NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	An observational cohort study to evaluate the risk of adverse pregnancy outcomes in patients treated with etanercept compared to those not treated with etanercept or other biologics using merged data from Sweden, Denmark and Finland
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Procedure number	EMEA/H/C/000262/MEA/167
Marketing Authorisation Holder (MAH)	Pfizer Limited Ramsgate Road, Sandwich, Kent CT13 9NJ United Kingdom
Joint PASS	No

Research question and objectives	To compare the risk of adverse pregnancy outcomes, including major birth defects, in infants born to mothers with rheumatoid arthritis (RA), psoriatic arthritis (PsA) or ankylosing spondyloarthritis (AS) who have been treated with etanercept during pregnancy with a similar population with the same diseases who have not been treated with etanercept or other biologic therapies in 3 Nordic countries
Country(-ies) of study	Sweden, Denmark and Finland
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AS	Ankylosing spondylitis
ATC	Anatomical Therapeutic Chemical
ARTIS	AntiRheumatic Therapies In Sweden
BMI	Body mass index
cIA	Chronic inflammatory arthritis
DMBR	Danish Medical Birth Register
DPDR	Danish National Prescription Registry
DNPR	Danish National Patient Registry
EMA	European Medicines Agency
EUROCAT	European Surveillance of Congenital Anomalies
FMBR	Finnish Medical Birth Register
FDPR	Finnish Register on Prescribed Medicine
HILMO	Finnish National Care Register for Health Care Institutions
ICD	International classifications of diseases
JIA	Juvenile arthritis
LMP	Last menstrual period
MAH	Marketing Authorization Holder
OR	Odds ratio
OSL	Public Access to Information and Secrecy Act
OTIS	Organization of Teratology Information Specialists
PAR	Swedish Patient Register

PASS	Post Authorisation Safety Study
PL	Package Leaflet
PsA	Psoriatic arthritis
PsO	Psoriasis
RA	Rheumatoid arthritis
RMP	Risk management plan
ROB-FIN	National register for biologic treatment in rheumatic diseases in Finland
SGA	Small for gestational age
SmPC	Summary of Product Characteristics
SMBR	Swedish Medical Birth Register
SPDR	Swedish Prescribed Drug Register
STORK	Systematic Tracking of Real Kids
TNF	Tumour necrosis factor

2. RESPONSIBLE PARTIES

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3. ABSTRACT

Protocol B1801396, version 3.0 – 20 March, 2017

An observational cohort study to evaluate the risk of adverse pregnancy outcomes in patients treated with etanercept compared to those not treated with etanercept or other biologics using merged data from Sweden, Denmark and Finland

Principal Investigator:

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Rationale and background

The introduction of tumor necrosis factor (TNF)-alpha inhibitor drugs has greatly improved the treatment of patients with rheumatoid arthritis (RA) and psoriasis (PsO).

There are limited data on the risk of adverse pregnancy outcomes in etanercept exposed patients from large population-based studies. Hyrich KL et al summarized the information available with regard to the use of biologic therapies during conception, pregnancy and breastfeeding. The collective evidence suggests that exposure to anti-TNF therapies at the time of conception or during the first trimester does not result in an increased risk of adverse pregnancy and fetal outcomes (8). The British Society for Rheumatology Biologics Register (BSRBR) collected data on 130 pregnancies in 118 patients with RA, who received anti-TNF therapy (etanercept, infliximab or adalimumab) (9). There were 2 (2/32=6.25%) reports of birth defects (congenital dislocation of the hip and pyloric stenosis) in patients exposed to anti-TNF therapy [without methotrexate (MTX) or LEF] at conception, and 2 (2/46=4.35%) (winking jaw syndrome and strawberry birth mark) in patients exposed to anti-TNF therapy before conception.

In a recent prospective, observational, cohort study, Weber-Schoendorfer et al compared pregnancy outcomes of 495 women treated with tumor necrosis factor-alpha (TNF-α) inhibitors (including adalimumab, infliximab, etanercept, certolizumab pegol or golimumab) with 1532 women unexposed to anti-TNF therapy who were referred for teratological evaluation between 1998 and 2013. (10) It was reported that there may be a moderately increased risk of birth defects associated with prenatal TNF-α inhibitor exposure for maternal chronic inflammatory conditions [adjusted odds ratio (aOR) = 2.20 (95% CI: 1.01, 4.8)] without a distinct pattern of malformations.

In a cohort using data from the national registers in Denmark and Sweden and including more than 22 000 women with chronic inflammatory disease there were 344 live-born infants to mothers with a recorded treatment of etanercept in early pregnancy. When compared to those with no treatment of a TNF-α inhibitor, 24 (7.0 %) vs 1019 (4.7 %) infants had any major birth defect, corresponding to an aOR of 1.49 (95% CI: 0.92 - 2.28). (11)

In the Organization of Teratology Information Specialists (OTIS) pregnancy registry in North America, which is a prospective, observational, cohort study to evaluate pregnancy outcomes in women with RA (including juvenile arthritis (JIA)), PsO, PsA or AS, any major malformation was prevalent in 30 of 319 (9.4%) of etanercept-exposed live-born infants

compared with 5 of 144 (3.5%) unexposed live-born infants, with an odds ratio (OR) of 2.88 (adjusted odds ratio [aOR] = 2.77 [95% confidence interval, CI: 1.04 to 7.35]).

In STORK (Systematic Tracking of Real Kids), a retrospective cohort study using a large insurance database affiliated with OptumInsight (Optum), there were no notable differences in the proportion of claims-identified or chart-identified MCMs across the chronic inflammatory arthritis (cIA) and psoriasis cohorts.

On the basis of the above information (from the OTIS and STORK studies) and the results from other studies, the Marketing Authorisation Holder (MAH) submitted a Type II labeling variation (EMEA/H/C/262/II/0184) to the European Medicines Agency (EMA) proposing updates to the information regarding pregnancy outcomes in section 4.6 of the Summary Product Characteristics (SmPC) and the corresponding section of the Package Leaflet (PL). The MAH was requested to provide further information to support the assessment of the variation, and to provide details of other observational data sources, which could be used to further investigate the relationship between etanercept exposure and major birth defects. In response to this request, the MAH proposed to use merged pregnancy outcome data from linked registries in Sweden, Finland and Denmark, and describe the approximate size of the etanercept and comparison cohorts that could be provided by such sources.

To further investigate the relationship between etanercept exposure and the outcome of major birth defects, it is proposed to conduct an observational cohort study by using merged pregnancy outcome data for etanercept that will be made available from three Nordic countries (in Sweden, Finland and Denmark), where national registries including patient registers, medical birth registers, prescribed drug registers and disease-specific quality registers may be linked.

This non-interventional (NI) study is designated as a post-authorisation safety study (PASS) and is a commitment to the EMA.

Research question and objectives

The primary objective of this observational cohort study is to compare the risk of major birth defects in infants born to mothers with rheumatoid arthritis (RA), psoriatic arthritis (PsA) or ankylosing spondyloarthritis (AS) who were treated with etanercept during pregnancy with a similar population with the same diseases who were not treated with etanercept or other biologic therapies in 3 Nordic countries (Sweden, Denmark and Finland).

Study design

This study is a population-based, multi-country, observational, cohort study using existing merged pregnancy outcome data from registries in 3 Nordic countries (Sweden, Finland and Denmark) to evaluate the risks of adverse pregnancy and birth outcomes of etanercept treatment during pregnancy in patients with RA, PsA and AS compared to those not treated with etanercept or other biologic therapies.

Study Population

The study population comprises all women and infants in the etanercept exposed cohort or in the non-biologic therapy cohort, identified from an existing database built at Karolinska Institutet, which includes births from July 2006 to December 2013 in Sweden and Denmark

and to December 2012 in Finland. Most of the included women had RA (84% in etanercept exposed cohort and 74% in non-biologic systemic cohort), while others had either PsA (8% in etanercept exposed cohort and 9% in non-biologic systemic cohort) or AS (8% in etanercept exposed cohort and 16% in non-biologic systemic cohort).

Data sources

The design for this registry study will utilize data on pregnancy and birth outcomes available from the Swedish Medical Birth Register (SMBR), the Danish Medical Birth Register (DMBR), and the Finnish Medical Birth Register (FMBR). The national medical birth registers will be used to identify all women who gave birth from July 2006 to December 2013 in Sweden and Denmark and to December 2012 in Finland. The registers have collected nationwide information on births for several decades with almost complete coverage. In addition, data on drug exposure and diseases will be obtained from national patient registers and registers on prescribed drugs in Sweden, Denmark and Finland, including the Swedish Patient Register (PAR), the Danish National Registry of Patients (DNRP), the Finnish National Care Register for Health Care Institutions (HILMO), Swedish Cause of Death Register, Danish Registry of Causes of Death, Finnish Cause of Death Register, Swedish Prescribed Drug Register (SPDR), Danish Registry of Medicinal Product Statistics (DPDR), Finnish Register on Prescribed Medicine (FPDR), and the quality registers ARTIS (Sweden) and ROB-FIN (Finland).

Variables

The main exposure variable is maternal etanercept treatment including gestational age at the time of exposure to etanercept and etanercept treatment dose. The outcome variables include information on all births, such as birth defects, viability, preterm birth, low birth weight and small for gestational age (SGA). In addition, data on patients' demographic and clinical characteristics including maternal comorbidities, smoking during pregnancy, body mass index (BMI), previous preterm delivery, any previous child(ren) with birth defect(s) will be considered.

Study size

Based on the number of exposed children to date in the pregnancy outcome database at Karolinska Institutet, including data from all three countries (435 in the etanercept cohort vs 2588 in the non-biologic systemic cohort) and a prevalence of major birth defects of 4.5% in the non-biologic systemic cohort, a 1.78-times higher frequency of major birth defects can be detected in the etanercept treated cohort compared to the non-biologic systemic treatment cohort with an 80% power at a 5% significance level (2-sided test). An alternative calculation, conservatively addressing the potential dependence between children with the same mother, assumes that each mother only contributes one child (378 in the etanercept cohort vs 2149 in the non-biologic systemic cohort) and yields a corresponding detectable relative increase of 1.84. When restricting exposure to etanercept within 3 months prior to the last menstrual period or during the 1st trimester of pregnancy (240 exposed children), a power calculation suggests a detectable relative risk of 2.04.

Data analyses

Data from Sweden, Denmark and Finland will be pooled. Analyses stratified by country will also be presented. Chi-square or Fishers exact test will be used for the crude analyses for the comparison between etanercept exposed cohort and non-biologic control cohort. The prevalence of adverse pregnancy outcomes will be assessed in the etanercept exposed and non-biologic cohorts. Univariate and multivariate logistic regression will be used to estimate the crude and adjusted odds ratios and 95% confidence intervals when comparing the risk of adverse pregnancy outcomes between the two cohorts.

Milestones

A final study report after study completion will be prepared. The proposed timeline for submission of the final report accounts for the data linking process, data analysis and development of the report. The estimated timeline for submission of the final report to the EMA is 30 November 2017.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned date
Start of data collection	01 July 2006
End of data collection	31 December 2013 in Sweden & Denmark 31 December 2012 in Finland
Registration in the EU PAS register	After CHMP endorsement of the final protocol
Final study report	30 November 2017

6. RATIONALE AND BACKGROUND

Etanercept and birth defects

Etanercept is a tumour necrosis factor-alpha (TNF-alpha) inhibitor. It is a bioengineered fusion protein incorporating tumour necrosis factor (TNF) receptor p75 and the crystallisable fragment (Fc) component of immunoglobulin G1 (IgG1), which binds specifically to TNF-alpha and lymphotoxin, inhibiting their interaction with cell surface receptors. In the EU, etanercept is indicated for the treatment of rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis, pediatric plaque psoriasis and psoriatic arthritis.

Etanercept would appear to have a low probability of crossing the placenta during the first trimester, owing to its molecular size, making potential adverse effects on early fetal viability or organogenesis unlikely. Significant fetal effects, such as preterm delivery or fetal growth restriction, would more reasonably be expected to manifest either later in pregnancy, when active transplacental transport of similar antibody molecules has been documented, or following delivery. In the current EU SmPC for Etanercept (Enbrel) there is a recommendation that women of childbearing potential should be advised to use appropriate contraception to avoid becoming pregnant during therapy, and for three weeks after discontinuation. The SmPC (section 4.6) also states that "Etanercept is not recommended during pregnancy".

Adverse pregnancy outcomes are listed as an important potential risk in the current etanercept risk management plan (RMP). Additional pharmacovigilance activities for this safety concern, include observational studies, notably the Rheumatic Diseases and Psoriasis Pregnancy Registry study conducted by the Organization of Teratology Information Specialists (OTIS) and the STORK (Systematic Tracking of Real Kids) study, a retrospective study to evaluate pregnancy outcomes associated with and without etanercept treatment among pregnant women with chronic inflammatory arthritis or psoriasis.

Birth defects in connection with disease severity and other systemic treatment

The prevalence of birth defects among neonates of women with RA has been reported to be between 0 to 4.3% in Sweden and Denmark. (1) When compared with neonates of women without the disease, a non-statistically significant association was observed for the incidence of congenital anomalies among women with RA (aOR = 1.32; 95% CI: 0.98, 1.79). However, women who were seropositive for rheumatoid factor (OR = 1.66; 95% CI: 1.15, 2.40) and had at least 1 previous hospital admission associated with RA (OR = 1.43; 95% CI: 1.00, 2.05) were shown to have an increased risk of giving birth to infants with birth defects than those without RA. When stratified by period of birth, the risk for birth defects decreased from 2.57 (95% CI: 1.59, 4.16) in 1994 to 1997 to 1.00 (95% CI: 0.64, 1.56) in 2002 to 2006. (1) Disease activity, seropositivity for rheumatoid factor, severity of disease (measured by surgery performed and/or hospitalization), and medication use seem to play an important role in pregnancy outcomes among patients with RA. However, limited information is available regarding adjustment for disease severity or use of medications during pregnancy in most of the studies referenced.

Methotrexate, designated pregnancy category X by the FDA and category D in Europe, can cause fetal death or teratogenic effects when administered to pregnant women. The use of

methotrexate in the first trimester has been associated with a specific pattern of birth defects, including malformations of the infants' head, face, and bones. There is a recognized association between high-dose methotrexate and spontaneous abortion. A systemic review found that 23% of pregnancies exposed to methotrexate in the first trimester resulted in spontaneous abortion and 5% of pregnancies resulted in reported minor neonatal malformations. (2)

Leflunomide is also designated pregnancy category X by the FDA and category D in Europe. Women should not conceive for 2 years after the last dose of leflunomide or undergo cholestyramine washout. Among 45 women who took leflunomide while pregnant, 2 infants of mothers exposed to leflunomide during the first trimester of pregnancy had major structural defects (12.5%). (3)

Isolated cleft palate among infants born to mothers exposed to any corticosteroid therapy during the first trimester of pregnancy has been associated with a prevalence of 0.54 per 1,000 live births. (4) A non-statistically significant increased risk of septal cardiac defects after exposure to multiple NSAIDs has been reported (OR = 3.9; 95% CI: 0.9, 15.7). (5) In an ongoing prospective study in Sweden, the total malformation rate was similar to the expected rate (OR = 1.04; 95% CI: 0.84, 1.29). However, the risk for cardiac defects was higher than expected (OR = 1.86, 95% CI: 1.32, 2.62). (6, 7) In addition, the risk for orofacial cleft defects was also increased (OR = 2.61; 95% CI: 1.01, 6.78).

There are limited data on the risk of adverse pregnancy outcomes in etanercept exposed patients from large population-based studies. Hyrich KL et al summarized the information available with regard to the use of biologic therapies during conception, pregnancy and breastfeeding. The collective evidence suggested that exposure to anti-TNF therapy in inflammatory arthritis and inflammatory bowel disease at the time of conception or during the first trimester does not result in an increased risk of adverse pregnancy and fetal outcomes. (8) The British Society for Rheumatology Biologics Register (BSRBR) collected data on 130 pregnancies in 118 patients with RA, who received anti-TNF therapy (etanercept, infliximab or adalimumab). (9) The pregnancy outcomes in the anti-TNF exposed patients were compared with those in RA patients who received non-biologic DMARDs. There were 2 (2/32=6.25%) reports of birth defects (congenital dislocation of the hip and pyloric stenosis) in patients exposed to anti-TNF therapy (without MTX or LEF) at conception, and 2 (2/46=4.35%) (winking jaw syndrome and strawberry birth mark) in patients exposed to anti-TNF therapy before conception.

In a recent prospective, observational, cohort study, Weber-Schoendorfer et al compared pregnancy outcomes of 495 women treated with tumor necrosis factor-alpha (TNF-α) inhibitors (including adalimumab, infliximab, etanercept, certolizumab pegol or golimumab) with 1532 women unexposed to TNF-α inhibitors who were referred for teratological evaluation between 1998 and 2013. (10) It was reported that there may be a moderately increased risk of birth defects associated with prenatal TNF-α inhibitor exposure for maternal chronic inflammatory conditions [adjusted odds ratio (aOR) = 2.20 (95% CI: 1.01, 4.8)] without a distinct pattern of malformations. There may be an increased risk of preterm birth and reduced birth weight, but no increased risk of spontaneous abortion. One of the

limitations of this study is that exposed pregnancies with chronic inflammatory conditions were only compared with a general comparison cohort, which may leave open the possibility of confounding by indication.

In a cohort using data from the national registers in Denmark and Sweden and including more than 22 000 women with chronic inflammatory disease there were 344 live-born infants to mothers with a recorded treatment of etanercept in early pregnancy. When compared to those with no treatment of a TNF-α inhibitor, 24 (7.0 %) vs 1019 (4.7 %) infants had any major birth defect, corresponding to an aOR of 1.49 (95% CI: 0.92 - 2.28). (11)

In the OTIS pregnancy registry in North America, which was a prospective, observational, cohort study to evaluate pregnancy outcomes in women with RA (including juvenile rheumatoid arthritis, JRA), PsO PsA or AS, it was found that any major birth defect was prevalent in 30 of 319 (9.4%) etanercept-exposed live-born subjects compared with 5 of 144 (3.5%) unexposed live-born infants, resulting in an odds ratio (OR) of 2.88 (adjusted odds ratio [aOR] = 2.77 [95% confidence interval, CI: 1.04 to 7.35]). A higher rate of major birth defects was also observed when comparing all pregnancies exposed to etanercept during the first trimester, with all pregnancies not exposed to etanercept or other TNF-antagonists (adjusted OR= 2.37, 95% CI: 1.02 – 5.52). When 4 of the 30 live-born exposed malformed subjects with chromosomal or genetic anomalies were excluded, the proportion of major birth defects in the first trimester exposed group decreased to 8.3%, reducing the aOR to 2.49 (95% CI: 0.92 to 6.68). However, no pattern of major birth defects was observed among the exposed subjects. Other adverse pregnancy outcomes such as spontaneous abortion, preterm birth, stillbirth and serious or opportunistic infections were not increased in the etanercept-exposed group.

The STORK study, a retrospective cohort study using a large insurance database affiliated with OptumInsight (Optum), compared pregnancy and birth outcomes among women with chronic inflammatory arthritis (cIA) and psoriasis (PsO) who were treated with etanercept during pregnancy with women with cIA and PsO who were not treated with etanercept or any anti-TNF during pregnancy. Thirty-one (18.7%) of 166 live born infants whose mothers had cIA and exposed to etanercept had claims for major congenital malformations (MCMs), while one hundred ninety (19.1%) had at least one claim for MCMs among 997 live born infants whose mother had cIA but without exposure to etanercept or other anti-TNFs. Eight (15.7%) of 51 live born infants whose mothers had claims for psoriasis and were exposed to etanercept had claims for MCMs, while one hundred thirty seven (14.5%) had at least one claim for MCMs among 943 live born infants whose mother had psoriasis but without exposure to etanercept or other anti-TNFs. In summary, the STORK study examined 6 mutually exclusive cohorts of pregnant women defined by claims-based evidence of cIA, PsO and etanercept exposure. There were no notable differences in the proportion of claims-identified or chart-identified MCMs across the 3 cIA cohorts (women with cIA and exposed to etanercept, women with cIA and unexposed to etanercept or any anti-TNF during pregnancy, and those without cIA and unexposed to etanercept or other anti-TNFs). The proportion of enrolled infants with LBW birth was highest in the etanercept-exposed cIA cohort and lowest in the non-diseased/non-exposed comparator cohort. Proportions of preterm birth were higher in both etanercept exposed and unexposed cIA disease cohorts than in the comparator cohort. There were no notable differences in the proportion of most outcomes between the PsO cohorts, however the numbers were insufficient to draw reliable conclusions.

On the basis of the information summarised above from the OTIS and STORK studies and the results from other studies, the MAH submitted a Type II labeling variation (EMEA/H/C/262/II/0184) to the EMA proposing updates to the information regarding pregnancy outcomes in section 4.6 of the SmPC and the corresponding section of the package leaflet (PL). The MAH was requested to provide further information to support the assessment of the variation, and to provide details of other observational data sources, for example existing disease registries, which could be used to further investigate the relationship between etanercept exposure and the outcome of major birth defects. In response to this request, the MAH proposed to use merged pregnancy outcome data from linked registries in Sweden, Finland and Denmark, and described the approximate size of the etanercept and comparison cohorts that could be provided by such sources. An estimate of the likely timelines to obtain an analysis and overall feasibility of such an investigation was also provided.

To further investigate the relationship between etanercept exposure and the outcome of major birth defects, the MAH proposes to conduct an observational cohort study by using merged pregnancy outcome data for etanercept that will be made available from three Nordic countries (in Sweden, Finland and Denmark), where various national registries are linked, by collaborating with the investigators from the ARTIS (AntiRheumatic Therapies In Sweden) registry and the Centre for Pharmacoepidemiology (CPE) at Karolinska Institutet who have been in charge of the previous/ongoing assessments of pregnancy outcomes following immunomodulator treatments. This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is a commitment to the EMA.

7. RESEARCH QUESTION AND OBJECTIVES

The primary objective is to compare the prevalence of major birth defects in infants born to mothers with rheumatoid arthritis (RA), psoriatic arthritis (PsA) or ankylosing spondyloarthritis (AS) who have received etanercept during pregnancy with a similar population with the same diseases who have not received etanercept or other biologic therapies in Sweden, Denmark and Finland.

The secondary objectives of this study are to:

- Compare the prevalence of all birth defects in infants born to mothers in the etanercept exposed cohort with a similar population with the same diseases in the non-biologic systemic cohort in Sweden, Denmark and Finland

- Compare the risk of other adverse pregnancy outcomes including stillbirth and preterm birth in the etanercept exposed cohort with a similar population with the same diseases in the non-biologic systemic cohort in Sweden, Denmark and Finland.

- Compare the risk of low birth weight, of small for gestational age, and in the first year of life the incidence rates of serious and opportunistic infections among infants in the etanercept exposed cohort with a similar population with the same disease in the non-biologic systemic cohort in Sweden, Denmark and Finland.

8. RESEARCH METHODS

8.1. Study design

This study is a population-based, multi-country, observational, cohort study conducted to evaluate the risk of adverse birth outcomes of etanercept treatment during pregnancy in patients with RA, PsA and AS compared to those not treated with etanercept or other biologic therapy.

This register-based study will be conducted including information on women and their infants up to 1 year of age. Data will be obtained from national medical birth registers, patient registers, and registers on prescribed drugs in Sweden, Denmark and Finland. Additional information on drug treatment can also be obtained from the Antirheumatic therapies in Sweden (ARTIS) and the ROB-FIN in Finland. Data in these registers in each country can be linked using the unique personal identification number assigned at birth or upon immigration to all residents of Sweden, Denmark and Finland.

8.2. Setting

The national medical birth registers will be used to identify all women who gave birth from July 2006 to December 2013 in Sweden and Denmark and to December 2012 in Finland. The registers have collected nationwide information on births for several decades with almost complete coverage. Midwives and physicians record information about the pregnancy, the delivery, and the neonatal period using structured forms. (12-13)

Based on the data derived from the database built at Karolinska Institute, currently there are 378 women who gave birth to 435 infants in the etanercept exposed cohort, and 2149 women who gave birth to 2588 infants in the non-biologic systemic cohort. Most of these women had rheumatoid arthritis (RA) (84% in etanercept exposed cohort and 74% in non-biologic systemic cohort), while others had either psoriatic arthritis (8% in etanercept exposed cohort and 9% in non-biologic systemic cohort) or ankylosing spondyloarthritis (8% in etanercept exposed cohort and 16% in non-biologic systemic cohort). A total of 216 women were exposed to etanercept from 3 months prior to the last menstrual period until the end of first trimester. These women gave birth to 240 infants.

8.2.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Have a diagnosis of RA, PsA or AS

2. For the etanercept treated cohort, have had any treatment with etanercept within 3 months prior to the first day of the last menstrual period (LMP) or any time during pregnancy.

8.2.2. Exclusion criteria

Patients exposed to the following drugs/drug classes will be excluded in the sensitivity analyses due to their known teratogenicity:

Exposure to acitretin, mycophenylate mofetil, methotrexate, leflunomide or anti-epileptics within 3 months prior to the first day of LMP or during pregnancy as recorded in the registers providing the information will disqualify a women frominclusion in the study

due to the known teratogenicity of these medications and/or the extremely long half-life of these medications (12-16)

8.3. Data sources

Medical Birth Registries

The design for this register study will utilize birth outcome information available from the Swedish Medical Birth Register (SMBR), the Danish Medical Birth Register (DMBR), and the Finnish Medical Birth Register (FMBR).

The SMBR is a comprehensive pregnancy outcome database established in 1973 for the purpose of compiling information on pre- and perinatal risk factors and their significance for infant health. Statistics from SMBR data have formed the basis for more than 300 published scientific studies during the past decade (17-18). The EMA "*Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post- Authorisation Data*" (EMA/CHMP/313666/2005, p. 8) specifically endorses the use of information from the SMBR for European registry studies.

The SMBR is administered by the Swedish National Board of Health and Welfare, whose responsibilities include maintenance of high quality epidemiologic registries, production of national reports on public health and social conditions, and coordination of statistics within the areas of health and social services. Women whose birth outcome information is contained in the SMBR are identified by the unique personal identification number (PIN) assigned to every legal resident of Sweden, which makes it possible to establish links between data contained in different Swedish national health registries. The PIN of a newborn is also included in the Medical Birth Register and is linked with the mother's PIN. The register includes information on all live births and still births from gestational week 22. Before July 2008 the cut-off for inclusion of still births was gestational week 28. ("Research Report from EpC: The Swedish Medical Birth Register--A Summary of Content and Quality" [Article no: 2003-112-3]).

The DMBR comprises information on all live births and stillbirths by women who are permanent residents of Denmark. Established in 1968 and computerized since 1973, the DMBR was originally intended to provide a means of monitoring newborn health and the quality of pre- and perinatal care services (19), but has also come to be used extensively for epidemiologic research (20-22). As for the Swedish national health registries, the unique PINs of mothers and newborns make possible the linkage of DMBR data with those available in other Danish health information databanks.

The FMBR, established in 1987 and administered by the National Institute for Health and Welfare (http://www.THL.fi/en_US/web/en), is a register that includes data on all live births and stillbirths of fetuses weighing at least 500 grams or having a gestational age of at least 22 weeks. Social and medical information about the mother is also included in the FMBR. The purpose of the FMBR is to provide data for statistical research on the development of maternity, obstetrical, and neonatal care in Finland. The FMBR collects baseline data on care and interventions for the mother during pregnancy and delivery and on newborn outcome through the first 7 days. Data for less than 1% of the newborn population is missing from the FMBR, and information on those cases is routinely obtained from the Central Population Register and the Cause-of-Death Register (23-24).

Among categories of maternal data captured in the SMBR, the DMBR, and the FMBR are as follows (Table 1):

- Maternal identification number
- Maternal age category
- Parity
- Date of admission to delivery unit, duration of pregnancy, mode of delivery, hospital code, and maternal delivery diagnoses (recorded as International Classification of Diseases [ICD] codes).

The following categories of infant data are captured in the SMBR, the DMBR, and the FMBR (Table 1):

- Infant identification number
- Mode of delivery, sex, birth weight, and Apgar score at 5 minutes
- Singleton or multiple birth
- Liveborn or stillborn
- Infant date of discharge (or date and time of death, if applicable, and whether autopsy was done), operations, and other procedures at delivery, and infant diagnoses. In Finland, information concerning autopsy results can be obtained from the Cause-of-Death Register.

Maternal diseases

Information on maternal disease for women who gave birth in Sweden is captured in the SMBR and in the Swedish Patient Register. Maternal information is readily available for Danish patients via linkages between the DMBR and the Danish National Patient Registry. Information on all diseases diagnosed during pregnancy in Finland is collected in the FMBR, and in addition information can be linked to the Finnish National Care Register for Health Care Institutions (HILMO), which contains data on all inpatient and out-patient care provided in public hospitals. Information on reimbursed prescribed medications is obtained from the Social Insurance Institution (SII) in Finland.

Maternal medication

For the Swedish cohort, information concerning maternal medication can be obtained from SMBR, the Swedish Prescribed Drug Register (SPDR) and the Swedish Patient Register (PAR). Similarly, the Danish National Registry of Patients (DNRP) and the Danish Registry of Medicinal Product Statistics (DPDR) provide information for the Danish cohort. For Finland, the information on maternal medication is mainly provided by the Finnish Register on Prescribed Medicine (FPDR). For the Swedish and Finnish cohorts, additional information on use of biologics can be obtained from the quality register of AntiRheumatic Therapies In Sweden (ARTIS) and the national register for biologic treatment in rheumatic diseases in Finland (ROB-FIN), respectively.

An inherent limitation of this study design is that data for early spontaneous pregnancy loss or voluntary termination of pregnancy is not available. Only information on live births or concerning still births occurring after 22 weeks of gestation is included in the database. Due to ethical-legal reasons, the Swedish registers do not include information at the individual level concerning spontaneous pregnancy loss or voluntary termination of pregnancy.

Distinct advantages of this study design are the comprehensive nature of the prenatal and pregnancy outcomes data that are available from the birth registers for both mothers and neonates, and the potential to obtain additional maternal information as well as reasonably robust infant follow-up information due to the linkages between maternal and infant PIN numbers and among the several Swedish, Danish, and Finnish national registers. To ensure good coverage of data, information on some variables will be obtained from several data sources (Table 1). For maternal disease during pregnancy information can be obtained from both the national birth registers and the patient registers. Similarly, information on systemic treatment for chronic inflammatory diseases can be obtained from the drug registers and for certain treatments also from the patient registers or the disease specific registers (ARTIS and ROB-FIN). In the proposed study we will use all available information that can be obtained from the various data sources.

Most manifestations of immunodeficiency result from frequent infections, usually beginning with recurrent respiratory infections (though many immunologically normal infants have 6 to 8 respiratory infections per year, particularly when exposed to older siblings or other children), and most patients with immunodeficiency eventually develop 1 or more severe bacterial infections that persist, recur, or lead to complications (e.g., sinusitis, chronic otitis and bronchitis following repeated upper respiratory infections) (Merck Manual of Diagnosis and Therapy, Seventeenth Edition [on-line]). Infections with opportunistic organisms and infections of the skin and mucous membranes may also occur, and malabsorption, failure to thrive and diarrhea are also common (ibid). In light of the above, and as information concerning antibiotic usage and hospitalization has been used previously in the evaluation of infant health status and immune function (25-27). We propose as noted below the use of infant hospitalization and of antibiotic usage data during the first year of life as surrogate markers for infant health status in this study.

More detailed information concerning the Swedish, Danish, and Finnish Medical Birth Registers may be found in **Appendix A, Appendix B**, and **Appendix C**, respectively.

Table 1. Data sources for key variables

Name of Register	Information
Swedish Medical Birth Register (SMBR) Danish Medical Birth Register (DMBR) Finnish Medical Birth Register (FMBR)	Maternal and infant characteristics, pregnancy and birth outcomes, birth defects, maternal diseases during pregnancy and infant diseases
Swedish Patient Register(PAR) Danish National Registry of Patients (DNRP) Finnish National Care Register for Health Care Institutions (HILMO)	Maternal and infant diseases, birth defects, maternal medication administered at hospital [a]
Swedish Cause of Death Register Danish Registry of Causes of Death Finnish Cause of Death Register	Infant death

Swedish Prescribed Drug Register (SPDR) Danish Registry of Medicinal Product Statistics (DPDR) Finnish Register on Prescribed Medicine (FPDR)	Maternal medication Infant use of antibiotics
ARTIS	Systemic antirheumatic treatment
ROB-FIN	Systemic antirheumatic treatment

[a] Only certain systemic treatments in Denmark and in Sweden

Use of data from Swedish, Danish, and Finnish national prescription and hospitalization registries

As noted above, the assignment in Sweden, Denmark, and Finland of unique PIN numbers makes possible cross-linkages between the birth registers and other national medical registers, including those tracking prescription drug use and hospitalizations (17-18, 22-24, 28). In this study, such registers will be utilized to obtain information concerning maternal disease states and maternal medication use. (Information regarding the use of TNF-α inhibitors in Denmark, for example, is captured in the Danish National Patient Registry). They will also provide information concerning infant hospitalization and/or antibiotic usage data during the first year of life, which will be utilized as surrogate markers for infant health status. These categories of information will be accessible via available linkages to the following national registers:

- the Swedish Prescribed Drug Register
- the Swedish Patient Register
- the Danish Register of Medicinal Product Statistics
- the Danish National Patient Registry
- the Finnish Register on Prescribed Medicine
- the Finnish National Care Register for Health Care Institutions

This study is potentially limited by the fact that hospital-prescribed drugs such as etanercept may not be reliably captured in the drug registers. In Denmark, exposure is assessed through filled prescriptions in the Danish Prescribed Drug Register (DPDR) and/or through codes for drug administration in the Danish National Patient Registry. In Sweden, exposure is assessed by filled prescriptions in the Swedish Prescribed Drug Register (SPDR) and/or through drug treatment recorded mainly in early and to a lesser degree in late pregnancy in the SMBR, or as treatments registered in ARTIS (Quality register: Anti Rheumatic Treatment in Sweden). In Finland, etanercept is recorded in the Finnish Register on Prescribed Medicine (FDPR) and may even be captured through linkage with ROB-FIN (Register of Biologics Treatment Among Rheumatic Patients in Finland). Exposure to other anti-TNF treatments is also captured as treatment notifications in ROB-FIN.

Additional information regarding these national registers is provided in **Appendix A** (Swedish registries), **Appendix B** (Danish registries), and **Appendix C** (Finnish registries).

8.4. Variables

The following data will be available for the analysis. Study variables, their roles and operational definitions are described in Table 2.

Exposure and cohort requirements

To determine the diagnosis/indication that led to initiation of etanercept/non-biologic treatment, information on the diseases as International Classification of Diseases (ICD), 10th revision, codes recorded at any time before or during pregnancy has been obtained from the patient registers, ARTIS and the medical birth registers from 1998 and onward (ICD-10 codes: M05–M06 for RA; L405, M070–M073, M090 for PsA; M45 for AS). For patients diagnosed with more than one disease, the latest diagnosis of a chronic inflammatory disease was used.

Qualification for the etanercept exposed cohort will require a combination of relevant ICD-10 or ICD-9 diagnoses of RA, PsA or AS and treatment with etanercept as identified by at least one prescribed ATC L04AB01 (treatment code BOHJ18A2 in the Danish National Patient Register) as shown in Table 2.

Timing of exposure to etanercept during pregnancy (from 90 days before the first day of the LMP until date of birth) is mainly based on data concerning filled prescriptions. For the Swedish cohort, additional data such as start/stop dates for specific anti-rheumatic drugs has been obtained from the ARTIS registry and for Finland, the ROB-FIN provided similar information.

For the primary objective, that is to compare the prevalence of major birth defects in infants born to mothers who have received etanercept during pregnancy with a similar population with the same diseases who have not received etanercept or other biologic therapies, the exposure period for the primary analysis is during the first trimester (from the first day of LMP until 90 days after LMP). In the sensitivity analyses, various other exposure periods (from 90 days before the first day of LMP until 90 days after LMP and from 30 days before LMP until 90 days after LMP) will be assessed.

For the secondary objective, comparing the prevalence of all birth defects in infants born to mothers in the etanercept exposed cohort with a similar population with the same diseases in the non-biologic systemic cohort in Sweden, Denmark and Finland, similar approaches as those used to address the primary objective concerning definition of exposure periods will be used.

For the other secondary objectives concerning adverse pregnancy outcomes other than birth defects, the exposure period is from 90 days before the first day of LMP until birth. In sensitivity analyses, various other exposure periods (from 90 days before the first day of LMP to LMP, during the first, second and third trimester) will be assessed.

Qualification for the non-biologic cohort will require a combination of relevant ICD-10 or ICD-9 diagnoses of RA, PsA or AS and at least one prescription of treatment with non-biologic systemic therapy (such as azathioprine, ciclosporin, cyclophosphamide, chloroquine, hydroxychloroquine and sulfalsalazine, etc.). The non-biologic cohort must have no ATC

codes for etanercept or any other biologics (ATC codes shown in Attachment A1).

Birth outcomes:

The primary outcome for this study will be major birth defects as defined according to the EUROCAT classification and based on ICD-codes (as shown in Attachment A2). The secondary outcomes will be all birth defects, live birth, stillbirth, preterm birth, low birth weight, small for gestational age, and infections during infancy.

Occurrence of birth defects, in general and by organ system–specific subgroups, and hospital visits in infants up to 1 year of age were ascertained from ICD-10 codes in the medical birth registers and in the patient registers (see Attachment A2), except for the birth defects in Finland, where the ICD-9 code has been used (specific definitions for each outcome are shown in Table 2).

Pregnancy and birth outcomes are recorded in birth registers held by each of the Nordic countries. The Nordic birth registers are collaborating in the Nordic Association of Medical Birth Registers (29).

The Swedish Medical Birth Register includes data on all births in Sweden, including stillbirths after gestational week 22 from 2008. Before that, live births and stillbirths occurring after gestational week 28 were recorded. Information is forwarded electronically to the register through standardized and generally used antenatal, obstetrical and pediatric records. Information includes delivery hospital, maternal socio-demographic characteristics and data on pregnancy, delivery and the neonatal period including birth defects until the mother and newborn infant are discharged from the hospital. In Sweden birth defects are also recorded in the Patient Register and information on birth defects until one year of age will be obtained.

The Danish Medical Birth Register is part of the Danish National Patient Register and includes data on live births, stillbirths of fetuses with a gestational age of at least 22 weeks and data on the mothers. Birth defects are reported to the register until one year of age.

The Finnish Medical Birth Register includes data on live births and stillbirths of fetuses with a birth weight of at least 500 grams or with a gestational age of at least 22 weeks, as well as data on the mothers. A data collection form is completed for each newborn in the maternity hospital, at the latest seven days after the delivery, which is sent to the register. Birth defects are identified through the Register on Congenital Malformations, which was started in 1963 and is run by THL. The data is collected from multiple sources, such as mandatory notifications by hospitals and physicians, other registers, and the Cause-of-Death Register. This register contains information on all observed malformations in spite of the type of pregnancy endpoint (miscarriage, induced abortion, still birth, and live birth), and it includes the personal identification numbers of the mother and the live newborns. Information on malformations in the register is completed over the first year of life. The register also includes diagnoses according to ICD-9 codes, as well as all exposures and risk factors related to the malformation. The data on all congenital malformations is collected; however, reporting is done on major congenital malformations only. Minor anomalies are excluded according to the exclusion list of European Registration of Congenital Anomalies (EUROCAT).

Covariates

Patient characteristics to be considered in the analysis include the following:

Demographics (such as age and country of residence), maternal and infant characteristics (such as infant sex, year and country of birth, mode of delivery) for both the etanercept treated and non-biologic systemic cohorts.

For those patients who were treated with etanercept during pregnancy:
Gestational age at the time of exposure to etanercept, maternal age at delivery, etanercept treatment dose, other treatments received during pregnancy, and the extent of use, prednisone and/or systemic oral corticosteroid use.

Other maternal characteristics include maternal comorbidities, previous maternal prosthetic surgery, smoking during pregnancy, previous preterm delivery, any previous child (ren) with birth defect (s).

Table 2. Study variables, their roles and operational definitions

Variable	Role	Operational definition	Data Source		
			Sweden	Denmark	Finland
Exposure variables					
Etanercept use (Yes/No)	Main exposure	Prescribed ATC= L04AB01 Treatment code in the Danish National Patient Register=BOHJ18A2 Recorded in ARTIS by start/stop date	SPDR ARTIS PAR	DPDR DNRP	FPDR ROB-FIN
RA (Yes/No)		ICD-10 codes: M05–M06	PAR SMBR	DNRP DMBR	HILMO FMBR
PsA (Yes/No)		ICD-10 codes: L405, M070–M073, M090	PAR SMBR	DNRP DMBR	HILMO FMBR
AS (Yes/No)		ICD-10 codes: M45	PAR SMBR	DNRP DMBR	HILMO FMBR
Gestational age at the time of exposure to etanercept	Main exposure	All prescriptions filled during the period from 3 months before LMP to date of birth will be identified in the national prescription registries. Based on the number of syringes prescribed and their strength (25/50 mg) exposure will be assigned to four periods: LMP-90 days to LMP; and trimesters 1 to 3. Assignment in the four periods will be based on the assumption of weekly administration irrespective of the strength.	SMBR	DMBR	FMBR

Etanercept treatment dose	Main exposure	Treatment dose in the four periods will be calculated as the cumulative dose in mg in each period assuming weekly administrations irrespective of strength.	SPDR ARTIS PsoReg PAR	DPDR DNRP	FPDR ROB-FIN
Other treatments received during pregnancy	Other exposure	Attachment A1	SPDR	DPDR	FPDR
Prednisone and/or systemic oral corticosteroid	Other exposure	Prescribed ATC= H02AB Dosing will not be assessed. Corticosteroid will be divided into subgroups (prednisone/others). Gestational age at exposure will be based on the date of filling the prescription.	SPDR	DPDR	FPDR
Outcome variables					
Major birth defects	Primary outcome	According to EUROCAT (Attachment A2)	SMBR PAR	DMBR DNRP	FMBR HILMO
All birth defects	Secondary outcome	ICD-10= Q-chapter, D215, D821, D1810, P350,P351,P371	SMBR PAR	DMBR DNRP	FMBR HILMO
Minor birth defects	Secondary outcome	All birth defects not defined as major (according to Attachment A2)	SMBR PAR	DMBR DNRP	FMBR HILMO
Stillbirth	Secondary outcome	Country specific indicator variable in national medical birth registries	SMBR	DMBR	FMBR
Preterm birth	Secondary outcome	Preterm=Gestational week < 37 Very Preterm=Gestational week < 32	SMBR	DMBR	FMBR
Birth size	Secondary outcome	Low= ≤ 2500 g Very low= ≤ 1500 g	SMBR	DMBR	FMBR
Serious infections (Yes/No, type of infection) in the first year of life	Secondary outcome	Attachment A3	PAR	DNRP	HILMO
Opportunistic infections (Yes/No, type of infection) in the first year of life	Secondary outcome	Including tuberculosis, pneumonia requiring antibiotic treatment and/or hospitalization, neonatal sepsis, meningitis, invasive fungal infection , pneumocystis, septic arthritis, osteomyelitis, abscess (deep tissue) (Attachment A3)	PAR	DNRP	HILMO

Covariates					
Demographic (age, country)	Baseline characteristics	Country specific variable in national medical birth registries	SMBR	DMBR	FMBR
Maternal indications	Baseline characteristics	Attachment A4 (codes for TNF-indication)	SMBR PAR	DMBR DNRP	FMBR HILMO
Smoking in early pregnancy	Baseline characteristics	Country specific variable in national medical birth registries (yes/no/missing)	SMBR	DMBR	FMBR
Previous preterm delivery	Baseline characteristics	Linkage to previous pregnancies identified in national medical birth registries (nullipara/ multipara without history/multipara with history)	SMBR	DMBR	FMBR
Any previous child (ren) with birth defect (s)	Baseline characteristics	Linkage to previous pregnancies identified in national medical birth registries (nullipara/ multipara without history/multipara with history)	SMBR	DMBR	FMBR
Maternal comorbidities	Baseline characteristics	Diagnosis of hypertension or diabetes, antihypertensive treatment, antidiabetic treatment (Attachment A5a)	SMBR PAR	DMBR DNRP	FMBR HILMO
Prosthetic surgery	Baseline characteristics	Surgery code for prosthetic joint surgery before pregnancy (Attachment A5b)	PAR	DNRP	HILMO

8.5. Study size

Based on the number of exposed children in the pooled dataset with information from Sweden, Denmark and Finland (435 in the etanercept cohort vs 2588 in the non-biologic systemic cohort) and the prevalence of major birth defects of 4.5% in the non-biologic systemic cohort, a 1.78-times higher frequency of major birth defect can be detected in the etanercept exposed cohort compared to non-biologic systemic treatment cohort with 80% power at a 5% significance level (2-sided test).

An alternative calculation, conservatively addressing the potential dependence between children with the same mother, assumes that each mother only contributes with one child (378 in the etanercept cohort vs 2149 in the non-biologic systemic cohort) and yields a corresponding detectable relative increase of 1.84. When restricting exposure to etanercept within 3 months prior to the last menstrual period or during the 1st trimester of pregnancy (240 exposed children), a power calculation suggests a detectable relative risk of 2.04.

Table 3. Power calculations given 80% power at a 5% significance level (2-sided test)

Non-biologic vs. Etanercept	Background Rate	Detectable Event Rate Increase
All 2588 vs. 435	4.5%	1.78-fold
	3%	2.00-fold
	1%	3.00-fold
	0.5%	4.00-fold
One infant per woman 2149 vs. 378	4.5%	1.84-fold
	3%	2.07-fold
	1%	3.10-fold
	0.5%	4.40-fold
Exposure within 3 months prior to LMP to 90 days after LMP 2588 vs. 240	4.5%	2.04-fold
	3%	2.33-fold
	1%	3.70-fold
	0.5%	5.40-fold

8.6. Data management

Within each research center, standard operating procedures (SOPs) will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. All key study documents, such as the statistical analysis plan, abstraction forms, and study reports will undergo quality-control review, senior scientific review, and editorial review.

Procedures will be consistent with the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) and guidelines provided by each of the 3 collaborating parties.

8.7. Data analysis

Data from the database, including information from the pooled dataset and for each of the three countries will be presented. Each of the above baseline characteristics will be summarized for the etanercept exposed cohort and the comparator cohort. Descriptive data are presented as the number and percentage of patients in each group for categorical variables. Means, median, range and standard deviations of the continuous variables will be provided in tables.

Chi-square or Fishers exact test will be used for the crude analyses for the comparison between etanercept exposed and non-biologic controls. The prevalence of adverse pregnancy outcomes will be assessed in the etanercept exposed and non-biologic cohorts. Univariate and multivariate logistic regression will be used to estimate the crude and adjusted odds ratios and 95% confidence intervals when comparing the risk of adverse pregnancy outcomes between the two cohorts. All potential confounders are pre-specified including: country, severity of maternal disease, parity, maternal age, smoking, history of surgery, hospitalization during pregnancy and additional drug treatments, and they will all be included in the multivariate analyses. Since women of childbearing potential may contribute multiple pregnancies during

the study period, adjustments will in addition be made by the generalized estimating equation (GEE) methods. Analyses will be performed on a complete case basis, adding covariates with known missing data such as smoking and BMI in the final model.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

Several sensitivity analyses will be performed, evaluating:

- Various exposure periods (for major birth defects and all birth defects: from 90 days before the first day of the LMP until 90 days after LMP and from 30 days before the LMP until 90 days after LMP; for adverse pregnancy outcomes other than birth defects, from 90 days before the first day of the LMP to LMP, during the first, second and third trimester)
- Two or more prescription fills
- Exclusion of known teratogenic drugs
- Disease severity (only women included in ARTIS by disease scores) and by adjusting for proxies for disease severity (history of surgery, hospitalization during pregnancy, and additional drug treatments)

8.8. Quality control

The Sponsor and Karolinska Institutet does not control and/or monitor the entry of data into the national registers. Karolinska Institutet can assure the quality of the data within the analytic dataset, since they are responsible for cross-linking the multiple datasets into one analytic dataset.

Results of validation tests and proofreading of programming codes will be documented, according to the guidelines for quality assurance at the Centre for Pharmacoepidemiology (CPEQD01_ v2.0, dated Feb 11, 2016). The guidelines align with the regulations that govern research at Karolinska Institutet and the pharmacoepidemiology guidelines issued by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the International Society of Pharmacoepidemiology (ISPE). Results of validation tests and proofreading of programming codes will be printed from Statistical Analysis System software and placed into a binder, which will be stored at the Karolinska Institutet.

8.9. Limitations of the research methods

This large population-based, observational cohort study will provide important, additional knowledge regarding the effect of etanercept exposure on pre-specified pregnancy and infant outcomes in patients with RA, PsA and AS. The strengths of this study are its large size by including all infants born to women who have been exposed to etanercept treatment in Sweden, Denmark and Finland. The accuracy and completeness of data from the national registers ensures the quality of the study. Valid information on covariates which may confound the results will also be obtained from the registers.

One limitation of this study is that the data is based on births, which means that the database does not have information on spontaneous or voluntary abortions. In addition, etanercept exposure before/during pregnancy will be based primarily on data from filled prescriptions. Since etanercept is a self-administered drug, some uncertainty will ultimately remain regarding the reliability of the exposure. However, considering the strict evaluation of the need of biological treatment for qualified patients, the fact that etanercept is not recommended to be used during pregnancy and the high costs of treatment, it is rather unlikely that etanercept is not administered when a prescription has been filled during pregnancy. To further elucidate on timing and the extent of exposure, sensitivity analyses including information on various exposure periods and repeated fillings of prescriptions will be performed. Drugs administered in the hospital setting are not captured by prescriptions, which may be another limitation of the study design. Information on anti-TNF therapy may, nevertheless, be found in the Danish and the Swedish patient registers and in the Swedish and the Finnish quality registers (ARTIS and ROB-FIN). As etanercept is mainly administered by prescription, the fact that hospital treatments are not fully captured is considered a minor limitation. Some disease characteristics (e.g., disease severity, duration) and personal information (e.g., maternal education, socioeconomic status, alcohol use), which may be potential risk factors for adverse pregnancy outcomes, but are unavailable in these register databases. Intake of folic acid in the pre-pregnancy and the embryonic period may reduce the risk of birth defects, such as neural tube defects, but as folic acid may be bought over the counter, information on folic acid use is not fully captured in the drug registers and therefore not included in the data base. In the database there are also missing data (5-15%) for some of the available covariates, such as BMI and smoking in early pregnancy.

Validation of outcomes lies within the responsibility of the register holders and will not be part of the proposed study. Several validation studies of data recorded in the Nordic national registers have demonstrated good positive predictive values for outcomes of relevance to the study (30). In addition, using information from 3 different countries provides us the possibility to compare rates of outcomes across the 3 registers, which may help assess if the outcomes data are valid.

8.10. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

While there are no assigned interventions in this registry study, the study will be performed following the required approval of the protocol by the Ethics Committee of Karolinska Institutet in Stockholm, Sweden and/or Aarhus University in Aarhus, Denmark, and/or the THL (National Institute for Health and Welfare) in Finland, and as required by any relevant government agencies, and will be conducted in conformance with all applicable Swedish, Danish, and Finnish regulatory safeguards of patient confidentiality. In the event of a health authority audit, Karolinska Institutet would make available the de-identified analytic datasets. The health authority would request approval from the Swedish, Danish, and Finnish National Boards of Health and Welfare to audit patient identified data.

De-identified pregnancy outcome information will be obtained from the Swedish, Danish, and Finnish Medical Birth Registries for all women with the indications of interest who have and who have not been exposed to etanercept during pregnancy during the specified study time period. De-

identified information will be obtained from Swedish, Danish, and Finnish national hospitalization and prescription pharmacy registers concerning the health status of the infants of these women during their first year of life. Information from all of these sources will be obtained with the collaboration and assistance of Dr. Helle Kieler of the Karolinska Institutet in Stockholm, Sweden, Dr. Henrik Toft-Sorensen of Aarhus University Hospital in Aarhus, Denmark, and Dr. Mika Gissler (or designees) at THL (National Institute for Health and Welfare) in Finland.

9.1. Patient Information and Consent

Not Applicable.

9.2. Patient withdrawal

Not Applicable.

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

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

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study includes unstructured data (e.g., narrative fields in the database) that will be converted to structured (i.e., coded) data solely by a computer using automated/algorithmic methods and/or data that already exist as structured data in an electronic database. In these data sources, 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 (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual adverse event reports.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The proposed timeline for submission of the final report account for the data lag time/availability of data to the investigators, data linking process time, data analysis and development of the report.

The final report including complete data from 1 July, 2006 through 31 December, 2013 in Sweden and Denmark and through 31 December 2012 in Finland is expected to be submitted to the EMA by 30 November 2017.

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.

12. REFERENCES

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13. LIST OF TABLES

Table 1. Data sources for key variables.

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14. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Appendix A: Swedish National Registries

I. Swedish Medical Birth Register

The Swedish Medical Birth Register was established in 1973 by an act of the Swedish Parliament, for the purpose of compiling information on ante- and perinatal factors and their importance for infant health. The basic structure of the register has remained unchanged since 1973, but there have been major modifications to content and methods of data collection over the years. From 1973 to 1982, the register was constructed by summarizing "Medical Birth Reports" prepared by secretaries at obstetric clinics. Starting in 1982, use of these reports was abandoned and copies of the 3 medical records of primary interest (the basic record of prenatal care of the mother, the delivery record, and the record for the pediatric examination of the newborn infant) were sent to the National Board of Health for computerization. At the same time, the register's content was expanded and other changes were instituted, 1 of which concerned the capture of information pertaining to diseases during pregnancy. Previously, specific diagnoses had been noted with ICD (International Classification of Diseases) codes; in the new modification, information concerning a number of serious conditions (and certain other categories of information, eg, administration of analgesics) was captured by means of check boxes. This general procedure has been followed since 1982, although the content of the register was modified again in 1990, 1994, and 1998. Since 1995, a copy of an additional record form has been requested from prenatal care centers to supply more information on the care provided.

The following is a summary of the register content and the time periods for which information on each item is available:

A. Identification of patient
Maternal personal identification number (PIN), infant PIN, maternal place of residence (parish) at delivery, delivery hospital, prenatal-care centre (1998-).

B. Social factors
Cohabitation, work outside home (1982-), occupation (1982-), parents' nationality, mother's country/county of birth, year of immigration (-1998), year of emigration (-1998); smoking before pregnancy (1998-), in early pregnancy (1982-), in late pregnancy (1990-); use of snuff before, in early pregnancy, in late pregnancy (1998-)

C. Maternal history

Previous pregnancies: induced abortions (-1981), spontaneous abortions, stillbirths, live births, perinatally dead infants, later dead infants; pre-pregnancy weight (1982-), weight increase (1982.1993), weight at delivery (1982.1989, 1994-) , height (1982-); involuntary childlessness, number of years (1982-); method for assisted conception (1994-); use of contraceptive pills or IUD before pregnancy (1982-); previous cesarean section, including year (1999-).

D. Pregnancy

Last menstrual period (LMP) date; expected date of delivery according to LMP and sonography (1982-); chorionic villus sampling (CVS) or amniocentesis, including date and outcome (1994-); selected diseases at first visit to prenatal clinic; drugs used during pregnancy (1995-); number of prenatal visits (1998-); date of first prenatal visit (1998-)

E. Delivery

Date of admission to delivery unit; pregnancy duration (weeks, days); presentation of infant; delivery diagnoses; operations at delivery: cesarean section, forceps, vacuum extraction, other; analgesia, anesthesia with specification; induction of delivery (1998-); placental weight (-1982); number of umbilical arteries (-1982); ruptures (1999-) perineotomia (1999-).

F. Infant
date and time of birth; stillborn/live-born; date of death, underlying cause of death; sex; birth weight; birth length; head circumference; multiple birth, including number; Apgar score at 1, 5, and 10 minutes; infant diagnoses; operations and other treatments of infant.

Abridged from: "Research Report from EpC: The Swedish Medical Birth Register--A Summary of Content and Quality" [Article no: 2003-112-3].

II. Swedish Prescribed Drug Register

The parliamentary decision to create the Prescribed Drug Register, the most recently-developed of Sweden's "national person identified health registries," was made on April 27, 2005. The Prescribed Drug Register includes information on all prescription drugs sold in Sweden since July 1, 2005.

The national person identified health registries are kept in a separate division of the National Board of Health and Welfare's Center for Epidemiology (EpC). Only a handful of the staff within this division has access to person identified data. The physical and virtual security and data protection facilities are generally kept at a very high level. The health data registries are essential for national and international health research and provide the basis for the Swedish health information system. The other national person identified health registries maintained by EpC include the Patient Discharge Register (encompassing all health care episodes in public and private hospitals since1987), the Cancer Register (all malignant primary tumours since 1958), the Medical Birth Register (medical data on all births since 1973) and the Cause of Death Register (with information concerning all deaths since 1952 recorded in a database, as well as extensive earlier paper records).

III. Swedish Patient Register

In the 1960s, the National Board of Health and Welfare started to collect data on individual in-patients at public hospitals. In 1984 the Ministry of Health and Welfare together with the Federation of County Councils decided to make reporting to the Hospital Discharge Register compulsory. Since 1987, the Register has covered all public, in-patient care in Sweden and since 2002 the coverage of out-patient hospital care is almost complete. The National Board of Health and Welfare also has data for earlier years. For the period 1964-2003, the register includes 47 million discharges.

The PAR contains data on both in-patient and out-patient populations in Sweden. However, since data collection for patients who are treated on an out-patient basis has improved over time, the Swedish National Patient Register was introduced as a separate register apart from the Swedish Hospital Discharge Register. These registers have been combined and are now known as PAR.

Information available in the Swedish Patient Register (PAR) includes the following:

Patient data (personal identification number, sex, age and place of residence)

Hospital data (county council, hospital and department)

Administrative data, including:

- date of admission or visit
- date of discharge
- length of stay
- acute/planned admission
- admitted from
- discharged to

Medical data, including:

- main diagnosis
- secondary diagnoses
- external cause of injury and poisoning
- surgical procedures

Information to PAR is delivered once a year to the National Board of Health and Welfare from each of the 21 county councils in Sweden. The National Board of Health and Welfare gets a magnetic tape or disc with 1 data file for the whole county council. Every discharge during 1 year corresponds to 1 record in that file.

Regarding quality of data and underreporting, very rapid changes of hospital organization in Sweden make estimations of underreporting difficult, especially for psychiatric and geriatric care. The total number of drop-outs for somatic short-time care for the period 1987-1991 has been estimated to be less than 2 per cent. For all records reported to PAR a data control is run. A check is made that compulsory variables are reported, eg personal identification number, hospital, and main diagnosis. A check is also made that codes for different variables and dates have valid values. Some obviously incorrect data is corrected in connection with the quality controls.

Abridged from “The Swedish Patient Register,” Swedish National Board of Health and Welfare [Socialstyrelsen] Web site. Available at: http://www.socialstyrelsen.se/register/halsodataregister/patientregistret/inenglish. Accessed 26 September 2011.

Appendix B: Danish National Registries

I. Danish Medical Birth Register

The Danish Medical Birth Register, established in 1968 and computerized since 1973, is kept and maintained by the Danish National Board of Health. Its primary purpose is to monitor the health of newborns and quality of prenatal and delivery care services, but the registry has also increasingly been used in research. Major revisions were made to the registry's content in 1978 and 1991.

The information contained in the Danish Medical Birth Register includes the following: maternal sociodemographic variables (PIN; date and year of birth; age at child's birth date; place of birth, citizenship and marital status; residence; occupation; smoking history); data on all newborns (PIN; maternal obstetric history/parity; number of prenatal visits; gestational age; hour and place of birth; complications during delivery; interventions prior to onset of labor or during delivery; type of anesthesia: presentation; whether single or multiple birth; sex, birth weight, length, and Apgar scores at 1 and 5 minutes: number of malformations diagnosed); and data on stillbirths and on live born infants dying within the first year of life.

Reference: Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Dan Med Bull* 1998;45:320-323.

II. Register of Medicinal Product Statistics

Since 1994, the Danish Medicines Agency has run the Register of Medicinal Product Statistics, which contains information on the total sale of medicinal products in Denmark. Each month, the sale from pharmacies, hospital pharmacies, the National Central Laboratory of the Danish Health System, the National Veterinary Laboratory, the Royal Veterinary and Agricultural University and authorized distributors of liberalized over-the-counter medicinal products (grocery stores, service stations etc.) is reported. Each year, the Register receives information on approximately 35 million sales of prescription-only products, approximately 20 million sales of over-the-counter products and approximately 18 million sales of free-trade goods. Information is available at the level of individual person, general practitioner, package, and company. In addition to the information reported, the Register contains information related to each medicinal product, for instance substance, current prices, product registration holder etc.

In mid-March 2003, researchers were given access to data in the Register of Medicinal Product Statistics at the Danish Medicines Agency via Statistics Denmark. An anonymous copy of the Register of Medicinal Product Statistics was transferred to Statistics Denmark and given the name 'Lægemiddeldatabasen' (the medicinal product database).

This type of registry offers the possibility of tracking the individual person's consumption of medicine over such a long period of time. By gaining access to the register via Statistics Denmark, researchers are offered a unique opportunity to pool data on the consumption of medicinal products with information from other registers. Such registers include the national patient register, the cause-of-death register, registers of social conditions or results of studies carried out by the researcher. Statistics Denmark is responsible for the pooling, and data are made available to researchers in a way that prevents identification of patient, doctor, and pharmacy. In 2003, 14 research projects covering a wide range of patients applied for access to the data in the medicinal products database, and more addressed either Statistics Denmark or the Danish Medicines Agency to request information for use in future projects.

To gain access to the data in the medicinal products database, a project protocol must be submitted to the researcher service unit (FSE) at Statistics Denmark. The project protocol should include, as a minimum, a description of the aim of the project, sample size and the type of information (variables) to be included in the data set. The data content of all projects that wish to use information from the medicinal products database must be approved by the Danish Medicines Agency. In its approval, the Danish Medicines Agency emphasizes the importance of a significant social aim of the project. FSE is responsible for approving the project protocol at the Danish Medicines Agency.

III. Danish National Patient Registry (Danish National Hospital Register)

The primary purposes of the Danish National Patient Registry are to provide information for the production of statistical data, to monitor hospital utilization and to support the planning process. The registry has also been used increasingly for monitoring diseases and treatments as well as for medical research and quality assurance in the hospital sector.

The Danish National Patient Registry contains information on all patient contact with clinical hospital departments in Denmark (ie, discharge, conclusion of out-patient treatment or report from emergency room visit). Data on all somatic hospital admissions have been submitted to the registry since its creation in 1977; since 1995, data on out-patients and emergency patients (and data on contacts with psychiatric hospital departments) have also been submitted. The data have been submitted to the registry in accordance with a declared national standard. The National Board of Health frequently publishes statistics based on the National Patient Registry.

For each entry in the registry, the following variables, among others, are included:
· unique personal identification number
· hospital department admitting the patient
· diagnoses
· surgical procedures
· date of admission/starting date for out-patient treatment
· date of discharge/date of conclusion of out-patient treatment
· mode of admission (acute/non-acute)

In the existing literature, the registry has been referred to alternately as:
· The National Hospital Register
· The National Patient Registry
· The National Register of In-patients
· The National In-patients Register
· The National Discharge Register
· The National Hospital Discharge Register

Several other registries form part of the National Patient Registry: The Medical Birth Register, the Congenital Malformation Registry (in operation during the period from 1983 to 1995), the Registry of Legally Induced Abortions and the Cancer Registry.

Ref: Andersen TF, Madsen M, Jorgensen J, Mellemkjoerl L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:263- 268.

Appendix C: Finnish National Registries

I. Finnish Medical Birth Register

This register was started in 1987 and is run by THL (National Institute for Health and Welfare). The reporting is mandatory for all hospital and home births. The register includes the mother's and child's unique, personal identification numbers, and information on maternal background, on care and interventions during pregnancy and delivery and on the newborn's outcome until the age of 7 days. The medical birth register data is collected from all delivery hospitals, and in case of home births, is collected by the assisting health care personnel. Less than 1% of all newborns are missing from the medical birth register; information on them can be obtained by making data linkages to the Central Population Register and the Cause-of–Death Register kept by Statistics Finland. After this data linkage, the medical birth register is considered to be complete in terms of numbers of births and newborns. According to data quality studies, the majority of the medical birth register content corresponds well or satisfactorily with hospital records. Since 2004, information on all diseases diagnosed during pregnancy is being collected in the FMBR.

II. Register on Prescribed Medicine

All Finnish citizens are entitled to reimbursement of medications under certain conditions. The reimbursement system of the Social Insurance Institution (SII) of Finland is organized through the National Health Insurance, which is maintained by the state, and is financed through tax revenues. The costs of prescribed medicines are reimbursable partly, or completely. Patients pay a fixed deductible per purchase, and of the balance remaining, reimbursement is percentage-based and divided into 3 categories: basic refund category (50%), the lower special refund category (75%), and the higher special refund category (100%). The register data includes data on all prescribed medicine since 1995 and on special refunded medicine since 1964. The special pharmaceutical reimbursement system currently covers a total of 36 chronic diseases in the complete reimbursement category. This reimbursement requires a medical certificate demonstrating that the diagnosis is based on clinical examinations, and fulfils national criteria. The register includes information on identification number, the medicine (ATC/DDD) and the purchase date. For special reimbursement rights, the register also includes information in the starting and ending date of this right.

III. National Care Register for Health Care Institutions

The National Care Register for Health Care Institutions (HILMO), also known as the Finnish National Care Register for Health Care Institutions was started in 1967 and is run by THL. It collects information on all episodes of institutionalized care (including both health and social care), and the reporting is mandatory for all public and private hospitals. The PAR includes all surgical procedures since 1996 (all hospitals) and all hospital out-patient visits since 1998 (public hospitals only). The register contains information on the patient's identification number, background, hospitalization period, procedures, and the main diagnosis by ICD (International Classification of Diseases) code with revision number (ICD-8 in 1967-1986, ICD-9 in 1987-1995, and ICD-10 since 1996). A 1986 data quality study found that 95% of the hospitalizations were registered and 97% of the main diagnoses concerning pregnancy, birth, and puerperium had been correctly reported at the 3-digit ICD-code level.

IV. Register on Congenital Malformations

This register was started in 1963 and is run by THL. The data is collected from multiple sources, such as mandatory notifications by hospitals and physicians, other registers, and the Cause-of-Death Register. This register contains information on all observed malformations in spite of the type of pregnancy endpoint (miscarriage, induced abortion, still birth, and live birth), and it includes the personal identification numbers of the mother and the live newborns. Information on malformations in the register is completed over the first year of life. The register also includes diagnoses according to ICD-9 codes, as well as all exposures and risk factors related to the malformation. The data on all congenital malformations is collected; however, reporting is done on major congenital malformations only. Minor anomalies are excluded according to the exclusion list of European Registration of Congenital Anomalies (EUROCAT).

Andersen TF, Madsen M, Jorgensen J, Mellemkjoerl L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999;46:263-268. Gissler M, Klemetti R, Sevon T, Hemmink E. Monitoring of IVF birth outcomes in Finland: a data quality study. BMC Med Inform Decis Mak. 2004 Mar 10;4:3.

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Knudsen LB, Olsen J. The Danish Medical Birth Registry. Dan Med Bull 1998;45:320-323.

ANNEX 2. ADDITIONAL INFORMATION

ATTACHMENT A1: ATC CODES IDENTIFYING ADDITIONAL TREATMENTS

ETANERCEPT COHORT	
Etanercept	L04AB01

NON-BIOLOGIC SYSTEMIC THERAPY COMPARISON COHORT	
Azathioprine	L01BB01
Azathioprine	L04AX01
Mercaptopurine	L01BB02
Corticosteroids for systemic use	H02*
Ciclosporin	L04AD01
Ciclosporin	L04AA01
Cyclophosphamide	L01AA01
Tacrolimus	L04AA05
Tacrolimus	L04AD02
Hydroxycarbamide/Hydrea	L01XX05
Alitretinoin	D11AH04
Tioguanin/Lanvis	L01BB03
Phototherapy, PUVA, oral	DQ010
Phototherapy, PUVA, bath	DQ011
Chloroquine	P01BA01
Hydroxychloroquine	P01BA02
Sulfalsalazine	A07EC

ATC CODES FOR EXCLUSION IN SENSITIVITY ANALYSES	
Methotrexate	L01BA01
Methotrexate	L04AX03
Leflunomide	L04AA13
Acitretin	D05B
Mycophenolic acid	L04AA06
Anti-epileptics	N03A
OTHER BIOLOGIC THERAPIES	
Anakinra	L04AC03
Tocilizumab	L04AC07
Rituximab	L01XC02
Abatacept	L04AA24
Efalizumab	L04AA21
Ustekinumab	L04AC05
Alefacept	L04AA15
Infliximab	L04AB02
Adalimumab	L04AB04
Certolizumab pegol	L04AB05
Golimumab	L04AB06
COMORBIDITY THERAPIES	
Antihypertensives	C02-C09
Antidiabetics	A10

ATTACHMENT A2: ICD-10 CODES IDENTIFYING MAJOR BIRTH DEFECTS [a]

EUROCAT SUBGROUPS OF MAJOR BIRTH DEFECTS		
		Exclusion diagnoses
Nervous system	Q00-Q07	
Eye, Ear, face and neck	Q11-Q16, Q100, Q104, Q106, Q107, Q178, Q183, Q187, Q188	Q135
Congenital heart defects	Q20-Q26	Q250
Respiratory	Q30-Q34	Q314, Q320
Oro-facial clefts	Q35-Q37	
Digestive system	Q41-Q45, Q402-Q409, Q38, Q39, Q790, Q792, Q793, Q795	Q381, Q382, Q3850, Q4021, Q43 Q4381, Q4382
Urinary	Q60-Q64, Q794	Q627, Q633
Genital organs	Q50, Q51, Q52, Q54, Q55, Q56	Q523, Q525
Limb	Q69-Q74, Q650, Q651, Q652, Q658, Q659, Q660, Q681, Q682, Q688	Q6821
Musculoskeletal system	Q750, Q751, Q754, Q755, Q756, Q757, Q758, Q759, Q761, Q762, Q763, Q764, Q766, Q767, Q768, Q769, Q77, Q78, Q796, Q797, Q798, Q799	
Chromosomal abnormalities	Q90, Q91, Q92, Q93, Q96, Q97, Q98, Q99	Q936
Others	Q80-Q87, Q27, Q28, Q89, Q936	Q270, Q825, Q8280, Q833, Q845

[a] For Finnish data, type of malformation is already grouped by the EUROCAT

ATTACHMENT A3: ICD-10 CODES FOR INFECTIONS

INFECTIOUS PATHOGENS IN FIRST YEAR OF LIFE (ICD-10 code)	
Intestinal infectious diseases	A00-A09
Tuberculosis	A15-A19
Certain zoonotic bacterial diseases	A20-A28
Infection due to other mycobacteria	A31
Listeriosis	A32
Tetanus neonatorum	A33
Other tetanus	A35
Diphtheria	A36
Whooping cough	A37
Scarlet fever	A38
Meningococcal infection	A39
Streptococcal sepsis	A40
Other sepsis	A41
Actinomycosis	A42
Nocardiosis	A43
Bartonellosis	A44
Erysipelas	A46
Other bacterial diseases, not elsewhere classified	A48
Bacterial infection of unspecified site	A49
Congenital syphilis	A50
Early syphilis	A51
Late syphilis	A52
Other and unspecified syphilis	A53
Gonococcal infection	A54
Acute poliomyelitis	A80
Atypical virus infections of central nervous system	A81
Mosquito-borne viral encephalitis	A83
Tick-borne viral encephalitis	A84
Other viral encephalitis, not elsewhere classified	A85
Unspecified viral encephalitis	A86
Viral meningitis	A87
Other viral infections of central nervous system, not elsewhere classified	A88
Unspecified viral infection of central nervous system	A89
Herpesviral [herpes simplex] infections	B00
Varicella [chickenpox]	B01
Zoster [herpes zoster]	B02
Measles	B05
Rubella [German measles]	B06
Other viral infections characterized by skin and mucous membrane lesions, not elsewhere classified	B08

Unspecified viral infection characterized by skin and mucous membrane lesions	B09
Viral hepatitis	B15-B19
Human immunodeficiency virus [HIV] disease	B20-B24
Cytomegaloviral disease	B25
Mumps	B26
Infectious mononucleosis	B27
Other viral diseases, not elsewhere classified	B33
Viral infection of unspecified site	B34
Mycoses	B35-B49
Toxoplasmosis	B58
Pneumocystosis	B59+
Sequelae of infectious and parasitic diseases	B90-B94
Streptococcus and staphylococcus as the cause of diseases classified to other chapters	B95
Other specified bacterial agents as the cause of diseases classified to other chapters	B96
Viral agents as the cause of diseases classified to other chapters	B97
Other specified infectious agents as the cause of diseases classified to other chapters	B98
Other and unspecified infectious diseases	B99
Inflammatory diseases of the central nervous system	G00-G09
Polyneuropathy in infectious and parasitic diseases classified elsewhere	G630
Myopathy in infectious and parasitic diseases classified elsewhere	G734
Other disorders of brain in diseases classified elsewhere	G940
Abscess of external ear	H600
Cellulitis of external ear	H601
Malignant otitis externa	H602
Other infective otitis externa	H603
Disorders of external ear in diseases classified elsewhere	H62
Suppurative and unspecified otitis media	H66
Otitis media in diseases classified elsewhere	H67
Mastoiditis and related conditions	H70
Infective pericarditis	I301
Acute and subacute infective endocarditis	I330
Infective myocarditis	I400
Myocarditis in bacterial diseases classified elsewhere	I410
Myocarditis in other infectious and parasitic diseases classified elsewhere	I412
Cardiomyopathy in infectious and parasitic diseases classified elsewhere	I430
Other heart disorders in bacterial diseases classified elsewhere	I520
Other heart disorders in other infectious and parasitic diseases classified elsewhere	I521
Acute upper respiratory infections	J00-J06
Influenza and pneumonia	J09-J18
Other acute lower respiratory infections	J20-J22

Chronic sinusitis	J32
Peritonsillar abscess	J36
Other abscess of pharynx	J391
Other diseases of pharynx	J392
Suppurative and necrotic conditions of lower respiratory tract	J85-J86
Pulpitis	K040
Acute apical periodontitis of pulpal origin	K044
Periapical abscess without sinus	K047
Acute gingivitis	K050
Acute periodontitis	K052
Abscess of salivary gland	K113
Cellulitis and abscess of mouth	K122
Acute appendicitis	K35
Other appendicitis	K36
Unspecified appendicitis	K37
Abscess of anal and rectal regions	K61
Infections of the skin and subcutaneous tissue	L00-L08
Pyogenic arthritis	M00
Direct infections of joint in infectious and parasitic diseases classified elsewhere	M01
Reactive arthropathies	M02
Osteomyelitis of vertebra	M462
Infection of intervertebral disc (pyogenic)	M463
Other infective spondylopathies	M465
Spondylopathy in other infectious and parasitic diseases classified elsewhere	M493
Myositis in bacterial diseases classified elsewhere	M630
Myositis in other infectious diseases classified elsewhere	M632
Necrotizing fasciitis	M726
Osteomyelitis	M86
Acute tubulo-interstitial nephritis	N10
Tubulo-interstitial nephritis, not specified as acute or chronic	N12
Pyonephrosis	N136
Acute cystitis	N300
Urinary tract infection, site not specified	N390
Salpingitis and oophoritis	N70
Other inflammation of vagina and vulva	N76
Infections specific to the perinatal period	P35-P39

ATTACHMENT A4: DISEASE CODES FOR MATERNAL CHRONIC INFLAMMATORY DISEASES

Disease State	ICD-10 Code
Rheumatoid arthritis	M05, M06
Juvenile rheumatoid arthritis	M08
Ankylosing spondylitis	M45
Arthropathic psoriasis	L40.5, M07.0, M07.1, M07.2, M07.3, M09.0
Psoriasis	L40

ATTACHMENT A5a: DISEASE CODES FOR MATERNAL COMORBIDITIES

Disease State	ICD-10 Code
Hypertension	I10-I13
Diabetes	E10-E14

ATTACHMENT A5b: SURGERY CODES FOR PROSTHETIC SURGERY

History of prosthetic surgery	NOMESCO [a] Codes
Knee prosthesis	NGB
Hip prosthesis	NFB
Shoulder prosthesis	NBB
Foot surgery	NHB, NHC, NHE, NHF, NHG
Hand surgery	NDB, NDC, NDE, NDF, NDG

[a] The Nordic Medico Classification of Surgical Procedures

ANNEX 3. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

An observational cohort study to evaluate the risk of adverse pregnancy outcomes in patients treated with etanercept compared to those not treated with etanercept or other biologics using merged data from Sweden, Denmark and Finland

Study reference number:

B1801396

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	12
1.1.2 End of data collection[2]	☒	☐	☐	12
1.1.3 Study progress report(s)	☐	☐	☒	-

[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 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1.4 Interim progress report(s)	☐	☐	☒	-
1.1.5 Registration in the EU PAS register	☒	☐	☐	12
1.1.6 Final report of study results.	☒	☐	☐	12

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	16
2.1.2 The objective(s) of the study?	☒	☐	☐	16
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	17
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	16
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	-

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	17
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	22-23
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	27-28

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	17
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	17
4.2.2 Age and sex?	☒	☐	☐	17

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.2.3 Country of origin?	☒	☐	☐	17-22
4.2.4 Disease/indication?	☒	☐	☐	17-22
4.2.5 Co-morbidity?	☒	☐	☐	17-22
4.2.6 Seasonality?	☐	☐	☒	-
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	17

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	22
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	22
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	22
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	22
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	22

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	22-23
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	22-23

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	23, 25-26, 27
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	-

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	19-21
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	18-21
8.1.3 Covariates?	☒	☐	☐	19-21
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	19-21
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	18-21
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	19-21
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	22
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	18-21
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	22
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	18-20

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	26-27

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	-
10.2 Is the choice of statistical techniques described?	☒	☐	☐	27-28
10.3 Are descriptive analyses included?	☒	☐	☐	27-28
10.4 Are stratified analyses included?	☒	☐	☐	27-28
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	27-28
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	-

Comments:

The protocol provides the outline of the data analysis. Detailed data analysis to address the study objective will be documented in a separate statistical analysis plan (SAP).

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☒	☐	-
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	27
11.3 Are methods of quality assurance described?	☒	☐	☐	28
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	28
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	-

Comments:

The management of missing data will be described in the statistical analysis plan

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	28-29
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	28-29
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	26-27
12.3 Does the protocol address other limitations?	☒	☐	☐	28-29

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	30
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	-
13.3 Have data protection requirements been described?	☒	☐	☐	30

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	11

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	31
15.2 Are plans described for disseminating study results externally, including publication?	☐	☒	☐	-

Comments:

Name of the main author of the protocol: Yun Gu

_____

Date: 20/3/2017

Signature: _____  _____