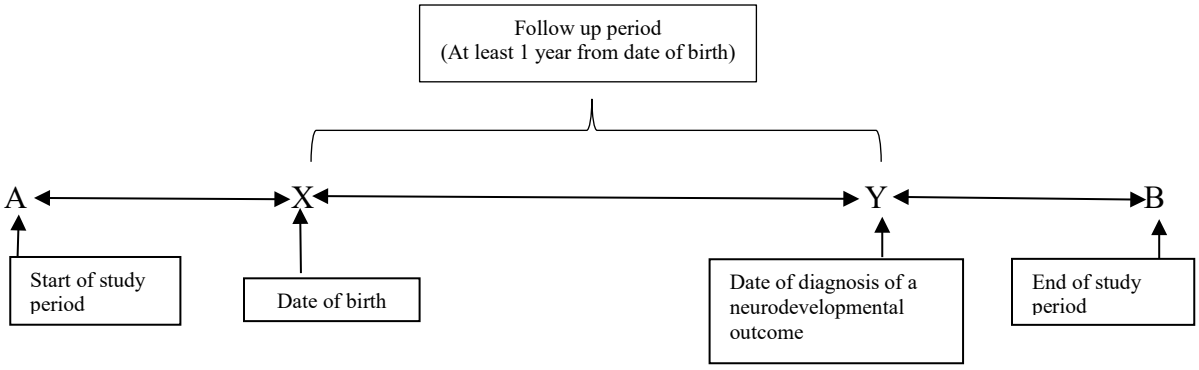
Full list of the study variables and their operational definitions are provided in Annex 3.

Figure 2. Examples of follow up period for neurodevelopmental outcomes during the study period

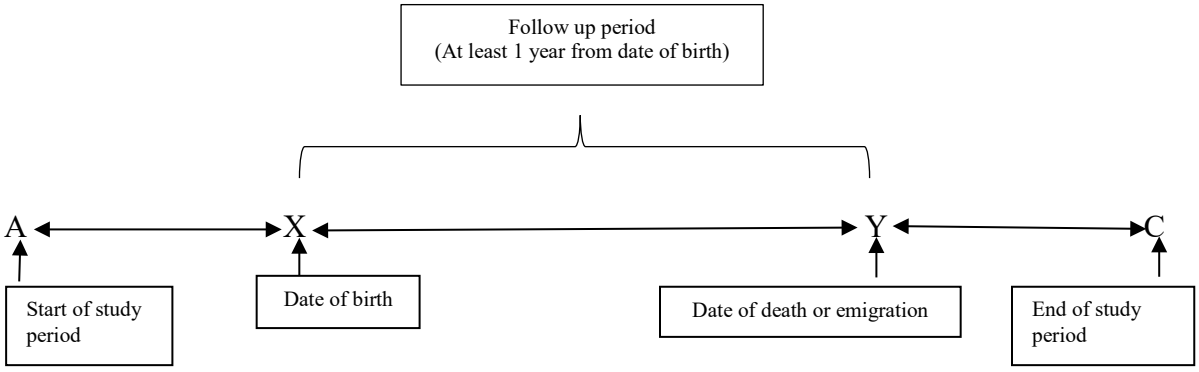
1.



2.



3.



8.4. Data sources

Data sources used to construct the analysis data set for this study are presented in Table 3. Within each country, records from all registries are linkable at the individual level by a unique national person identifier. For births recorded in the birth registries, a maternal unique identifier is a variable on the record of the offspring, enabling exact linkage between a given offspring and maternal history of medication dispensing or diagnoses before or during pregnancy.

Diagnosis in all countries are registered based on the ICD-10 coding system and accessed through registers as specified in Table 3. Similarly medications are classified according to the ATC coding system and accessed through prescription registers. The medical birth registers in the included countries furthermore contain similar information other relevant covariates (calendar year of delivery, maternal age at conception, parity; marital/cohabiting status; pregravid body mass index (BMI); smoking during pregnancy; single or multiple pregnancy; and child's sex.)

Validity of routine data in Nordic national registries has been found to be high in all countries.[22-37] In Denmark, positive predictive value of diagnoses of cardiac malformations is 89%.[38] For drugs used chronically, there is also high level of agreement between general practitioner and dispensing records.[39] An agreement between dispensing records and drug use reported in the standard medical antenatal records included in the birth register was 69% for antiepileptics in Sweden.[40]

Table 3. National registries in Denmark, Finland, Norway and Sweden and type of data available from each registry

Study variable/role	Type of data	Data source(s)	Coding system(s) used
Person identification (mothers and children)	Unique personal identifier for data linkage	Danish Civil Danish Civil Registration System[41] Finnish Medical Birth Register* National Registry of Norway Swedish Total Population Register[42]	N/A
Study population	Pregnancies ending in singleton/multiple live birth or stillbirth	Danish Medical Birth Registry Finnish Medical Birth Register* Medical Birth Registry of Norway Swedish Medical Birth Register	A specific variable in each birth registry
	Pregnancies ending in therapeutic 2nd trimester induced abortion	Danish National Patient Registry[43,44] Finnish Register on Induced Abortions* Norwegian Register of Pregnancy Terminations (part of the Medical Birth Registry of Norway) Not available in Sweden	ICD-10

Table 3. National registries in Denmark, Finland, Norway and Sweden and type of data available from each registry

Study variable/role	Type of data	Data source(s)	Coding system(s) used
Exposure (for full list see Section 8.3.1)	Maternal dispensings of pregabalin, lamotrigine, duloxetine	Danish National Health Services Prescription Database[45,46] Finnish Prescription Register[45] Norwegian Prescription Database[45] Swedish Prescribed Drug Register[45]	ATC
Outcome (for full list see Section 8.3.2)	Major congenital malformations	Danish Medical Birth Registry (stillbirths)/ Danish National Patient Registry (livebirths/induced abortions) Finnish Medical Birth Register* Finnish Register of Congenital Malformations* Finnish Register on Induced Abortions* Finnish Care Register for Health Care Medical Birth Registry of Norway Swedish Medical Birth Register Swedish National Patient Register	ICD-10, local codes (Denmark)
	Birth weight, gestational age, Apgar score at 5 minutes, head circumference, stillbirth	Danish Medical Birth Registry Finnish Medical Birth Register* Medical Birth Registry of Norway Swedish Medical Birth Register	A specific variable in each birth registry
	Neurodevelopmental outcomes	Danish National Patient Registry[43] Danish Psychiatric Central Research Register[47] Danish Psychiatric Central Register Finnish Care Register for Health Care Finnish Register of Primary Health Care visits Norwegian Patient Registry[48±] Swedish National Patient Register[29,49] Danish National Health Services Prescription Database[45,46] Finnish Prescription Register[45] Norwegian Prescription Database[45] Swedish Prescribed Drug Register[45]	ICD-10 for diagnoses, ATC codes for drug proxies
Characteristic of study population and covariates (for full list see Section 8.3.3)	Mother: age, parity, marital/cohabiting status, mode of delivery, smoking during pregnancy, BMI Offspring: sex, multiplicity of gestation	Danish Medical Birth Registry Finnish Medical Birth Register* National Registry of Norway[50] Swedish Medical Birth Register[42]	A specific variable in each birth registry

Table 3. National registries in Denmark, Finland, Norway and Sweden and type of data available from each registry

Study variable/role	Type of data	Data source(s)	Coding system(s) used
	Maternal morbidity (including indication for pregabalin) Markers of health care utilisation	Danish National Patient Registry,[43] Finnish Care Register for Health Care Finnish Register of Primary Health Care visits Norwegian Patient Registry[48] Swedish National Patient Register[29,49] Danish National Health Services Prescription Database[45,46] Finnish Prescription Register[45] Norwegian Prescription Database[45] Swedish Prescribed Drug Register[45]	ICD-10 for diagnoses, ATC for medication proxies
	Maternal medications	Danish National Health Services Prescription Database[45,46] Finnish Prescription Register[45] Norwegian Prescription Database[45] Swedish Prescribed Drug Register[45]	ATC
Loss to follow-up	Death, emigration[†]	Danish Civil Danish Civil Registration System[41] Finnish Causes of Death Register Finnish Population Register Centre National Registry of Norway Swedish Cause of Death Register	A specific variable in each registry

*Data for the Medical Birth Register, the Register on Induced Abortions, the Malformation Register and the Prescription Register (3 months before last menstrual period) can be obtained from the Finnish Drugs and Pregnancy Project (DPP) database.
[†]Emigration data not available in the Swedish or the Norwegian dataset
[±]Data available from 2008 onwards in Norway

8.5. Study size

Table 4 shows estimated number of total pregnancies ending in live or stillbirth and pregnancies with exposures and indications potentially relevant for analysis.

Table 4. Estimated numbers of pregnancies ending in live or still birth for potentially analysis-relevant categories

	Denmark (2005-2016)	Finland (2005-2014)	Norway* (2005-2016)	Sweden (2006-2013)
Pregnancies ending in live/still birth	730,000	580,000	650,000	800,000
Pregnancies with dispensation of				
Pregabalin, first trimester	200	700	200	400
Pregabalin, any time during pregnancy	350	900	350	800
Lamotrigine, first trimester	2000	900	2000	1300
Lamotrigine, any time during pregnancy	2700	1100	2700	1800
Duloxetine, first trimester	400	500	400	500
Duloxetine, any time during pregnancy	800	600	800	1000

*Pilot data not available; estimated based on pilot data from Denmark due to similar s population size.

The estimated numbers of pregnancies ending in live or still birth for potentially analysis-relevant categories for Norway were unavailable at the time of the protocol writing but are estimated in Table 4 by imputing data from Denmark, where the number of pregabalin users was the lowest, to provide the most conservative estimate. Based on this and on each country's population size, conservatively estimated achievable size for this study will be more than 1000 pregnancies exposed to pregabalin during the first trimester.[20,51] Table 5 shows the maximum upper limit of the 95% confidence interval of risk ratio that can be ruled out with 80% probability, for different scenarios with respect to the size of the exposed and comparator groups conservatively assuming N=1000 to be the size of pregabalin-exposed pregnancies. This analysis assumes that the true underlying risk ratio is 1.0 (no association between pregabalin exposure and an endpoint). For example, assuming the background prevalence of major congenital malformations to be 3%, underlying pregabalin-associated RR, and allocation ratio of comparator to pregabalin of 119:1 (corresponding to pregabalin exposure prevalence 0.8%), the analysis will rule out a RR with an upper confidence limit of 1.65845.

Table 5. Maximum upper limits of 95% confidence interval for risk or prevalence ratios depending on the prevalence of selected outcomes representative of prevalence of various study outcomes

Outcome	Estimated prevalence of outcome	Maximum upper limit of 95% confidence interval for risk ratio can be ruled out with at least 80% probability (unexposed:exposed allocation ratio= 119:1; approximate the analysis with pregabalin-unexposed as a comparator*)
Malformations of the nervous system[20,45], mental retardation	0.2%	7.2
Stillbirth, postnatal outcomes, ASD	0.6%	3.1
Cardiac congenital malformations, postnatal outcomes[18,20], ADHD	1%	2.4
Any major congenital malformation[18,20]	3%	1.7
Preterm birth/SGA	10%	1.3

Assumes true risk ratio =1.0, size of the pregabalin-exposed group N=1000 for first-trimester exposure and N=1000 for any exposure in pregnancy with minimum 6 years follow-up.
*The expected size of the pregabalin-unexposed pregnancies is about ten-fold of that used in the above calculations and the size of the pregabalin-exposed group during pregnancy is expected to be larger than that exposed in the first trimester. The computations were done using SAS software based on the 'Study size' worksheet of the Episheet.[52]

8.6. Data management

Data retrieval and management will be conducted separately in each country. Investigator in each country will obtain all necessary permissions and prepare a data application to its country-specific data custodian. A data manager in each country will ensure correctness of the delivered raw data before data management start. Records from different registries will be merged by unique personal identifier or its pseudonym and de-identified before the analysis. Data will be cleaned and coded, and harmonised analytic datasets will be prepared according

to the specifications provided in Annex 3. All four countries use similar coding systems for medications, diagnoses and procedures, and codes will be shared whenever feasible. There may be slight between-country variations in the specific diagnostic or procedure codes, which will be addressed in consultation with clinicians on a country-specific basis. Patient level data are kept on secure servers within each respective country. Patient-level data from Finland, Norway, or Sweden will not be made available to researchers at the 'vendor organizing institution' (Aarhus University Hospital, Denmark) or the MAH (Pfizer).

For data management and analyses, SAS version 9.3 or later and/or R version 3.1.1 or later will be used.

8.7. Data analysis

All steps of the country-specific data analyses will be conducted separately in each participating country according to the description below. Each country will generate a set of identical analytic tables, according to the table shells, provided in Annex 3.

After conducting the country-specific data analyses, country-specific datasets containing crude and adjusted estimates of association will be transferred to Aarhus University Hospital, Denmark, for meta-analyses.

8.7.1. Calculation of prevalences of birth outcomes

Prevalence of each birth outcome will be computed as number of newborns with a given outcome divided by the total number of newborns at risk. For the outcomes of congenital malformations and stillbirth in the analysis not including pregnancies ending in 2nd trimester abortion the number of newborns at risk will be the total number of live or stillborn children. For the outcomes of congenital malformations and stillbirth in the analysis including pregnancies ending in a 2nd trimester abortion the number of newborns at risk will be the number of live or stillborn children and the number of pregnancies ending in a 2nd trimester abortion. For the other birth outcome the number of newborns at risk will the number of liveborn newborns.

8.7.2. Calculation of incidence rates of postnatal outcomes

Incidence rate of each postnatal outcome will be computed as the number of first-recorded events during the follow-up divided by the total person-time at risk contributed by each liveborn infant. The follow-up for each newborn will begin on the date of birth and will end on the date of a given postnatal outcome, emigration, death, or the end of the observation period.

8.7.3. Estimation of prevalence ratios and hazard ratios

Crude and adjusted prevalence ratios and 95% Wald confidence intervals (CIs) for each birth outcome and a given population/contrast will be estimated using log-binomial regression.

Crude and adjusted incidence rate ratios and 95% Wald CIs will be estimated Cox's proportional-hazards regression for each postnatal outcome.
.

8.7.3.1. Computation of propensity scores

To account for confounding by the measured covariates, adjusted analysis will be conducted using propensity score (PS) stratification, following the approach by Patorno et al.[4] For each pregnancy, a PS will be computed, using logistic regression, as the probability being exposed to pregabalin vs. given comparator conditional on the measured covariates listed in Section 8.3.3 and Annex 3.[53]

PS will be estimated for each pregnancy using a generic-outcome model, meaning that all prespecified covariates will be included in the PS-estimating model, regardless of the outcome. Wyss et al showed, in a simulation study, that such model performs well when multiple outcomes are being examined;[54] furthermore, it is reasonable to assume in this study that all confounders distort the association in the same direction for all outcomes. In case of model non-convergence, covariates with the smallest cell counts (corresponding to the lowest prevalence of covariates) will be removed one-by-one until convergence is achieved.

A separate PS will be estimated for each study population and contrast. To summarise, the following sets of propensity scores will be estimated:

1. First-trimester pregabalin vs. first-trimester unexposed
2. First-trimester pregabalin vs. first-trimester lamotrigine
3. First-trimester pregabalin vs. first-trimester duloxetine
4. First-trimester pregabalin vs. first-trimester duloxetine or lamotrigine
5. First trimester pregabalin monotherapy vs. first-trimester unexposed
6. First trimester pregabalin monotherapy vs. first-trimester lamotrigine monotherapy
7. First trimester pregabalin monotherapy vs. first-trimester duloxetine monotherapy
8. First-trimester pregabalin monotherapy vs. first-trimester duloxetine or lamotrigine monotherapy
9. Any-trimester pregabalin vs. any-trimester unexposed
10. Any-trimester pregabalin vs. any-trimester lamotrigine
11. Any-trimester pregabalin vs. any-trimester duloxetine
12. Any-trimester pregabalin vs. any-trimester duloxetine or lamotrigine

13. Any-trimester pregabalin monotherapy vs. unexposed
14. Any-trimester pregabalin monotherapy vs. any-trimester lamotrigine monotherapy
15. Any-trimester pregabalin monotherapy vs. any-trimester duloxetine monotherapy
16. Any-trimester pregabalin monotherapy vs. any-trimester duloxetine or lamotrigine monotherapy

After estimation of each PS, the following steps will be taken in each country:

- a graph showing distribution of PS of the exposed and unexposed pregnancies will be produced and pregnancies with PS in non-overlapping areas will be deleted (trimming).

- based on the trimmed distributions, strata of PS will be defined using boundaries of the pregabalin-exposed pregnancies. Number of strata will be determined by the number of exposed pregnancies and will vary across countries.

- all exposed and unexposed pregnancies included in a given PS estimation will be classified into these strata based on their PS.

- A weight will be assigned to each unexposed pregnancy based on its stratum; each exposed pregnancy will assigned the weight of 1.

- A weighted regression analysis will be performed, in which adjusted prevalence ratios or adjusted hazards ratios are estimated using a weighted regression model.

Balance of the covariates following trimming and stratifications-strata specific weights will be assessed in each country's dataset using standardised mean differences. Covariates with standardised mean differences <0.1 will be considered balanced. Initially only first-order variables will be entered into the PS models; if imbalance persists, use of interaction terms will be considered. PS will be estimated by an analyst in each country and the final PS models that achieve acceptable covariate balance may be different in each country.

The crude and the adjusted country-specific estimates of association will be reported separately and combined in a meta-analysis (described in Section 8.7.7).

If feasible, prevalence ratios will be estimated among women with >1 pregnancies discordant with respect to pregabalin exposure in country-specific analyses only (not in meta-analyses).

8.7.4. Primary analyses

The primary analyses will be conducted in the following study population/analysis set: pregnancies ending in singleton/multiple live birth, stillbirth. The assessment of the outcomes stillbirth and major congenital malformations will include stillbirths; the other primary outcomes assessment will exclude stillbirths.

8.7.4.1. Descriptive analysis

- Pregabalin use in pregnancy will be described as the number and proportion of pregnancies exposed in the first trimester, and in any trimester. Number and proportion of pregnancies with pregabalin monotherapy will be reported. Cumulative dose during first trimester and any trimester will be described based on the amount of dispensings during a relevant period. Use of lamotrigine and duloxetine will be similarly described.

- Distributions of the characteristics of the study population will be tabulated according to pregabalin exposure categories: first trimester (exposed/unexposed); any trimester (exposed unexposed) and separately for the monotherapy subgroup. Categorical variables will be summarized using frequencies and proportions; continuous variables using either mean and standard deviation (SD), or median and interquartile range (IQR) as appropriate.
- Distribution of maternal and offspring characteristics in the study population will be tabulated according to pregabalin and the active comparator categories, as above. All descriptive tables will be constructed including stillbirths.
- Crude prevalence of the major congenital malformations will be reported according to first-trimester exposure to pregabalin (overall and in the subcategory of monotherapy) and each comparator (overall for all comparators including not exposed and in the subcategory of monotherapy for lamotrigine and duloxetine). In addition overall prevalence of malformations in the whole general population will be presented. Crude prevalence of the other birth outcomes (stillbirth, low birth weight, small for gestational age (SGA), preterm birth, low Apgar score at 5 minutes and microcephaly) will be reported according to any trimester exposure to pregabalin and each comparator, in the same fashion.

Major congenital malformation outcomes

Major congenital malformations (any, each major malformation type sample size permitting), among pregnancies ending in a live or a stillbirth pregnancies exposed to pregabalin during the first trimester will be compared against each of the comparators estimating crude and adjusted prevalence ratios in log-binomial regression.

Birth outcomes other than major congenital malformations

For birth outcomes other than major congenital malformations, any-trimester pregabalin exposed pregnancies will be compared against each of the comparators estimating crude and adjusted prevalence ratios in log-binomial regression. With the exception of stillbirth, all remaining birth outcomes will be assessed in pregnancies ending in a live birth

8.7.5. Secondary analyses

The secondary analyses will be conducted in the following study population/analysis set: pregnancies ending in singleton/multiple live birth. In these analyses any trimester pregabalin exposure will be considered versus each of the comparators as above. The monotherapy subset will be examined, sample size permitting.

Incidence rates (number of events/person-time contributed by live-born infants) of the postnatal neurodevelopmental outcomes will be reported according to any exposure to pregabalin and the predefined comparators. All incidence rates will be reported for any pregabalin therapy and the subset with pregabalin monotherapy.

For the postnatal neurodevelopmental outcomes, exposure will be defined at any time during pregnancy and the same comparators as above. Crude and PS-adjusted hazard ratios will be

estimated using Cox's proportional-hazards regression. In the event that too few postnatal outcomes are observed to estimate association, the number of cases and crude rates will be reported to the extent allowed by the data protection regulation.

8.7.6. Sensitivity analyses

To reduce the potential bias in the analysis of congenital malformations from not including pregnancies terminated due to known malformations, a sensitivity analysis including these will be conducted in the countries where this information is available (Denmark, Norway and Finland). The sensitivity analyses will be conducted in the following study population/analysis set: pregnancies ending in singleton/multiple live birth, stillbirth, or in therapeutic 2nd trimester induced abortion. The analyses in this population will assess the association of the first-trimester exposure to pregabalin and major congenital malformations, including all the comparators above. Separate descriptive tables will be produced and separate sets of PS will be estimated as appropriate for each contrast in the sensitivity analyses.

In another sensitivity analysis, crude estimates of association for the birth outcomes will be provided defining monotherapy of pregabalin, lamotrigine, and/or duloxetine by absence of other AED, selective serotonin reuptake inhibitors or benzodiazepines. By comparing magnitude and direction of change in the estimates of association obtained in this analysis and those in the main analyses of monotherapy, it will be possible to infer the direction and the amount of any potential unmeasured confounding, thus aiding interpretation of the results (triangulation[55]).

All estimates of association will be reported with Wald 95% confidence intervals (CIs).

8.7.7. Meta-analyses

After the separate analyses in each participating country as specified in the tables in Annex 3, aggregated level data on crude and adjusted estimates of association will be transferred to Aarhus University Hospital, Denmark for meta-analyses. Because of the similarities between the healthcare systems in the Nordic countries and the use of a common study protocol with well-defined selection of exposures, outcomes and covariates, the MAH does not expect the associations between the exposures and outcomes to vary substantially between countries and therefore a fixed-effects meta-analysis will be applied.[56] Country-specific crude and adjusted estimates of association for each prespecified contrast will be combined in a meta-analysis.[57] For each outcome the MAH will use the inverse variance method in the fixed effects meta-analyses, which is weighting the country-specific estimates of association by the inverse of the within-country variances. Heterogeneity of the estimates will be verified and a random-effects meta-analysis will be considered as an alternative should the estimates be found to vary significantly between countries. Results of the meta-analyses will be presented using a standard forest plot, reporting the country-specific overall crude and adjusted point estimates, and the pooled overall point estimate, all with 95% CIs.

8.8. Quality control

Data storage, management and analyses will be conducted according to each institution's standard procedures. At a minimum, all study documents (protocol, report, publications) will be reviewed by the entire research team. A senior epidemiologist in each institution will review the report before submission to the sponsor. Clinical expertise is available for appropriate interpretation of results. At the start of the project, a kick-off meeting will establish a regular communication plan (via e-mail and regular teleconferences); and internal timelines will be established to allow review and quality control before submitting each deliverable. Each institution will also follow its internal quality control procedures and will ensure the necessary compliance with local data protection, storage and archiving, and patient privacy laws and regulations and will obtain all permission necessary to conduct this study.

8.9. Limitations of the research methods

All epidemiologic studies are subject to biases that may include confounding, information bias, and selection bias. As with most pharmacoepidemiologic studies, confounding by indication may be introduced since epilepsy itself is known to be associated with adverse pregnancy outcomes. Other sources of confounding include residual confounding by unmeasured characteristics and resulting from misclassification of confounders. Even though this study proposed to use not only unexposed pregnancies but pregnancies exposed to medications with indications similar to pregabalin, those latter comparisons may still be confounded. As suggested by the feasibility analyses (pilot data), the distribution of the indications for the comparator drugs may not be identical to that of pregabalin and this could also result in confounding. Furthermore, validity of diagnostic codes used to identify GAD have not been studied in any of the registers; in fact, most patients who actually do have such a disorder do not get that specific diagnosis, and may be assigned a less specific anxiety diagnosis instead. Assessing safety of pregabalin within each indication of use does not appear feasible as data on indication are available for a minority of pregnancies according to the pilot data.

Information bias manifests as misclassification of exposure, outcome or confounders (discussed above). Dispensing records may not accurately represent the actual amount and timing of medication intake (exposure misclassification) and estimation of dose response patterns is limited by the small number of exposed pregnancies. Hospital diagnoses, used in identifying indications, covariates, and outcomes are imperfect measures of true events they purport to measure. Furthermore, as is common in such studies, malformations in pregnancies ending in spontaneous and first-trimester induced abortions cannot be observed, resulting in underestimation of the number of cases. If such selective dropout (i.e. selection bias) is associated with pregabalin exposure, associations based on prevalent outcomes will be biased. Given its design of a fixed study period, the study will be unable to provide equal follow up for live births regarding post neurodevelopmental outcomes. Children of mothers diagnosed and treated for epilepsy during pregnancy may undergo more medical surveillance compared to children of the general population, potentially leading to spurious association observed owing to this detection bias. Due to the limitations of the measurement and case

ascertainment, the study objective and analyses of postnatal outcomes was designated as secondary. Selection bias stemming from inclusion of all eligible pregnancies is of less concern in this study, as study entry for each woman is the estimated conception date of pregnancy and ends for each outcome of interest with the event (e.g. date of live birth, stillbirth). Selection of an appropriate reference group is challenging since no single drug is known to have all the indications of pregabalin and the unexposed population is likely to be healthier than the exposed population. Finally, full feasibility assessment of the postnatal neurodevelopmental outcomes cannot be performed at this time of writing the protocol and prior to review of the data, as those are diagnosed primarily at school age. Not all live-born infants will have follow-up into the school age, and the number of pregabalin exposed pregnancies in the earlier study period may not be sufficient to yield stable estimates of association, as specified in the provided feasibility counts in Table 5 and Annex 3. Emigration data (censoring variable) are not available in the Swedish or the Norwegian datasets, however, the impact of this is likely to be negligible.

The models proposed to analyse data including propensity score stratification performs well when multiple outcomes are being examined [54] However, in case of model non-convergence, actions have been described in section 8.7.3.1 to achieve convergence. The study is performed in the Nordic countries where >90 % is of Caucasian ethnicity, and thus the available data on other ethnic groups are too limited to do stratified analyses, but the MAH has no reason to believe that the associations between pregabalin exposure and the studied outcome should be different in other ethnic groups or in other countries.

8.10. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient information and consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

Registry-based studies in the Nordic countries do not require patient consent, but they need to be approved by each country's relevant authority (Data Protection Agency and/or Ethics Committees).[51,58] Investigators in each of the four countries will be responsible for obtaining all required approvals and compliance with all relevant local laws. Investigators will not have access to the personal identification numbers since those will be transferred to study-specific dummy-IDs by the data holders.

9.2. Patient withdrawal

Not applicable.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

In Denmark, no IRB/IEC approval is required for studies based on data from routine registries. An approval from the Danish Data Protection Agency, required for all studies, will be obtained.

In Finland, the protocol will be subjected to the Ethics Committee of the Hospital District of Helsinki and Uusimaa for review and approval. In addition, a register notification of the forming study register will be sent to the Office of the Data Protection Ombudsman.

In Norway, the protocol needs to be approved by the Data Inspectorate.

In Sweden, an IEC approval will be obtained from the Regional Ethical Review Board in Stockholm.

9.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), and European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and an ENCePP study seal will be obtained. The study protocol as well as results will be published in EU PAS register maintained by EMA.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study includes data that already exist as structured data in an electronic database. In these data sources, it is not possible to link (i.e., establish whether causal relation was reported between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual adverse event (AE) reports.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

At the end of this study a single report based on analysis of combined results (meta-analysis) from the four countries (and country-specific results) will be prepared and submitted to the EMA. The investigators may subsequently present results from this study at scientific

conferences and publish the results in a peer-reviewed journal. At least one joint publication will be produced, but several publications are likely due to the large number of outcomes studied. The investigators have the right to publish the results independent of the sponsor.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information, which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

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13. LIST OF TABLES

14. LIST OF FIGURES

Figure 2. Examples of follow up period for neurodevelopmental outcomes during the study period

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: A Non-Interventional Post-Authorisation Safety Study (PASS) of Pregabalin to Characterize Pregnancy Outcomes

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☒	☐	☐	5
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	5

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)	☒	☐	☐	6
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	7
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[1] 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.

[2] 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, new or alternative design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.4
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	8.7
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	8.7
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)	☐	☐	☒	10

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	8.4
	4.2.2 Age and sex?	☒	☐	☐	8.4
	4.2.3 Country of origin?	☒	☐	☐	8.4
	4.2.4 Disease/indication?	☒	☐	☐	8.4
	4.2.5 Duration of follow-up?	☒	☐	☐	8.4
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2.1 8.2.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.4 8.4
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	8.9
5.3	Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	8.7

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	8.7

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	8.9
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	8.3.2

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	8.7
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	8.7
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	8.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	8.9
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	8.9

Comments:

Section 8: Effect modification	Yes	No	N/A	Section Number

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

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.4
	9.1.3 Covariates?	☒	☐	☐	8.4
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)	☒	☐	☐	8.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.4
	9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Annex 3
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Annex 3
	9.3.3 Covariates?	☒	☐	☐	Annex 3
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	8.4

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Is the choice of statistical techniques described?	☒	☐	☐	8.7
10.2	Are descriptive analyses included?	☒	☐	☐	8.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.3 Are stratified analyses included?	☒	☐	☐	8.7
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	8.7
10.5 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	8.5

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)	☒	☐	☐	8.6-8.8
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Re 11.3: There is a peer review publication plan

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	8.9
12.1.2 Information bias?	☒	☐	☐	8.9
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)	☒	☐	☐	8.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	8.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	9

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.3 Have data protection requirements been described?	☒	☐	☐	9

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?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

Name of the main author of the protocol: Kofi Asomaning, PhD

Date: dd/Month/year 02/07/2018

Signature: 

ANNEX 3. ADDITIONAL INFORMATION

Codes used to identify study variables

Table shells