TecGistry: An Interim Analysis of the Dimethyl Fumarate Pregnancy Exposure Registry in the UK and Ireland

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Conclusions

- Among the 161 pregnancy outcomes reported worldwide, 9 were in the UK/Ireland. Four birth defects have been reported worldwide, 1 of which occurred in the UK/Ireland. Consistent with previous reports,[4,6] there was no safety signal for DMF exposure on pregnancy outcomes based on data from an interim analysis of this ongoing registry.
  - The rate of spontaneous abortions from the interim analysis was similar to the rate observed in clinical trials of DMF (8%)[6] and below the estimated rates (12–16%)[7] in the general global population.
  - The rate of birth defects from the interim analysis was similar to the rate observed in the MS population (4%)[8] and the general population (2–5%).[9-11]
- Final results, including additional enrolment in the UK/Ireland, will provide information for women concerning DMF safety during pregnancy.
- Networks of MS specialists throughout the UK/Ireland continue to be valuable in identifying and referring potential patients into this registry.

Introduction

- Delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) demonstrated strong efficacy and a favourable benefit-risk profile in Phase 3 studies of patients with relapsing-remitting multiple sclerosis (MS).[1,2]
- Nearly two-thirds of patients with MS are women,[3] many of them in their childbearing years.
- Available data from clinical trials and post-marketing reports have not demonstrated any safety signals with DMF exposure during pregnancy; however, experience remains limited.
  - In clinical trials, no increased risk of foetal abnormalities or adverse pregnancy outcomes was observed; pregnancy outcomes have been reported in 93 DMF-treated patients as of 26 March 2017: n=62 (67%) live births, n=9 (10%) spontaneous abortions and n=14 (15%) elective terminations.[4]
- Given the limited available data at the time of approval, the DMF product label recommends use during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Objectives

- An interim analysis of 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.
- The objective of this poster is to report on pregnancy outcomes in patients enrolling in the registry from the UK and Ireland.

Methods

Patients and Registry Design

- This prospective observational registry is anticipated to enrol a minimum of 300 pregnant women with MS (Figure 1); this interim analysis included data as of 24 April 2018.

Endpoints and Outcome Measures

- Women participating in the registry who were exposed to DMF from the first day of their last menstrual period before conception, or at any time during pregnancy, are prospectively evaluated for:
  - Live births (premature birth and full-term birth);
  - Pregnancy loss (elective or therapeutic pregnancy terminations, spontaneous abortions and foetal 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 and any maternal death occurring ≤12 weeks post delivery.
- Potential birth defects are adjudicated by an external teratology expert. Other negative pregnancy outcomes will be similarly examined as the sample size permits.

Statistical Analysis

- Gestational size was classified based on World Health Organization or country-specific growth charts, if available.
- The prevalence of birth defects and spontaneous abortions and 95% CIs for the registry population were calculated for this interim analysis.

Results

Patient Demographics and DMF Exposure

- As of 24 April 2018, 220 women (11 from the UK/Ireland) were enrolled in the registry; mean (SD) age was 32 (4) years (Table 1).
- Globally, 23 women discontinued from the registry, 14 due to loss of foetus, 7 due to consent withdrawn and 2 due to other; 50 have a pregnancy in progress or had a pregnancy with an unknown outcome (Figure 2).
- Earliest DMF exposure occurred in the first (100%; 214/215), second (<1%; 1/215) and third (0%) trimesters in the 215 women with a known exposure date (Table 1).

Pregnancy Outcomes

- In this interim analysis, 161 pregnancy outcomes were reported, including 147 (91%) live births and 14 (9%) loss of foetus. In the UK/Ireland, 9 pregnancy outcomes were reported (Table 2).
- No ectopic or molar pregnancies were reported. No maternal, neonatal, perinatal or infant deaths or still births were reported (Table 2).

Infant Status

- Of the 147 live births reported in this interim analysis, the majority, 133 (90%), were full term. Of the 9 pregnancy outcomes reported in the UK/Ireland, all were live births; 8 were full term and none were premature (details on 1 case pending; Figure 2).
- Four (2%) infants had adjudicator-confirmed birth defects: 1 with pyloric stenosis, 1 with transposition of the great vessels and 2 with ventricular septal defect (including 1 in the UK/Ireland). For context, prevalence of ventricular septal defect is estimated to be 42/10,000 live births.[5]
- Of the 122 infants with gestational size data, the majority, 102 (84%), were classified as appropriate (Figure 3).

Registry Information

- The UK Coordinating Centre, based at the Manchester Centre for Clinical Neurosciences, and the Ireland Coordinating Centre, based at St. Vincent's University Hospital, Dublin, liaise directly with DMF-exposed patients and their healthcare professionals in their respective countries. All registry centres and lead investigators are listed in Table 3. To register a patient for the pregnancy registry or to learn more, please contact the centre in your country or, if in the United States, visit https://www.tecfiderapregnancyregistry.com/.

Figure 1. Patients and registry design

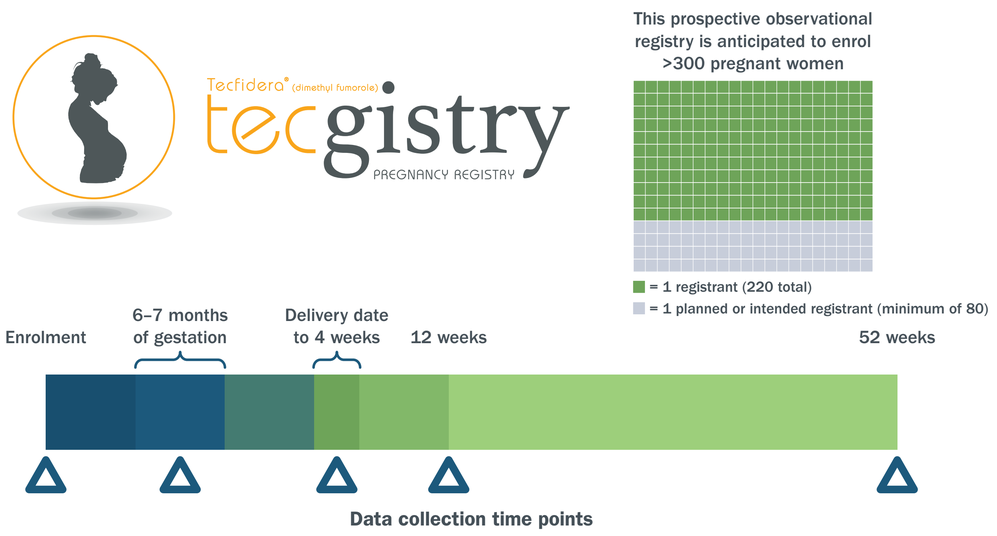
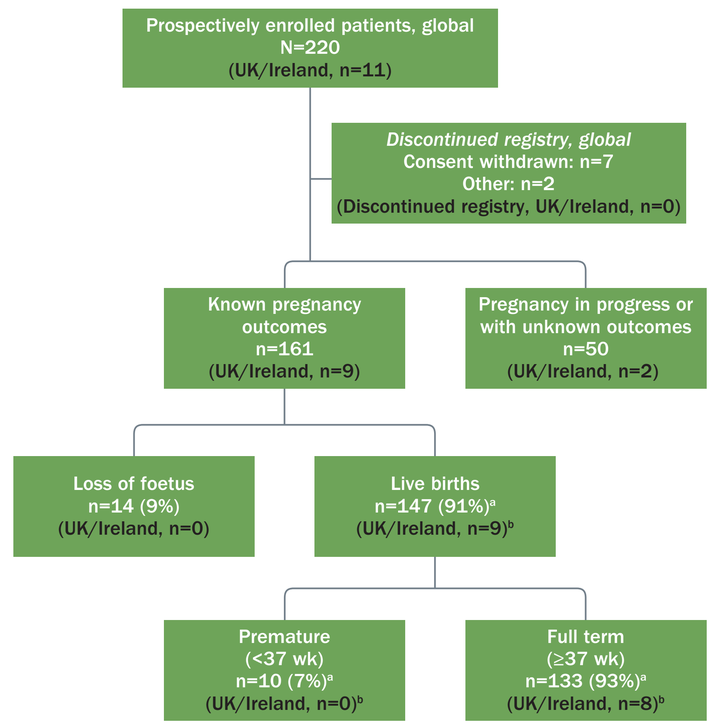


Table 1. Patient characteristics and DMF exposure

Characteristic	Patients in the UK/Ireland n=11	All patients N=220
Age, y[a]		
Mean (SD)	34 (4)	32 (4)
Median (min, max)	35 (29, 39)	32 (22, 42)
Race, n (%)[a]		
White	0	38 (17)
Black	0	10 (5)
Other	0	4 (2)
Not reported due to confidentiality regulations	11	168 (76)
Education, y[b]		
Mean (SD)	13 (1)	14.6 (2.6)
Median (min, max)	13 (11, 14)	14 (10, 23)
Employment status, n (%)[c]		
Full time	3 (27)	108 (51)
Part time	4 (36)	54 (26)
Unemployed	4 (36)	50 (24)
Earliest DMF exposure, n (%)[d]		
First	–	214 (100)
Second	–	1 (1)
Third	–	0

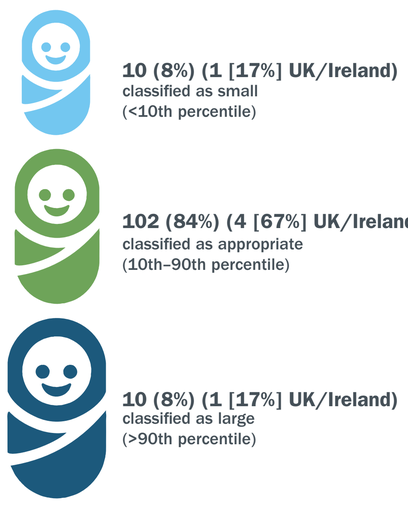
DMF = delayed-release dimethyl fumarate; max = maximum; min = minimum
[a]n=220
[b]n=90
[c]n=212
[d]n=215; 5 patients did not have a date of first exposure to DMF reported

Figure 2. Pregnancy outcomes update



[a]Percentages based on births with available premature or full-term birth status; 4 births were not reported as full-term or premature
[b]Percentages based on births with available premature or full-term birth status; 1 birth was not reported as full-term or premature

Figure 3. Gestational size, global patients and UK/Ireland patient cohort[a]



[a]Percentages based on births with available gestational size data; gestational size was classified based on World Health Organization or country-specific growth charts

Table 2. Incidence of maternal and foetal deaths and birth defects[a]

	Enrolled patients N=220	Patients in the UK/Ireland n=11
Elective or therapeutic pregnancy termination	0	0
Spontaneous abortion, n (%)[b,c]	13 (6)	0
Ectopic pregnancy	0	0
Molar pregnancy	0	0
Maternal death	0	0
Neonatal death	0	0
Perinatal death	0	0
Infant death	0	0
Still birth	0	0
Adjudicator-confirmed birth defects, n (%)[c]	4 (2)	1 (1)
Ventricular septal defect	2	1
Pyloric stenosis	1	–
Transposition of the great vessels	1	–

[a]As of the interim data cut
[b]Spontaneous abortion was defined as any loss of a foetus due to natural causes at <22 weeks of gestation
[c]n=161 (known pregnancy outcomes)

Table 3. Registry centres[a]

Country	Lead investigator	Centre name	No. of sites	Enrolled patients, n (%)
Australia	Helmut Butzkueven	Box Hill Hospital	1	5 (2)
Canada	Kristen Hahn	IQVIA North American Coordinating Center	1	2 (1)
Germany	Kerstin Hellwig	St. Josef-Hospital Universitaetsklinikum	1	147 (67)
Ireland	Christopher McGuigan	St Vincent's University Hospital	1	1 (<1)
Italy	Maria Pia Amato Lucia Moiola Antonio Uccelli Salvatore Cottone Claudio Gasperini	Azienda Ospedaliera Universitaria Careggi Ospedale San Raffaele Azienda Ospedaliera Universitaria San Martino AO Ospedali Riuniti Cervello - Presidio Villa Sofia Azienda Ospedaliera San Camillo Forlanini	2	5 (2)
Spain	Fernandez Sanchez Victoria Eugenia	Hospital Regional Universitario de Malaga	0	0
United Kingdom	David Rog	Salford Royal NHS Foundation Trust Manchester Centre for Clinical Neurosciences	1	10 (5)
United States	Kristen Hahn	IQVIA North American Coordinating Center	1	50 (23)

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

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