NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	A Population-based Study of the Safety of Gabapentin Use During Pregnancy
Protocol number	A9451182
Protocol version identifier	1
Date	02 October 2020
EU Post Authorisation Study (PAS) register number	Study to be registered before start of data collection
Active substance	Gabapentin (ATC N03AX12)
Medicinal product	Neurontin®
Product reference	DE/H/0899 MRP (Neurontin®) DE/H/2852 DCP (Gabapentin Pfizer) 20000710/11 Bulgaria National (Neurontin®) HR-H-198579675/HR-H-227912224 Croatia National (Neurontin®)
Procedure number	DE/H/XXXX/WS/682
Joint PASS	No
Research question and objectives	The study objectives are to: 1. Describe the use of gabapentin in pregnancy. 2. Estimate the risk of major congenital malformations, other birth outcomes, and selected postnatal neurodevelopmental outcomes in pregnancies with exposure to gabapentin as compared with pregnancies

	with: no exposure to antiepileptic drugs (AEDs); exposure to pregabalin; exposure to lamotrigine; exposure to pregabalin or lamotrigine.
Countries of study	Denmark, Finland, Norway, Sweden
Authors	Vera Ehrenstein, MPH, DSc Kofi Asomaning, PhD

Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s) in Reference Member State (RMS) - Germany	Pfizer Pharma PFE GmbH, Linkstr. 10, 10785 Berlin
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2. 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
DCP	Decentralised Procedure
DDD	Defined daily dose
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
EURAP	The European Registry of Antiepileptic Drugs and Pregnancy
EUROCAT	European Network of Congenital Anomaly Registers
GAD	General anxiety disorder
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practice
HCP	Health Care Professional
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
MRP	Mutual Recognised Procedure
NA AED	North American Antiepileptic Drug registry
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
SmPC	Summary of product characteristics
TIS	Teratology information services
TOP	Termination of pregnancy
UK	United Kingdom
USA	United States of America
VSD	Ventricular Septal Defect

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Protocol: A9451182 Version: 1.0 Date: 02 October 2020

Main Authors: Vera Ehrenstein MPH, DSc, Aarhus University;
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Title: A Population-based Study of the Safety of Gabapentin Use During Pregnancy

Rationale and background: Gabapentin (Neurontin®) received first regulatory approval on 05 February 1993 in the United Kingdom (UK) and is currently marketed in 96 countries. In the European Union (EU), gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 6 years and above; as monotherapy in the treatment of partial seizures with and without secondary generalization in adults and adolescents aged 12 years and above; and for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults.

Per the current summary of product characteristics (SmPC), gabapentin should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

To date, gabapentin exposure has been relatively low. As per the most recent (2019) Periodic Safety Update Report (PSUR), there have been 10,617,907 cumulative patient years of exposure worldwide.

Few population-based pregnancy outcome studies have been published to date. The two studies including the largest number of pregnancies exposed to gabapentin monotherapy did not report an increased risk of major congenital malformations (Hernández-Díaz S. et al., Källén B. et al.). A population-based study designed to assess the comparative risk of spontaneous abortions, terminations of pregnancy (TOPs), major congenital malformations, preterm births and small for gestational age (SGA) newborns following intrauterine gabapentin and pregabalin exposure concluded that it was underpowered to provide information on the risks associated with single antiepileptic drugs (AEDs) (Mostacci B. et al.). The current study aims to evaluate the effects of gabapentin use in pregnancy on outcomes including malformations, foetal growth indicators, and neurologic morbidity in a large population-based setting.

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:

1. Describe the use of gabapentin in pregnancy

2. Estimate the risk of major congenital malformations, other birth outcomes, and selected postnatal neurodevelopmental outcomes of pregnancies with exposure to gabapentin as compared with pregnancies with: no exposure to AEDs; exposure to pregabalin; exposure to lamotrigine; exposure to pregabalin or lamotrigine.

The primary objectives of the study are to:

- Describe use of gabapentin, pregabalin, and lamotrigine during pregnancy overall (for any therapeutic use), and by:
  - trimester of pregnancy,
  - indication,
  - cumulative dose,
  - calendar year of delivery;

  Description of exposure will be performed for all pregnancies, including pregnancies with monotherapy exposure (defined as no concomitant administration with other AEDs) and pregnancies with polytherapy exposure (defined as concomitant administration with other AEDs), as well as the subset of only pregnancies with monotherapy exposure.
- Calculate the prevalence of major congenital malformations in pregnancies with first-trimester exposure to:
  - gabapentin;
  - pregabalin;
  - lamotrigine;
  - pregabalin or lamotrigine.
  - Perform a sensitivity analysis to calculate the prevalence of major congenital malformations that includes stillbirth and pregnancies ending in therapeutic 2nd trimester induced abortion in the definition of prevalence in pregnancies with first-trimester exposure to:
    - gabapentin;
    - pregabalin;
    - lamotrigine;
    - pregabalin or lamotrigine.
- Estimate the associations between first-trimester exposure to gabapentin and prevalence of major congenital malformations, as compared with:
  - no exposure to AEDs during the first trimester;
  - exposure to pregabalin during the first trimester;
  - exposure to lamotrigine during the first trimester;
  - exposure to pregabalin or lamotrigine during the first trimester.
- Calculate the prevalence of pre-specified birth outcomes, including stillbirth, low birth weight, small for gestational age (SGA), preterm birth, low Apgar score, microcephaly, among pregnancies with any trimester exposure to:
  - gabapentin;
  - pregabalin;
  - lamotrigine;
  - pregabalin or lamotrigine.

- Estimate the associations between exposure to gabapentin any time during pregnancy and other pre-specified birth outcomes, including stillbirth, low birth weight, small for gestational age (SGA), preterm birth, low Apgar score, microcephaly, as compared with:
  - no exposure to AEDs any time during pregnancy;
  - exposure to pregabalin any time during pregnancy;
  - exposure to lamotrigine any time during pregnancy;
  - exposure to pregabalin or lamotrigine any time during pregnancy.

The secondary objectives of the study are to:

- Calculate the incidence rates of pre-specified postnatal neurodevelopmental outcomes with any trimester exposure to:
  - gabapentin;
  - pregabalin;
  - lamotrigine;
  - pregabalin or lamotrigine.
- Estimate the associations between exposure to gabapentin any time during pregnancy and the pre-specified postnatal neurodevelopmental outcomes, as compared with:
  - no exposure to AEDs any time during pregnancy;
  - exposure to pregabalin any time during pregnancy;
  - exposure to lamotrigine any time during pregnancy;
  - exposure to pregabalin or lamotrigine any time during pregnancy.

All prevalence and incidence rate calculations will be determined for all pregnancies, including pregnancies with monotherapy exposure and pregnancies with polytherapy exposure, as well as the subset of only pregnancies with monotherapy exposure. The prevalence of major congenital malformations does not include stillbirth and pregnancies ending in therapeutic 2nd trimester induced abortion, unless otherwise specified in sensitivity analyses.

Study design: This post-authorisation safety study (PASS) is a population-based study using national administrative registries from four Nordic countries: Denmark, Finland, Norway, and Sweden.

Population: The study population consists of all births identified in the respective administrative registries from 1 January 2005 to 31 December 2015 in Denmark, Finland, and Norway and all births identified from 1 July 2006 to 31 December 2016 in Sweden.

Variables: Exposure to the medications under study is defined as follows:
Gabapentin exposure- At least one maternal dispensing of gabapentin during the first trimester for the analyses of major congenital malformations and during any trimester for all remaining outcomes.

Comparators/reference groups:

No exposure to AEDs-This reference group consists of births with no maternal dispensing of any AED during the first trimester for the outcome of major congenital malformations and during any trimester for all remaining outcomes.

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

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

Pregabalin or lamotrigine exposure – At least one maternal dispensing of pregabalin and/or lamotrigine during the first trimester for the outcome of major congenital malformations and during any trimester for all remaining outcomes.

For analyses that use pregabalin as the comparator, pregnancies exposed to both gabapentin and lamotrigine in the same relevant exposure window will be excluded. For analyses that use lamotrigine as the comparator, pregnancies exposed to both gabapentin and pregabalin in the same relevant exposure window will be excluded.

Primary Outcomes:
Birth outcomes

- Major congenital malformations
- 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 disorders;
- Pervasive developmental disorders (autism spectrum disorders);
- Learning disorders (Specific developmental disorders of speech and language, and Specific developmental disorders of scholastic skills) and intellectual disabilities (mental retardation).

Follow-up for the postnatal neurodevelopmental outcomes, when available, will be a minimum of 1 year postnatally and for the maximum period available in the dataset for each birth. However, for a variety of reasons (e.g. emigration, death), follow-up could be infeasible in individual cases. It should be noted that not all livebirths will have available follow-up information into the school age, and as postnatal neurodevelopmental disorders are

diagnosed after the first year of age, primarily at school age, the number of events in gabapentin exposed (and other comparator groups) pregnancies in the study period may not be sufficient to yield stable estimates of association.

Covariates:
Characteristics of the study population that are to be described will include calendar year of delivery, maternal age at conception, parity (number of live and still births prior to the on-study pregnancy); indication for AED use, 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.

The covariates to be included in the propensity-score model are:

- calendar year of delivery;
- maternal 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;
- indicators of maternal health care utilisation in the 12 months pre-LMP (number of inpatient and specialised outpatient encounters);
- for congenital malformations outcome: maternal medication use, each as a dichotomous variable.

Data source: Data from national population-based administrative registries in Denmark, Finland, Norway, and Sweden will be used in this study. These national registries include patient, birth, prescription, and total population registries. 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.

Study size: The study size is estimated at greater than 3,000,000 pregnancies, including approximately 1743 exposed to gabapentin at any time. A study of this size will rule out a relative risk with a 95% upper confidence limit of 1.5 with 80% probability, assuming the following: gabapentin vs. 'unexposed to AEDs' as comparator, background prevalence of major congenital malformations is 3%; gabapentin exposure prevalence is 0.8%; and the true underlying risk ratio is 1.0.

Data analyses:
For all data analyses, the birth (not the patient/mother) will be the unit of analysis. Given that a woman could have more than one birth during the study period, data analyses will account for correlated observations using GEE (generalized estimating equation) or robust variance

estimates. All analyses will be conducted separately in each participating country according to the description below. Each country will generate a set of identical analytic tables. Results of comparative analyses will also be combined across countries.

Primary analyses:

- Use of gabapentin, pregabalin and lamotrigine will be characterized in terms of pregnancy trimester, indication, cumulative dose, and calendar year of delivery within two pregnancy groups: (i) all pregnancies, including pregnancies with monotherapy exposure (defined as no concomitant administration with other AEDs) and pregnancies with polytherapy exposure (defined as concomitant administration with other AEDs), and (ii) subset of only pregnancies with monotherapy exposure.
- Distributions of the maternal and offspring characteristics in the study population will be tabulated according to gabapentin and the active comparator exposure categories. The defined daily dose (DDD) of gabapentin is 1800 mg (WHO Collaborating Centre for Drug Statistics Methodology). In the EU, the recommended/approved daily dose of gabapentin is 900-3600 mg (gabapentin summary of product characteristics (SmPC)) (equivalent of 0.5-2.0 times the DDD). Three (3) gabapentin cumulative dose (DDD) categories of < 1.0, 1.0-2.0, and > 2.0 times the DDD, will be used to stratify select descriptive analyses of major congenital malformations. The number of major congenital malformation events, the total number of newborns at risk and the prevalence of major congenital malformation events for each of the 3 gabapentin dose categories will be provided.
- Prevalence of study outcomes in pregnancies exposed to gabapentin and comparators will be calculated by trimester of exposure (first-trimester only for major congenital malformations, any trimester exposure for other outcomes).
- Crude and propensity-score adjusted prevalence ratios will be estimated for the birth outcomes comparing pregnancies exposed to gabapentin during relevant exposure period (first trimester only for major congenital malformations, any trimester exposure for other birth outcomes) with the four comparison groups.
    - Separate analyses will be conducted for AED monotherapy if study size permits (i.e. separate exposure variables will be created for gabapentin (and pregabalin, and lamotrigine) polytherapy and monotherapy).
    - Prevalence ratios comparing the frequency of major congenital malformations in patients with first-trimester gabapentin exposure (monotherapy or polytherapy) and patients with no first-trimester exposure to AEDs will be estimated within the <1.0, 1.0-2.0, and >2.0 DDD categories; however these estimates are likely to be unstable due to small counts.

Secondary analyses:

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

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, where data on pregnancies ending in 2nd trimester therapeutic induced abortions is unavailable).

In the primary analyses, patients with at least one dispensing within the relevant timeframe will be classified as exposed. In sensitivity analyses, two (2) gabapentin dispensing categories of '1 dispensing', and '>1 dispensing', will be used to stratify select descriptive analyses of major congenital malformations (it is anticipated that patient counts will not be high enough to support stratified comparative analyses). The number of major congenital malformation events, the total number of newborns at risk and the prevalence of major congenital malformation events for each of the 2 gabapentin dispensing categories will be provided.

Combining country-specific results
Country-specific crude and adjusted estimates of association will first be calculated and presented; then these results will be combined using meta-analysis or another suitable method that allows incorporation of combined estimates of associations when no exposed events are observed, such as Mantel-Haenszel pooling methods (Selmer R et al., Desai RJ et al).

Milestones: Pfizer will initiate the study upon endorsement of the protocol by the EMA. Data collection is estimated to start in December 2020, with the final study report submitted in March 2022.

References:

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Desai RJ, Rothman KJ, Bateman BT, Hernandez-Diaz S, Huybrechts KF. A Propensity-score-based Fine Stratification Approach for Confounding Adjustment When Exposure Is Infrequent. Epidemiology. 2017;28(2):249-257.

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned date*
Draft protocol submission to the EMA	February 2020
Registration in the EU PAS register	30 November 2020
Start of data collection†	30 December 2020
End of data collection‡	30 April 2021
Final study report to the EMA	March 2022

EU: European Union; PAS: post-authorization study.
*Subject to change due to protocol 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).

7. RATIONALE AND BACKGROUND

Gabapentin (Neurontin®) received first regulatory approval on 05 February 1993 in the United Kingdom (UK) and is currently marketed in 96 countries. In the European Union (EU), gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 6 years and above, as monotherapy in the treatment of partial seizures with and without secondary generalization in adults and adolescents aged 12 years and above, and for the treatment of peripheral neuropathic pain (such as painful diabetic neuropathy and post-herpetic neuralgia) in adults.

Per the current EU Mutual Recognition Procedure (MRP) Reference Member States (RMS) summary of product characteristics (SmPC), gabapentin should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

To date, gabapentin exposure has been relatively low. As per the most recent (2019) Periodic Safety Update Report (PSUR), (PSUSA/00001499/201902 covering the period 02 February 2016 to 01 February 2019 and with data lock point of 1st February 2019), there have been 10,617,907 cumulative patient years of exposure worldwide.

To the best of the MAH's knowledge, the North American Antiepileptic Drug (NA AED) Registry is the largest existing AED registry worldwide. To date, over 11,594 women, including 1,220 women unexposed to any AEDs, have been enrolled. The 2019 annual report (available upon request) of the NA AED Registry provided data from 207 gabapentin monotherapy-exposed pregnancies (out of the 10,939 women whose estimated date of delivery was before January 1, 2019). In total, major congenital malformations were diagnosed, between birth and 12 weeks of age, in 3 of the 207 gabapentin monotherapy-exposed pregnancies, with the risk of 1.5% (95% CI: 0.39 to 4.7). The prevalence of major congenital malformations at birth in the general population is 2-4%.[1,2] In comparison to the neonates in the internal comparison group (pregnant women, not taking an AED, who were recruited from among the friends and family members of the enrolled women taking an AED) the relative risk for any type of malformation was 1.4 (95% CI: 0.37 to 5.1). In summary, the NA AED Registry gabapentin report concluded that there is no increased risk of major congenital malformations with gabapentin monotherapy.

Few population-based pregnancy outcome studies have been published to date. The two studies including the largest number of pregnancies exposed to gabapentin monotherapy (n = 145 prospective register; n = 119 by retrospective cross-comparison of registers) did not report an increased risk of major congenital malformations, with malformation prevalence of 0.7% (0.02 – 3.8)[3] and 1.7%.[4] In addition, the study conducted in 2017 by aGeNCe NatioNale de SéCUrité dU MédiCameNt et des prodUits de santé (ANSM) and Caisse NatioNale de l'AssUraNCe maladie (CNAM) reported that of the 26 major congenital malformations studied, the risk was no different between neonates born from pregnancies exposed to gabapentin monotherapy and neonates unexposed to AEDs.[5] A population-based study to assess the comparative risk of spontaneous abortions, terminations of pregnancy (TOPs), major congenital malformations, preterm births and small for gestational age (SGA)

newborns following intrauterine gabapentin and pregabalin exposure in Northern Italy had the following results: Among 145 243 pregnancies (111,284 deliveries, 112,845 live births and 279 stillbirths, 16,408 spontaneous abortions and 17,551 TOP), 21 (0.014%) were exposed to gabapentin (GBP), 30 (0.02%) to pregabalin and 1 was exposed to both drugs. Among pregnancies exposed to gabapentin only, two ended in spontaneous abortion (9.5% vs 11.3% in unexposed-OR=0.83, CI 95%=0.09 to 3.43; p=0.6), and eight in TOP (38% vs 12% in unexposed- OR=4.51, CI 95%=1.62 to 11.75; p=0.0021). Among the 11 newborns exposed to gabapentin only, 6 were born preterm (54.5% vs 14%-OR=7.37, CI 95%=1.87 to 30.54; p=0.0018) and 4 were SGA (36.3% vs 10%, OR=5.14, CI 95%=1.10 to 20.23; p=0.018). Among the nine newborns exposed to gabapentin during the first trimester, two had a major congenital malformation, an isolated ventricular septal defect (VSD) in both cases, while one of the two was also SGA. The study's authors concluded that the study was underpowered to provide information on the risks associated with single antiepileptic drugs.[6] Further studies of the effects of gabapentin use in pregnancy on outcomes including malformations, foetal growth indicators, and neurologic morbidity in large sample size settings are warranted.

This non-interventional study will evaluate the use and safety of gabapentin in pregnancy using data on pregnancies identified from national population-based registries in Denmark, Finland, Norway, and Sweden. To reduce confounding by indication and underlying disease severity[7] (as compared with previous studies), in addition to assessing the risk of study outcomes according to exposure to gabapentin during pregnancy, the study outcomes will also be assessed in pregnancies exposed to agents with similar indications as gabapentin: namely, pregabalin (epilepsy, neuropathic pain), and lamotrigine (epilepsy).

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

8. RESEARCH QUESTION AND OBJECTIVES

The study objectives are to:

1. Describe the use of gabapentin in pregnancy.

2. Estimate the risk of major congenital malformations, other birth outcomes, and selected postnatal neurodevelopmental outcomes of pregnancies with exposure to gabapentin as compared with pregnancies with: no exposure to antiepileptic drugs (AEDs); exposure to pregabalin; exposure to lamotrigine; exposure to pregabalin or lamotrigine.

The primary objectives of the study are to:

- Describe use of gabapentin, pregabalin, and lamotrigine during pregnancy overall (for any therapeutic use), and by:
  - trimester of pregnancy,
  - indication,
  - cumulative dose,
  - calendar year of delivery;

Description of exposure will be performed for all pregnancies, including pregnancies with monotherapy exposure (defined as no concomitant administration with other AEDs) and pregnancies with polytherapy exposure (defined as concomitant administration with other AEDs), as well as the subset of only pregnancies with monotherapy exposure.

- Calculate the prevalence of major congenital malformations in pregnancies with first-trimester exposure to:
  - gabapentin;
  - pregabalin;
  - lamotrigine;
  - pregabalin or lamotrigine.
  - Perform a sensitivity analysis to calculate the prevalence of major congenital malformations that includes stillbirth and pregnancies ending in therapeutic 2nd trimester induced abortion in the definition of prevalence in pregnancies with first-trimester exposure to:
    - gabapentin;
    - pregabalin;
    - lamotrigine;
    - pregabalin or lamotrigine.
- Estimate the associations between first-trimester exposure to gabapentin and prevalence of major congenital malformations, as compared with:
  - no exposure to AEDs during the first trimester;
  - exposure to pregabalin during the first trimester;
  - exposure to lamotrigine during the first trimester;
  - exposure to pregabalin or lamotrigine during the first trimester.
- Calculate the prevalence of pre-specified birth outcomes including stillbirth, low birth weight, small for gestational age (SGA), preterm birth, low Apgar score, microcephaly, among pregnancies with any trimester exposure to:
  - gabapentin;
  - pregabalin;
  - lamotrigine;
  - pregabalin or lamotrigine.
- Estimate the associations between exposure to gabapentin any time during pregnancy and other pre-specified birth outcomes, including stillbirth, low birth weight, small for gestational age (SGA), preterm birth, low Apgar score, microcephaly, as compared with:
  - no exposure to AEDs any time during pregnancy;
  - exposure to pregabalin any time during pregnancy;
  - exposure to lamotrigine any time during pregnancy;
  - exposure to pregabalin or lamotrigine any time during pregnancy.

The secondary objectives of the study are to:

- Calculate the incidence rates of pre-specified postnatal neurodevelopmental outcomes (attention-deficit hyperactivity disorders, pervasive developmental disorders, learning disorders and intellectual disabilities) with any trimester exposure to:
  - gabapentin;
  - pregabalin;
  - lamotrigine;
  - pregabalin or lamotrigine.
- Estimate the associations between exposure to gabapentin any time during pregnancy and the pre-specified postnatal neurodevelopmental outcomes, as compared with:
  - no exposure to AEDs any time during pregnancy;
  - exposure to pregabalin any time during pregnancy;
  - exposure to lamotrigine any time during pregnancy;
  - exposure to pregabalin or lamotrigine any time during pregnancy.

The calculations of 'prevalence' and 'incidence rate' are further described in section 9.7.1 and section 9.7.2 respectively. All prevalence and incidence rate calculations will be determined for all pregnancies, including pregnancies with monotherapy exposure and pregnancies with polytherapy exposure, as well as the subset of only pregnancies with monotherapy exposure. The prevalence of major congenital malformations does not include stillbirth and pregnancies ending in therapeutic 2nd trimester induced abortion, unless otherwise specified in sensitivity analyses (see section 9.7.6.).

9. RESEARCH METHODS

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

This PASS is a population-based study and is based on routinely collected data from national administrative and medical registers in four Nordic countries. All births from 1 January 2005 to 31 December 2015 in Denmark, Finland, and Norway, and during 1 July 2006 to 31 December 2016 in Sweden will be included. Follow-up for the postnatal neurodevelopmental outcomes, when available, will be a minimum of 1 year postnatally and for the maximum period available in the dataset for each birth (Table 1). However, for a variety reasons, either related to the individual or to the family (e.g. emigration, death), follow-up could be infeasible in individual cases. Each country has tax-supported universal health care;[8] 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).

Because indication may be related to the occurrence of the study outcomes, medications used to treat the same indications as gabapentin (epilepsy and neuropathic pain) are selected as comparators to control for potential confounding.

The birth outcomes chosen are standard outcomes used to evaluate the safety of prenatal medication exposure for offspring and have been examined in previous studies of medication safety in pregnancy.[4-6,8,10,12]

9.2. Setting

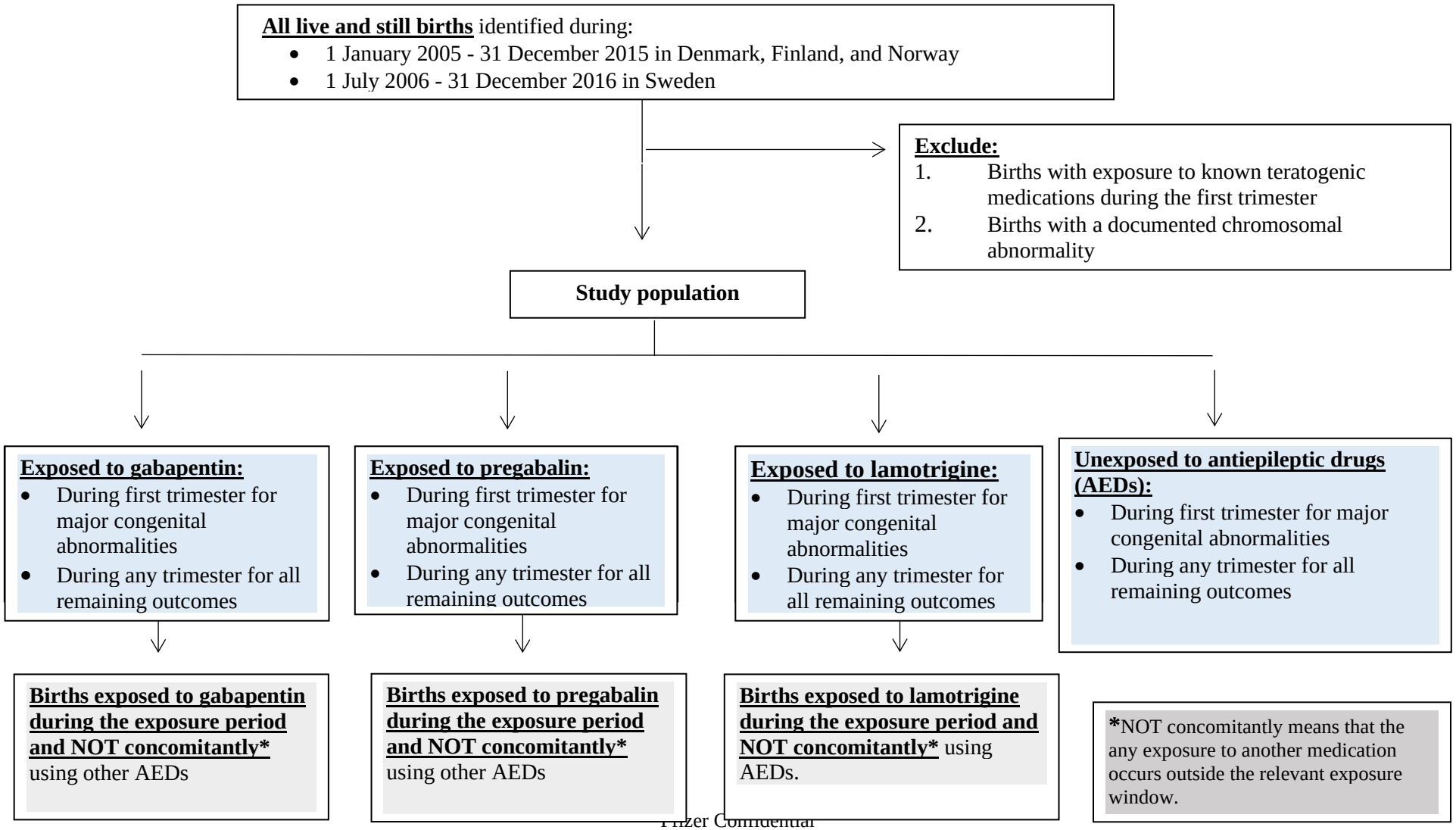
This study will be conducted using data from four Nordic countries: Denmark, Finland, Norway, and Sweden.[8] All live births and stillbirths are recorded in birth registries (in all countries except Sweden from gestational week 22 from July 2008 onwards; in Sweden, from gestational week 28 from July 2008 onwards). During the study period, there were approximately 580,000 – 730,000 live births in each of Denmark, Finland, and Norway, and 1,100,000 in Sweden.[9] The start of the study period in each country was selected to ensure availability of gabapentin and the comparators 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, clinically relevant birth and postnatal outcomes for this study; last menstrual period (LMP), depending on country is either directly recorded in the birth registry or estimated from gestational age; routine capture of dispensings of prescription medications to pregnant women; extensive information about maternal and offspring demographic information; and exact linkage between the maternal and the offspring record.

Study population

The study population will consist of all births identified in the respective registries from 1 January 2005 to 31 December 2015 in Denmark, Finland, and Norway and all births identified from 1 July 2006 to 31 December 2016 in Sweden, Figure 1 .

Figure 1. Study population flow diagram



As all birth outcomes will have occurred as of the date of delivery, prevalence will be used as a measure of outcome occurrence.[10] To allow for delayed reporting/diagnosis, all congenital malformations diagnosis recorded within one year of age will be included, according to the standard procedure used by the European Network of Congenital Anomaly Registers (EUROCAT)[11] through the end of 2016 in Denmark, Finland and Norway and through the end of 2017 in Sweden. In addition, available information on pregnancies ending in 2nd trimester therapeutic induced abortions will be identified in Denmark, Finland and Norway. Information on pregnancies ending in 2nd trimester therapeutic induced abortions is not available from Sweden for the specific study period. 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.[12]

Major congenital malformations and stillbirth prevalence will be described and compared using live and stillbirths as the denominator. For the birth outcomes other than major congenital malformations or stillbirth, prevalences at birth will be described and compared using live births as the denominator.

For the postnatal neurodevelopmental outcomes, livebirths of all gabapentin-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 2016 in Denmark, Finland, and Norway; 31 December 2017 in Sweden); 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, livebirths will be followed up to a minimum of 1 year and a maximum of 8 years in Norway, 10 years postnatally in Denmark, and Finland, and up to a maximum 11.5 years postnatally in Sweden (Figure 2).

9.2.1. Inclusion criteria

All births from 1 January 2005 through 31 December 2015 (both dates inclusive) in Denmark, Finland, and Norway and all births identified from 1 July 2006 through 31 December 2016 (both dates inclusive) in Sweden.

9.2.2. Exclusion criteria

Patients meeting any of the following criteria will be excluded from the study:

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

2. Births with a chromosomal abnormality diagnosis.

9.3. Variables

9.3.1. Exposures

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

- First trimester: 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).

LMP, depending on country is either directly recorded in the birth registry or estimated from gestational age. LMP will be determined using the following hierarchy/availability: ultrasound determined LMP (if recorded), self-reported LMP (if ultrasound-reported is unavailable); date of delivery minus gestational age in days (if LMP unavailable by ultrasound or self-report). If gestational age is missing, LMP will be imputed by subtracting 280 days from date of delivery.

Exposure during the first trimester
Gabapentin exposure during the first trimester is defined as at least one maternal dispensing of gabapentin during the first trimester.

Comparators/reference groups:
No exposure to AEDs-This reference group consists of births with no maternal dispensing of any AED during the first trimester.

Pregabalin exposure in the first trimester is defined by 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.

Lamotrigine exposure in the first trimester is defined by at least one maternal 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.

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

For analyses that use pregabalin as the comparator, pregnancies exposed to both gabapentin and lamotrigine in the same relevant exposure window will be excluded. For analyses that use lamotrigine as the comparator, pregnancies exposed to both gabapentin and pregabalin in the same relevant exposure window will be excluded.

Exposure any time during pregnancy
Gabapentin exposure any time during pregnancy is defined by at least one maternal dispensing of gabapentin during any trimester. Gabapentin monotherapy any time during

pregnancy will be defined as any-pregnancy exposure to gabapentin and no dispensing for any other AED during any trimester.

Comparators:
No exposure to AEDs-This reference group consists of births with no maternal dispensing of any AED during any trimester.

Pregabalin exposure any time during pregnancy is defined by at least one maternal 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.

Lamotrigine exposure any time during pregnancy is defined by at least one maternal 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.

Pregabalin or lamotrigine exposure any time during pregnancy defined by at least one maternal dispensing of pregabalin and/or lamotrigine during any trimester. Pregabalin or lamotrigine monotherapy any time during pregnancy will be defined as any pregnancy exposure to pregabalin and/or lamotrigine and no dispensing for any other AED during any trimester.

For analyses that use pregabalin as the comparator, pregnancies exposed to both gabapentin and pregabalin in the same relevant exposure window will be excluded. For analyses that use lamotrigine as the comparator, pregnancies exposed to both gabapentin and lamotrigine in the same relevant exposure window will be excluded.

9.3.2. Outcomes

For each outcome defined below, the population (denominator), period of pregnancy identification, and follow-up for outcome assessment are described in Table 1.

Table 1. 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 1Jul2006-31Dec2016 inclusive	Prevalence at birth with outcomes identified at birth, and until the first birthday (inclusive) through 2016 in Denmark, Finland and Norway and through 2017 in Sweden
	Stillbirth	Pregnancies ending in singleton/multiple live birth, stillbirth, 1Jan2005 - 31Dec2015 inclusive			Pregnancies ending in singleton/multiple live birth or stillbirth 1Jul2006-31Dec2016 inclusive	Prevalence at birth
	Low birth weight SGA[13] 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 1Jul2006-31Dec2016 inclusive	Prevalence at birth
Secondary analyses	Attention-deficit hyperactivity disorders Pervasive developmental disorders Learning disorders and intellectual disabilities	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 1Jul2006-31Dec2016 inclusive	Minimum 1 year postnatally. Maximum available postnatally, 31Dec 2016 Denmark, Finland, Norway; 31Dec 2017 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

Table 1. 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	
Sensitivity analyses	Major congenital malformations (overall)	Pregnancies ending in singleton/multiple live birth, stillbirth, 1Jan2005 - 31Dec2015 inclusive			Pregnancies ending in singleton/multiple live birth or stillbirth 1Jul2006-31Dec2016 inclusive	Prevalence of major congenital malformation events for each of the 2 gabapentin dispensing categories of '1 dispensing', and '>1 dispensing'.

SGA, Small for gestational age; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorders.
* In the Patient Registry of Norway, the source of data for the postnatal outcomes has existed from 2008.

9.3.2.1. Primary Outcomes (Birth outcomes)

- Major congenital malformations, any and specific malformation type, according to the EUROCAT classification[14]
- 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.[13,15] 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

9.3.2.2. Secondary Outcomes (Postnatal neurodevelopmental outcomes)

Postnatal neurodevelopmental outcomes (ICD-10 (International Classification of Diseases, Tenth Revision) codes):

- Attention-deficit hyperactivity disorders (F90);
- Pervasive developmental disorders (autism spectrum disorders) (F84);

- Learning disorders (Specific developmental disorders of speech and language (F80), and Specific developmental disorders of scholastic skills (F81)) and Intellectual disabilities (mental retardation) (F70-F79).

Follow-up for the postnatal neurodevelopmental outcomes, when available, will be a minimum of 1 year postnatally and for the maximum period available in the dataset for each birth. However, for a variety of reasons (e.g. emigration, death), follow-up could be infeasible in individual cases. It should be noted that not all livebirths will have available follow-up information into the school age, and as postnatal neurodevelopmental disorders are diagnosed primarily at school age, the number of events in gabapentin exposed (and other comparator groups) pregnancies in the study period may not be sufficient to yield stable estimates of association.[16]

9.3.2.3. Sensitivity Analysis (Major congenital malformations)

The analyses of major congenital malformations (overall, not for specific malformations due to expected low counts) will be repeated with the inclusion of pregnancies ending in 2nd trimester therapeutic induced abortions (in all countries except Sweden, where data on pregnancies ending in 2nd trimester therapeutic induced abortions is unavailable).

Some patients may have obtained a single dispensing (prescription) of an antiepileptic drug. Possible reasons for this may be that the drug was prescribed for an indication other than epilepsy, treatment was stopped due to an adverse reaction, etc. Two (2) gabapentin dispensing categories of '1 dispensing', and '>1 dispensing', will be used to stratify select descriptive analyses of major congenital malformations (it is anticipated that patient counts will not be high enough to support stratified comparative analyses). The definition that will be used in the primary analyses is at least 1 dispensing. If patient counts within both these dispensing categories are sufficiently high, the number of major congenital malformation events, the total number of newborns at risk and the prevalence of major congenital malformation events for each of the 2 gabapentin dispensing categories will be provided. As noted above, given the very small sample size of gabapentin first trimester-exposed pregnancies ending in a live or still birth, and the low prevalence of major congenital malformations, it will not be feasible to conduct any further stratified analyses (i.e., analyses simultaneously stratified by dispensing and other variables).

9.3.3. Covariates and other population characteristics

Characteristics of the study population that are to be described will include calendar year of delivery, maternal age at conception, parity (number of live and still births prior to the on-study pregnancy); indication for AED use, 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 gabapentin (and other AEDs) use in 12-months pre-LMP (epilepsy, neuropathic pain, 'other' indications) will be reported

descriptively but will not be used for adjustment as administrative data available for this study have low sensitivity in identifying relevant indications for all pregnancies.

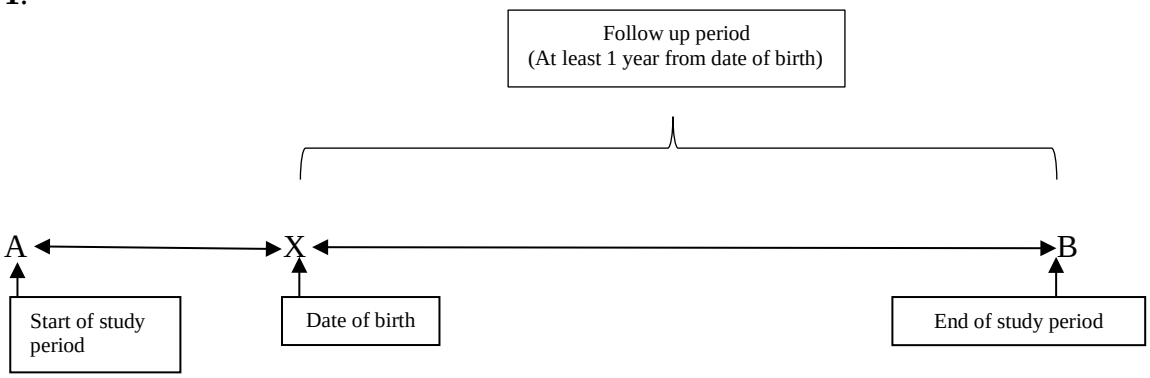
The covariates to be included in the propensity-score model are:

- calendar year of delivery;
- maternal 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).

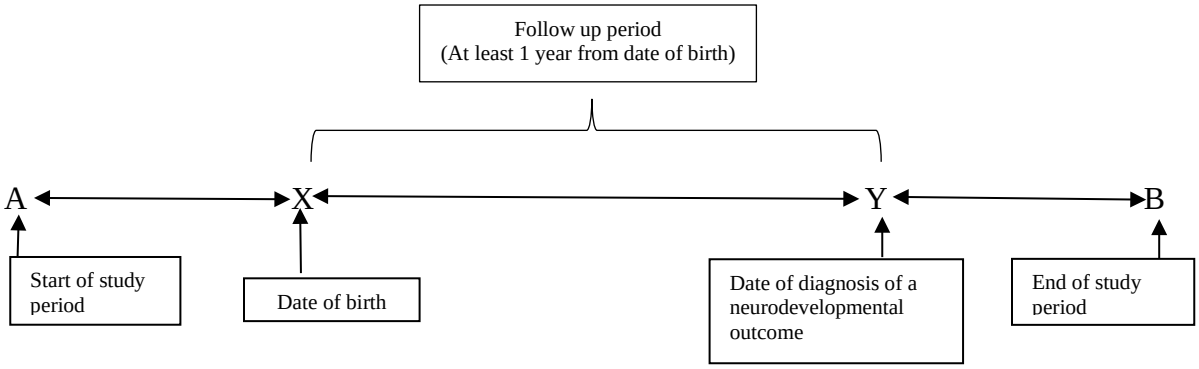
Full list of the study variables and their operational definitions are provided in Annex 3.

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

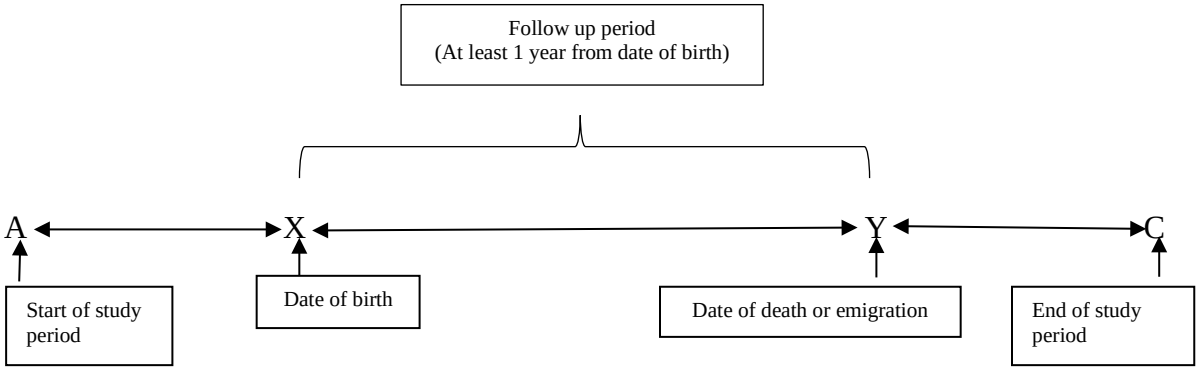
1.



2.



3.



9.4. Data sources

Data sources used to construct the analysis dataset for this study are presented in Table 2. 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.

Diagnoses 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 on 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.[17-26] In Denmark, positive predictive value of diagnoses of cardiac malformations is 89%.[27] For drugs used chronically, there is also high level of agreement between general practitioner and dispensing records.[28] 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.[29]

Table 2. 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[30] Finnish Medical Birth Register* National Registry of Norway Swedish Total Population Register[31]	N/A
Study population	Pregnancies ending in singleton/multiple live birth or stillbirth	Danish Medical Birth Registry[26] Finnish Medical Birth Register*[26] Medical Birth Registry of Norway[26] Swedish Medical Birth Register[26]	A specific variable in each birth registry
	Pregnancies ending in therapeutic 2nd trimester induced abortion	Danish National Patient Registry[32,33] 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 2. 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 9.3.1)	Maternal dispensings of gabapentin, pregabalin, lamotrigine	Danish National Prescription Registry[34] Finnish Prescription Register[35] Norwegian Prescription Database[35] Swedish Prescribed Drug Register[35]	ATC
Outcome (for full list see Section 9.3.2)	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[32] Danish Psychiatric Central Research Register[36] Danish Psychiatric Central Register Finnish Care Register for Health Care Finnish Register of Primary Health Care visits Norwegian Patient Registry[37,38±] Swedish National Patient Register[22,39] Danish National Prescription Registry[34] Finnish Prescription Register[35] Norwegian Prescription Database[35] Swedish Prescribed Drug Register[35]	ICD-10 for diagnoses, ATC codes for drug proxies
Characteristic of study population and covariates (for full list see Section 9.3.3)	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[40] Swedish Medical Birth Register[41,42] Swedish National Patient Register	A specific variable in each birth registry

Table 2. 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 gabapentin) Markers of health care utilisation	Danish National Patient Registry,[32] Finnish Care Register for Health Care Finnish Register of Primary Health Care visits Norwegian Patient Registry[37] Swedish National Patient Register[43] Danish National Prescription Registry[34] FinnishDatabase Finnish Prescription Register[35] Norwegian Prescription Database[35] Swedish Prescribed Drug Register[35]	ICD-10 for diagnoses, ATC for medication proxies
	Maternal medications	Danish National Prescription Registry[34] Finnish Prescription Register[35] Norwegian Prescription Database[35] Swedish Prescribed Drug Register[35]	ATC
Loss to follow-up	Death, emigration[†]	Danish Civil Danish Civil Registration System[30] Finnish Causes of Death Register Finnish Population Register Centre National Registry of Norway Swedish Cause of Death Register[44] Swedish Total Population 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 Norwegian dataset
[±]Data available from 2008 onwards in Norway

9.5. Study size

Table 3 shows estimated number of total pregnancies ending in live or stillbirth and pregnancies with AED exposure (any use, i.e., pregnancies exposed to monotherapy and pregnancies exposed to polytherapy).

Table 3. Estimated numbers of pregnancies ending in live or still birth (any use, i.e., pregnancies exposed to monotherapy and pregnancies exposed to polytherapy)*

	Denmark (2005-2016)	Finland (2005-2016)	Norway (2005-2016)	Sweden (2006-2016)	TOTAL
Live/still births	728,052	701,550	717,219 (657,451)	1,152,002	3,298,823

Table 3. Estimated numbers of pregnancies ending in live or still birth (any use, i.e., pregnancies exposed to monotherapy and pregnancies exposed to polytherapy)*

	Denmark (2005-2016)	Finland (2005-2016)	Norway (2005-2016)	Sweden (2006-2016)	TOTAL
Pregnancies with dispensation of					
Gabapentin, first trimester	374	374	344	500	1,592
Gabapentin, any time during pregnancy	388	388	467	500	1,743
Pregabalin, first trimester	372	1,020 (935)	248 (227)	1,230	2,870
Pregabalin, any time during pregnancy	377	1,053 (965)	225 (307)	1,275	2,930
Lamotrigine, first trimester	2,266	1,048 (961)	1,841 (1,688)	2,838	7,993
Lamotrigine, any time during pregnancy	2,379	1,104 (1,012)	2,110 (1,934)	2,991	8,584

*Number of exposed in Denmark and Sweden are the actual numbers for 2005-2016; estimated for Finland and Norway based on 2005-2015 data in parenthesis. No exclusion criteria are applied in this table.

The 2005-2016 estimated numbers of pregnancies ending in live or still birth for potentially analysis-relevant categories for Norway and Finland were unavailable at the time of writing the protocol but are estimated using data from 2005-2015 to provide the most conservative estimate.[14,45,46,47]

Table 4 shows the 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 based on counts provided in Table 3. The study size is estimated at greater than 3,000,000 pregnancies, including approximately 1743 exposed to gabapentin at any time. For example, a study of this size (1743 exposed to gabapentin at any time, 3,298,823 pregnancies in total) will rule out a relative risk with a 95% upper confidence limit of 1.5 with 80% probability, assuming the following: gabapentin vs. 'unexposed to AEDs' as comparator, background prevalence of major congenital malformations is 3%; gabapentin exposure prevalence is 0.8%; and the true underlying risk ratio is 1.0 (see Table 4).

Table 4. 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	Upper limit of 95% confidence interval for risk ratio can be ruled out with at least 80% probability (based on actual or estimated frequencies; approximate the analysis with **gabapentin-unexposed** as a comparator*)
Malformations of the nervous system[14,35], mental retardation	0.2%	4.801 (use first-trimester counts)
Stillbirth, postnatal outcomes, ASD	0.6%	2.373 (use any time during pregnancy counts)
Cardiac congenital malformations, postnatal outcomes[12,14], ADHD	1%	1.950 (use any time during pregnancy counts)
Any major congenital malformation[12,14]	3%	1.465 (use any time during pregnancy counts)
Preterm birth/SGA	10%	1.223 (use any time during pregnancy counts)
		Upper limit of 95% confidence interval for risk ratio can be ruled out with at least 80% probability (based on actual or estimated frequencies; approximate the analysis with **gabapentin-pregabalin** as a comparator*)
Malformations of the nervous system[14,35], mental retardation	0.2%	7.069 (use first-trimester counts)
Stillbirth, postnatal outcomes, ASD	0.6%	2.977 (use any time during pregnancy counts)
Cardiac congenital malformations, postnatal outcomes[12,14], ADHD	1%	2.324 (use any time during pregnancy counts)
Any major congenital malformation[12,14]	3%	1.619 (use any time during pregnancy counts)
Preterm birth/SGA	10%	1.289 (use any time during pregnancy counts)
		Upper limit of 95% confidence interval for risk ratio can be ruled out with at least 80% probability (based on actual or estimated frequencies; approximate the analysis with **gabapentin-lamotrigine** as a comparator*)
Malformations of the nervous system[14,35], mental retardation	0.2%	5.571 (use first-trimester counts)
Stillbirth, postnatal outcomes, ASD	0.6%	2.579 (use any time during pregnancy counts)
Cardiac congenital malformations, postnatal outcomes[12,14], ADHD	1%	2.080 (use any time during pregnancy counts)
Any major congenital malformation[12,14]	3%	1.520 (use any time during pregnancy counts)
Preterm birth/SGA	10%	1.247 (use any time during pregnancy counts)
		Upper limit of 95% confidence interval for risk ratio can be ruled out with at least 80% probability (based on actual or estimated frequencies; approximate the analysis with **gabapentin-pregabalin or lamotrigine** as a comparator*)
Malformations of the nervous system[14,35], mental retardation	0.2%	5.447 (use first-trimester counts)
Stillbirth, postnatal outcomes, ASD	0.6%	2.547 (use any time counts)
Cardiac congenital malformations, postnatal outcomes[12,14], ADHD	1%	2.060 (use any time counts)
Any major congenital malformation[12,14]	3%	1.511 (use any time counts)

Table 4. 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

Preterm birth/SGA	10%	1.243 (use any time counts)

*Can include exposed to other AEDs i.e., monotherapy or polytherapy; calculations made without applying any exclusion criteria. The computations were done using SAS software based on the 'Study size' worksheet of the Episheet.[48]

9.6. Data management

Data retrieval and management will be conducted separately in each country. Investigators 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 (within each country) 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.

9.7. Data analysis

For all data analyses, the birth (not the patient/mother) will be the unit of analysis. Given that a woman could have more than one birth during the study period, data analyses will account for correlated observations using GEE (generalized estimating equation) or robust variance estimates. 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. Registry data will not be provided for very low numbers (less than 5 events) due to data security and data confidentiality rules.

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.

Given that gabapentin has several indications and that administrative data available for this study have low sensitivity in identifying relevant indications for all pregnancies, in this study pregnancies exposed to gabapentin will be compared with pregnancies exposed to medications with similar sets of indications. Because confounding by indication or severity

of indication may persist even against an active comparator,[7] the amount of confounding may be inferred indirectly by examining whether estimates of association differ depending on the comparator. Here, pregabalin and lamotrigine, which are both indicated for epilepsy, have been identified as suitable active comparators.

In a 2019 publication from Sweden, all individuals aged 15 years or older and being dispensed at least 2 prescriptions of gabapentin in the period 2006-2013 were identified (N= 85,360).[49] The indication of use (i.e. health status before start of treatment) was 6.4% epilepsy, 20% psychiatric disorders, and 52.1% musculoskeletal disorders. In the same publication, the indication of use for pregabalin (n=120,664) was 5.4% epilepsy, 40.9% psychiatric disorders, and 46.2% musculoskeletal disorders. Published data on the most common gabapentin indication in pregnant women are unavailable at this time.

9.7.1. Calculation of prevalences of birth outcomes

Prevalence of each birth outcome will be computed as the 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 stillbirths. 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 stillbirths and the number of pregnancies ending in a 2nd trimester abortion. For all the other birth outcomes, the number of newborns at risk will the number of liveborn newborns.

9.7.2. 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 livebirth. 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.

9.7.3. 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. Crude and adjusted prevalence ratios and incidence rates ratios will be calculated for all pregnancies, including pregnancies with monotherapy exposure and pregnancies with polytherapy exposure, as well as the subset of only pregnancies with monotherapy exposure.

9.7.3.1. Computation of propensity scores

To account for confounding by all measured covariates, adjusted analysis will be conducted using propensity score (PS) stratification, following the approach by Patorno et al.[50] For each pregnancy, a PS will be computed, using logistic regression, as the probability being exposed

to gabapentin vs. given comparator conditional on the measured covariates listed in Section 9.3.3 and Annex 3.[51]

PS will be estimated for each birth using a generic-outcome model, meaning that all prespecified covariates will be included in the PS-estimating model, regardless of the association with the outcome. Wyss et al showed, in a simulation study, that such a model performs well when multiple outcomes are being examined;[52] 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. Categories of variables with small cell counts may be collapsed if applicable by an analyst in each country.

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

1. First-trimester gabapentin (monotherapy or polytherapy) vs. first-trimester unexposed to AEDs
2. First-trimester gabapentin (monotherapy or polytherapy) vs. first-trimester pregabalin (monotherapy or polytherapy)
3. First-trimester gabapentin (monotherapy or polytherapy) vs. first-trimester lamotrigine (monotherapy or polytherapy)
4. First-trimester gabapentin (monotherapy or polytherapy) vs. first-trimester pregabalin or lamotrigine (monotherapy or polytherapy)

5. First trimester gabapentin (monotherapy only) vs. first-trimester unexposed to AEDs
6. First trimester gabapentin (monotherapy only) vs. first-trimester pregabalin (monotherapy only)
7. First trimester gabapentin (monotherapy only) vs. first-trimester lamotrigine (monotherapy only)
8. First-trimester gabapentin (monotherapy only) vs. first-trimester pregabalin or lamotrigine (monotherapy only)

9. Any-trimester gabapentin (monotherapy or polytherapy) vs. any-trimester unexposed to AEDs
10. Any-trimester gabapentin (monotherapy or polytherapy) vs. any-trimester pregabalin (monotherapy or polytherapy)
11. Any-trimester gabapentin (monotherapy or polytherapy) vs. any-trimester lamotrigine (monotherapy or polytherapy)
12. Any-trimester gabapentin (monotherapy or polytherapy) vs. any-trimester pregabalin or lamotrigine (monotherapy or polytherapy)

13. Any-trimester gabapentin (monotherapy only) vs. unexposed to AEDs

14. Any-trimester gabapentin (monotherapy only) vs. any-trimester pregabalin (monotherapy only)
15. Any-trimester gabapentin (monotherapy only) vs. any-trimester lamotrigine (monotherapy only)
16. Any-trimester gabapentin (monotherapy only) vs. any-trimester pregabalin or lamotrigine (monotherapy only)

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 gabapentin-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 be 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 may 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 9.7.7).

9.7.4. Primary analyses

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

9.7.4.1. Descriptive analysis

- Gabapentin use in pregnancy will be described as the number and proportion of births exposed in the first trimester, and in any trimester. Number and proportion of pregnancies with gabapentin 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 pregabalin and lamotrigine will be similarly described.
- Distributions of the characteristics of the study population will be tabulated according to gabapentin 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 birth characteristics in the study population will be tabulated according to gabapentin and the active comparator categories, as above. Crude prevalence of the major congenital malformations will be reported according to first-trimester exposure to gabapentin (overall and in the subcategory of monotherapy) and each comparator (overall for all comparators including not exposed and in the subcategory of monotherapy for pregabalin and lamotrigine). In addition, overall prevalence of malformations in the unexposed group 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 gabapentin and each comparator, in the same fashion.
  The defined daily dose (DDD) of gabapentin is 1800 mg.[53] In the EU, the recommended/approved daily dose of gabapentin is 900-3600 mg [54] (equivalent of 0.5-2.0 times the DDD). Three (3) gabapentin cumulative dose (DDD) categories of < 1.0, 1.0-2.0, and > 2.0 times the DDD, will be used to stratify select descriptive analyses of major congenital malformations. The number of major congenital malformation events, the total number of newborns at risk and the prevalence of major congenital malformation events for each of the 3 gabapentin dose categories will be provided. In the study feasibility assessment, even after combining available data from the 4 Nordic countries to obtain a total of 3,298,823 first trimester exposed pregnancies ending in live or still birth, a conservative estimate of 1,592 gabapentin first trimester-exposed pregnancies ending in live or still birth were determined to be available (see Table 3). Given this very small sample size, and the low prevalence of major congenital malformations, it will not be feasible to conduct any extensive stratified analyses (i.e., analyses simultaneously stratified by dose and other variables) or dose dependency analyses. In addition, dose-stratified analyses on the combined dataset will not be possible since data will not be combined at the individual level.

9.7.4.2. Comparative analysis

<u>Major congenital malformation outcomes</u>

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

In summary, the following comparative analyses will be performed:

- First-trimester gabapentin (monotherapy or polytherapy) vs. first-trimester unexposed to AEDs
- First-trimester gabapentin (monotherapy or polytherapy) vs. first-trimester pregabalin (monotherapy or polytherapy)
- First-trimester gabapentin (monotherapy or polytherapy) vs. first-trimester lamotrigine (monotherapy or polytherapy)
- First-trimester gabapentin (monotherapy or polytherapy) vs. first-trimester pregabalin or lamotrigine (monotherapy or polytherapy)

- First trimester gabapentin (monotherapy only) vs. first-trimester unexposed to AEDs
- First trimester gabapentin (monotherapy only) vs. first-trimester pregabalin (monotherapy only)
- First trimester gabapentin (monotherapy only) vs. first-trimester lamotrigine (monotherapy only)
- First-trimester gabapentin (monotherapy only) vs. first-trimester pregabalin or lamotrigine (monotherapy only)

Prevalence ratios comparing the frequency of major congenital malformations in patients with first-trimester gabapentin exposure (monotherapy or polytherapy) and patients with no first-trimester exposure to AEDs will be estimated within the <1.0, 1.0-2.0, and >2.0 DDD categories; however these estimates are likely to be unstable due to small counts.

Birth outcomes other than major congenital malformations

For birth outcomes other than major congenital malformations, any-trimester gabapentin exposed births will be compared against each of the comparators estimating crude and adjusted prevalence ratios in log-binomial regression.

To summarise, the following comparative analyses will be performed for all outcomes:

- Any-trimester gabapentin (monotherapy or polytherapy) vs. any-trimester unexposed to AEDs
- Any-trimester gabapentin (monotherapy or polytherapy) vs. any-trimester pregabalin (monotherapy or polytherapy)
- Any-trimester gabapentin (monotherapy or polytherapy) vs. any-trimester lamotrigine (monotherapy or polytherapy)
- Any-trimester gabapentin (monotherapy or polytherapy) vs. any-trimester pregabalin or lamotrigine (monotherapy or polytherapy)

- Any-trimester gabapentin (monotherapy only) vs. unexposed to AEDs
- Any-trimester gabapentin (monotherapy only) vs. any-trimester pregabalin (monotherapy only)
- Any-trimester gabapentin (monotherapy only) vs. any-trimester lamotrigine (monotherapy only)
- Any-trimester gabapentin (monotherapy only) vs. any-trimester pregabalin or lamotrigine (monotherapy only)

9.7.5. Secondary analyses

The secondary analyses will be conducted among live-born children. In these analyses any trimester gabapentin 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-births) of the postnatal neurodevelopmental outcomes will be reported according to any prenatal exposure to gabapentin and the predefined comparators. All incidence rates will be reported for any gabapentin therapy and the subset with gabapentin monotherapy.

For the postnatal neurodevelopmental outcomes, exposure will be defined at any time during pregnancy. 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.

To summarise, the following comparative analyses will be performed for all outcomes:

- Any-trimester gabapentin (monotherapy or polytherapy) vs. any-trimester unexposed to AEDs
- Any-trimester gabapentin (monotherapy or polytherapy) vs. any-trimester pregabalin (monotherapy or polytherapy)
- Any-trimester gabapentin (monotherapy or polytherapy) vs. any-trimester lamotrigine (monotherapy or polytherapy)
- Any-trimester gabapentin (monotherapy or polytherapy) vs. any-trimester pregabalin or lamotrigine (monotherapy or polytherapy)

Sample size permitting:

- Any-trimester gabapentin (monotherapy only) vs. unexposed to AEDs
- Any-trimester gabapentin (monotherapy only) vs. any-trimester pregabalin (monotherapy only)
- Any-trimester gabapentin (monotherapy only) vs. any-trimester lamotrigine (monotherapy only)
- Any-trimester gabapentin (monotherapy only) vs. any-trimester pregabalin or lamotrigine (monotherapy only)

9.7.6. Sensitivity analyses

To evaluate the potential bias in the analysis of major congenital malformations from excluding pregnancies terminated due to known malformations, a sensitivity analysis including these terminated pregnancies 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: singleton/multiple live births, stillbirths, or pregnancies ending in therapeutic 2nd trimester induced abortion (these will be considered singleton pregnancies). The analyses in this population will assess the association of the first-trimester exposure to gabapentin and major congenital malformations (overall, not for specific malformations due to expected low counts), 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.

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

In the primary analyses, patients with at least one dispensing within the relevant timeframe will be classified as exposed. However, some patients may have obtained a single dispensing (prescription) of an antiepileptic drug. Possible reasons for this may be that the drug was

prescribed for an indication other than epilepsy, treatment was stopped due to an adverse reaction, etc. Two (2) gabapentin dispensing categories of '1 dispensing', and '>1 dispensing', will be used to stratify select descriptive analyses of major congenital malformations (it is anticipated that patient counts will not be high enough to support stratified comparative analyses). The number of major congenital malformation events, the total number of newborns at risk and the prevalence of major congenital malformation events for each of the 2 gabapentin dispensing categories will be provided. As noted above, given the very small sample size of gabapentin first trimester-exposed pregnancies ending in a live or still birth, and the low prevalence of major congenital malformations, it will not be feasible to conduct any further stratified analyses (i.e., analyses simultaneously stratified by dispensing and other variables).

9.7.7. Combining results

Crude and adjusted estimates of association from Sweden, Norway, and Finland will be transferred to Aarhus University, Aarhus, Denmark for meta-analyses or other combined 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, a fixed-effects meta-analysis is justifiable applied.[55] Country-specific crude and adjusted estimates of association for each prespecified comparison will first be calculated and presented. These results will then be combined in a meta-analysis, or, if deemed more suitable, another method that allows incorporation into combined estimates of associations with no exposed events, such as Mantel-Haenszel pooling methods.[56] For each outcome the coordinating centre 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. Homogeneity of the estimates will be verified, and a random-effects meta-analysis will be considered as an alternative should the estimates be found to be heterogeneous. The rejected model, i.e. the model not used as the primary model, will be checked in a sensitivity analysis. For example, if the fixed-effect model is used as the primary meta-analytical approach, the random-effects model will be checked in a sensitivity analysis, and vice versa. Results of combined analyses will be presented using a standard forest plot, reporting the country-specific overall crude and adjusted point estimates, and the pooled overall crude and adjusted point estimates, all with 95% CIs.

9.8. 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.

9.9. Limitations of the research methods

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, clinically relevant birth and postnatal outcomes for this study; last menstrual period (LMP), depending on country is either directly recorded in the birth registry or estimated from gestational age; routine capture of dispensings of prescription medications to pregnant women; extensive information about maternal and offspring demographic information; and exact linkage between the maternal and the offspring record. This study is designed to compare pregnancies with exposure to gabapentin not only with pregnancies not exposed to an AED, but also with pregnancies with exposure to pregabalin, and lamotrigine. Comparison with an exposed reference group will help reduce confounding by indication and severity, which was a major limitation in prior studies that had only used a reference group of pregnancies unexposed to AEDs.

Although the study has many strengths in its comprehensive structure and design, all epidemiologic studies are subject to biases that may include confounding, information bias, and selection bias. Here, confounding by indication may be introduced since epilepsy itself is known to be associated with adverse pregnancy outcomes.[57] Indication for gabapentin use in 12-months pre-LMP (epilepsy, neuropathic pain) will be reported descriptively but will not be used for adjustment as administrative data available for this study have low sensitivity in identifying all pregnancies with relevant indications. As suggested by the feasibility analyses (pilot data), the distribution of the indications for the comparator drugs may not be similar to that of gabapentin and this could also result in confounding. Assessing safety of gabapentin within each indication of use does not appear feasible as data on indication are available only for a minority of pregnancies according to the pilot data.

Information bias manifests as misclassification of exposure, outcome or confounders (discussed above). Unlike data from for example, teratology information services (TIS), with national healthcare registries, there is no risk of bias by self-referral, recall, or access to health care. Given the timelines, it is not feasible to confirm all malformations identified through medical record review. However, as stated in section 9.4, “Validity of routine data in Nordic national registries has been found to be high in all countries.[17-26] In Denmark, positive predictive value of diagnoses of cardiac malformations, the most common major congenital malformation, is 89%.[27]” Dispensings of medicines represent a better proxy of actual drug intake than do issued prescriptions (primary compliance), reducing misclassification of the actual drug exposure. However, 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.

Per EUROCAT, total prevalence (per 10,000 births) is defined as:

$$\frac{\text{Number of Cases (LB + FD + TOPFA)}}{\text{Number of Births (live and still)}} \times 10{,}000$$

Where:

Cases=Cases of congenital anomaly in population; LB=live birth; FD=Fetal deaths from 20 weeks' gestation; TOPFA=Termination of pregnancy for fetal anomaly after prenatal diagnosis, at any gestational age.

In the study sensitivity analyses, calculation of total prevalence (per 10, 000 births) is defined as:

$$\frac{\text{Number of Cases (LB + stillbirth + pregnancies ending in therapeutic 2nd trimester induced abortion)}}{\text{Number of Births (live and still)}} \times 10{,}000$$

The term 'termination of pregnancy for fetal anomaly (TOPFA)' is not included in the study definition of prevalence of major congenital malformations for the primary analyses. As is common in pregnancy studies, malformations in pregnancies ending in spontaneous and first-trimester induced abortions cannot be observed, resulting in underestimation of the number of cases. The extent of underestimation for major congenital malformations depends on the severity of, and lethality of, the malformation.[12] Termination of pregnancies (TOPs) or therapeutic abortions that are elective (for example, resulting from severe malformations) may not always be recorded accurately and it may not always be possible to distinguish between a TOP in the absence of pregnancy abnormality versus one that was terminated due to pregnancy abnormality. If such selective dropout (i.e. selection bias) is associated with gabapentin exposure, associations based on prevalent outcomes will be biased.

Given its design of a fixed study period, some children won't be followed-up long enough to observe 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. This surveillance bias is of lower relevance for the primary objective of analyzing major congenital malformations but cannot be totally excluded.

Selection bias stemming from inclusion of all eligible births 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 gabapentin and the unexposed population is likely to be healthier than the exposed population. Timing of exposure relies on accurate identification of LMP. Assuming that any misclassification of exposure that occurs is non-differential for a dichotomous

exposure variable (yes/no), it is more likely that this misclassification would result in biasing towards the null than away from the null. Not all livebirths will have follow-up into the school age, and as postnatal neurodevelopmental disorders are diagnosed after the first year of age, primarily at school age, the number of events in gabapentin exposed pregnancies in the study period may not be sufficient to yield stable estimates of association, as specified in the provided feasibility counts in Table 3 and Annex 3. Emigration data (censoring variable) are not available in the Norwegian dataset, however, the impact of this is likely to be minimal. In 2019, 7,583 Norwegian citizens of all ages immigrated, 9,256 emigrated and the net immigration was -1673.[60] Children of school going age, born in the study period (1Jan2005 - 31Dec2015), who were exposed to gabapentin (or any of the other comparators) in utero, and who emigrated over the study period, are expected to be few; in Norway, gabapentin exposed pregnancies during the study period are approximately 467/657,451 (0.07%) of all pregnancies (Table 3). In addition, it is unlikely that the emigration pattern of gabapentin exposed paediatric subjects differs substantially from that of paediatric subjects in the other comparator groups.

The methods proposed to analyse data including propensity score stratification perform well when multiple outcomes are being examined.[52] 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 gabapentin exposure and the studied outcome should be different in other ethnic groups or in other countries.

Finally, medication use during pregnancy is defined as a dichotomous variable (yes/no). This simple definition is the most feasible measure based on the study sample size. However, dichotomization may result in loss of information if there is a continuous (non-ordinal) relationship between the exposure dose/duration and the outcome risk. [59] The use of data-derived "optimal" cut-points can lead to serious bias and requires testing on independent observations to assess their validity. Adjustment for continuous covariates is more complex, as the shape of this association does need to be specified. Examples of continuous associations include linear, quadratic, logarithmic, or some other form.[59] With the exception of gabapentin, further specifying the nature of the effect of maternal medication use beyond a dichotomous variable is not feasible based on the anticipated number of exposed patients. With maternal gabapentin use, these estimates beyond a dichotomous variable are likely to be unstable due to small counts.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves data that exist in anonymized structured format and contain no patient personal information, e.g. name, date of birth, address.

Registry data will not be provided for very low numbers (less than 5 events) due to data security and data confidentiality rules.

10.2. Patient consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

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).[46,61] 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.

In the Nordic countries ethics committees (EC) are generally acknowledged to represent the public, and approval from the EC can largely replace individual approvals from study participants in registry-based research.[61] "It is assumed that the study participants do not object to registry-based research, provided that such research is deemed ethical by the EC. This assumed agreement to contribute personal data to research is part of the informal contract between the individual and the state (or where relevant, county councils or other suppliers of health care), given that health care is traditionally virtually free of charge (costs are covered through the tax bill). Registry-based data are maintained for the purpose of health care quality improvement and national statistics and are used in economic administration systems, and transfer of data is sometimes an integrated part of the reimbursement system (single individuals cannot opt out; instead, participation is compulsory)."[61]

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

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must 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, approval will be obtained from the Norwegian Data Inspectorate and from an Ethical Committee.

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

10.4. 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. The study protocol as well as results will be posted in EU PAS register maintained by EMA.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that already exist as structured data in an electronic database. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

At the end of this study a single report with country specific results as well as combined results (meta-analysis) from the four countries 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.

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.

13. REFERENCES

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14. LIST OF TABLES

15. LIST OF FIGURES

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 Gabapentin 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)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.7
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)	☒	☐	☐	9.7
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)	☐	☐	☒	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	9.4
	4.2.2 Age and sex?	☒	☐	☐	9.4
	4.2.3 Country of origin?	☒	☐	☐	9.4
	4.2.4 Disease/indication?	☒	☐	☐	9.4
	4.2.5 Duration of follow-up?	☒	☐	☐	9.4
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1 9.2.2

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)	☒	☐	☐	9.4 9.4
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.9

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.7
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.7

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?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
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)	☒	☐	☐	9.9
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)	☐	☐	☒	9.3.2

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.7
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.7
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.9

Comments:

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)	☒	☐	☐	9.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
	9.1.3 Covariates?	☒	☐	☐	9.4
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)	☒	☐	☐	9.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
	9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
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)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Is the choice of statistical techniques described?	☒	☐	☐	9.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7
10.5 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

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)	☒	☐	☐	9.6-9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
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?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
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)	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

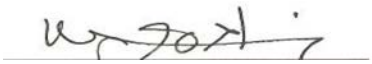
Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

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

Date: dd/Month/year 01/25/2019

Signature: 

ANNEX 3. ADDITIONAL INFORMATION

Codes used to identify study variables