Efficacy and Safety in Phase 3 EVOLVE-MS-1 After Switching from Glatiramer Acetate or Interferon or Continuing on Diroximel Fumarate

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OBJECTIVE

- **To evaluate efficacy, safety, and tolerability of diroximel fumarate (DRF) in patients with relapsing forms of multiple sclerosis (MS) in the Phase 3 EVOLVE-MS-1 study who had switched from prior glatiramer acetate (GA) or interferons (IFN).**

CONCLUSIONS

- **Patients who received GA or IFN as their most recent disease-modifying therapy (DMT) experienced improvements in clinical and radiological measures of disease activity with up to 2 years of DRF treatment.**
- **Rates of treatment discontinuation due to GI adverse events (AEs) were low (< 1%).**
- **These data suggest that transition to DRF from GA or IFN is a reasonable treatment strategy with low rates of discontinuation, similar to the favorable results observed after transition from DMF to DRF.[1]**

Introduction

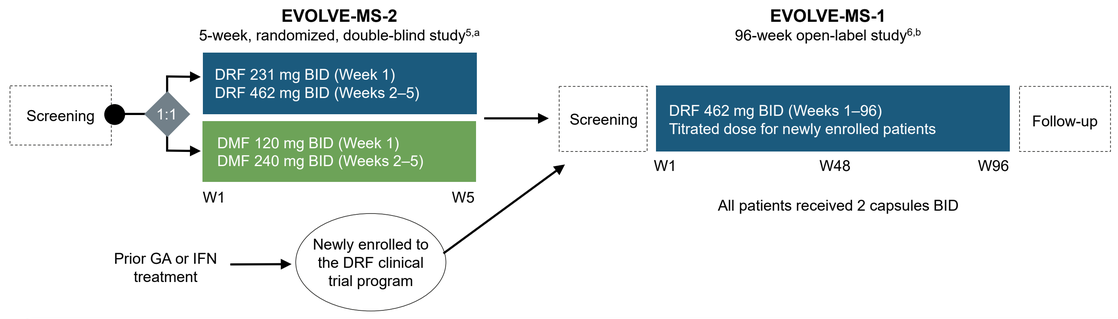
- DRF is a novel oral fumarate approved in multiple countries globally for patients with relapsing forms of MS.[2,3]
- Oral administration of DRF 462 mg and dimethyl fumarate (DMF) 240 mg produce bioequivalent exposure of the active metabolite monomethyl fumarate and, therefore, are expected to exhibit comparable efficacy and safety profiles.[2-5]
- DRF has an improved GI tolerability profile compared with DMF, with fewer patients discontinuing due to GI AEs.[5,6]

Methods

Study Design

- EVOLVE-MS-1 (NCT02634307) is an open-label, 2-year, phase 3 study evaluating DRF safety, tolerability, and efficacy over 96 weeks in adults with relapsing-remitting MS (Figure 1).
- This analysis evaluated:
  - Safety and tolerability in the overall patient population and in a subset of EVOLVE-MS-1 patients who received either GA or IFN as their most recent DMT (GA/IFN);
  - Efficacy in a subset of patients who received either GA or IFN as their most recent DMT (GA/IFN).
- Efficacy outcomes included annualized relapse rate (ARR), time to confirmed disability progression (CDP), number of gadolinium-enhancing (Gd+) lesions, and number of new/newly enlarging T2 lesions.
- Safety outcomes included treatment-emergent AEs (TEAEs) and absolute lymphocyte counts (ALC).
- Results from the DRF-rollover and DMF-rollover groups have previously been published.[1]

Figure 1. EVOLVE-MS-1 Study Design



EVOLVE-MS-1 key eligibility criteria
- 18–65 years old
- Confirmed RRMS diagnosis[7]
- No history of clinically significant recurring or active GI symptoms within 3 months of screening
- Neurologically stable with no evidence of relapse in the 30 days before screening
- Prior DMT use was permitted

BID = twice a day; DMF = dimethyl fumarate; DMT = disease-modifying therapy; DRF = diroximel fumarate; GI = gastrointestinal; RRMS = relapsing-remitting multiple sclerosis; W = week
EVOLVE-MS-1 was conducted from 10 December 2015 until 11 November 2021.
[a]Adapted from Naismith RT, et al. *CNS Drugs*. 2020;34(2):185-196; http://creativecommons.org/licenses/by-nc/4.0/.
[b]Adapted from Naismith RT, et al. *Mult Scler*. 2020;26(13):1729-1739; http://creativecommons.org/licenses/by-nc/4.0/.
[c]Exclusion criteria for newly enrolled patients included use of: teriflunomide within 2 years of Visit 2 (Week 1); natalizumab within 2 months of Visit 2; alemtuzumab; fingolimod within 90 days of Visit 2; daclizumab within 6 months of Visit 2; or B-cell therapies within 12 months of Screening.

Results

Patients

- As of 01 September 2020, 1057 patients were enrolled in EVOLVE-MS-1.
- Subgroup analysis included patients who had previously received GA or IFN (GA/IFN) as their most recent DMT (n = 343; Table 1).
  - Median exposure to prior GA or IFN was 2.1 (range, 0.0–21.9) years.
- A washout period was not defined.
  - Median (Q1, Q3) time from discontinuation of GA/IFN to DRF treatment initiation was:
    - For GA: 101 (38, 400) days.
    - For IFN: 171 (31, 1127) days.
- Baseline characteristics were generally similar between the overall population and the prior GA/IFN group.

Efficacy

- ARR was significantly reduced on treatment compared with 12 months before study entry for the overall and prior GA/IFN populations (Figure 2).
  - At Week 96, 82% of patients in the overall population and 82% in the prior GA/IFN population were relapse-free.
- Time to CDP (Figure 3) and time to first relapse (data not shown) were similar between the overall population and the subgroup of patients treated previously with GA or IFN.
- Gd+ lesion counts were significantly reduced at Week 96 versus Baseline for all populations (Figure 4).
  - At Week 96, 91% (621/681) of patients in the overall population and 94% (197/209) in the Prior GA/IFN population were Gd+ lesion free.
- Mean (SD) number of new/newly enlarging T2 lesions remained stable or declined slightly from Year 1 to Year 2 (Figure 5).

Safety and GI Tolerability

- The occurrence of any AE and AEs leading to treatment discontinuation were similar between groups (Table 2).
- The most common AEs for the subgroup that received prior GA/IFN occurred at similar rate in the overall population.
- Discontinuations due to GI AEs were low (<1%) in both groups.

Absolute Lymphocyte Count (ALC)

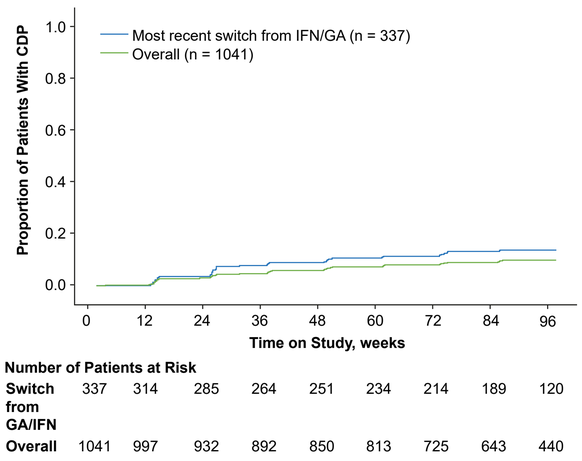
- Mean (SD) ALC decreased at a similar rate in both the overall group and prior GA/IFN group from baseline, 1.81 (0.58) versus 1.81 (0.60) × 10^9/L, through Week 96, 1.29 (0.52) versus 1.23 (0.51) × 10^9/L (Figure 6).
- Mean percent ALC reduction was –29% (overall) versus –30% (GA/IFN) from baseline to Week 96.

Table 1. Baseline Demographics and Disease Characteristics

	Overall population N = 1057	Prior GA/IFN n = 343
Mean (SD) age, y	42.5 (10.8)	43.9 (10.4)
Female, n (%)	762 (72)	257 (75)
Race, n (%)		
White	972 (92)	306 (89)
Black or African American	72 (7)	32 (9)
Other	13 (1)	5 (1)
Mean (SD) BMI, kg/m^2	26.6 (6.1)	27.8 (6.5)
Region, n (%)		
US	453 (43)	214 (62)
Germany and Poland	604 (57)	129 (38)
Mean (SD) time since diagnosis, y	7.6 (7.3)[a]	8.9 (7.1)
Mean (SD) no. of relapses in previous year	0.7 (0.8)	0.6 (0.7)
Mean (SD) EDSS score	2.7 (1.5)	2.6 (1.5)
Mean (SD) no. of Gd+ lesions	1.1 (3.5)[b]	0.8 (2.5)[c]
Gd+ lesion free, n (%)	741 (70)	266 (78)

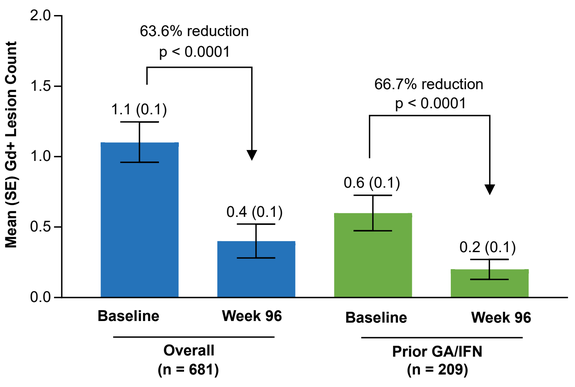
BMI = body mass index; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; Gd+ = gadolinium-enhancing; IFN = interferon
EVOLVE-MS-1 data cut: 01 September 2020.
[a]n = 1056. [b]n = 1053. [c]n = 340.

Figure 3. Time to 12-Week CDP



CDP = confirmed disability progression; GA = glatiramer acetate; IFN = interferon
Time to CDP was from Kaplan-Meier product-limit method.

Figure 4. Mean Number of Gd+ Lesions



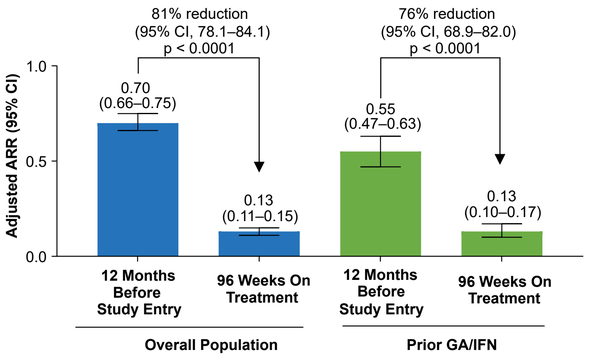
GA = glatiramer acetate; Gd+ = gadolinium-enhancing; IFN = interferon; SD = standard deviation

Table 2. Summary of safety

	Overall population N = 1057	Prior GA/IFN n = 343
Any TEAE, n (%)	932 (88.2)	310 (90.4)
Mild	307 (29.0)	94 (27.4)
Moderate	527 (49.9)	186 (54.2)
Severe	98 (9.3)	30 (8.7)
Most Common TEAEs in Prior GA/IFN group (≥ 10% patients in Prior GA/IFN), n (%)		
Flushing	288 (27)	111 (32)
MS relapse	201 (19)	67 (20)
Upper respiratory tract infection	151 (14)	54 (16)
Diarrhea	109 (10)	45 (13)
Urinary tract infection	102 (10)	42 (12)
Nasopharyngitis	136 (13)	41 (12)
Lymphopenia	118 (11)	35 (10)
AEs leading to treatment discontinuation, n (%)	85 (8.0)	37 (10.8)
GI AEs leading to treatment discontinuation, n (%)	7 (0.7)	1 (0.3)
SAEs, n (%)	120 (11.4)	38 (11.1)
Death[a]	4 (0.4)	0

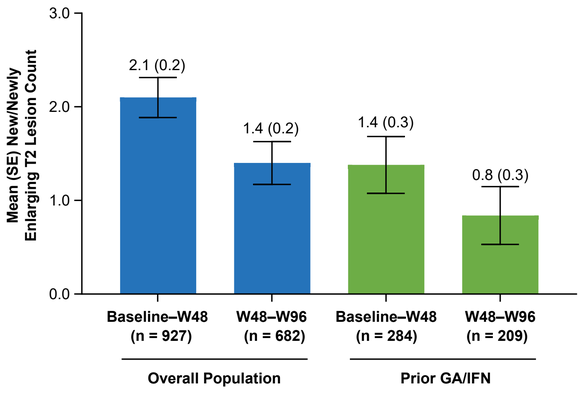
AE = adverse event; GA = glatiramer acetate; GI = gastrointestinal; IFN = interferon; SAE = serious adverse event; TEAE = treatment-emergent adverse event
EVOLVE-MS-1 data cut: 01 September 2020.
[a]Accidental fall, bacterial pneumonia, hypertensive heart disease, and cardiac arrest; none of the deaths were considered related to study drug by the Investigator.

Figure 2. ARR After 96 Weeks on Treatment Compared With the 12 Months Before Study Entry



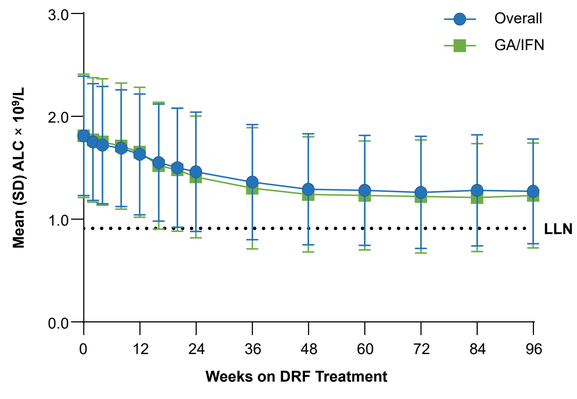
ARR = annualized relapse rate; CI = confidence interval; GA = glatiramer acetate; IFN = interferon
Calculation of ARR was based on patient-reported relapses in the 12 months before study entry compared with protocol-defined relapses during the study period.

Figure 5. Number of New/Newly Enlarging T2 Lesions



GA = glatiramer acetate; IFN = interferon; SD = standard deviation; W = week

Figure 6. Absolute lymphocyte count over time



ALC = absolute lymphocyte count; DRF = diroximel fumarate; LLN = lower limit of normal; SD = standard deviation
Lower limit of normal defined as 0.91 × 10^9/L.

References 1. Wray S, et al. *Adv Ther*. 2022;39(4):1810-1831. 2. Vumerity [prescribing information]. Cambridge, MA: Biogen; 2022. 3. Vumerity EPAR. Netherlands, B.V. 2022. 4. Tecfidera [prescribing information]. Cambridge, MA: Biogen; 2022. 5. Naismith RT, et al. *CNS Drugs*. 2020;34(2):185-196. 6. Naismith RT, et al. *Mult Scler*. 2020;26(13):1729-1739. 7. Polman CH, et al. *Ann Neurol*. 2011;69(2):292-302. Disclosures SW: consulting fees from and advisory boards for Biogen, Celgene, and EMD Serono; speaker bureaus for Biogen, Celgene, EMD Serono, Genentech-Roche, and Sanofi-Genzyme; research support from Biogen, Celgene, EMD Serono, Genentech-Roche, Novartis, Receptos, Sanofi-Genzyme, and TG Therapeutics; FTB: grant support from the German Research Foundation (DFG) and Federal Ministry of Education and Research (BMBF); has received, through his institution, grant support and travel support to attend scientific meetings from Actelion, Bayer, Biogen, Genzyme, Merck-Serono, and Novartis; speaker fees from and advisory boards for Actelion, Bayer, Genzyme, Merck-Serono, Novartis, and Roche; AW: advisor fees from AbbVie; research support from AbbVie, Alkermes, and Biogen; DLA: consulting fees from Albert Charitable Trust, Alexion Pharma, Biogen, Celgene, Frequency Therapeutics, Genentech, Med-Ex Learning, Merck, Novartis, Population Council, Receptos, Roche, and Sanofi-Aventis; grants from Biogen, Immunotec, and Novartis; equity interest in NeuroRx; JD: speaker fees from and advisory boards for Bayer, Biogen, Hemofarm, Medis, Merck, Novartis, Roche, Sanofi-Genzyme, Teva, and Zentiva; EJ: advisory boards for Biogen; speaker fees from Biogen, Novartis, Roche, and Sanofi; JDB: speaker/consulting/advisory fees from Alexion, Alkermes, Biogen, Celgene, EMD Serono, Genentech, Genzyme, Novartis, and TG Therapeutics; holds stock in Amgen; research support from Alexion, Alkermes, Biogen, Celgene, Genentech, Genzyme, Novartis, and TG Therapeutics; DN: research support from and consultant/advisory boards/speaker bureaus for Adamas, Alkermes, Alexion, Bayer, Biogen, Celgene/Bristol Myers Squibb, EMD Serono, Genentech-Roche, Janssen Pharmaceuticals, Novartis, and Sanofi-Genzyme; RTN: speaker/consulting/advisory fees from Alexion, Alkermes, Bayer, Biogen, Celgene, EMD Serono, Genentech, Lundbeck, NervGen, Novartis, Sanofi-Genzyme, Third Rock Therapeutics, and Viela Bio; SFH: consulting fees from AbbVie, Adamas, Biogen, BMS, Janssen-Actelion, Novartis, Osmotica, and Sanofi; research support from AbbVie, Actelion, Anokion, Biogen-Alkermes, BMS-Celgene, Novartis, Roche-Genentech, and Sanofi-Genzyme; speaker bureaus for Biogen, BMS, Roche-Genentech, and Sanofi-Genzyme; MG: consulting fees from Biogen, EMD Serono, Novartis, and Sanofi-Genzyme; research support from Alkermes; speaker bureaus for Biogen, EMD Serono, Genentech-Roche, and Sanofi-Genzyme; HC, SL, SLS, FB, and JPM: employees of and hold stock/stock options in Biogen; MEB and SK: former employees of and held stock/stock options in Biogen at time of analysis; BAS: speaker/consulting fees from AbbVie, Alexion, Biogen, Bristol Myers Squibb, EMD Serono, Janssen, Genentech, Greenwich Biosciences, Novartis, Roche, Sanofi-Genzyme, and TG Therapeutics; research support from AbbVie, Alkermes, Biogen, Greenwich Biosciences, MedImmune, Novartis, Roche, and Sanofi-Genzyme. Acknowledgments This study was sponsored by Biogen (Cambridge, MA, USA). Writing and editorial support for the preparation of this poster was provided by Excel Scientific Solutions (Fairfield, CT, USA): funding was provided by Biogen