INFORM

Interferon beta Exposure in the 2nd and 3rd Trimester of Pregnancy - a Register-based Drug Utilisation Study in Finland and Sweden

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DISCLOSURES

- ***Meritxell Sabidó*** is an employee of the healthcare business of Merck KGaA, Darmstadt, Germany.
- ***Kiliana Suzart-Woischnik*** is an employee of Bayer AG.
- ***Nydjie Grimes*** is a former employee of Biogen Netherlands B.V.
- ***Lisa M Prach*** is an employee of Novartis Pharma AG.
- ***Katja M Hakkarainen*** and ***Liwei Zhao*** are the employees of the Global Database Studies, IQVIA, which performs commissioned pharmacoepidemiological studies for pharmaceutical companies.
- The study is co-sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945), Bayer, Biogen, and Novartis.

INTRODUCTION

- A previous post-authorisation safety study (EUPAS13054) [1,2] in Finland and Sweden showed no increased risk of adverse pregnancy outcomes after exposure to interferon beta (IFN β) 6 months before or during pregnancy in women with multiple sclerosis (MS).
- The European Medicines Agency (EMA) approved a label change in 2019: treatment of MS with IFN β may be considered during pregnancy, if clinically needed.
- Uncertainty still exists over whether later-stage pregnancy (2nd and/or 3rd trimester) exposure to IFN β may increase the risk of adverse pregnancy outcomes.
- The EMA has requested a cohort study to assess the risk of IFN β exposure in later-stage pregnancy. As a result, this Drug Utilisation Study (DUS) (EUPAS38736) [3] will be conducted to determine if the number of exposed pregnancies is adequate for a cohort study.

[1] Hakkarainen et al., 2020, Ther Adv Neurol Disord 13, 1756286420951072.
[2] EU PAS register: EPID Multiple Sclerosis Pregnancy study (EUPAS13054), ENCePP, 2021.
[3] EU PAS register: INFORM (EUPAS38736), ENCePP, 2021.

OBJECTIVES

The primary objectives of this DUS are to determine:

- The number of pregnancies in women with MS exposed to IFN β in later-stage pregnancy in Finland and Sweden by 2022.
- Whether the number of pregnancies available in Finland and Sweden by 2022 is adequate to conduct a cohort study to assess the outcomes of IFN β exposure in later-stage pregnancy.

METHODS

Study design

- Observational DUS using secondary data from the national registers in Finland and Sweden.
- Data on mothers and pregnancies collected over 26 years in Finland (1996-2022) and 17 years in Sweden (2005-2022).

Study population

- Women with MS defined by having any record of MS (ICD-10 [International Classification of Diseases,10th revision] code: G35) in the national registers before pregnancy.
- Pregnancies defined as pregnancies that ended with live birth, stillbirth, elective termination, spontaneous abortion, or ectopic pregnancy in women with MS during the study period.

METHODS

Exposure status

- **Exposed to IFN β only**: any dispensation records of IFN β in the 2nd and/or 3rd trimesters without dispensation records of other MS disease-modifying drugs from 6 months before pregnancy to the end of pregnancy.
- **Unexposed**: No dispensation records of IFN β or MS disease-modifying drugs from 6 months before pregnancy to the end of pregnancy.

Analysis

- Descriptive analyses of pregnancies exposed to only IFN β and the unexposed pregnancies in 1996-2022 (Finland) and 2005-2022 (Sweden).
- Study size simulation for a cohort study of adverse pregnancy outcomes: The 95% confidence intervals (CI) were simulated by iterations of three assumptions:
    1) Number of exposed pregnancies: 100, 200, and 300;
    2) Detectable relative risks (RR): 1.5, 2.0, 2.5, 3.0, and 5.0;
    3) Proportion of pregnancies exposed to IFN β during the later stages of pregnancy: 4.0%.
- The width of the CIs indicates the precision of the detectable RR: the narrower the CI, the higher the precision.

METHODS

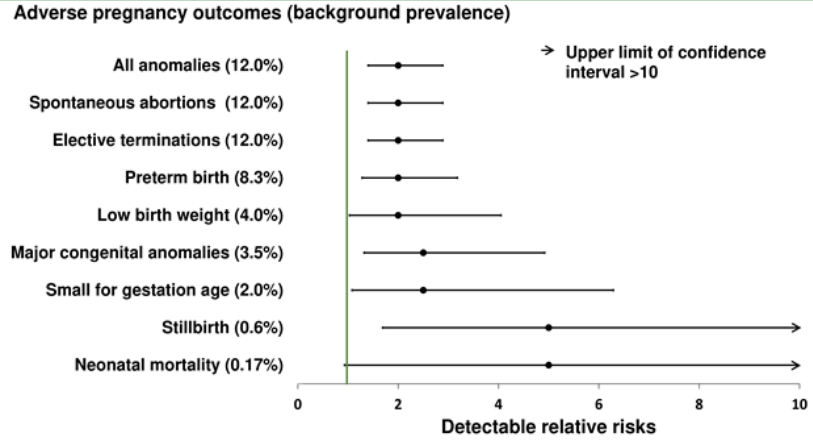

Figure 1. Minimum detectable relative risks of adverse pregnancy outcomes for 100 exposed later-stage pregnancies, with 95% confidence intervals.

- 100 exposed later-stage pregnancies are expected to be sufficient for detecting most of the adverse pregnancy outcomes with minimum detectable RRs of 2.00 or 2.50, without the 95% CIs overlapping 1.00 (**Figure 1**).
- With 100 exposed pregnancies, stillbirth and neonatal mortality can be detected at an RR of 5.0 or higher, but the precision is low.

RESULTS & DISCUSSION

- By 2014, 19 and 28 pregnancies were exposed to IFN β only during the 2nd and 3rd trimester, respectively, combined in Finland and Sweden.
- Based on the simulation, 100 exposed later-stage pregnancies are considered as the minimum number for conducting a cohort study for the adverse pregnancy outcomes.
- The required study size will be examined when the data of pregnancies (collected until the end of 2022) become available in 2024. In case of inadequate number of pregnancies, the DUS will be extended for an additional two years.
- It is unclear whether 100 pregnancies exposed to IFN β in the later stages of pregnancy will be available by the end of 2022.

RESULTS & DISCUSSION

- Additionally, other factors influence the interpretation of adequate precision of risk estimation, including:
  - Change of clinical practice of MS treatment during pregnancy
  - Any upcoming safety signals
  - Alternative therapies becoming available
- As opposed to traditional methods utilising and reporting study power, the study size simulation used precision-based statistics [4], which generated the CIs for the minimum detectable RRs. The CIs staying above 1.00 were of interest.

[4] Rothman, K. J. and Greenland, S, 2018, Epidemiology, 29 (5), pp. 599.

CONCLUSIONS

- A staggered approach is used to assess the sufficiency of data before evaluating the safety of IFN β exposure in the later-stage pregnancy among women with MS.
- As the first step, this DUS evaluates whether the accrued number of exposed pregnancies is adequate to conduct a cohort study.
- This DUS provides a strategy for studying pregnancy outcomes where achieving an adequate study size may be challenging for designing a cohort study.