Cumulative update on pregnancy outcomes after fingolimod treatment in patients with multiple sclerosis

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Poster Program: P1118

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Poster Presentation at the 8th Joint ACTRIMS-ECTRIMS Meeting, MSVirtual2020, September 11–13, 2020

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Disclosures

Kerstin Hellwig has received compensation for serving as a consultant or speaker, or the institution she works for has received research support from Bayer, Schering Healthcare, Teva, Sanofi Aventis, Biogen Idec, Merck Serono and Novartis.

Thomas M. MacDonald's institution received support from Menarini and has done observational studies funded by GSK and Shire pharmaceuticals. He has received compensation from Novartis in the past for work done in relation to the present study.

Helmut Butzkueven has received compensation for serving as a consultant or speaker, personal fees, or he or the institution he works for has received research support from Biogen Idec, Novartis, Merck Serono, Teva and Oxford Pharmagenesis. He is on the Australian advisory boards for Novartis, Biogen Idec, Merck Serono and Teva.

Hugh Tilson is a member of the Pregnancy Registry Boards for Seqiris, GSK and Jazz Pharmaceuticals; and he is a senior epidemiology consultant for the International Antiretrovirals in Pregnancy Registry, sponsored by all manufacturers of branded and generic ARV products.

Sandra Vukusic reports grants and personal fees from Biogen, Merck Serono, Novartis, Roche, Sanofi Genzyme and Teva; personal fees from Geneuro and Celgène; and grants from MedDay.

Morgane Guennec is an employee of IQVIA, France.

Lisa M. Prach, Alan Moore, Bita Rezaallah, Gregor McBride, Imran Ali Khan, Alit Bhatt, Yvonne Geissbuehler, Sandra Lopez-Leon are employees of Novartis.

The study was funded by Novartis Pharma AG, Basel, Switzerland.

Medical writing support was provided by **Ashwini Patil and Sreelatha Komatireddy** (employees of Novartis Healthcare Pvt. Ltd., Hyderabad, India). The final responsibility for the content lies with the authors.

Background and objective

- Multiple sclerosis (MS) treatment options include many disease-modifying therapies; however, most of them have safety concerns for use during pregnancy[1]
- Fingolimod (Gilenya®) is a sphingosine-1-phosphate receptor modulator formulated as a once-daily oral treatment and approved for treatment of relapsing MS[a] in adults, and children and adolescents aged ≥10 years[2,3]
  - Women should not become pregnant while on treatment with fingolimod and effective contraception is recommended during treatment and for 2 months after stopping treatment[3]
  - In the EU[b], fingolimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception[4]
- Assessment of the impact of fingolimod exposure on pregnancy outcomes is essential for the management of MS in pregnant women or those planning to conceive

Objective

To report the prevalence of major congenital malformations in infants following fingolimod exposure before (up to 8 weeks before last menstrual period) or during pregnancy

[a]The approved indication may vary from country to country. In the EU, fingolimod is approved for the treatment of patients with highly active relapsing- remitting MS. In the United States, it is approved for the treatment of patients with relapsing forms of MS; [b]Also contraindicated in other countries such as Montenegro, Serbia, Macedonia, Switzerland, Egypt and Canada. EMA, European Medicines Agency; MS, multiple sclerosis

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Methods

- This safety update reports cumulative pregnancy outcome data (cut-off: 28 February 2020) from prospective cases in:
  - **N**ovartis **S**afety **d**ata**b**ase (NSDB) and
  - Multinational **G**ilenya® **P**regnancy Exposure **R**egistry (GPR, cases in GPR are also in the NSDB)

Prospective cases defined as

- **For NSDB**: Prospective cases are those for which pregnancy outcome was unknown at the time of enrolment and prenatal testing was not performed; if performed, results must be either normal/not known
- **For GPR:** Prospective cases were those for which condition of the fetus was not assessed through prenatal testing at the time of enrolment and the pregnancy outcome was unknown at the time of enrolment

- **Outcomes assessed**: **Major congenital malformations**[a] and **overall pregnancy outcomes** (live births, still births, induced terminations and spontaneous abortions)

[a]Any structural defect with surgical, medical, or cosmetic importance recognized) are presented as a proportion of fetal cases in live births, or in live births, stillbirths, and termination of pregnancy due to fetal anomaly (TOPFA); the cases are adjudicated

TOPFA, Termination of Pregnancy due to Fetal Anomaly

Case disposition

NSDB
(Prospective cases: 1762)

- **Birth-type outcome known: 1064 (60.4%)**
  - Live births : 754 (70.9%)
- **Birth-type outcome pending: 149 (8.5 %)**
- **Birth-type outcome unknown: 549 (31.2%)**

GPR
(Prospective cases: 177)

- **Birth-type outcome known: 153 (86.4%)**
  - Live births: 130 (85%)
- **Birth-type outcome pending: 14 (7.9%)**
- **Birth-type outcome unknown:10 (5.6%)**

Data are expressed as n (%), unless stated otherwise
NSDB, Novartis Safety database; GPR, Gilenya® Pregnancy Exposure Registry

Overall pregnancy outcomes among prospective fetal cases

Outcome	NSDB N=1762	GPR N=177
Number of infants in pregnancies with known outcome	**1064**	**154**
Live births[a]	**754 (70.9)**	**131 (85.1)**
Congenital malformations[b]	37 (4.9)	10 (7.6)
No reported congenital maformations	717 (95.1)	121 (92.4)
Stillbirths	**3 (0.3)**	**1 (0.6)**
Congenital malformations[b]	1 (33.3)	0 (0.0)
No reported congenital malformations	2 (66.7)	1 (100.0)
Induced termination	**160 (15.0)**	**10 (6.5)**
Congenital malformations[b]	9 (5.6)	1 (10.0)
No reported congenital malformations	151 (94.4)	9 (90.0)
Spontaneous abortion	**143 (13.4)**	**11 (7.1)**
Ectopic pregnancies	**4 (0.4)**	**1 (0.6)**

Data are expressed as n (%), unless stated otherwise

[a]For the NSDB, the 'term', 'pre-term' and 'neonatal' deaths are included under 'live births' and not analyzed separately; [b]Includes major and minor malformations

N, total number of patients; n, number of patients; GPR, Gilenya® Pregnancy Exposure Registry; NA, not available; NSDB, Novartis Safety database

Prevalence of major and unspecified congenital malformations (EUROCAT classification) is consistent with the literature

Prevalence n/N % (95% CI)	NSDB[a]	GPR	Literature
Major congenital malformations in live births	25/753 **3.3% (2.2; 4.9)**	6/131 **4.6% (1.7; 9.7)**	**4.2% (2.7; 6.1)[1] in untreated MS population 2.04% (2.03; 2.05)[2] in general population**
Major congenital malformations in live births, stillbirths and TOPFA	35/765 **4.6% (3.2; 6.3)**	7/133 **5.3% (2.1;10.5)**	**2.6%(2.6; 2.6)[2] to 6.9% (6.6; 7.2)[3] in general population**

- In the NSDB, the estimate of the proportion of prospectively-reported live births with major cardiovascular anomalies (1.33% [95% CI: 0.64; 2.43]) was larger than but not significantly different from the corresponding EUROCAT prevalence estimate (0.69%). This may be attributable to the difference in data collection and processing methodologies between EUROCAT and the NSDB.

[a]The denominator is restricted to cases with known fetal outcome; The prevalence is calculated as the number of fetuses/infants with at least one major malformation per 100 fetuses/infants. If any infants had multiple anomalies, only the worst anomaly was counted. CI: Confidence Interval; EUROCAT, Surveillance of Congenital Anomalies; GPR, Gilenya® Pregnancy Exposure Registry; N, total number of patients; n, number of patients; NSDB, Novartis Safety database; TOPFA: Termination of Pregnancy due to Fetal Anomaly

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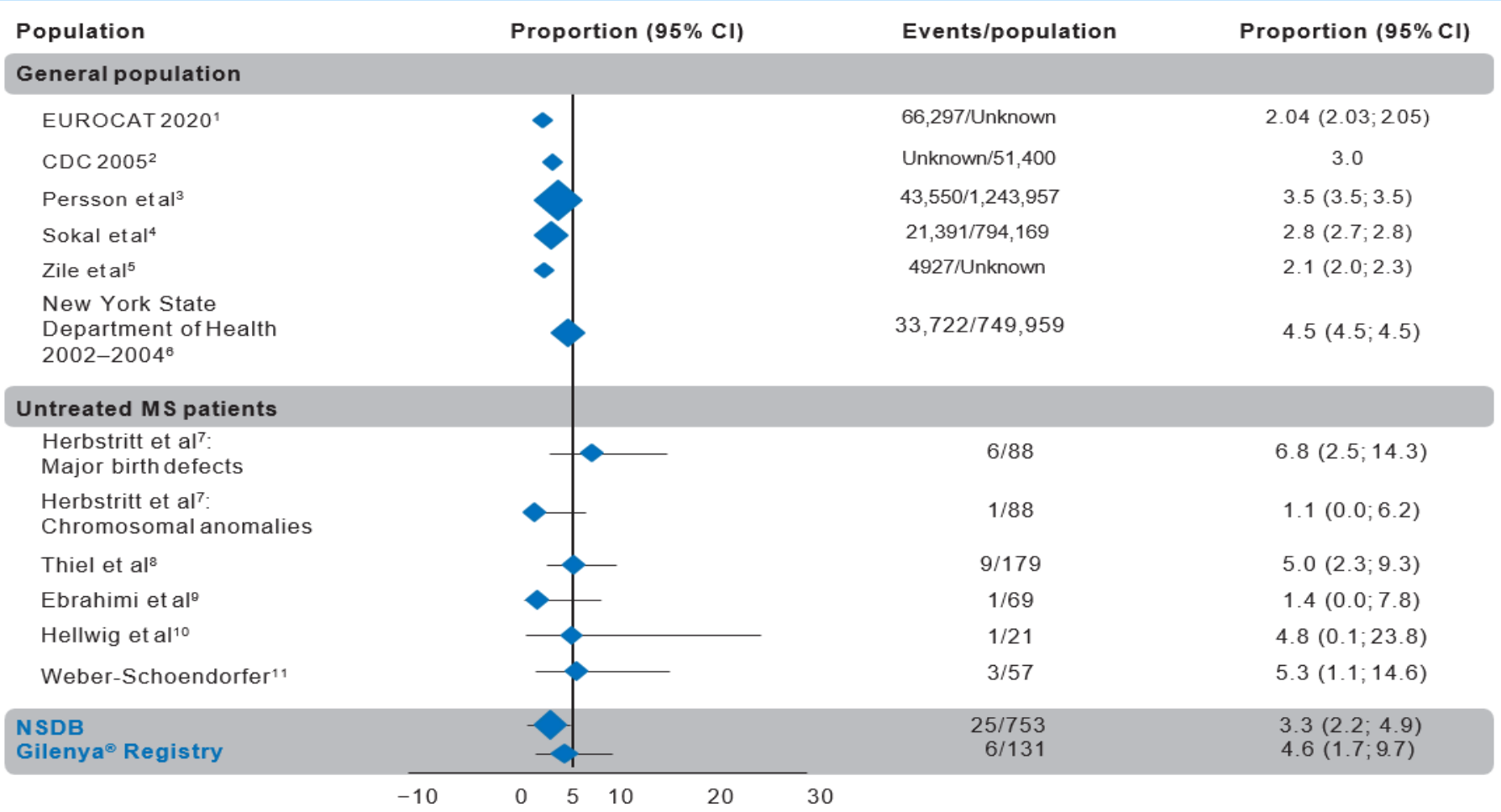
Prevalence of major congenital malformations in live births (EUROCAT classification) is consistent with the literature



The proportions reported in the figure are either retrieved directly from the reference or are derived from the information available in the reference; CI, confidence interval; EUROCAT, Surveillance of Congenital Anomalies; MS, multiple sclerosis

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Conclusions

- The prevalence of major congenital malformations among live births in the NSDB and GPR are similar to that from the untreated MS population
- The prevalence estimates in both NSDB and GPR are numerically higher than the prevalence reported in general population as per EUROCAT classification; however these are within 95% CIs for both databases
- The wide 95% CIs in the GPR prevent firm conclusions regarding increased risk of major congenital malformations in infants born to women exposed to fingolimod

CI, confidence interval; NSDB, Novartis Safety database; GPR, Gilenya® Pregnancy Exposure Registry

Thank you