NOVARTIS

Quantitative Safety and Epidemiology

FTY720D (Fingolimod)

REDACTED REPORT BODY

CFTY720D2404

Non-Interventional Study Final Report

The Multi-national Gilenya® Pregnancy Exposure Registry in Multiple Sclerosis

Author	[redacted] Novartis Pharma AG
Document Status	Final
Date of final version of the study report	04-Feb-2025
EU PAS register number	ENCEPP/SDPP/2569

NIS Report Template Version 4.0, Effective from 06-Aug-2021

PASS information

Title	The Multi-national Gilenya® Pregnancy Exposure Registry in Multiple Sclerosis
Version identifier of the final study report	Final report
Date of last version of the interim study report	22-May-2023
EU PAS register number	ENCEPP/SDPP/2569
NIS Type	NIS with Primary Data Collection
Active substance	Fingolimod hydrochloride ATC code: L04AE01 Pharmacotherapeutic group: Immunosuppressants, Sphingosine-1-phosphate (S1P) receptor modulators
Medicinal product	Gilenya®
Product reference	EMA reference number: EMEA/H/C/002202 US-FDA reference number: NDA 022527
Procedure number	EMA procedure: MEA 014 US-FDA procedure: PMR 1679-3
Marketing authorization holder	Novartis Europharm Limited (EU) Novartis Pharmaceutical Corporation (US)
Joint PASS	No

Research question and objectives	The overall goal is to prospectively collect and evaluate safety data on fingolimod exposure immediately before (up to 8 weeks before last menstrual period (LMP)) and during pregnancy on pregnancy outcomes for comparing the maternal, fetal, and infant outcomes in the registry to the background frequency from reference populations. The main (primary) objective is: • To describe the overall frequency of major and minor congenital malformations associated with exposure to fingolimod during pregnancy The other (secondary) objectives are: • To describe the frequency of specific types of major and minor congenital malformations associated with exposure to fingolimod during pregnancy • To characterize the nature of pregnancy and other fetal outcomes associated with exposure to fingolimod during pregnancy such as spontaneous abortions, stillbirths, and elective terminations • To describe the occurrence of physical developmental delays as well as adverse effects on immune system development in infants around 1-year of age associated with exposure to fingolimod during pregnancy
Country(-ies) of study	The following countries have enrolled women: Argentina, Australia, Austria, Belgium, Canada, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lebanon, Mexico, Netherlands, Poland, Portugal, Russia, Saudi Arabia, Spain, Sweden, Switzerland, United Arab Emirates, United Kingdom, and United States.
Main author	[redacted] MSc [redacted] Novartis Pharma AG Lichtstrasse 35 CH-4056 Basel, Switzerland.

Marketing authorization holder

Marketing authorization holder(s)	**European Union (EU):** Novartis Europharm Limited Vista Building Elm Park, Merrion Road Dublin 4 Ireland. **United States (US):** Novartis Pharmaceutical Corporation One Health Plaza East Hanover, NJ 07936 United States.
MAH contact person	**EU contact** [redacted] Novartis Pharma AG Lichtstrasse 35 CH-4056 Basel, Switzerland. **US contact** [redacted] Novartis Pharmaceutical Corporation One Health Plaza East Hanover, NJ 07936 United States.

Table of Contents

List of appendices

The appendices listed below are based on the ICH study report granulation. Some of the appendices may not be relevant for this report.

16.1 Study information

16.1.1 Protocol and protocol amendments

16.1.2 Sample case report form(s)

16.1.3 List of IECs or IRBs and sample consent form(s)

16.1.4 List and description of investigators and other important participants in the study

16.1.5 Signatures

16.1.6 Listing of participants receiving test drug(s) from specific batches

16.1.7 Randomization scheme and codes

16.1.8 Audit certificates and health authority inspections

16.1.9 Documentation of statistical methods

16.1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures

16.1.11 Publications based on the study

16.1.12 Important publications referenced in the report

16.2 Data listings

16.2.1 Discontinued participants

16.2.2 Protocol deviations

16.2.3 Participants excluded from the analysis

16.2.4 Demographic data

16.2.5 Compliance and/or drug concentration data

16.2.6 Individual efficacy response data

16.2.7 Adverse event listings

16.2.8 Laboratory measurements

16.2.9 Vital signs and other observations related to safety

16.3 Case Report Forms

16.4 Individual patient data listings (US archival listings)

1 Abstract

Title

The Multi-national Gilenya® Pregnancy Exposure Registry in Multiple Sclerosis

Version and date

Final report, 04-Feb-2025

NIS Type

NIS with Primary Data Collection

Name and affiliation of main author

[redacted] Novartis Pharma AG

Keywords

Fingolimod, Gilenya®, Multiple Sclerosis, Pregnancy Outcomes

Rationale and background

Fingolimod is a sphingosine-1-phosphate receptor modulator. It is indicated as a disease modifying therapy for the treatment of patients 10 years and older with relapsing multiple sclerosis (MS) to reduce the frequency of relapses and to delay the progression of disability. Fingolimod was first approved in Russia on 17-Aug-2010. As of 28-Feb-2024, fingolimod is registered in 92 countries worldwide.

Fingolimod was found to be teratogenic in rats, including the findings of persistent truncus arteriosus and ventricular septal defect. Although the embryo-fetal effects in rats and rabbits occurred at maternal exposures similar to human therapeutic exposures, these findings cannot be used to predict specific human effects. At the time of fingolimod registration, the available data in humans did not provide any firm conclusions regarding the safety of fingolimod in pregnancy. Therefore, a prospective follow-up of human pregnancies was deemed necessary and the Gilenya Pregnancy Registry (GPR) was implemented. Among the 39 countries where GPR recruited participants or has ever initiated a site for recruitment, fingolimod is contraindicated during pregnancy in 33 countries.

Due to recruitment challenges, changes in MS drug use, and the contraindication in pregnancy in most GPR recruiting countries, interactions with the United States (US) Food and Drug Administration (FDA) were undertaken. In Feb-2024, FDA agreed that the Registry could be closed and that currently enrolled prospective cases in the Registry should be followed until completion of the 12-month infant outcome datapoint. Since 12-month infant follow-up has been completed, this is the final GPR report.

Research question and objectives

Primary objective:

- To describe the overall frequency of major and minor congenital malformations associated with exposure to fingolimod during pregnancy.

Secondary objectives:

- To describe the frequency of specific types of major and minor congenital malformations associated with exposure to fingolimod during pregnancy
- To characterize the nature of pregnancy and other fetal outcomes associated with exposure to fingolimod during pregnancy such as spontaneous abortions, stillbirths, and elective terminations
- To describe the occurrence of physical developmental delays as well as adverse effects on immune system development in infants around 1-year of age associated with exposure to fingolimod during pregnancy

Study design

GPR was a multi-national, prospective, observational study collecting data regarding fingolimod exposure during or shortly before pregnancy and the maternal, fetal, and infant outcomes. Pregnancy outcomes were collected at selected gestational time points and at the estimated date of delivery (EDD). Structural and functional congenital malformations identified in the perinatal period through 1-year of life, in addition to the developmental status of infants, were collected and classified.

Setting

GPR was designed for open enrollment of all female patients meeting the following criteria:

Inclusion criteria:

- A woman with a diagnosis of MS
- Currently pregnant
- Exposure to fingolimod during pregnancy or up to 8 weeks before last menstrual period (LMP)
- Signed informed consent (IC)

Exclusion criteria:

- None

Pregnant women were classified as prospective or retrospective cases.

The criteria for prospective enrollment were:

- The condition of the fetus has NOT been assessed through prenatal testing at the time of enrollment and the outcome of the pregnancy was NOT known at the time of enrollment.

The criteria for retrospective enrollment were:

- The condition of the fetus has been assessed through prenatal testing at the time of enrollment and/or the outcome of the pregnancy was known at the time of enrollment.

Subjects and study size, including dropouts

GPR was initially planned to include approximately 500 pregnant women (as per protocol version 3.0 dated 10-Dec-2019). With 500 women exposed to fingolimod included, the study would have >80% power (two-sided test, α set at 0.05) to detect an 80% risk increase in the frequency of major malformations, assuming a background prevalence of 3%.

In September 2021, FDA agreed to decrease the enrollment target from 500 pregnancies to 300 live births (LBs). In Feb-2024, FDA concluded that the Registry could be closed.

Variables and data sources

The key safety endpoints included outcomes of interest related to:

- Major malformations (defined as any structural defect with surgical, medical, or cosmetic importance recognized)
- Minor congenital anomalies
- Overall pregnancy outcomes (i.e., LB, spontaneous fetal loss, stillbirth [SB], and elective termination)
- Pregnancy complications

Additional endpoints of interest included potential adverse effects on the physical and immune system development of the offspring, and any other adverse pregnancy complications and maternal outcomes.

Other safety assessments consisted of collecting all adverse events (AEs) and serious adverse events (SAEs), with their severity and relationship to fingolimod.

The data sources included the patient's medical records inclusive of information collected as part of the protocol specifications and/or routine medical practice, hospital discharge files, documentation of patient self-reporting, documentation of reporting from treating physicians to the participating investigator, etc.

Relevant data from source documents were recorded into electronic case report forms (eCRFs). Physician evaluations, recorded directly into the eCRF, were considered source data. If the pregnancy outcome included a congenital anomaly or other outcome for which there was evidence of a birth defect, patient data was forwarded to two independent adjudicators (e.g., teratologists) who completed a congenital anomaly evaluation. If a case was adjudicated differently by the two reviewers according to either European Registry of Congenital Anomalies and Twins (EUROCAT) or Metropolitan Atlanta Congenital Defects Program (MACDP) classification, then a third adjudicator reviewed the case. Either the assessment on which two of the three adjudicators agreed or the more severe/conservative result was retained (if all three adjudicators disagreed on assessment).

Statistical methods

This study was descriptive in nature.

The main measures of interest included frequency and percentage of fetal congenital malformations, exposure to fingolimod prior to (up to 8 weeks before LMP) and during pregnancy, other potential risk factors for the occurrence of major congenital malformations (MCM), baseline maternal characteristics, and AEs and SAEs reported after the start of fingolimod treatment, even if the event was not considered related to fingolimod.

The primary analysis consisted of the estimation of the prevalence of MCM (proportion and 95% confidence interval [CI]). Congenital anomaly definitions and classifications were consistent with the MACDP and EUROCAT surveillance programs. Two denominators were considered: LBs, and LBs, SBs and termination of pregnancy due to fetal anomaly (TOPFA). The MCM prevalence by organ system and the distribution by organ system are also provided.

Since potentially subject to different reporting bias, data were presented by enrollment type, categorized as prospective or retrospective.

Results

This is the final analysis on the 312 women enrolled in GPR up to 05-Jan-2023. Data accumulated up to 03-Jul-2024 (database lock date) are included, allowing one year of follow-up for each infant. Nine women were excluded due to protocol deviations, leading to 303 women analyzed (202 prospective and 101 retrospective).

The median age at LMP was 32.0 years (range 19-48). Overall, 70.6% of the women were from Europe and 21.5% from the US and Canada. The pre-pregnancy body mass index (BMI) classified 22.1% and 21.7% of the women as overweight and obese, respectively. Relapsing Remitting Multiple Sclerosis (RRMS) was the most common current type of MS (93.9%).

At least one active medical condition was reported by 104 (34.3%) women. The most reported conditions were depression (7.9%), thyroid disease (4.0%) and autoimmune disease (3.6%).

Among the women with available information, a majority (n=158, 52.7%) reported at least one previous medically recognized pregnancy. Among these, 26 (16.5%) reported at least one specific obstetric complication in a previous pregnancy.

Most women (88.8%) were exposed to fingolimod during at least the first trimester.

Among the 303 pregnancies, 286 recorded a known pregnancy outcome, involving 289 infants (189 in the prospective group and 100 in the retrospective group).

Overall, there were 263 (91.0%) LBs. Two (0.7%) women reported an ectopic pregnancy, 12 (4.2%) women reported a spontaneous abortion, and 11 (3.8%) reported an elective termination (including one due to fetal anomaly). One woman reported a SB.

Out of the 289 infants, 25 were confirmed to have a malformation by the adjudication panel. Per EUROCAT classification, in LBs, SBs, and TOPFA, 19 infants were adjudicated with MCMs (12 prospective and seven retrospective cases). The remaining six were adjudicated as minor malformations (four prospective and two retrospective cases).

No malformations were assessed as chromosomal anomalies or genetic defects.

Using the EUROCAT classification, the prevalences of MCM in infants exposed to fingolimod *in utero* were similar across pregnancy classification and denominator:

- in prospective LBs (n/N= 11/164): 6.7% (95% CI: 3.4, 11.7),
- in prospective LBs, SBs, and TOPFA (n/N= 12/166): 7.2% (95% CI: 3.8, 12.3),
- in all (prospective and retrospective) LBs (n/N = 18/263): 6.8% (95% CI: 4.1, 10.6),
- in all LBs, SBs and TOPFA (n/N = 19/265): 7.2% (95% CI: 4.4, 11.0).

Using the MACDP classification, the prevalences of MCM were:

- in prospective LBs (n/N=15/164): 9.1% (95% CI: 5.2, 14.6),
- in prospective LBs, SBs and TOPFA (n/N=16/166): 9.6% (95% CI: 5.6, 15.2).

The observed prevalence of major congenital malformations using the EUROCAT and MACDP classification systems in infants born to mothers with fingolimod exposure is higher than the prevalence observed in the general population (EUROCAT [excluding chromosomal/genetic anomalies]: 1.77% [LB+SB] and 2.03% [LB+SB+TOPFA]; MACDP: 3.0%).

For three organ systems, MCM prevalence in the GPR prospective group was higher compared to EUROCAT (LBs, SBs and TOPFA):

- congenital heart defects (GPR: 3.61% [95% CI: 1.34, 7.70] vs. EUROCAT: 0.69% [95% CI: 0.68, 0.69]),
- urinary malformations (GPR: 2.41% [95% CI: 0.66, 6.05] vs. EUROCAT: 0.32% [95% CI: 0.31, 0.32]), and
- limb/musculoskeletal malformations (GPR: 1.81% [95% CI: 0.37, 5.19] vs. EUROCAT: 0.34% [95% CI: 0.34, 0.35]).

The same was observed when all (i.e., prospective and retrospective combined) cases are considered.

Of the MCMs reported according to EUROCAT (prospective and retrospective combined among LB+SB+TOPFA), complete recovery was reported for five cardiac events in the nine cases involving major cardiac malformations (three events of ventricular septal defect [VSD] out of five cases with VSD and one event each of VSD and atrial septal defect [ASD] in one out of two cases with ASD+VSD), and for one further event (brachycephaly) in a case classified under “other anomalies”.

Of the MCMs reported according to EUROCAT (prospective and retrospective combined among LB+SB+TOPFA), complete recovery was reported for five cardiac events in the nine cases involving major cardiac malformations (three events of ventricular septal defect [VSD] out of five cases with VSD and one event each of VSD and atrial septal defect [ASD] in one out of two cases with ASD+VSD), and for one further event (brachycephaly) in a case classified under “other anomalies”.

In LB, SB, and TOPFA, the overall MCM prevalence was higher in participants from the US/Canada (13.0%) and when the participant self-reported (11.3%). Classifying the pregnancies by their risk profile (including active medical condition, family history, event during the pregnancy, age and BMI), 164 (62%) pregnancies had at least one risk factor. Among these, 14 (8.5%) had an infant with an MCM, leading to an odds ratio (OR) for MCM in pregnancies with at least one risk factor vs. MCM in pregnancies without a risk factor of 1.69 (95% CI: 0.61, 4.68).

One neonatal death, due to prematurity, was reported.

Of the 231 infants with 12-month follow-up, there were no significant findings in infant immune system development. Developmental delay was reported in five infants.

Overall, 83 SAEs (excluding pregnancy outcomes and malformation associated events only in LBs) were reported in 37 (14.5%) infants. The most frequently reported (≥3%) SAEs were related to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) of infections and infestations (9.0%) and respiratory, thoracic and mediastinal disorders (5.1%). One infant was reported with neonatal sepsis. Two babies had respiratory failure and one case was reported with Kernicterus.

Overall, 120 SAEs (excluding adverse pregnancy outcomes and associated events) were reported in 67 women. The most frequent SOCs for mother SAEs were pregnancy, puerperium and perinatal conditions (9.9% [n=30] of women), Nervous system disorders 6.6% (n=20) and infection and infestations 4.3% (n=13). Cervical incompetence, gestational diabetes and pre-eclampsia were the most reported SAEs in 1.7% (n=5) of women each. One maternal death was reported. Other notable SAEs reported include cervical cancer and severe allergic reaction to Copaxone.

Limitations

This study had several limitations. GPR was a single arm study, and no direct comparator was available. Comparing results in GPR to external data sources must be done with caution. The limited sample size of infants born to fingolimod-exposed women (164 prospective LBs) and the limited number of infants reported with MCMs resulted in a MCM prevalence estimate with a wide CI. In some instances, cases were conservatively classified as a major malformation when lacking detailed information. To fully assess the causal relation of fingolimod-exposure *in utero* and MCM, the effect of possible confounders would need to be isolated; based on the current data this is hard to establish since there is no definitive set of risk factors for MCMs and the information collected may be incomplete (e.g., details of family history).

Discussion

The prevalence of MCMs in infants exposed to fingolimod *in utero* was higher than the EUROCAT background prevalence in the general population. While the underlying maternal risk factors (such as maternal age, obesity, gestational diabetes) contributed to the observed increased MCM prevalence, the exact magnitude of this contribution remains unknown due to potential further unmeasured factors.

Per design, in the US/Canada the reporter was the patient herself. This may have led to enrollment and reporting biases, as suggested by the higher MCM prevalence in the US/Canada compared to other regions.

Conclusion

The prevalence of MCMs in prospective LBs in the GPR, using both the EUROCAT (6.7%; 95% CI: 3.4, 11.7) and MACDP (9.1%; 95% CI: 5.23, 14.6) classifications systems, was higher than in the general population (1.77% and 3.0%), with non-overlapping CIs. The same was observed when prospective and retrospective cases were combined.

Compared to EUROCAT data in LBs, SBs and TOPFA, the prevalence of congenital heart defects, urinary malformations, and limb/musculoskeletal malformations in GPR was greater than in the general population.

A high proportion of participants reported at least one risk factor for MCM, which contributed to the observed increased MCM prevalence.

The higher-than-expected prevalence of cardiovascular, urinary, and limb/musculoskeletal malformations was consistent with previous reports.

The prevalence of spontaneous abortions was at the lower end and that of SB in line with what would be expected in the general population and in untreated and treated women with MS with studies of similar designs (e.g., primary data collection with ongoing pregnancy at informed consent).

Marketing Authorization Holder(s)

Novartis Europharm Limited in the European Union (EU)

Novartis Pharmaceutical Corporation in the United States (US)

Name(s) and Affiliation(s) of Principal Investigator(s)

Dr. [redacted], ([redacted] Gilenya® Pregnancy Registry Steering Committee and National Coordinating Site in Germany), [redacted], Germany.

2 List of abbreviations

AE	Adverse Event
APGAR score	Appearance, Pulse, Grimace, Activity, and Respiration score
ASD	Atrial septal defect
BMI	Body mass index
CDC	Centers of Disease Control and Prevention
CI	Confidence Interval
COVID	Corona virus disease
CRF	Case Report/Record Form
CRO	Contract Research Organization
EDD	Estimated date of delivery
EDSS	Expanded disability status scale
EMEA	European Medicines Agency
EU	European Union
EUROCAT	European Registration of Congenital Anomalies and Twins
FDA	Food & Drug Administration
HCP	Health Care Provider
HPV	Human papilloma virus
ICF	Informed Consent Form
LB	Live birth
MAH	Marketing Authorization Holder
MACDP	Metropolitan Atlanta Congenital Defects Program
MCM	Major Congenital Malformation
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
OR	Odds Ratio
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PRIM	PRegnancy outcomes Intensive Monitoring
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SB	Still birth
TOPFA	Termination of pregnancy for fetal anomaly
VSD	Ventricular septal defect
WHO	World Health Organisation

3 Investigators

Principal Investigator: Dr. [redacted], ([redacted] Gilenya® Pregnancy Registry Steering Committee and National Coordinating Site in Germany), [redacted] Germany.

4 Other responsible parties

The administrative structure of the study, including internal and external participants, is described in Appendix 16.1.4-Section 1.

[redacted] analyzed this study and Novartis authored this report. The signatures of the principal or coordinating investigator, the sponsor's responsible medical officer, and the report authors are provided in Appendix 16.1.5.

5 Milestones

Table 5-1 Study milestones

Milestone	Planned date	Actual date
Start of data collection	13-May-2011	15-Oct-2011
End of data collection	Q4 2030	03-Jul-2024
Interim reports		
Interim report 1	04-Apr-2012	28-Mar-2012
Interim report 2	25-Jun-2013	11-Jun-2013
Interim report 3	30-Jun-2014	19-Jun-2014
Interim report 4	15-Jun-2015	04-Jun-2015
Interim report 5	01-Jul-2016	30-Jun-2016
Interim report 6	26-Jun-2017	05-Jun-2017
Interim report 7	29-Jun-2018	19-Jun-2018
Interim report 8	19-Jun-2019	14-Jun-2019
Interim report 9	02-Jun-2020	04-Jun-2020
Interim report 10	04-Jun-2021	26-May-2021
Interim report 11	24-May-2022	03-Jun-2022
Interim report 12	01-Jun-2023	22-May-2023
Final report	-	04-Feb-2025

6 Rationale and background

Multiple sclerosis (MS) is a chronic, demyelinating, immune-mediated disease of the central nervous system characterized by inflammation and destruction of myelin and axons (Trapp et al 1998, Sosperdra and Martin 2005). MS affects two to three times more women than men and the average age of onset of MS is 29.2 years (inter-quartile range, 25.3 to 31.8 years; (World Health Organization (WHO) 2008 and Leray et al 2016), indicating that many women living with MS are of childbearing potential when diagnosed.

Based on the evidence to date, including a meta-analysis (Finkelsztejn et al 2011), MS has no discernable effects on the risk of adverse pregnancy outcomes, including spontaneous abortion,

stillbirth (SB), neonatal death, delivery complications, low birth weight, abnormal head circumference, and congenital malformations (Worthington et al 1994, Houtchens et al 2007, Dahl et al 2008, Kelly et al 2009, Liguori et al 2009, Finkelsztejn et al 2011 and MacDonald et al 2019a). However, a recent systematic review found results pointing towards an increased risk of preterm birth and small for gestational age (SGA) among women with MS (Andersen et al 2023). Two out of eight studies were sufficiently powered to draw a conclusion and observed a statistically significantly increased risk of preterm birth in women with MS compared to a non-MS population. For SGA, three studies observed a statistically significantly increased risk of SGA in women with MS compared to a non-MS population, while three other studies did not find any significant differences (Andersen et al 2023).

Fingolimod (Gilenya®/FTY720) is an oral sphingosine-1-phosphate (S1P) receptor modulator approved for the treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations, and to delay the accumulation of physical disability (Volpi et al 2019). Fingolimod is registered in 92 countries worldwide as of the data lock point (DLP) of 28-Feb-2024 for this report. Mitsubishi Tanabe Pharma Corporation is the license partner for fingolimod in Japan.

In animal models, fingolimod was teratogenic in rats when given at doses of 0.1 mg/kg or higher. A dose of 0.1 mg/kg in rats corresponds to 2 times the exposure in humans at the recommended dose of 0.5 mg. The most common fetal visceral malformations included persistent truncus arteriosus and ventricular septum defect (Gilenya CDS). Furthermore, the receptor affected by fingolimod (the S1P receptor) is known to be involved in vascular formation during embryogenesis (Mendelson et al 2014). An increase in post-implantation loss was observed in rats at 1 mg/kg and higher and a decrease in viable fetuses at 3 mg/kg. Fingolimod was not teratogenic in rabbits, however an increased embryo-fetal mortality was seen at doses of 1.5 mg/kg and higher, and a decrease in viable fetuses as well as fetal growth retardation at 5 mg/kg. A dose of 1.5 mg/kg in rabbits corresponds to similar exposure in humans at the recommended dose of 0.5 mg (Gilenya CDS).

Due to the potential teratogenic risk of fingolimod, a prospective follow up of human pregnancies in a registry was deemed necessary. The pregnancy status of females of reproductive potential should be verified prior to starting treatment with fingolimod. The use of fingolimod in women who are or may become pregnant should only be considered if the potential benefit justifies the potential risk to the fetus. Since 2019, fingolimod has been contraindicated for use during pregnancy in 33 of 39 countries where the Gilenya Pregnancy Report (GPR) recruited or has ever initiated a site for recruitment. The countries with initiated recruiting sites that did not have a contraindication for use during pregnancy are Argentina, Australia, Brazil, Colombia, Israel and the US.

Due to recruitment challenges, changes in MS drug use, and the contraindication in pregnancy in most GPR recruiting countries, interactions with Food and Drug Administration (FDA) were undertaken. In February 2024, FDA agreed that the Registry could be closed. Since all enrolled pregnancies have completed the 12-month infant follow-up, this is the Final Report for Study CFTY720D2404 (referred to GPR). The database lock date was 03-Jul-2024 and analyses include all data until that point in time.

7 Research question and objectives

The overall goal was to prospectively collect and evaluate safety data on fingolimod exposure immediately before (up to 8 weeks before last menstrual period (LMP)) and during pregnancy and associated pregnancy outcomes for comparing the maternal, fetal, and infant outcomes in the registry to the background frequency from reference populations.

Primary objective:

- To describe the overall frequency of major and minor congenital malformations associated with exposure to fingolimod during pregnancy.

Secondary objectives:

- To describe the frequency of specific types of major and minor congenital malformations associated with exposure to fingolimod during pregnancy
- To characterize the nature of pregnancy and other fetal outcomes associated with exposure to fingolimod during pregnancy such as spontaneous abortions, stillbirths and elective terminations
- To describe the occurrence of physical or developmental delays, as well as adverse effects on immune system development in infants around one year of age associated with exposure to fingolimod during pregnancy

Impact of the COVID-19 pandemic

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified by the World Health Organization (WHO) in December 2019. GPR was ongoing during this pandemic. It is assumed that the pandemic had limited impact since pregnancy related assessments were most likely maintained. The exact impact of the COVID-19 pandemic on this study remains unknown.

8 Amendments and updates to the protocol

Date	Amendment or update	Reason
15-Apr-2011	1	The rationale for Amendment 1 was based on comments received from the FDA on 24-Feb-2011. The major changes included clarifying the enrollment and informed consent (IC) timing and procedures for the patient and her infant, reason for discontinuation, and contact information needed to minimize the number of patients lost to follow-up. Some assessment time points were relabeled and visit windows were better defined to keep in line with common practice. Sections representing characterization of weight relative to pregnancy outcome and documentation procedures for gestational age (GA) were also updated. Novartis confirmed that it would try to collect pathology reports if done for cases of spontaneous or elective abortion. In order to further characterize infant development, developmental milestones were added at the 1-year follow-up and assessed during routine clinical care. Amendment 1 was implemented prior to recruitment of patients into the registry.
05-Jul-2012	2	The rationale for Amendment 2 was based on comments received from the FDA requiring better clarification of the main (primary) versus other (secondary) objectives for the registry. Changes to the protocol were also aimed to increase enrollment by allowing remote patient consenting and data collection directly by the clinical/contract research organization (CRO) and

		through patients' in countries where this practice is acceptable by local country law. To remain compliant with safety reporting duties while reducing site workload, the pharmacovigilance and registry data flows were streamlined. Amendment 2 was implemented after patient enrollment had begun and 1 patient was enrolled into the registry.
10-Dec-2019	3	The rationale for Amendment 3 was to reflect the update in the Gilenya® (fingolimod) core datasheet or local product information regarding use of fingolimod in pregnancy. At the time of writing this amendment, 260 patients were enrolled in the registry.
Source: Appendix 16.1.1-Study Protocol		

9 Research methods

9.1 Study design

This was a multi-national, prospective, observational study which collected data regarding fingolimod exposure during pregnancy and the maternal, fetal, and infant outcomes.

GPR was initially planned to include approximately 500 pregnant women exposed to fingolimod immediately before or during pregnancy. In September 2021, FDA agreed to decrease the enrollment target from 500 pregnancies to 300 live births (LBs).

Pregnancy outcomes were collected at selected gestational time points and at the estimated date of delivery (EDD). Structural and functional congenital malformations identified in the perinatal period through one year of life and developmental status of infants were collected and classified.

Women taking fingolimod were advised to enroll in GPR as soon as their pregnancy was known, preferably in the first trimester before the condition of the fetus was assessed through targeted prenatal testing (i.e., prospective patients).

In cases where the condition of the fetus was assessed as a result of prenatal testing at the time of enrollment, the participant was still eligible for enrollment but was considered retrospective. Data collection for retrospective and prospective participants was similar; however, retrospective cases were analyzed separately.

The following baseline and follow-up data were collected for prospective and retrospective patients:

- Baseline assessment (at enrollment): maternal information, including demographics, prenatal test results, information on fingolimod and other exposures, medical and obstetrical history.
- Mid-second trimester (21 weeks gestational age +/- two weeks): any additional prenatal testing, maternal (and fetal) outcomes, updated exposure information on fingolimod, and other exposures.
- Post-partum (from birth up to three months post EDD): maternal and infant outcome (including gestational age), type of major and minor malformation (if any), obstetrical complications, updated exposure information on fingolimod and other exposures, and adverse events (AEs).

- 3-month follow up (EDD + three months to infant age nine months): infant outcome details, major and minor malformations not recorded at birth, and AEs.
- One-year follow up (infant age 10 to 14 months): infant outcome details, major and minor malformations not recorded at birth, infant height, weight and head circumference, infant medical conditions, including testing/procedures and diagnoses, neurodevelopmental milestones and AEs.

9.2 Setting

The registry was designed for open enrollment of all patients meeting the inclusion criteria described in Section 9.3. To reduce the bias that could have occurred when some outcome information was known prior to enrollment, women were enrolled in the registry as soon as their pregnancy was known, preferably in the first trimester, or before the condition of the fetus had been assessed through prenatal testing. Targeted prenatal testing was considered an outcome assessment since this testing may have provided knowledge about structural malformations. First trimester dating ultrasounds were not generally considered as a potential assessment of outcome.

Cases for which the condition of the fetus was known because of prenatal testing at the time of enrollment were considered retrospective cases. Section 9.7.1.1 provides the definition of prospective and retrospective cases. The time of enrollment is defined as the time when the participant signed the informed consent (IC) form.

9.3 Patients

Participants eligible for enrollment were required to fulfill all of the following criteria:

Inclusion criteria:

- A woman with a diagnosis of MS
- Currently pregnant
- Exposure to fingolimod during pregnancy or up to 8 weeks before LMP
- Signed IC

Exclusion criteria:

None.

9.4 Variables

9.4.1 Patient demographics/characteristics

Patient baseline demographics, pregnancy information, and MS disease characteristics were recorded upon enrollment. In addition, patient obstetric history, family history, and information on environmental exposures were collected at enrollment.

9.4.2 Drug exposure

The exposure of interest was fingolimod treatment immediately prior to becoming pregnant (up to 8 weeks before LMP), and during pregnancy.

Exposure to fingolimod during pregnancy was categorized in two different ways:

- A patient may contribute data to more than one category (peri-LMP, first trimester, after first trimester, second trimester, and third trimester).
- Exposure was categorized in mutually exclusive categories (peri-LMP, first trimester and after first trimester), based on the first and last use of fingolimod to define the earliest and latest exposures.

Cumulative exposure was calculated in days and in milligrams. Exposure to other medications and other environmental exposures (i.e., smoking, alcohol, and recreational drugs) during pregnancy was also collected.

9.4.3 Outcomes of interest

Primary outcome measures were major and minor congenital malformations. Major Congenital Malformation (MCMs) were defined as any structural defects with recognized surgical, medical, or cosmetic importance. Data on minor congenital anomalies and overall pregnancy outcomes were collected (i.e., live birth, spontaneous fetal loss, stillbirth, and elective termination). In cases of live births involving a congenital anomaly or other outcome for which there was evidence of a congenital anomaly, patient data were forwarded to two independent adjudicators (e.g., teratologists) who completed a congenital anomaly evaluation according to the EUROCAT (European Registration of Congenital Anomalies and Twins) and MACDP (Metropolitan Atlanta Congenital Defects Program) classifications. If a case was adjudicated differently by the two reviewers according to either EUROCAT or MACDP classification, then a third adjudicator reviewed the case and either the assessment on which two of the three adjudicators agreed or the most severe/conservative result was retained (if all three adjudicators disagree).

Complications during pregnancy along with data on potential adverse effects of fingolimod on the physical and immune system development of the infant, and any other pregnancy complications and maternal outcomes were also collected. The following minor congenital anomalies and adverse pregnancy outcomes were collected:

- Minor anomalies, i.e., anomalies with no serious medical or cosmetic consequence to the child
- Positional deformities, i.e., a positional deformity that usually normalizes spontaneously after about three months of age, e.g., abnormal head shape, torticollis
- Features of pre-maturity
- Chromosome abnormalities
- Genetic disorders

Infant and maternal AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) lower-level terms. MedDRA coding modules and MedDRA dictionary Version 26.1 Mixed were used. An infant may have had multiple anomalies resulting in more than one preferred term per case and therefore more anomalies than infant cases may have been presented for adjudication.

9.5 Data sources and measurement

9.5.1 Data sources

The data sources for this pregnancy registry study included the patient's medical records, inclusive of information collected as part of the protocol specifications and/or routine medical practice, hospital discharge files, documentation of patient self-reporting, documentation of reporting from treating physicians to the participating investigator, etc. (Table 9-1). Relevant data from source documents were recorded into electronic case report forms (eCRFs). Physician evaluations that were recorded directly into the eCRF were considered source data.

Findings from GPR, including prevalence of MCM, were compared to data from external sources in general surveillance systems, such as EUROCAT and MACDP, as well as the treated and untreated MS populations. Background prevalence information was retrieved from the literature. Details are provided in Appendix 16.1.1-Protocol-Section 3.5.

9.5.2 Data collection/measurement

Data was captured during different assessment periods: baseline (at enrollment), mid-second trimester (21 weeks GA ± two weeks), postpartum (up to three months after EDD), three month infant follow-up (from three months after EDD up to infant age nine months), one year infant follow up (infant age 10 to 14 months), and at discontinuation (including early termination/end of study). Data was entered directly into the eCRF by the investigator (or on paper (CRFs) and centrally entered) and stored in the electronic data capture (EDC) system.

If the participant's health care provider (HCP) was unable to provide the information needed, information was solicited directly from the participant by the registry team (where permitted according to local regulations) and recorded as medically unconfirmed by an HCP. For any safety topics, all efforts were made to obtain a confirmation by an HCP.

The data collected in each eCRF/CRF are specified in the Appendix 16.1.1-Protocol-Section 3.4.1 to Appendix-16.1.1-Protocol-Section-3.4.6 and summarized in Table 9-1 for the patient/fetus and in Table 9-2 for the infant.

Note: some changes were introduced in the eCRF over time to improve data capture leading to some elements being only partially available.

Table 9-1 Recommended schedule of data collection: maternal and fetal exposure and outcomes

Visit	Baseline	Mid-second trimester	Postpartum	End of registry or premature discontinuation
Window	At enrollment	21 weeks gestational age ± 2 weeks	Up to 3 months after EDD	At the end of patient's participation
IC	X			
Maternal demographics	X			
MS disease and treatment history	X			
Gestational age at enrollment (by LMP or ultrasound)	X			

Visit	Baseline	Mid-second trimester	Postpartum	End of registry or premature discontinuation
Obstetrical history, including previous pregnancy outcomes and sibling information	X			
Relevant maternal/paternal family history of pregnancy complications/congenital abnormalities	X			
Medical history/newly diagnosed conditions of mother	X			
Fingolimod dosing and administration	X	X	X	X
Prenatal test results	X	X	X	X
Other exposures, including lifestyle factors and concomitant medications	X	X	X	X
Participation in fingolimod studies[1]	X			
Obstetric and delivery complications			X	X
Pregnancy outcome, including gestational age at outcome			X	X
Major and minor malformations	X	X	X	X
AEs	X	X	X	X
Reason for premature discontinuation				X

[1]FTY720 clinical trials and any non-interventional studies (NIS) with FTY720.
Source: Appendix 16.1.1-Protocol-Table 3-1

Table 9-2 Recommended schedule of data collection: infant outcomes

Visit	Postpartum	3 months follow-up	1-year follow-up	Premature discontinuation
Window	Up to 3 months after EDD	EDD + 3 months to infant age 9 months	Infant age 10 to 14 months	At the end of infant's participation
IC for infant	X			
Infant outcome details	X	X	X	X
Major and minor malformations[1]	X	X	X	X
Infant height, weight and head circumference	X		X	X
Infant medical conditions, including testing/procedures and diagnoses	X		X	X
Breastfeeding history and duration			X	X

Visit	Postpartum	3 months follow-up	1-year follow-up	Premature discontinuation
Neurodevelopmental milestone status			X	X
AEs	X	X	X	X
Reason for early discontinuation				X

[1]In addition to occurrence, detailed information on major and minor malformations (e.g., diagnostic or pathology results) is collected when available.
Source: Appendix 16.1.1-Study Protocol-Table 3-2

9.5.3 Safety related measurements

Safety assessments consisted of collecting all AEs and SAEs, with their severity and relationship to fingolimod.

Full information about the definition and reporting procedures of AEs and SAEs is provided in Appendix 16.1.1-Protocol-Section 4.

9.5.4 Other assessments

Data on environmental exposure (i.e., smoking, alcohol, drug use), family history, and medical history were also collected.

9.6 Bias

As reporting of pregnancies was voluntary, there could have been bias in the type of pregnancies reported, such as low- versus high-risk pregnancy or favorable versus unfavorable outcomes. Due to a participant's personal reasons, accurate data on voluntary pregnancy termination or stillbirth could have been difficult to obtain, and as a result, identifying the percentage of pregnancies with normal outcome or birth defects with any certainty was difficult.

To reduce selection bias that could have occurred when outcome information was known prior to enrollment, women were advised to enroll in GPR as soon as their pregnancy was known, preferably in the first trimester or before the condition of the fetus was assessed through targeted prenatal testing.

To reduce the potential for loss to follow-up that may have led to differential response bias, multiple contact attempts via different contact modalities (e.g., phone, fax, and registered letter) were systematically mandated as per protocol.

9.7 Statistical methods

All analyses were performed using Statistical Analysis System® (SAS) Version 9.4 and run by [redacted] Data collection methods are provided in Section 9.5.2.

9.7.1 Main summary measures

The main measures of interest included fetal congenital malformations, exposure to fingolimod prior to (up to 8 weeks before LMP) and during pregnancy, other potential risk factors for the occurrence of congenital anomalies, baseline maternal characteristics, and AEs and SAEs

reported after the start of fingolimod treatment, even if the event was not considered related to fingolimod.

The primary analysis consisted of the estimation of the prevalence of MCM (proportion and 95% CI). Congenital anomaly definitions and classifications were consistent with the MACDP and EUROCAT surveillance programs.

Further details can be found in Appendix 16.1.1-Protocol-Section 5.1 and Appendix 16.1.9-SAP.

9.7.1.1 Determination of enrollment type

Enrollment type was categorized as prospective or retrospective (Section 9.2).

The criteria for prospective enrollment were:

- The condition of the fetus was NOT assessed through prenatal testing such as targeted ultrasound, amniocentesis, nuchal scan or chorionic villus sampling at the time of enrollment
- The outcome of the pregnancy was NOT known at the time of enrollment

The criteria for retrospective enrollment were:

- The condition of the fetus had been assessed through prenatal testing such as targeted ultrasound amniocentesis, nuchal scan or chorionic villus sampling at the time of enrollment and/or
- The outcome of the pregnancy was known at the time of enrollment

For more information on the determination of enrollment type, refer to Appendix 16.1.1-Protocol-Section 3.1.

9.7.1.2 Definition and measurement of pregnancy outcome

Pregnancy outcomes, including LB (term LB, pre-term LB, and neonatal death), ectopic pregnancy, spontaneous abortion, fetal death/SB, and elective terminations were defined based on the data recorded on the Pregnancy Outcome CRF. Neonatal death was defined as death of a live newborn during the first 28 days of life. Neonatal death was categorized as a live birth and neonatal death.

The primary pregnancy outcome of interest was congenital malformation classified by the adjudication panel as described in Section 9.4.3. MCMs were the main outcome of interest and were defined as any structural defects with recognized surgical, medical, or cosmetic importance.

The following minor congenital anomalies and adverse pregnancy outcomes were collected but not recorded as MCMs: minor anomalies (i.e., anomalies with no serious medical or cosmetic consequence to the child), positional deformities (i.e., a positional deformity that usually normalizes spontaneously after about three months of age (e.g., abnormal head shape, torticollis)), features of pre-maturity, chromosome abnormalities, and genetic disorders.

Adverse pregnancy outcomes included spontaneous fetal loss, SB, and induced abortion/elective termination, complications during pregnancy, adverse effects on physical and

immune system development of the fetus/infant, and any other adverse pregnancy and maternal outcomes observed in clinical assessments.

Since the number of multiple births remained low (n=three sets of twins), these were counted as singleton births in the analysis.

Small and large birth weight for gestational age (GA) were derived variables and were assessed (since interim report 11) using United States national reference data (Aris et al 2019) for participants enrolled in US or Canada and World Health Organization data (Kiserud et al 2017) for participants enrolled in other countries. For this report, small and large for GA for infants from Germany were assess using German national reference data (Voigt et al 2014). Infants were considered small for GA if their weight was less than the 10th percentile of the standard GA data.

9.7.1.3 Definition and measurement of exposure

9.7.1.3.1 Exposure to fingolimod

The exposure of interest was fingolimod exposure immediately prior to becoming pregnant (up to 8 weeks before LMP), and during pregnancy. Four exposure periods were considered: Peri-LMP, first trimester, second trimester, and third trimester. Based on the first and last use of fingolimod, exposure to fingolimod was categorized in two different ways.

In the first categorization, a participant may have contributed data to more than one category: Peri-LMP, first trimester, after first trimester, second trimester, and third trimester. In the second categorization, categories were taken as mutually exclusive: Peri-LMP only, At least first trimester vs. Only after first trimester. "During all pregnancy" was considered and applied to participants exposed at least from LMP to the third trimester or pregnancy outcome date, whatever came first. This category overlapped with the category "At least first trimester."

For additional information on the definition and measurement of fingolimod exposure, refer to Appendix 16.1.9-SAP.

9.7.1.3.2 Environmental exposure

Maternal environmental exposures (i.e., smoking, alcohol, and recreational drugs) were characterized as detailed in Appendix 16.1.9-SAP.

9.7.1.4 Definition of pregnancy periods

The following periods were used when describing periods of potential exposure:

- Peri-LMP: the 8 weeks prior to the first day of the LMP (the first day of the LMP - 56 days – < the first day of LMP)
- First Trimester: From the first day of the LMP to <14 weeks gestation (meaning ≤ 13 weeks) (the first day of the LMP - ≤ 91 days gestation)
- Second Trimester: From 14 to 27 weeks gestation (92 to 189 days gestation)
- Third Trimester: ≥ 28 weeks gestation until end of pregnancy (≥ 190 days gestation)
- After First Trimester: ≥ 14 weeks gestation until end of pregnancy (≥ 92 days gestation)

- During all pregnancy: From the first day of the LMP and up to the third trimester of pregnancy or the end of pregnancy, whichever occurs first

The estimated LMP for missing LMP is described in Appendix 16.1.9-SAP.

9.7.1.5 Adverse event and serious adverse event

The number of serious adverse events (SAEs) reported during the follow-up period and the total number of SAEs were described in mothers and in infants:

- Overall by severity, action taken and relationship to fingolimod
- By System Organ Class (SOC) and Preferred Term (PT)

If a mother or infant experienced more than one SAE by category, she/he was counted only once in the patient-level summary statistics, but each event was counted separately in the event-level summary statistics.

To further characterize SAEs, a medical review was undertaken and SAEs, excluding pregnancy outcomes and malformation events, were presented by SOC and PT for the mother and the infant.

For additional information on Novartis AE and SAE reporting standards and definitions refer to Appendix 16.1.9-SAP.

9.7.1.6 Baseline maternal characteristics

A critical element for understanding the potential association of maternal, fetal, and infant outcomes with fingolimod exposure was the inclusion of appropriate maternal characteristics in the analyses. The following maternal characteristics and exposures with the potential to affect pregnancy outcomes were collected:

Maternal demographics:

- Age at LMP
- Race (Note: from interim report 11 ethnicity will no longer be summarized due to change in local laws and difficulties to capture relevant and complete information)

Behavior/lifestyle factors:

- Smoking (current and past history)
- Alcohol (current and past history)
- Recreational drugs (current and past history)
- BMI (calculated using pre-pregnancy weight and height)

Medical and obstetric history:

- Number and outcome of previous pregnancies
- Previous obstetric complications
- Previous adverse fetal outcomes
- Other major maternal medical conditions
- Family history of congenital anomalies
- Family history of other significant pregnancy/fetal complications

Factors related to current pregnancy:

- Singleton versus multiple births
- Other medication and supplements taken, by trimester

9.7.2 Main statistical methods

Participant demographic and baseline characteristics were described by means of absolute and relative frequencies for categorical variables and mean, standard deviation (SD), minimum and maximum values for continuous variables. Categorical variables included race and region. Continuous variables included age at LMP, height, pre-pregnancy weight, and pre-pregnancy BMI. Relevant medical history/current condition data, MS history and current status, maternal obstetric history data and exposure to fingolimod based on start and stop date of fingolimod treatment (Peri-LMP only, at least first trimester, only after first trimester, during all pregnancy) were summarized by frequency. Duration of MS at baseline and the cumulative exposure to fingolimod (in days and in mg) was described with mean, median, SD, minimum, and maximum.

Pregnancy outcomes and infant measures were described overall and stratified by fingolimod exposure.

The prevalence (proportion, 95% CI) of MCM in LBs and in LBs, SBs, and TOPFA (termination of pregnancy for fetal anomaly) were estimated. Prevalence was calculated using both EUROCAT and MACDP classification systems. In addition, a more conservative approach was considered and the prevalence provided including chromosomal anomalies/genetic disorders. To minimize reporting bias, data obtained from prospectively reported cases was the main estimate of interest. To further characterize MCMs, the distribution of the MCM events by organ system (per EUROCAT classification system) was also provided (events were the unit of analysis).

Additional pregnancy outcomes (e.g., spontaneous abortions, SBs, elective terminations, adverse effects on immune system development, and any other adverse pregnancy outcomes) were summarized using frequency and prevalence (proportion). For overall pregnancy outcomes, prevalence was calculated out of the total number of infants with known pregnancy outcome. For additional details refer to Appendix 16.1.9-SAP. Results were reported overall and by timing of fingolimod exposure.

Retrospective cases were analyzed separately from prospective cases. For more information, refer to Appendix 16.1.9-SAP.

9.7.2.1 Methods used to examine subgroups and association

The main subgroup was the reporting type. Prospective and retrospective cases were presented separately.

Multiple versus singleton gestation and documented exposure versus indeterminate exposure are provided in Appendix 16.1.9-SAP.

The association between the occurrence of MCMs according to EUROCAT and potential risk factors was assessed as follows:

- The region (US/Canada, Germany, and "Other") and the initial reporter type (Patient or HCP) were taken as characteristics (i.e., stratification factors).
- A medical review was performed to determine if a least one risk factor for MCM per EUROCAT was present during the pregnancy. The following items were assessed, reviewed and included as medically relevant: family history of congenital abnormalities/birth defects, family history of pregnancy complications or poor outcomes, obstetric complications in previous pregnancies, adverse fetal outcomes in previous pregnancies, exposure to drug(s) with moderate or high-risk teratogenic effect during pregnancy (i.e., pregnancy exposed to known teratogen, accounting for 5 half-lives, between Peri-LMP to pregnancy outcome date), pre-pregnancy obesity/BMI, active significant condition(s) during pregnancy (condition marked as active and with a diagnosis date before pregnancy outcome date). These factors were combined rather than taken individually due to the limited sample size. Risk of MCM per EUROCAT was considered overall rather than organ specifically. Maternal smoking history was not included since data collection remained sparse.
- The occurrence of MCM by stratification factor and potential risk factor category (yes/no) was provided by pregnancy type in LB and LB, SB, and TOPFA.
- The association between the occurrence of MCM according to EUROCAT and potential risk factors was assessed in LB, SB, and TOPFA among all (i.e., prospective and retrospective combined) cases. The most inclusive denominator (LB+SB+TOPFA for all) was considered since no notable prevalence differences were observed in the previous report. Using a univariate logistic regression with the occurrence of MCMs as the outcome and the potential risk factor as a covariate (yes/no), the odds ratio (OR) and 95% CI were determined. To mitigate the possibility of rare events, Firth's Penalized Likelihood option was used. Given the low number of MCM cases, no multivariate logistic model was fitted.

9.7.3 Missing values

In general, no imputations of missing values were performed in this study, except for change in environmental exposures and partial AE dates as described in Appendix 16.1.9-SAP.

Unless otherwise specified, prevalence was provided for cases with known pregnancy outcome.

If the participant did not complete the follow-up visit, the missing values were considered missing and are not imputed. Missing was not added as a separate level for categorical variables. Summaries and percentages were provided among non-missing data.

Refer to Appendix 16.1.9-SAP for additional information.

9.7.4 Sensitivity analyses

FDA suggested that since prenatal testing had become routine, excluding women with a pre-natal test available prior to enrollment from the prospective definition may have decreased the sample size. FDA recommended revising the definition of prospective cases to also include women who had prenatal testing, regardless of result. The FDA named this the "traditional" prospective group, and it corresponded to all enrolled participants in GPR. The GPR prospective group qualified per FDA's terminology as the "pure" prospective group. On recommendation of the GPR Steering Committee, Novartis based its conclusions on the prevalence of the "pure"

prospective (the current prospective) group. Per FDA request, both prospective and all enrolled patients are presented in the results.

9.7.5 Amendments to the statistical analysis plan

For each yearly interim report, a dedicated SAP was developed as described in Appendix 16.1.9-SAP.

The SAP was further updated before the current database lock:

- For family history of congenital abnormality/birth and family history of pregnancy complication or poor outcome, a medical review was performed to summarize risk factors for EUROCAT MCM or other poor pregnancy outcome (SB/SGA/pre-term), with focus on 1st degree relatives. All reported terms are listed. Medically confirmed terms were included in the analysis.
- Risk factor analysis (as described above) to put into perspective the confounders included in the medical review was added.
- A summary of SAEs, except pregnancy outcomes, was added to allow interpretation of the mother and infant SAE tables.

A full list of amendments is presented in Appendix 16.1.9-SAP.

9.8 Study size

The GPR targeted sample size was originally 500 women exposed to fingolimod during pregnancy.

At the time of registry protocol development, a review of the literature reported that in the US, 3,030 infants with birth defects were reported per 100,000 live births (CDC 2008) and EUROCAT reported a prevalence of 2,334.2 congenital malformations per 100,000 live births (EUROCAT 2010). Worldwide, about 6% of all newborn infants have serious birth defects of genetic or partially genetic origin and the annual prevalence of congenital malformations was 3,650 per 100,000 births (Christianson et al 2006). From these three sources, the average congenital malformation prevalence was estimated to be approximately 3% (or 3,000 per 100,000 live births).

If 500 women were included, then the study would have had an >80% power (2-sided test, α set to 0.05) to detect an 80% risk increase, assuming a background prevalence of MCMs of 3%.

In September 2021, FDA agreed to decrease the enrollment target from 500 pregnancies to 300 LBs. In February 2024, FDA concluded that GPR could be closed.

9.9 Data transformation

Variables derived based on the data collected in the CRF are provided in Section 9.4. These variables further characterize GA, lifestyle factors, and relevant medicinal products analyzed in the study.

9.10 Quality control

The GPR database was housed at the offices of the clinical/contract research organization (CRO) [redacted] within a computer system environment maintained in accordance with sponsor reviewed written security policies.

The Outcome System® met approved and established standards for the security of health information and is validated. The system also met the standards of the International Council for Harmonisation guideline E6 (R1) and 21 Code of Federal Regulations Part 11 regarding electronic registry data handling and was available for audit upon request. Patient confidentiality was strictly maintained. For details refer to: The multi-national Gilenya Pregnancy exposure Registry in MS Data Management Plan (Version 6.0; Dated 16-Nov-2023).

Post database lock, two data errors were identified:

- Subject [redacted] had two adverse events ("relative pulmonary stenosis" and "relative pulmonic stenosis") recorded. After confirmation with the site, the event "relative pulmonary stenosis" was confirmed to be a duplicate and only the event "relative pulmonic stenosis" was retained.
- Subject [redacted] had a change in the reported name for a congenital malformation event. The site misread a query and renamed the event "heart murmur" to "persistent foramen ovale". The site confirmed that, per source documents, heart murmur is recorded and should be retained.

These terms were documented and hard coded.

10 Results

This is the final GPR report and supersedes all previous interim reports. This report includes cumulative data up to 03-Jul-2024, the final database lock date. This time allowed one year of follow-up on all pregnancies recruited from 15-Oct-2011 to 05-Jan-2023 (last informed consent, Listing 16.2.4-1.1).

Since the previous interim report (dated 22-May-2023), newly retrieved data and data cleaning led to changes in several previously reported cases, including changes in case classification (i.e., prospective vs. retrospective) and malformation classification (major vs. minor vs. none). Therefore, cases may be categorized differently from previous reports:

- Case classification changed from prospective to retrospective for four subjects (Subject [redacted], Subject [redacted], Subject [redacted] and Subject [redacted]) due to additional prenatal test results and additional number of tests. This included one set of twins (Subject [redacted]).
- The pregnancy outcome for one case (Subject [redacted]) was previously categorized as a termination and was reclassified to a LB.
- One prospective LB with a minor congenital malformation was removed after it was discovered that the malformation, a hernia, occurred in the mother and not the infant (Subject [redacted]).
- One new retrospective MCM case (Subject [redacted]) was reported since the previous interim report.

10.1 Participants

As of 05-Jan-2023 (last informed consent, Listing 16.2.4-1.1), a total of 312 pregnancies were enrolled in GPR, of which nine women were excluded from the analysis due to protocol deviations. Analyses include 303 women (202 prospective and 101 retrospective) (Table 10-1).

Of the 303 women analyzed, 255 (84.2%) completed registry participation (i.e., data collection up to the time of the pregnancy outcome and for LBs up to the one-year follow-up was completed) and 48 women (15.8%) discontinued participation (Table 10-1).

Two women participated twice in the registry; these women contributed twice to Table 10-1:

- Subject [redacted] and Subject [redacted] involve the same woman with both pregnancies prospectively reported (Listing 16.2.1-1.1)
- Subject [redacted] and Subject [redacted] involve the same woman, reported prospectively and retrospectively, respectively (Listing 16.2.1-1.1).
  Subject [redacted] reported one MCM of cystic kidney disease and
  Subject [redacted] was a TOPFA with MCMs reported in several organs (Table 10-12).

Pregnancy outcome was reported for 286 women (188 prospective and 98 retrospective women) (Table 10-1) and included 260 LBs (163 prospective and 97 retrospective). For 87.7% (n=228) of these, the 1-year follow-up was completed.

Table 10-1 Case disposition

	Prospective Cases	Retrospective Cases	All cases
Number of enrolled women, n	-	-	312
Number of women excluded from the analysis[1], n	-	-	9
Number of analyzed women, n	202	101	303
Women status in the registry, n (%)[2]			
Completed[3]	167 (82.7%)	88 (87.1%)	255 (84.2%)
Discontinued	35 (17.3%)	13 (12.9%)	48 (15.8%)
Reason for discontinuation, n (%)[4]			
Withdrew consent	3 (10.7%)	1 (9.1%)	4 (10.3%)
Death of mother	1 (3.6%)	0 (0.0%)	1 (2.6%)
Death of infant	1 (3.6%)	0 (0.0%)	1 (2.6%)
Lost to follow-up	22 (78.6%)	9 (81.8%)	31 (79.5%)
Other reason	1 (3.6%)	1 (9.1%)	2 (5.1%)
Missing	7	2	9
Pregnancy status in the registry, n (%)[2]			
Unknown pregnancy outcome[5]	14 (6.9%)	3 (3.0%)	17 (5.6%)
Known pregnancy outcome	188 (93.1%)	98 (97.0%)	286 (94.4%)
Non live births[6]	25 (13.3%)	1 (1.0%)	26 (9.1%)
Live births[7]	163 (86.7%)	97 (99.0%)	260 (90.9%)
1-year follow-up completed[8]	142 (87.1%)	86 (88.7%)	228 (87.7%)
1-year follow-up not performed[8]	16 (9.8%)	9 (9.3%)	25 (9.6%)
ICF not signed for infant[8]	5 (3.1%)	2 (2.1%)	7 (2.7%)

ICF: Informed Consent Form

[1]Reasons for study exclusion are described in Listing 16.2.1-1.2.

[2]Number of women. Percentages computed among analyzed women.

[3]Completed means data collection up to the time of the pregnancy outcome and for live births up to the 1-year follow-up.

[4]Number of women. Percentages computed among women who discontinued.

[5]Women discontinued from the study before pregnancy outcome was known.

[6]Number of pregnancies. A pregnancy involving multiples is only counted if no live birth is observed. Percentages computed among women with known pregnancy outcome.

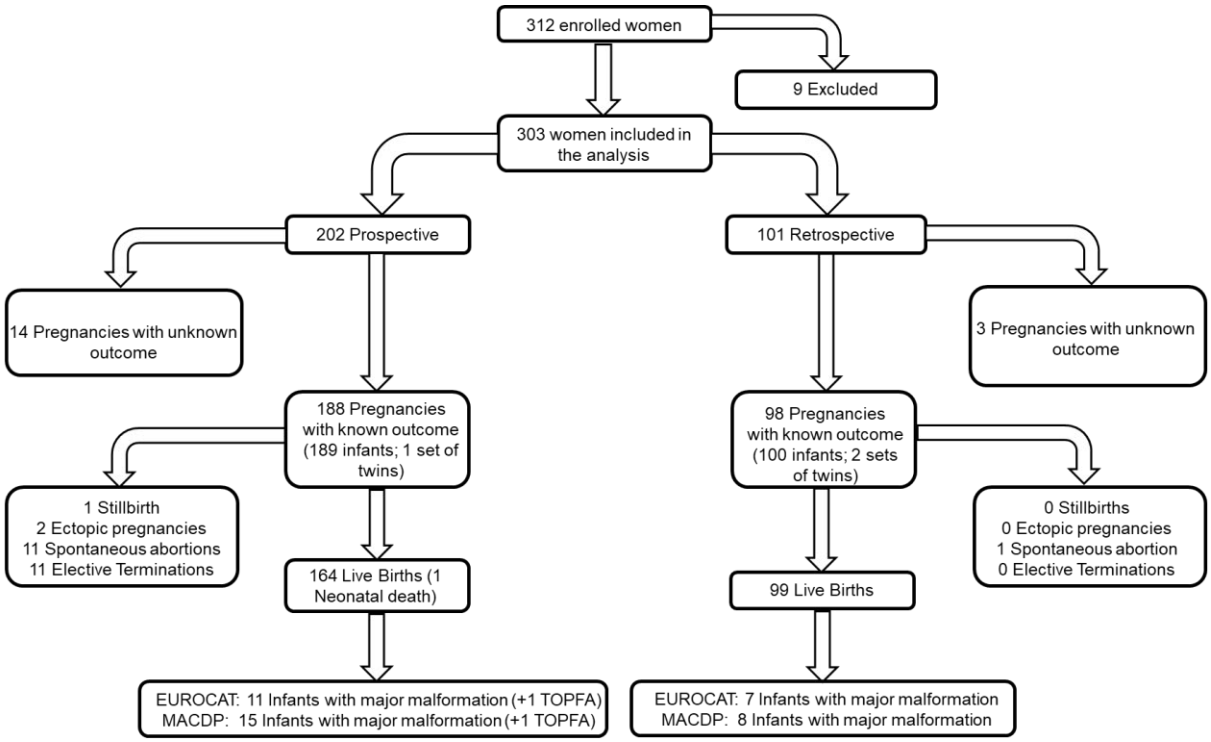
[7]Number of pregnancies. A pregnancy involving multiples is only counted if at least one live birth is observed. Percentages computed among women with known pregnancy outcome.

[8]Percentages computed among pregnancies resulting in at least one live birth.

Source: Table 14.1-1.1.

Pregnancy outcome was reported for 286 women (188 prospective and 98 retrospective women) and involved three twin pregnancies (1 prospective and 2 retrospective), leading to 289 infants (189 prospective and 100 retrospective infants) (Table 14.3-1.1). The total number of women included in the analysis and pregnancy outcomes are presented in Figure 10-1.

Figure 10-1 Pregnancy outcomes



Source: Table 14.1-1.1 and Table 14.3-1.9

EUROCAT: European Registry of Congenital Anomalies and Twins – MACDP: Metropolitan Atlanta Congenital Defects Program

Among live births, [redacted] (retrospective), [redacted] (retrospective) and [redacted] (prospective) reported two fetuses for each pregnancy (Table 14.3-1.1).

Two women participated twice to the registry; these women contribute to this figure for each of their pregnancies ([redacted] prospective & [redacted] prospective, [redacted] prospective & [redacted] retrospective).

Exclusion from the analysis

Nine women did not fulfill inclusion/exclusion criteria leading to excluding them from analysis (Listing 16.2.1-1.2):

- Three women had no exposure to fingolimod during pregnancy or up to 8 weeks before LMP (Subject [redacted], Subject [redacted], and Subject [redacted])
- One woman was not currently pregnant (Subject [redacted])
- Three women did not sign the informed consent form (Subject [redacted], Subject [redacted], and Subject [redacted])
- Two women signed the informed consent form, had no data entered and were immediately marked as lost to follow-up (Subject [redacted] and Subject [redacted])

Further protocol deviations, not leading to exclusion of the patients, are presented in Table 14.1-1.2.

10.2 Descriptive data

10.2.1 Demographics and baseline characteristics

The median age at LMP was 32.0 years (range 19 to 48 years). Overall, 70.6% of the women were from Europe and 21.5% were from the US and Canada. Median pre-pregnancy BMI was similar in the prospective and retrospective groups (24.04 and 23.62 kg/m^2, respectively). According to BMI, 22.1% of participants were overweight and 21.7% were obese (Table 10-2).

A full listing of patient demographics is provided in Listing 16.2.4-1.1.

Table 10-2 Women demographics

	Prospective Cases (N=202)[1]	Retrospective Cases (N=101)[1]	All cases (N=303)[1]
Age at last menstrual period (LMP) (years)[2]			
n (%)[3]	199 (98.5%)	101 (100.0%)	300 (99.0%)
Mean (SD)	31.7 (4.85)	32.3 (4.82)	31.9 (4.84)
Median	32.0	32.0	32.0
Min, Max	19, 44	19, 48	19, 48
Region			
n (%)[3]	202 (100.0%)	101 (100.0%)	303 (100.0%)
U.S. and Canada	30 (14.9%)	35 (34.7%)	65 (21.5%)
Europe	153 (75.7%)	61 (60.4%)	214 (70.6%)
Asia	15 (7.4%)	0 (0.0%)	15 (5.0%)
Other	4 (2.0%)	5 (5.0%)	9 (3.0%)
Pre-pregnancy Body Mass Index (kg/m2)[5]			
n (%)[3]	198 (98.0%)	101 (100.0%)	299 (98.7%)
Mean (SD)	25.68 (6.764)	25.63 (6.492)	25.66 (6.662)
Median	24.04	23.62	23.88
Min, Max	16.4, 54.2	16.3, 45.2	16.3, 54.2
Underweight (<18.5), n (%)[4]	16 (8.1%)	12 (11.9%)	28 (9.4%)
Normal weight (≥18.5-<25), n (%)[4]	97 (49.0%)	43 (42.6%)	140 (46.8%)
Overweight (≥25-<30), n (%)[4]	44 (22.2%)	22 (21.8%)	66 (22.1%)
Obese (≥30.0), n (%)[4]	41 (20.7%)	24 (23.8%)	65 (21.7%)

Max: Maximum - Min: Minimum - SD: Standard Deviation.

[1]Number of women enrolled and analyzed.

[2]Age at last menstrual period (LMP) is computed as the difference between the year of the derived LMP and the year of birth (if both available) or the age at LMP (if collected).

[3]Number of women with available information. Percentage computed among analyzed women.

[4]Percentage computed among women with available information.

[5][redacted] is [redacted] inches and [redacted] lbs. leading to a BMI of 54.2 kg/m^2. Values and units were queried and confirmed.

Source: Table 14.1-1.3.

10.2.2 Gestational age at enrollment

As expected, median gestational age (GA) at enrollment was earlier for the prospective group (61.0 days) than the retrospective group (168.0 days) (Table 10-3). In the prospective group, 77.4% enrolled during the first trimester of pregnancy and 3.5% during the third trimester. In

the retrospective group, 64.4% enrolled during the second trimester and 32.7% during the third trimester.

A full data listing of GA at enrollment is provided in Listing 16.2.4-2.1.

Table 10-3 Gestational age at enrollment

	Prospective Cases (N=202)[1]	Retrospective Cases (N=101)[1]	All cases (N=303)[1]
Gestational age (days)[2]			
n (%)[3]	199 (98.5%)	101 (100.0%)	300 (99.0%)
Mean (SD)	73.7 (43.50)	169.0 (51.65)	105.7 (64.66)
Median	61.0	168.0	85.0
Min, Max	24, 265	72, 278	24, 278
First trimester, n (%)[4]	154 (77.4%)	3 (3.0%)	157 (52.3%)
Second trimester, n (%)[5]	38 (19.1%)	65 (64.4%)	103 (34.3%)
Third trimester, n (%)[6]	7 (3.5%)	33 (32.7%)	40 (13.3%)

Max: Maximum - Min: Minimum - SD: Standard Deviation.

[1]Number of women enrolled and analyzed.

[2]Gestational age at enrollment is computed as the difference between enrollment date and derived last menstrual period (LMP) date.

[3]Number of women with available information. Percentage computed among analyzed women.

[4]Gestational age at enrolment ≤ 13 weeks (91 days).

[5]Gestational age at enrolment > 13 weeks (91 days) and ≤ 27 weeks (189 days).

[6]Gestational age at enrolment > 27 weeks (189 days).

Source: Table 14.1-1.4

10.2.3 Multiple sclerosis history and additional medical history

Multiple sclerosis history

Overall, the median age at MS diagnosis was 24.0 years (range 9 to 46 years). Relapsing Remitting Multiple Sclerosis (RRMS) was the most common current type of MS (93.9%). Overall, the median disease duration since MS diagnosis was 7.3 years (range 0 to 21 years) at the time of enrollment. The median time since the most recent relapse prior to enrollment was 18.04 months (16.56 and 20.70 months in prospective and retrospective, respectively). In women with an expanded disability status scale (EDSS) score prior to enrollment (n=159), the overall median EDSS score was 2.0 (Table 10-4).

The full data listing of patient MS history is provided in Listing 16.2.4-2.3.

Table 10-4 Multiple sclerosis history

	Prospective cases (N = 202)[1]	Retrospective cases (N =101)[1]	All enrolled (N = 303)[1]
Age at MS diagnosis (years)			
n (%)[2]	199 (98.5%)	100 (99.0%)	299 (98.7%)
Mean (SD)	24.4 (5.35)	24.9 (5.59)	24.6 (5.43)
Median	24.0	25.0	24.0
Min, Max	9, 41	11, 46	9, 46

	Prospective cases (N = 202)[1]	Retrospective cases (N =101)[1]	All enrolled (N = 303)[1]
Duration of MS since diagnosis at enrollment (years)[3]			
n (%)[2]	199 (98.5%)	100 (99.0%)	299 (98.7%)
Mean (SD)	7.6 (4.27)	8.0 (4.54)	7.8 (4.36)
Median	7.0	7.7	7.3
Min, Max	0, 21	0, 20	0, 21
Time since the most recent relapse (month) prior to enrollment[4]			
n (%)[2]	143 (70.8%)	74 (73.3%)	217 (71.6%)
Mean (SD)	22.60 (20.882)	29.04 (27.312)	24.79 (23.412)
Median	16.56	20.70	18.04
Min, Max	0.1, 103.1	0.1, 110.6	0.1, 110.6
Current type of MS[5]			
n (%)[2]	153 (100.0%)	77 (100.0%)	230 (100.0%)
Primary Progressive MS (PPMS)	2 (1.3%)	0 (0.0%)	2 (0.9%)
Relapsing Remitting MS (RRMS)	145 (94.8%)	71 (92.2%)	216 (93.9%)
Secondary Progressive MS (SPMS)	1 (0.7%)	0 (0.0%)	1 (0.4%)
Other[6]	2 (1.3%)	1 (1.3%)	3 (1.3%)
Unknown	3 (2.0%)	5 (6.5%)	8 (3.5%)
Most recent Expanded Disability Status Scale (EDSS) score prior to enrollment			
n (%)[2]	113 (55.9%)	46 (45.5%)	159 (52.5%)
Mean (SD)	2.00 (1.759)	2.42 (1.844)	2.12 (1.788)
Median (Q1, Q3)	2.00 (0.00, 3.00)	2.00 (1.00, 3.50)	2.00 (0.00, 3.00)
Min, Max	0.0, 6.5	0.0, 6.5	0.0, 6.5
EDSS ≤4.5, n (%)[7]	103 (91.2%)	40 (87.0%)	143 (89.9%)
EDSS ≥5.0, n (%)[7]	10 (8.8%)	6 (13.0%)	16 (10.1%)

CRF: Case Report Form; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation.

[1]Number of women enrolled and analyzed.

[2]Number of women with available information. Percentage computed among analyzed women.

[3]Duration defined as the difference between enrollment date and MS diagnosis date plus one day divided by 365.25.

[4]Time defined as the difference between enrollment date and the date of the most recent relapse plus one day divided by 30.4.

[5]Percentages computed among women with baseline visit performed on or after 11-Oct-2014.

[6]Other specified current types: 'Acting', 'In Remission', 'Clinically isolated syndrome'.

[7]Percentage computed among women with available information.

Source: Table 14.1-1.5

Further medical history

At least one active medical condition was reported by 104 (34.3%) women. Table 10-5 presents the active medical conditions reported by at least four women in the “all enrolled” column. The active medical conditions most often reported were depression (7.9%), thyroid disease (4.0%) and autoimmune disease (3.6%).

Table 10-5 Active medical conditions (reported by at least four women)

Active medical condition, n (%)	Prospective cases (N = 202)[1]	Retrospective cases (N =101)[1]	All enrolled (N = 303)[1]
At least one	64 (31.7%)	40 (39.6%)	104 (34.3%)
Depression	17 (8.4%)	7 (6.9%)	24 (7.9%)
Thyroid disease	6 (3.0%)	6 (5.9%)	12 (4.0%)
Autoimmune disease	8 (4.0%)	3 (3.0%)	11 (3.6%)
Asthma	5 (2.5%)	4 (4.0%)	9 (3.0%)
Migraine	5 (2.5%)	3 (3.0%)	8 (2.6%)
Anxiety	4 (2.0%)	3 (3.0%)	7 (2.3%)
Obesity	5 (2.5%)	1 (1.0%)	6 (2.0%)
Psychiatric disorder other than depression	2 (1.0%)	3 (3.0%)	5 (1.7%)
Seasonal allergy	4 (2.0%)	1 (1.0%)	5 (1.7%)
Anxiety disorder	3 (1.5%)	1 (1.0%)	4 (1.3%)
Chronic hypertension (>140/90 mmHg)	3 (1.5%)	1 (1.0%)	4 (1.3%)
Epilepsy	4 (2.0%)	0 (0.0%)	4 (1.3%)

The table presents any medical conditions (significant or not significant) marked as active during pregnancy; medical conditions with diagnosis date after pregnancy outcome are excluded.
The table excludes Multiple Sclerosis and relapse history.
Percentage computed among women enrolled and analyzed.
[1]Number of women enrolled and analyzed.
Source: Table 14.1-1.12

10.2.4 Maternal obstetric history

Among the 300 women with available information on the number of previous medically recognized pregnancies, 158 (52.7%) women had at least one previous medically recognized pregnancy, and 142 (47.3%) women had no previous pregnancy. Of the 158 women with previous pregnancies, 126 (79.7%) had at least one term LB, 13 (8.2%) had at least one pre-term LB, 29 (18.4%) had at least one elective termination, 40 (25.3%) had at least one spontaneous abortion, and one (0.6%) had history of SB (Table 10-6).

Table 10-6 Maternal Obstetric History

	Prospective cases (N=202)[1]	Retrospective cases (N=101)[1]	All enrolled (N=303)[1]
Number of women with previous medically recognized pregnancies			
n (%)[2]	199 (98.5%)	101 (100.0%)	300 (99.0%)
0	98 (49.2%)	44 (43.6%)	142 (47.3%)
1	49 (24.6%)	26 (25.7%)	75 (25.0%)
2	24 (12.1%)	18 (17.8%)	42 (14.0%)
3 or more	28 (14.1%)	13 (12.9%)	41 (13.7%)
Number of women with previous term live births (≥37 weeks)			
n (%)[3]	101 (100.0%)	57 (100.0%)	158 (100.0%)
0	17 (16.8%)	15 (26.3%)	32 (20.3%)
1	49 (48.5%)	23 (40.4%)	72 (45.6%)
2	24 (23.8%)	17 (29.8%)	41 (25.9%)

	Prospective cases (N=202)[1]	Retrospective cases (N=101)[1]	All enrolled (N=303)[1]
3 or more	11 (10.9%)	2 (3.5%)	13 (8.2%)
Number of women with previous pre-term live births (<37 weeks)			
n (%)[3]	101 (100.0%)	57 (100.0%)	158 (100.0%)
0	96 (95.0%)	49 (86.0%)	145 (91.8%)
1	4 (4.0%)	8 (14.0%)	12 (7.6%)
2	1 (1.0%)	0 (0.0%)	1 (0.6%)
3 or more	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of women with previous elective terminations[4]			
n (%)[3]	101 (100.0%)	57 (100.0%)	158 (100.0%)
0	83 (82.2%)	46 (80.7%)	129 (81.6%)
1	16 (15.8%)	8 (14.0%)	24 (15.2%)
2	2 (2.0%)	2 (3.5%)	4 (2.5%)
3 or more	0 (0.0%)	1 (1.8%)	1 (0.6%)
Number of women with previous spontaneous losses/miscarriages (<20 weeks gestation)			
n (%)[3]	101 (100.0%)	57 (100.0%)	158 (100.0%)
0	78 (77.2%)	40 (70.2%)	118 (74.7%)
1	15 (14.9%)	11 (19.3%)	26 (16.5%)
2	5 (5.0%)	3 (5.3%)	8 (5.1%)
3 or more	3 (3.0%)	3 (5.3%)	6 (3.8%)
Number of women with previous fetal deaths/stillbirths (≥20 weeks gestation)			
n (%)[3]	101 (100.0%)	57 (100.0%)	158 (100.0%)
0	100 (99.0%)	57 (100.0%)	157 (99.4%)
1	1 (1.0%)	0 (0.0%)	1 (0.6%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)
3 or more	0 (0.0%)	0 (0.0%)	0 (0.0%)

[1]Number of women enrolled and analyzed.
[2]Number of women with available information. Percentage computed among analyzed women.
[3]Percentage computed among women with at least one previous pregnancy.
[4]The reasons for elective termination are listed in Listing 16.2.4-2.4.
A woman can contribute to several pregnancy outcome sections.
Source: Table 14.1-1.6

History of obstetric complication

Among women with at least one previously medically recognized pregnancy (N=158), 26 (16.5%) reported at least one specific obstetric complication in a previous pregnancy. The most reported term was non-elective C-section in three (3.0%) prospective and four (7.0%) retrospective pregnancies. Gestational diabetes was reported in four pregnancies (2.5%). Pre-eclampsia/eclampsia and pregnancy induced hypertension were reported in three pregnancies (1.9%) overall. No obstetric complications in previous pregnancies were reported in 83 (82.2%) prospective participants, and 39 (68.4%) retrospective participants (Table 14.1-1.7).

At least one adverse fetal outcome (Table 14.1-1.7) was reported in 12 previous pregnancies (7.6%), mainly low birth weight (n=3, 1.9%).

Family (i.e., first degree relatives) history of congenital abnormalities/birth defects and family history of pregnancy complications or poor outcomes were medically reviewed to identify risk

factors for MCM and other poor pregnancy outcomes (Listing 16.2.4-2.6). Family history of congenital abnormality/birth defect, considered a risk factor, was reported in five (2.5%) prospective and three (3.0%) retrospective pregnancies. Further terms were reported by 24 participants (Listing 16.2.4-2.6).

Family history of pregnancy complications or poor outcomes, considered as a risk factor, was reported by one (0.3%) woman (Table 14.1-1.8). Further terms were reported by 38 participants (Listing 16.2.4-2.6).

Full patient data listings of maternal obstetric history and previous pregnancy obstetric complications are provided in Listing 16.2.4-2.4 and Listing 16.2.4-2.5, respectively.

10.2.5 Maternal environmental exposure

Of the 303 women analyzed, 286 women reached the pregnancy outcome visit and were included in the analysis of maternal environmental exposure (Table 14.1-1.9).

Smoking history

Most women (n=169; 59.1%) had never smoked and 60 (21.0%) women were former smokers. Of the remaining women, 38 (13.3%) women smoked during the first trimester only, two (0.7%) women smoked during the first and second trimester, and 15 (5.2%) women smoked throughout pregnancy (Table 14.1-1.9).

Alcohol use

Of the women with available information (n=286), 23 women (8.0%; 12 prospective and 11 retrospective) reported alcohol use during the first trimester only. Alcohol use was rare after the first trimester, with one (0.3%) in the second trimester only, one (0.3%) in the first and second trimester, and three (1.0%) throughout pregnancy (Table 14.1-1.9).

Recreational drug use

Of the women with available information (n=286), most women (n=265, 92.7%) did not report any recreational drug use and 16 (5.6%) reported former use (Table 14.1-1.9). Three (1%) declined to answer. Two women (0.7%) reported use in the first trimester only.

A full patient data listing of maternal environmental exposures (enrollment to postpartum) is available in Listing 16.2.4-2.7.

10.2.6 Fingolimod exposure

Since pregnancies with unknown outcome did not allow for exposure assessment at the end of pregnancy, presentation on fingolimod exposure was restricted to pregnancies with known outcome.

Most women (88.8%) were exposed to fingolimod during at least the first trimester.

The median cumulative exposure to fingolimod (between 8 weeks prior to LMP and end of pregnancy) was 89.0 days (range 3 to 328 days) (Table 10-7).

Table 10-7 Fingolimod exposure since 8 weeks prior to LMP (Patients with known pregnancy outcome)

	Prospective Cases (N=188)[1]	Retrospective Cases (N=98)[1]	All cases (N=286)[1]
Timing of exposure[2]			
n (%)[3]	188 (100.0%)	98 (100.0%)	286 (100.0%)
Peri-LMP only[4,5]	20 (10.6%)	11 (11.2%)	31 (10.8%)
At least First trimester[5,6]	167 (88.8%)	87 (88.8%)	254 (88.8%)
Only after First trimester[5,7]	0 (0.0%)	0 (0.0%)	0 (0.0%)
During all pregnancy[5,8]	9 (4.8%)	0 (0.0%)	9 (3.1%)
Exact timing of exposure unknown[5,9]	1 (0.5%)	0 (0.0%)	1 (0.3%)
Cumulative exposure (days)[10]			
n (%)[3]	184 (97.9%)	93 (94.9%)	277 (96.9%)
Mean (SD)	84.7 (37.94)	90.4 (44.66)	86.6 (40.33)
Median	88.0	90.0	89.0
Min, Max	3, 328	3, 313	3, 328
Cumulative exposure (mg)[11]			
n (%)[3]	183 (97.3%)	93 (94.9%)	276 (96.5%)
Mean (SD)	41.4 (19.34)	44.3 (22.40)	42.4 (20.43)
Median	43.5	44.5	44.0
Min, Max	2, 164	2, 157	2, 164

LMP: Last menstrual period - Max: Maximum - Min: Minimum - SD: Standard Deviation
[1] Number of women enrolled and analyzed.
[2] A woman may fall into multiple exposure categories.
[3] Number of women with non-missing information. Percentage computed among analyzed women.
[4] Exposed only during the period starting 56 days prior to the first day of LMP and ending one day prior to the first day of LMP.
[5] Percentage computed among women with non-missing timing of exposure.
[6] Exposed during the Period starting on the first day of the LMP and ending on day 91 of gestation, but can also include exposure during other pregnancy periods.
[7] Exposed only during the Period starting on day 92 of gestation until end of pregnancy.
[8] 'During all pregnancy' is the period starting on LMP date and ending during the 3rd trimester or on the pregnancy outcome date, whatever occurs first. The definition applies to all women regardless of the pregnancy outcome. This period may overlap with 'At least First trimester', therefore categories are not mutually exclusive.
[9] [redacted] (prospective) has fingolimod start and stop dates missing.
[10] Cumulative exposure in days is computed as the sum of each period of Fingolimod exposure in days, from 8 weeks (56 days) prior to derived LMP date to the date of pregnancy outcome.
[11] Cumulative exposure in mg is computed as sum of each duration of Fingolimod exposure × corresponding daily dose, from 8 weeks (56 days) prior to derived LMP date to the date of pregnancy outcome.
Source: Table 14.1-1.10

10.3 Main results

10.3.1 Pregnancy outcomes

Pregnancy outcome was known for 286 women (188 prospective and 98 retrospective women). Overall, there were 263 (91.0%) LBs, including 32 pre-term births. Three women (1.1%) reported LB twins, of which two women had pre-term deliveries (Table 10-8 and Table 14.3-1.1), leading to 289 fetuses/infants (189 prospective and 100 retrospective fetuses/infants).

Overall, two (0.7%) women reported an ectopic pregnancy, 12 (4.2%) women reported a spontaneous abortion, and 11 (3.8%) reported an elective termination. Out of the 11 elective terminations, three were due to psychosocial/non-medical reasons, one was due to severe multiple malformations of the fetus (Subject [redacted]), which is counted in the remaining tables as a TOPFA, and seven were due to "other" reasons reported as wish/personal decision of the patient or fear of malformations. Details are provided in Table 14.3-1.1 and Listing 16.2.9-1.2. One woman (Subject [redacted]) reported a SB (details provided in Section 14.3.3).

Individual patient information on prenatal testing, pregnancy information at mid-second trimester follow-up, and pregnancy outcomes are provided in Listing 16.2.8-1.1, Listing 16.2.9-1.1, and Listing 16.2.9-1.2, respectively.

Table 10-8 Pregnancy outcomes

	Prospective cases (N=202)[1]	Retrospective cases (N=101)[1]	All enrolled (N=303)[1]
Number of women with filled pregnancy outcome CRF, n	188	98	286
Number of pregnancies with known pregnancy outcome, n	188	98	286
Number of infants in pregnancies with known outcome, n	189	100	289
Ectopic pregnancy, n (%)[2]	2 (1.1%)	0 (0.0%)	2 (0.7%)
Spontaneous abortion, n (%)[2]	11 (5.8%)	1 (1.0%)	12 (4.2%)
Elective termination, n (%)[2]	11 (5.8%)	0 (0.0%)	11 (3.8%)
Stillbirths, n (%)[3]	1 (0.6%)	0 (0.0%)	1 (0.4%)
Live births, n (%)[2]	164 (86.8%)	99 (99.0%)	263 (91.0%)
Pre-term live birth, n	13	19	32
Type of pregnancy[4]			
n (%)	188 (100.0%)	98 (100.0%)	286 (100.0%)
Singleton	187 (99.5%)	96 (98.0%)	283 (99.0%)
Multiple[5]	1 (0.5%)	2 (2.0%)	3 (1.0%)

CRF: Case Report Form.

Live births include term live births, pre-term live births and neonatal deaths. Congenital malformations (CMs) are the cases adjudicated as a malformation according to either EUROCAT or MACDP.

[1]Number of women enrolled and analyzed.

[2]Percentage computed among infants for whom the pregnancy outcome was known.

[3]Percentage computed among infants for whom the pregnancy outcome was known, excluding spontaneous abortion cases.

[4]Number of pregnancies. Percentages are based on the number of pregnancies with known pregnancy outcome.

[redacted] (retrospective), [redacted] (retrospective) and [redacted] (prospective) reported two fetuses for each pregnancy. The outcome for [redacted] and [redacted] is pre-term live birth for all infants, and for [redacted] term live birth for all infants.

Source: Table 14.3-1.1

10.3.2 Current pregnancy obstetric complications

Of 286 women reporting pregnancy complication information, 234 (81.8%) reported no pregnancy complications. Complications reported in five or more women included: gestational

diabetes (n=8, 15.4%), bacterial infection (n=8, 15.4%), pre-term labor (n=7, 13.5%), pre-eclampsia/eclampsia (n=6, 11.5%), cervical incompetence (n=5, 9.6%), and pregnancy-induced hypertension (n=5, 9.6%). Other obstetrical complications were reported in 28.8% (n=15) of participants (Table 14.3-1.4).

A full patient data listing on pregnancy obstetric complications (post-partum) is provided in Listing 16.2.9-1.3.

10.3.3 Infant outcomes and follow-up

One prospective neonatal death, due to prematurity, was reported (Subject [redacted]). The gestational age at pregnancy outcome was 24 weeks and 3 days. Details of the case can be found in Section 14.3.3.

10.3.3.1 Infant measurements at post-partum visit

The following details on LBs were available at post-partum visits (Table 14.3-1.5):

Gender and birth weight

There were 133 (55.0%) male and 109 (45.0%) female infants. The mean birth weight for all live births was 3137.7 g (SD 599.01) (Table 14.3-1.5).

APGAR score

Infant mean APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) scores at 1, 5 and 10 minutes after birth were 8.5, 9.5, and 9.8, respectively (Table 14.3-1.5). No infant had an APGAR score below seven at 10 minutes after birth.

Gestational age

The median GA at pregnancy outcome among all LBs was 39.0 weeks (range 23 to 43 weeks) for prospective cases and 39.0 weeks (range 28 to 41 weeks) for retrospective cases (Table 14.3-1.5).

Small and large birth weight for GA was assessed using US national reference data for infants born in the US or Canada (Aris et al 2019), German national reference data for infants born in Germany (Voigt et al 2014) and World Health Organization fetal growth charts (Kiserud et al 2017) for infants born in the rest of the world (Listing 16.2.9-1.4). A complete listing of small for GA is provided in Listing 16.2.9-1.4. Among 240 infants with birth weight measurements, 47 (19.6%) infants were small for gestational age (26 prospective and 21 retrospective).

Low birth weight (defined as < 2500 grams) and very low birth weight (< 1500 grams) was reported in 25 (10.4%) infants and four (1.7%) infants, respectively. Most of these were pre-term births (n=19).

Small for GA and low/very low birth weight are non-exclusive categories: eight prospective and eight retrospective infants, respectively, were both small for GA and had low birth weight, while no prospective and three retrospective infants (two sets of twins) were small for GA and had very low birth weight.

Large for gestation was reported in 23 (9.6%) infants (Table 10-9).

Table 10-9 Birth weight in live births

	Prospective cases	Retrospective cases	All enrolled
N live born with CRF	**151**	**91**	**242**
With birth weight n (%)[1]	150 (99.3%)	90 (98.9%)	240 (99.2%)
Small for gestational age, n (%)[2]	26 (17.3%)	21 (23.3%)	47 (19.6%)
	m^=3	*m^=7*	*m^=10*
Low birth weight, n (%)	12 (8.0%)	13 (14.4%)	25 (10.4%)
	m=7	*m=12*	*m^=19*
Very low birth weight, n (%)	0 (0.0%)	4 (4.4%)	4 (1.7%)
	m^=0	*m^=4*	*m^=4*
Large for gestational age, n (%)[2]	17 (11.3%)	6 (6.7%)	23 (9.6%)

Live birth includes term live birth, pre-term live birth and neonatal death.

The table presents data for infants of women enrolled and analyzed and for whom Informed Consent was obtained.

[1]Number of infants with available information. Percentage computed among infants of women enrolled and analyzed and for whom Informed Consent was obtained.

[2]Small for gestational age defined as birth weight < 10th percentile for the GA and large for gestational age defined as birth weight > 90th percentile for the

GA.*m^* number of preterms

Source: Table 14.3-1.5, Listing 16.2.9-1.4

10.3.3.2 Infant one year follow up

The infant one-year follow-up assessment was available for 231 infants (143 among the 164 prospective LBs and 88 among the 99 retrospective LBs).

For five infants, developmental delay was reported. Three had motor delay, one had language delay, and one was reported as "other" delay (reported as "[redacted]") :

- Subject [redacted], Subject [redacted] and Subject [redacted] are mentioned as motor delay with no information (Listing 16.2.9-1.6, Listing 16.2.7-1.2),
- Subject [redacted] is referred as language delay with comment [redacted] (Listing 16.2.7-1.2),
- Subject [redacted] is referred as "Other" and reported as [redacted] (Listing 16.2.9-1.6).

All cases were reported by the infant's parent/guardian and were not confirmed by a healthcare provider (Listing 16.2.9-1.10 and Listing 16.2.9-1.6).

At 1-year follow-up, two infants were reported with serious infections requiring hospitalization that may suggest an impact on the infant's immune system (see Section 14.3.3) (Table 10-10):

- Subject [redacted] had Bocavirus infection along with respiratory syncytial virus ([redacted]; ~[redacted] months of age).
- Subject [redacted] was reported with pneumonia (Listing 16.2.9-1.10) (start date unknown). This infant experienced bacterial infections resulting in respiratory problems and coronavirus infection (start date: [redacted]; at approximately [redacted]months of age), and haemophilus influenzae test positive and metapneumovirus (start date unknown) (Listing 16.2.9-1.6).

Other relevant illnesses, surgeries or hospitalizations were reported in 39 (16.9%) infants (Table 10-10) with the majority of events related to infections (Listing 16.2.9-1.6 and Listing 16.2.9-10).

Neonatal sepsis was reported for one infant (Subject [redacted]).

Further SAEs in infants up to one year of age are discussed in Section 10.5.2.

A complete patient data listing of infant information at the 3-month follow-up and infant age at which the infant reached the development milestones is provided in Listing 16.2.9-1.5 and Listing 16.2.9-1.7, respectively.

Table 10-10 Infant measurements at one year follow-up visit in all live births[1]

Characteristic	Prospective cases	Retrospective cases	All enrolled
Number of infants with Infant Information CRF filled	**143**	**88**	**231**
Vital status			
n (%)[2]	143 (100.0%)	88 (100.0%)	231 (100.0%)
Alive	143 (100.0%)	88 (100.0%)	231 (100.0%)
Infant weight (kg)			
n (%)[3]	135 (94.4%)	85 (96.6%)	220 (95.2%)
Mean (SD)	9.82 (1.309)	10.03 (1.377)	9.90 (1.336)
Median	10.00	10.00	10.00
Min, Max	7.0, 18.0	6.8, 14.0	6.8, 18.0
Infant height (cm)[4]			
n (%)[3]	132 (92.3%)	80 (90.9%)	212 (91.8%)
Mean (SD)	75.9 (4.26)	75.9 (4.58)	75.9 (4.37)
Median	75.0	76.0	76.0
Min, Max	58, 98	61, 86	58, 98
Serious infection requiring hospitalization that may suggest an impact on the infant's immune system[5]			
n (%)[3]	143 (100.0%)	88 (100.0%)	231 (100.0%)
Yes	2 (1.4%)	0 (0.0%)	2 (0.9%)
No	139 (97.2%)	88 (100.0%)	227 (98.3%)
Unknown	2 (1.4%)	0 (0.0%)	2 (0.9%)
Other relevant illnesses, surgeries or hospitalizations[6]			
n (%)[3]	143 (100.0%)	88 (100.0%)	231 (100.0%)
Yes	27 (18.9%)	12 (13.6%)	39 (16.9%)
No	115 (80.4%)	76 (86.4%)	191 (82.7%)
Unknown	1 (0.7%)	0 (0.0%)	1 (0.4%)
Developmental delay[7]			
n (%)[3]	131 (91.6%)	83 (94.3%)	214 (92.6%)
Yes	2 (1.5%)	3 (3.6%)	5 (2.3%)
No	127 (96.9%)	79 (95.2%)	206 (96.3%)
Unknown	2 (1.5%)	1 (1.2%)	3 (1.4%)
Type of developmental delay[7]			
n (%)[8]	2 (1.4%)	3 (3.4%)	5 (2.2%)
Motor development	2 (100.0%)	1 (33.3%)	3 (60.0%)
Language development	0 (0.0%)	1 (33.3%)	1 (20.0%)

Characteristic	Prospective cases	Retrospective cases	All enrolled
Social/emotional development	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	1 (33.3%)	1 (20.0%)

CRF: Case Report Form - Max: Maximum - Min: Minimum - SD: Standard Deviation.

The table presents data from infants of women enrolled and analyzed and for whom Informed Consent was obtained.

[1]Excludes live births resulting in neonatal deaths.

[2]Number of infants with available information. Percentage computed among infants with Infant Information at birth CRF filled.

[3]Number of infants with available information. Percentage computed among infants alive at 1- year follow-up.

[4][redacted] has height at 1-year follow-up recorded as [redacted] inches ([redacted] cm). This value has been queried and confirmed. [redacted] has height at 1-year follow-up recorded as [redacted] inches, this value is disregarded in the analysis

[5]Percentage computed among infants alive at 1-year follow-up. The details of specified serious infections requiring hospitalization are listed in Listing 16.2.9-1.10.

[6]Percentage computed among infants alive at 1-year follow-up. The details of specified relevant illnesses, surgeries, or hospitalizations are listed in Listing 16.2.9-1.6.

[7]Percentage computed among infants alive at 1-year follow-up with developmental delay. The details of specified developmental delay are listed in Listing 16.2.9-1.6.

[8]Percentage computed among infants with developmental delay.

Source: Table 14.3-1.7

10.3.4 Congenital malformations

Congenital malformations were adjudicated using the EUROCAT and MACDP classifications by an independent adjudication committee. If an infant had more than one congenital malformation, the most severe level was considered to categorize the infant. The frequency of pregnancy outcomes, including major or minor malformations, are presented in Table 10-11. A full listing of the cases that were adjudicated for infant/fetal complications is presented in Listing 16.2.9-1.11.

Chromosomal/mendelian anomaly/genetic disorder

No chromosomal/mendelian anomaly/genetic disorder was reported (Table 14.3-1.9).

Prematurity related anomalies and positional defects

No prematurity related malformation was reported (Table 14.3-1.9).

Clubfoot was reported in one prospective LB (Subject [redacted]) and was adjudicated as a positional deformity.

Major and minor congenital malformations

Congenital malformations were assessed by the adjudication panel as major or minor using EUROCAT and MACDP definitions (Table 10-11).

The events cardiac murmur (Subject [redacted], retrospective), brain edema (Subject [redacted], prospective) and hemangioma right upper lip (Subject [redacted], prospective) were adjudicated and assessed as no malformations. These terms are counted under 'Other' in Table 10-11.

Out of the 289 infants, 25 were confirmed to have a malformation by the adjudication panel.

Per EUROCAT classification, in LBs, SBs, and TOPFA, 19 infants were adjudicated with MCMs (12 prospective and seven retrospective cases). The remaining six were adjudicated as minor malformations (four prospective and two retrospective cases) (Table 14.3-1.9).

Using the MACDP classification, in LBs, SBs, and TOPFA, 24 were adjudicated with MCMs (16 prospective and eight retrospective cases) and one with minor malformation (a retrospective case). A full list of congenital malformations or fetal anomalies is provided in Listing 16.2.9-1.11, Annex 1 Table 15-1 and Section 14.3.3.

Among the 11 elective terminations, one was reported with MCMs (Subject [redacted]) and is counted in the remaining tables as a TOPFA. Full details are provided in Section 14.3.3.

Two women participated twice in the registry, contributing to Table 10-11 for each of their pregnancies:

- In woman Subject [redacted] (prospective)/ Subject [redacted] (prospective), both pregnancies were term LBs.
- In woman Subject [redacted] (prospective)/ Subject [redacted] (retrospective) (Listing 16.2.1-1.1), Subject [redacted] was reported with one MCM of cystic kidney disease and Subject [redacted] was a TOPFA with MCMs reported in several organs (Table 10-12).

Table 10-11 Category of malformation by pregnancy outcome

	Prospective cases (N=202)[1]	Retrospective cases (N=101)[1]	All cases (N=303)[1]
Number of pregnancies with known pregnancy outcome, n	188	98	286
Number of infants in pregnancies with known outcome, n	189	100	289
Ectopic pregnancy, n (%)[2]	2 (1.1%)	0 (0.0%)	2 (0.7%)
Spontaneous abortion, n (%)[2]	11 (5.8%)	1 (1.0%)	12 (4.2%)
Live births, stillbirths and elective terminations, n (%)[3]	**176 (93.1%)**	**99 (99.0%)**	**275 (95.2%)**
No malformation, n (%)[4]	160 (90.9%)	90 (90.9%)	250 (90.9%)
None[5]	157 (89.2%)	89 (89.9%)	246 (89.5%)
Positional deformity	1 (0.6%)	0 (0.0%)	1 (0.4%)
Other	2 (1.1%)	1 (1.0%)	3 (1.1%)
Malformations using EUROCAT, n (%)[4]	16 (9.1%)	9 (9.1%)	25 (9.1%)
Major malformation	12 (6.8%)	7 (7.1%)	19 (6.9%)
Minor malformation	4 (2.3%)	2 (2.0%)	6 (2.2%)
Malformations using MACDP, n (%)[4]	16 (9.1%)	9 (9.1%)	25 (9.1%)
Major malformation	16 (9.1%)	8 (8.1%)	24 (8.7%)
Minor malformation	0 (0.0%)	1 (1.0%)	1 (0.4%)
Not applicable[6]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Elective terminations, n (%)[2]	11 (5.8%)	0 (0.0%)	11 (3.8%)
No malformation, n (%)[4]	10 (90.9%)	0 (0.0%)	10 (90.9%)
None[5]	10 (90.9%)	0 (0.0%)	10 (90.9%)
Positional deformity	0 (0.0%)	0 (0.0%)	0 (0.0%)
Prematurity related	0 (0.0%)	0 (0.0%)	0 (0.0%)

	Prospective cases (N=202)[1]	Retrospective cases (N=101)[1]	All cases (N=303)[1]
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)
Malformations using EUROCAT, n (%)[4]	1 (9.1%)	0 (0.0%)	1 (9.1%)
Major malformation	1 (9.1%)	0 (0.0%)	1 (9.1%)
Minor malformation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Malformations using MACDP, n (%)[4]	1 (9.1%)	0 (0.0%)	1 (9.1%)
Major malformation	1 (9.1%)	0 (0.0%)	1 (9.1%)
Minor malformation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not applicable[6]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stillbirths, n (%)[2, 7]	**1 (0.6%)**	**0 (0.0%)**	**1 (0.4%)**
No malformation, n (%)[4]	1 (100.0%)	0 (0.0%)	1 (100.0%)
None[5]	1 (100.0%)	0 (0.0%)	1 (100.0%)
Malformations using EUROCAT, n (%)[4]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Malformations using MACDP, n (%)[4]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Live births, n (%)[3]	**164 (86.8%)**	**99 (99.0%)**	**263 (91.0%)**
No malformation, n (%)[4]	149 (90.9%)	90 (90.9%)	239 (90.9%)
None[5]	146 (89.0%)	89 (89.9%)	235 (89.4%)
Positional deformity	1 (0.6%)	0 (0.0%)	1 (0.4%)
Other	2 (1.2%)	1 (1.0%)	3 (1.1%)
Malformations using EUROCAT, n (%)[4]	15 (9.1%)	9 (9.1%)	24 (9.1%)
Major malformation	11 (6.7%)	7 (7.1%)	18 (6.8%)
Minor malformation	4 (2.4%)	2 (2.0%)	6 (2.3%)
Malformations using MACDP, n (%)[4]	15 (9.1%)	9 (9.1%)	24 (9.1%)
Major malformation	15 (9.1%)	8 (8.1%)	23 (8.7%)
Minor malformation	0 (0.0%)	1 (1.0%)	1 (0.4%)
Not applicable[6]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Live births, Stillbirths, and TOPFA, n (%)[3]	166 (87.8%)	99 (99.0%)	265 (91.7%)
No malformation, n (%)[4]	150 (90.4%)	90 (90.9%)	240 (90.6%)
None[5]	147 (88.6%)	89 (89.9%)	236 (89.1%)
Positional deformity	1 (0.6%)	0 (0.0%)	1 (0.4%)
Other	2 (1.2%)	1 (1.0%)	3 (1.1%)
Malformations using EUROCAT, n (%)[4]	16 (9.6%)	9 (9.1%)	25 (9.4%)
Major malformation	12 (7.2%)	7 (7.1%)	19 (7.2%)
Minor malformation	4 (2.4%)	2 (2.0%)	6 (2.3%)
Malformations using MACDP, n (%)[4]	16 (9.6%)	9 (9.1%)	25 (9.4%)
Major malformation	16 (9.6%)	8 (8.1%)	24 (9.1%)
Minor malformation	0 (0.0%)	1 (1.0%)	1 (0.4%)
Not applicable[6]	0 (0.0%)	0 (0.0%)	0 (0.0%)

EUROCAT: European Registration of Congenital Anomalies and Twins - MACDP: Metropolitan Atlanta Congenital Defects Program - TOPFA: Termination of Pregnancy due to Fetal Anomaly

[1]Number of women enrolled and analyzed.

[2]Percentage computed among infants for whom the pregnancy outcome was known.

[3]Percentage computed among infants for whom the pregnancy outcome was known. Live births include term live births, pre-term live births and neonatal deaths.

[4]Malformations based on adjudication. If an infant had multiple anomalies, the infant is only counted once and the worst category is retained. Percentage computed among infants in the category of pregnancy outcome.

	Prospective cases (N=202)[1]	Retrospective cases (N=101)[1]	All cases (N=303)[1]

[5]No congenital malformation documented in the Congenital Malformation CRF.

[6]Malformations categorized as reportable according to EUROCAT classification but as not reportable according to MACDP classification.

[7]Percentage computed among infants for whom the pregnancy outcome was known, excluding spontaneous abortion cases.

Source: Table 14.3-1.9

Congenital malformation events

Table 10-12 lists the infants that were adjudicated to have at least one major and/or minor congenital malformation per EUROCAT or MACDP.

Using the EUROCAT definition, 16 prospective fetuses/infants (15 LBs and one TOPFA) and nine retrospective fetuses/infants (all LBs) were adjudicated to have a malformation. Of these, major malformations were reported in 12 prospective and 7 retrospective infants with 3 and 2 contributing MCMs to more than one organ system, respectively. Of the MCMs reported, complete recovery was reported for five cardiac events in the nine cases involving major cardiac malformations (three events of ventricular septal defect [VSD] out of five cases with VSD and one event each of VSD and atrial septal defect [ASD] in one out of two cases with ASD+VSD), and for one further event (brachycephaly) in a case classified under “other anomalies”.

Using the MACDP definition, 16 prospective infants/fetuses (15 LBs and one TOPFA) and nine retrospective infants/fetuses (all LBs) were adjudicated to have a malformation. Of these, major malformations were reported in 16 prospective and eight retrospective infants (Section 14.3.3, Annex 1 Table 15-1 and Listing 16.2.9-1.11).

Note that some infants reported multiple major and/or minor malformations, within and across different organs systems; these are marked with the superscript “1” in Table 10-12. The event driving the infant EUROCAT classification as major and related to the organ system under investigation is underlined in bold. Malformation cases which were adjudicated as EUROCAT minor are marked with a **; these are included for completeness.

Table 10-12 Adjudicated major or minor congenital malformation events (according to EUROCAT or MACDP classification) by organ system

Infant ID	Enrol-ment type	EUROCAT /MACDP category	Maternal age (years)	All reported malformations	Risk factors/ confounders	Adjudication notes	Action and Outcome
Cardiovascular							
[redacted]	Prosp	Major/Major	[redacted]	**VSD**	Blood folate decrease	Cardiac anomalies are relatively common, about 0.8% of infants. Could be unrelated to treatment. The other drugs are not considered teratogenic. It may be related to Gilenya but this is a common anomaly and it is impossible to know.	VSD: no action taken; outcome unknown
[redacted][1]	Prosp	Major/Major	[redacted]	**VSD, ASD**	Gestational diabetes Gestational hypertension	None.	All malformations: no action taken; outcome unknown
[redacted]	Prosp	Major/Major	[redacted]	**ASD**	-	A relatively common cardiac malformation often the etiology is unknown.	No action taken; still present and unchanged
[redacted]	Prosp	Major/Major	[redacted]	**VSD**	Maternal obesity (pre-pregnancy BMI = 35.8) Teratogen	Could be associated with maternal obesity or with the drug; could also close spontaneously in the first year and then it can be considered a minor malformation.	Non-drug therapy; completely recovered
[redacted]	Prosp	Major/Major	[redacted]	**VSD, ASD**	Pre-term birth (30 weeks/3 days)	This is a relatively common anomaly of the heart that may close spontaneously. May be related to Gilenya. Atrial septal defect may represent a patent foramen ovale in a preterm infant, which would not be a malformation. There is insufficient information to judge the reliability of the diagnosis.	Hospitalization; VSD, relative pulmonary stenosis, ASD outcome: completely recovered; combined heart failure: improving

Infant ID	Enrol-ment type	EUROCAT /MACDP category	Maternal age (years)	All reported malformations	Risk factors/ confounders	Adjudication notes	Action and Outcome
[redacted]	Prosp	Major/Major	[redacted]	**VSD**	Adipositas Maternal smoking (in first trimester) Maternal obesity (pre-pregnancy BMI = 35.4) Age >35 years	Relation to Gilenya cannot be excluded.	Hospitalization; outcome: still present and unchanged
[redacted]	Retro	Major/Major	[redacted]	Patent foramen ovale; **High take-off of right coronary artery**	Alcohol use during 1st trimester [redacted] Gestational diabetes Maternal obesity (pre-pregnancy BMI = 34.9)	Generally, patent foramen ovale closes spontaneously and is therefore considered functional. In this case it apparently did not close and should therefore be considered an anatomical/structural malformation.	Both malformations: no action taken; still present and unchanged
[redacted]	Retro	Major/Major	[redacted]	**VSD**	Maternal obesity (pre-pregnancy BMI = 34.3)	(1) VSD is the most common cardiac malformation, often etiology is unknown; maternal obesity; These transient VSDs are common in the general population. (2) Patient BMI = 34 but no clear epi evidence that obesity increases risk of VSD. [Some evidence of association with septal defects overall, but likely driven by the more common ASDs].	Action taken not reported; outcome: completely recovered
[redacted]	Retro	Major/Major	[redacted]	**VSD**	Smoking during first trimester	(1) The small VSD is noted as an adverse event on [redacted]. The date of diagnosis of the VSD is [redacted],	Non-drug therapy given; outcome: completely recovered [redacted]

Infant ID	Enrol-ment type	EUROCAT /MACDP category	Maternal age (years)	All reported malformations	Risk factors/ confounders	Adjudication notes	Action and Outcome
					Gabapentinoid during pregnancy	the due date was [redacted]. If the baby was born <37 weeks gestation, this septal defect could be related to prematurity. (2) Most ventricular septal defects are minor and resolve on their own.	
Urinary							
[redacted]	Prosp	Major/Major	[redacted]	**Hydronephrosis**	Age >35 years	The other drugs taken by this mother are not considered teratogenic. Hence, it may be related to Gilenya. However, size of hydronephrosis is unknown and is considered a major malformation only if more than 10 mm.	No action taken; still present and unchanged; hydronephrosis is stable; no need for further follow up
[redacted]	Prosp	Major/Major	[redacted]	**Pelvic kidney**	Gestational diabetes Gestational hypertension	Abnormal location of the kidney is generally due to a problem in the development of the kidney that is rarely due to teratogens. The child also had 2 other malformations: patent foramen ovale and pelvic kidney. may be related to gilenya	No action taken; outcome unknown
[redacted]	Prosp	Major/Major	[redacted]	**Cystic kidney disease**	-	The mother did not take any other drugs but generally cystic disease of the kidney has a strong genetic etiology	No action taken; still present and unchanged
[redacted]1	Prosp	Major/Major	[redacted]	**Suspicion of renal agenesis, right; suspicion of doubleniere, left**	Maternal obesity (pre-pregnancy BMI = 35.4) Smoking during 1st trimester	This is often a malformation of genetic origin/ Maternal obesity	Hospitalization; still present and unchanged
[redacted]**	Prosp	**Minor**/Major	[redacted]	Renal pelvic dilation (7.3 mm) on right side	BMI >25	This finding is a normal variant; judged as a malformation based on EUROCAT and MACDP. The recorded dilatation was 7.3 mm. dilation of pelvis is considered a major	Unknown (ICF for infant was not signed, see Listing 16.2.1-1.3)

Infant ID	Enrol-ment type	EUROCAT /MACDP category	Maternal age (years)	All reported malformations	Risk factors/ confounders	Adjudication notes	Action and Outcome
						anomaly by EUROCAT only if it is 10 mm or more. hence, this is a minor malformation. It is quite common and it is unlikely that it is related to Gilenya. Follow up studies may give more information	
[redacted]**	Prosp	**Minor**/Major	[redacted]	Renal cyst right side	Smoking throughout pregnancy Maternal obesity (pre-pregnancy BMI = 32.7)	A single cyst of the kidney does not seem to affect kidney function and can therefore be considered by EUROCAT a minor anomaly most probably not related to the drug./ Cysts right kidney, most probably unrelated to treatment	No action taken; still present and unchanging
[redacted]1	Retro	Major/Major	[redacted]	**Ectopic kidney**	Pre-term birth (33 weeks/0 days) Tizanidine Pre-eclampsia	None.	No action taken; still present and unchanging
[redacted]	Retro	Major/Major	[redacted]	**Cystic kidney disease**	Congenital abnormality in previous pregnancy	Cystic kidneys can be genetic, impossible to say with the information available in case.	Not reported
Limb/Musculoskeletal							
[redacted]	Prosp	Major/Major	[redacted]	**Clubfoot**	[redacted] Maternal smoking (throughout pregnancy) Chronic depression	This is a relatively common anomaly, sometimes positional and often with etiology unknown.	Surgery performed; recovered with sequelae

Infant ID	Enrol-ment type	EUROCAT /MACDP category	Maternal age (years)	All reported malformations	Risk factors/ confounders	Adjudication notes	Action and Outcome
[redacted]	Prosp	Major/Major	[redacted]	**Tibia bowing, left**	Age > 35	Etiology unknown. May be positional. Probably unrelated to any specific cause	Condition improving through physiotherapy.
[redacted][1,2]	Prosp	Major/Major	[redacted]	Syndactylia of feet Syndactylia of fingers Slightly inflected big toe	-	Could be a chromosomal anomaly, but there is no data on that and no clinical diagnosis of the syndrome Broad prominent toes are characteristic of Rubinstein Taybi syndrome that is genetic, and may also have all other anomalies of this fetus Syndactyly of hands-probably not related to any teratogenic action. This is one of 5 anomalies that probably constitute a syndrome of multiple malformations	No action taken; death of fetus
[redacted][1]	Retro	Major/Major	[redacted]	Limb reduction defects	Pre-term birth (33 weeks/0 days) Pre-eclampsia	Hypoplastic thumbs often go with renal anomalies, and are unrelated to teratogenic events, no obvious factor seen/ Resembles Duane-radial ray syndrome, an X-linked genetic disorder, although the female sex would argue against that diagnosis	No action taken; still present and unchanging
[redacted]**	Retro	**Minor**/Major	[redacted]	Bilateral hip dysplasia	Maternal obesity (pre-pregnancy BMI = 32.0) Teratogen (Iodine)	In most cases of bilateral hip dysplasia the etiology is unknown and there is no known association with drugs taken by the mother during pregnancy. The possibility that it is related to gilenya treatment is remote.	Non-drug therapy; completely recovered
[redacted]	Retro	Major/Major	[redacted]	Polydactyly: Extra finger on left hand Extra toe on left foot	Alcohol use in the 1st trimester Maternal obesity (pre-pregnancy BMI = 39.1)	Most probably an error in embryogenesis (genetic), not related to Gilenya, as both extra fingers are on the left side/ If infant was of African ancestry and extra digit is postaxial, the condition is likely genetic.	The infant's extra finger was removed through surgery (action reported only in ARGUS, refer to narratives in Section 14.3.3)

Infant ID	Enrol-ment type	EUROCAT /MACDP category	Maternal age (years)	All reported malformations	Risk factors/ confounders	Adjudication notes	Action and Outcome
					History of polydactyly in the mother	Most probably not related to any teratogen	
[redacted][1]	Retro	Major/Major	[redacted]	**Pes eginus (Peroneal nerve palsy)**	Smoking during first trimester Gabapentinoid during pregnancy Previous preterm live birth	May be related to treatment.	No action taken; still present and unchanged
Nervous system							
[redacted][1,2]	Prosp	Major/Major	[redacted]	**Corpus callosum agenesis**	-	Could be a chromosomal anomaly, but there is no data on that and no clinical diagnosis of the syndrome Broad prominent toes are characteristic of Rubinstein Taybi syndrome that is genetic, and may also have all other anomalies of this fetus Syndactyly of hands-probably not related to any teratogenic action. This is one of 5 anomalies that probably constitute a syndrome of multiple malformations	No action taken; death of fetus
Genital							
[redacted]	Prosp	Major/Major	[redacted]	**Hypospadias**	Age > 35	None.	Hospitalization; still present and unchanged
[redacted]-[redacted]**	Prosp	**Minor**/Major	[redacted]	[redacted]	BMI >25	This is a common anomaly probably unrelated to treatment or disease. The use of surgery makes this condition a major malformation in MACDP.	Uncomplicated surgery; completely recovered
Other anomalies/syndrome							

Infant ID	Enrol-ment type	EUROCAT /MACDP category	Maternal age (years)	All reported malformations	Risk factors/ confounders	Adjudication notes	Action and Outcome
[redacted][1,2]	Prosp	Major/Major	[redacted]	**Mesocardia**	-	Could be a chromosomal anomaly, but there is no data on that and no clinical diagnosis of the syndrome Broad prominent toes are characteristic of Rubinstein Taybi syndrome that is genetic, and may also have all other anomalies of this fetus Syndactyly of hands-probably not related to any teratogenic action. This is one of 5 anomalies that probably constitute a syndrome of multiple malformations	No action taken; death of fetus
[redacted]**	Prosp	**Minor**/Major	[redacted]	Torticollis	Aortic valve stenosis [redacted] Alcohol use during 1st trimester	The mother was also using other medications including topamax that may be teratogenic. However, congenital torticollis is not related to possible teratogenic effects of any drug	Action taken not reported; outcome unknown
[redacted]	Retro	Major/Major	[redacted]	**Brachycephaly**	BMI >25 Maternal use of sertraline	This is often a positional malformation with no clinical relevance Brachycephaly was diagnosed months after birth.	Non-drug therapy (Doc Band); completely recovered
NA- not malformation							
[redacted]**	Prosp	**Minor**/Minor	[redacted]	Inguinal hernia	Pre-term birth (30 weeks/3 days)	Prematurity is associated with inguinal hernia./ Although inguinal hernia is more common in premature infants, it is still a minor congenital malformation, not reportable according to the MACDP in premature infants	Hospitalization; outcome: completely recovered

Infant ID	Enrol-ment type	EUROCAT /MACDP category	Maternal age (years)	All reported malformations	Risk factors/ confounders	Adjudication notes	Action and Outcome
[redacted]**	Retro	**Minor**/Minor	[redacted]	Pigeon toes	-	This is a minor anomaly that might be related. Probably not related to other medications as they are not teratogenic	Non-drug therapy/ Condition improving

ASD: atrial septal defect; BMI: body mass index; EUROCAT: European Registry of Congenital Anomalies and Twins; [redacted]; MACDP: Metropolitan Atlanta Congenital Defects Program; Prosp: prospective; Retro: retrospective; VSD: ventricular septal defect.

[1]Infant had a malformation reported in more than one organ system.

[2]Termination of pregnancy due to fetal anomaly.

**EUROCAT minor malformation.

Source: Table 14.3-1.16, Listing 16.2.9-1.13 (for risk factors/ confounders), Listing 16.2.9-1.11 (for adjudication notes), Listing 16.2.7-1.2 (for outcome and action)

Risk factors

Of the nine cases reported with cardiac malformations (6 prospective and 3 retrospective), relevant risk factors were identified in eight cases and included maternal obesity (n=4), gestational diabetes (n=2), smoking intake in first trimester (n=2), maternal alcohol intake in first trimester (n=1), gestational hypertension (n=1), [redacted], gabapentinoid use (n=1), blood folate decrease (n=1) and prematurity (n=1) for one case with VSD and ASD. In three of these cases, the infant recovered from VSD; in one further case with ASD/VSD, both the VSD and ASD resolved (Table 10-12).

Of the eight cases reported with congenital malformations in the urinary organ system (including two minor cases), relevant risk factors included maternal obesity and smoking (n=2), gestational diabetes and hypertension (n=1) and pre-maturity (n=1) (Table 10-12).

In the seven malformations reported in the musculoskeletal/limb organ system (including one minor), relevant risk factors included [redacted] maternal smoking (n=1), history of polydactyly in the mother with maternal obesity and alcohol use (n=1), pre-maturity and pre-eclampsia (n=1), maternal obesity (n=1) and pre-maturity, smoking during pregnancy and gabapentinoid use (n=1) (Table 10-12). One case was reported as recovered with sequelae after surgical treatment, and one case was reported as recovered by non-surgical treatment. To further assess the impact of risk factors, a systematic evaluation was undertaken and is presented in Section 10.3.4.1.

Prevalence of major congenital malformations

Using the EUROCAT definition, the prevalence of MCMs in prospective LBs (n/N = 11/164) with exposure to fingolimod in utero was 6.7% (95% CI: 3.4, 11.7) and in prospective LBs, SBs, and TOPFA (n/N = 12/166), it was 7.2% (95% CI: 3.8, 12.3).

The prevalence of MCMs in all cases (prospective and retrospective) ending in LB (n/N = 18/263; 6.8% [95% CI: 4.1, 10.6]) or LB, SB, or TOPFA (n/N = 19/265; 7.2% [95% CI: 4.4, 11.0]) was similar to that of prospective cases.

Using the MACDP definition, the prevalence of MCMs in prospective LBs (n/N = 15/164) with exposure to fingolimod in utero was 9.1% (95% CI: 5.2, 14.6) and in prospective LBs, SBs, and TOPFA (n/N= 16/166) it was 9.6% (95% CI: 5.6, 15.2) (Table 10-13).

Table 10-13 Prevalence of major congenital malformations (MCM)

Classification/ Population	Prospective cases		All cases	
	Fetuses/ infants with major malformations / Total n / N	Prevalence (%)[1] (95% CI)	Fetuses/infants with major malformations / Total n / N	Prevalence (%)[1] (95% CI)
EUROCAT classification				
Live births	11 / 164	6.7 (3.4, 11.7)	18 / 263	6.8 (4.1, 10.6)
Live births, stillbirths, and TOPFA	12 / 166	7.2 (3.8, 12.3)	19 / 265	7.2 (4.4, 11.0)
MACDP classification				
Live births	15 / 164	9.1 (5.2, 14.6)	23 / 263	8.7 (5.6, 12.8)
Live births, stillbirths, and TOPFA	16 / 166	9.6 (5.6, 15.2)	24 / 265	9.1 (5.9, 13.2)

CI: Confidence Interval; TOPFA: Termination of Pregnancy due to Fetal Anomaly; EUROCAT: European Registry of Congenital Anomalies and Twins; MACDP: Metropolitan Atlanta Congenital Defects Program.

Malformations based on adjudication. Major malformations excluding Chromosomal Anomalies/Genetic Disorders. If an infant had multiple anomalies, the infant is only counted once and the worst category is retained.

[1]The prevalence is calculated as the number of fetuses/infants with at least one major malformation per 100 fetuses/infants (n*100/N).

Source: Table 14.3-1.12

EUROCAT vs MACDP classification

As expected, based on the more inclusive nature of the classification, some infants were classified as having an MCM with MACDP but were classified as having a minor malformation according to EUROCAT. This was the case for the following five infants (Table 10-12):

- Subject [redacted]: Torticollis
- Subject [redacted]: Renal pelvic dilation
- Subject [redacted]: Renal cyst right side
- Subject [redacted]: [redacted] (uncomplicated surgery; complete recovery)
- Subject [redacted] (retrospective): Bilateral hip dysplasia

Prevalence of EUROCAT major congenital malformations in live births, stillbirths, and TOPFA by organ system

Table 10-14 provides the prevalence of MCM by organ system using the EUROCAT classification system, and the EUROCAT prevalence in the general population as reference population. Organ systems are presented using the most inclusive denominator i.e., LBs, SBs and TOPFA. The background prevalences of MCMs excluding genetic anomalies are taken as reference.

Compared to EUROCAT, in LBs, SBs and TOPFA, the prevalence of all anomalies (2.03% [95% CI: 2.02, 2.04] vs. 7.23% [95% CI: 3.79, 12.29]), congenital heart defects (0.69% [95% CI: 0.68, 0.69] vs. 3.61% [95% CI: 1.34, 7.70]), urinary malformations (0.32% [95% CI: 0.31, 0.32] vs. 2.41% [95% CI: 0.66, 6.05]), and limb/musculoskeletal malformations (0.34% [95% CI: 0.34, 0.35] vs. 1.81% [95% CI: 0.37, 5.19]) in GPR prospective cases is higher than would

be expected in the general population. The same was observed when all (i.e., prospective and retrospective combined) cases were considered. The higher-than-expected prevalence of cardiovascular, urinary, limb/musculoskeletal malformations was similar to what was observed in previous reports.

Table 10-14 Major congenital malformations in live births, stillbirths, and TOPFA in prospective and all cases (prospective and retrospective) per EUROCAT classification

Organ system	EUROCAT reference[1] Prevalence (95% CI) per 100 cases	GPR prospective cases (N=166) N cases	GPR prospective cases (N=166) Prevalence (95% CI) per 100 cases	GPR all cases (N=265) N cases	GPR all cases (N=265) Prevalence (95% CI) per 100 cases
All anomalies	**2.03 (2.02-2.04)**	**12**	**7.23 (3.79,12.29)**	**19**	**7.17 (4.37,10.97)**
Congenital heart defects	**0.69 (0.68, 0.69)**	**6**	**3.61 (1.34, 7.70)**	**9**	**3.40 (1.56, 6.35)**
Limb	**0.34 (0.34, 0.35)**	3	**1.81 (0.37, 5.19)**	**6**	**2.26 (0.84, 4.86)**
Urinary	**0.32 (0.31, 0.32)**	**4**	**2.41 (0.66, 6.05)**	**6**	**2.26 (0.84, 4.86)**
Nervous system	0.23 (0.22, 0.23)	1	**0.60** (0.02, 3.31)	1	**0.38** (0.01, 2.08)
Genital	0.21 (0.20, 0.21)	1	**0.60** (0.02, 3.31)	1	**0.38** (0.01, 2.08)
Digestive system	0.16 (0.16, 0.16)	0	0.00 (0.00, 2.20)	0	0.00 (0.00, 1.38)
Eye	0.03 (0.03, 0.03)	0	0.00 (0.00, 2.20)	0	0.00 (0.00, 1.38)
Other anomalies/ syndromes	NA	1	0.60 (0.02, 3.31)	2	0.75 (0.09, 2.70)

CI: Confidence Interval; TOPFA: Termination of Pregnancy due to Fetal Anomaly; EUROCAT: European Registry of Congenital Anomalies and Twins; NA: not available

[1] EUROCAT 2023: Data using all full registry data from 2010 to 2020 (including birth year 2020), excluding genetic anomalies. EUROCAT data were last updated on 20-Dec-2022 and can be found here: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en; access date: 08-Feb-2023.

If an infant has malformations in more than one system organ class, the infant is counted once in "All anomalies" and once in each organ.

Source: Table 14.3-1.17

Distribution of major congenital malformations per EUROCAT by organ and preferred term

Table 10-15 provides the distribution of MCM events (i.e., events are counted rather than fetuses/infants) by organ system and preferred term (PT). In the 19 infants/fetuses with at least one MCM, 30 MCM events were reported (20 prospective and 10 retrospective). Congenital heart defects represented 36.7% of the reported events, with VSD (23.3%) and ASD (10.0%) being the most reported cardiac PT. Important to note is that except in 2 cases (Subject [redacted] and Subject [redacted]), ASD and VSD were reported in isolations (Table 10-12).

Limb malformations represented 30.0% (n=9) of reported events, with one patient contributing with three events (Subject [redacted]). For some infants, more than one event with the

same PT was reported: Syndactyly was reported twice in Subject [redacted] and Polydactyly was reported twice in Subject [redacted] (Table 10-12).

Urinary malformations represented 20.0% (n=6) of reported events, with two events of congenital cystic kidney disease.

All other events were reported in isolated infants/fetuses.

Table 10-15 Major congenital malformation events per EUROCAT summary by organ system and preferred term

Organ system, n (%) Preferred term (PT), n (%)	Prospective Cases	Retrospective Cases	All cases
Any major malformation, N[1]	**20**	**10**	**30**
Congenital heart defects	**8 (40.0%)**	**3 (30.0%)**	**11 (36.7%)**
Ventricular septal defect	5 (25.0%)	2 (20.0%)	7 (23.3%)
Atrial septal defect	3 (15.0%)	0 (0.0%)	3 (10.0%)
Coronary artery disease	0 (0.0%)	1 (10.0%)	1 (3.3%)
Limb	**5 (25.0%)**	**4 (40.0%)**	**9 (30.0%)**
Polydactyly	0 (0.0%)	2 (20.0%)	2 (6.7%)
Syndactyly	2 (10.0%)	0 (0.0%)	2 (6.7%)
Congenital bowing of long bones	1 (5.0%)	0 (0.0%)	1 (3.3%)
Foot deformity	1 (5.0%)	0 (0.0%)	1 (3.3%)
Limb reduction defect	0 (0.0%)	1 (10.0%)	1 (3.3%)
Peroneal nerve palsy	0 (0.0%)	1 (10.0%)	1 (3.3%)
Talipes	1 (5.0%)	0 (0.0%)	1 (3.3%)
Urinary	**4 (20.0%)**	**2 (20.0%)**	**6 (20.0%)**
Congenital cystic kidney disease	1 (5.0%)	1 (10.0%)	2 (6.7%)
Ectopic kidney	0 (0.0%)	1 (10.0%)	1 (3.3%)
Hydronephrosis	1 (5.0%)	0 (0.0%)	1 (3.3%)
Pelvic kidney	1 (5.0%)	0 (0.0%)	1 (3.3%)
Renal aplasia	1 (5.0%)	0 (0.0%)	1 (3.3%)
Other anomalies / syndromes	**1 (5.0%)**	**1 (10.0%)**	**2 (6.7%)**
Brachycephaly	0 (0.0%)	1 (10.0%)	1 (3.3%)
Cardiac malposition	1 (5.0%)	0 (0.0%)	1 (3.3%)
Genital	**1 (5.0%)**	**0 (0.0%)**	**1 (3.3%)**
Hypospadias	1 (5.0%)	0 (0.0%)	1 (3.3%)
Nervous system	**1 (5.0%)**	**0 (0.0%)**	**1 (3.3%)**
Congenital central nervous system anomaly	1 (5.0%)	0 (0.0%)	1 (3.3%)

EUROCAT: European Registry of Congenital Anomalies and Twins

[1]Number of events reported in the Congenital malformation CRF and adjudicated as major per EUROCAT.

Percentage among the total number of malformations (N).

Patient [redacted] had one extra finger and one extra toe, which is counted as 2 separate malformations, both classified under Polydactyly Preferred Term.

Patient [redacted] had syndactyly of finger and feet, which is counted as 2 separate malformations, both classified under Syndactyly Preferred Term.

Source: Table 14.3-1.15a

Prevalence of major congenital malformations by timing of fingolimod exposure

Table 14.3-1.12b provides the prevalence of MCM by timing of fingolimod exposure for all exposure categories, for both MACDP and EUROCAT classifications.

No fetuses/infants with MCMs were reported with peri-LMP only exposure or with exposure only after the first trimester (Table 10-16).

A majority (88.8%) of pregnancies were exposed to fingolimod during at least the first trimester (Table 10-7). Using the EUROCAT definition, the prevalence of MCMs in prospective LBs with exposure to fingolimod at least during the first trimester was (11/145) 7.6% (95% CI: 3.9, 13.2) and in prospective LBs, SBs, and TOPFA, it was (12/147) 8.2% (95% CI: 4.3, 13.8). Using the MACDP definition, the prevalence of MCMs in prospective LBs with exposure to fingolimod at least during the first trimester was (15/145) 10.3% (95% CI: 5.9, 16.5) and in prospective LBs, SBs, and TOPFA it was (16/147) 10.9% (95% CI: 6.4, 17.1).

Table 10-16 Prevalence of major congenital malformations by fingolimod exposure

	Prospective Cases			All cases		
Timing of fingolimod exposure[1] Classification/ Population	**Fetuses (infants) with major malformations (n)/ Total (N)**		**Prevalence (%)[2] (95% CI)**	**Fetuses (infants) with major malformations (n)/ Total (N)**		**Prevalence (%)[2] (95% CI)**
Peri-LMP only	0	18	0.0 (0.0, 18.5)	0	11	0.0 (0.0, 28.5)
At least first trimester						
EUROCAT						
LB	11	145	7.6 (3.9, 13.2)	7	88	8.0 (3.3, 15.7)
LB, SB, and TOPFA	12	147	8.2 (4.3, 13.8)	7	88	8.0 (3.3, 15.7)
MACDP						
LB	15	145	10.3 (5.9, 16.5)	8	88	9.1 (4.0, 17.1)
LB, SB, and TOPFA	16	147	10.9 (6.4, 17.1)	8	88	9.1 (4.0, 17.1)
Only after first trimester	0	0	NA	0	0	NA
During all pregnancy	0	2	0.0 (0.0, 84.2)	0	0	NA
Exact timing of exposure unknown	0	1	0.0 (0.0, 97.5)	0	0	NA

CI: Confidence Interval; EUROCAT: European Registry of Congenital Anomalies and Twins; LMP: Last Menstrual Period; MACDP: Metropolitan Atlanta Congenital Defects Program; NA: Not available; TOPFA: Termination of Pregnancy due to Fetal Anomaly; LB: live births; SB: stillbirths

Malformations based on adjudication. Major malformations excluding Chromosomal Anomalies/Genetic Disorders.

If an infant had multiple anomalies, the infant is only counted once, and the worst category is retained.

[1]Peri-LMP only: Exposed only during the period starting 56 days prior to the first day of LMP and ending one day prior to the first day of LMP.

At least first trimester: Exposed during the Period starting on the first day of the LMP and ending on day 91 of gestation, but can also include exposure during other pregnancy periods.

	Prospective Cases		All cases	
Timing of fingolimod exposure[1] Classification/ Population	**Fetuses (infants) with major malformations (n)/ Total (N)**	**Prevalence (%)[2] (95% CI)**	**Fetuses (infants) with major malformations (n)/ Total (N)**	**Prevalence (%)[2] (95% CI)**

Only after first trimester: Exposed only during the Period starting on day 92 of gestation until end of pregnancy.

During all pregnancy: From the first day of the LMP and up to the third trimester of pregnancy or the end of pregnancy, whichever occur first. This period may overlap with 'At least First trimester', therefore categories are not mutually exclusive.

[2]The prevalence is calculated as the number of fetuses/infants with at least one major malformation per 100 fetuses/infants (n*100/N).

Source: Table 14.3-1.12b

10.3.4.1 Risk factor analysis

Since most pregnancies were exposed during at least the first trimester, with few pregnancies exposed during peri-LMP only and none only after the first trimester (Table 10-7), any association between MCM prevalence and timing of fingolimod exposure would be difficult to establish.

Since no definite list of risk factors for MCM (per EUROCAT) exists, a medical review was performed to determine if at least one risk factor for MCM per EUROCAT was present for the pregnancy (Section 9.7.2.1). The search criteria applied to qualify the pregnancy as "at risk" are described in Listing 16.2.9-1.12; the results of the criteria application are provided in Listing 16.2.9-1.13.

Table 10-17 provides the stratified prevalence by characteristics and risk factors in LBs, SBs, and TOPFA.

In the US and Canada, when prospective and retrospective cases are combined, the MCM prevalence was higher than in Other or Germany (13.0% vs. 6.4% and 5.3%, respectively). The odds ratio (OR) of US/Canada vs. Germany was 2.66 (95% CI: 0.91, 7.78).

More MCMs were reported when the initial reporter was the patient compared to an HCP (11.3% vs. 5.7%; OR: 2.14 [95% CI: 0.84, 5.45]).

In total, 164 (62%) pregnancies were identified with at least one risk factor for MCM (Listing 16.2.9-1.13). More MCMs were reported in pregnancies with at least one risk factor compared to pregnancies with no risk factor (8.5% vs. 5.0%; OR: 1.69 [95% CI: 0.61, 4.68]). Of the 19 infants with MCM, in 14 (74%) cases the mother had at least one risk factor for MCM.

Table 10-17 Occurrence of major congenital malformations according to EUROCAT by potential characteristics/risk factor in Live birth, stillbirth and TOPFA

Characteristics/ risk factor	Prospective cases (N=166) Fetuses/infants with EUROCAT MCM / Total n / N (%)	All cases (N=265) Fetuses/infants with EUROCAT MCM / Total n / N (%)	Odd Ratio[1] (95% CI)
Region			
Germany	6 / 97 (6.2%)	7 / 133 (5.3%)	Reference
Other	3 / 49 (6.1%)	5 / 78 (6.4%)	1.26 (0.40, 3.96)
US and Canada	3 / 20 (15.0%)	7 / 54 (13.0%)	2.66 (0.91, 7.78)
Initial reporter			
HCP	8 / 136 (5.9%)	11 /194 (5.7%)	Reference
Patient	4 / 30 (13.3%)	8 /71 (11.3%)	2.14 (0.84, 5.45)
At least one risk factor for MCM			
No	4 / 62 (6.5%)	5 / 101 (5.0%)	Reference
Yes*	8 / 104 (7.7%)	14 / 164 (8.5%)	1.69 (0.61, 4.68)

*'Yes' based on medical review. List of criteria as per Listing 16.2.9-1.12; identified patients as per Listing 16.2.9-1.13.

[1]Unadjusted logistic models fitted with the occurrence of at least one MCM according to EUROCAT as the outcome with firth correction.

Source: Table 14.3-1.19, Table 14.3-1.21

10.4 Literature Review

The source data for published studies that assess adverse pregnancy outcomes in the general population, untreated and treated MS populations vary greatly. These sources (as noted in the figures) include national health registries, nationwide cohorts, claims databases, pregnancy registries, pharmacovigilance databases, single hospital cohorts, and other sources.

Data collection methods also vary between studies. For example, some studies required an informed consent process for their primary data collection, while others did not since it was a secondary use of data study. Inclusion and exclusion criteria vary by study, as well as the time of inclusion (e.g., definition and timing of gestation at index date) and geography covered. These data collection methods can lead to biases in the outcomes captured, especially for spontaneous abortions, which typically occur early in pregnancy.

Furthermore, no universal definitions exist for spontaneous abortions and SB (Tavares Da Silva et al 2016) and different spontaneous abortion and SB definitions are applied in the EUROCAT registries (EUROCAT Guide 1.5 2022 and EUROCAT 2024).

The size of the data sources also varies, with some studies including millions of observations in the denominator while others include fewer than 100 women in the population, leading to differences in CI widths.

The classification system used to assess MCMs (noted in the figures) also varies by study, which makes comparisons between studies difficult.

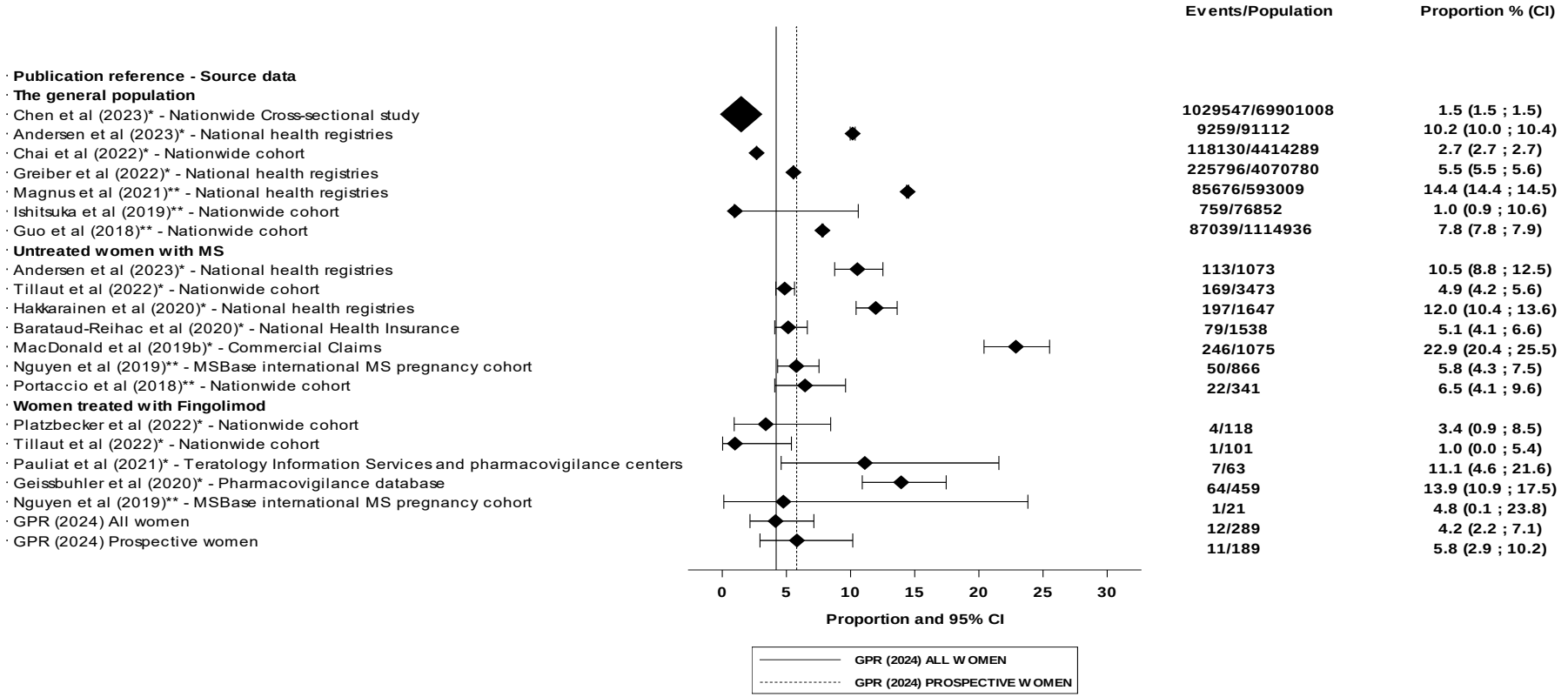
Due to the differences in data source and study methodologies, outcome estimates and confidence intervals can vary, and comparisons between these external data sources and GPR must be done with caution.

10.4.1 Spontaneous abortions

Spontaneous abortion prevalences are affected by the timing of the index date and are typically underreported when informed consents are in place and in studies based on claims data.

The prevalence of spontaneous abortions ranges from 1.0% to 14.4% in the general population, 4.9% to 22.9% in the untreated MS population (Figure 10-2), and 0.0% to 21.2% in the treated MS population (excluding Fingolimod) (Figure 10-3). In prospective cases in GPR, the prevalence of spontaneous abortions was 5.8% (95% CI: 2.9, 10.2), which is at the lower end of what would be expected in the general population, untreated and treated MS populations.

Figure 10-2 Studies assessing spontaneous abortion in the general population, in untreated women with Multiple Sclerosis and in fingolimod treated women with Multiple Sclerosis



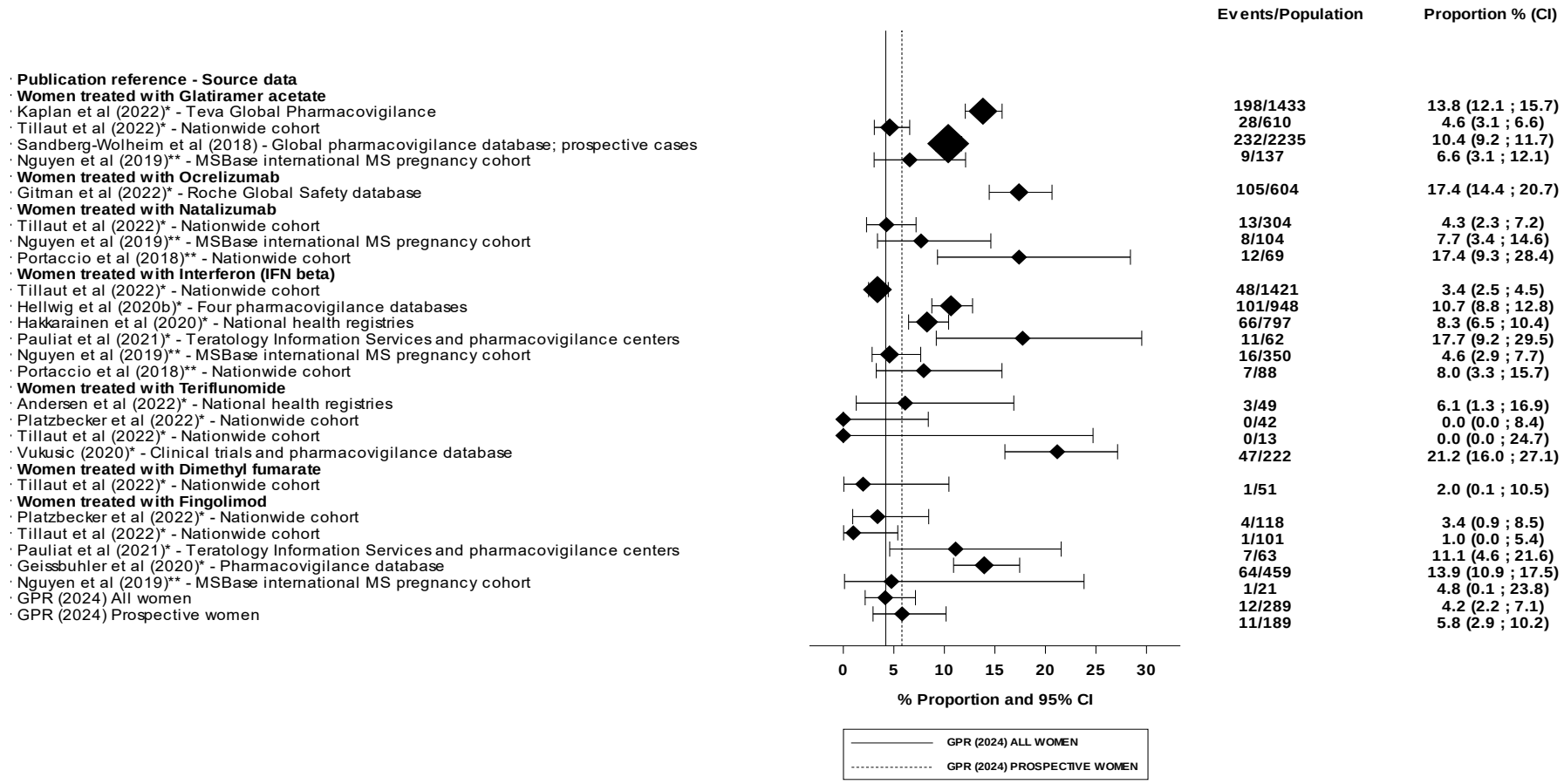
CI: Confidence Interval, GPR: Gilenya pregnancy Registry, MS: Multiple Sclerosis.

* The Clopper-Pearson 95% CI was calculated based on information in the publication.

**The prevalence and the Clopper-Pearson 95% CI were calculated based on information in the publication.

Source: Figure 2.1

Figure 10-3 Studies assessing spontaneous abortion in treated women with Multiple Sclerosis



CI: Confidence Interval, GPR: Gilenya pregnancy Registry, MS: Multiple Sclerosis.

* The Clopper-Pearson 95% CI was calculated based on information in the publication.

**The prevalence and the Clopper-Pearson 95% CI were calculated based on information in the publication.

Source: Figure 2.2

10.4.2 Major congenital malformations

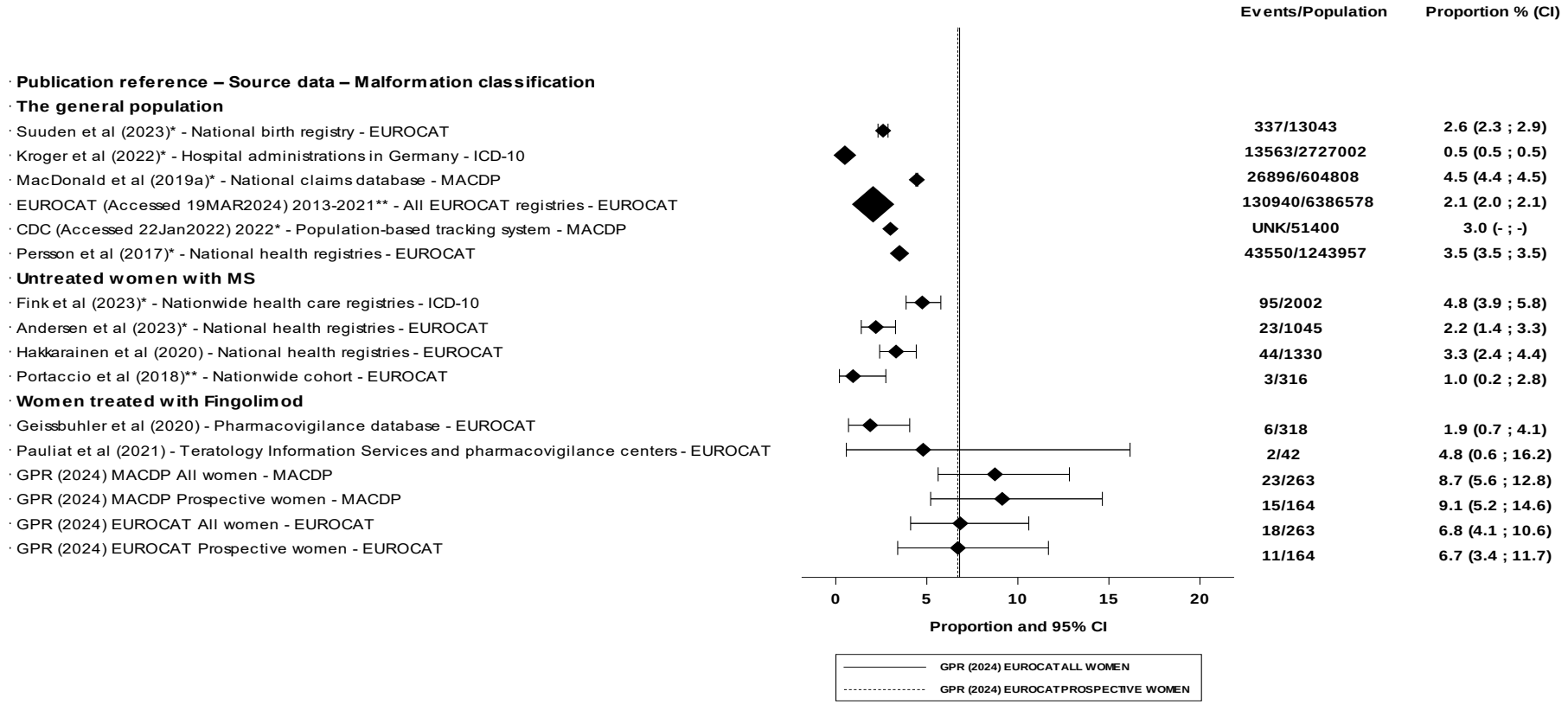
Major congenital malformation prevalences are affected by the classification system used (e.g., EUROACT vs. MACDP), the information available for the classification and the population under study.

The prevalence of MCMs in LBs ranges between 0.5% and 4.5% in the general population, between 1.0% and 4.8% in untreated MS populations (Figure 10-4), and between 0.0% and 3.7% in the MS population treated with other disease modifying drugs (Figure 10-5).

The following literature references used the MACDP classification system: MacDonald et al (2019b), Henson et al (2020) and Kaplan et al (2023) and the following literature references used the ICD-10 classification system: Fink et al (2023), Kroger et al (2022) and Andersen et al (2022). All other references used the EUROCAT classification system, except for Hellwig et al (2020b), which did not specify the malformation classification system used.

The prevalence of MCMs in LBs in GPR was 6.7% (95% CI: 3.4, 11.7) for prospective cases using the EUROCAT classification and 9.1% (95% CI: 5.2, 14.6) using the MACDP classification. Using either EUROCAT or MACDP, the prevalence of MCMs in LBs in GPR is higher than would be expected in the general population and the CIs do not overlap.

Figure 10-4 Studies assessing major congenital malformations in live births in the general population and in untreated women for Multiple Sclerosis and in women treated with fingolimod



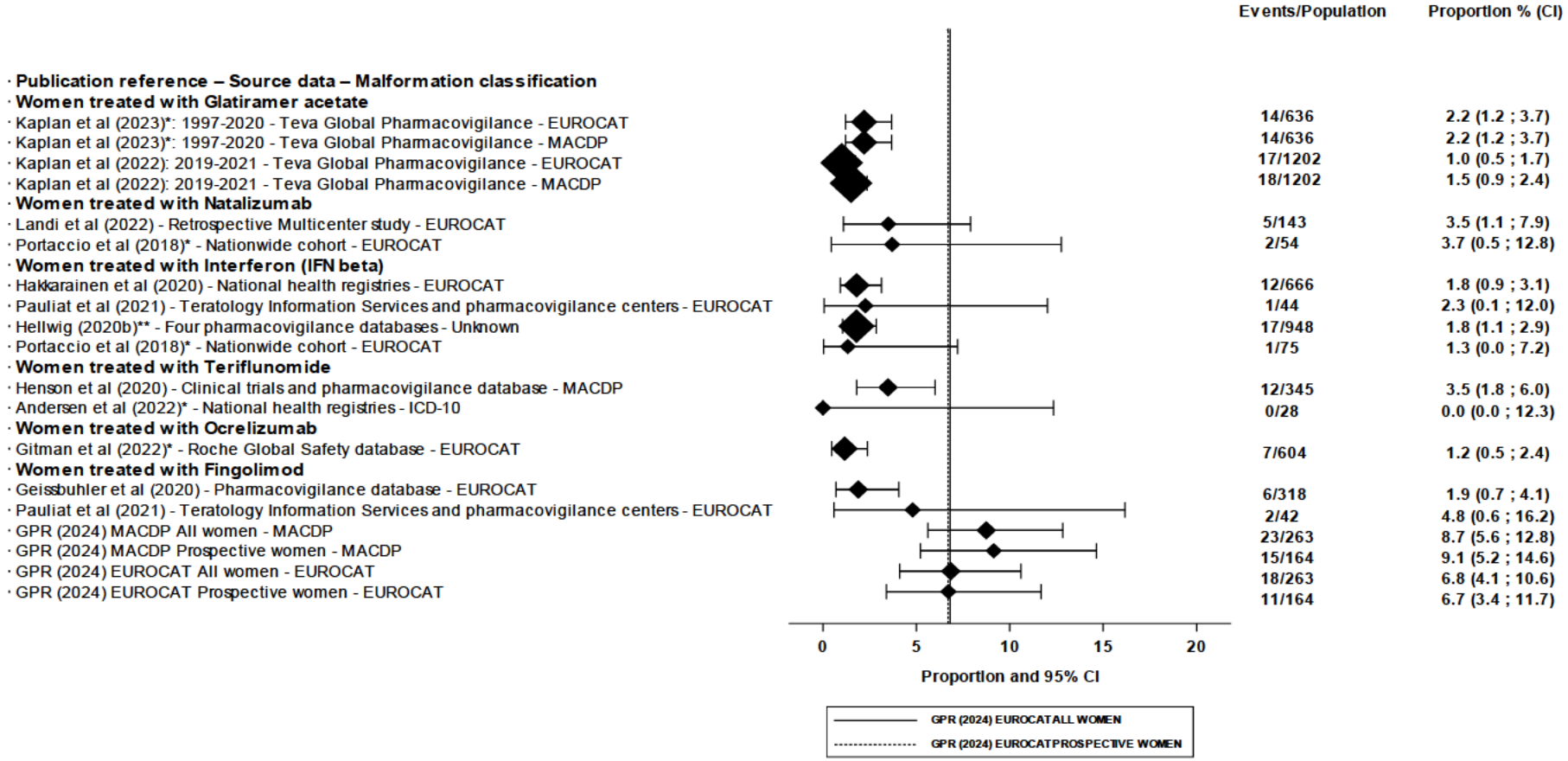
CDC: Centers of Disease Control and Prevention, CI: Confidence Interval, EUROCAT: European Registry of Congenital Anomalies and Twins, GPR: Gilenya pregnancy Registry, ICD: International Classification of Diseases, MACDP: Metropolitan Atlanta Congenital Defects Program, MS: Multiple Sclerosis, UNK: Unknow.

* The Clopper-Pearson 95% CI was calculated based on information in the publication.

**The prevalence and the Clopper-Pearson 95% CI were calculated based on information in the publication.

Source: Figure 9.1

Figure 10-5 Studies assessing major congenital malformations in live births, in women treated for Multiple Sclerosis



CI: Confidence Interval, EUROCAT: European Registry of Congenital Anomalies and Twins, GPR: Gilenya pregnancy Registry, ICD: International Classification of Diseases, IFN: Interferon, MACDP: Metropolitan Atlanta Congenital Defects Program.

* The Clopper-Pearson 95% CI was calculated based on information in the publication.

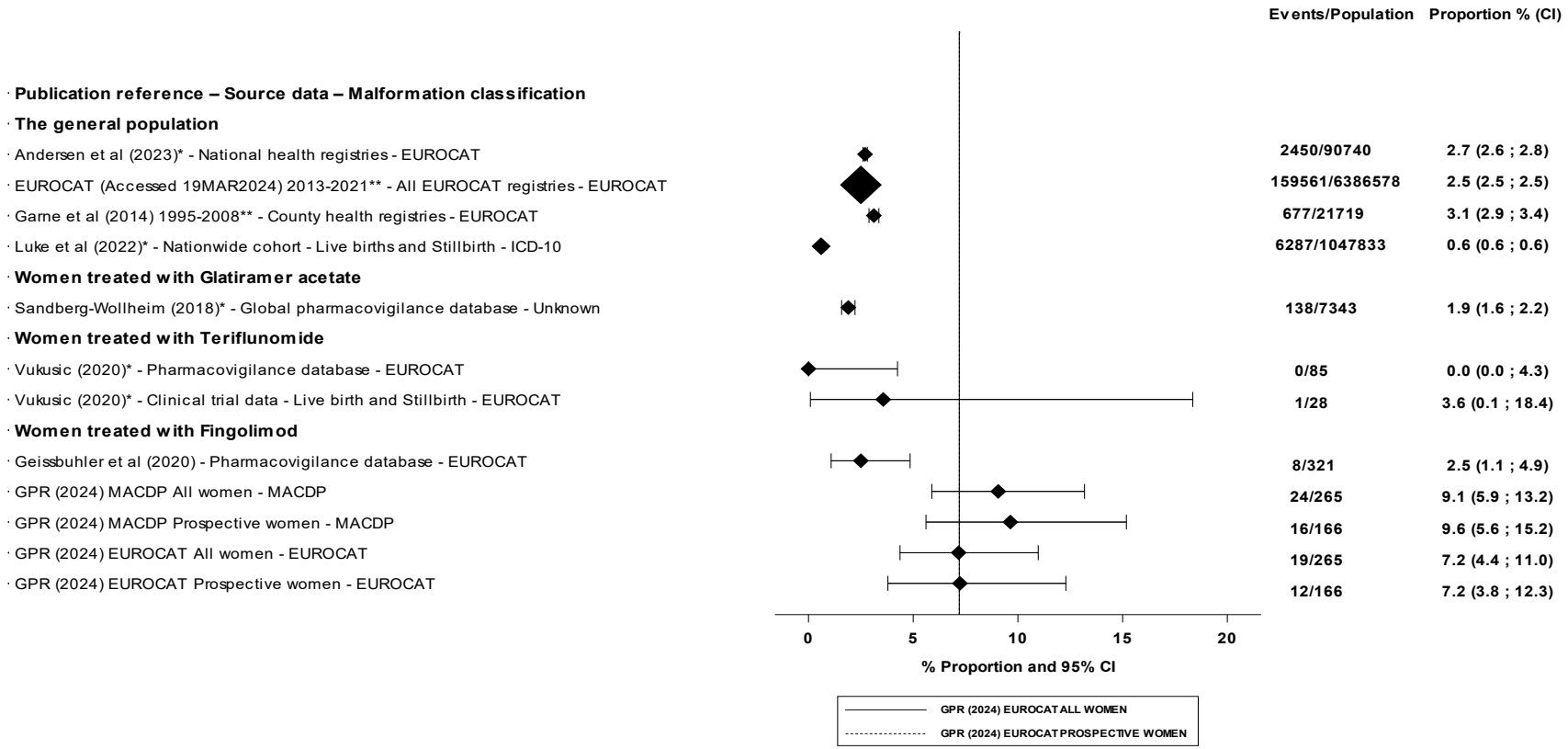
**The prevalence and the Clopper-Pearson 95% CI were calculated based on information in the publication.

Source: Figure 9.2

In LBs, SBs and TOPFA, the prevalence of MCMs ranged from 0.6% to 3.1% in the general population and from 0.0% to 3.6% in the treated (with other disease modifying drugs) MS populations (Figure 10-6).

In LBs, SBs and TOPFA, the prevalence of MCMs in prospective cases from the GPR was 7.2% (95% CI: 3.8, 12.3) and 9.6% (95% CI: 5.6, 15.2) using EUROCAT and MACDP definitions, respectively.

Figure 10-6 Studies assessing major congenital malformations in live births, stillbirths and TOPFA in the general population and in women treated for Multiple Sclerosis



CI: Confidence Interval, EUROCAT: European Registry of Congenital Anomalies and Twins, GPR: Gilenya pregnancy Registry, ICD: International Classification of Diseases, MACDP: Metropolitan Atlanta Congenital Defects Program, TOPFA: Termination Of Pregnancy for Fetal Anomaly.

* The Clopper-Pearson 95% CI was calculated based on information in the publication.

**The prevalence and the Clopper-Pearson 95% CI were calculated based on information in the publication.

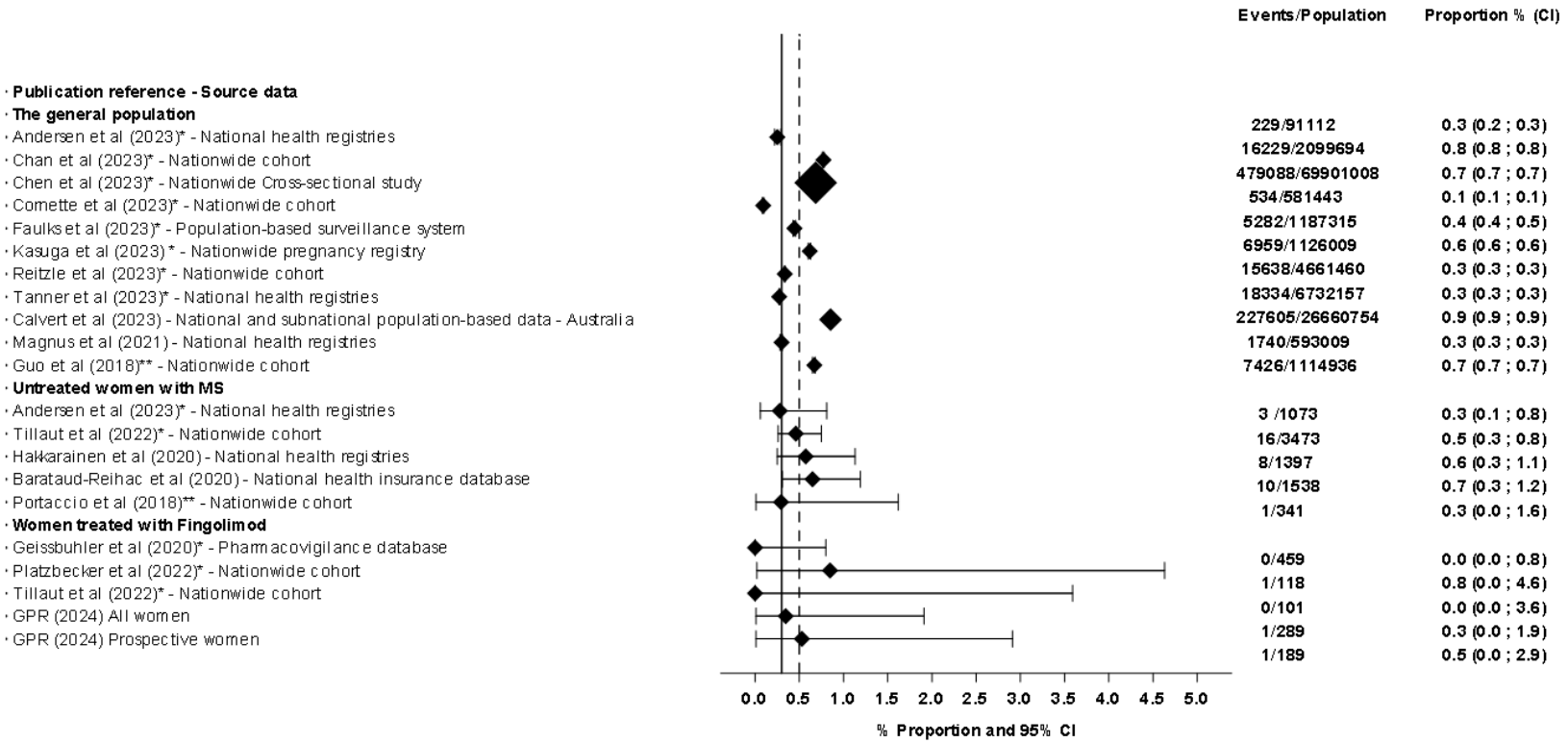
Source: Figure 8

10.4.3 Stillbirth

The prevalence of SB ranged from 0.1% to 0.9% in the general population, from 0.3% to 0.7% in the untreated MS population (Figure 10-7), and from 0.0% to 0.5% in the treated MS population (excluding Fingolimod) (Figure 4-2).

The prevalence of SB was 0.5% (95% CI: 0.0, 2.9) in prospective GPR cases (Figure 10-7), which is in line with the prevalence in the general population and untreated and treated MS populations.

Figure 10-7 Studies assessing stillbirth in the general population, in untreated women with Multiple Sclerosis and in fingolimod treated women with Multiple Sclerosis



CI: Confidence Interval, GPR: Gilenya pregnancy Registry, MS: Multiple Sclerosis

For GPR, prevalence is computed among infants with pregnancy outcome known, excluding spontaneous abortion cases.

* The Clopper-Pearson 95% CI was calculated based on information in the publication.

**The prevalence and the Clopper-Pearson 95% CI were calculated based on information in the publication.

Source: Figure 4.1

10.5 Safety results

10.5.1 Serious adverse events in mothers

Serious adverse events (with seriousness assessed by reporter) in the mother were medically reviewed and divided into three tables:

- Table 14.3-1.13a provides all SAEs
- Table 14.3-1.13b is restricted to SAEs excluding pregnancy outcomes and associated events
- Table 14.3-1.13c is restricted to SAEs of pregnancy outcomes and associated events

Table 10-18 presents SAEs in the mother, excluding adverse pregnancy outcomes and associated events, by SOC and PT for SAEs that occurred in two or more women in the 'All cases' column.

Overall, 120 SAEs (excluding adverse pregnancy outcomes and associated events) were reported in 67 (22.1%) women. The most frequent SOCs were pregnancy, puerperium and perinatal conditions (9.9% of women, n=30), Nervous system disorders (6.6%, n=20) and infection and infestations (4.3%, n=13). Cervical incompetence, gestational diabetes and pre-eclampsia were the most reported SAEs in 1.7% (n=5) of women each. Multiple sclerosis relapse was reported for 5.6% (n=17) of women. Other notable SAEs reported include cervix carcinoma (Subject [redacted]) and severe allergic reaction to Copaxone (Subject [redacted]).

In addition, one maternal SAE (Subject [redacted]) was reported as death (verbatim "[redacted]" coded with PT "death [redacted]" [redacted]) (Table 14.3-1.13), fully described in Section 14.3.3.

The complete list of SAEs by SOC and PT is in Table 14.3-1.13, which also includes details on severity, action taken, and outcome.

Table 10-18 Serious adverse events in women, excluding adverse pregnancy outcomes and associated events (terms reported in two or more women)

System Organ Class Preferred Term	Prospective Cases (N=202)[1]		Retrospective Cases (N=101)[1]		All cases (N=303)[1]	
	Number of SAEs n	Women with SAE n (%)	Number of SAEs n	Women with SAE n (%)	Number of SAEs n	Women with SAE n (%)
All types	73	40 (19.8%)	47	27 (26.7%)	120	67 (22.1%)
Pregnancy, puerperium and perinatal conditions	17	15 (7.4%)	17	15 (14.9%)	34	30 (9.9%)
Cervical incompetence	4	4 (2.0%)	1	1 (1.0%)	5	5 (1.7%)
Gestational diabetes	2	2 (1.0%)	3	3 (3.0%)	5	5 (1.7%)
Pre-eclampsia	1	1 (0.5%)	4	4 (4.0%)	5	5 (1.7%)
Premature labour	1	1 (0.5%)	3	3 (3.0%)	4	4 (1.3%)
Premature rupture of membranes	2	2 (1.0%)	1	1 (1.0%)	3	3 (1.0%)

System Organ Class Preferred Term	Prospective Cases (N=202)[1]		Retrospective Cases (N=101)[1]		All cases (N=303)[1]	
	Number of SAEs n	Women with SAE n (%)	Number of SAEs n	Women with SAE n (%)	Number of SAEs n	Women with SAE n (%)
Oligohydramnios	1	1 (0.5%)	1	1 (1.0%)	2	2 (0.7%)
Nervous system disorders	16	12 (5.9%)	9	8 (7.9%)	25	20 (6.6%)
Multiple sclerosis relapse	13	11 (5.4%)	6	6 (5.9%)	19	17 (5.6%)
Dizziness	2	2 (1.0%)	1	1 (1.0%)	3	3 (1.0%)
Infections and infestations	**12**	**9 (4.5%)**	**4**	**4 (4.0%)**	**16**	**13 (4.3%)**
Amniotic cavity infection	2	1 (0.5%)	1	1 (1.0%)	3	2 (0.7%)
Beta haemolytic streptococca	1	1 (0.5%)	1	1 (1.0%)	2	2 (0.7%)
Reproductive system and breast disorders	**4**	**4 (2.0%)**	**1**	**1 (1.0%)**	**5**	**5 (1.7%)**
Vaginal hemorrhage	2	2 (1.0%)	0	0 (0.0%)	2	2 (0.7%)
Investigations	**2**	**2 (1.0%)**	**2**	**2 (2.0%)**	**4**	**4 (1.3%)**
Gastrointestinal disorders	**4**	**4 (2.0%)**	**0**	**0 (0.0%)**	**4**	**4 (1.3%)**
Surgical and medical procedures	**4**	**3 (1.5%)**	**1**	**1 (1.0%)**	**5**	**4 (1.3%)**
Injury, poisoning and procedural complications	**1**	**1 (0.5%)**	**4**	**2 (2.0%)**	**5**	**3 (1.0%)**
Vascular disorders	**2**	**2 (1.0%)**	**2**	**1 (1.0%)**	**4**	**3 (1.0%)**
Renal and urinary disorders	**3**	**3 (1.5%)**	**0**	**0 (0.0%)**	**3**	**3 (1.0%)**
Kidney congestion	3	3 (1.5%)	0	0 (0.0%)	3	3 (1.0%)
General disorders and administration site conditions	**0**	**0 (0.0%)**	**2**	**2 (2.0%)**	**2**	**2 (0.7%)**
Endocrine disorders	**1**	**1 (0.5%)**	**1**	**1 (1.0%)**	**2**	**2 (0.7%)**
Blood and lymphatic system disorders	**1**	**1 (0.5%)**	**1**	**1 (1.0%)**	**2**	**2 (0.7%)**
Thrombocytopenia	1	1 (0.5%)	1	1 (1.0%)	2	2 (0.7%)
Eye disorders	**1**	**1 (0.5%)**	**1**	**1 (1.0%)**	**2**	**2 (0.7%)**
Diplopia	1	1 (0.5%)	1	1 (1.0%)	2	2 (0.7%)

Serious Adverse Events (SAEs) occurring after the woman has provided informed consent and until 30 days after the end of registry participation are described.

If a woman experiences more than one SAE by category, she is counted only once in the woman-level summary statistics, but each event is counted separately in the event-level summary statistics.

System Organ Classes and Preferred Terms are sorted in the descending order of frequency for All Cases.

Percentage computed among the number of analyzed women.

[1]Number of women enrolled and analyzed.

Source: Table 14.3-1.13b

10.5.2 Serious adverse events in infants

The complete list of SAEs by SOC and PT in infants/fetuses is provided in Table 14.3-1.14, which also includes details on severity, action taken, and outcome.

Serious adverse events (with seriousness assessed by reporter) in the infants were medically reviewed and divided into three tables:

- Table 14.3-1.14a provides all SAEs in infants/fetuses (irrespective of birth type)
- Table 14.3-1.14b is restricted to SAEs in infants (birth type as LB) excluding adverse pregnancy outcomes and malformation events
- Table 14.3-1.14c is restricted to SAEs in infants/fetuses (irrespective of birth type) of adverse pregnancy outcomes and malformation events

Death

In total, 8 events are coded with outcome as death (Table 14.3-1.14, Listing 16.2.4-2.1) in the following 4 infants/fetuses. These deaths were also counted in Table 14.3-1.14 and Table 14.3-1.14c as consequence of the pregnancy outcome. Further description is provided in Section 14.3.3:

- Subject [redacted] with the event coded as PT 'Death neonatal' on [redacted] due to prematurity. The patient delivered a [redacted] baby weighing [redacted] grams on [redacted] (24 weeks and 3 days of GA). The estimated delivery date was [redacted].
- Subject [redacted] with the event coded as PT 'Abortion induced' refers to a patient who had an elective abortion due to fear of malformation.
- Subject [redacted] with the event coded as PT 'Still birth'.
- Subject [redacted] refers to a patient who had termination of pregnancy due to fetal anomaly (TOPFA). On [redacted], ultrasound on 22 weeks gestation was performed and the baby was found to have corpus callosum agenesia, mesocardia, syndactylia finger, syndactylia of the feet and prominent slightly inflected big toes. On [redacted], the mother planned for abortion due to severe multiple malformations of fetus. For this case, a total of five events were reported with outcome 'Death': PT "foot deformity" in SOC 'Musculoskelatal and connective tissue disorder', 'Syndactyly' (reported for both hand and feet), 'Cardiac malposition' and 'Congenital central nervous system anomaly' all in the SOC 'Congenital, familial and genetic disorder'.

Other SAEs

Table 10-19 presents SAEs in the infants (birth type as LB) excluding adverse pregnancy outcomes and congenital malformations, by SOC and PT if they occurred in two or more infants in the 'all cases' column.

Overall, 83 SAEs (excluding pregnancy outcome and malformation events only in LBs) were reported in 37 (14.5%) infants. The most frequently reported (≥3%) SAEs were related to the SOC of infections and infestations (9.0%) and respiratory, thoracic and mediastinal disorders (5.1%). One infant (Subject [redacted]) was reported with neonatal sepsis. Two babies had respiratory failure (Subject [redacted] and Subject [redacted]) and one case was reported with Kernicterus (Subject [redacted]).

All narratives for SAEs occurring in infants are provided in Section 14.3.3.

Table 10-19 Serious adverse events in infants, excluding adverse pregnancy outcomes and congenital malformations (birth type of Live births) (terms reported in two or more infants)

	Prospective Cases (N=159)[1]		Retrospective Cases (N=97)[1]		All cases (N=256)[1]	
System organ class Preferred term	SAEs, n	Infants with SAE, n (%)	SAEs, n	Infants with SAE, n (%)	SAEs, n	Infants with SAE, n (%)
All types	47	24 (15.1%)	36	13 (13.4%)	83	37 (14.5%)
Infections and infestations	**23**	**16 (10.1%)**	**9**	**7 (7.2%)**	**32**	**23 (9.0%)**
Neonatal infection	3	3 (1.9%)	1	1 (1.0%)	4	4 (1.6%)
Bronchitis	3	3 (1.9%)	0	0 (0.0%)	3	3 (1.2%)
Pneumonia	3	3 (1.9%)	0	0 (0.0%)	3	3 (1.2%)
Influenza	0	0 (0.0%)	2	2 (2.1%)	2	2 (0.8%)
Respiratory syncytial virus infection	1	1 (0.6%)	1	1 (1.0%)	2	2 (0.8%)
Respiratory, thoracic and mediastinal disorders	**7**	**5 (3.1%)**	**11**	**8 (8.2%)**	**18**	**13 (5.1%)**
Respiratory disorder	0	0 (0.0%)	3	3 (3.1%)	3	3 (1.2%)
Apnoea	1	1 (0.6%)	1	1 (1.0%)	2	2 (0.8%)
Infantile apnoea	1	1 (0.6%)	1	1 (1.0%)	2	2 (0.8%)
General disorders and administration site conditions	**1**	**1 (0.6%)**	**6**	**4 (4.1%)**	**7**	**5 (2.0%)**
Hypothermia	0	0 (0.0%)	3	2 (2.1%)	3	2 (0.8%)
Pyrexia	0	0 (0.0%)	3	2 (2.1%)	3	2 (0.8%)
Pregnancy, puerperium and perinatal conditions	**2**	**2 (1.3%)**	**3**	**3 (3.1%)**	**5**	**5 (2.0%)**
Jaundice neonatal	0	0 (0.0%)	2	2 (2.1%)	2	2 (0.8%)
Blood and lymphatic system disorders	**2**	**2 (1.3%)**	**2**	**1 (1.0%)**	**4**	**3 (1.2%)**
Cardiac disorders	**1**	**1 (0.6%)**	**2**	**2 (2.1%)**	**3**	**3 (1.2%)**
Bradycardia	1	1 (0.6%)	2	2 (2.1%)	3	3 (1.2%)
Metabolism and nutrition disorders	**1**	**1 (0.6%)**	**2**	**2 (2.1%)**	**3**	**3 (1.2%)**
Dehydration	1	1 (0.6%)	1	1 (1.0%)	2	2 (0.8%)
Nervous system disorders	**1**	**1 (0.6%)**	**1**	**1 (1.0%)**	**2**	**2 (0.8%)**
Gastrointestinal disorders	**2**	**2 (1.3%)**	**0**	**0 (0.0%)**	**2**	**2 (0.8%)**
Hepatobiliary disorders	**3**	**2 (1.3%)**	**0**	**0 (0.0%)**	**3**	**2 (0.8%)**

SAE: Serious Adverse Event.

Serious Adverse events occurring from birth and until 30 days after the end of registry participation are described.

If an infant experiences more than one SAE by category, she/he is counted only once in the infant-level summary statistics, but each event is counted separately in the event-level summary statistics.

System Organ Classes and Preferred Terms are sorted in the descending order of frequency for All cases.

Percentage computed among the number of analyzed infants.

[1]Number of analyzed infants.

Source: Table 14.3-1.14b

10.5.3 Narratives for adverse events

Narratives for fetal/infant and maternal deaths, abortions, congenital malformations, small for GA, developmental delays, serious infections and other serious events in both mothers and infants are provided in Appendix 14.3.3.

11 Discussion

11.1 Key results

Disposition

This is the final analysis on the 312 women enrolled in GPR up to 05-Jan-2023. Data accumulated up to 03-Jul-2024 (database lock date) are included, allowing one year of follow-up for each infant. Nine women were excluded due to protocol deviations, leading to 303 women analyzed (202 prospective and 101 retrospective).

Demographics and exposure

The median age at LMP was 32.0 years (range 19 to 48 years). Overall, 70.6% of the women were from Europe and 21.5% from the US and Canada. The pre-pregnancy BMI classified 22.1% and 21.7% of the women as overweight or obese, respectively. Relapsing Remitting Multiple Sclerosis (RRMS) was the most common current type of MS (93.9%).

At least one active medical condition was reported by 104 (34.3%) women. The most reported conditions were depression (7.9%), thyroid disease (4.0%) and autoimmune disease (3.6%).

Among the women with available information, a majority (n=158, 52.7%) of women reported at least one previous medically recognized pregnancy. Among these, 26 (16.5%) reported at least one specific obstetric complication in a previous pregnancy.

Most women (88.8%) were exposed to fingolimod during at least the first trimester.

Outcomes

Among the 303 pregnancies, a known pregnancy outcome was recorded for 286, involving 289 infants (189 in the prospective group and 100 in the retrospective group).

Overall, there were 263 (91.0%) LBs. Two (0.7%) women reported an ectopic pregnancy, 12 (4.2%) women reported a spontaneous abortion, and 11 (3.8%) women reported an elective termination (including one due to fetal anomaly). One woman reported a SB.

Congenital malformations

Out of the 289 infants, 25 infants had an adjudicated reportable malformation.

Using the EUROCAT classification, in LBs, SBs and TOPFA, 19 infants reported MCMs (12 prospective and 7 retrospective cases). Of the MCMs reported, complete recovery was reported for five cardiac events in the nine cases involving major cardiac malformations (three events of VSD out of five cases with VSD and one event each of VSD and ASD in one out of two cases

with ASD+VSD), and for one further event (brachycephaly) in a case classified under "other anomalies".

No malformations were assessed as chromosomal anomalies or genetic defects.

Using the EUROCAT classification, the prevalences of MCM in infants exposed to fingolimod *in utero* were similar across pregnancy classification and denominator:

- in prospective LBs (n/N= 11/164): 6.7% (95% CI: 3.4, 11.7),
- in prospective LBs, SBs, and TOPFA (n/N= 12/166): 7.2% (95% CI: 3.8, 12.3),
- in all (prospective and retrospective) LBs (n/N = 18/263): 6.8% (95% CI: 4.1, 10.6),
- in all LBs, SBs and TOPFA (n/N = 19/265): 7.2% (95% CI: 4.4, 11.0).

Using the MACDP classification, the prevalences of MCM were:

- in prospective LBs (n/N=15/164): 9.1% (95% CI: 5.2, 14.6),
- in prospective LBs, SBs and TOPFA (n/N=16/166): 9.6% (95% CI: 5.6, 15.2).

The observed prevalence of MCMs using the EUROCAT and MACDP classification systems in infants born to mothers with fingolimod exposure is higher than the prevalence observed in the general population (EUROCAT [excluding chromosomal/genetic anomalies]: 1.77% [LB+SB] and 2.03% [LB+SB+TOPFA]; MACDP: 3.0%).

For three organ systems, the MCM prevalence in the GPR prospective group was higher compared to EUROCAT (LBs, SBs and TOPFA):

- congenital heart defects (GPR: 3.61% [95% CI: 1.34, 7.70] vs. EUROCAT: 0.69% [95% CI: 0. 68, 0.69]),
- urinary malformations (GPR: 2.41% [95% CI: 0.66, 6.05] vs. EUROCAT: 0.32% [95% CI: 0.31, 0.32]), and
- limb/musculoskeletal malformations (GPR: 1.81% [95% CI: 0.37, 5.19] vs. EUROCAT: 0.34% [95% CI: 0.34, 0.35]).

The same was observed when all cases (prospective and retrospective) are considered.

In LB, SB, and TOPFA, the overall MCM prevalence was higher in participants from the US/Canada (13.0%) and when the participant self-reported (11.3%). Classifying the pregnancies by their risk profile (including active medical condition, family history, event during the pregnancy, age and BMI), 164 (62%) pregnancies had at least one risk factor. Among these, 14 (8.5%) resulted in an infant with an MCM, leading to an OR for MCM in pregnancies with at least one risk factor vs. MCM in pregnancies without a risk factor of 1.69 (95% CI: 0.61, 4.68).

Further safety observations in infant and mothers

One neonatal death due to prematurity was reported.

Developmental delays were reported in five infants who completed the one-year follow-up. In three cases, these were motor delays and there was one language and one "other" (reported as "[redacted]") delay. All five cases were reported by a parent/guardian and were not confirmed by a healthcare provider.

Overall, there were no significant findings in infant immune system development.

Overall, 83 SAEs (excluding pregnancy outcomes and malformation associated events only in LBs) were reported in 37 (14.5%) infants. The most frequently reported (≥3%) SAEs were related to the SOC of infections and infestations (9.0%) and respiratory, thoracic and mediastinal disorders (5.1%). One infant reported neonatal sepsis. Two babies had respiratory failure and one case was reported with Kernicterus.

Overall, 120 SAEs (excluding adverse pregnancy outcomes and associated events) were reported in 67 women. The most frequent SOCs for mother SAEs were pregnancy, puerperium and perinatal conditions (9.9% of women, n=30), Nervous system disorders (6.6%, n=20) and infection and infestations (4.3%, n=13). Cervical incompetence, gestational diabetes and pre-eclampsia were the most reported SAEs in 1.7% (n=5) of women each. One maternal death was reported. Other notable SAEs reported include cervical cancer and severe allergic reaction to Copaxone.

11.2 Limitations

There are several limitations to this study.

- GPR was a single arm study. No direct comparator was available to put these results into context.
- 312 women were enrolled in GPR and nine were excluded from the analysis. The limited sample size of infants born to fingolimod-exposed women (164 prospective LBs) and the limited number of infants reported with MCMs result in a MCM prevalence estimate with a wide CI.
    - While this study involves a limited sample size, the study data can be complemented with data obtained from the Novartis pharmacovigilance system, i.e., via the PRegnancy outcomes Intensive Monitoring (PRIM). PRIM has a different study design, but larger sample size (N=1481 pregnancy cases).
- In some instances, cases were conservatively classified as a major malformation when lacking detailed information. When a case was reported by a participant, the reported term was often vague, making adjudication assessment difficult (see Table 10-12). In addition, if a malformation had spontaneously resolved at the 12-month infant follow up, no re-adjudication was performed.
- Comparing results in GPR to external data sources must be done with caution.
    - The source data for published studies that assess adverse pregnancy outcomes in the general population, untreated and treated MS populations vary greatly. These sources include national health registries, nationwide cohorts, claims databases, pregnancy registries, pharmacovigilance databases, single hospital cohorts, and other sources. Data collection methods vary between studies, including primary data collection with an informed consent process, analyzing pharmacovigilance data, and secondary use of claims data. Inclusion and exclusion criteria, time period of data collection and geography covered also vary by study. The MCM classification system used to assess malformations varies by study, making comparisons between studies difficult.
- Per design, selection bias could have occurred, in particular in the US/Canada where the patient self-reported.

- To fully assess the causal relation between fingolimod-exposure *in utero* and MCM, the effect of possible confounders would need to be isolated; based on the current data, this is hard to establish since there is no definitive set of risk factors for MCMs and the information collected may be incomplete (e.g., details of family history).
  - A systematic medical review approach was undertaken to identify risk factors for MCMs. Medical history, active conditions, BMI, age and AEs were reviewed and risk factors identified, irrespective of the outcome in the infant.
  - Smoking and alcohol use, since only partially recorded, were not accounted for.
  - Rather than considering each factor in isolation, risk factors were combined into a composite and the comparison established between patients reported with at least one risk factor vs. no risk factor.
  - Residual confounding (from history of smoking, history of alcohol use during pregnancy or other unmeasured confounding factors) that may have contributed to the MCM cannot be excluded.

11.3 Interpretation

In this registry study, the prevalence of major congenital malformations in infants exposed to fingolimod *in utero* was higher than the EUROCAT background prevalence in the general population. While underlying maternal risk factors (such as maternal age, obesity, gestational diabetes) contributed to the observed increased MCM prevalence, the exact magnitude of this contribution remains unknown due to potential further unmeasured factors.

11.4 Generalizability

A high (91% overall) percentage of LBs was reported. This could be due to the study's required informed consent process and could have excluded early spontaneous abortions from being recruited.

Per design, in the US/Canada the reporter was the patient herself. This may have led to enrollment and reporting biases, as suggested by the higher MCM prevalence in the US/Canada compared with other regions.

To increase the generalizability of GPR, further contextualization using pharmacovigilance data (PRIM study) and the fingolimod unexposed cohort from the German MS Pregnancy Registry will be performed. These additional analyses will help elucidate the contribution of risk factors to MCM prevalence after fingolimod exposure.

12 Conclusion

The prevalence of MCMs in prospective LBs in the GPR, using both the EUROCAT (6.7%; 95% CI: 3.4, 11.7) and MACDP (9.1%; 95% CI: 5.23, 14.6) classification systems, was higher than in the general population (1.77% and 3.0%, respectively), with non-overlapping CIs. The same was observed when prospective and retrospective cases were combined.

Compared to EUROCAT data in LBs, SBs and TOPFA, the prevalence of congenital heart defects, urinary malformations, and limb/musculoskeletal malformations in GPR was greater than in the general population.

A high proportion of participants reported at least one risk factor for MCM, which contributed to the observed increased MCM prevalence.

The higher-than-expected prevalence of cardiovascular, urinary, and limb/musculoskeletal malformations was consistent with previous reports. The prevalence of spontaneous abortions was at the lower end and that of SB in line with what would be expected in the general population and in untreated and treated women with MS with studies of similar designs (e.g., primary data collection with ongoing pregnancy at informed consent).

13 References

Available upon request.

Andersen J B, Wandall-Holm M F, Magyari M, et al (2022) Pregnancy outcomes following maternal or paternal exposure to teriflunomide in the Danish MS population. Multiple sclerosis and related disorders; 59:103529.

Andersen, Johanna Balslev et al (2023) Pregnancy outcomes after early fetal exposure to injectable first-line treatments, dimethyl fumarate, or natalizumab in Danish women with multiple sclerosis. European journal of neurology; 30(1):162-171.

Aris IM, Kleinman KP, Belfort MB, et al (2019) A 2017 US reference for singleton birth weight percentiles using obstetric estimates of gestation. Pediatrics; 144(1): e20190076.

Barataud-Reilhac, A., Kerbrat, S., Roux, J., et al (2020). Teriflunomide-exposed pregnancies in a French cohort of patients with multiple sclerosis. Neurology. Clinical practice; 10(4), 287–297.

Calvert, Clara et al (2023) Changes in preterm birth and stillbirth during COVID-19 lockdowns in 26 countries. Nature human behaviour; 7(4):529-544.

CDC (2008) Update on Overall prelevance of Major Birth Defects-Atlanta, Georgia, 1978-2005. MMWR; 57(1):1-5. Available from:

<https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm> (Accessed 21-Jan-2025).

Chai, Jian et al (2022) Preconception alcohol consumption and risk of miscarriage in over 4.5 million Chinese women aged 20-49 years. BMJ sexual & reproductive health; 48,e1: e53-e59.

Chan, Tien-Ming et al (2023) Fetal-neonatal and maternal outcomes in women with Sjögren syndrome: a population-based registry linkage study. Rheumatology (Oxford, England); 62(8): 2820-2828.

Chen, Po-Hung et al (2023) Trends in the Prevalence of Hepatitis C Infection During Pregnancy and Maternal-Infant Outcomes in the US, 1998 to 2018. JAMA network open; 6,7 e2324770.

Cornette, Jérôme et al (2023) Perinatal mortality and neonatal and maternal outcome per gestational week in term pregnancies: A registry-based study. Acta obstetricia et gynecologica Scandinavica; 102(1): 82-91.

Christianson A, Howson CP, Modell B (2006) March of dimes. Global report on birth defects. The hidden toll of dying and disabled children (Internet) Available from: <http://www.marchofdimes.com/MOD-Report-PF.pdf> (Accessed 10 June 2010).

Dahl J, Myhr KM, Daltveit AK, et al (2005) Pregnancy, delivery, and birth outcome in women with multiple sclerosis. Neurology; 65(12):1961-3.

Dahl J, Myhr KM, Daltveit AK, et al (2008) Pregnancy, delivery and birth outcome in different stages of maternal multiple sclerosis. J Neurol; 255(5):623-7.

EUROCAT (2010) European Surveillance of Congenital Anomalies (EUROCAT). Prevalence data tables (Internet) Available from: <http://www.eurocat-network.eu/accessprevalencedata/prevalencetables > (Accessed 10-June-2010).

EUROCAT (2023) European Surveillance of Congenital Anomalies (EUROCAT). Prevalence data tables (Internet) Available from: <https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en> (Accessed 08-Feb-2023).

EUROCAT Guide 1.5 (2022) European Surveillance of Congenital Anomalies (EUROCAT). Guide 1.5 Chapter 2.2.2 Coding Instructions for Variables (Internet) Available from: https://eu-rd-platform.jrc.ec.europa.eu/system/files/public/eurocat/Guide_1.5_Chapter_2.2.2.pdf (Accessed 19-Sep-2024).

EUROCAT (2024) European Surveillance of Congenital Anomalies (EUROCAT) Population definitions tables. Available from: Available from: <https://eu-rd-platform.jrc.ec.europa.eu/system/files/public/eurocat/Population_definition_%20geographic%20area_stillbirth_definition_upper_TOPFA_limit_max_age_at_diagnosis.pdf> (Accessed 28-Nov-2024)

Faulks, Fiona et al (2023) Perinatal outcomes of socially disadvantaged women in Australia: A population-based retrospective cohort study. BJOG : an international journal of obstetrics and gynaecology;130(11): 1380-1393.

Fink K, Gorczyca A, Alping P, et al (2023) Multiple sclerosis, disease-modifying drugs and risk for adverse perinatal and pregnancy outcomes: Results from a population-based cohort study. Multiple sclerosis journal; 29(6): 731-40.

Finkelsztejn A, Brooks JBB, Paschoal FM, et al (2011) What can we really tell women with multiple sclerosis regarding pregnancy? A systematic review and meta-analysis of the literature. BJOG; 118:790-7.

Garne E, Hansen AV, Birkelund AS, et al (2014) Major congenital anomalies in a Danish region. Dan Med J; 61(6):A4825.

Geissbühler, Y., Rezaallah, B., & Moore, A. (2020) An alternative to product-specific pregnancy registries? PRIM; PRegnancy outcomes Intensive Monitoring. Reproductive toxicology (Elmsford, N.Y.); 94, 13–21.

Gilenya® (fingolimod) (2020) Core data sheet (CDS), Novartis Pharma AG (v4.2, revised December 2020).

Gitman, Victor et al (2022) Pregnancy outcomes of women with multiple sclerosis treated with ocrelizumab in Canada: A descriptive analysis of real-world data. Multiple sclerosis and related disorders; 62: 103792.

Guo T, Wang Y, Zhang H, et al (2018) The association between ambient temperature and the risk of preterm birth in China. Sci Total Environ; 613-614: 439-46.

Greiber, Iben Katinka et al (2022) Cancer in pregnancy and the risk of adverse pregnancy and neonatal outcomes: A nationwide cohort study. BJOG : an international journal of obstetrics and gynaecology; 129(9): 1492-1502.

Hakkarainen, K. M., Juuti, R., Burkill, S., Geissbühler, Y., et al (2020) Pregnancy outcomes after exposure to interferon beta: a register-based cohort study among women with MS in Finland and Sweden. Therapeutic advances in neurological disorders; 13, 1756286420951072.

Hellwig K, Geissbuehler Y, Sabidó M, et al (2020b) Pregnancy outcomes in interferon-beta-exposed patients with multiple sclerosis: results from the European Interferon-beta Pregnancy Registry. J Neurol; 267(6):1715-23.

Henson L J., Afsar S, Davenport L, et al (2020) Pregnancy outcomes in patients treated with leflunomide, the parent compound of the multiple sclerosis drug teriflunomide. Reproductive toxicology; 95:45–50.

Houtchens MK (2007) Pregnancy and multiple sclerosis. Semin Neurol; 27(5):434-41.

Ishitsuka, K., Yamamoto-Hanada, K., Ayabe, T., et al (2019) Risky Health Behaviors of Teenage Mothers and Infant Outcomes in the Japan Environment and Children's Study: A Nationwide Cohort Study. Journal of pediatric and adolescent gynecology; 32(2), 146–152.

Kaplan, Sigal et al (2022) Pregnancy, Fetal, and Infant Outcomes Following Maternal Exposure to Glatiramer Acetate During Pregnancy and Breastfeeding. Drug safety; 45(4): 345-357.

Kaplan S Zeygarnik M, Stern T, et al (2023) Pregnancy and fetal outcomes following maternal exposure to glatiramer acetate in all three trimesters of pregnancy. European journal of neurology; 30(12): 3890-5.

Kelly VM, Nelson LM, Chakravarty EF (2009) Obstetric outcomes in women with multiple sclerosis and epilepsy. Neurology; 73:1831-6.

Kiserud T, Piaggio G, Carroli G, et al (2017) The World Health Organization Fetal Growth Charts: A Multinational Longitudinal Study of Ultrasound Biometric Measurements and Estimated Fetal Weight. PLoS medicine, 14(1):e1002220.

Kröger J, Gunster C, Heller G, et al (2022) Prevalence and Infant Mortality of Major Congenital Malformations Stratified by Birthweight. Neonatology; 119(1): 41-59.

Landi, Doriana et al (2022) Exposure to natalizumab throughout pregnancy: effectiveness and safety in an Italian cohort of women with multiple sclerosis. Journal of neurology, neurosurgery, and psychiatry, jnnp-2022-329657. 30 Sep.

Leray E, Moreau T, Fromont A, et al (2016) Epidemiology of multiple sclerosis. Rev Neurol (Paris); 172(1):3-13.

Liguori N, Klajn D, Acion L, et al (2009) Epidemiological characteristics of pregnancy, delivery, and birth outcome in women with multiple sclerosis in Argentina (EMEMAR study). Mult Scler; 15:555-62.

Luke, Sabrina et al (2022) Cannabis use in pregnancy and maternal and infant outcomes: A Canadian cross-jurisdictional population-based cohort study. PloS one 17,11 e0276824. 23 Nov.

MacDonald SC, McElrath TF, Hernandez-Diaz S (2019a) Pregnancy outcomes in women with multiple sclerosis. Am J Epidemiol; 188(1):57-66.

MacDonald SC, McElrath TF, Hernández-Díaz S (2019b) Use and safety of disease-modifying therapy in pregnant women with multiple sclerosis. Pharmacoepidemiology and drug safety; 28(4), 556–60.

Magnus MC, Morken NH, Wensaas KA, et al (2021) Risk of miscarriage in women with chronic diseases in Norway: A registry linkage study. PLoS medicine; 18(5), e1003603.

Mendelson K, Evans T, Hla T (2014) Sphingosine 1-phosphate signalling. Development; 141: 5-9.

Nguyen AL, Havrdova EK, Horakova D, et al (2019) Incidence of pregnancy and disease-modifying therapy exposure trends in women with multiple sclerosis: A contemporary cohort study. Mult Scler Relat Disord; 28: 235-43.

Pauliat, E., Onken, M., Weber-Schoendorfer, C., et al (2021) Pregnancy outcome following first-trimester exposure to fingolimod: A collaborative ENTIS study. Multiple sclerosis (Houndmills, Basingstoke, England); 27(3), 475–478.

Persson M, Cnattingius S, Villamor E, et al (2017) Risk of major congenital malformations in relation to maternal overweight and obesity severity: cohort study of 1.2 million singletons. BMJ; 357:j2563.

Platzbecker, Katharina et al (2022) Fingolimod, teriflunomide and cladribine for the treatment of multiple sclerosis in women of childbearing age: description of drug utilization and exposed pregnancies in Germany. Multiple sclerosis and related disorders; 67: 104184.

Portaccio E, Annovazzi P, Ghezzi A, et al (2018) Pregnancy decision-making in women with multiple sclerosis treated with natalizumab: I: Fetal risks. Neurology; 90: e823-e831.

Reitzle, Lukas et al (2023) Pregnancy Complications in Women With Pregestational and Gestational Diabetes Mellitus. Deutsches Arzteblatt international; 120(6): 81-86.

Sandberg-Wollheim, M, Neudorfer, O, Grinspan, A, et al. (2018) Pregnancy Outcomes from the Branded Glatiramer Acetate Pregnancy Database. Int J MS Care; 20(1), 9–14.

Sospedra M, Martin R (2005) Immunology of multiple sclerosis. Annu Rev Immunol; 23:683-747.

Süüden, Eva-Liina et al (2023) The prevalence of congenital anomalies: nationwide study in 2020 in Estonia. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians; 36(2): 2259050.

Tanner, Darren et al (2023) Risk factors for late (28+ weeks' gestation) stillbirth in the United States, 2014-2015. PloS one; 18,8 e0289405. 30 Aug.

Tavares Da Silva F, Gonik B, McMillan M, et al (2016) Brighton Collaboration Stillbirth Working Group. Stillbirth: Case definition and guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine; 34(49):6057-68.

Tillaut, Hélène et al (2022) Pregnancy in women with multiple sclerosis in France from 2010 to 2015: Incidence, outcomes, and exposure to disease-modifying therapies. Multiple sclerosis (Houndmills, Basingstoke, England); 28(5): 778-789.

Trapp BD, Peterson J, Ransohoff RM, et al (1998) Axonal transection in the lesions of multiple sclerosis. N Engl J Med; 338(5):278-85.

Voigt M, Rochow N, Schneider KTM, et al (2014) New percentile values for the anthropometric dimensions of singleton neonates: analysis of perinatal survey data of 2007-2011 from all 16 states of Germany. Gerburtsh Neonatol; 218: 210-7.

Volpi C, Orabona C, Macchiarulo A, et al (2019) Preclinical discovery and development of fingolimod for the treatment of multiple sclerosis. Expert Opin Drug Discov; 14(11):1199-212.

Vukusic, S., Coyle, P. K., Jurgensen, S., et al (2020) Pregnancy outcomes in patients with multiple sclerosis treated with teriflunomide: Clinical study data and 5 years of post-marketing experience. Mult Scler; 26(7), 829–836.

Weber-Schoendorfer C, Schaefer C (2009) Multiple sclerosis, immunomodulators, and pregnancy outcome: a prospective observational study. Mult Scler; 15(9):1037-42.

World Health Organization (WHO) (2008) Atlas. Multiple sclerosis resources in the world 2008 (Internet) Available from:

<https://iris.who.int/bitstream/handle/10665/43968/9789241563758_eng.pdf?sequence=1> (Accessed 28-Nov-2024)

Worthington J, Jones R, Crawford M, et al (1994) Pregnancy and multiple sclerosis--a 3-year prospective study. J Neurol; 241(4):228-33.

Zīle I, Villeruša A, Gissler M (2014) Monitoring of Congenital Anomalies in Latvia. Cent Eur J Public Health; 22(3):147-152.

Reason for signing: I confirm this document is ready for submission/publication	Name: [redacted] Role: Author Date of signature: 18-Feb-2025 14:01:51 GMT+0000
Reason for signing: I confirm this document is ready for submission/publication	Name: [redacted] Role: Approver Date of signature: 18-Feb-2025 14:54:32 GMT+0000
Reason for signing: I confirm this document is ready for submission/publication	Name: [redacted] Role: Approver Date of signature: 18-Feb-2025 18:11:43 GMT+0000

Signature Page for: cfty720d2404--report-body
VV-TMF-7988805 v 1 . 0