Study Design of a Multinational Gilenya™ (Fingolimod) Pregnancy Exposure Registry

GILENYA Pregnancy Registry

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CONCLUSIONS

- **No structural or functional defects have been reported to date in any of the few known pregnancy outcomes of patients enrolled in the Gilenya Pregnancy Registry.**
- **Due to limited sample size from fingolimod clinical trials, postmarketing settings, and registry data, it is not yet possible to draw any firm conclusions regarding pregnancy outcomes.**
- **The Gilenya Pregnancy Registry is still ongoing, and the findings will provide further reliable safety data on the effect of fingolimod on pregnancy and fetal outcomes.**
- **These findings will be useful to physicians for treating and counseling women with multiple sclerosis who have been on fingolimod or may be exposed to fingolimod during pregnancy.**

INTRODUCTION

- Multiple sclerosis (MS) is a chronic inflammatory neurologic condition with average onset age of 29 years[1] and is approximately 3-fold more common in women than in men; thus, many patients are of childbearing age when diagnosed with the disease.
- Fingolimod, a first-in-class sphingosine 1-phosphate receptor modulator, was the first oral therapy approved in the United States and more than 60 other countries for treatment of relapsing MS.[a]
- Preclinical data suggest a potential fetal risk; however, currently available data are insufficient to draw reliable conclusions regarding the effect of fingolimod on the human fetus.
- As per current label, use of effective contraception during, and for 2 months after stopping, fingolimod therapy is recommended.
- As of August 2012, 219 pregnancies have been reported from fingolimod clinical trials and postmarketing settings with the following outcomes:
  - 59 normal newborns
  - 60 abortions (39 induced, 21 spontaneous)
  - 80 pregnancies are ongoing for which outcome is unknown
  - 12 pregnancies lost to follow-up
  - 5 congenital anomalies (1 case each of unilateral congenital posteromedial bowing of tibia, acrania, tetralogy of Fallot [led to induced abortion], premature birth with large patent ductus arteriosus, and vesicoureteric reflux)
  - 3 other pregnancy abnormalities (1 blighted ovum, 2 ectopic pregnancies)
- The rate of congenital anomalies reported in the Novartis safety database are: 2.3% having all pregnant patients as denominator; 3.9% when excluding patients with ongoing pregnancies, pregnancy outcome unknown or lost to follow-up; and 6.3% when considering only live births.
  - Depending on denominator definitions, corresponding rates from the general population are approximately 6.9% (including live births, stillbirths, spontaneous and induced abortions[2]) and 3% (in live births[3,4]).
  - As a note of caution, passive monitoring systems like EUROCAT tend to capture only approximately 50% of the true number of congenital malformations as active birth registries do.[2]
- Due to small sample size, no firm conclusions can be drawn (n=127, excluding patients with unknown pregnancy outcome, and n=63 considering only live births).
- The Gilenya Pregnancy Registry will help obtain prospectively and systematically collected data on the potential pregnancy outcome and fetal effects associated with exposure to fingolimod during pregnancy, as opposed to relying only on spontaneous adverse event reports.

OBJECTIVE

- The main objective of the registry is to prospectively collect and evaluate safety data on maternal, fetal, and infant outcomes associated with exposure to fingolimod before (up to 8 weeks before last menstrual period [LMP]) and during pregnancy and compare it with an external reference population.

[a]The approved indication may vary from country to country. In the United States, it is approved for the treatment of patients with relapsing forms of MS. In the EU, fingolimod is approved for treatment of patients with highly active relapsing-remitting MS.

METHODS

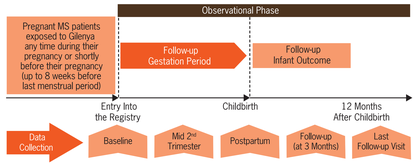
Patients

- Pregnant MS patients with confirmed or suspected maternal exposure to fingolimod any time during pregnancy or shortly before pregnancy willing to participate in the registry are included; no specific exclusion criteria.

Registry Design

- Multinational, prospective, observational study in collaboration between National Coordinating Sites, Sentinel Sites and Quintiles Outcome, a contract research organization conducting this registry on behalf of Novartis Pharma AG **(Figure 1)**
  - Approximately 500 pregnant women will be enrolled.

Figure 1. Registry design



Outcomes

The following and more data will be collected:

- Family history of congenital anomalies/birth defects and pregnancy complications or poor outcomes; maternal smoking history, alcohol use, and recreational drug use
- Overall pregnancy outcomes: spontaneous fetal loss, stillbirth and induced abortion, and other complications during pregnancy
- Major malformations: any structural defect with surgical, medical, or cosmetic importance recognized
- Minor congenital anomalies: anomalies with no serious medical or cosmetic consequence to the offspring
- Adverse effects on the physical and immune system development of the offspring up to 1 year post partum

Analysis

- Descriptive statistics will be used to summarize the findings, specifically, overall frequency (proportion, 95% confidence interval) of major malformations, which will be compared with prevalence reported in national surveillance programs and registries.[2-4]

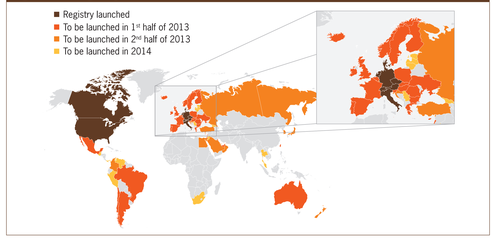
Enrollment

- Any eligible patient who wants to participate or any health care professional with an eligible patient is invited to contact the registry team. Contacting the team at the beginning of the pregnancy is appreciated to allow prospective enrollment.
- **Registry contact information**
  - Website: www.gilenyapregnancyregistry.com or www.gpregnancy.com
  - Email: gpr@outcome.com
  - Telephone numbers
    - For North America: +1-877-598-7237 (toll-free)
    - For outside North America: +800-688-266-37 (toll-free)
- Further details on the study and the enrollment procedures will be provided on contact.

RESULTS

- As of February 2013, the Gilenya Pregnancy Registry has been launched in 10 countries: United States, Canada, Czech Republic, Germany, Austria, Denmark, Netherlands, Switzerland, Italy, and Liechtenstein **(Figure 2)**.

Figure 2. Registry launch worldwide



- As of February 28, 2013, 16 women aged 24–43 years at LMP have been enrolled (9 US, 7 EU) **(Table 1)**.
  - 14 women still participating, 1 completed the study (elective termination), and 1 withdrew consent, which led to discontinuation from the registry
- Information on maternal demographics and pregnancy information **(Table 1)**, MS history **(Table 2)**, and pregnancy history **(Table 3)** at enrollment are presented.
- Out of 5 known pregnancy outcomes (1 elective termination and 4 full-term births), no congenital anomalies were reported.

Table 1. Pregnancy information at enrollment

	Patients enrolled prospectively (N=6)	Patients enrolled retrospectively (N=10)	All enrolled (N=16)
Age at LMP, y			
n	5	5	10
Mean (SD)	31.7 (7.0)	32.2 (4.2)	31.9 (5.7)
Gestational age, d			
n	5	4	9
Mean (SD)	89.8 (30.9)	147.8 (73.0)	115.6 (61.1)
Timing of exposure in pregnancy, n (%)*			
n	4	4	8
Peri-LMP	4 (100.0)	2 (50.0)	6 (75.0)
First trimester	3 (75.0)	4 (100.0)	7 (88.0)
After first trimester	1 (25.0)	1 (25.0)	2 (25.0)
During all pregnancy	1 (25.0)	0 (0.0)	1 (13.0)

Note: Patients enrolled signed informed consent form, but data for some of these patients are not available.
**One patient can be in more than one category. The patient exposed during all pregnancy had a planned elective termination.*
LMP=last menstrual period; N=number of patients enrolled; n=number of patients with available data.

Table 2. Multiple sclerosis disease history

	Patients enrolled prospectively (N=6)	Patients enrolled retrospectively (N=10)	All enrolled (N=16)
Age at MS diagnosis, y			
n	5	5	10
Mean (SD)	25.4 (7.6)	26.6 (4.8)	26.0 (6.4)
Age at onset of MS symptoms, y			
n	5	5	10
Mean (SD)	24.4 (8.1)	25.8 (5.6)	25.1 (7.0)
Duration of MS since diagnosis at enrollment, y			
n	5	4	9
Mean (SD)	6.5 (3.0)	5.0 (3.6)	5.8 (3.3)
Time since the most recent relapse prior to enrollment, mo			
n	5	4	9
Mean (SD)	20.9 (8.8)	10.4 (2.1)	16.2 (8.5)
Most recent EDSS score prior to enrollment			
n	1	2	3
Mean (SD)	3.0 (0.0)	2.5 (0.5)	2.7 (0.5)

Note: Patients enrolled signed informed consent form, but data for some of these patients are not available.
EDSS=Expanded Disability Status Scale; MS=multiple sclerosis; N=number of patients enrolled; n=number of patients with available data.

Table 3. Pregnancy history*

	Patients enrolled prospectively (N=6)	Patients enrolled retrospectively (N=10)	All enrolled (N=16)
Previous medically recognized pregnancies, n (%)			
n	5	5	10
0	3 (60.0)	1 (20.0)	4 (40.0)
1	1 (20.0)	1 (20.0)	2 (20.0)
2	0 (0.0)	3 (60.0)	3 (30.0)
3 or more	1 (20.0)	0 (0.0)	1 (10.0)
Term live births (≥37 wk), n (%)			
n	2	4	6
0	0 (0.0)	2 (50.0)	2 (33.3)
1	1 (50.0)	0 (0.0)	1 (16.7)
2	1 (50.0)	2 (50.0)	3 (50.0)
3 or more	0 (0.0)	0 (0.0)	0 (0.0)
Elective terminations, n (%)			
n	2	4	6
0	1 (50.0)	2 (50.0)	3 (50.0)
1	1 (50.0)	2 (50.0)	3 (50.0)
2 or more	0 (0)	0 (0)	0 (0)
Obstetric complications in previous pregnancies, n (%)			
n	2	3	5
None	2 (100.0)	2 (66.7)	4 (80.0)
Pre-eclampsia/eclampsia	0 (0.0)	1 (33.3)	1 (20.0)
Rh incompatibility	0 (0.0)	1 (33.3)	1 (20.0)
Viral infection	0 (0.0)	0 (0.0)	0 (0.0)
Bacterial infection	0 (0.0)	0 (0.0)	0 (0.0)
Adverse fetal outcomes in previous pregnancies, n (%)			
n	2	3	5
None	2 (100.0)	2 (66.7)	4 (80.0)
Congenital anomalies/birth defects	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1† (33.3)	1 (20.0)

Note: Patients enrolled signed informed consent form, but data for some of these patients are not available.
**No cases reported for spontaneous losses/miscarriages and fetal death/stillbirths.*
†In one previous pregnancy, amblyopia, patent ductus arteriosus, and torticollis were reported as adverse fetal outcome.
N=number of patients enrolled; n=number of patients with available data.

References

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Disclosures

Yvonne Geissbuehler is an employee of Novartis Pharma AG, Basel, Switzerland.
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Ron Hashmonay and **Simrat Randhawa** are employees of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.

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