Karolinska Institutet

Pharmacoepidemiological report for the non-interventional post-authorisation safety study ER-9430

Pregnancy outcomes in Multiple Sclerosis populations exposed and unexposed to interferon beta – a register-based study in the Nordic countries

Authors: Hanna Gyllensten, Rosa Juuti, Katja Hakkarainen, Pasi Korhonen

Study ID: ER-9430

Sponsor: Bayer AG

Biogen Netherlands B.V.

Merck Europe B.V.

Novartis Europharm Limited

Report version: 2.0

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PASS information

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Report version	2.0
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EU PAS register number	EUPAS13054
Active substances	interferon beta-1a (L03AB07), interferon beta-1b (L03AB08), peginterferon beta-1a (L03AB13)
Medicinal products	Avonex, Betaferon, Extavia, Plegridy, Rebif
Product references	Avonex: EU/1/97/033/002 – EU/1/97/033/006 Betaferon: EU/1/95/003/005- EU/1/95/003/012 Extavia: EU/1/08/454/008 - EU/1/08/454/014 Plegridy: EU/1/14/934/001 - EU/1/14/934/006 Rebif: EU/1/98/063/001 - EU/1/98/063/021
Procedure numbers	Avonex: EMEA/H/C/000102 Betaferon: EMEA/H/C/000081 Extavia: EMEA/H/C/000933 Plegridy: EMEA/H/C/002827 Rebif: EMEA/H/C/000136
Marketing authorisation holders	Avonex, Plegridy: Biogen Netherlands B.V. Betaferon: Bayer AG Extavia: Novartis Europharm Limited Rebif: Merck Europe B.V.
Joint PASS	Yes
Research question and objectives	The overall research question of this study is to determine if exposure to interferon beta (IFN-beta) before or during pregnancy has an adverse effect on pregnancy outcomes in patients with Multiple Sclerosis (MS) including, as requested by the Committee for the Medicinal Products for Human Use (CHMP), the identification of the prevalence of adverse pregnancy outcomes in women with MS unexposed to IFN-beta.
Countries of study	Finland and Sweden
Authors of the report	Hanna Gyllensten, Rosa Juuti, Katja Hakkarainen, Pasi Korhonen

Marketing authorization holders

Marketing authorisation holders	Bayer AG 51368 Leverkusen Germany Biogen Netherlands B.V. Prins Mauritslaan 13, 1171LP Badhoevedorp The Netherlands Merck Europe B.V. Gustav Mahlerplein 102 1082 MA Amsterdam The Netherlands Novartis Europharm Limited Vista Building, Elm Park, Merrion Road, Dublin 4, D04 A9N6 Ireland
MAH contact person	[redacted] Biogen Netherlands B.V. (on behalf of all MAHs)

Abstract

Title: Pregnancy outcomes in Multiple Sclerosis populations exposed and unexposed to interferon beta – a register-based study in the Nordic countries

Keywords: pregnancy, multiple sclerosis, interferon-beta, congenital malformations, stillbirths, spontaneous abortions, live births

Rationale and background: Multiple Sclerosis (MS) is the most common chronic neurologic disability-causing disease in young adult females in their childbearing ages. Little evidence is available regarding the association between exposure to interferon beta (IFN-beta) and adverse pregnancy outcomes.

Upon request from the European Medicines Agency (EMA), the four marketing authorisation holders of IFN-beta carried out a European IFN-beta Pregnancy Registry, now completed. In addition, the Committee for Medicinal Products for Human Use (CHMP) requested a study to estimate pregnancy outcomes in the MS population unexposed to IFN-beta.

Research question and objectives: The research questions this study addressed are: a) to determine if exposure to IFN-beta before or during pregnancy has an adverse effect on pregnancy outcomes in patients with MS, and b) to estimate the prevalence of pregnancy outcomes in women with MS unexposed to IFN-beta. The primary objectives are 1) to estimate the prevalence of serious adverse pregnancy outcomes and other pregnancy outcomes in Cohorts 1-4 (either exposed or unexposed to IFN-beta) and 2) to compare the prevalence of serious adverse pregnancy outcomes and other pregnancy outcomes between women with MS exposed to IFN-beta only (Cohort 1) and unexposed to any MS disease modifying drugs (MSDMDs) (Cohort 3) and between women with MS exposed to IFN-beta only (Cohort 1) and unexposed to IFN-beta regardless of exposure to other MSDMDs (Cohort 4). The cohort of women unexposed to any MSDMDs (Cohort 3) also provides background prevalence estimates for pregnancy outcomes in MS that will serve as a reference to the estimates obtained from the European IFN-beta Pregnancy Registry.

Study design: The present study is a population-based cohort study using register data from two Nordic countries: Finland (FIN) and Sweden (SWE). Norway (NOR) was originally planned to be included but it was proposed to be removed from the study due to major delays in the data permit processes for this study.

Population and setting: The target study population consists of Finnish and Swedish women diagnosed with MS who were pregnant during the study period from 1996 to 2014. The pregnancy could result in an elective termination (information not available in Sweden), spontaneous abortion, ectopic pregnancy, stillbirth, or live birth during the study period. A pregnancy was considered unexposed if exposure was stopped at least three months prior to the last menstrual period (LMP) (exceptions: six months for mitoxantrone and cladribine). MSDMDs that were considered aside from IFN beta-1a, IFN beta-1b and Peg IFN-beta-1a: human normal immunoglobulin (Anatomical Therapeutic Chemical (ATC) code, J06BA02), cyclophosphamide (L01AA01), methotrexate (L01BA01, L04AX03), cladribine (L01BB04), mitoxantrone (L01DB07), alemtuzumab (L01XC04), glatiramer acetate (L03AX13), leflunomide (L04AA13), natalizumab (L04AA23), fingolimod (L04AA27), teriflunomide (L04AA31), azathioprine (L04AX01), dimethyl fumarate (N07XX09).

2831 pregnancy outcome events (including pregnancies ending in elective termination, spontaneous abortion, ectopic pregnancy, stillbirth or live birth) were examined among 1983 pregnant women with MS in FIN and SWE.

Primary outcome variables: The primary outcome variables were serious adverse pregnancy outcomes (defined as a composite endpoint including elective terminations of pregnancy due to foetal anomaly (TOPFA), major congenital anomalies (MCA) in live births, or stillbirths), elective TOPFA or elective termination due to other reasons, MCA, and live birth.

Data sources: The study database was constructed through record linkage from health registers in FIN and SWE: Drugs and Pregnancy Project (DPP) (FIN), patient registers, MS registers, prescription registers, medical birth registers, Malformation Register (FIN), Causes of Death Register, and population registers.

Statistical methods: Log-binomial regression was used to analyse relative risks (RR) with 95% confidence intervals (CI) for the outcomes of interest. In addition, odds ratios (OR) from the models were reported, when the log-binomial model could not be fitted. The base model was adjusted for the following other covariates: country, year of pregnancy outcome, maternal age at LMP, number of previous pregnancies, any chronic diseases, and exposure to any teratogenic medications including steroids. Additional analyses were conducted to explore assumptions underlying the model definitions and the robustness of the results.

Results: The prevalence of serious adverse pregnancy outcomes among all pregnant women with MS was 3.2% (95% CI 2.6-4.0), of which most were MCAs in live births (prevalence 2.7%, 95% CI 2.0-3.4), followed by elective TOPFAs (0.7%, 95% CI 0.2-1.5) and stillbirths (0.5%, 95% CI 0.3-0.8). The prevalence of elective terminations for other reasons was 13.6% (95% CI 11.4-16.0), MCA (total; in live or stillbirths or elective terminations) 2.9% (95% CI 2.3-3.6), and live births 94.4% (95% CI 93.4-95.2).

The prevalence of MCAs in live births, and MCA (total) was lower among women with MS exposed to IFN-beta (Cohort 1), compared with those unexposed to IFN-beta (Cohort 3 and 4). An indication of a higher prevalence of elective termination for reasons other than foetal anomaly was detected among the INF-beta exposed. The prevalence of the other pregnancy outcomes was similar between the Cohorts. After adjusting for covariates, no evidence was found for an increased risk of the following adverse pregnancy outcomes after exposure to IFN-beta only (Cohort 1), compared with women with MS who were unexposed to IFN-beta (Cohort 3): serious adverse pregnancy outcomes (adjusted base model RR 0.55, 95% CI 0.31-0.96), elective TOPFAs (RR 1.94, 95% CI 0.35-10.85), MCAs in live births (RR 0.52, 95% CI 0.27-0.99), stillbirths (RR 0.41, 95% CI, 0.09-1.93), MCA (total) (RR 0.57, 95% CI 0.31-1.03), and non-live birth (OR 1.47, 95% CI 0.95-2.28). Similar results were obtained comparing Cohort 1 to Cohort 4, and when model definitions were varied. In contrast to the other outcomes, the risk of elective terminations for reasons other than foetal anomaly was increased (OR 1.71, 95% CI 1.06-2.78) among women with MS exposed to only IFN-beta (Cohorts 1), compared with those unexposed (Cohorts 3).

Conclusions: This study found no evidence of an increased risk of the composite outcome of serious adverse pregnancy outcomes, TOPFAs, MCAs, stillbirths, or non-live births after exposure to IFN-beta prior to or during pregnancy compared with women with MS that were unexposed to IFN-beta (regardless of exposure to other MSDMDs). However, the results suggest that women with MS exposed to IFN-beta may terminate their pregnancy for other reasons than fetal anomaly more often than those unexposed.

Marketing Authorization Holders: Avonex, Plegridy: Biogen Netherlands B.V.; Betaferon: Bayer AG; Extavia: Novartis Europharm Limited; Rebif: Merck Europe B.V.

Name and affiliation of principal investigator: Pasi Korhonen, PhD, Adjunct Professor of Biostatistics, EPID Research Oy, Metsänneidonkuja 12, FI-02130 Espoo, Finland.

The full study report will be published in the EU PAS Register® at latest one month after EMA endorsement of the full report.