Avonex and Plegridy Additional Analyses for Pregnancy outcomes in Multiple Sclerosis populations exposed and unexposed to interferon β – a register-based study in the Nordic countries

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

Authors: Henrik Svanström

Study ID: 2589353 (original study code ER-9430)

Sponsor: Biogen Netherlands B.V.

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PASS information

Title	Avonex and Plegridy Additional Analyses for Pregnancy outcomes in Multiple Sclerosis populations exposed and unexposed to interferon β – a register-based study in the Nordic countries
Study ID	2589353 (original study code ER-9430)
Report version	1.0
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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, Plegridy
Product references*	Avonex: EU/1/97/033/002 – EU/1/97/033/006 Plegridy: EU/1/14/934/001 - EU/1/14/934/006
Procedure numbers*	Avonex: EMEA/H/C/000102 Plegridy: EMEA/H/C/002827
Marketing authorisation holders*	Biogen Netherlands B.V.
Joint PASS*	Yes
Research question and objectives	The objective of this study was to investigate if exposure to interferon β before or during pregnancy has an adverse effect on pregnancy outcomes in patients with multiple sclerosis MS, using inverse-probability of treatment weighting based on propensity scores.
Countries of study	Finland and Sweden
Authors of the report	Henrik Svanström

**This abstract describes the additional analyses that were completed as part of the pharmacoepidemiological study "Pregnancy outcomes in Multiple Sclerosis populations exposed and unexposed to interferon β – a register-based study in the Nordic countries" (MS Preg, EUPAS13054). These analyses were explicitly requested by the Marketing Authorisation Holder of the medicinal products Avonex and Plegridy. All impacted stakeholders (research partners and MAHs) have been informed accordingly.*

Marketing authorization holders

Marketing authorisation holders	Biogen Netherlands B.V. Prins Mauritslaan 13, 1171LP Badhoevedorp The Netherlands
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Abstract

Title: Avonex and Plegridy Additional Analyses for Pregnancy outcomes in Multiple Sclerosis populations exposed and unexposed to interferon β – a register-based study in the Nordic countries

Keywords: pregnancy, multiple sclerosis, interferon-beta, congenital malformations, stillbirths, spontaneous abortions, live births, propensity score, inverse-probability of treatment weighting

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- β) and adverse pregnancy outcomes.

In the study report V1.0 *"Pregnancy outcomes in Multiple Sclerosis populations exposed and unexposed to interferon β – a register-based study in the Nordic countries"*, it was investigated whether exposure to IFN-β prior to or during pregnancy has an adverse effect on pregnancy outcomes in women with MS. Upon review of the report, the U.S. Food and Drug Administration raised concerns regarding the potential for unmeasured confounding and requested that the marketing authorisation holder provides additional analyses using propensity score methods.

Research question and objectives: To investigate whether exposure to IFN-β before or during pregnancy has an adverse effect on pregnancy outcomes in women with multiple sclerosis MS, using inverse-probability of treatment weighting (IPTW) based on propensity scores.

Study design: Population-based cohort study using register data from Finland and Sweden.

Population and setting: The study population consisted of Finnish and Swedish women diagnosed with MS who were pregnant during the study period (1996-2014).

Primary outcome variables: The primary outcomes were serious adverse pregnancy outcomes (composite endpoint including elective terminations of pregnancy due to foetal anomaly, major congenital anomalies [MCAs] in live births, and stillbirth), elective termination, MCAs, stillbirth, and non-live birth.

Data sources: The study database was constructed through record linkage of national register data in Finland and Sweden, including medical birth registers, patient registers, prescription registers, population registers, the Swedish MS register, the Finnish Drugs and Pregnancy Project, and the Finnish malformation register.

Statistical methods: Pregnancies exposed to IFN-β only were compared with, respectively, pregnancies not exposed to any MS disease modifying drugs (MSDMDs) and pregnancies not exposed to IFN-β but exposed to other MSDMDs. The analyses were conducted using log-binomial and logistic regression models, to estimate the relative risks and odds ratios associated with exposure to IFN-β. The results were adjusted using IPTW based on propensity scores.

Results: The study included a total of 797 pregnancies exposed to IFN-β only, 1647 not exposed to any MSDMDs, and 107 not exposed to IFN-β but exposed to other MSDMDs. In the IPTW-weighted analyses, exposure to IFN-β was not associated with a statistically significant increased risk of any of the outcomes, compared with non-exposure to any MSDMDs. Similarly, there was no statistically significant increased risk of any outcome associated with exposure to IFN-β, compared with exposure to other MSDMDs.

Conclusions: This study found no evidence of increased risk of adverse pregnancy outcomes associated with exposure to IFN-β. The results of these additional analyses using propensity score methods align with previous data showing no increased risk of adverse pregnancy outcomes after exposure to IFN-β prior to or during pregnancy.

Marketing Authorization Holder: Biogen Netherlands B.V

Name and affiliation of principal investigator: Pasi Korhonen