# Pregnancy outcomes from the global pharmacovigilance database on interferon beta-1b exposure

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## Introduction

- Multiple sclerosis (MS) is a chronic demyelinating disease that is more common in women than in men and is most often diagnosed in young patients during their reproductive years[1]
- Although MS does not increase the rate of adverse pregnancy outcomes,[2] information regarding the potential pregnancy risks associated with disease-modifying therapies (DMTs) for MS is limited
- Interferon beta-1b (Betaferon®/Betaseron®, Bayer AG) is known to be efficacious in treating patients with clinically isolated syndrome suggestive of MS, relapsing MS and secondary progressive MS.[3-7] Clinical trial experience and safety data have been collected on interferon beta-1b since the pivotal study in 1988[3-7]
- DMTs are frequently discontinued in women who intend to become pregnant. Concerns arise when patients are confirmed with an unplanned pregnancy during treatment[8]
- Randomized controlled trials in pregnant women are not possible. Information on drug exposure during pregnancy is crucial. Therefore, pharmacovigilance safety data can provide important information for decision-making around family-planning while on treatment
- Bayer's global pharmacovigilance database contains data on more than 3800 pregnancies with exposure to interferon beta-1b collected over more than 20 years since January 1995. It is the largest dataset available on interferon beta-1b to date

## Objective

- To review pregnancy outcomes of patients who have been exposed to interferon beta-1b during pregnancy

## Methods

- Pregnancy cases with exposure to interferon beta-1b reported prospectively from worldwide sources up to February 2018 were retrieved from Bayer's pharmacovigilance database (Figure 1)
- To avoid recall or reporting bias, only prospective cases were included in this analysis (Figure 2). Prospective cases were defined as those for which the data were acquired prior to the knowledge of the pregnancy outcome or prior to the detection of a congenital malformation at prenatal examination
- Outcomes and follow-up information were collected from patients and their health care providers
- The calculations of rates for pregnancy losses were based on the total number of pregnancies (N=1348) and the rates of events after birth among the total live births with known health status (n=981)
- Congenital malformations were classified according to ICD-10. Rates of pregnancies resulting in congenital disorders in Bayer's database were compared with rates from the general population and more specifically from the following sources:
  - EUROCAT, a European network of population-based registries for the epidemiologic surveillance of congenital anomalies (2012-2016)[9]
  - Metropolitan Atlanta Congenital Defects Program (MACDP), a US population–based system that surveilles birth defects (1978-2005)[10]
- Pregnancy outcomes such as spontaneous abortions were compared with reference rates of abnormal pregnancy outcomes from the general population

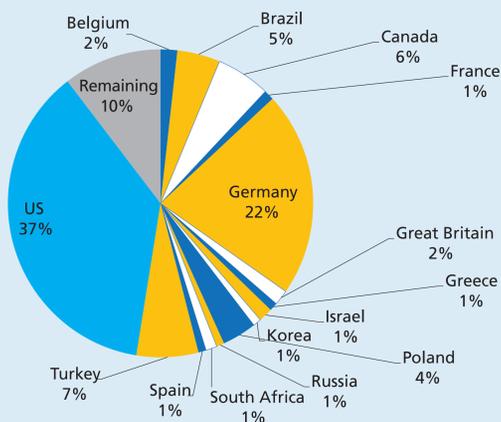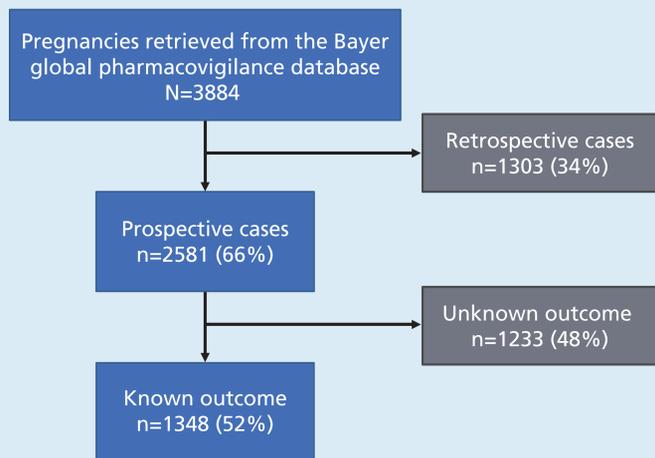### Figure 1. Distribution of pregnancy cases by country



Belgium 2%, Brazil 5%, Canada 6%, France 1%, Remaining 10%, Germany 22%, Great Britain 2%, Greece 1%, US 37%, Israel 1%, Korea 1%, Poland 4%, Turkey 7%, Spain 1%, South Africa 1%, Russia 1%

### Figure 2. Distribution of cases



Pregnancies retrieved from the Bayer global pharmacovigilance database N=3884
→ Retrospective cases n=1303 (34%)
Prospective cases n=2581 (66%)
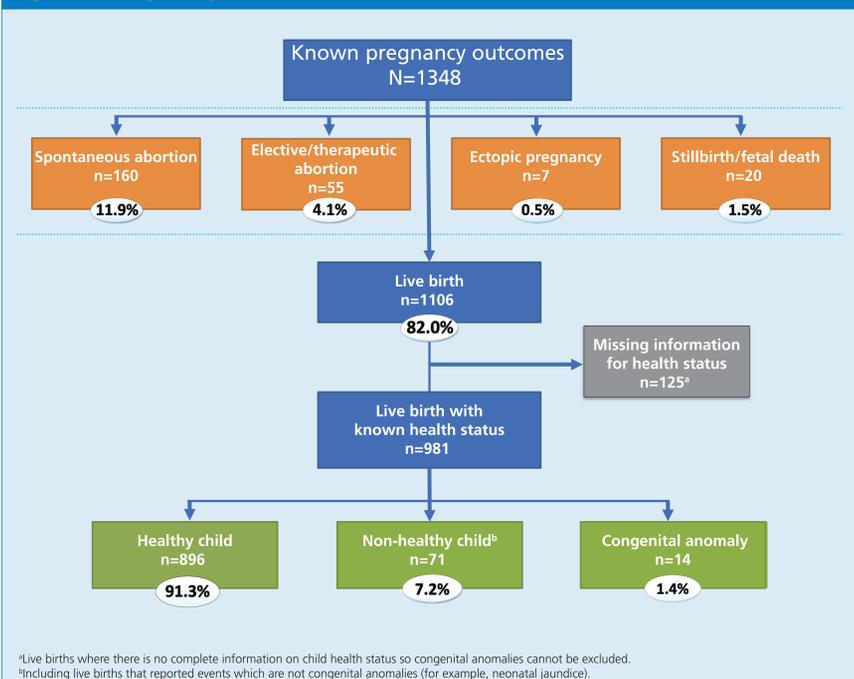→ Unknown outcome n=1233 (48%)
Known outcome n=1348 (52%)

## Results

- As of February 2018, there were a total of 3884 pregnancy cases of which 2581 were prospective pregnancies exposed to interferon beta-1b retrieved from 2548 individual case safety reports. A total of 1348 pregnancies had documented outcomes
- The majority of cases came from North America (43%, including 37% from the US) and Europe (41%, including 22% from Germany)
- The majority of the outcomes (82.0%) were live births: 1106/1348 (Figure 3)
- 896 cases (91.3%) were live births of healthy children without a congenital anomaly
- Spontaneous abortion occurred in 160 (11.9%) cases out of 1348 pregnancies
  - This rate is comparable to rates reported in the general population, ranging from 12% to 21%[11,13]
- Major and minor birth defects (Table 1) were observed in 14 (1.4%) of 981 live births with known health status, which is consistent with rates reported in the general population (2.1- 4.1%[14,15])
  - This rate of birth defects of the sample (1.4%) was comparable to the MACDP database reference rate of major congenital anomalies in the US population (2.8%) and also comparable to the EUROCAT database (3%) (Table 2)
  - The standardized incidence ratio was 0.41

## Results (cont'd)

### Figure 3. Pregnancy outcomes



Known pregnancy outcomes N=1348
- Spontaneous abortion n=160 — 11.9%
- Elective/therapeutic abortion n=55 — 4.1%
- Ectopic pregnancy n=7 — 0.5%
- Stillbirth/fetal death n=20 — 1.5%

Live birth n=1106 — 82.0%
Missing information for health status n=125[a]

Live birth with known health status n=981
- Healthy child n=896 — 91.3%
- Non-healthy child[b] n=71 — 7.2%
- Congenital anomaly n=14 — 1.4%

[a]Live births where there is no complete information on child health status so congenital anomalies cannot be excluded.
[b]Including live births that reported events which are not congenital anomalies (for example, neonatal jaundice).

### Table 1. Congenital anomalies by system

| System | Observed events,[a] No. |
| --- | --- |
| Musculoskeletal | 5 |
| Urinary | 3 |
| Circulatory | 2 |
| Deformation and chromosomal abnormalities | 1 |
| Ear | 1 |
| Cleft palate | 1 |
| Other congenital malformations | 3 |

[a]Total of 16 congenital anomalies (>1 malformation may have occurred in the same infant)

### Table 2. Congenital anomalies in the interferon beta-1b sample vs the MACDP and EUROCAT databases

| Interferon beta-1b database sample Rate of congenital anomalies | MACDP database Rate of major congenital anomalies |
| --- | --- |
| 1.4%[a] | 2.8%[b] |
| Interferon beta-1b database sample Observed number of cases | EUROCAT database Expected number of cases |
| 14[c] | 25[d] |
| Standardized incidence ratio=0.56 | |

[a]Proportion of sample from prospective cases of pregnancies with exposure to interferon beta-1b.
[b]Number of infants and fetuses with a major birth defect that were delivered during a specified period divided by the number of live births during that period.
[c]Number of pregnancies with congenital anomalies in the sample from prospective cases of pregnancies with exposure to interferon beta-1b.
[d]Calculated per the EUROCAT reference prevalence rate of congenital anomalies (2012-2016): 2558.2/100,000 births. Rate calculated as the number of cases with congenital anomalies, divided by the number of cases resulting in birth (live birth, fetal death/stillbirth, and termination of pregnancy for fetal anomaly after prenatal diagnosis).

## Discussion

- Data contained in Bayer's global pharmacovigilance database include reports from patients and healthcare professionals; thus, data may not be complete and the report may not be precise, depending on the individual reporting
- The majority of exposures occurred in the first trimester of pregnancy (56.9%)

## Conclusions

- This is the largest sample of exposure to interferon beta-1b during pregnancy
- Pregnancies exposed to interferon beta-1b were not associated with an increased risk for spontaneous abortion or congenital anomalies when compared with the general population

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