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

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Study ID: ER-9430

Sponsor: Bayer AG

Biogen Netherlands B.V.

Merck Europe B.V.

Novartis Europharm Limited

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PASS information

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

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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 terminations for reasons other than foetal anomaly was detected among the IFN-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.

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1 List of abbreviations

AGA	Average for gestational age
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CS	Caesarean section
DPP	Drugs and Pregnancy Project
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EUROCAT	European Surveillance of Congenital Anomalies
FASS	Swedish National Drug Formulary
FIN	Finland
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
ICD-10	International Classification of Diseases, 10th revision
IFN-beta	Interferon beta
ISPE	International Society for Pharmacoepidemiology
LBL	Low birth length
LBW	Low birth weight
LGA	Large for gestational age
LMP	Last menstrual period
MAH	Marketing authorization holder
MBR	Medical Birth Register
MCA	Major congenital anomaly
MS	Multiple Sclerosis
MSDMD	MS disease modifying drug
NOR	Norway
oMSDMD	Other MS disease modifying drug than interferon beta
OR	Odds ratio
PIN	Personal identification number
RR	Relative risk
SAP	Statistical Analysis Plan
SD	Standard deviation
SGA	Small for Gestational Age
SID	Study Identification Number

SWE	Sweden
THL	Finnish National Institute for Health and Welfare
TOPFA	Termination of pregnancy due to foetal anomaly

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We have reviewed this pharmacoepidemiological study report (ER-9430 Version 2.0, dated 07 June 2019) and confirm it by signing it.

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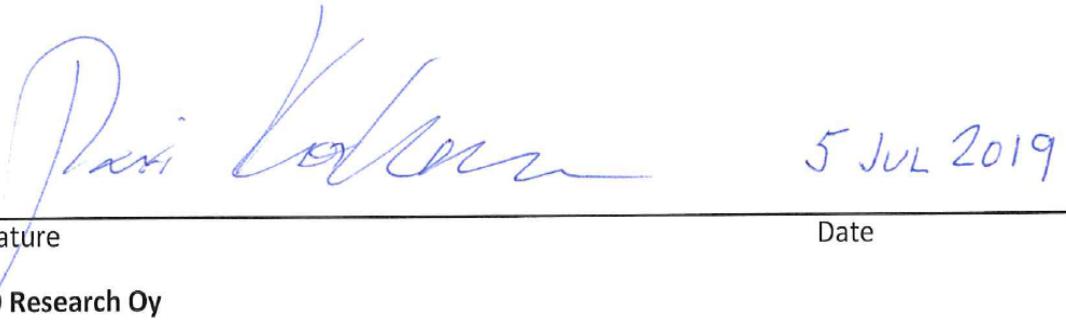

5 JUL 2019

Signature Date

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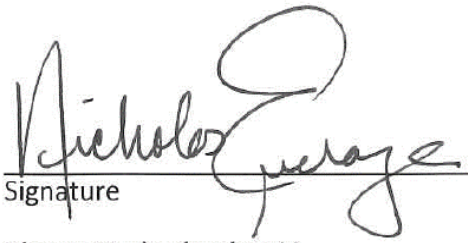

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Novartis Europharm Limited, Yvonne Geissbühler, PhD

Steering committee: Not applicable in this study.

4 Milestones

Milestone	Planned date	Actual date	Comments
Signing study agreement	n/a	5 December 2012[1]	
Power calculations completed based on feasibility study data	9 October 2013	16 October 2013	
Feasibility study report including study outline approved		25 September 2014	
CHMP feedback to study outline received		25 September 2014	
Study protocol ready		18 August 2015	
Study protocol submitted to EMA		27 February 2015	
EMA/CHMP approved the study protocol		1 April 2016	
Registration in the EU PAS register	31 October 2015[2]	15 April 2016	
Start of data permit process	15 May 2016[2]	3 May 2016	Dates of approval from each Ethics committee are listed in Annex 2 (Data permit approval information).
End of data permit process		25 August 2017	
Start of data collection	15 May 2016[2]	2 May 2016	In the protocol, this was defined as "Data permit applications sent". The actual date is the date from which data extraction started (according to Good Pharmacovigilance Practices (GVP) Module VIII for Post-authorisation safety studies).
End of data collection	15 April 2017[2]	25 January 2018	In the protocol, this was defined as "Data received". The actual date is the date from which the analytical dataset was completely available (according to GVP Module VIII).
Start of data analysis		1 November 2017	
End of data analysis		05 September 2018	
Final report of study results	15 April 2018[2]	01 October 2018	

[1] Effective date of the agreement

[2] In the protocol

5 Rationale and background

Multiple Sclerosis (MS) is the most common chronic neurologic disability causing disease in young adult females of childbearing age of 20-45 years [1]. Several studies suggest that MS itself is not associated with negative effect on foetal outcomes [2,3], but women with MS are confronted with questions relating to pregnancy and pharmacological MS therapy. It is commonly understood that MS relapses are fewer during pregnancy [3], but also that medication taken before conception or in early pregnancy could negatively affect the outcome of the pregnancy. Interferon beta (IFN-beta) was the first introduced MS disease modifying drug (MSDMD), after which other MSDMDs have entered the market, including glatiramer acetate, natalizumab, alemtuzumab, mitoxantrone (a cytostatic agent approved as an MS drug in 2006), teriflunomide and fingolimod [4,5]. Experience with exposure to IFN-beta during pregnancy has shown no clear association of adverse outcomes such as low birth weight (LBW), congenital anomaly or spontaneous abortion [6,7], and there was a paucity of systematic studies. According to the EU product information, initiation of treatment with IFN-beta during pregnancy is contraindicated.

The newer MSDMD substances could be potential alternative treatments during pregnancy, but little is known about them possibly increasing the risk of adverse pregnancy outcomes [7]. Current evidence, however, suggests that although more research is still needed, IFN-beta, glatiramer acetate, natalizumab, and alemtuzumab may not induce adverse pregnancy outcomes, while e.g. teriflunomide is contraindicated because of reproductive toxicity in humans or animal models. Adverse events in the infant following in utero exposure to MSDMD need to be also considered.

However, withdrawing MSDMD treatment that benefits the woman planning pregnancy or being pregnant is a concern as disease activity may return [7].

Thus, women with MS currently pregnant or planning pregnancy and their treating physician need to balance the possible increase in MS disease activity before or during pregnancy and the potential risks of adverse pregnancy outcomes associated with the use of MSDMDs [3].

The European Medicines Agency (EMA) requested the four marketing authorization holders of IFN-beta to initiate a European IFN-beta Pregnancy Registry, and this has now been completed. In addition, the Committee for Medicinal Products for Human Use (CHMP) requested a study to enable identification of pregnancy outcomes in the MS population unexposed to IFN-beta that will serve as a reference to the estimates obtained from the European register.

This pharmacoepidemiological study addresses the request from the CHMP, to identify pregnancy outcomes in the MS population unexposed to IFN-beta for reference to the separately ongoing European IFN-beta Pregnancy Registry sponsored by the four European Marketing authorization holders (MAH) of IFN-beta. The study does not, however, include a direct comparison of results to those from the European IFN-beta Pregnancy Registry. This is because available information on disease severity and other confounding factors differs between the health registers and the European IFN-β Pregnancy Registry and in some cases is missing, such that the rates cannot be adjusted to be comparable. In addition, the pregnancy cases included in the Nordic health registers are population-wide and are not based on a sample, whereas the European IFN-β Pregnancy Registry is based on spontaneous reports.

6 Research questions and objectives

The overall research question of this study is to determine if exposure to IFN-beta before or during pregnancy has an adverse effect on pregnancy outcomes in patients with MS. In addition, as requested by the CHMP, the prevalence of adverse pregnancy outcomes in women with MS unexposed to IFN-beta is studied. The different study cohorts (defined in section 9.3.3) from this study will provide background prevalence information and context for pregnancy outcomes in MS for the European IFN-beta Pregnancy Registry.

6.1 Primary objectives

1. To estimate the prevalence of the following pregnancy outcomes in the four study Cohorts 1 – 4, as further detailed below in sections 6.1 (2.) and 6.2:
   - Serious adverse pregnancy outcome defined as a composite endpoint including
     - elective termination of pregnancy due to foetal anomaly (TOPFA) (assessment not possible in SWE as no register available)
     - major congenital anomaly (MCA) in live birth or
     - stillbirth
   - Elective termination for other reasons than TOPFA (assessment not possible in SWE as no register available)
   - MCA (total) (in live or stillbirths or elective terminations)
   - Live birth
2. To compare the prevalence of each of the outcomes in objective 1 between:
   a. Women with MS exposed to IFN-beta only (Cohort 1) vs. unexposed to any MSDMDs (Cohort 3)

      and

   b. Women with MS exposed to IFN-beta only (Cohort 1) vs. unexposed to IFN-beta regardless of exposure to other MSDMDs (Cohort 4)

6.2 Secondary objectives

3. To compare the prevalence of the following pregnancy outcomes between women with MS exposed to IFN-beta regardless of exposure to other MSDMDs (Cohort 2) vs. unexposed to any MSDMDs (Cohort 3):
   - Serious adverse pregnancy outcome
     - elective TOPFA (not possible in SWE)
     - MCA in live birth or
     - stillbirth
   - Elective termination for other reasons than TOPFA (not possible in SWE)
   - MCA (total) (in live or stillbirths or elective terminations)
   - Live birth
4. To estimate the prevalence of a) ectopic pregnancies and b) spontaneous abortions in the study Cohorts 1, 2, 3 and 4 and to compare the prevalence of them separately between:
   a. Women with MS exposed to IFN-beta only (Cohort 1) vs. unexposed to any MSDMDs (Cohort 3)

b. Women with MS exposed to IFN-beta only (Cohort 1) vs. unexposed to IFN-beta regardless of exposure to other MSDMDs (Cohort 4), and

c. Women with MS exposed to IFN-beta regardless of exposure to other MSDMDs (Cohort 2) vs. unexposed to any MSDMDs (Cohort 3).

5. To estimate the prevalence of the pregnancy outcomes (i.e. serious adverse pregnancy outcomes, elective TOPFAs (not possible in SWE), stillbirths, live births and MCAs) in Cohorts 1 – 4 stratified by country, year of pregnancy outcome, maternal age at last menstrual period (LMP), chronic diseases (list of diagnoses in Annex 5), exposure to any teratogenic medications including steroids, time since MS diagnosis, duration of MS treatment, gestational age and weight of the newborn as relevant for specific pregnancy outcomes.

6.3 Exploratory objectives

6. To describe the following additional characteristics about pregnancy in Cohorts 1 – 4:
   - Mode of delivery (Caesarean section (CS)/vaginal)
   - Preterm birth
   - Birth weight and LBW
   - Birth length and low birth length (LBL), according to country-specific standards
   - Birth weight (small for gestational age (SGA) and large for gestational age (LGA)), length and head circumference when compared to average for gestational age (AGA)
   - Sex of the newborn
   - Head circumference and low head circumference, according to country-specific standards
   - Apgar score (at 1 and 5 minutes)
   - Defect cases (3 or more minor congenital anomalies)

7. To estimate the prevalence of
   - MCA (total) (in live or stillbirths or elective terminations),
   - Ectopic pregnancies,
   - Spontaneous abortions, and
   - Stillbirths

   in the general population without MS diagnosis (Cohort 6) in FIN and SWE for each pregnancy outcome separately as available in each country. The observed numbers of pregnancy outcomes in Cohort 3, matched for age and country, are compared with the expected numbers through indirect standardisation (using standardised prevalence ratios) under the assumption that Cohort 3 had experienced the same prevalence as women in the general population without MS diagnosis (Cohort 6).

7 Amendments and updates

7.1 Study protocol

No.	Date	Section of study protocol	Amendment or update	Reason
0	18 February 2015 (Original protocol)			
1	18 August 2015	Several	Update	Comments received during EMA review process.

A single study protocol was used across the countries. The following changes were made to protocol version 2.0 during the EMA review process (see section 5 in the Study protocol version 2.0; the presented section numbers refer to the sections of the protocol):

- Due to more data becoming available during the protocol development, end of the study period has been extended to 31 Dec 2014 in each country. Estimated cohort sizes and power calculations have been updated accordingly.
    - Dimethyl fumarate (N07XX09) has been added to MSDMD list and removed from study limitations, as it gained market authorisation in EU on 30 January 2014.
    - Peginterferon beta-1a (L03AB13) has been added to MSDMD list as it gained market authorisation in EU on 18 July 2014.

- Potential confounding factors
    - Maternal age has been defined at LMP also for spontaneous abortion and ectopic pregnancy. Missing information with regards to maternal age at LMP in pregnancies ending in spontaneous abortion or ectopic pregnancy has been described in Section 9.9.

- Missing data (section 9.7.7)
    - Robustness of the variable selection procedure (section 9.7.3) to missing data was tested as part of the sensitivity analyses.

7.2 Study report

No.	Date	Section of study report	Amendment or update	Reason
1	8 April 2019 (to study report version 2.0)	Abstract 9 Results 10 Discussion 11 Conclusion	Quality deviation 1: correction to estimate odd ratio (OR) of elective termination for other reasons than foetal anomaly, instead of all elective terminations (previously the OR was mistakenly estimated for all elective terminations), influencing all OR for the outcome while prevalence remained unaffected by the quality deviation.	Quality deviation 1
2	8 April 2019 (to study	Abstract 9 Results 10 Discussion	Quality deviation 2: correction to exclude Swedish pregnancies outside the study period (pregnancies before 1 July 2005),	Quality deviation 2

	report version 2.0)	11 Conclusion	influencing descriptive prevalence and prevalence comparison for all outcomes with Swedish data.	
3	8 April 2019 (to study report version 2.0)	Abstract 8.9.5 Changes after adopting the protocol 9 Results 10 Discussion 11 Conclusion	Amending the definition of maternal age in Finnish data closer to the protocol definition, as defined in 8.9.5 Changes after adopting the protocol.	Amending maternal age
4	8 April 2019 (to study report version 2.0)	Abstract 8.9.5 Changes after adopting the protocol 9 Results 10 Discussion 11 Conclusion	Improving the model fits for the adjusted base models and the further adjusted models, as defined in 8.9.5 Changes after adopting the protocol.	Improving the model fits
5	8 April 2019 (to study report version 2.0)	Abstract 8.9.5 Changes after adopting the protocol 9 Results 10 Discussion 11 Conclusion	Requiring at minimum 6 months of drug register data before LMP, as defined in 8.9.5 Changes after adopting the protocol.	Requiring at minimum 6 months of drug register data before LMP

8 Research methods

8.1 Study design

This study is a population-based cohort study using register data from two Nordic countries: Finland and Sweden.

8.2 Setting

8.2.1 Study periods

- FIN: 1 January 1996 – 31 December 2014
- SWE: 1 July 2005 – 31 December 2014

8.2.2 Cohort entry date and follow-up

Cohort entry date was the date of LMP. This date was considered as the beginning of pregnancy. LMP was available from the Medical Birth Register (MBR) in each country if pregnancy was identified as live birth, stillbirth or elective termination. For spontaneous abortions, LMP was defined to be 9 weeks [8] (63 days) before the date of diagnosis. For ectopic pregnancies, LMP was defined to be 8 weeks [8] (56 days) before the date of diagnosis.

Pregnancies were followed until pregnancy outcome. Live births were further followed-up for a maximum of 12 months for registration of MCAs. Follow-up for the MCA varies between the countries (12 months in FIN and 6 months in SWE). These lag times were considered in the study design phase by allowing enough follow-up time for the MCA before data collection. Because the registers do the follow-up for the MCA, this does not need to be considered when managing or analysing the data.

8.3 Subjects

The main study population consisted of women with MS with reported pregnancy outcome, as per study protocol, in FIN or SWE during the study period. The main study population was identified according to the inclusion criteria below. In addition to the main study population, general birth statistics among all women in FIN and SWE was used as a reference for indirect comparisons.

8.3.1 Inclusion criteria

1. Women with MS, recorded during the study period as follows:
   - FIN: MS diagnosis (International Classification of Diseases, 10th revision (ICD-10) G35) in the Patient Register or special reimbursement code 109 for MS in the Reimbursement Register
   - SWE: MS diagnosis in the Patient Register (ICD-10 G35) or the Swedish MS Register
2. Pregnancy with a recorded outcome during the study period and after indication of MS, identified as follows:
   - Elective termination of pregnancy – the Medical Birth Register (the term elective termination is used in this study report, instead of induced abortion)
   - Spontaneous abortion – ICD-10 O03 diagnosis in the Patient Register
   - Ectopic pregnancy – ICD-10 O00 diagnosis in the Patient Register
   - Live birth or stillbirth – the Medical Birth Register

8.3.2 Exclusion criteria

None.

8.3.3 Study Cohorts

The pregnancy outcomes were compared between study cohorts that were formed from the main study population of all pregnant women with MS. The study cohorts differed by exposure to IFN-beta and to other MS disease modifying drugs (MSDMDs) (Table 1).

Cohort 1 consisted of pregnant MS patients with exposure to exclusively IFN-beta (no exposure to other MS disease modifying drug than IFN-beta (oMSDMD); Cohort 1 [IFN-beta(+)/oMSDMD(-)]), while Cohort 2 consisted of those with IFN-beta exposure regardless of exposure to other MSDMDs (Cohort 2 [IFN-beta(+)/oMSDMD(+/-)]). The Cohort 3 consisted of pregnant MS patients without exposure to any MSDMDs (Cohort 3 [IFN-beta(-)/oMSDMD(-)]). The Cohort 4 represented pregnant MS patients with no exposure to IFN-beta regardless of exposure to other MSDMDs (Cohort 4 [IFN-beta(-)/oMSDMD(+/-)]), and Cohort 5 those with no exposure to IFN-beta and exposure to exclusively other MSDMDs (Cohort 5 [IFN-beta(-)/oMSDMD(+)]). (+)]). Cohort 6 consisted of women from the general population, without MS diagnosis.

As presented in Table 1, the Cohort 2 [IFN-beta(+)/oMSDMD(+/-)] represented the total of all pregnant MS patients exposed to IFN-beta, and thus included also the Cohort 1 [IFN-beta(+)/oMSDMD(-)]. Similarly, Cohort 4 [IFN-beta(-)/oMSDMD(+/-)] represented the total of all pregnant MS patients unexposed to IFN-beta, and thus included also the Cohort 3 [IFN-beta(-)/oMSDMD(-)].

Table 1 Study Cohorts.

Exposure status by IFN-beta and other MSDMD	**Main study population: All pregnant women with MS**			**Women without MS (only summary statistics used)**
	Unexposed to other MSDMD	**Exposed to other MSDMD**	**Total**	
Exposed to IFN-beta	**Cohort 1: IFN-beta(+)/ oMSDMD(-)** Exposure to IFN-beta only	Exposed to both IFN-beta and other MSDMD (group not studied)	**Cohort 2: IFN-beta(+)/ oMSDMD(+/-)** All patients with IFN-beta exposure regardless of exposure to other MSDMDs	NA
Unexposed to IFN-beta	**Cohort 3: IFN-beta(-)/ oMSDMD(-)** No exposure to any MSDMDs	**Cohort 5** [1] **IFN-beta(-)/ oMSDMD(+)** Only other MSDMD exposure excluding IFN-beta or glatiramer acetate (Copaxone®) or dimethyl fumarate (Tecfidera®) (for sensitivity analysis only)	**Cohort 4: IFN-beta(-)/ oMSDMD(+/-)** All patients with no IFN-beta exposure regardless of exposure to other MSDMDs	**Cohort 6: MS(-)** Women from the general population without MS diagnosis

IFN-beta, interferon beta; MCA, major congenital anomalies; MS, multiple sclerosis; MSDMD, multiple sclerosis disease modifying drug; NA, not applicable; oMSDMD, other multiple sclerosis disease modifying drug than interferon beta.
[1] Cohort 5 was created to represent a Cohort of patients who have more aggressive MS, explored in the sensitivity analyses, and thus excludes patients on first line therapies.

8.4 Variables

Variables used for defining the population are presented in the Statistical Analysis Plan (SAP; Annex 3, Table 2), together with definitions for these variables. Furthermore, the variable for describing the use of category C or D teratogenic medications was divided into two separate variables for category C and D, respectively (updated list of medications provided in Annex 6 of this report; not listed in the SAP). The categorical variables describing time since MS started and since the start of MSDMD treatment were defined in years, while continuous variables for these characteristics were defined in number of weeks since each event. Variables used for the characterisation of pregnancy events are defined in the SAP (Annex 3, Table 3). In addition, full-term pregnancy was defined as birth at gestational week ≥37 (see also section 8.9.5). Variables used for defining the drug exposure are detailed in the SAP (Annex 3, Table 4) and a list of MSDMDs is provided in Table 2. Definitions of the outcome variables are presented in the Table 3 in this report and other outcome variables at birth are detailed in the SAP (Annex 3, Table 5).

Table 2 Study MSDMDs

MSDMDs	ATC code(s)	Notes
IFN-beta products		
IFN-beta natural	L03AB02	Not included as MSDMD in Cohort 5 [1]
IFN-beta-1a	L03AB07	Not included as MSDMD in Cohort 5 [1]
IFN-beta-1b	L03AB08	Not included as MSDMD in Cohort 5 [1]
Peg IFN-beta-1a	L03AB13	Not included as MSDMD in Cohort 5 [1]
Other MSDMDs than IFN-beta products		
Intravenous immunoglobulin	J06BA02	
Cyclophosphamide	L01AA01	
Methotrexate	L01BA01, L04AX03	
Cladribine	L01BB04	Uses MS Pregnancy extended exposure period
Mitoxantrone	L01DB07	Uses MS Pregnancy extended exposure period
Alemtuzumab	L01XC04	
Glatiramer acetate	L03AX13	Not included as MSDMD in Cohort 5 [1]
Leflunomide	L04AA13	
Natalizumab	L04AA23	
Fingolimod	L04AA27	
Teriflunomide	L04AA31	
Azathioprine	L04AX01	
Dimethyl fumarate	N07XX09	Not included as MSDMD in Cohort 5 [1]

ATC, Anatomical Therapeutic Chemical; IFN-beta, interferon beta; MS, multiple sclerosis; MSDMD, multiple sclerosis disease modifying drug,

[1] Cohort 5 was created to represent a Cohort of patients who have more aggressive MS, explored in the sensitivity analyses, and thus excludes patients on first line therapies.

Table 3 Definitions of the outcome variables, including pregnancy outcome and other outcome variables at birth.

Outcome variable	Description / definition
Serious adverse pregnancy outcome	Categorical: 1, 0; Composite endpoint including: • Elective TOPFA (not included in Sweden) • Live birth with MCA • Stillbirth Has value 1 (=Yes) if any of the above pregnancy outcomes occurred and 0 (=No) otherwise.
Elective termination due to fetal anomaly (TOPFA)	Categorical: 1, 0; Has value 1 (=Yes) if pregnancy outcome was elective TOPFA and 0 (=No) otherwise.
Elective termination for other reasons	Categorical: 1, 0; Has value 1 (=Yes) if pregnancy outcome was elective termination without foetal defect or with an unknown reason and 0 (=No) otherwise.
Stillbirth	Categorical: 1, 0; Has value 1 (=Yes) if pregnancy outcome was stillbirth (similarly for sub-events) and 0 (=No) otherwise.
Live birth	Categorical: 1, 0; Has value 1 (=Yes) if pregnancy outcome was live birth and 0 (=No) otherwise.
MCA (total) (in live or stillbirths or elective terminations)	Categorical: 1, 0; Has value 1 (=Yes) if pregnancy outcome was MCA and 0 (=No) otherwise
MCA in live births	Categorical: 1, 0; Has value 1 (=Yes) if pregnancy outcome was MCA in live birth and 0 (=No) otherwise.
Ectopic pregnancy	ICD-10 code O00 Categorical: 1, 0; Has value 1 (=Yes) if pregnancy outcome was ectopic pregnancy and 0 (=No) otherwise.
Spontaneous abortion	ICD-10 code O03 Categorical: 1, 0; Has value 1 (=Yes) if pregnancy outcome was spontaneous abortion and 0 (=No) otherwise.

Ectopic pregnancies and spontaneous abortions were recorded in the same register: A woman could have several visits due to one event in a relatively short time period and the diagnosis could change from spontaneous abortion to ectopic pregnancy (or vice versa) during the period. This is because it may initially be difficult to know if e.g., bleeding results from miscarriage or ectopic pregnancy, and there may be a need for additional tests before the exact nature of the event may be known. Thus, visits within 3 months after the first visit were combined, the first visit defined the event date but the last diagnosis identified during the 3-month period determined the diagnosis for the event, which were used for the analyses However, in indirect comparisons all visits were included (max 1 record/day), with the registered diagnosis. Thus, the total number of events and pregnancies were higher in the indirect comparisons than in the descriptive tables and analyses.

8.5 Data sources and measurement

All Nordic countries being studied have well developed population-wide register systems with tens of years of longitudinal follow-up data. The persons are identified in the registers with a unique personal identification number (PIN) and thus the records can be linked for research purposes at the individual level between the various registers.

In all of the Nordic countries, births are covered by three different databases [9]. First, all live births are registered to the central population registers, which are the basis for vital statistics. Second, all deaths of live born children are registered in the causes of death registers, maintained by statistical or health authorities.

Third, all Nordic countries have introduced a separate MBR for more detailed collection of parturitions, deliveries and newborns.

The present study was based on data on births complemented with data obtained from the patient registers, the prescription registers and the population registers. Data sources used in the study in relation to outcomes, exposures and population definition by country are listed in the SAP (Annex 3, Table 1).

Study permits were applied for by EPID Research in FIN and together with academic collaborators in SWE. After being granted the permits, EPID Research and the collaborators requested data from the data holders, who identified the study population according to the inclusion criteria. The original data holders used the unique PINs to extract all the relevant data for the study population. The data holders created a unique dummy study identification number (SID) for each PIN. The researchers received data without direct identifiers, as the PINs had been replaced by SIDs, and these were used for data linkage at the patient level.

The Nordic national health registers have population-wide coverages within each country, and the overall quality of the registers is high. The large size of the health register databases of these countries enable the precise estimates of a number of different health indicators, and combined together, they also enable evaluation of rare exposures and outcomes. Use of PINs increases the validity of the information, and the register-based method helps to avoid certain biases, such as recall or reporting bias.

8.6 Bias

This cohort study aimed towards describing pregnancy outcomes after exposure to MS treatment before and during pregnancy. However, any effects identified in observational studies are prone to different types of bias and should not be interpreted as causal effects. There may be other factors that differ between the studied Cohorts and that introduce bias to the outcomes assessment, and some factors that also have an impact on the probability of following a specific treatment strategy (introducing confounding).

The study was conducted based on register data from two Nordic countries with known high coverage in national registers. However, there is variation in the coverage of registers included in the analyses, and register-based studies are influenced by how the data are collected into each register. Such registers are not usually designed for research but are collected for administrative or clinical purposes.

8.6.1 Selection bias

8.6.1.1 Elective terminations under-represented in the SWE population

The Swedish registers do not include systematically collected information on elective terminations on individual-level. Thus, the SWE study population (cohorts 1-5) does not include pregnancy events that ended in an elective termination.

In estimating the prevalence of MCA (total), the denominator included the number of elective terminations, together with the number of births (still or live).

To counterbalance the unavailability of data on elective terminations in SWE, the prevalence of MCA (total) was calculated exclusively using FIN data. Thereafter, the prevalence of MCAs was re-calculated to include MCAs identified from SWE, however excluding the elective TOPFAs identified from FIN.

8.6.1.2 Detection of stillbirths, by country

In both Swedish and Finnish data, information on stillbirths was available from gestational week 22 onwards throughout the study period. It has also been reported that there is underreporting of stillbirths (1-2%) in the Swedish Medical Birth Register [10]. As this could results in a lower prevalence of stillbirths and a smaller denominator in SWE, country-specific prevalence rates were estimated for outcomes, where stillbirths were included as numerator, or denominator.

8.6.2 Information bias (misclassification bias)

8.6.2.1 Time-related exposure misclassification, for detecting MCAs

Of the pregnancy outcomes, the risk of MCAs can generally be increased only if teratogenic exposure occurs by the end of the first trimester. In the main analyses, women with MS were assigned to the cohorts based on exposure to the MSDMD study drugs within six months prior to LMP (nine months for mitoxantrone and cladribine) or during the pregnancy, when the possible differences in the risk of MCA between the cohorts may be diluted by the presence of the exposures that took place only in the second and third trimesters. To explore the influence of this possible bias to the results, the ***sensitivity analysis 3*** on the risk of MCA between the cohorts restricted the exposure period to the end of the first trimester.

8.6.2.2 Misclassification of women with MS exposed to hospital administrated MSDMDs as unexposed to MSDMDs

Information on patient-level data on MSDMD used in hospitals and other institutions is not included in the data from prescription databases in FIN or SWE [11]. This creates observation gaps and therefore there may be some cases classified as MSDMD unexposed, who are actually treated in hospitals. Some drugs are dispensed only through outpatient clinics (for example, antiretroviral drugs), and some new drug groups including some biological drugs (for example, infliximab) are mainly administered in hospitals, and are therefore not usually included in the prescription databases. Nonetheless, in FIN information on patients who have a special reimbursement for i.e. intramuscular injection, and who want to be injected by a professional instead of themselves, is included in the prescription register as the patient buys the medicine from pharmacy (personal communication with Leena Saastamoinen[1], 5 January 2015). In similar situation with infusion, the medicine is always obtained from the hospital pharmacy, and therefore information is not included in the Prescription Register.

The influence of this limitation on the risk of pregnancy outcomes was investigated in the ***sensitivity analysis 6***, where women with intravenous medical treatment administered in hospital were considered as exposed to oMSDMDs.

8.6.2.3 Misclassification of women with MS exposed to rituximab as women with MS unexposed to MSDMDs

During the later years of this study, a newer MSDMD rituximab (Mabthera®) has become a common MS treatment in SWE [12] albeit prescribed off-label since MS is not an approved indication for rituximab and has not been studied in approved international preclinical or clinical trials of MS. Consequently, a majority of Finnish neurologists do not prescribe rituximab for MS and without a few exceptions [13] it has not been used in MS in most Finnish MS clinics (personal communication with Auli Verkkoniemi-Ahola[2], 13 May 2018). In SWE, rituximab is generally distributed and administered through outpatient clinics and thus recorded if the person is registered in the MS Register but not registered in the Swedish Prescribed Drug Register. Although the MS Register is reported to cover over 80% of all patients with MS in SWE [14], and should thus include most MS patients exposed to rituximab, rituximab was not considered in the design phase of this study, and was not included in the study protocol nor the register data requested for this study. Thus, women with MS exposed to rituximab, who were not exposed to other MSDMDs, were in the current study classified as women with MS unexposed to any MSDMDs (Cohort 3). This possible misclassification was investigated in the ***post hoc sensitivity analyses on rituximab users***.

[1]Leena Saastamoinen works as researcher at the Social Insurance Institute (Kela, Finland) and has been consulted as an expert for this study.

[2]Auli Verkkoniemi-Ahola is a Finnish neurologist and has acted as a clinical expert in this study.

8.6.2.4 Follow-up period to detect MCA

For detecting MCAs, the follow-up periods in the national registers vary between Finland and Sweden: In FIN the follow-up period for the registration of MCA is 12 months after birth, and in SWE 6 months. To address this, analyses were stratified by country.

8.6.3 Confounding

8.6.3.1 Confounders in the adjusted base model and further adjusted model – Missingness

Available information on disease severity and other confounding factors differs between the health registers and the European IFN-beta Pregnancy Registry, and in some cases is missing, hence the rates cannot be adjusted to be comparable. However, the following confounding factors and effect modifiers were considered in the analyses according to availability and available time period from each register source: any chronic diseases, exposure to any teratogenic medications including steroids, country of residence of the mother, university hospital district, maternal age at LMP, year of pregnancy outcome, pre-pregnancy weight, pre-pregnancy body mass index (BMI), number of previous pregnancies, time since MS diagnosis, duration of MS treatment, number of previous abortions, smoking status during pregnancy and number of foetuses in the pregnancy (single or multiple).

However, because some of the covariates included had partial missing data, the ***sensitivity analysis 8*** investigated whether the results on the risk of the pregnancy outcomes were robust when missing variables in the regression models were imputed using multiple imputations.

8.6.3.2 Differing study periods

The study periods differed in the countries, depending on data availability, which may have influenced both the prevalence and risk of the studied pregnancy outcomes. To account for possible developments in e.g., diagnostic criteria and treatment patterns over time, the influence of the different study periods was investigated in the ***sensitivity analysis 4***, where the study period was limited to 2005-2014 when data from all countries were available.

8.6.3.3 Residual confounding by other drug exposures

In this study, the MSDMDs of interest include both drugs that have MS in their label as indication as well as drugs that do not. This off-label use includes the following medicinal products: human normal immunoglobulin, methotrexate, azathioprine, cyclophosphamide and leflunomide. Many of these drugs used as off-label for treatment of MS are cytostatic agents and have been e.g., in FIN only used in the rare occasions when there are no other treatment options. These drugs may have very long-term effects (personal communication with clinical expert, Auli Verkkoniemi-Ahola, 13 May 2018). Thus, ***an additional post hoc sensitivity analysis*** was run to investigate whether removing users of these off-label drugs from the analysis in this study impacts the prevalence of adverse pregnancy outcomes.

8.7 Study size

Based on a feasibility study it was estimated that a total of 1671 MS pregnancies would be available for the current study from FIN, SWE and NOR*. This total sample size was estimated as follows: In FIN 433 MS pregnancies were observed between 1 January 1996 and 31 December 2010 of which 86 were in 2010. For the actual study, data from FIN from 1 January 2011 to 31 December 2014 was also used, and therefore the total number of available MS pregnancies was estimated to be 777 (433 + 4x86, where 86 is the number of MS pregnancies in 2010). In SWE, 329 MS pregnancies were observed during the time period 1 July 2005 – 31 December 2011 (329/6.5 years = 51 per year). Because the study period in SWE was from 1 January 2005 to 31 December 2014, the estimated number of MS pregnancies in SWE was 482 (329 + 3x1). In NOR, 330 MS births were expected to occur in the time period 1 January 2004 – 31 December 2014, which was

estimated to be 80% of all MS pregnancies excluding terminations of pregnancies. The number of MS pregnancies available in the study from NOR was thus estimated to be 412 (330/0.8). The total number of 1671 MS pregnancies available for the study was obtained as the sum of these estimated numbers (777 + 482 + 412).

From the 433 MS pregnancies in FIN, 102 (24%) and 331 (76%) were identified as exposed and unexposed to any MSDMD, respectively (in SWE, the proportion of unexposed to any MSDMDs was 77%). Furthermore, of the 433 MS pregnancies in FIN, 95 (22%) and 338 (78%) were identified as exposed and unexposed to IFN-beta regardless of exposure to other MSDMDs, respectively (personal communication with Anna-Maria Lahesmaa-Korpinen[3], Finnish National Institute for Health and Welfare (THL), 15 May 2014). Based on these numbers, it was estimated that 76% (= 331/433) of all MS pregnancies would be unexposed to any MSDMD and 78% (= 338/433) of all MS pregnancies would be unexposed to IFN-beta (regardless of exposure to other MSDMDs). Based on a systematic review of MSDMD usage[15], it was estimated that 80% of those identified as exposed to IFN-beta would not be using other MSDMDs (368*0.8 = 294). The study population size by exposure to IFN-beta based on these assumptions is presented in the study protocol.

The estimated background prevalence for the composite endpoint of serious adverse pregnancy outcome, consisting of TOPFAs, live births with MCA and all stillbirths, was 6.5% (personal communication with Anna-Maria Lahesmaa-Korpinen, THL, 15 May 2014) and 7.3% (= 24/331, result in the feasibility study report) in women with MS unexposed to IFN-beta (regardless of exposure to other MSDMDs) and unexposed to any MSDMD, respectively. Because these numbers best correspond to the study setting, they were taken as the most relevant baseline prevalence of serious adverse pregnancy outcomes in the sample size calculations. Lower outcome prevalence was investigated to test how sensitive the findings of minimum detectable effect sizes are to these assumptions. For comparison, in the Finnish feasibility study the prevalence of serious adverse outcomes was 3.7% = (38384/1031778) among all women, and according to European Surveillance of Congenital Anomalies (EUROCAT) 2015, the prevalence of malformation outcome among all women in the EU is 2.6%. The anticipated sample sizes in study Cohorts 1-6 were:

- Cohort 1: 294 (80% of 368) for MS pregnancies exposed only to IFN-beta.
- Cohort 2: 368 (22% of 1671) for MS pregnancies exposed to IFN-beta regardless of exposure to other MSDMDs.
- Cohort 3: 1270 (76% of 1671) for MS pregnancies unexposed to any MSDMD.
- Cohort 4: 1303 (78% of 1671) for MS pregnancies unexposed to IFN-beta.
- Cohort 5: 33 (Cohort 4 size – Cohort 3 size = 1303 – 1270 = 33) for MS pregnancies exposed to MSDMDs except IFN-beta or glatiramer acetate (Copaxone®) or dimethyl fumarate (Tecfidera®).
- Cohort 6: Approximately 2.9 Million pregnancies for women from the general population in FIN, SWE and NOR without MS diagnosis based on the feasibility study (cf. Annex 1).

*Norway was decided to be removed from the study due to major delays in the data permit processes for this study.

With the original sample sizes and baseline outcome prevalence given above, the minimum detectable effect size between the MS women exposed to IFN-beta only (Cohort 1) vs. MS women unexposed to any MSDMDs (Cohort 3) was 1.72 in terms of relative risk (RR) using 80% power and a 5% two-sided significance level. Based on the observed cohort sizes in Finland and Sweden, post-hoc power calculations for the comparison of Cohorts 1 and 3 were also performed. With observed background prevalence of 3.9% in Cohort 3, the minimum detectable effect size between Cohorts 1 and 3 was 1.71 in terms of RR whilst using the same power and significance levels. The study is thus sufficiently powered with data from Finland and Sweden.

[3] Anna-Maria Lahesmaa-Korpinen has acted as the Project Manager of the DPP project (THL, Finland) and has been consulted as an expert for this study.

If the original background prevalence calculated among MS pregnancies unexposed to any MSDMD's would be closer to that in the general population, e.g. 6%, 5%, 4% or 3%, the respective minimum detectable effect sizes would be 1.81, 1.91, 2.04, and 2.23. Regarding the comparison of a composite serious adverse pregnancy outcome between women with MS exposed to IFN-beta only (Cohort 1) vs. unexposed to IFN-beta regardless of exposure to other MSDMDs (Cohort 4), the minimum detectable effect size (RR) was approximately 1.77. Regarding the comparison of the composite serious adverse pregnancy outcome between women with MS exposed to IFN-beta regardless of exposure to other MSDMDs (Cohort 2) vs. unexposed to any MSDMD (Cohort 3), the minimum detectable effect size (RR) was approximately 1.66.

The sample size calculations were performed using the bpower function of the R programming language (http://www.r-project.org).

8.8 Data transformation and management

Data cleaning and verification was performed on the raw data during the analysis dataset building process. All steps and modifications applied during the analysis dataset building process are documented.

Data management, tabulations, graphics, and statistical modelling were carried out with R language (http://www.r-project.org). R language is described more detailed in report "R: Regulatory Compliance and Validation Issues: A Guidance Document for the Use of R in Regulated Clinical Trial Environments" (http://www.r-project.org/doc/R-FDA.pdf).

Data from Finland and Sweden were pooled into one dataset that was analysed using the methods and approaches described in full in the SAP (Annex 3).

8.9 Statistical methods

8.9.1 Main summary measures

All pregnancy events (one woman may have multiple events) were characterised by the descriptive statistics presented in the SAP (Annex 3, section 7.2), in the main study population of all pregnant women with MS and separately in Cohorts 1-4.

All outcomes, including pregnancy outcomes and other outcomes at birth, were characterised in the main study population as described in the SAP (Annex 3, Table 6), including information about denominators used to calculate proportions (%).

8.9.2 Main statistical methods

8.9.2.1 Primary objective 1: Prevalence of pregnancy outcomes

The number and the prevalence, with 95% confidence interval (CI), of the following pregnancy outcomes

- Serious adverse pregnancy outcome
    - Elective TOPFA
    - MCA in live births
    - Stillbirth
- Elective termination for other reasons
- MCA (total)
- Live birth

were determined in the main study population of all pregnant women with MS and separately in Cohorts 1-4. The denominator for the calculation of the prevalence is provided in **Table 4**. The prevalence was determined combined in FIN and SWE, and by country.

8.9.2.2 Primary objective 2: Comparing pregnancy outcomes in Cohort 1 [IFN-beta(+)/oMSDMD (-)] vs. Cohort 3 [IFN-beta(-)/oMSDMD(-)] and in Cohort 1 [IFN-beta(+)/oMSDMD(-)] vs. Cohort 4 [IFN-beta(-)/oMSDMD(+/-)]

The binary (0 for no and 1 for yes) variables of the following pregnancy outcomes

- Serious adverse pregnancy outcome
  - Elective TOPFA
  - MCA in live births
  - Stillbirth
- Elective termination for other reasons
- MCA (total)
- Live birth

were compared using the log-binomial regression between

- Cohort 1 [IFN-beta(+)/oMSDMD(-)] and Cohort 3 [IFN-beta(-)/oMSDMD(-)]
- Cohort 1 [IFN-beta(+)/oMSDMD(-)] and Cohort 4 [IFN-beta(-)/oMSDMD(+/-)].

Two multivariate models, an adjusted base model and a further adjusted model, were used in the log-binomial regression. RRs with 95% CIs were reported for the outcomes of interest, combined in FIN and SWE, and by country. In addition, odds ratios (OR) from the models were reported (see also section 8.9.5).

In the adjusted base model, the exposures of interest were the exposures to MS drugs as defined for each respective Cohort, and the 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.

The further adjusted model was determined through a variable selection procedure described below. Candidate covariates for the further adjusted model were those in the adjusted base model and the following additional ones: university hospital district, pre-pregnancy weight, pre-pregnancy BMI, number of previous abortions, smoking status during pregnancy, number of foetuses in pregnancy (single vs. multiple), time since MS diagnosis and duration of MS treatment as available in the data sources. Variable selection started by applying first the unadjusted model and proceeded as follows:

1. Each candidate covariate was considered a potential confounder if there was a univariate association between the covariate and the serious adverse pregnancy outcome, tested with the Wald test for logistic regression with P-value cut-point of 0.25.

2. All candidate covariates identified as potential confounders in step 1 were added simultaneously to the model. After this, additional covariates not identified as potential confounders in step 1 were added to the model one at a time and the model fit comparing each null vs. alternative model was assessed by the likelihood-ratio test. Variables in the alternate model were retained at a likelihood ratio test of P-value <0.1.

3. An iterative process of reducing the model in step 2 was performed by refitting and verifying model fit comparing null vs. alternative models by likelihood ratio test of P-value <0.1 to determine the main effects model.

4. Model fit results and the effect of adding and removing variables in step 2 and step 3 were reported at each step. If a low number of outcomes was identified, the final further adjusted model was limited to a covariate-outcome ratio of 1 covariate: 10 outcomes to avoid over-adjustment. If the number of covariates

was higher than the covariate-outcome ratio allows, then the covariates with the least significant effect to the model fit were omitted.

Full results including estimates for the adjusting variables were also generated.

8.9.2.3 Secondary objective 3: Comparing pregnancy outcomes in Cohort 2 [IFN-beta(+)/oMSDMD(+/-)] vs. Cohort 3 [IFN-beta(-)/oMSDMD(-)]

The binary (0 for no and 1 for yes) variables of the following pregnancy outcomes

- Serious adverse pregnancy outcome
    - Elective TOPFA
    - MCA in live births
    - Stillbirth
- Elective termination for other reasons
- MCA (total)
- Live birth

were compared using the log-binomial regression between

- Cohorts 2 and 3

Two multivariate models, an adjusted base model and a further adjusted model, were used in the log-binomial regression, as described above for primary objectives. RRs with 95% CIs were reported for the outcomes of interest, combined in FIN and SWE, and by country.

8.9.2.4 Secondary objective 4: Prevalence of ectopic pregnancies and spontaneous abortions

The number and the prevalence, with 95% CI, of the following pregnancy outcomes

- Ectopic pregnancy
- Spontaneous abortion

were determined in the main study population of all pregnant women with MS and separately in Cohorts 1-4. The denominator for the calculation of the prevalence is provided in **Table 4**. The prevalence was determined combined in FIN and SWE, and by country.

This objective is subject to available data from each country, as information only on ectopic pregnancies or spontaneous abortions requiring treatment in hospitals is available in the study.

8.9.2.5 Secondary objective 4a-c: Comparing ectopic pregnancies and spontaneous abortions between Cohorts

The binary variables of ectopic pregnancy and spontaneous abortion were compared using the adjusted base and further adjusted models presented above for the primary objectives. Comparison was done between

- Cohorts 1 and 3
- Cohorts 1 and 4
- Cohorts 2 and 3

RRs with 95% CIs were reported for the outcomes of interest, combined in FIN and SWE, and by country.

8.9.2.6 Secondary objective 5: Stratified prevalence of pregnancy outcomes

The number and the prevalence, with 95% CI, of the following pregnancy outcomes

- Serious adverse pregnancy outcome
    - Elective TOPFA
    - MCA in live births
    - Stillbirth
- Elective termination for other reasons
- MCA (total)
- Live birth

were determined in the whole study population and separately in Cohorts 1-4, stratified by country, year of pregnancy outcome, maternal age at LMP, any chronic diseases, exposure to any teratogenic medications including steroids, time since MS diagnosis, duration of MS treatment, gestational age and weight of the newborn as relevant for specific pregnancy outcomes and as the number of events allow. The number and proportion are given. The denominator for calculation of the proportion is provided in **Table 4**.

8.9.3 Missing values

If a variable was completely missing from a database, it was excluded from the analysis. If a variable was missing for only some of the patients, a missing data category was added and used in the analysis.

In addition, to investigate the robustness of the variable selection procedure to missing data (sensitivity analysis 8, section 8.9.4), when a candidate covariate was missing from over one quarter of patients in Cohorts 1, 3 or 4, missing values were imputed for all candidate covariates multiple times and the variable selection was re-performed using each of the complete (imputed) data sets. Thus, multiple imputations were performed when investigating serious adverse pregnancy outcome in Cohorts 1 vs 3 and 1 vs 4. Multiple imputation was performed using the R library "mi" [16]. Five complete datasets were created by imputing the missing values in the incomplete data (original data with missing values). In the imputation phase, missing covariate values were predicted based on observed data. Imputed values were drawn using an iterative conditional regression approach with 30 iterations for each dataset. The variable selection was performed on each of the complete datasets as a sensitivity analysis to variable selection on incomplete data. Results for models including predictors that appear in i) any, ii) at least half, and iii) all models selected using the imputed data sets are reported as part of the sensitivity analyses. Using these 3 sets of adjusting variables, log-binomial and logistic regression models were fitted using the incomplete data.

8.9.4 Sensitivity analyses

To assess the robustness of results, the following pre-planned sensitivity analyses were undertaken:

1. **Cross-country comparison of MCAs between cohorts, by country**: The MCA outcome among i) all live births and ii) among live births, stillbirths and elective terminations (MCA (total)) in FIN and NOR (both countries separately and also combined) was originally planned to be compared between Cohorts 1 and 3 and Cohorts 1 and 4 using the adjusted base log-binomial model.

   This sensitivity analysis was not performed, as data from Norway was not received.

2. **Comparison of elective TOPFAs between cohorts, by trimester**: Elective TOPFAs were compared between Cohorts 1 and 3 and Cohorts 1 and 4 using the adjusted base log-binomial model, but only including pregnancy events that happen during each trimester (weeks 0-12, 13-27 and >27). That is, for each trimester a separate comparison was made.
3. **Comparison of MCAs between cohorts when exposure restricted to pre-pregnancy or first trimester**: MCAs among i) all live births and ii) among live births, stillbirths and elective terminations (MCA (total)) were compared between Cohorts 1 and 3 and Cohorts 1 and 4 with a modified exposure definition for MSDMDs. In particular, exposure was defined as “Yes” only when a purchase happened

6 months (cladribine and mitoxantrone 9 months) prior to LMP or during the first trimester of pregnancy (exposures happening only after 1st trimester was excluded). The comparison was made using the adjusted base log-binomial model.

4. **Restricting study period to 2005-2014**: Serious adverse pregnancy outcomes, elective TOPFAs, stillbirths, live births, the MCAs in live births and the MCAs (total) occurring only in time period 1st January 2005 – 31st December 2014 were compared between Cohorts 1 and 3 and Cohorts 1 and 4 using the adjusted base log-binomial model.
5. **Proportion of women using cladribine, mitoxantrone and teriflunomide**: The proportion of women using cladribine, mitoxantrone and teriflunomide during the extended pregnancy period was reported, separately for each of the Cohorts 1 – 4. The duration of these treatments prior to LMP was also determined and reported (similarly as duration of MS treatment). In addition, the serious adverse pregnancy outcomes, elective TOPFAs, stillbirths, live births, MCAs in live births and MCAs (total) were compared between Cohorts 1 and 3 and Cohorts 1 and 4, using the adjusted base log-binomial model adjusted additionally for i) never / ever exposure of cladribine, mitoxantrone and teriflunomide and ii) duration of cladribine, mitoxantrone and teriflunomide exposure prior to LMP (categories as for duration of MS treatment).
6. **Classifying hospital administrated drugs as exposed to MSDMDs**: Serious adverse pregnancy outcome, elective TOPFA, stillbirth, live birth MCA in live births and MCA (total) outcomes was compared between Cohorts 1 and 3 and Cohorts 1 and 4, using the adjusted base log-binomial model, with redefined Cohort inclusion / exclusion criteria. In particular, all those with procedures related to intravenous medical treatment administered in a hospital (Table 4) during the MS pregnancy exposure period were considered exposed to other MSDMDs (not exposed to IFN-beta).
7. **Pregnancy outcomes in women with MS exposed to exclusively oMSDMD (Cohort 5), with assumedly more serious MS**: Serious adverse pregnancy outcome, elective TOPFA, stillbirth, live birth MCA in live births and MCA (total) were described with the descriptive statistics (Table 6) in Cohort 5. These outcomes were also compared between Cohorts 3 and 5 using the adjusted base log-binomial model.
8. **Robustness of the variable selection procedure to missing data**: Sensitivity analysis was also conducted to account for alternative model definitions in the performed multiple imputations, as described in the Missing data section.

8.9.5 Changes after adopting the protocol

Data permit processes for this study had major delays in Norway, and for this reason Norway was proposed to be removed from the study. EMA approved the proposed approach on August 15, 2018. The rationale behind this proposal is herewith summarized:

- It is expected that the exclusion of Norway data only has a minimal impact on the statistical power knowing that the study sample size has been already achieved (and exceeded) with data from Finland and Sweden, due to higher number of pregnancy events than expected in the sample size estimation. In addition, the anticipated background prevalence of serious adverse pregnancy outcomes was only based on the Finnish feasibility data.
- The MAHs acknowledge that information on elective termination is not available in Sweden. As data from Norway is not included, the final number of patients with information on elective termination is reduced. However, the sample size calculation was not designed with the objective to have a complete sample size of elective terminations. If this was the case, the study would have needed to have 1671 pregnancies only with Finland and Norway. In addition, as stated in the protocol (Section 9.9. Limitations), information on pregnancy terminations is available only from gestational week 12 onwards in Norway, so this information would also not be complete if obtained from Norway.

- Finally, to obtain data from Norway data would have resulted in prolonged study duration.

Changes made after the protocol

No.	Date	Section of study protocol	Protocol deviation	Reason
1.	30 June 2016	9.4	Definition for any chronic diseases included comorbidity "Severe psychosis and other severe mental disorders and related conditions" that in turn included ICD-10 code G35 (MS). This ICD-10 code for MS was removed from this variable.	All study participants would have had any chronic diseases variable status "Yes".
2	28 November 2017	Annex 3	ATCs related to study drugs (any MSDMDs) were removed. The list was updated according to Swedish National Drug Formulary (FASS) 2017 / The table was omitted from the analyses.	The FASS reference was outdated and there was inaccuracy in listing ATC codes. In addition, the table included ATCs of MSDMSs, which would have caused an interaction in the model.

The following changes, in addition to those described above, were made after the statistical analysis plan:

- A definition of full-term pregnancy was missing from protocol and SAP. In the analyses, birth at ≥37 gestational weeks was used.
- For outcomes elective termination for other reasons and live birth, it was not possible to fit the log-binomial model and to produce RRs. Therefore, ORs produced by the logistic model were presented for these two outcomes.
- The rare disease assumption does not hold for live birth outcome in the regression models, thus non-live birth (the reverse of live birth) was used instead. In descriptive tables, the prevalence of live birth is reported.
- Two variables not defined in the study protocol were added (thus dividing the previous variable for any exposure to teratogenic medications, including both category C and D, into two variables):
    - The variable Exposure to any category C teratogenic medications excluding study MSDMD drugs; defined as Yes, if during the pregnancy or 6 months before LMP a purchase of any category C teratogenic medication (excluding study MSDMD drugs) according to FASS, and No elsewise, based on ATC codes listed in the study protocol (Annex 3).
    - The variable Exposure to any category D teratogenic medications excluding study MSDMD drugs; defined as Yes, if during the pregnancy or 6 months before LMP a purchase of any category D teratogenic medication (excluding study MSDMD drugs) according to FASS, and No elsewise, based on ATC codes listed in the study protocol (Annex 3).
- To investigate the influence of including off-label drugs as oMSDMD, a **post hoc sensitivity analysis** was performed, where the number of mothers and pregnancies exposed to off-label drugs (human normal immunoglobulin, methotrexate, azathioprine, cyclophosphamide or leflunomide) were described by country. Further, the prevalence of pregnancy outcomes without and with exposure to the off-label drugs was described, as well as the prevalence of pregnancy outcomes by cohort in pregnancies without exposure to the off-label drugs.

- To investigate the influence of excluding rituximab as a study drug, another **post hoc sensitivity analysis** was performed, where the number pregnancies exposed to rituximab and the observed outcomes of these pregnancies were described.
- For sensitivity analyses 6, the procedure codes used to extract the data in Sweden were updated. The following codes were used in Sweden: DT016 (drug administered intravenously) and DV033 (immunotherapy).
- In data received from Finland, maternal age was only available at birth (not at LMP) for live births and stillbirths, and at procedure date (not at LMP) for elective TOPFA, ectopic pregnancies and spontaneous abortions. According to the protocol definition, however, maternal age shall be evaluated at LMP. In the absence of maternal age at LMP from the received data, maternal age at LMP was derived using mothers' date of birth (recorded in MBR or anomalies register) when available. If not available, maternal age at birth (for live births and stillbirths) or at procedure date (for elective TOPFA, ectopic pregnancies, spontaneous abortions) was used. For elective termination for other reasons, maternal age was completely unavailable from abortion register, but could be derived from other patient register data.
- To improve the model fits of the adjusted base models and the further adjusted models, adjusting variables with 100% missingness for the specific outcome-cohort comparison at study were removed from the regression models.
- Requiring at minimum 6 months of drug register data before LMP: As exposure was defined as at least one dispensation of the study drugs during 6 months before LMP, or during pregnancy, only pregnancies with available drug exposure data at least 6 months before LMP were included in the analyses. In Sweden, the study period started on 1 July 2005, according to the study protocol and the SAP. However, pregnancies with LMP between 1 July and 31 December 2005 were excluded from the analyses, because the drug register in Sweden was established on 1 July 2005 and therefore drug data during the 6-month period before LMP were unavailable for pregnancies with LMP before 31 December 2005. In Finland, the study period started on 1 January 1996, according to the study protocol and the SAP. As Finnish drug data were available since 1993, pregnancies with LMP from 1 January 1996 onwards had drug data available 6 months before LMP and thus could be included in the analyses.

8.10 Quality control

The study was performed by following the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct and the Guideline for Good Pharmacoepidemiology Practices (GPP) by the International Society for Pharmacoepidemiology (ISPE). The study protocol was registered (registration number EUPAS13054) and results will be published in the EU PAS register maintained by the EMA.

All study data and supporting documents will be retained for ten years after the end of the study and then destroyed. As the register holder of the study register EPID Research is responsible of archiving and deleting the data. Secure archives are maintained for the orderly storage and retrieval of all study related material. An index was prepared to identify the archived contents and their locations. Access to the archives is controlled and limited to authorised personnel only.

9 Results

9.1 Participants

The main study population consisted of 1983 women with MS who had been pregnant in FIN or SWE during the study period (Figure 1). Of this main study population, 755 pregnant women with MS resided in FIN and 1228 in SWE.

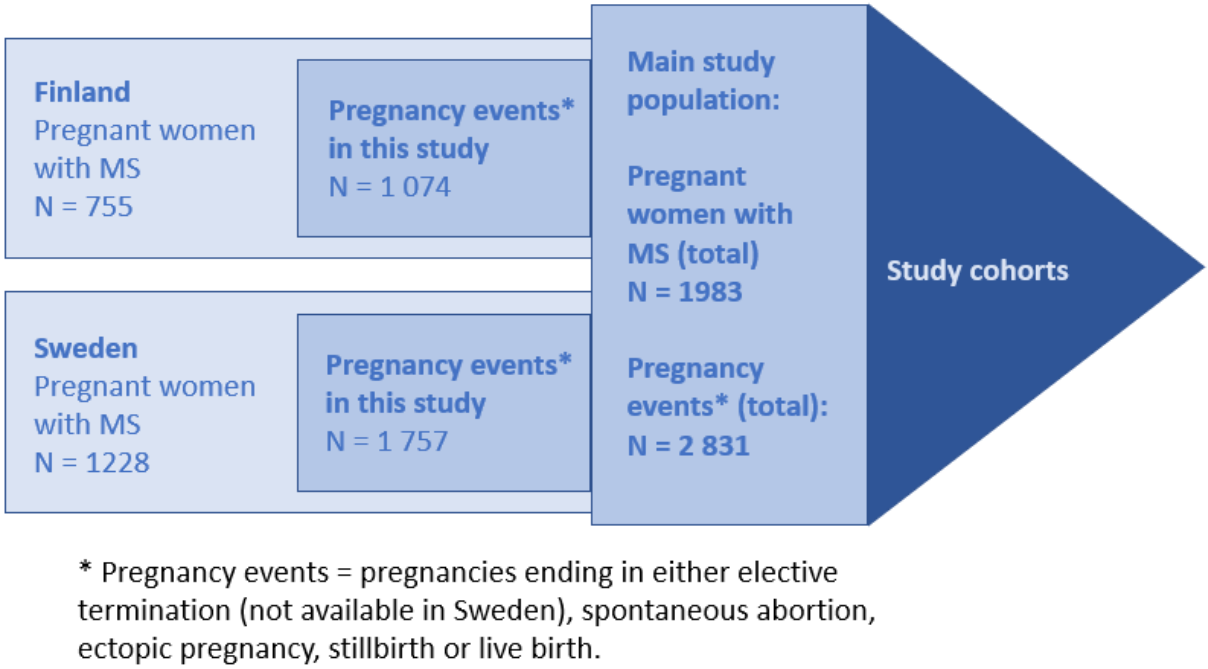

Figure 1 The formation of the main study population.

9.2 Descriptive data

Among the 1983 pregnant women with MS in FIN and SWE, in total 2831 pregnancy events ending in either elective termination, spontaneous abortion, ectopic pregnancy, stillbirth or live birth were identified (**Table 4**). The distribution of the number of pregnancy events between the Cohorts is presented in **Table 4**, together with the frequency of other denominators used in the study.

Table 5 presents the characteristics of the pregnancy events and outcomes in the main study population, combined in FIN and SWE, and by Cohort. **Table 6** describes also pregnancy characteristics in each Cohort (Exploratory objective 6).

Table 4 Used denominators in the study, by Cohort and combined in Finland and Sweden.

Denominator	Number (n), by Cohort and combined in Finland and Sweden					Outcome for which used as denominator
	All pregnant women with MS (Cohorts 1-4)	Women exposed to IFN-beta		Women unexposed to IFN-beta		
		Cohort 1 IFN-beta(+)/ oMSDMD(-)	Cohort 2 IFN-beta(+)/ oMSDMD(+/-)	Cohort 3 IFN-beta(-)/ oMSDMD(-)	Cohort 4 IFN-beta(-)/ oMSDMD(+/-)	
All pregnancy events (elective termination[1], spontaneous abortion, ectopic pregnancy, stillbirth or live birth[2])	2831	797	856	1647	1975	Ectopic pregnancies, spontaneous abortions
Elective terminations, stillbirths and live births[2]	2466	718	774	1397	1692	Serious adverse pregnancy outcome, elective TOPFA or elective termination for other reasons, stillbirths (with or without foetal defects), live births, MCA (total), defect cases[3]
Finland only	890	295	307	474	583	
Live births[2]	2327	666	722	1330	1605	MCA in live birth, mode of delivery, preterm birth, birth length, birth weight, birth weight for gestational age, sex of the newborn
Single pregnancies	2255	646	702	1284	1553	
Multiple pregnancies	72	20	20	46	52	
Full-term live births	2146	619	673	1219	1473	Head circumference, Apgar score at 1 and 5 minutes, low Apgar score
Single pregnancies	2114	609	663	1203	1451	
Multiple pregnancies	32	10	10	16	22	

Source: Result Report (Annex 4), Table 2.1 (presented as **Table 6** *in this report)*

IFN-beta, interferon beta; MCA, major congenital anomaly; oMSDMD, other multiple sclerosis disease modifying drug than interferon beta, TOPFA, termination of pregnancy due to foetal anomaly.

[1] Unavailable in Sweden.

[2] Including both pre-term and full-term live births.

[3] Defect case refers to a child with 3 or more minor congenital anomalies.

Table 5 Characterisation of the pregnancy events, combined in Finland and Sweden, and by Cohort.

Variable	All pregnant women with MS (Cohorts 1-4)	Women exposed to IFN-beta		Women unexposed to IFN-beta	
		Cohort 1 IFN-beta(+)/ oMSDMD(-)	Cohort 2 IFN-beta(+)/ oMSDMD(+/-)	Cohort 3 IFN-beta(-)/ oMSDMD(-)	Cohort 4 IFN-beta(-)/ oMSDMD(+/-)
Pregnancy events, N	**2831**	**797**	**856**	**1647**	**1975**
Country of residence					
Finland, n (%)	1074 (37.9)	320 (40.2)	332 (38.8)	614 (37.3)	742 (37.6)
Sweden, n (%)	1757 (62.1)	477 (59.8)	524 (61.2)	1033 (62.7)	1233 (62.4)
Country and university hospital district					
Finland					
Etelä-Karjala, n (%)	17 (0.6)	7 (0.9)	7 (0.8)	9 (0.5)	10 (0.5)
Etelä-Pohjanmaa, n (%)	31 (1.1)	8 (1.0)	8 (0.9)	20 (1.2)	23 (1.2)
Etelä-Savo, n (%)	10 (0.4)	3 (0.4)	3 (0.4)	7 (0.4)	7 (0.4)
Helsinki and Uusimaa, n (%)	310 (11.0)	107 (13.4)	110 (12.9)	165 (10.0)	200 (10.1)
Itä-Savo, n (%)	4 (0.1)	1 (0.1)	2 (0.2)	2 (0.1)	2 (0.1)
Kainuu, n (%)	9 (0.3)	3 (0.4)	3 (0.4)	6 (0.4)	6 (0.3)
Kanta-Häme, n (%)	46 (1.6)	9 (1.1)	9 (1.1)	34 (2.1)	37 (1.9)
Keski-Pohjanmaa, n (%)	7 (0.2)	3 (0.4)	3 (0.4)	2 (0.1)	4 (0.2)
Keski-Suomi, n (%)	39 (1.4)	19 (2.4)	19 (2.2)	18 (1.1)	20 (1.0)
Kymenlaakso, n (%)	29 (1.0)	9 (1.1)	11 (1.3)	13 (0.8)	18 (0.9)
Länsi-Pohja, n (%)	13 (0.5)	7 (0.9)	7 (0.8)	6 (0.4)	6 (0.3)
Lappi, n (%)	25 (0.9)	9 (1.1)	10 (1.2)	13 (0.8)	15 (0.8)
Päijät-Häme, n (%)	25 (0.9)	11 (1.4)	11 (1.3)	12 (0.7)	14 (0.7)
Pirkanmaa, n (%)	64 (2.3)	17 (2.1)	18 (2.1)	34 (2.1)	46 (2.3)
Pohjois-Karjala, n (%)	21 (0.7)	5 (0.6)	6 (0.7)	13 (0.8)	15 (0.8)
Pohjois-Pohjanmaa, n (%)	71 (2.5)	24 (3.0)	25 (2.9)	37 (2.2)	46 (2.3)
Pohjois-Savo, n (%)	25 (0.9)	8 (1.0)	8 (0.9)	12 (0.7)	17 (0.9)
Satakunta, n (%)	21 (0.7)	4 (0.5)	5 (0.6)	10 (0.6)	16 (0.8)
Vaasa, n (%)	27 (1.0)	6 (0.8)	6 (0.7)	14 (0.9)	21 (1.1)
Varsinais-Suomi, n (%)	94 (3.3)	34 (4.3)	35 (4.1)	46 (2.8)	59 (3.0)
Sweden					
Dalarna-Gävleborg, n (%)	78 (2.8)	19 (2.4)	21 (2.5)	45 (2.7)	57 (2.9)
Mälardalen, n (%)	59 (2.1)	142 (17.8)	150 (17.5)	423 (25.7)	481 (24.4)
Mellannorrland, n (%)	631 (22.3)	20 (2.5)	23 (2.7)	31 (1.9)	36 (1.8)
Norra Sverige, n (%)	90 (3.2)	26 (3.3)	31 (3.6)	46 (2.8)	59 (3.0)
Östergötaland, n (%)	90 (3.2)	19 (2.4)	22 (2.6)	50 (3.0)	68 (3.4)
Småland, n (%)	108 (3.8)	27 (3.4)	29 (3.4)	67 (4.1)	79 (4.0)

Variable	All pregnant women with MS (Cohorts 1-4)	Women exposed to IFN-beta		Women unexposed to IFN-beta	
		Cohort 1 IFN-beta(+)/ oMSDMD(-)	Cohort 2 IFN-beta(+)/ oMSDMD(+/-)	Cohort 3 IFN-beta(-)/ oMSDMD(-)	Cohort 4 IFN-beta(-)/ oMSDMD(+/-)
Pregnancy events, N	**2831**	**797**	**856**	**1647**	**1975**
Södra Götaland, n (%)	263 (9.3)	83 (10.4)	99 (11.6)	134 (8.1)	164 (8.3)
Västra Götaland, n (%)	344 (12.2)	118 (14.8)	125 (14.6)	177 (10.7)	219 (11.1)
Västra Svealand, n (%)	90 (3.2)	21 (2.6)	22 (2.6)	58 (3.5)	68 (3.4)
Missing, n (%)	190 (6.7)	28 (3.5)	28 (3.3)	143 (8.7)	162 (8.2)
Time since MS diagnosis at LMP					
≤2 years, n (%)	817 (28.9)	249 (31.2)	270 (31.5)	471 (28.6)	547 (27.7)
3 – 5 years, n (%)	985 (34.8)	285 (35.8)	307 (35.9)	560 (34.0)	678 (34.3)
> 5 years, n (%)	1029 (36.3)	263 (33.0)	279 (32.6)	616 (37.4)	750 (38.0)
Range, years (min - max)	(–0.8-20.5)	(-0.7-16.0)	(-0.7-16.0)	(-0.8-20.5)	(-0.8-20.5)
Mean, years (+/-SD)	4.5 (3.6)	4.2 (3.2)	4.1 (3.1)	4.6 (3.8)	4.6 (3.8)
Median, years (Q1 - Q3)	3.7 (1.7-6.5)	3.4 (1.7-6.1)	3.4 (1.6-6.0)	3.8 (1.7-6.6)	3.8 (1.6-6.6)
Duration of MS treatment at LMP[1]					
≤2 years, n (%)	1025 (36.2)	342 (42.9)	371 (43.3)	552 (33.5)	654 (33.1)
3 – 5 years, n (%)	795 (28.1)	252 (31:.6)	269 (31.4)	393 (23.9)	526 (26.6)
> 5 years, n (%)	683 (24.1)	199 (25.0)	212 (24.8)	378 (23.0)	471 (23.8)
Missing, n (%)	328 (11.6)	4 (0.5)	4 (0.5)	324 (19.7)	324 (16.4)
Range, years (min - max)	(0.0-20.1)	(0.0-14.0)	(0.0-14.0)	(0.0-18.9)	(0.0-20.1)
Mean, years (+/-SD)	3.5 (3.2)	3.3 (2.8)	3.3 (2.8)	3.5 (3.4)	3.5 (3.4)
Median, years (Q1 - Q3)	2.7 (0.8- 5.3)	2.5 (1.1-5.0)	2.5 (1.1-5.0)	2.7 (0.0-5.4)	2.8 (0.5-5.4)
Year of pregnancy outcome					
1996 – 1999, n (%)	59 (2.1)	1 (0.1)	1 (0.1)	58 (3.5)	58 (2.9)
2000 – 2004, n (%)	106 (3.7)	32 (4.0)	32 (3.7)	70 (4.3)	74 (3.7)
2005 – 2009, n (%)	896 (31.6)	240 (30.1)	260 (30.4)	538(32.7)	636 (32.2)
≥2010, n (%)	1770 (62.5)	524 (65.7)	563 (65.8)	981 (59.6)	1207 (61.1)
Maternal age at LMP					
≤20 years, n (%)	27 (1.0)	8 (1.0)	9 (1.1)	15 (0.9)	18 (0.9)
21 – 25 years, n (%)	295 (10.4)	100 (12.5)	113 (13.2)	144 (8.7)	182 (9.2)
26 – 30 years, n (%)	907 (32.0)	273 (34.3)	294 (34.3)	495 (30.1)	613 (31.0)
31 – 35 years, n (%)	1073(37.9)	325 (40.8)	342 (40.0)	613 (37.2)	731 (37.0)
36 – 40 years, n (%)	457(16,1)	71 (8.9)	78 (9.1)	336 (20.4)	379 (19.2)
> 40 years, n (%)	72 (2.5)	20 (2.5)	20 (2.3)	44 (2.7)	52 (2.6)
Range (min - max)	(17.0-57.0)	(18.0-48.0)	(18.0-48.0)	(18.0-57.0)	(17.0 -57.0)
Mean (+/-SD)	31.3 (4.7)	30.6 (4.5)	30.5 (4.5)	31.8 (4.7)	31.6 (4.8)
Median (Q1, Q3)	31.0 (28.0-34.0)	31.0 (28.0-33.0)	31.0 (28.0-33.0)	32.0 (29.0-35.0)	32.0 (28.0-35.0)

Variable	All pregnant women with MS (Cohorts 1-4)	Women exposed to IFN-beta		Women unexposed to IFN-beta	
		Cohort 1 IFN-beta(+)/ oMSDMD(-)	Cohort 2 IFN-beta(+)/ oMSDMD(+/-)	Cohort 3 IFN-beta(-)/ oMSDMD(-)	Cohort 4 IFN-beta(-)/ oMSDMD(+/-)
Pregnancy events, N	**2831**	**797**	**856**	**1647**	**1975**
Pre-pregnancy maternal weight					
≤39 kg, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
40 – 54 kg, n (%)	259 (9.1)	76 (9.5)	87 (10.2)	142 (8.6)	172 (8.7)
55 – 75 kg, n (%)	1373 (48.5)	397 (49.8)	427 (49.9)	777 (47.2)	946 (47.9)
76 – 90 kg, n (%)	342 (12.1)	88 (11.0)	97 (11.3)	195 (11.8)	245 (12.4)
>90 kg, n (%)	164 (5.8)	55 (6.9)	58 (6.8)	88 (5.3)	106 (5.4)
Missing, n (%)	693 (24.5)	181 (22.7)	187 (21.8)	445 (27.0)	506 (25.6)
Range (min - max)	(41.0-139.0)	(42.0-139.0)	(42.0-139.0)	(41.0-130.0)	(41.0-133.0)
Mean (+/-SD)	68.3 (14.2)	68.4 (14.8)	68.2 (14.7)	68.1 (13.8)	68.3 (13.9)
Median (Q1 - Q3)	65.0 (59.0-75.0)	65.0 (59.0-75.0)	65.0 (58.0-75.0)	65.0 (59.0-75.0)	65.0 (59.0-75.0)
Pre-pregnancy BMI					
≤18.5 kg/m² (underweight), n (%)	74 (2.6)	18 (2.3)	25 (2.9)	40 (2.4)	49 (2.5)
18.6 – 25 kg/m² (normal), n (%)	1319 (46.6)	385 (48.3)	413 (48.2)	751 (45.6)	906 (45.9)
25.1 – 30 kg/m² (overweight), n (%)	487 (17.2)	134 (16.8)	145 (16.9)	268 (16.3)	342 (17.3)
>30 kg/m² (obesity), n (%)	249 (8.8)	77 (9.7)	83 (9.7)	138 (8.4)	166 (8.4)
Missing, n (%)	702 (24.8)	183 (23.0)	190 (22.2)	450 (27.3)	512 (25.9)
Range (min - max)	(15.4-49.2)	(15.4-49.2)	(15.4-49.2)	(16.6-47.6)	(16.6-48.9)
Mean (+/-SD)	24.5 (4.8)	24.5 (5.0)	24.5 (5.0)	24.4 (4.7)	24.4 (4.7)
Median (Q1 - Q3)	23.3 (21.2-26.4)	23.1 (21.1-26.7)	23.1 (21.1-26.6)	23.3 (21.1-26.3)	23.4 (21.2-26.4)
Number of previous pregnancies					
0, n (%)	1178 (41.6)	347 (43.5)	367 (42.9)	669 (40.6)	811 (41.1)
1 – 2, n (%)	1406 (49.7)	390 (48.9)	423 (49.4)	828 (50.3)	983 (49.8)
≥3, n (%)	247 (8.7)	60 (7.5)	66 (7.7)	150 (9.1)	181 (9.2)
Number of previous induced abortions[2]					
0, n (%)	918 (32.4)	264 (33.1)	273 (31.9)	531 (32.2)	645 (32.7)
1 – 2, n (%)	136 (4.8)	50 (6.3)	53 (6.2)	71 (4.3)	83 (4.2)
≥3, n (%)	20 (0.7)	6 (0.8)	6 (0.7)	12 (0.7)	14 (0.7)
Missing, n (%)	1757 (62.1)	477 (59.8)	524 (61.2)	1033 (62.7)	1233 (62.4)
Smoking status during pregnancy					
Yes, n (%)	211 (7.5)	52 (6.5)	58 (6.8)	129 (7.8)	153 (7.7)
No, n (%)	2047 (72.3)	595 (74.7)	644 (75.2)	1157 (70.2)	1403 (71.0)
Missing, n (%)	573 (20.2)	150 (18.8)	154 (18.0)	361 (21.9)	419 (21.2)
Number of foetuses in pregnancy					
Single, n (%)	2267 (80.1)	648 (81.3)	704 (82.2)	1292 (78.4)	1563 (79.1)

Variable	All pregnant women with MS (Cohorts 1-4)	Women exposed to IFN-beta		Women unexposed to IFN-beta	
		Cohort 1 IFN-beta(+)/ oMSDMD(-)	Cohort 2 IFN-beta(+)/ oMSDMD(+/-)	Cohort 3 IFN-beta(-)/ oMSDMD(-)	Cohort 4 IFN-beta(-)/ oMSDMD(+/-)
Pregnancy events, N	**2831**	**797**	**856**	**1647**	**1975**
Multiple, n (%)	72 (2.5)	20 (2.5)	20 (2.3)	46 (2.8)	52 (2.6)
NA[3], n (%)	492 (17.4)	129 (16.2)	132 (15.4)	309 (18.8)	360 (18.2)
Gestational age at pregnancy outcome[4]					
<28 weeks, n (%)	509 (18.0)	135 (16.9)	138 (16.1)	317 (19.2)	371 (18.8)
28 – 36 weeks, n (%)	169 (6.0)	42 (5.3)	44 (5.1)	105 (6.4)	125 (6.3)
≥37 weeks, n (%)	2153 (76.1)	620 (77.8)	674 (78.7)	1225 (74.4)	1479 (74.9)
Range (min - max)	(4.9-45.0)	(4.9-44.9)	(4.9-44.9)	(5.7-45.0)	(4.9-45.0)
Mean (+/-SD)	33.8 (11.7)	34.2 (11.5)	34.4 (11.3)	33.3 (11.9)	33.5 (11.9)
Median (Q1 - Q3)	39.0 (37.0-40.0)	39.0 (37.0-40.0)	39.0 (37.2-40.0)	39.0 (36.3-40.0)	39.0 (36.6-40.0)
Any chronic disease before or during pregnancy (excl. MS)					
Yes, n (%)	1059 (37.4)	282 (35.4)	307 (35.9)	621 (37.7)	752 (38.1)
No, n (%)	1772 (62.6)	515 (64.6)	549 (64.1)	1026 (62.3)	1223 (61.9)
Exposure to any group C teratogenic medications before[5] or during pregnancy[6]					
Yes, n (%)	1626 (57.4)	520 (65.2)	558 (65.2)	864 (52.5)	907 (45.9)
No, n (%)	1205 (42.6)	277 (34.8)	298 (34.8)	783 (47.5)	907 (45.9)
Exposure to any group D teratogenic medications before[5] or during pregnancy[6]					
Yes, n (%)	427 (15.1)	149 (18.7)	167 (19.5)	216 (13.1)	260 (13.2)
No, n (%)	2404 (84.9)	648 (81.3)	689 (80.5)	1431 (86.9)	1715 (86.8)

Source: Result Report (Annex 4), Table 1.1

BMI, body mass index; IFN-beta, interferon beta; MS, multiple sclerosis; n, number of pregnancy events; oMSDMD, other multiple sclerosis disease modifying drug than interferon beta; LMP, last menstrual period; MS, multiple sclerosis; SD, standard deviation.

[1] Duration of MS treatment at LMP refers to refers to any MS treatment they patient may have ever received

[2] Records of induced abortions are not available from SWE.

[3] NA for the variable "number of foetuses in pregnancy" refers to pregnancies for which the outcome was either ectopic pregnancy, spontaneous abortion or elective termination.

[4] Includes all pregnancy outcomes.

[5] Six months prior to LMP.

[6] Teratogenic C and D drugs are based on year 2017 list in SWE (Appendix 5).

Table 6 Characterisation of birth outcomes, combined in FIN and SWE, and by Cohort, excluding the studied pregnancy outcomes (described in **Table 7** and **Table 9**).

Variable	All pregnant women with MS (Cohorts 1-4)	Women exposed to IFN-beta		Women unexposed to IFN-beta	
		Cohort 1 IFN-beta (+)/ oMSDMD (-)	Cohort 2 IFN-beta (+)/ oMSDMD (+/-)	Cohort 3 IFN-beta (-)/ oMSDMD (-)	Cohort 4 IFN-beta (-)/ oMSDMD (+/-)
Mode of delivery					
CS, n/N (%, 95% CI)	509/2327 (21.9; 20.2-23.6)	136/666 (20.4; 17.4-23.7)	148/722 (20.5; 17.6-23.6)	309/1330 (23.2; 21.0-25.6)	361/1605 (22.5; 20.5-24.6)
Vaginal, n/N (%, 95% CI)	1626/2327 (69.9; 68.0-71.7)	478/666 (71.8; 68.2-75.2)	520/722 (72.0; 68.6-75.3)	905/1330 (68.0; 65.5-70.5)	1106/1605 (68.9; 66.6-71.2)
Missing, n/N (%, 95% CI)	192/2327 (8.3; 7.2-9.4)	52/666 (7.8; 5.9-10.1)	54/722 (7.5; 5.7-9.6)	116/1330 (8.7; 7.3-10.4)	138/1605 (8.6; 7.3-10.1)
Mode of delivery among single pregnancies					
CS, n/N (%, 95% CI)	470/2255 (20.8; 19.2-22.6)	126/646 (19.5; 16.5-22.8)	138/702 (19.7; 16.8-22.8)	282/1284 (22.0; 19.7-24.3)	332/1553 (21.4; 19.4-23.5)
Vaginal, n/N (%, 95% CI)	1597/2255 (70.8; 68.9-72.7)	468/646 (72.4; 68.8-75.9)	510/702 (72.6; 69.2-75.9)	890/1284 (69.3; 66.7-71.8)	1087/1553 (70.0; 67.6-72.3)
Missing, n/N (%, 95% CI)	188/2255 (8.3; 7.2-9.6)	52/646 (8.0; 6.1-10.4)	54/702 (7.7; 5.8-9.9)	112/1284 (8.7; 7.2-10.4)	134/1553 (8.6; 7.3-10.1)
Mode of delivery among multiple pregnancies					
CS, n/N (%, 95% CI)	39/72 (54.2; 42.0-66.0)	10/20 (50.0, 27.2-72.8)	10/20 (50.0, 27.2-72.8)	27/46 (58.7; 43.2-73.0)	29/52 (55.8; 41.3-69.5)
Vaginal, n/N (%, 95% CI)	29/72 (40.3; 28.9-52.5)	10/20 (50.0, 27.2-72.8)	10/20 (50.0, 27.2-72.8)	15/46 (32.6; 19.5-48.0)	19/52 (36.5; 23.6-51.0)
Missing, n/N (%, 95% CI)	4/72 (5.6; 1.5-13.6)	0/20 (0.0, 0.0-16.8)	0/20 (0.0, 0.0-16.8)	4/46 (8.7; 2.4-20.8)	4/52 (7.7; 2.1-18.5)
Preterm birth among all live births					
No, n/N (%, 95% CI)	2146/2327 (92.2; 91.1-93.3)	619/666 (92.9; 90.7-94.8)	673/722 (93.2; 91.1-94.9)	1219/1330 (91.7; 90.0-93.1)	1473/1605 (91.8; 90.3-93.1)
Yes, n/N (%, 95% CI)	181/2327 (7.8; 6.7-8.9)	47/666 (7.1; 5.2-9.3)	49/722 (6.8; 5.1-8.9)	111/1330 (8.3; 6.9-10.0)	132/1605 (8.2; 6.9-9.7)
Preterm birth among single pregnancies					
No, n/N (%, 95% CI)	2114/2255 (93.7; 92.7-94.7)	609/646 (94.3; 92.2-95.9)	663/702 (94.4; 92.5-96.0)	1203/1284 (93.7; 92.2-95.0)	1451/1553 (93.4; 92.1-94.6)
Yes, n/N (%, 95% CI)	141/2255 (6.3; 5.3-7.3)	37/646 (5.7; 4.1-7.8)	39/702 (5.6; 4.0-7.5)	81/1284 (6.3; 5.0-7.8)	102/1553 (6.6; 5.4-7.9)
Preterm birth among multiple pregnancies					
No, n/N (%, 95% CI)	32/72 (44.4; 32.7-56.6)	10/20 (50.0, 27.2-72.8)	10/20 (50.0, 27.2-72.8)	16/46 (34.8; 21.4-50.2)	22/52 (42.3; 28.7-56.8)
Yes, n/N (%, 95% CI)	40/72 (55.6; 43.4-67.3)	10/20 (50.0, 27.2-72.8)	10/20 (50.0, 27.2-72.8)	30/46 (65.2; 49.8-78.6)	30/52 (57.7; 43.2-71.3)
Birth height[1]					
Low, n/N (%)	80/2327 (3.4)	23/666 (3.5)	24/722 (3.3)	47/1330 (3.5)	56/1605 (3.5)
Normal, n/N (%)	2149/2327 (92.4)	618/666 (92.8)	671/722 (92.9)	1219/1330 (91.7)	1478/1605 (92.1)
High, n/N (%)	79/2327 (3.4)	19/666 (2.9)	21/722 (2.9)	52/1330 (3.9)	58/1605 (3.6)
Missing, n/N (%)	19/2327 (0.8)	6/666 (0.9)	6/722 (0.8)	12/1330 (0.9)	13/1605 (0.8)
Range (min - max)	(29.0-57.0)	(29.0-57.0)	(29.0-57.0)	(33.0-56.0)	(32.0-57.0)
Mean (+/-SD)	49.8 (2.8)	49.8 (2.9)	49.9 (2.9)	49.8 (2.7)	49.8 (2.7)
Median (Q1 - Q3)	50.0 (49.0-51.0)	50.0 (49.0-51.0)	50.0 (49.0-51.0)	50.0 (49.0-51.0)	50.0 (49.0-51.0)

Variable	All pregnant women with MS (Cohorts 1-4)	Women exposed to IFN-beta		Women unexposed to IFN-beta	
		Cohort 1 IFN-beta (+)/ oMSDMD (-)	Cohort 2 IFN-beta (+)/ oMSDMD (+/-)	Cohort 3 IFN-beta (-)/ oMSDMD (-)	Cohort 4 IFN-beta (-)/ oMSDMD (+/-)
Birth height among single pregnancies[1]					
Low, n/N (%)	78/2255 (3.5)	22/646 (3.4)	23/702 (3.3)	46/1284 (3.6)	55/1553 (3.5)
Average, n/N (%)	2087/2255 (92.5)	600/646 (92.9)	653/702 (93.0)	1181/1284 (92.0)	1434/1553 (92.3)
High, n/N (%)	76/2255 (3.4)	19/646 (2.9)	21/702 (3.0)	49/1284 (3.8)	55/1553 (3.5)
Missing, n/N (%)	14/2255 (0.6))	5/646 (0.8)	5/702 (0.7)	8/1284 (0.6)	9/1553 (0.6)
Range (min - max)	(29.0-57.0)	(29.0-57.0)	(29.0-57.0)	(33.0-56.0)	(32.0-57.0)
Mean (+/-SD)	49.9 (2.6)	50.0 (2.6)	50.0 (2.6)	49.9 (2.5)	49.9 (2.6)
Median (Q1 - Q3)	50.0 (49.0-51.0)	50.0 (49.0-51.0)	50.0 (49.0-51.8)	50.0 (49.0-51.0)	50.0 (49.0-51.0)
Birth height among multiple pregnancies[1]					
Low, n/N (%)	2/72 (2.8)	1/20 (5.0)	1/20 (5.0)	1/46 (2.2)	1/52 (1.9)
Normal, n/N (%)	62/72 (86.1)	18/20 (90.0)	18/20 (90.0)	38/46 (82.6)	44/52 (84.6)
High, n/N (%)	3/72 (4.2)	0/20 (0.0)	0/20 (0.0)	3/46 (6.5)	3/52 (5.8)
Missing, n/N (%)	5/72 (6.9)	1/20 (5.0)	1/20 (5.0)	4/46 (8.7)	4/52 (7.7)
Range (min - max)	(34.0-52.0)	(34.0-51.0)	(34.0-51.0)	(34.0-52.0)	(34.0-52.0)
Mean (+/-SD)	45.4 (4.4)	44.3 (5.5)	44.3 (5.5)	45.6 (4.1)	45.8 (3.8)
Median (Q1 - Q3)	47.0 (42.5-48.0)	46.0 (39.5-49.0)	46.0 (39.5-49.0)	47.0 (43.0-48.0)	47.0 (43.0-48.0)
Birth weight[2]					
Very low, n/N (%)	25/2327 (1.1)	8/666 (1.2)	8/722 (1.1)	15/1330 (1.1)	17/1605 (1.1)
Low, n/N (%)	101/2327 (4.3)	26/666 (3.9)	27/722 (3.7)	64/1330 (4.8)	74/1605 (4.6)
Normal, n/N (%)	1876/2327 (80.6)	536/666 (80.5)	581/722 (80.5)	1074/1330 (80.8)	1295/1605 (80.7)
High, n/N (%)	278/2327 (11.9)	82/666 (12.3)	90/722 (12.5)	153/1330 (11.5)	188/1605 (11.7)
Very high, n/N (%)	43/2327 (1.8)	13/666 (2.0)	15/722 (2.1)	21/1330 (1.6)	28/1605 (1.7)
Missing, n/N (%)	4/2327 (0.2)	1/666 (0.2)	1/722 (0.1)	3/1330 (0.2)	3/1605 (0.2)
Range (min - max)	(580.0-5285.0)	(580.0-5160.0)	(580.0-5160.0)	(685.0-5100.0)	(670.0-5285.0)
Mean (+/-SD)	3405.5 (593.8)	3416.7 (606.4)	3429.2 (602.8)	3389.6 (587.6)	3394.8 (589.5)
Median (Q1 - Q3)	3430.0 (3088.0-3790.0)	3440.0 (3110.0-3810.0)	3450.0 (3110.0-3820.0)	3405.0 (3070.0-3780.0)	3412.5 (3076.2-3780.0)
Birth weight among single pregnancies[2]					
Very low, n/N (%)	13/2255 (0.6)	3/646 (0.5)	3/702 (0.4)	8/1284 (0.6)	10/1553 (0.6)
Low, n/N (%)	75/2255 (3.3)	20/646 (3.1)	21/702 (3.0)	44/1284 (3.4)	54/1553 (3.5)
Normal, n/N (%)	1842/2255 (81.7)	527/646 (81.6)	572/702 (81.5)	1055/1284 (82.2)	1270/1553 (81.8)
High, n/N (%)	278/2255 (12.3)	82/646 (12.7)	90/702 (12.8)	153/1284 (11.9)	188/1553 (12.1)
Very high, n/N (%)	43/2255 (1.9)	13/646 (2.0)	15/702 (2.1)	21/1284 (1.6)	28/1553 (1.8)
Missing, n/N (%)	4/2255 (0.2)	1/646 (0.2)	1/702 (0.1)	3/1284 (0.2)	3/1553 (0.2)
Range (min - max)	(580.0-5285.0)	(580.0-5160.0)	(580.0-5160.0)	(685.0-5100.0)	(670.0-5285.0)
Mean (+/-SD)	3439.9 (556.8)	3453.0 (563.4)	3462.9 (562.3)	3429.5 (544.3)	3429.5 (554.1)
Median (Q1 - Q3)	3445.0 (3120.0-3800.0)	3460.0 (3142.0-3830.0)	3470.0 (3145.0-3834.0)	3430.0 (3110.0-3790.0)	3435.0 (3110.0-3790.0)

Variable	All pregnant women with MS (Cohorts 1-4)	Women exposed to IFN-beta		Women unexposed to IFN-beta	
		Cohort 1 IFN-beta (+)/ oMSDMD (-)	Cohort 2 IFN-beta (+)/ oMSDMD (+/-)	Cohort 3 IFN-beta (-)/ oMSDMD (-)	Cohort 4 IFN-beta (-)/ oMSDMD (+/-)
Birth weight among multiple pregnancies[2]					
Very low, n/N (%)	12/72 (16.7)	5/20 (25.0)	5/20 (25.0)	7/46 (15.2)	7/52 (13.5)
Low, n/N (%)	26/72 (36.1)	6/20 (30.0)	6/20 (30.0)	20/46 (43.5)	20/52 (38.5)
Normal, n/N (%)	34/72 (47.2)	9/20 (45.0)	9/20 (45.0)	19/46 (41.3)	25/52 (48.1)
High, n/N (%)	0/72 (0.0)	0/20 (0.0)	0/20 (0.0)	0/46 (0.0)	0/52 (0.0)
Very high, n/N (%)	0/72 (0.0)	0/20 (0.0)	0/20 (0.0)	0/46 (0.0)	0/52 (0.0)
NA, n/N (%)	0/72 (0.0)	0/20 (0.0)	0/20 (0.0)	0/46 (0.0)	0/52 (0.0)
Range (min - max)	(970.0-3680.0)	(1050.0-3290.0)	(1050.0-3290.0)	(970.0-3590.0)	(970.0-3680.0)
Mean (+/-SD)	2329.4 (703.5)	2248.4 (781.3)	2248.4 (781.3)	2279.2 (665.9)	2360.5 (676.7)
Median (Q1 - Q3)	2457.5 (1639.0-2897.5)	2420.0 (1520.0-2875.0)	2420.0 (1520.0-2875.0)	2308.0 (1645.2-2830.0)	2465.0 (1827.5-2897.5)
Birth weight for gestational age[3]					
SGA, n/N (%)	45/2327 (1.9)	14/666 (2.1)	16/722 (2.2)	26/1330 (2.0)	29/1605 (1.8)
AGA, n/N (%)	2209/2327 (94.9)	631/666 (94.7)	685/722 (94.9)	1263/1330 (95.0)	1524/1605 (95.0)
LGA, n/N (%)	18/2327 (0.8)	5/666 (0.8)	5/722 (0.7)	11/1330 (0.8)	13/1605 (0.8)
Missing, n/N (%)	55/2327 (2.4)	16/666 (2.4)	16/722 (2.2)	30/1330 (2.3)	39/1605 (2.4)
Birth weight for gestational age among single pregnancies[3]					
SGA, n/N (%)	40/2255 (1.8)	11/646 (1.7)	13/702 (1.9)	24/1284 (1.9)	27/1553 (1.7)
AGA, n/N (%)	2149/2255 (95.3)	616/646 (95.4)	670/702 (95.4)	1224/1284 (95.3)	1479/1553 (95.2)
LGA, n/N (%)	14/2255 (0.6)	4/646 (0.6)	4/702 (0.6)	8/1284 (0.6)	10/1553 (0.6)
Missing, n/N (%)	52/2255 (2.3)	15/646 (2.3)	15/702 (2.1)	28/1284 (2.2)	37/1553 (2.4)
Birth weight for gestational age among multiple pregnancies					
SGA, n/N (%)	5/72 (6.9)	3/20 (15.0)	3/20 (15.0)	2/46 (4.3)	2/52 (3.8)
AGA, n/N (%)	60/72 (83.3)	15/20 (75.0)	15/20 (75.0)	39/46 (84.8)	45/52 (86.5)
LGA, n/N (%)	4/72 (5.6)	1/20 (5.0)	1/20 (5.0)	3/46 (6.5)	3/52 (5.8)
Missing, n/N (%)	3/72 (4.2)	1/20 (5.0)	1/20 (5.0)	2/46 (4.3)	2/52 (3.8)
Sex of the newborn					
Female, n/N (%)	1132/2327 (48.6)	330/666 (49.5)	362/722 (50.1)	635/1330 (47.7)	770/1605 (48.0)
Male, n/N (%)	1195/2327 (51.4)	336/666 (50.5)	360/722 (49.9)	695/1330 (52.3)	835/1605 (52.0)
Sex of the newborn among single pregnancies					
Female, n/N (%)	1104/2255 (49.0)	321/646 (49.7)	353/702 (50.3)	616/1284 (48.0)	751/1553 (48.4)
Male, n/N (%)	1151/2255 (51.0)	325/646 (50.3)	349/702 (49.7)	668/1284 (52.0)	802/1553 (51.6)
Sex of the newborn among multiple pregnancies					
Female, n/N (%)	28/72 (38.9)	9/20 (45.0)	9/20 (45.0)	19/46 (41.3)	19/52 (36.5)
Male, n/N (%)	44/72 (61.1)	11/20 (55.0)	11/20 (55.0)	27/46 (58.7)	33/52 (63.5)
Head circumference[3]					

Variable	All pregnant women with MS (Cohorts 1-4)	Women exposed to IFN-beta		Women unexposed to IFN-beta	
		Cohort 1 IFN-beta (+)/ oMSDMD (-)	Cohort 2 IFN-beta (+)/ oMSDMD (+/-)	Cohort 3 IFN-beta (-)/ oMSDMD (-)	Cohort 4 IFN-beta (-)/ oMSDMD (+/-)
Low, n/N (%)	27/2146 (1.3)	12/619 (1.9)	12/673 (1.8)	13/1219 (1.1)	15/1473 (1.0)
Normal, n/N (%)	1966/2146 (91.6)	567/619 (91.6)	620/673 (92.1)	1106/1219 (90.7)	1346/1473 (91.4)
High, n/N (%)	63/2146 (2.9)	21/619 (3.4)	21/673 (3.1)	36/1219 (3.0)	42/1473 (2.9)
Missing, n/N (%)	90/2146 (4.2)	19/619 (3.1)	20/673 (3.0)	64/1219 (5.3)	70/1473 (4.8)
Range (min - max)	(30.0-40.0)	(31.5-39.0)	(31.5-39.0)	(30.0-40.0)	(30.0-40.0)
Mean (+/-SD)	35.0 (1.5)	35.0 (1.4)	35.1 (1.4)	35.0 (1.5)	35.0 (1.5)
Median (Q1 - Q3)	35.0 (34.0-36.0)	35.0 (34.0-36.0)	35.0 (34.0-36.0)	35.0 (34.0-36.0)	35.0 (34.0-36.0)
Head circumference among single pregnancies[3]					
Low, n/N (%)	27/2114 (1.3)	12/609 (2.0)	12/663 (1.8)	13/1203 (1.1)	15/1451 (1.0)
Normal, n/N (%)	1936/2114 (91.6)	558/609 (91.6)	611/663 (92.2)	1091/1203 (90.7)	1325/1451 (91.3)
High, n/N (%)	62/2114 (2.9)	20/609 (3.3)	20/663 (3.0)	36/1203 (3.0)	42/1451 (2.9)
Missing, n/N (%)	89/2114 (4.2)	19/609 (3.1)	20/663 (3.0)	63/1203 (5.2)	69/1451 (4.8)
Range (min - max)	(30.0-40.0)	(31.5-39.0)	(31.5-39.0)	(30.0-40.0)	(30.0-40.0)
Mean (+/-SD)	35.0 (1.5)	35.1 (1.4)	35.1 (1.4)	35.0 (1.5)	35.0 (1.5)
Median (Q1 - Q3)	35.0 (34.0-36.0)	35.0 (34.0-36.0)	35.0 (34.0-36.0)	35.0 (34.0-36.0)	35.0 (34.0-36.0)
Head circumference among multiple pregnancies[3]					
Low, n/N (%)	0/32 (0.0)	0/10 (0.0)	0/10 (0.0)	0/16 (0.0)	0/22 (0.0)
Normal, n/N (%)	30/32 (93.8)	9/10 (90.0)	9/10 (90.0)	15/16 (93.8)	21/22 (95.5)
High, n/N (%)	1/32 (3.1)	1/10 (10.0)	1/10 (10.0)	0/16 (0.0)	0/22 (0.0)
Missing, n/N (%)	1/32 (3.1)	0/10 (0.0)	0/10 (0.0)	1/16 (6.2)	1/22 (4.5)
Range (min - max)	(32.0-37.0)	(32.0-36.0)	(32.0-36.0)	(33.0-37.0)	(33.0-37.0)
Mean (+/-SD)	34.5 (1.1)	34.1 (1.1)	34.1 (1.1)	34.6 (1.1)	34.6 (1.0)
Median (Q1 - Q3)	34.0 (34.0-35.0)	34.0 (34.0-34.9)	34.0 (34.0-34.9)	34.0 (34.0-35.2)	35.0 (34.0-35.0)
Apgar score at 1 minute[4]					
Low, n/N (%)	111/2146 (5.2)	38/619 (6.1)	38/673 (5.6)	63/1219 (5.2)	73/1473 (5.0)
Normal, n/N (%)	2027/2146 (94.5)	580/619 (93.7)	634/673 (94.2)	1151/1219 (94.4)	1393/1473 (94.6)
Missing, n/N (%)	8/2146 (0.4)	1/619 (0.2)	1/673 (0.1)	5/1219 (0.4)	7/1473 (0.5)
Range (min - max)	(0.0-10.0)	(1.0-10.0)	(1.0-10.0)	(0.0-10.0)	(0.0-10.0)
Mean (+/-SD)	8.7 (1.2)	8.6 (1.2)	8.7 (1.2)	8.7 (1.2)	8.7 (1.2)
Median (Q1 - Q3)	9.0 (9.0-9.0)	9.0 (9.0-9.0)	9.0 (9.0-9.0)	9.0 (9.0-9.0)	9.0 (9.0-9.0)
Apgar score at 5 minutes[4]					
Low, n/N (%)	24/2146 (1.1)	9/619 (1.5)	9/673 (1.3)	14/1219 (1.1)	15/1473 (1.0)
Normal, n/N (%)	1934/2146 (90.1)	546/619 (88.2)	598/673 (88.9)	1095/1219 (89.8)	1336/1473 (90.7)
Missing, n/N (%)	188/2146 (8.8)	64/619 (10.3)	66/673 (9.8)	110/1219 (9.0)	122/1473 (8.3)
Range (min - max)	(0.0-10.0)	(3.0-10.0)	(3.0-10.0)	(0.0-10.0)	(0.0-10.0)

Variable	All pregnant women with MS (Cohorts 1-4)	Women exposed to IFN-beta		Women unexposed to IFN-beta	
		Cohort 1 IFN-beta (+)/ oMSDMD (-)	Cohort 2 IFN-beta (+)/ oMSDMD (+/-)	Cohort 3 IFN-beta (-)/ oMSDMD (-)	Cohort 4 IFN-beta (-)/ oMSDMD (+/-)
Mean (+/-SD)	9.6 (0.8)	9.5 (0.9)	9.5 (0.8)	9.6 (0.9)	9.6 (0.8)
Median (Q1 - Q3)	10.0 (9.0-10.0)	10.0 (9.0-10.0)	10.0 (9.0-10.0)	10.0 (9.0-10.0)	10.0 (9.0-10.0)
Low Apgar score[5]					
No, n/N (%, 95% CI)	1938/2146 (90.3; 89.0-91.5)	547/619 (88.4; 85.6-90.8)	599/673 (89.0; 86.4-91.3)	1098/1219 (90.1; 88.3-91.7)	1339/1473 (90.9; 89.3-92.3)
Yes, n/N (%, 95% CI)	20/2146 (0.9; 0.6-1.4)	8/619 (1.3; 0.6-2.5)	8/673 (1.2; 0.5-2.3)	11/1219 (0.9; 0.5-1.6)	12/1473 (0.8; 0.4-1.4)
Missing, n/N (%, 95% CI)	188/2146 (8.8; 7.6-10.0)	64/619 (10.3; 8.1-13.0)	66/673 (9.8; 7.7-12.3)	110/1219 (9.0; 7.5-10.8)	122/1473 (8.3; 6.9-9.8)
Apgar score at 1 minute among single pregnancies[4]					
Low, n/N (%)	110/2114 (5.2)	38/609 (6.2)	38/663 (5.7)	62/1203 (5.2)	72/1451 (5.0)
Normal, n/N (%)	1996/2114 (94.4)	570/609 (93.6)	624/663 (94.1)	1136/1203 (94.4)	1372/1451 (94.6)
NA, n/N (%)	8/2114 (0.4)	1/609 (0.2)	1/663 (0.2)	5/1203 (0.4)	7/1451 (0.5)
Range (min - max)	(0.0-10.0)	(1.0-10.0)	(1.0-10.0)	(0.0-10.0)	(0.0-10.0)
Mean (+/-SD)	8.7 (1.2)	8.6 (1.2)	8.7 (1.2)	8.7 (1.2)	8.7 (1.2)
Median (Q1 - Q3)	9.0 (9.0-9.0)	9.0 (9.0-9.0)	9.0 (9.0-9.0)	9.0 (9.0-9.0)	9.0 (9.0-9.0)
Apgar score at 5 minutes among single pregnancies[4]					
Low, n/N (%)	24/2114 (1.1)	9/609 (1.5)	9/663 (1.4)	14/1203 (1.2)	15/1451 (1.0)
Normal, n/N (%)	1904/2114 (90.1)	538/609 (88.3)	590/663 (89.0)	1079/1203 (89.7)	1314/1451 (90.6)
Missing, n/N (%)	186/2114 (8.8)	62/609 (10.2)	64/663 (9.7)	110/1203 (9.1)	122/1451 (8.4)
Range (min - max)	(0.0-10.0)	(3.0-10.0)	(3.0-10.0)	(0.0-10.0)	(0.0-10.0)
Mean (+/-SD)	9.6 (0.8)	9.5 (0.9)	9.5 (0.8)	9.6 (0.9)	9.6 (0.8)
Median (Q1 - Q3)	10.0 (9.0-10.0)	10.0 (9.0-10.0)	10.0 (9.0-10.0)	10.0 (9.0-10.0)	10.0 (9.0-10.0)
Low Apgar score among single pregnancies[5]					
No, n/N (%, 95% CI)	1908/2114 (90.3; 88.9-91.5)	539/609 (88.5; 85.7-90.9)	591/663 (89.1; 86.5-91.4)	1082/1203 (89.9; 88.1-91.6)	1317/1451 (90.8; 89.2-92.2)
Yes, n/N (%, 95% CI)	20/2114 (0.9; 0.6-1.5)	8/609 (1.3; 0.6-2.6)	8/663 (1.2; 0.5-2.4)	11/1203 (0.9; 0.5-1.6)	12/1451 (0.8; 0.4-1.4)
NA, n/N (%, 95% CI)	186/2114 (8.8; 7.6-10.1)	62/609 (10.2; 7.9-12.9)	64/663 (9.7; 7.5-12.2)	110/1203 (9.1; 7.6-10.9)	122/1451 (8.4; 7.0-10.0)
Apgar score at 1 minute among multiple pregnancies[4]					
Low, n/N (%)	1/32 (3.1)	0/10 (0.0)	0/10 (0.0)	1/16 (6.2)	1/22 (4.5)
Normal, n/N (%)	31/32 (96.9)	10/10 (100.0)	10/10 (100.0)	15/16 (93.8)	21/22 (95.5)
Missing, n/N (%)	0/32 (0.0)	0/10 (0.0)	0/10 (0.0)	0/16 (0.0)	0/22 (0.0)
Range (min - max)	(3.0-10.0)	(8.0-10.0)	(8.0-10.0)	(3.0-10.0)	(3.0-10.0)
Mean (+/-SD)	8.8 (1.2)	9.1 (0.6)	9.1 (0.6)	8.6 (1.6)	8.7 (1.4)
Median (Q1 - Q3)	9.0 (9.0-9.0)	9.0 (9.0-9.0)	9.0 (9.0-9.0)	9.0 (9.0-9.0)	9.0 (9.0-9.0)

Variable	All pregnant women with MS (Cohorts 1-4)	Women exposed to IFN-beta		Women unexposed to IFN-beta	
		Cohort 1 IFN-beta (+)/ oMSDMD (-)	Cohort 2 IFN-beta (+)/ oMSDMD (+/-)	Cohort 3 IFN-beta (-)/ oMSDMD (-)	Cohort 4 IFN-beta (-)/ oMSDMD (+/-)
Apgar score at 5 minutes among multiple pregnancies[4]					
Low, n/N (%)	0/32 (0.0)	0/10 (0.0)	0/10 (0.0)	0/16 (0.0)	0/22 (0.0)
Normal, n/N (%)	30/32 (93.8)	8/10 (80.0)	8/10 (80.0)	16/16 (100.0)	22/22 (100.0)
Missing, n/N (%)	2/32 (6.2)	2/10 (20.0)	2/10 (20.0)	0/16 (0.0)	0/22 (0.0)
Range (min - max)	(8.0-10.0)	(9.0-10.0)	(9.0-10.0)	(8.0-10.0)	(8.0-10.0)
Mean (+/-SD)	9.6 (0.6)	9.8 (0.5)	9.8 (0.5)	9.4 (0.6)	9.5 (0.7)
Median (Q1 - Q3)	10.0 (9.0-10.0)	10.0 (9.8-10.0)	10.0 (9.8-10.0)	9.5 (9.0-10.0)	10.0 (9.0-10.0)
Low Apgar score among multiple pregnancies[5]					
No, n/N (%, 95% CI)	30/32 (93.8; 79.2-99.2)	8/10 (80.0, 44.4-97.5)	8/10 (80.0, 44.4-97.5)	16/16 (100.0, 79.4-100.0)	22/22 (100.0; 84.6-100.0)
Yes, n/N (%, 95% CI)	0/32 (0.0; 0.0-10.9)	0/10 (0.0, 0.0-30.8)	0/10 (0.0, 0.0-30.8)	0/16 (0.0, 0.0-20.6)	0/22 (0.0; 0.0-15.4)
Missing, n/N (%, 95% CI)	2/32 (6.2; 0.8-20.8)	2/10 (20.0, 2.5-55.6)	2/10 (20.0, 2.5-55.6)	0/16 (0.0, 0.0-20.6)	0/22 (0.0; 0.0-15.4)
Defect case[6]					
Defect case among all elective terminations, still or live births, n/N (%, 95% CI)[3]	0/2466 (0.0; 0.0-0.1)	0/718 (0.0; 0.0-0.5)	0/774 (0.0; 0.0-0.5)	0/1397 (0.0; 0.0-0.3)	0/1692 (0.0; 0.0-0.2)

Source. Result Report (Annex 4), Table 2.1

AGA, average for gestational age; CI, confidence interval, CS, caesarean section; IFN-beta, interferon beta; LGA, large for gestational age; MCA, major congenital anomaly; MS, multiple sclerosis; n, number of pregnancy events; N, denominator for the specific analysis; oMSDMD, other multiple sclerosis disease modifying drug than interferon beta; SGA, small for gestational age; SD, standard deviation; TOPFA, termination of pregnancy due to foetal anomaly.

The denominator for head circumference and Apgar scores is full time live birth. That is defined to be at least 37 gestational weeks.

[1] Birth length, according to national reference [17].

[2] Birth weight categories. Very Low. <1500g, Low. 1500 – 2499g, Average. 2500 – 3999g, High. 4000 - 4500g, Very high. >4500g

[3] SGA is defined as being below reference value minus 2 times standard deviation (SD) and LGA as reference value plus 2 times standard deviation. AGA is defined as being between SGA and LGA (reference values listed in SAP Annex 4).

[4] Apgar score categories. <7 low, 7-10 normal

[5] Low Apgar score. Less than 7 in 1 and 5 minutes

[6] Defect case refers to a child with 3 or more minor congenital anomalies. Defect cases are not available in Finnish data for year 2014.

9.3 Main results

9.3.1 Serious adverse pregnancy outcomes, elective termination for other reasons, MCA and live birth (Primary objective 1)

9.3.1.1 Prevalence, combined in FIN and SWE and by Cohort

The total prevalence of serious adverse pregnancy outcomes among all women with MS (Cohorts 1-4) was 3.2% (95% CI 2.6-4.0%) (**Table 7**). Among women exposed to IFN-beta, the prevalence was 2.2% (95% CI 1.3-3.6%) in Cohort 1 without exposure to oMSDMDs and 2.2% (95% CI 1.3-3.6%) in Cohort 2 which could be exposed to oMSDMDs in addition to IFN-beta. Among women unexposed to IFN-beta, the prevalence of serious adverse pregnancy outcomes was 4.0% (95% CI 3.0-5.2%) in Cohort 3 without exposure to any oMSDMDs and 3.7% (95% CI 2.9-4.7%) in Cohort 4 which could be exposed to oMSDMDs.

Of the serious adverse pregnancy outcomes (**Table 7**), MCA in live births was the most common, with a prevalence of 2.7% (95% CI 2.0-3.4%) among all women with MS (Cohorts 1-4). Among women exposed to IFN-beta, the prevalence of MCAs in live births was 1.8% (95% CI 0.9-3.1%) in Cohort 1 without exposure to oMSDMDs and also 1.8% (95% CI 1.0-3.1%) in Cohort 2 which could be exposed to oMSDMDs in addition to IFN-beta. Among women unexposed to IFN-beta, the prevalence of MCAs in live births was 3.3% (95% CI 2.4-4.4%) in Cohort 3 without exposure to any oMSDMDs and 3.1% (95% CI 2.3-4.0%) in Cohort 4 which could be exposed to oMSDMDs.

Table 7 Prevalence of serious adverse pregnancy outcomes, elective terminations for other reasons, MCA and live births, combined in FIN and SWE, and by Cohort.

Pregnancy outcome	Prevalence n/N (%) combined in FIN and SWE, and by Cohort				
	All pregnant women with MS (Cohorts 1-4)	Women exposed to IFN-beta		Women unexposed to IFN-beta	
		Cohort 1 IFN-beta(+)/ oMSDMD(-)	Cohort 2 IFN-beta(+)/ oMSDMD(+/-)	Cohort 3 IFN-beta(-)/ oMSDMD(-)	Cohort 4 IFN-beta(-)/ oMSDMD(+/-)
Serious adverse pregnancy outcome[1,2], n/N (%, 95% CI)	80/2466 (3.2, 2.6-4.0)	16/718 (2.2, 1.3-3.6)	17/774 (2.2, 1.3-3.5)	56/1397 (4.0, 3.0-5.2)	63/1692 (3.7, 2.9-4.7)
Elective TOPFA[2,3], n/N (%, 95% CI)	6/890 (0.7, 0.2-1.5)	2/295 (0.7, 0.1-2.4)	2/307 (0.7, 0.1-2.3)	4/474 (0.8, 0.2-2.1)	4/583 (0.7, 0.2-1.7)
MCA in live birth[4,5], n/N (%,95% CI)	62/2327 (2.7, 2.0-3.4)	12/666 (1.8, 0.9-3.1)	13/722 (1.8, 1.0-3.1)	44/1330 (3.3, 2.4-4.4)	49/1605 (3.1, 2.3-4.0)
Stillbirth[2], n/N (%,95% CI)	12/2466 (0.5, 0.3-0.8)	2/718 (0.3, 0.0-1.0)	2/774 (0.3, 0.0-0.9)	8/1397 (0.6, 0.2-1.1)	10/1692 (0.6, 0.3-1.1)
Elective termination for other reasons[2,3], n/N (%,95% CI)	121/890 (13.6, 11.4-16.0)	48/295 (16.3, 12.2-21.0)	48/307 (15.6, 11.8-20.2)	55/474 (11.6, 8.9-14.8)	73/583 (12.5, 9.9-15.5)
MCA (total)[5,6], n/N (%,95% CI)	71/2466 (2.9, 2.3-3.6)	14/718 (1.9, 1.1-3.2)	15/774 (1.9, 1.1-3.2)	49/1397 (3.5, 2.6-4.6)	56/1692 (3.3, 2.5-4.3)
Live birth[2], n/N (%,95% CI)	2327/2466 (94.4, 93.4-95.2)	666/718 (92.8, 90.6-94.5)	722/774 (93.3, 91.3-94.9)	1330/1397 (95.2, 93.9-96.3)	1605/1692 (94.9, 93.7-95.9)

Source: Result Report (Annex 4), Tables 5.1-5.7.

CI, confidence interval; IFN-beta, interferon beta; MCA, major congenital anomaly; MS, multiple sclerosis; n, number of pregnancy events; N, denominator for the specific analysis; oMSDMD, other multiple sclerosis disease modifying drug than interferon beta; TOPFA, termination of pregnancy due to foetal anomaly.

[1] Composite endpoint defined as elective TOPFA, MCA in live birth, or stillbirth. However, elective TOPFA was unavailable in SWE.

[2] Denominator: live births, stillbirths and terminations.

[3] Finnish data, records of terminations are not available from SWE.

[4] Denominator: Number of live births.

[5] MCA is not available for year 2014 in the Finnish data.

[6] Denominator: the number of live births and stillbirths in Swedish and Finnish data and terminations in Finnish data. In Swedish data termination due to foetal defect (TOPFA) is not included in MCA (total).

Of the other serious adverse pregnancy outcomes (**Table 7**), the prevalence of elective TOPFAs was 0.7% (95% CI 0.2-1.5%) and stillbirths 0.5% (95% CI 0.3-0.8%) among all women with MS (Cohorts 1-4), with a similar prevalence in the Cohorts 1-4.

Among all women with MS (Cohorts 1-4), 13.6% (95% CI 11.4-16.0%) of pregnancy events ended with elective terminations without foetal anomaly or with an unknown reason (**Table 7**), with a higher prevalence in Cohorts 1-2 compared with Cohorts 3-4 (overlapping confidence intervals).

The prevalence of MCA (total) was 2.9% (95% CI 2.3-3.6%) among all women with MS (Cohorts 1-4) (**Table 7**). The distribution of MCA (total) was similarly to MCA in live births. Among women with MS exposed to IFN-beta, the prevalence of MCA (total) was 1.9% (95% CI 1.1-3.2%) in Cohort 1 and 1.9% (95% CI 1.1-3.2%) Cohort 2, while among women unexposed to IFN-beta the prevalence was 3.5% (95% CI 2.6-4.6%) in Cohort 3 and 3.3% (95% CI 2.5-4.3%) in Cohort 4.

The prevalence of live births was 94.4% (95% CI 93.4-95.2%) combined in Cohorts 1-4 (**Table 7**). Among pregnant women with MS exposed to IFN-beta, the pregnancy ended in a live birth for 92.8% (95% CI 90.6-94.5%) in Cohort 1 and 93.3% (95% CI 91.3-94.9%) in Cohort 2. Among women with MS unexposed to IFN-beta, the prevalence of live births was 95.2% (95% CI 93.9-96.3%) when the women were unexposed to any MSDMDs (Cohort 3) and 94.9% (95% CI 93.7-95.9%) when the women could be exposed to oMSDMDs (Cohort 4).

9.3.1.2 Women with MS exposed to IFN-beta only (Cohort 1) vs. unexposed to any MSDMDs (Cohort 3) (Primary objective 2a)

In the adjusted base model, the risk of the composite endpoint of serious adverse pregnancy outcomes was lower among women with MS exposed to IFN-beta only (Cohort 1) compared with those unexposed to any MSDMDs (Cohort 3) (RR 0.55, 95% CI 0.31-0.96) (**Table 8**). As part of the composite endpoint, the risk of MCAs in live births was in the adjusted base model also lower in Cohort 1 than in Cohort 3 (RR 0.52, 95% CI 0.27-0.99). In the adjusted base model, the risk of MCA (total) appeared decreased in Cohort 1 compared with Cohort 3, although the difference was not statistically significant (RR 0.57, 95% CI 0.31-1.03).

In the further adjusted model, the decreased risk of the composite endpoint of serious adverse pregnancy outcomes in Cohort 1 compared with Cohort 3 remained statistically significant (RR 0.55, 95% CI 0.31-0.95), as did the risk of MCAs in live births (RR 0.52, 95% CI 0.28-0.98) (**Table 8**).The decreased risk of MCA (total) in Cohort 1 compared with Cohort 3 did not reach statistical significance in the further adjusted model (RR 0.55, 95% CI 0.31-1.00) (**Table 8**).

No statistically significant differences were observed in the risk of elective TOPFAs, stillbirths, or non-live births, when comparing pregnant women with MS exposed to IFN-beta only (Cohort 1) to those unexposed to any MSDMDs (Cohort 3) (**Table 8**). However, the risk of stillbirths was generally decreased in Cohort 1 compared with Cohort 3, without reaching statistical significance.

The risk of elective terminations for other reasons than TOPFA appeared increased among pregnant women with MS exposed to IFN-beta only (Cohort 1) to those unexposed to any MSDMDs (Cohort 3), both in the adjusted base model (OR 1.71, 95% CI 1.06-2.78) and in the further adjusted model (OR 1.65, CI 95% 1.02-2.67) (**Table 8**).

Table 8 Odds ratios (OR) and relative risks (RR) of serious adverse pregnancy outcomes, elective terminations for other reasons, MCAs and non-live births in women with MS exposed IFN-beta only (Cohort 1) compared with those unexposed to any MSDMDs (Cohort 3) or unexposed to IFN-beta regardless of exposure to other MSDMDs (Cohort 4), and in women with MS exposed to IFN-beta regardless of exposure to other MSDMDs (Cohort 2) compared with those unexposed to any MSDMDs (Cohort 3).

Pregnancy outcome	Primary objective 2a: Cohort 1 vs. 3 (reference)				Primary objective 2b: Cohort 1 vs. 4 (reference)				Secondary objective 3: Cohort 2 vs. 3 (reference)			
	Adjusted base model[1]		Further adjusted model[2]		Adjusted base model[1]		Further adjusted model[2]		Adjusted base model[1]		Further adjusted model[2]	
	OR (95% CI)	**RR (95% CI)**	OR (95% CI)	**RR (95% CI)**	OR (95% CI)	**RR (95% CI)**	OR (95% CI)	**RR (95% CI)**	OR (95% CI)	**RR (95% CI)**	OR (95% CI)	**RR (95% CI)**
Serious adverse pregnancy outcome[3,4]	0.54 (0.30-0.96)	**0.55 (0.31-0.96)**	0.53 (0.30-0.95)	**0.55 (0.31-0.95)**	0.59 (0.33-1.04)	**0.60 (0.35-1.04)**	0.59 (0.34-1.04)	**0.60 (0.35-1.04)**	0.53 (0.30-0.93)	**0.54 (0.31-0.94)**	0.53 (0.30-0.93)	**0.54 (0.32-0.93)**
Elective TOPFA[3]	1.89 (0.28-12.96)	**1.94 (0.35-10.85)**	0.80 (0.15-4.41)	**0.80 (0.15-4.36)**	2.14 (0.32-14.57)	**2.17 (0.39-11.97)**	0.99 (0.18-5.42)	**0.99 (0.18-5.36)**	1.84 (0.27-12.63)	**1.88 (0.33-10.64)**	0.77 (0.14-4.23)	**0.77 (0.14-4.19)**
MCA in live births[4]	0.51 (0.26-0.99)	**0.52 (0.27-0.99)**	0.51 (0.27-0.98)	**0.52 (0.28-0.98)**	0.57 (0.29-1.09)	**0.57 (0.30-1.08)**	0.57 (0.30-1.07)	**0.58 (0.31-1.08)**	0.51 (0.27-0.97)	**0.52 (0.28-0.97)**	0.51 (0.27-0.96)	**0.53 (0.29-0.97)**
Stillbirth	0.40 (0.08-1.94)	**0.41 (0.09-1.93)**	0.48 (0.10-2.29)	**0.49 (0.10-2.28)**	0.39 (0.09-1.83)	**0.40 (0.09-1.82)**	0.47 (0.10-2.15)	**0.47 (0.10-2.15)**	0.37 (0.08-1.80)	**0.38 (0.08-1.80)**	0.45 (0.10-2.12)	**0.45 (0.10-2.12)**
Elective termination for other reasons[5]	**1.71 (1.06-2.78)**	NA	**1.65 (1.02-2.67)**	NA	**1.54 (0.99-2.41)**	NA	**1.51 (0.97-2.36)**	NA	**1.60 (0.99-2.58)**	NA	**1.53 (0.95-2.45)**	NA
MCA (total)[4]	0.55 (0.30-1.03)	**0.57 (0.31-1.03)**	0.54 (0.29-1.00)	**0.55 (0.31-1.00)**	0.59 (0.32-1.08)	**0.60 (0.33-1.08)**	0.59 (0.32-1.08)	**0.60 (0.34-1.08)**	0.55 (0.30-1.01)	**0.56 (0.31-1.01)**	0.54 (0.30-0.99)	**0.56 (0.31-0.99)**
Non-live birth[6]	**1.47 (0.95-2.28)**	NA	**0.47 (0.10-2.22)**	NA	**1.36 (0.90-2.05)**	NA	**0.45 (0.10-2.08)**	NA	**1.37 (0.89-2.12)**	NA	**0.43 (0.09-2.06)**	NA

Source: Result Report (Annex 4), Tables 3.1 and 3.2

CI, confidence interval; OR, odds ratio; MCA, major congenital anomaly; RR, relative risk; TOPFA, termination of pregnancy due to foetal anomaly.

The main results (RR results except where unavailable) are **bolded** in the table, to make it easier to read.

[1] 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. The adjusted base model uses a predefined set of adjusting variables.

[2] Further adjusted for additional variable selected through variable selection, from the following candidate variables: university hospital district, pre-pregnancy weight, pre-pregnancy BMI, number of previous abortions, smoking status during pregnancy, number of foetuses in pregnancy (single vs. multiple), time since MS diagnosis and duration of MS treatment as available in the data sources. The further adjusted model includes a step by step adjusting method based on a larger set of variables and their correlation with each outcome.

[3] Elective TOPFA not available in the Swedish data.

[4] MCA not available for year 2014 in the Finnish data.

[5] The Swedish data not included.

[6] As the rare disease assumption did not hold for live birth, non-live birth was used as an outcome.

9.3.1.3 Women with MS exposed to IFN-beta only (Cohort 1) vs. unexposed to IFN-beta regardless of exposure to other MSDMDs (Cohort 4) (Primary objective 2b)

When women with MS exposed to IFN-beta only (Cohort 1) were compared with women unexposed to IFN-beta regardless of exposure to other MSDMDs (Cohort 4), the results were similar when compared with women unexposed to any MSDMDs (**Table 8**). However, none of the observed decreased risks of pregnancy outcomes among women with MS exposed to IFN-beta reached statistical significance in the adjusted base model nor in the further adjusted model.

9.3.1.4 Women with MS exposed to IFN-beta regardless of exposure to other MSDMDs (Cohort 2) vs. unexposed to any MSDMDs (Cohort 3) (Secondary objective 3)

Similar to the comparison between Cohorts 1 and 3, the adjusted base model showed a decreased risk of the composite endpoint of serious adverse pregnancy outcomes (RR 0.54, 95% CI 0.31-0.94) and MCA in live births (RR 0.52, 95% CI 0.28-0.97) among the IFN-beta exposed in Cohort 2 compared with those entirely unexposed to MSDMDs in Cohort 3 (**Table 8**). In the further adjusted model, the decreased risk in Cohort 2 compared with Cohort 3 remained statistically significant both for the composite endpoint of serious adverse pregnancy outcomes (RR 0.54, 95% CI 0.32-0.93) and for MCA in live births (RR 0.53, 95% CI 0.29-0.97).

No statistically significant differences were observed in the risk of elective TOPFAs, stillbirths, elective terminations for other reasons than TOPFA, or non-live births, when comparing women with MS exposed to IFN-beta regardless of exposure to other MSDMDs (Cohort 2) to those unexposed to any MSDMDs (Cohort 3) (**Table 8**). However, in the adjusted base and further adjusted models the risk of stillbirths was generally decreased, and in the adjusted base model the risk of elective terminations for other reasons than TOPFA increased in Cohort 2 compared with Cohort 3, without reaching statistical significance.

9.3.2 Ectopic pregnancy and spontaneous abortion (Secondary objective 4)

9.3.2.1 Prevalence, combined in FIN and SWE and by Cohort

Among all women with MS (Cohorts 1-4), the prevalence of ectopic pregnancies was 2.6% (95% CI 2.1-3.3%), with similar prevalence in Cohorts 1-4 (**Table 9**; overlapping confidence intervals). The prevalence of spontaneous abortions combined in FIN and SWE was 10.3% (95% CI 9.2-11.5%), being 8.3% (95% CI 6.5-10.4%) in Cohort 1 and 8.1% (95% CI 6.3-10.1%) Cohort 2, and 12.0% (95% CI 10.4-13.6%) in Cohort 3 and 11.2% (95% CI 9.9-12.7%) in Cohort 4.

Table 9 Prevalence of ectopic pregnancies and spontaneous abortions, combined in FIN and SWE, and by Cohort.

Pregnancy outcome	Prevalence n,%; combined in FIN and SWE, and by Cohort				
	All pregnant women with MS (Cohorts 1-4)	Women exposed to IFN-beta		Women unexposed to IFN-beta	
		Cohort 1 IFN-beta(+)/ oMSDMD(-)	Cohort 2 IFN-beta(+)/ oMSDMD(+/-)	Cohort 3 IFN-beta(-)/ oMSDMD(-)	Cohort 4 IFN-beta(-)/ oMSDMD(+/-)
Ectopic pregnancy	74/2831 (2.6, 2.1-3.3)	13/797 (1.6, 0.9-2.8)	13/856 (1.5, 0.8-2.6)	53/1647 (3.2, 2.4-4.2)	61/1975 (3.1, 2.4-3.9)
Spontaneous abortion	291/2831 (10.3, 9.2-11.5)	66/797 (8.3, 6.5-10.4)	69/856 (8.1, 6.3-10.1)	197/1647 (12.0, 10.4-13.6)	222/1975 (11.2, 9.9-12.7)

Source: Result Report (Annex 4), Table 2.1
IFN-beta, interferon beta; MCA, major congenital anomaly; MS, multiple sclerosis; n, number of pregnancy events; N, denominator for the specific analysis; oMSDMD, other multiple sclerosis disease modifying drug than interferon beta; TOPFA, termination of pregnancy due to foetal anomaly.

9.3.2.2 *Comparing ectopic pregnancies and spontaneous abortions between Cohorts*

Based on the adjusted base models and the further adjusted models, a trend towards decreased risk of ectopic pregnancies was observed when comparing women with MS exposed to IFN-beta (Cohorts 1 and 2) to those unexposed to IFN-beta (Cohorts 3 and 4) (**Table 10**). The decreased risk reached statistical significance only in the adjusted base models, and when women with MS exposed to IFN-beta (Cohorts 1 or 2) were compared to those unexposed any MSDMDs (Cohort 3), while comparison to Cohort 4 did not reach statistical significance. In the further adjusted models, the risk decease did not reach statistical significance and the numerical risk decrease was smaller (point estimate RR closer to 1).

No statistically significant differences in the risk of spontaneous abortions were observed between any of the Cohorts, not in the adjusted base model nor in the further adjusted model (**Table 10**).

Table 10 Odds ratios (OR) and relative risks (RR) of ectopic pregnancy and spontaneous abortion in women with MS exposed IFN-beta only (Cohort 1) compared with those unexposed to any MSDMDs (Cohort 3) or unexposed to IFN-beta regardless of exposure to other MSDMDs (Cohort 4), and in women with MS exposed to IFN-beta regardless of exposure to other MSDMDs (Cohort 2) compared with those unexposed to any MSDMDs (Cohort 3).

Pregnancy outcome	Cohort 1 vs. 3 (reference)				Cohort 1 vs. 4 (reference)				Cohort 2 vs. 3 (reference)			
	Adjusted base model[1]		Further adjusted model[2]		Adjusted base model[1]		Further adjusted model[2]		Adjusted base model[1]		Further adjusted model[2]	
	OR (95% CI)	**RR (95% CI)**	OR (95% CI)	**RR (95% CI)**	OR (95% CI)	**RR (95% CI)**	OR (95% CI)	**RR (95% CI)**	OR (95% CI)	**RR (95% CI)**	OR (95% CI)	**RR (95% CI)**
Ectopic pregnancy	0.52 (0.27-0.97)	**0.53 (0.29-0.98)**	0.96 (0.49-1.88)	**0.91 (0.52-1.61)**	0.54 (0.29-1.00)	**0.55 (0.30-1.00)**	0.95 (0.49-1.84)	**0.90 (0.51-1.58)**	0.49 (0.26-0.93)	**0.51 (0.27-0.93**	0.92 (0.47-1.81	**0.89 (0.50-1.57)**
Spontaneous abortion	0.75 (0.55-1.02)	**0.78 (0.60-1.02)**	1.15 (0.81-1.63)	**1.14 (0.94-1.38)**	0.79 (0.59-1.06)	**0.81 (0.62-1.05)**	1.22 (0.87-1.72)	**1.17 (0.98-1.41)**	0.74 (0.55-1.00)	**0.77 (0.59-1.00)**	1.11 (0.79-1.56)	**1.12 (0.93-1.36)**

Source: Result Report (Annex 4), Tables 3.1 and 3.2

CI, confidence interval; OR, odds ratio; MCA, major congenital anomaly; RR, relative risk; TOPFA, termination of pregnancy due to foetal anomaly.

The main results (RR results except where unavailable) are **bolded** in the table, to make it easier to read.

[1] 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.

[2] Further adjusted for additional variable selected through variable selection, from the following candidate variables: university hospital district, pre-pregnancy weight, pre-pregnancy BMI, number of previous abortions, smoking status during pregnancy, number of foetuses in pregnancy (single vs. multiple), time since MS diagnosis and duration of MS treatment as available in the data sources.

9.3.3 Stratified prevalence of pregnancy outcomes and associations with adjusting variables (Secondary objective 5)

The prevalence of serious adverse pregnancy outcomes among all pregnant women with MS (Cohorts 1-4) was 4.6% in FIN and 2.5% in SWE (**Table 11**). The same pattern of higher prevalence in FIN compared with SWE was also observed for the other pregnancy outcomes: MCAs in live births, stillbirths, and MCAs (total); and lower prevalence of live births in FIN. The prevalence of elective TOPFAs (0.7%) and elective terminations for other reasons (13.6%) were available exclusively in FIN. In both FIN and SWE, the pattern of a lower prevalence of adverse pregnancy outcomes in women exposed to IFN-beta (Cohorts 1 and 2) than those unexposed to IFN-beta (Cohorts 3 and 4) was observed. In SWE, the prevalence of live births was, however, similar between the Cohorts. Thus, the lower prevalence of live births in Cohorts 1 and 2 than in Cohorts 3 and 4, combined for the countries, was driven by differences in the prevalence between the Cohorts in the Finnish data.

The prevalence of pregnancy outcomes among all pregnant women and by characteristics and Cohort are presented in Tables 5.1-5.4 and 5.7 in Result Report. The prevalence of serious adverse pregnancy outcomes differed by duration of MS treatment. With shorter duration of MS treatment at LMP (<2 years and 3-5 years), the prevalence of serious adverse pregnancy outcomes was lower in Cohorts 1 and 2 (<2 years: 1.3% and 1.2%; 3-5 years: 1.7% and 2.0%), compared with Cohorts 3 and 4 (<2 years: 4.6% and 4.4%; 3-5 years: 4.9% and 4.5%), respectively (Table 5.1; Result Report). With an MS treatment of >5 years at LMP, on the contrary, the prevalence of serious adverse pregnancy outcomes appeared higher in Cohorts 1 and 2 (4.3% and 4.0%), compared with Cohorts 3 and 4 (2.7% and 2.1%), respectively.

Associations between the covariates in the adjusted models and serious adverse pregnancy outcomes are presented in **Table 12**, and the covariates and MCAs (total) in **Table 13**. Residing in FIN and having chronic diseases other than MS increased the risk of both serious adverse pregnancy outcomes and MCAs (total). Associations between the covariates in the adjusted models and all of the outcomes are presented in Tables 4.1-4.12 in Result Report.

Cohorts 1 and 2 were to a larger extent exposed to any group C and/or D teratogenic medications before or during pregnancy than were Cohorts 3 and 4 (**Table 5**), but this difference in exposure was not associated with the adverse pregnancy outcomes being studied (**Table 12**).

Table 11 Prevalence of serious pregnancy outcomes, elective terminations for other reasons, MCAs and live births, by country and Cohort.

Pregnancy outcome	Prevalence n/N (%), by country and cohort									
	FIN					SWE				
	All pregnant women with MS (Cohorts 1-4)	Women exposed to IFN-beta		Women unexposed to IFN-beta		All pregnant women with MS (Cohorts 1-4)	Women exposed to IFN-beta		Women unexposed to IFN-beta	
		Cohort 1 IFN-beta(+)/ oMSDMD(-)	Cohort 2 IFN-beta(+)/ oMSDMD(+/-)	Cohort 3 IFN-beta(-)/ oMSDMD(-)	Cohort 4 IFN-beta(-)/ oMSDMD(+/-)		Cohort 1 IFN-beta(+)/ oMSDMD(-)	Cohort 2 IFN-beta(+)/ oMSDMD(+/-)	Cohort 3 IFN-beta(-)/ oMSDMD(-)	Cohort 4 IFN-beta(-)/ oMSDMD(+/-)
Serious adverse pregnancy outcome[1,2]	41/890 (4.6)	8/295 (2.7)	8/307 (2.6)	29/474 (6.1)	33/583 (5.7)	39/1576 (2.5)	8/423 (1.9)	9/467 (1.9)	27/923 (2.9)	30/1109 (2.7)
Elective TOPFA[1]	6/890 (0.7)	2/295 (0.7)	2/307 (0.7)	4/474 (0.8)	4/583 (0.7)	NA[1]	NA[1]	NA[1]	NA[1]	NA[1]
MCA in live births[2]	28/756 (3.7)	5/244 (2.0)	5/256 (2.0)	21/411 (5.1)	23/500 (4.6)	34/1571 (2.2)	7/422 (1.7)	8/466 (1.7)	23/919 (2.5)	26/1105 (2.4)
Stillbirth	7/890 (0.8)	1/295 (0.3)	1/307 (0.3)	4/474 (0.8)	6/583 (1.0)	5/1576 (0.3)	1/423 (0.2)	1/467 (0.2)	4/923 (0.4)	4/1109 (0.4)
Elective termination for other reasons[3]	121/890 (13.6)	48/295 (16.3)	48/307 (15.6)	55/474 (11.6)	73/583 (12.5)	NA[3]	NA[3]	NA[3]	NA[3]	NA[3]
MCA (total)[2]	37/890 (4.2)	7/295 (2.4)	7/307 (2.3)	26/474 (5.5)	30/583 (5.1)	34/1576 (2.2)	7/423 (1.7)	8/467 (1.7)	23/923 (2.5)	26/1109 (2.3)
Live birth	756/890 (84.9)	244/295 (82.7)	256/307 (83.4)	411/474 (86.7)	500/583 (85.8)	1571/1576 (99.7)	422/423 (99.8)	466/467 (99.8)	919/923 (99.6)	1105/1109 (99.6)

Source: Result Report (Annex 4), Tables 5.1 - 5.7

IFN-beta, interferon beta; MCA, major congenital anomaly; MS, multiple sclerosis; n, number of pregnancy events; N, denominator for the specific analysis; NA, not applicable; oMSDMD, other multiple sclerosis disease modifying drug than interferon beta; TOPFA, termination of pregnancy due to foetal anomaly.

[1] Elective TOPFA not available in the Swedish data.

[2] MCA not available for year 2014 in the Finnish data.

[3] The Swedish data not available.

Table 12 Prevalence of serious adverse pregnancy outcomes, by covariates in the adjusted models and by Cohort, and associations between the outcome and the covariates in the different cohort comparisons.

Variable	Serious adverse pregnancy outcome									
	Prevalence n/N (%)				Cohort 1 vs. 3 (reference)		Cohort 1 vs. 4 (reference)		Cohort 2 vs. 3 (reference)	
	Women exposed to IFN-beta		Women unexposed to IFN-beta							
	Cohort 1 IFN-beta(+)/ oMSDMD(-)	Cohort 2 IFN-beta(+)/ oMSDMD(+/-)	Cohort 3 IFN-beta(-)/ oMSDMD(-)	Cohort 4 IFN-beta(-)/ oMSDMD(+/-)	Adjusted base model RR (95% CI)	Further adjusted model RR (95% CI)	Adjusted base model RR (95% CI)	Further adjusted model RR (95% CI)	Adjusted base model RR (95% CI)	Further adjusted model RR (95% CI)
VARIABLES EXCLUSIVELY IN ADJUSTED BASE MODEL										
Country of residence										
FIN	8/295 (2.7)	8/307 (2.6)	29/474 (6.1)	33/583 (5.7)	2.77 (1.65-4.63)	2.52 (1.54-4.13)	2.75 (1.69-4.48)	2.47 (1.55-3.94)	2.72 (1.63-4.53)	2.49 (1.52-4.06)
SWE	8/423 (1.9)	9/467 (1.9)	27/923 (2.9)	30/1109 (2.7)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Year of pregnancy outcome										
1996 – 1999	0/1 (0.0)	0/1 (0.0)	4/44 (9.1)	4/44 (9.1)	1.5 (0.52-4.34)	1.35 (0.46-3.90)	1.66 (0.58-4.75)	1.7 (0.60-4.84)	1.55 (0.54-4.47)	1.37 (0.47-3.97)
2000 – 2004	0/26 (0.0)	0/26 (0.0)	0/32 (0.0)	0/35 (0.0)	NA	NA	NA	NA	NA	NA
2005 – 2009	5/207 (2.4)	5/225 (2.2)	18/468 (3.8)	20/557 (3.6)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
≥2010	11/484 (2.3)	12/522 (2.3)	34/853 (4.0)	39/1056 (3.7)	0.93 (0.57-1.52)	0.89 (0.54-1.47)	0.92 (0.58-1.48)	0.92 (0.57-1.48)	0.94 (0.58-1.55)	0.90 (0.55-1.49)
Maternal age at LMP										
≤20 years	0/7 (0.0)	0/8 (0.0)	0/13 (0.0)	1/15 (6.7)	NA	Not selected	1.26 (0.17-9.22)	Not selected	NA	Not selected
21 – 25 years	3/90 (3.3)	3/102 (2.9)	6/129 (4.7)	7/164 (4.3)	Ref.	Not selected	Ref.	Not selected	Ref.	Not selected
26 – 30 years	6/253 (2.4)	7/273 (2.6)	16/435 (3.7)	17/545 (3.1)	0.81 (0.38-1.73)	Not selected	0.75 (0.36-1.56)	Not selected	0.86 (0.40-1.83)	Not selected
31 – 35 years	6/291 (2.1)	6/307 (2.0)	22/528 (4.2)	26/633 (4.1)	0.83 (0.39-1.76)	Not selected	0.89 (0.44-1.79)	Not selected	0.86 (0.41-1.82)	Not selected
36 – 40 years	1/60 (1.7)	1/67 (1.5)	11/267 (4.1)	11/303 (3.6)	0.81 (0.34-1.95)	Not selected	0.79 (0.34-1.84)	Not selected	0.84 (0.35-2.02)	Not selected
> 40 years	0/17 (0.0)	0/17 (0.0)	1/25 (4.0)	1/32 (3.1)	0.62 (0.08-4.78)	Not selected	0.53 (0.07-4.06)	Not selected	0.65 (0.08-5.01)	Not selected
Number of previous pregnancies										
0	NA[1]	NA[1]	NA[1]	NA[1]	Ref.	Not selected	Ref.	Not selected	Ref.	Not selected
1 – 2	NA[1]	NA[1]	NA[1]	NA[1]	1.23 (0.74-2.03)	Not selected	1.16 (0.72-1.86)	Not selected	1.17 (0.71-1.93)	Not selected

Variable	Serious adverse pregnancy outcome									
	Prevalence n/N (%)				Cohort 1 vs. 3 (reference)		Cohort 1 vs. 4 (reference)		Cohort 2 vs. 3 (reference)	
	Women exposed to IFN-beta		Women unexposed to IFN-beta							
	Cohort 1 IFN-beta(+)/ oMSDMD(-)	Cohort 2 IFN-beta(+)/ oMSDMD(+/-)	Cohort 3 IFN-beta(-)/ oMSDMD(-)	Cohort 4 IFN-beta(-)/ oMSDMD(+/-)	Adjusted base model RR (95% CI)	Further adjusted model RR (95% CI)	Adjusted base model RR (95% CI)	Further adjusted model RR (95% CI)	Adjusted base model RR (95% CI)	Further adjusted model RR (95% CI)
≥3	NA[1]	NA[1]	NA[1]	NA[1]	0.95 (0.41-2.24)	Not selected	0.87 (0.38-2.02)	Not selected	0.91 (0.39-2.12)	Not selected
Any chronic disease before or during pregnancy (excl. MS)										
Yes	10/256 (3.9)	11/279 (3.9)	25/542 (4.6)	28/665 (4.2)	2.14 (1.30-3.52)	2.12 (1.31-3.46)	2.04 (1.27-3.28)	1.98 (1.25-3.14)	2.18 (1.33-3.57)	2.17 (1.34-3.52)
No	6/462 (1.3)	6/495 (1.2)	31/855 (3.6)	35/1027 (3.4)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Exposure to any group C teratogenic medications before[5] or during pregnancy										
Yes	10/469 (2.1)	11/504 (2.2)	30/733 (4.1)	34/917 (3.7)	0.78 (0.49-1.26)	Not selected	0.74 (0.47-1.17)	Not selected	0.80 (0.50-1.29)	Not selected
No	6/249 (2.4)	6/270 (2.2)	26/664 (3.9)	29/775 (3.7)	Ref.	Not selected	Ref.	Not selected	Ref.	Not selected
Exposure to any group D teratogenic medications before[5] or during pregnancy										
Yes	3/131 (2.3)	3/148 (2.0)	10/171 (5.8)	11/210 (5.2)	1.56 (0.86-2.85)	Not selected	1.53 (0.86-2.73)	Not selected	1.48 (0.82-2.70)	Not selected
No	13/587 (2.2)	14/626 (2.2)	46/1226 (3.8)	52/1482 (3.5)	Ref.	Not selected	Ref.	Not selected	Ref.	Not selected
VARIABLES ADDED IN FURTHER ADJUSTED MODEL										
Number of foetuses in pregnancy[6]										
Single	NA[1]	NA[1]	NA[1]	NA[1]	-	Not selected	-	Not selected	-	Not selected
Multiple	NA[1]	NA[1]	NA[1]	NA[1]	-	Not selected	-	Not selected	-	Not selected
Missing	NA[1]	NA[1]	NA[1]	NA[1]	-	Not selected	-	Not selected	-	Not selected
Time since MS diagnosis at LMP										
≤2 years	2/220 (0.9)	2/240 (0.8)	12/396 (3.0)	15/463 (3.2)	-	Ref.	-	Not selected	-	Ref.
3-5 years	6/254 (2.4)	7/274 (2.6)	28/464 (6.0)	29/572 (5.1)	-	2.02 (1.09-3.74)	-	Not selected	-	2.09 (1.13-3.85)

Variable	Serious adverse pregnancy outcome									
	Prevalence n/N (%)				Cohort 1 vs. 3 (reference)		Cohort 1 vs. 4 (reference)		Cohort 2 vs. 3 (reference)	
	Women exposed to IFN-beta		Women unexposed to IFN-beta							
	Cohort 1 IFN-beta(+)/ oMSDMD(-)	Cohort 2 IFN-beta(+)/ oMSDMD(+/-)	Cohort 3 IFN-beta(-)/ oMSDMD(-)	Cohort 4 IFN-beta(-)/ oMSDMD(+/-)	Adjusted base model RR (95% CI)	Further adjusted model RR (95% CI)	Adjusted base model RR (95% CI)	Further adjusted model RR (95% CI)	Adjusted base model RR (95% CI)	Further adjusted model RR (95% CI)
>5 years	8/244 (3.3)	8/260 (3.1)	16/537 (3.0)	19/657 (2.9)	-	1.26 (0.65-2.43)	-	Not selected	-	1.27 (0.66-2.45)

Source: Result Report (Annex 4), Tables 4.1 - 4.6, 5.1 - 5.7

CI, confidence interval; OR, odds ratio; IFN-beta, interferon beta; MS, multiple sclerosis; n, number of pregnancy events; N, denominator for the specific analysis; NA, not applicable; oMSDMD, other multiple sclerosis disease modifying drug than interferon beta; RR, relative risk.

[1] Prevalence not calculated.

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Table 13 Prevalence of MCAs (total), by covariates in the adjusted models and by Cohort, and associations between the outcome and the covariates in the different cohort comparisons.

Variable	MCA (total)									
	Prevalence n/N (%)				Cohort 1 vs. 3 (reference)		Cohort 1 vs. 4 (reference)		Cohort 2 vs. 3 (reference)	
	Women exposed to IFN-beta		Women unexposed to IFN-beta		Adjusted base model RR (95% CI)	Further adjusted model RR (95% CI)	Adjusted base model RR (95% CI)	Further adjusted model RR (95% CI)	Adjusted base model RR (95% CI)	Further adjusted model RR (95% CI)
	Cohort 1 IFN-beta(+)/ oMSDMD(-)	Cohort 2 IFN-beta(+)/ oMSDMD(+/-)	Cohort 3 IFN-beta(-)/ oMSDMD(-)	Cohort 4 IFN-beta(-)/ oMSDMD(+/-)						
VARIABLES EXCLUSIVELY IN ADJUSTED BASE MODEL										
Country of residence										
FIN	7/295 (2.4)	7/307 (2.3)	26/474 (5.5)	30/583 (5.1)	2.81 (1.61-4.90)	2.51 (1.48-4.27)	2.83 (1.68-4.75)	2.49 (1.51-4.10)	2.75 (1.59-4.77)	2.47 (1.46-4.18)
SWE	7/423 (1.7)	8/467 (1.7)	23/923 (2.5)	26/1109 (2.3)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Year of pregnancy outcome										
1996 – 1999	0/1 (0.0)	0/1 (0.0)	4/44 (9.1)	4/44 (9.1)	1.57 (0.54-4.57)	1.38 (0.47-4.02)	1.71 (0.59-4.92)	1.72 (0.60-4.94)	1.63 (0.56-4.74)	1.40 (0.48-4.11)
2000 – 2004	0/26 (0.0)	0/26 (0.0)	0/32 (0.0)	0/35 (0.0)	NA	NA	NA	NA	NA	NA
2005 – 2009	5/207 (2.4)	5/225 (2.2)	17/468 (3.6)	19/557 (3.4)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
≥2010	9/484 (1.9)	10/522 (1.9)	28/853 (3.3)	33/1056 (3.1)	0.80 (0.48-1.35)	0.77 (0.46-1.30)	0.81 (0.50-1.34)	0.81 (0.49-1.33)	0.82 (0.49-1.37)	0.78 (0.46-1.32)
Maternal age at LMP										
≤20 years	0/7 (0.0)	0/8 (0.0)	0/13 (0.0)	1/15 (6.7)	NA	Not selected	1.24 (0.17-9.17)	Not selected	NA	Not selected
21 – 25 years	3/90 (3.3)	3/102 (2.9)	6/129 (4.7)	7/164 (4.3)	Ref.	Not selected	Ref.	Not selected	Ref.	Not selected
26 – 30 years	5/253 (2.0)	6/273 (2.2)	12/435 (2.8)	13/545 (2.4)	0.62 (0.28-1.38)	Not selected	0.59 (0.27-1.25)	Not selected	0.67 (0.30-1.48)	Not selected
31 – 35 years	5/291 (1.7)	5/307 (1.6)	20/528 (3.8)	24/633 (3.8)	0.75 (0.35-1.61)	Not selected	0.81 (0.40-1.66)	Not selected	0.78 (0.36-1.66)	Not selected
36 – 40 years	1/60 (1.7)	1/67 (1.5)	10/267 (3.7)	10/303 (3.3)	0.75 (0.31-1.84)	Not selected	0.73 (0.31-1.74)	Not selected	0.78 (0.32-1.90)	Not selected
> 40 years	0/17 (0.0)	0/17 (0.0)	1/25 (4.0)	1/32 (3.1)	0.64 (0.08-4.97)	Not selected	0.56 (0.07-4.29)	Not selected	0.67 (0.09-5.19)	Not selected
Number of previous pregnancies										
0	NA[1]	NA[1]	NA[1]	NA[1]	Ref.	Not selected	Ref.	Not selected	Ref.	Not selected

Variable	MCA (total)									
	Prevalence n/N (%)				Cohort 1 vs. 3 (reference)		Cohort 1 vs. 4 (reference)		Cohort 2 vs. 3 (reference)	
	Women exposed to IFN-beta		Women unexposed to IFN-beta		Adjusted base model RR (95% CI)	Further adjusted model RR (95% CI)	Adjusted base model RR (95% CI)	Further adjusted model RR (95% CI)	Adjusted base model RR (95% CI)	Further adjusted model RR (95% CI)
	Cohort 1 IFN-beta(+)/ oMSDMD(-)	Cohort 2 IFN-beta(+)/ oMSDMD(+/-)	Cohort 3 IFN-beta(-)/ oMSDMD(-)	Cohort 4 IFN-beta(-)/ oMSDMD(+/-)						
1 – 2	NA[1]	NA[1]	NA[1]	NA[1]	1.22 (0.71-2.1)	Not selected	1.14 (0.69-1.89)	Not selected	1.16 (0.68-1.98)	Not selected
≥3	NA[1]	NA[1]	NA[1]	NA[1]	0.95 (0.38-2.4)	Not selected	0.84 (0.34-2.08)	Not selected	0.9 (0.36-2.25)	Not selected
Any chronic disease before or during pregnancy (excl. MS)										
Yes	8/256 (3.1)	9/279 (3.2)	21/542 (3.9)	24/665 (3.6)	2.01 (1.18-3.45)	1.96 (1.16-3.32)	1.93 (1.16-3.21)	1.84 (1.12-3.01)	2.06 (1.21-3.51)	2.01 (1.20-3.39)
No	6/462 (1.3)	6/495 (1.2)	28/855 (3.3)	32/1027 (3.1)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Exposure to any group C teratogenic medications before[5] or during pregnancy										
Yes	8/469 (1.7)	9/504 (1.8)	25/733 (3.4)	29/917 (3.2)	0.70 (0.42-1.15)	Not selected	0.67 (0.41-1.08)	Not selected	0.72 (0.43-1.18)	Not selected
No	6/249 (2.4)	6/270 (2.2)	24/664 (3.6)	27/775 (3.5)	Ref.	Not selected	Ref.	Not selected	Ref.	Not selected
Exposure to any group D teratogenic medications before[5] or during pregnancy										
Yes	3/131 (2.3)	3/148 (2.0)	8/171 (4.7)	9/210 (4.3)	1.54 (0.80-2.98)	Not selected	1.53 (0.82-2.86)	Not selected	1.46 (0.76-2.81)	Not selected
No	11/587 (1.9)	12/626 (1.9)	41/1226 (3.3)	47/1482 (3.2)	Ref.	Not selected	Ref.	Not selected	Ref.	Not selected
VARIABLES ADDED IN FURTHER ADJUSTED MODEL										
Number of foetuses in pregnancy[6]										
Single	NA[1]	NA[1]	NA[1]	NA[1]	-	Not selected	-	Not selected	-	Not selected
Multiple	NA[1]	NA[1]	NA[1]	NA[1]	-	Not selected	-	Not selected	-	Not selected
Missing	NA[1]	NA[1]	NA[1]	NA[1]	-	Not selected	-	Not selected	-	Not selected

Variable	MCA (total)									
	Prevalence n/N (%)				Cohort 1 vs. 3 (reference)		Cohort 1 vs. 4 (reference)		Cohort 2 vs. 3 (reference)	
	Women exposed to IFN-beta		Women unexposed to IFN-beta		Adjusted base model RR (95% CI)	Further adjusted model RR (95% CI)	Adjusted base model RR (95% CI)	Further adjusted model RR (95% CI)	Adjusted base model RR (95% CI)	Further adjusted model RR (95% CI)
	Cohort 1 IFN-beta(+)/ oMSDMD(-)	Cohort 2 IFN-beta(+)/ oMSDMD(+/-)	Cohort 3 IFN-beta(-)/ oMSDMD(-)	Cohort 4 IFN-beta(-)/ oMSDMD(+/-)						
Time since MS diagnosis at LMP										
≤2 years	2/220 (0.9)	2/240 (0.8)	10/396 (2.5)	13/463 (2.8)	-	Ref.	-	Not selected	-	Ref.
3-5 years	5/254 (2.0)	6/274 (2.2)	25/464 (5.4)	26/572 (4.5)	-	2.11 (1.09-4.10)	-	Not selected	-	2.19 (1.13-4.24)
>5 years	7/244 (2.9)	7/260 (2.7)	14/537 (2.6)	17/657 (2.6)	-	1.33 (0.66-2.70)	-	Not selected	-	1.34 (0.66-2.73)

Source: Result Report (Annex 4), Tables 4.1 - 4.6, 5.1 - 5.7

CI, confidence interval; OR, odds ratio; IFN-beta, interferon beta; MCA, major congenital anomaly; MS, multiple sclerosis; n, number of pregnancy events; N, denominator for the specific analysis; NA, not applicable; oMSDMD, other multiple sclerosis disease modifying drug than interferon beta; RR, relative risk.

[1] Prevalence not calculated.

9.3.4 Indirect comparison of selected pregnancy outcomes in women with MS unexposed to IFN-beta (Cohort 3) compared with general populations (Cohort 6) (Exploratory objective 7)

Comparing the observed pregnancy outcomes among women unexposed to IFN-beta (Cohort 3) to those in the general population (Cohort 6), results differed between the countries (**Table 14**). For FIN, the prevalence ectopic pregnancies and spontaneous abortions was higher than expected in Cohort 3, while for MCA (total) and stillbirths a difference in the observed and expected prevalence did not reach statistical difference. For SWE, there was no statistically significant difference in the prevalence of these pregnancy outcomes between the women with MS unexposed to IFN-beta and the general population. In the total study population, the prevalence of ectopic pregnancies and spontaneous abortion was higher than expected among women with MS, mainly driven by FIN data (**Table 14**).

Table 14 Prevalence of outcomes in women unexposed to any IFN-beta (Cohort 3) and in the general population (Cohort 6).

	FIN Observed total n / expected total n : standardised prevalence ratio (95% CI)	**SWE** Observed total n / expected total n : standardised prevalence ratio (95% CI)	**Combined** Observed total n / expected total n : standardised prevalence ratio (95% CI)
Cohort 3 observed vs. expected			
Stillbirths	4/1.3 : 3.10 (0.84-7.94)	4/3.5 : 1.14 (0.31-2.92)	8/4.8 : 1.67 (0.72-3.28)
MCA (total)	20/12.9 : 1.55 (0.95-2.40)	28/28.6 : 0.80 (0.51-1.21)	43/41.5 : 1.04 (0.75-1.40)
Ectopic pregnancies	80/30.0 : 2.66 (2.11-3.32)	19/22.5 : 0.84 (0.51-1.32)	99/52.6 : 1.88 (1.53-2.29)
Spontaneous abortions	155/67.5 : 2.30 (1.95-2.69)	138/143.3 : 0. 96 (0.81-1.14)	293/210.8 : 1.39 (1.24-1.56)

Source: Result Report (Annex 4), Tables 6.1-6.5
CI, Confidence interval; FIN, Finland; MCA, Major congenital anomaly
Note: The "observed total n" numbers presented in this tables for ectopic pregnancies and spontaneous abortions differ from those presented in Table 6. In the descriptive tables and analyses, visits within 3 months after the first visit were combined, so that the first visit defined the event date but the last diagnosis identified during the 3-month period determining the diagnosis for the event. However, in indirect comparisons this type of combination of events was not possible for the data on general population and thus all visits were included (max 1 record/day), with the registered diagnosis. Thus, the total number of events and pregnancies were higher in the indirect comparisons than in the descriptive tables and analyses.

9.3.5 Sensitivity analyses

9.3.5.1 Sensitivity analysis 1: Cross-country comparison of MCAs between cohorts, by country

Cross-country comparisons between FIN and NOR were not possible to conduct due to delay in data permit processes In Norway.

9.3.5.2 Sensitivity analysis 2: Comparison of elective TOPFA between cohorts, by trimester

Among pregnancies ending with TOPFA, all six events occurred during the second trimester. Thus, comparisons between the cohorts, separately for the first and third trimesters, could not be conducted (Tables 8.1-8.3, 8.7-8.12, 8.16-18; Results Report). In addition, only 20 other pregnancy events were identified during the second trimester, making the comparison within that trimester insufficiently powered to identify any differences (n = 26) (Tables 8.4-8.6, 8.13-8.15; Results Report).

9.3.5.3 Sensitivity analysis 3: Comparison of MCA between cohorts when exposure restricted to pre-pregnancy or first trimester

Using an alternative exposure definition, limiting the comparison of MCA outcomes to those with use of IFN-beta or oMSDMDs just before or during the first trimester of pregnancy, the decreased risk of MCA in live births among women with MS exposed to IFN-beta only (Cohort1) remained statistically significant compared

with women with MS unexposed to any MSDMDs (Cohort 3) (RR 0.48, 95% CI 0.25-0.94) (Table 8.19; Results Report). For MCA (total), the decreased risk was significant with, however, the upper limit of the CI close to 1 (RR 0.53, 95% CI 0.29-0.98). The effect size of MCA (in live births or total) was similar for the comparison between women with MS exposed to IFN-beta only (Cohort 1) and women with MS unexposed to IFN-beta regardless of exposure to oMSDMDs (Cohort 4), but that decreased risk did not reach statistical significance (MCA live births RR 0.52, 95% CI 0.27-1.01; MCA (total) RR 0.56, 95% CI 0.30-1.02).

9.3.5.4 Sensitivity analysis 4: Restricting study period to 2005-2014

In the sensitivity analysis limiting the study period to 1st January 2005 – 31st December 2014 (Table 8.25; Result Report), thus only including the period with overlapping data from both countries, was found that results were the same or very similar for serious adverse pregnancy outcome, stillbirth, live birth, MCA in live births and total MCA.

9.3.5.5 Sensitivity analysis 5: Proportion of women using cladribine, mitoxantrone and teriflunomide

No women were exposed to the new immunomodulating MS treatments (i.e., cladribine, mitoxantrone, and teriflunomide) before or during pregnancy (Table 8.31; Result Report).

9.3.5.6 Sensitivity analysis 6: Including intravenous medical treatment administered in a hospital to other MSDMDs

According to the adjusted base model, the risk of the composite endpoint of serious adverse pregnancy outcomes was lower in Cohort 1 than in Cohort 3 (RR 0.54, 95% CI 0.30-0.95) and with borderline significance also for the comparison to Cohort 4 (RR 0.57, 95% CI 0.33-1.00) (Table 8.45; Result Report), after considering women with intravenous medical treatment administered in hospital as exposed to oMSDMDs. Such injections could indicate oMSDMDs or steroids being administered e.g., during healthcare visits/hospitalizations not included in the registers. Additionally, the risk of MCA in live births was lower in Cohort 1 than in Cohort 3, in line with the main analysis. The risk of MCA (total and in live births) was increased in Cohort 1 also in the other comparisons to Cohorts 3 and 4, however, without reaching statistical significance. Also, in line with the main analyses, no statistically significant differences in the risk of the other investigated pregnancy outcomes (elective TOFPA, stillbirth) were observed between the cohorts.

9.3.5.7 Sensitivity analysis 7: Pregnancy outcomes in women with MS exposed to exclusively oMSDMD (Cohort 5), with assumedly more serious MS

In Cohort 5, in women treated exclusively with oMSDMDs, indicating a supposedly more aggressive MS (excluding those exposed to IFN-beta, glatiramer acetate or dimethyl fumarate), 3.2% had serious adverse pregnancy outcomes, all of which were MCAs in live births (Table 8.57; Result Report). The risk of serious adverse pregnancy outcomes, MCAs in live births, or MCA (total) did not differ in Cohort 5 compared with women with MS unexposed to any oMSDMDs (Cohort 3) (Table 8.58 and 8.60; Result Report).

9.3.5.8 Sensitivity analysis 8: Robustness of the variable selection procedure to missing data

The models for serious adverse pregnancy outcomes were robust to alternative model building after multiple imputation, as the trend toward decreased risk in women with MS exposed to IFN-beta (Cohort 1) remained, compared with those unexposed to IFN-beta (Cohorts 3 and 4) (Tables 8.62-8.73; Result Report).

9.3.5.9 Additional post hoc sensitivity analysis: Off-label users among oMSDMDs

The results of these additional analyses are presented in the Result Report, Tables 9.1-9.3. Shortly, 126 pregnancies in total (9 in FIN, 117 in SWE) were found to be exposed to either human normal immunoglobulin, methotrexate or azathioprine. No exposure to cyclophosphamide or leflunomide was

found. Among women with off-label use, the numbers of cases of pregnancy outcomes were very small, e.g. in total 2 serious adverse pregnancy outcomes. When the analysis was restricted to those without off-label use, the prevalence of the pregnancy outcomes was identical to the main analyses (Result Report, Tables 9.3 and 9.4). Thus, the inclusion of the off-label drugs is unlikely to influence risk estimates.

9.3.5.10 Additional post hoc sensitivity analysis: Rituximab users

Even though rituximab is now in common use in the Swedish MS population, additional analyses showed that the study population of this study included five pregnancies exposed to rituximab (data not shown). The outcomes of these pregnancies were 1 spontaneous abortion and 4 full-time births with no malformations.

9.4 Adverse events

The nature of this non-interventional study does not meet the criteria for adverse event reporting.

10 Discussion

10.1 Key results

10.1.1 Serious adverse pregnancy outcomes, elective terminations for other reasons, MCAs and live births

10.1.1.1 Prevalence, combined in FIN and SWE, by cohort and country

In this study, serious adverse pregnancy outcomes occurred in 3.2% of all pregnancy events with MS, of which MCAs in live births were the most common (2.7% of all live births). Of other serious adverse pregnancy outcomes, the prevalence of elective TOPFAs was 0.7% and stillbirth 0.5%, among all women with MS included in the study.

Among Finnish women with MS, pregnancy ended in an elective termination for other reasons than TOPFA for 13.6%. Among all women with MS, the prevalence of all MCAs including still and live births (MCA (total)) was 2.9%. The prevalence of live births was 94.4%.

Of the above outcomes, the prevalence of serious adverse pregnancy outcomes, MCAs in live births, and MCA (total) were lower among women with MS exposed to IFN-beta (Cohorts 1 and 2), compared with those unexposed to IFN-beta (Cohorts 3 and 4). An indication of a higher prevalence of elective terminations for other reasons than foetal anomaly was detected in Cohorts 1-2 compared with Cohort 3-4. The prevalence of the other pregnancy outcomes was similar between the cohorts.

Specifically, among women with MS without any exposure to MSDMDs (Cohort 3), the observed prevalence of serious adverse pregnancy outcomes was 4.0%, among which the prevalence of MCAs in live births was 3.3%, elective TOPFA 0.8%, and stillbirth 0.6%. The prevalence of elective terminations for reasons other than TOPFA was 11.6% among these women without any exposure to MSDMDs. In Cohort 3, the prevalence of MCA (total) was 3.5% and the prevalence of live births 95.2%. Based on the indirect standardised comparisons, the observed prevalence of MCAs total and stillbirths in women with untreated MS (Cohort 3) combined in the two countries did not differ from the expected in the general population (Cohort 6), although the result differed between the countries.

10.1.1.2 Women exposed to IFN-beta compared with those unexposed

In this study, no increased risk of adverse pregnancy outcomes was observed among women with MS exposed to IFN-beta only (Cohort 1) or among those exposed to IFN-beta regardless of exposure to oMSDMDs (Cohort 2), compared with those unexposed to any MSDMDs (Cohort 3) or those unexposed to IFN-beta regardless of exposure to oMSDMDs (Cohort 4). However, according to data available from Finland only the risk of elective terminations for other reasons than foetal anomaly appeared numerically increased among the IFN-beta exposed, reaching statistical significance only when Cohort 1 was compared to Cohort 3.

According to the multivariate models in this study, the lower prevalence of serious adverse pregnancy outcomes, , MCAs in live births, and MCA (total) among women with MS exposed to IFN-beta (Cohort 1 or 2) remained borderline significant after covariate adjustment, compared with women with MS unexposed to any MSDMDs (Cohort 3). For these outcomes, the point estimates (RRs, ORs) for the IFN-beta exposed women were protective with statistical significance either in the adjusted base model, the further adjusted model, or both. However, upper limits of the confidence intervals were close to 1.0.

The descriptive prevalence of serious adverse pregnancy outcomes, MCAs in live births, and MCA (total) was lower among women with MS exposed to IFN-beta only (Cohort 1) compared with those unexposed to IFN-beta and possible exposure to oMSDMDs (Cohort 4), and the association was only borderline non-significant after adjusting for covariates.

Although the higher prevalence of elective terminations for other reasons than foetal anomaly reached statistical significance only when Cohort 1 was compared to Cohort 3, the point estimates (ORs) were increased also when Cohort 1 was compared to Cohort 4 and Cohort 2 to Cohort 3, with lower limits of the confidence intervals close to 1.0. This result was the same for both used regression models, the adjusted base model and the further adjusted model.

10.1.2 Ectopic pregnancy and spontaneous abortion

10.1.2.1 Prevalence, combined in FIN and SWE and by cohort

Among all women with MS included in this study, the prevalence of ectopic pregnancies was 2.6% and spontaneous abortions 10.3%. The prevalence of them was similar between the cohorts.

Specifically, among women with MS unexposed to any MSDMDs (Cohort 3), the observed prevalence of ectopic pregnancies was 3.2% and spontaneous abortions 12.0%. Based on the indirect standardised comparisons, a higher than expected prevalence of ectopic pregnancies and spontaneous abortions was observed in women with untreated MS (Cohort 3) compared with those in the general population (Cohort 6).

10.1.2.2 Women exposed IFN-beta compared with those unexposed

In the adjusted base models and the further adjusted models, a trend towards decreased risk of ectopic pregnancy among women with MS exposed to IFN-beta (Cohorts 1 and 2), compared with those unexposed (Cohorts 3 and 4) was detected. However, only the adjusted base model comparing Cohorts 1 and 2 to Cohort 3 reached statistical significance, with an upper limit of the confidence interval close to 1.0.

No statistically significant differences in the risk of spontaneous abortions were observed between any of the cohorts, not in the adjusted base model or the further adjusted model.

10.1.3 Secondary objective 5

The prevalence of the adverse pregnancy outcomes was by large higher in FIN than in SWE, and in pregnancy events associated with chronic diseases other than MS.

10.2 Limitations

10.2.1 Study power

The comparisons in this study were performed between MS patients exposed to IFN-beta (with/without exposure to oMSDMDs) and women unexposed to IFN-beta (with/without oMSDMDs), and the study has been powered for these comparisons using the serious adverse pregnancy outcome as the endpoint. However, the study was not powered for comparisons made using individual pregnancy outcomes or for comparisons that only employed a subset of the cohorts in the primary comparisons. In the power calculations, the anticipated background prevalence of serious adverse pregnancy outcomes was based on feasibility data from FIN, which due to differences in the overall prevalence of adverse pregnancy outcomes between the countries and due to differences in what is registered was high compared with the prevalence in SWE. Thus, the prevalence of serious adverse pregnancy outcomes observed in this study was higher in FIN than in SWE. However, regardless of country, the prevalence was always lower in Cohort 1 as compared with Cohort 3, which increases the confidence in these results. In the actual comparison of Cohort 1 vs. Cohort 3, the prevalence of serious adverse pregnancy outcomes was lower in Cohort 1 than in Cohort 3. The original power calculations were made assuming higher prevalence in women treated with IFN-beta (Cohort 1) compared with untreated women with MS (Cohort 3). The minimum detectable (80% power) effect size for decrease was 0.45, which corresponds to prevalence 1.7% in Cohort 1. In summary, the study has insufficient statistical power to detect decreases with these numbers for the individual pregnancy outcomes,

but the results are able to show with good statistical confidence that the risk of serious adverse pregnancy outcomes were not increased in Cohort 1 as compared with Cohort 3.

The direction of the effect in comparisons between Cohort 1 and Cohort 3 were in line with the findings in the feasibility study, both for pregnancy outcomes (i.e., lower prevalence of adverse pregnancy outcomes among all women with MS compared with those with untreated MS) and for country comparison (i.e., higher prevalence of adverse pregnancy outcomes in FIN compared with SWE).

10.2.2 Generalisability: Findings limited to MSDMDs on market and used on MS

There is a variation between the countries regarding MSDMDs on market. Some of the products are not on market and some of the products are new to market. For example, teriflunomide was licensed in the European Union in 2013. New MS immunomodulatory therapies (e.g. cladribine, mitoxantrone and teriflunomide) can have long-term side effects. In this study, no women were exposed to these new MSDMDs and therefore we were unable to evaluate their long-term effects.

In FIN, most of the MSDMDs are included in the prescription databases and are included in the study database. In FIN or SWE, IFN-beta natural (L03AB02) is not on market. Furthermore, human normal immunoglobulin (J06BA02), cyclophosphamide (L01AA01), some products of methotrexate (L01BA01, L04AX03), cladribine (L01BB04), mitoxantrone (L01DB07), alemtuzumab (L01XC04) and natalizumab (L04AA23) are on market, but they are not under the special reimbursement and are given in hospitals. Information on glatiramer acetate (L03AX13) is available since 2004, when the product was approved in EU and in NOR. Dimethyl fumarate (N07XX09) is not included in the study, since it was approved in EU and in NOR in 2014 and was launched after the lock point for the data collected.

10.2.3 Selection bias

10.2.3.1 Elective terminations under-represented in the SWE population

As noted in the bias section (8.6), elective terminations were unavailable in SWE, and could therefore not be considered in the numerator or denominator for estimating the prevalence of MCAs.

In addition, the unavailability of data on elective terminations in SWE influenced the prevalence of stillbirths and live births when elective terminations were intended to be included in the denominator. Namely, the obtained results on the prevalence of both stillbirths and live births would have been lower in SWE than observed in this study, if elective terminations could have been included in the dominator (making the denominator larger).

Because the unavailability of data elective terminations in SWE influenced both the prevalence of MCAs and stillbirths, the limitation also influenced the composite endpoint serious adverse pregnancy outcomes.

Due to the unavailability of elective terminations in SWE, elective TOPFA or elective terminations for other reasons could not be evaluated in SWE at all.

10.2.3.2 Spontaneous abortions underrepresented in the population

Information on spontaneous abortions was incomplete in this study, as only women treated in hospitals due to spontaneous abortions are included in the register data. Usually spontaneous abortions are in the early pregnancy and women may not even know yet about the pregnancy. Therefore, estimates based on hospital records lead to underestimation of the actual number of spontaneous abortions.

In addition, the study population in Sweden has been limited to women who have had MS and a pregnancy event recorded in the MBR (birth-related event after gestational week 22) during the study period. Therefore, women with MS and a spontaneous abortion but no records in the MBR would not appear in the dataset. Thus, it is likely that spontaneous abortions in Sweden are underreported in this study. However, it is

expected, but not certain, that the underestimation of spontaneous abortions would be comparable across cohorts.

Furthermore, spontaneous abortions were intended to be used as the denominator in the prevalence of ectopic pregnancies. The absence of this denominator data decreased the denominator, and thereby increased the observed prevalence of ectopic pregnancies in SWE.

10.2.3.3 Ectopic pregnancies underreported in the SWE population

In Sweden, the study population has been limited to women who have had MS and a pregnancy event recorded in the MBR (birth-related event after gestational week 22) during the study period. Therefore, women with MS and an ectopic pregnancy but no records in the MBR would not appear in the dataset. Thus, it is likely that ectopic pregnancies in Sweden are underreported in this study. However, it is expected that the underestimation of ectopic pregnancies in SWE would be comparable across the cohorts.

10.2.3.4 Detection of stillbirths, by country

As noted in the section on bias (8.6), information on stillbirths was available from gestational week 22 onwards from both Finnish and Swedish data. In addition, stillbirths are underreported in SWE [10]. This probably contributed in the higher prevalence of stillbirths in FIN compared to SWE.

10.2.3.5 Detection of MCAs, by country

In this study, MCAs were detected from the Malformation register in Finland and the Medical Birth Register in Sweden. There are, however, several sources of information on congenital malformations available in Sweden, the use of which would have increased the number of identified MCAs, such as the diagnosis codes reported in medical records (can be identified through the National Patient Register) or the the Swedish Birth Defects Registry (previously the Swedish Registry of Congenital Malformations), held by the National Board of Health and Welfare. The Swedish Birth Defects Registry is today expected to be covering almost all MCAs, after a change in identification practices made in 2013 [18]. During the study period, excluding data from the Swedish Birth Defects Registry should have mainly affected the prevalence of MCA in stillbirths, while the addition of diagnoses from the Patient Register could have increased in particular the prevalence of MCA in live births [19]. This would probably have made the identified prevalence of MCA in SWE more similar to the prevalence in FIN. The alternative methods for detecting MCA should, however, not have affected to a large extent the comparisons between cohorts.

10.2.4 Information bias (misclassification bias)

10.2.4.1 Time-related exposure misclassification, for detecting MCAs

As described in the section on bias (8.6), time-related exposure misclassification for detecting MCAs was explored in ***sensitivity analysis 3***. As the results were in line with the main analyses, restricting the exposure period to the end of the first trimester did not influence the risk of MCAs.

10.2.4.2 Misclassification of women with MS exposed to hospital administrated MSDMDs as unexposed to MSDMDs

As described in the section on bias (8.6), women with MS exposed to hospital administrated MSDMDs were to some extent misclassified as unexposed to MSDMDs. In the ***sensitivity analysis 6***, where all women with hospital administrated drugs were classified as exposed to MSDMDs, the results of main analyses remained the same or very similar.

10.2.4.3 Misclassification of women with MS exposed to rituximab as women with MS unexposed to MSDMDs

As described under the section on Bias (8.6), rituximab users were classified as unexposed to MSDMDs, per protocol. The ***post hoc sensitivity analyses on rituximab users*** revealed, however, a low number of women with MS exposed to rituximab (n=5) in the study population, probably because rituximab became more common during the later years of the study period. The number of rituximab users was potentially limited because the women trying to conceive. A recent literature review identified no major safety signals in studies of rituximab use during pregnancy [20], although few of the patients included in that study had MS. Assuming that the finding of the study is representative to women with MS using rituximab before or during pregnancy and considering the low number of rituximab users, the categorisation of rituximab users under women unexposed to MSDMDs is unlikely to have affected the results of this study.

10.2.4.4 Follow-up period to detect MCA

As described under the section on Bias (8.6), the follow-up periods for detecting MCAs in the national registers vary between countries, being 12 months after birth in FIN and 6 months in SWE. In the stratified analyses, the prevalence of MCAs was indeed higher in FIN than in SWE, which was most likely contributed by this difference in registration of MCAs.

10.2.4.5 Misclassification of women without MS under women with MS unexposed to MSDMDs

It has been suggested that MS status as identified from the national patient registers may include some patients without a MS diagnosis, as the ICD code for MS is sometimes mistakenly recorded during e.g., investigatory visits, before determining the final diagnosis. As a result, the women with MS unexposed MSDMSs may include some patients with no MS diagnosis, or possibly some patients treated for other similar diagnoses but not MS being included in the cohorts of patients exposed to oMSDMDs (since some of the study drugs are used also for other diagnoses). For example, patients with Lyme's disease may have initially been misdiagnosed as MS patients. If the unexposed women included patients who in fact were not MS patients, they may confound the analyses, if they for example were instead diagnosed with another disease which itself or treatments for it influenced the risk of adverse pregnancy outcomes.

10.2.5 Confounding

10.2.5.1 Confounders in the adjusted base model and further adjusted model – Missingness

As described under the section on Bias (8.6), the covariates included in the adjusted base model and further adjusted model included partial missing data. According to the ***sensitivity analysis 8***, the results on the risk of the investigated pregnancy outcomes remained in line with the main analyses, when several models with multiple imputations were used, suggesting that the main results were robust to the missingness.

10.2.5.2 Differing study periods

As described under the section on Bias (8.6), the different study periods between the countries could influence both the prevalence and risk of the studies pregnancy outcomes. The results of the ***sensitivity analysis 4*** indicated, however, that even when limiting the study period to 2005-2014, when data were available both countries, the results were similar to the results during the whole study period. Thus, the main result appeared to be robust to the differing time periods.

10.2.5.3 Residual confounding by other drug exposures

As described under the section on Bias (8.6), the inclusion of off-label drugs under MSDMD users may have confounded the analyses. When women with and without off-label use were analysed separately in the ***additional post hoc sensitivity analysis***, women with off-label use had few pregnancy outcomes. However,

the observed number of the off-label users in FIN (9) was probably lower than in reality, because Finnish data does not include data on hospital-administered drugs. Among women without off-label use, the prevalence of the pregnancy outcomes was close to identical to the main analyses. Thus, the inclusion of off-label drug users among users of MSDMDs in the main analyses was unlikely to influence risk estimates.

Mycophenolate mofetil is also used off-label for MS [21], but was not included in this study. However, it was not included as a MSDMD in a recent review of the MSDMDs used in SWE [12], which may implicate that its use is rather limited.

In the main analyses, confounding by teratogenic drugs commonly used in MS, other than MSDMDs, cannot be ruled out, even though use of teratogenic drugs was considered as a confounder in the further adjusted models of the main analyses. The variable on teratogenic drugs was namely not selected in the final models based on the variables selection process, perhaps due the variable including a wide range of teratogenic drugs, possibly diluting the effect of teratogenic drugs commonly used in MS patients, such as methylprednisolone or gabapentin. Women unexposed to any MSDMDs are probably commonly exposed to such teratogenic drugs, especially cortisone, as the women unexposed to any MSDMDs were most likely in an earlier disease stage and cortisone is used before proceeding to MSDMDs. Thus, the adjustment for use of teratogenic drugs in the current study may not have adequately distinguished teratogenic drugs commonly used in MS for symptomatic treatment, such as methylprednisolone or gabapentin, possibly resulting in higher risk of MCA among women unexposed to MSDMDs. Albeit the study did not include any detailed analyses of specific teratogenic drugs, the overall findings were that exposure to at least one teratogenic drug was more common in Cohorts 1 and 2, compared with Cohorts 3 and 4, which would have been expected to result in an increased risk of adverse pregnancy outcomes in the cohorts using IFN-beta.

10.2.5.4 Other residual confounding

Although several important confounders were considered in the analyses, residual confounding from other factors cannot be ruled out.

Among potential confounding factors, information on maternal alcohol use or other substance abuse was not available in this study. Heavy alcohol use may affect the risk for spontaneous abortion, and also other pregnancy outcomes. Considering that women with MS unexposed to IFN-beta, compared with those exposed, were slightly younger, slightly more commonly smokers and also had slightly more commonly BMI>30, the women with MS unexposed to IFN-beta may have also used more alcohol and other substances increasing risk of adverse pregnancy outcomes. If this was true, risk of adverse pregnancy outcomes would be decreased in women with MS exposed to IFN-beta, compared with those unexposed.

Furthermore, paternal age and other paternal factors were not available in the data, and thus they could not be adjusted for in the analyses, potentially influencing the risk of adverse birth outcomes. Information on family history of pregnancies was also not available in MBRs. Therefore, for example, heredity in multiple pregnancies cannot be evaluated in this study.

As for information on age at MS onset, disease status, and disease severity were not available from the MS data sources of these countries, the effect of MS and MSDMDs on these pregnancy outcomes in patients with different types of MS cannot be distinguished in this study. Therefore, confounding by indication is possible. In the further adjusted models, however, duration of MS treatment was used as a candidate variable, which may also have functioned as a proxy for severity of MS.

Finally, although the candidate variables for the adjusted regression models included country and region, the models may not have been optimally adjusted for regional variation in healthcare delivery, practice and behaviour.

10.2.6 Other limitations

For FIN, information on MCAs were not available for the year 2014 due to delays at the register holder, explained by organizational restructuring and cut-down resources for the malformation register in FIN (National Institute of Health and Welfare, THL). Data are still not available until this date.

When the aggregated national statistics for the indirect comparisons with the general population (Cohort 6) were retrieved, in FIN general population MCA statistics were available only during 1996-2011 and from SWE statistics were not available by maternal age group. Swedish MCA records for the general population were retrieved from a publication from the National Board of Health and Welfare [22] (Table 1: Fosterskador/kromosomavvikelser, totalt). It is possible, that definition of MCA in Finnish THL register and the Swedish register has some differences.

Regional and international differences in prevalence and incidence of MS have been reported, often suggesting a latitudinal gradient, with suggested higher prevalence in the Northern European countries than in southern part of Europe. This gradient has been associated with for example vitamin D levels [23] but has also been contested based on data from the Nordic countries [24,25]. It is unlikely that drug-related effects are due to the prevalence of the disease, but the large study population increases the likelihood of observed rare adverse outcomes.

10.3 Interpretation

10.3.1 Prevalence of pregnancy outcomes

10.3.1.1 Composite endpoint serious adverse pregnancy outcomes

In the current study in FIN and SWE, the total prevalence of serious adverse pregnancy outcomes among all women with MS (3.2%) expectedly constituted mainly of MCA in live births (prevalence 2.7%), considering that the prevalence of MCAs is generally higher than the prevalence of elective TOPFAs and stillbirths, as discussed below.

10.3.1.2 MCA in live births and total

The prevalence of MCA (total) (2.9%) among all women with MS was lower in this study than reported in the general population, as reported for cohort 6, in SWE (3.6%) [22] and FIN (3.0%; data from THL). When divided by country, however, a different trend was observed between the countries. The Finnish prevalence of MCA (total) among all women with MS (4.2%) was higher than in the general population (3.0%; data from THL). In SWE on the contrary, the observed prevalence of MCA (total) among all women with MS (2.2%) was lower than in the general population (3.6%) [22], which was expected considering that the observed prevalence excluded and the national statistics included TOPFA. However, even when the prevalence of MCAs in SWE is considered exclusively in live and stillbirths of the general population (3.1%), the prevalence observed in this study was lower. Thus, this study found that compared with the general populations the observed MCA prevalence among women with MS was comparably higher in FIN, lower in SWE, and lower when combined in the two countries.

Moreover, the indirect comparison of pregnancy outcomes revealed that in FIN the observed prevalence of MCA (total) in women with MS unexposed to any MSDMDs (Cohort 3) was higher than expected in the general population. This indicates that other factors than MS increased the prevalence on MCA in women with MS unexposed to any MSDMDs, as MS does not influence the prevalence of MCAs [3]. For example, it is possible that the known high proportion of comorbidities among patients with MS could be related to an increase in MCA [26], which can also be related to the prevalent use of teratogenic drugs identified in the study population. Comorbidities have also been shown to increase the probability of receiving MSDMDs [27]. In SWE and combined in the two countries, no increase in the prevalence of MCAs for women with MS unexposed to MSDMDs (Cohort 3) was found compared with the general population, although the analysis of MCAs was also subject to limitations with regards to data availability for the Swedish study population.

Of the 2.9% prevalence of MCAs total among all women with MS in this study, the prevalence was expectedly higher in FIN (4.2%) than in SWE (2.2%). The same pattern was observed for MCA in live births. The higher prevalence in FIN was expected, because MCAs are registered 12 months after birth in FIN and 6 months after birth in SWE, and the prevalence of MCAs in SWE excluded TOPFA as elective terminations are unavailable in SWE. The differing MCA prevalence between FIN and SWE may also be contributed by otherwise differing MCA recording. On the other hand, the observed prevalence of MCAs in FIN would have been even higher if the observation period had been the same as in SWE (2005-2015), because the prevalence of MCAs in FIN has increased over time [28]. Thus, the inclusion of women in FIN since 1996, when the prevalence was lower, decreases the observed prevalence in our study. In Finland, MCA data from 2014 is unavailable, and thus potentially an even higher prevalence might have been seen, had it been included. In SWE, the prevalence of MCA has been similar since the 1990's [18]. Nonetheless, due to the partially incomplete data from SWE, the actual prevalence of MCAs in live births alone and in total is probably higher than observed in this study in SWE alone and combined for FIN and SWE.

10.3.1.3 Elective TOPFA and elective termination for other reasons

In the current study, the prevalence of elective TOPFAs in FIN (0.7%) was similar than in the general population in FIN (0.6%; data from THL termination statistics). Among all women with MS in FIN (Cohorts 1-4), 13.6% of pregnancy events ended with elective terminations without foetal anomaly or with an unknown reason, which was of similar magnitude as in the general population in 1999-2014 (15.2%; data from THL). As this study and the used national Finnish statistics had no difference in the recording or calculations of TOPFA, our results indicate that the prevalence of elective TOPFAs among women with MS is of similar magnitude to that of in the Finnish general population. In SWE, the prevalence of elective TOPFAs and elective terminations for other reasons could not be assessed.

10.3.1.4 Stillbirths and live births

The observed prevalence of stillbirths among all women with MS in this study, combined in the cohorts and in the two countries (0.5%), was similar to the prevalence in the general populations of the two countries (0.3-0.4% in each country, based on data retrieved for Cohort 6). According to the indirect comparison of pregnancy outcomes in this study, the observed prevalence of stillbirths in women with MS unexposed to any MSDMDs (Cohort 3) also did not differ from the expected prevalence in the general population.

However, the observed prevalence of stillbirths in women with MS appeared to differ between the countries, with a higher prevalence in FIN (SWE 0.3%, FIN 0.8%). The discrepancy between FIN and SWE could partially be explained by the study period starting earlier in FIN than in SWE, considering the declining prevalence of stillbirths in the Nordic countries over time (data from THL). An additional explanation for the lower prevalence of stillbirths in SWE is the possible under-recording of stillbirths in the Medical Birth Register in SWE, although the underreporting is expected to be low [10]. On the other hand, the prevalence of stillbirths in SWE would be even lower, if the denominator included elective terminations, which were unavailable in SWE. Even with the possible reasons for the difference between the countries, the difference may also be by chance, considering the low number of events. Nonetheless, the results of this study revealed higher prevalence of stillbirths in FIN compared with SWE, among all women with MS, which is probably due to difference in recording stillbirths.

The prevalence of live births among all women with MS in this study was 94.4%, and the prevalence was lower in FIN (84.9%) than in SWE (99.7%), in accordance with the prevalence in the general populations of the two countries. The lower prevalence in FIN in our study and in population statistics is partially explained by the denominator in FIN including elective terminations, while in SWE data on elective terminations were unavailable for the denominator. Otherwise, the potential reasons for the discrepancy in the prevalence of live births between FIN and SWE are the same as for stillbirths.

10.3.2 Pregnancy outcomes in women with MS exposed to IFN-beta compared with those unexposed

The result of this study is in line with previous research [3] which has also found that exposure to IFN-beta during pregnancy is not expected to negatively impact pregnancy outcomes.

10.3.2.1 Composite endpoint serious adverse pregnancy outcomes

The observation that exposure to IFN-beta during pregnancy did not increase the risk of serious adverse pregnancy outcomes in women with MS supports the results of previous research [3]. According to the multivariate models in this study, the lower prevalence of serious adverse pregnancy outcomes among women with MS exposed to IFN-beta compared with those unexposed remained borderline significant after covariate adjustment. However, the inverse association for IFN-beta may have been contributed by the unavailability of relevant confounders, such as alcohol and substance use, socioeconomic status, paternal factors, co-morbidities causing adverse birth outcomes, or by inadequate adjustment for teratogenic drug use, as discussed under limitations (10.2). If it had been possible to better control for confounding, the point estimates would probably have been closer to 1.0. Moreover, the study was powered to detect an increase in the point estimates (see 8.7 Study size), which hinders drawing conclusions on the observed inverse association.

10.3.2.2 MCA in live births and total

As for the composite endpoint of serious pregnancy outcomes, exposure to IFN-beta in women with MS during pregnancy did not according to this study increase the risk of MCA in live births or in both live and stillbirth (MCA (total)), in line with previous research [3]. Similarly to all serious pregnancy outcomes, the lower prevalence of MCAs among women with MS exposed to IFN-beta remained borderline significant compared with those unexposed to any MSDMDs, according to the multivariate models in this study. These findings are comparable with previous research, with non-significant changes in the risk of major congenital anomalies (crude OR 0.53, 95% CI 0.20-1.41) [29], or birth defects (RR 2.1, 95% CI 0.9-4.9) [30]. The borderline inverse association for IFN-beta in our study is probably explained by residual confounding, as for the composite endpoint of serious pregnancy outcomes. Nonetheless, this study strengthens the evidence that the risk of MCA is not increased by the IFN-beta exposure.

10.3.2.3 Elective TOPFA and elective termination for other reasons

The risk of elective TOPFAs was not according to this study increased among women with MS exposed to IFN-beta. The descriptive prevalence of elective TOPFAs and elective terminations for other reasons was similar between the cohorts. The same findings remained after adjusting for covariates in multivariate models: no differences in the risk of elective TOPFAs were observed between women with MS exposed to IFN-beta and those unexposed.

The higher prevalence of elective terminations for other reasons than foetal anomaly was detected among women with MS exposed to IFN-beta, both as descriptive prevalence and after adjustments for covariates, reaching however statistical significance only when Cohort 1 was compared to Cohort 3. Previous research on elective terminations in IFN-beta exposed women with MS is hampered by small study populations, few reported cases, and typically lack of a comparator group [29–33]. This larger study with, however, exclusively Finnish data on elective terminations suggests that in real-world settings pregnant women with MS exposed to IFN-beta may terminate the pregnancy for other reasons foetal anomaly more commonly than unexposed women. The finding potentially indicates that those pregnancies under medication were more likely unplanned than those unexposed. The result shall, however, be interpreted with caution as residual confounding probably remained despite the confounder adjustment and the result was exclusively based on data from Finland.

10.3.2.4 Stillbirths and live births

According to this study, the risk of stillbirths was not increased or the risk of live births decreased among women with MS exposed to IFN-beta. The descriptive prevalence of stillbirths and live birth did not differ between the cohorts. After adjusting for covariates in multivariate models, the same findings remained: no differences in the risk of stillbirths and live births were observed between women with MS exposed to IFN-beta and those unexposed. These findings that exposure to IFN-beta does not increase stillbirths are strengthened by the similarly results reported in a previous study from the German Multiple Sclerosis and Pregnancy Registry [29] and findings from a previous literature review in which IFN-beta was not associated with an increased abortive risk [6].

10.3.3 Ectopic pregnancies and spontaneous abortions

The observed prevalence of ectopic pregnancies (2.6%) and spontaneous abortions (10.3%) among all pregnant women with MS in this study, combined in the cohorts and the two countries, was of similar magnitude than reported in the general population in FIN (data from THL) and SWE [10].

In this study, no evidence of an increased risk of ectopic pregnancies in women exposed to IFN-beta was found, compared with women unexposed to IFN-beta. While the descriptive prevalence of ectopic pregnancies was similar between the cohorts, the adjusted multivariate models revealed a borderline significant deceased risk of ectopic pregnancies in women exposed to IFN-beta, compared with women unexposed to IFN-beta. As with serious adverse pregnancy outcomes, however, the inverse association for IFN-beta was probably contributed by the unavailability of relevant confounders, such as alcohol and substance use, socioeconomic status, paternal factors, co-morbidities causing adverse birth outcomes, or by inadequate adjustment for teratogenic drug use, as discussed under limitations (10.2). If it had been possible to better control for confounding, the point estimates would probably have been closer to 1.0. Nonetheless, this study provides additional evidence on that IFN-beta exposure does not increase the risk of ectopic pregnancies.

The risk of spontaneous abortions was not either according to this study increased among women with MS exposed to IFN-beta, which complements the inconsistent findings of previous studies [7]. In the current study, the descriptive prevalence of spontaneous abortions was similar between the cohorts. After adjusting for covariates in the multivariate models, the same finding remained: no differences in the risk of spontaneous abortions were observed between women with MS exposed to IFN-beta, compared with those unexposed.

10.4 Generalisability

The study included almost all women with treated MS during pregnancy in the studied countries and it is therefore representative for this population in the two countries. Although heterogeneity was identified across countries in the overall prevalence of the pregnancy outcomes, with higher prevalence in FIN than in SWE, the fact that also in country specific comparisons Cohort 1 always had lower prevalence than Cohort 3 provides confidence to believe these results would also be relevant for other similar countries. In addition, the difference between countries could at least partly be explained by the difference in recording the pregnancy outcome.

10.4.1 Relevance of results to the European IFN-beta Pregnancy Registry

Available information on disease severity and other potential confounding factors differs between the health registers and the European IFN-beta Pregnancy Registry and in some cases is missing, such that the rates cannot be adjusted to be comparable. In addition, the pregnancies included in the Nordic health registers are population-wide and are not based on a sample, whereas the European IFN-beta Pregnancy Registry is based on post-marketing spontaneous and solicited reports.

Furthermore, study and exposure periods differ between the countries in this study and follow-up periods in the European IFN-beta Pregnancy Registry. Also, it is known that there are regional and international differences in MSDMD treatment practices, MSDMDs on market and prevalence of MS. Where possible, the analyses were conducted to control for some of these variations by stratification and adjustment; for country, hospital district, year of pregnancy outcome, maternal age, time since MS diagnosis and duration of IFN-beta treatment. As a conclusion, results of this retrospective cohort study are not directly comparable with the information derived from the European IFN-beta Pregnancy Registry, but can serve as reference to the estimates obtained from European registry.

11 Conclusion

The total prevalence of serious adverse pregnancy outcomes among all women with MS was 3.2%, of which most were MCAs in live births. The prevalence of MCA (total) among all women with MS was 2.9%, lower than in the general populations of Finland and Sweden. In this study, the prevalence of elective TOPFAs (0.7%) and terminations for other reasons (13.6%) among women with MS in FIN was of similar magnitude than in the Finnish general population, while in SWE information on elective terminations were unavailable. Among all women with MS, the prevalence of stillbirths was 0.5% and live births 94.4%. The prevalence of MCA and stillbirths appeared higher and live births lower in FIN than in SWE, however may have been due to difference in recording practices and the availability of register data.

Of the above-mentioned outcomes, the prevalence of serious adverse pregnancy outcomes, MCAs in live births, and MCAs in live and stillbirths and elective terminations (MCA (total)) were lower among women with MS exposed to IFN-beta, compared with those unexposed to IFN-beta. An indication of a higher prevalence of elective terminations for other reasons than foetal anomaly was detected the IFN-beta exposed. The prevalence of the other pregnancy outcomes was similar between the cohorts. After adjusting for covariates, this study found no evidence for an increased risk of the serious adverse pregnancy outcomes, MCAs, TOPFAs, stillbirths or non-live births after exposure to IFN-beta during pregnancy, compared with women with MS who were unexposed to IFN-beta, regardless of exposure to other MSDMDs. However, the prevalence of elective terminations for other reasons than foetal anomaly appeared increased among the IFN-beta exposed compared to those unexposed suggesting that women exposed to IFN-beta may terminate their pregnancy more often than those unexposed.

The prevalence of ectopic pregnancies among all women with MS was 2.6%, and spontaneous abortions 10.3%, with a similar prevalence between the cohorts. After adjusting for covariates, this study found no evidence for an increased risk of ectopic pregnancies or spontaneous abortions after exposure to IFN-beta during pregnancy, regardless of exposure to other MSDMDs, compared with women with MS who were unexposed to IFN-beta.

12 Other information

None.

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Annexes

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	Annex 2	22 October 2018	ER-9430_Study Report_Annex 2_Data permit approval information_20181022.pdf
2	Annex 3	14 October 2016	ER-9430_Study Report_Annex 3_MS preg SAP_v1.0 2016-10-14 Signed.pdf
3	Annex 4	23 April 2019	ER-9430_Study Report_Annex 4_ Result Report_2019-04-23.pdf

Annex 5. List of chronic diseases diagnosed before LMP and during pregnancy

Comorbidities	ICD-10
Asthma and related conditions	E84.0, J41–J45, P27.1
Hypothyroidism (thyroid insufficiency)	C73, E03, E89.0
Epilepsy	C71, G40, G41
Rheumatoid arthritis and related conditions	A04.6, A39.8, A50.5, D76.0, D76.3, H20.1, H30, I33.0, J84, K50.9, K51.9, K73.2, K74.3, K83.0, L40.5, M02, M05, M06, M08, M13.9, M30–M35, M45, M46.1, M46.9, M94.1, N03, Q44.2
Diabetes Mellitus (type I and type II will be considered separately)	E10-E14, E89.1
Colitis Ulcerosa, Crohn´s disease	K50, K51
Hypertensive diseases	I10–I13, I15, I27.0
Severe psychosis and other severe mental disorders and related conditions	A52.1, A69.2, A81.0, B22.0, B56.9, B57.2, E01.8, E03.9, E52, E53.8, E75.6, E83.0, E83.5, F01, F03, F06.0-F06.3, F20-F25, F28, F29, F30.1, F30.2, F31, F32.3, F33.3, F84, G10, G20, G30.0, G30.1, G30.8, G30.9, G31.0, G35, G40.9, M30.0, M32.8
Leukaemia and related conditions	C81–C85, C88, C90–C96, D45–D47, D72.1, D75
Hypercholesterolemia and mixed hyperlipidemia	E78.0, E78.2
Hypogonadism	E28.3, E29.1, E89.4, E89.5, Q96, Q98
Hypertensive heart disease with heart failure and related conditions	I11.0, I13, I50, I97.1, P29.0
Chronic arrhythmia of the heart	I47–I49
Glaucoma	H40
Pernicious anemia and deficiency of specified B group vitamins	C16, D51, E53.8
Hypothyroidism parathyroid gland, chronic (parathyroid insufficiency)	E20, E31.0, E89.2
Deficiency of coagulation, hemophilia	D66, D67, D68.0–D68.2
Myasthenia gravis	G70.0
Maternal pregnancy-related disorders	O10-O29
Other malignancies	C00-C80

Annex 6. Potentially or clearly harmful drugs during pregnancy

Definitions for the risk categories in the Swedish Catalogue of Approved Drugs during pregnancy (FASS, 2017) classification system are given below. This classification comprises 4 separate categories (A, B, C, D): A includes the safest drugs; B is divided into 3 subgroups (B1, B2, B3); and C and D categories are used for drugs which may have different risks for the foetus depending on the evidence on which the risk is based.

Risk category	Description
A	Medicinal products which may be assumed to have been used by a large number of pregnant women and women of child-bearing age without any identified disturbance in the reproductive process, e.g. an increased incidence of malformations or other direct or indirect effects on the foetus. This category comprises: drugs that have been available for many years; those that have been used by many pregnant women and women of child-bearing age and; drugs for which satisfactory retrospective studies in pregnant women are considered to have been carried out.
B	Medicinal products which may be assumed to have been used only by a limited number of pregnant women and women of child-bearing age without any identified disturbance in the reproductive process having been noted so far, e.g. an increased incidence of malformations or other direct or indirect harmful effects on the foetus. As experience of effects of medicinal products in man is limited in this category, results of reproduction toxicity studies in animals are indicated by allocation to one of 3 subgroups B1, B2 or B3 according to the following definitions: **B1**: Reproduction toxicity studies have not given evidence of an increased incidence of foetal damage or other deleterious effects on the reproductive process. **B2**: Reproduction toxicity studies are inadequate or lacking, but available data do not indicate an increased incidence of foetal damage or other deleterious effects on the reproductive process. **B3**: Reproduction toxicity studies in animals have revealed an increased incidence of foetal damage or other deleterious effects on the reproductive process, the significance of which is considered uncertain in humans.
C	Medicinal products, which by their pharmacological effects have caused or must be suspected of causing, disturbances in the reproductive process that may involve risk to the foetus without being directly teratogenic. If experimental studies in animals have indicated an increased occurrence of foetal injuries or other disturbances of the reproductive process of uncertain insignificance in humans, these findings are to be stated for drugs in this category.
D	Medicinal products, which have caused an increased incidence of foetal malformations or other permanent damage in humans or which, on the basis of e.g. reproduction toxicity studies, must be suspected of doing so. This category comprises drugs with primary teratogenic effects that may directly or indirectly have a harmful effect on the foetus.

In this study, the following drugs (ATC codes) from categories C and D will be included in this study as potentially teratogenic drugs or teratogenic drugs.

	ATC codes						
Potentially teratogenic drugs – risk category C	A01AB11	C07AB07	G02CB03	J01XC01	M01AE02	N03AX15	N06BA04
	A01AC01	C07AB09	G03AA07	J01XE01	M01AE03	N03AX16	N06CA01
	A02BC02	C07AG01	G03AA09	J01XX08	M01AE51	N05AA01	N06DA03
	A03AB02	C07AG02	G03AA10	J02AB02	M01AG01	N05AB02	N06DA04
	A03FA01	C07FB02	G03AA11	J02AC01	M01AH01	N05AB03	N06DX01
	A04AA03	C08CA01	G03AA12	J02AC02	M01AH04	N05AB04	N07AA02
	A04AD12	C08CA02	G03AA13	J02AC03	M01AH05	N05AD01	N07AA51
	A05AA02	C08CA03	G03AB03	J02AX04	M01AX01	N05AD03	N07AX01
	A07DA03	C08CA05	G03AB05	J04AB02	M01CB03	N05AE03	N07BA01
	A07EA02	C08CA06	G03AB06	J04AB04	M02AA07	N05AE04	N07BB04
	A07EA06	C08CA07	G03AC01	J05AB01	M02AA10	N05AF01	N07BC02
	A10BB01	C08CA13	G03AC03	J05AB11	M02AA15	N05AF03	N07XX02
	A10BB07	C08DA01	G03AC08	J05AE02	M02AC	N05AF05	P01BA01
	A10BB12	C08DB01	G03AC09	J05AE03	M03AB01	N05AH03	P01BA02
	A10BG02	C10AA03	G03CX01	J05AE07	M03AX01	N05AX08	P01BB51
	A10BG03	C10AA04	G03FA01	J05AF01	M03BX02	N05AX12	P01BC02
	A10BH01	C10AB02	G03FA12	J05AF05	M05BA03	N05BA01	P02CA01
	A10BX02	C10AB04	G03FA17	J05AF06	M05BA04	N05BA02	R01AC02
	A10BX03	C10AB05	G03FB05	J05AF08	M05BA06	N05BA04	R01AC03
	A11HA30	D01AA02	G03FB06	J05AR01	M05BA07	N05BA06	R01AD01
	B01AC06	D01AC07	G03GA01	J07BA02	M05BA08	N05BA09	R01AD08
	B01AC11	D01AC08	G03GB02	J07BK01	M05BC01	N05BA12	R01AD09
	B01AC30	D01AE16	G03HB01	L01XX23	N01AB07	N05BB01	R01AD11
	B01AD02	D05AX03	H01CA02	L02AB01	N01AH01	N05CD02	R01AD12
	B01AD07	D05AX52	H01CB02	L02AE01	N01AH02	N05CD05	R03AC13
	B01AE07	D06BB03	H01CB03	L02AE02	N01AH06	N05CD07	R03AK06
	B03XA01	D06BB04	H01CC02	L02AE04	N01AX01	N05CD08	R03AK07
	C01BC03	D07AB01	H02AA02	L02BA02	N01AX10	N05CF01	R03BA01
	C01BC04	D07AB02	H02AB01	L02BG03	N01BB10	N05CF02	R03BA05
	C01BD01	D07AB08	H02AB02	L02BG06	N01BB58	N05CF03	R03BB04
	C01BD05	D07AC01	H02AB04	L03AA02	N02AA01	N06AA04	R05DA20
	C01CA04	D07AC03	H02AB06	L03AA10	N02AA05	N06AA06	S01AD03

	C01CX08	D07AC13	H02AB07	L03AA13	N02AA59	N06AA09	S01AX11
	C01EA01	D07AD01	H02AB08	L03AB05	N02AB03	N06AA10	S01AX19
	C02AC05	D07BC01	H03BB01	L03AB11	N02AE01	N06AA12	S01BA01
	C03AA03	D07CC01	H05AA02	L04AA10	N02AX02	N06AB03	S01BA13
	C03BA11	D07XC01	J01CA08	L04AB02	N02BA01	N06AB04	S01BC03
	C03CA01	D08AG02	J01EA01	L04AB04	N02BA51	N06AB05	S01EC01
	C03EA01	D10AD01	J01EE01	L04AD02	N02BG08	N06AB06	S01ED51
	C04AD03	D10AD03	J01EE02	M01AB01	N02CA01	N06AB10	S01EE03
	C07AA03	D11AH01	J01FA15	M01AB05	N02CA52	N06AX03	S01EE04
	C07AA05	D11AX01	J01MA01	M01AB08	N02CC07	N06AX05	S01GX06
	C07AA07	D11AX18	J01MA02	M01AB15	N03AG06	N06AX11	S01JA01
	C07AB02	G01AF08	J01MA06	M01AB51	N03AX09	N06AX16	
	C07AB03	G02AB01	J01MA12	M01AC06	N03AX12	N06AX18	
	C07AB05	G02BB01	J01MA14	M01AE01	N03AX14	N06AX21	
ATC codes							
Teratogenic drugs – risk category D	A02BB01	C09BA05	C09DB01	G03FA14	L01CD01	L01XX14	N03AE01
	A16AX03	C09BA06	C10AA01	G03FB08	L01CD02	L01XX17	N03AF01
	B01AA03	C09BA15	C10AA02	G03GA06	L01DB01	L01XX19	N03AF02
	B01AD11	C09CA01	C10AA05	G03HA01	L01DB03	L01XX32	N03AG01
	C01BA01	C09CA02	C10AA07	G03XB01	L01DB06	L02AE03	N03AG04
	C02KX01	C09CA03	D05BB02	G03XC01	L01DC01	L02BA01	N03AX11
	C09AA01	C09CA06	D06AX04	G04CB01	L01DC03	L02BA03	N05AN01
	C09AA02	C09CA07	D10AD04	J01FA09	L01XA01	L02BB03	S01EE01
	C09AA03	C09CA08	D10BA01	J01GB01	L01XA02	L02BG04	S01LA04
	C09AA04	C09DA01	D11AX10	L01BC02	L01XC07	L03AB10	
	C09AA05	C09DA02	G03BA03	L01BC05	L01XE01	L04AX02	
	C09AA06	C09DA03	G03DA02	L01BC06	L01XE06	M01AB55	
	C09BA02	C09DA06	G03DC02	L01CA04	L01XX05	N03AB02	
	C09BA03	C09DA07	G03DC03	L01CB01	L01XX11	N03AB05	