An International Registry Tracking Pregnancy Outcomes in Women Treated With Dimethyl Fumarate

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Conclusions

- Consistent with previous reports,[4,5] no safety signal was observed for DMF exposure in relation to pregnancy outcomes based on data from an interim analysis of this ongoing international registry.
- The rate of spontaneous abortions from the interim analysis was similar to the rate observed in clinical trials of DMF (8%)[5] and below the estimated rates (12–16%)[10] in the general population.
- The rate of birth defects from the interim analysis was similar to the rate observed in the MS population (4%)[11] and the general population (2–5%).[12-14]
- Ongoing recruitment to this registry, including additional enrollment in the United Kingdom and Ireland, will provide essential information on pregnancy outcomes among women exposed to DMF during pregnancy.

Introduction

- Delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) demonstrated strong efficacy and a favorable benefit-risk profile in Phase 3 studies of patients with relapsing-remitting multiple sclerosis (MS).[1,2]
- As of 30 June 2019, > 415,000 patients have been treated with DMF, representing > 780,000 patient-years of exposure. Of these, 6335 patients (14,065 patient-years) were from clinical trials.
- Nearly two-thirds of patients with MS are women,[3] many of whom are in their childbearing years.
- Available data from clinical trials and postmarketing reports have not demonstrated any safety signals with DMF exposure during pregnancy; however, experience remains limited.
  - In clinical trials, no increased risk of fetal abnormalities or adverse pregnancy outcomes was observed; pregnancy outcomes have been reported in 142 DMF-treated patients as of 26 March 2018: n = 97 (68%) live births, n = 5 (4%) preterm births, n = 16 (11%) spontaneous abortions, and n = 24 (17%) elective terminations.[4]
  - In the postmarketing setting, less than half of all known pregnancies have outcomes reported, suggesting potential reporting biases[5]; however, in the total pregnancy outcomes reported (n = 1481), no increased risk of fetal abnormalities or adverse pregnancy outcomes has been observed.[4]
- The DMF product label recommends use during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Objectives

- The objective of this interim analysis is to assess pregnancy outcomes in an ongoing international registry (NCT01911767) of women with MS exposed to DMF since the first day of their last menstrual period before conception, or at any time during pregnancy. Overall, as well as UK- and Ireland-specific, pregnancy outcomes are presented.

Methods

Patients and Registry Design

- This prospective observational registry is anticipated to enroll a minimum of 300 pregnancy outcomes among 310–375 pregnant women with MS (Figure 1); this interim analysis included data as of 08 April 2019.

Endpoints and Outcome Measures

- Women who were exposed to DMF from the first day of their last menstrual period before conception or at any time during pregnancy and who are participating in the registry are prospectively evaluated for:
  - Live births (premature birth and full-term birth)
  - Pregnancy loss (elective or therapeutic pregnancy terminations; spontaneous abortions; and fetal death, including stillbirth)
  - Ectopic and molar pregnancies, birth defects, or congenital anomalies (including minor anomalies) occurring at ≤ 52 weeks of age
  - Any infant death occurring at ≤ 52 weeks of age
  - Any maternal death occurring ≤ 12 weeks after delivery.
- Potential birth defects are adjudicated by an external teratology expert.

Statistical Analysis

- Gestational weight was classified based on World Health Organization or country-specific growth charts as small (birth weights < 2500 grams), appropriate (birth weights 2500–4000 grams); and large (birth weights > 4000 grams).
- The prevalence of birth defects, spontaneous abortions, and 95% CIs for the registry population were calculated for this interim analysis.

Results

Patient Demographics and DMF Exposure

- As of 08 April 2019, 263 women (12 from the United Kingdom and 2 from Ireland) were enrolled in the registry; mean (SD) age was 32 (4) years (Table 1).
- A total of 71 women had a pregnancy with incomplete follow-up (Figure 2).
- Earliest DMF exposure occurred in the first (99.6%; 251/252), second (0.4%; 1/252), and third (0%) trimesters in the 252 women with a known exposure date (Table 1).
  - Median gestational week at first DMF exposure was 1 (range, 0.7–12.7) week and mean (SD) was 1.2 (1.1) weeks. All but 1 infant had exposure in the first trimester.

Pregnancy Outcomes

- In this interim analysis, 214 pregnancy outcomes were reported, including 197 (92%) live births (Figure 2), 16 (7%) spontaneous abortions, and 1 stillbirth at ≥ 28 weeks of gestational age (Table 2). There were 4 sets of twins born.
  - Of the 12 births reported in the United Kingdom and Ireland, all were live births.
- One ectopic pregnancy was reported, although an outcome has not been reported. One neonatal death was reported and no maternal or perinatal deaths were reported.

Infant Status

- Of the 197 births with known gestational age reported in this interim analysis, the majority, 176 (89%), were full term (Figure 2). All United Kingdom and Ireland births were full term (n = 12).
- Seven (4%) infants had adjudicator-confirmed birth defects: 2 with ventricular septal defect (including 1 in the United Kingdom/Ireland); 1 with congenital hydronephrosis; 1 with pyloric stenosis; 1 with transposition of the great vessels; 1 with unilateral developmental dysplasia of the hip (from the United Kingdom/Ireland); and 1 premature newborn had multiple birth defects. For context, the prevalence of ventricular septal defect is estimated to range from 192 to 1045 per 100,000 live births.[6-9]
- Of the 163 infants with neonatal weight data, the majority, 134 (82%), were classified as appropriate (birth weights 2500–4000 grams; Figure 3).

Registry Information

- The UK coordinating center, based at the Manchester Centre for Clinical Neurosciences, and the Ireland coordinating center, based at St. Vincent's University Hospital, Dublin, liaise directly with DMF-exposed patients and their health care professionals in their respective countries. All registry centers and lead investigators are listed in Table 3.

Figure 1. Patients and Registry Design

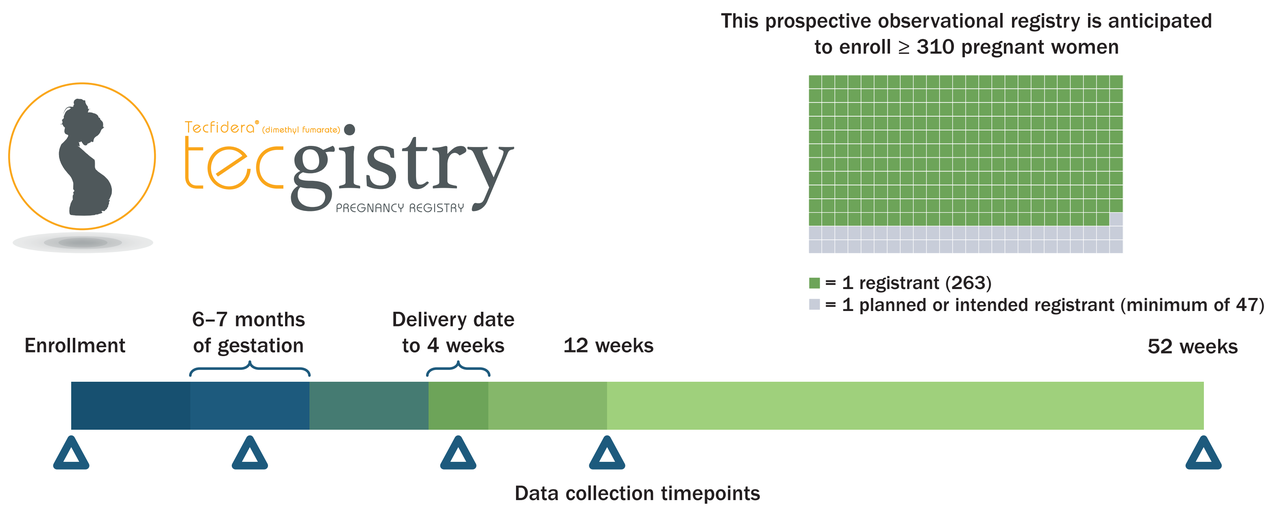
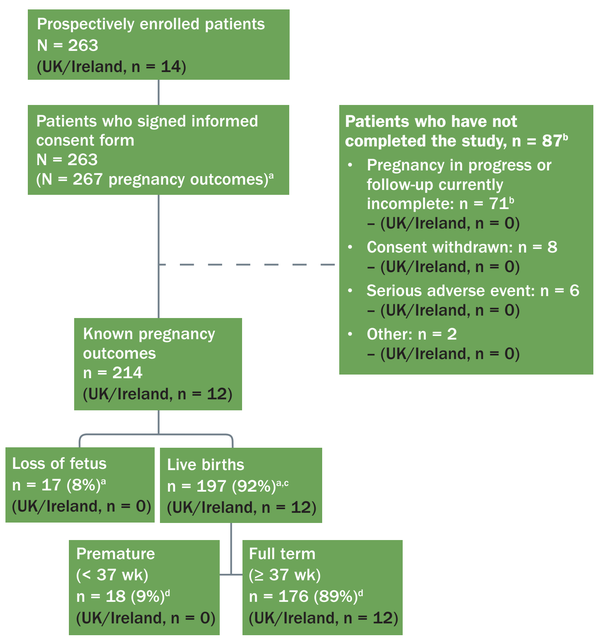
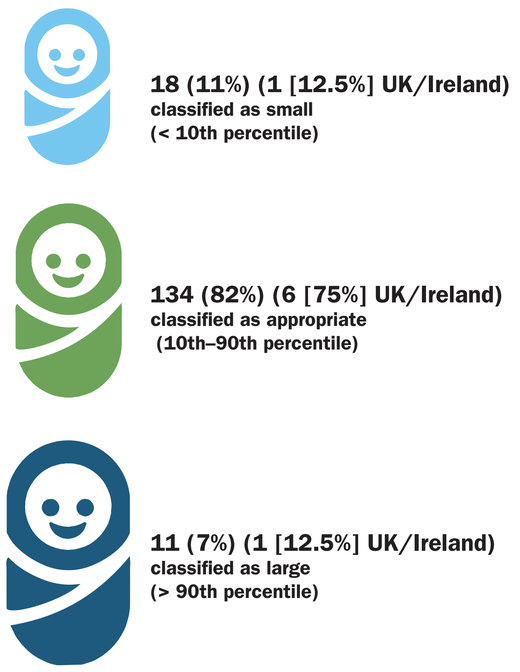


Figure 2. Pregnancy Outcomes Update



[a]Four pregnancies resulted in multiple (twin) births.
[b]Some patients may have known pregnancy outcomes but further follow-up is in progress or not yet complete. For the UK/Ireland data, there are 12 known outcomes and 2 patients where the data were unavailable in the database at the time of the data cut.
[c]Percentages based on births with available premature or live birth status; n = 194 because 3 patients had missing data.
[d]Percentages based on live births with known gestational age (n = 197).

Figure 3. Gestational Size[a]



[a]Percentages were based on births with available gestational size data; gestational size was classified based on World Health Organization or country-specific growth charts.
Total n = 197; 34 infants were missing gestational data; 163 infants had gestational size data.
Size for gestational age: small (birth weights < 2500 grams); appropriate (birth weights 2500–4000 grams); large (birth weights > 4000 grams).

Table 1. Patient Characteristics and DMF Exposure

Characteristic	Patients From the UK/Ireland n = 14	All Patients N = 263
Age, y		
Mean (SD)	33 (4)	32 (4)
Range	25–39	22–43
Race, n (%)		
White		40 (15)
Black		14 (5)
Other		5 (2)
Not reported due to confidentiality regulations	14 (100)	204 (78)
Education, y		
Mean (SD)	13 (1)	14 (3)[a]
Range	11–14	9–23[a]
Employment status, n (%)		
Full-time	4 (29)	135 (53)[b]
Part-time	4 (29)	65 (25)[b]
Unemployed	6 (43)	55 (22)[b]
Earliest DMF exposure, n (%)		
First	14 (100)	251 (99.6)[c]
Second	0	1 (0.4)[c]
Third	0	0

DMF = delayed-release dimethyl fumarate
[a]n = 113.
[b]n = 255.
[c]n = 252.

Table 2. Incidence of Maternal and Fetal Deaths and Birth Defects[a]

Parameter, n (%)	Known Pregnancy Outcomes: Patients From the UK/Ireland n = 12	Known Pregnancy Outcomes: Overall N = 214
Elective or therapeutic pregnancy termination	0	0
Spontaneous abortion, n (%)[b]	0	16 (7)
Stillbirth[c]	0	1 (0.4)
Molar pregnancy	0	1 (0.4)
Ectopic pregnancy	0	0
Maternal death	0	0
Neonatal death[d]	0	1 (0.5)[d]
Perinatal death	0	0
Infant death	0	0
Adjudicator-confirmed birth defects, n (%)[e]		7 (4)
Ventricular septal defect	1	2
Congenital hydronephrosis	0	1
Premature newborn with multiple birth defects	0	1
Pyloric stenosis	0	1
Transposition of the great vessels	0	1
Unilateral developmental dysplasia of the hip	1	1

[a]As of the interim data cut.
[b]Spontaneous abortion was defined as any loss of a fetus due to natural causes at < 22 weeks of gestation; percentage based on 259 reported pregnancy outcomes.
[c]Late fetal loss = fetal death at ≥ 28 weeks of gestation; percentage based on 259 reported pregnancy outcomes.
[d]Percentage based on 197 live births.
[e]Multiple defects applied to 1 infant; there were 7 affected infants of the 200 births known from all data sources (3.5%; 95% CI, 1.4–7.1).

Table 3. Registry Centers[a]

Country	Lead Investigator	Center Name
Australia	Helmut Butzkueven	Box Hill Hospital
Canada	Kristen Hahn	IQVIA North American Coordinating Center
Germany	Kerstin Hellwig	St. Josef-Hospital Universitaetsklinikum
Ireland	Christopher McGuigan	St. Vincent's University Hospital
Italy	Maria Pia Amato Lucia Moiola Antonio Uccelli Salvatore Cottone Claudio Gasperini	Azienda Ospedaliera Universitaria Careggi Ospedale San Raffaele Azienda Ospedaliero Universitaria San Martino AO Ospedali Riuniti Cervello - Presidio Villa Sofia Azienda Ospedaliera San Camillo Forlanini
Spain	Fernandez Sanchez Victoria Eugenia	Hospital Regional Universitario de Malaga
United Kingdom	David Rog	Salford Royal NHS Foundation Trust Manchester Centre for Clinical Neurosciences
United States	Kristen Hahn	IQVIA North American Coordinating Center

[a]To register a patient for the pregnancy registry or learn more, please contact the center in your country or, if in the United States, visit https://www.tecfiderapregnancyregistry.com/.

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