Diroximel Fumarate in Young Adults With Relapsing-Remitting Multiple Sclerosis: Interim Safety and Efficacy Results From the Phase 3 EVOLVE-MS-1 Study

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*At time this work was conducted

OBJECTIVE

- To assess interim safety, GI tolerability, and efficacy of DRF in young adults (aged 18–29 years) participating in the EVOLVE-MS-1 study.

CONCLUSIONS

- In this interim analysis of EVOLVE-MS-1, safety and efficacy profiles of DRF over 2 years in the young adult population were consistent with those in the overall study population.
- No discontinuations due to GI AEs were seen; GI AEs occurred in 37.4% of patients, in line with the overall patient population.
- Data suggest that DRF is an effective treatment option for young adults aged 18–29 years with MS.

Introduction

- Young adults with multiple sclerosis (MS) reach disability milestones at an earlier age[1] and experience a more inflammatory disease course than older patients with MS.[2]
- Diroximel fumarate (DRF) is an oral fumarate for the treatment of relapsing MS.[3] DRF has better gastrointestinal (GI) tolerability and lower rates of discontinuation due to GI adverse events (AEs) compared with dimethyl fumarate (DMF).[3]
- Although other disease-modifying therapies have been shown to treat young adults with MS safely and effectively,[4] outcomes have not previously been shown for treatment with DRF.

Methods

Study Population

- Patients aged 18–29 entered the open-label, 96-week EVOLVE-MS-1 study either as newly enrolled in the DRF clinical development program or after completing the randomized, double-blind, 5-week, Phase 3 EVOLVE-MS-2 study of DRF or DMF.
- Patients received 462 mg of DRF twice daily and were titrated if newly enrolled.
- Key eligibility criteria included age of 18–65 years, confirmed relapsing-remitting MS diagnosis, no history of clinically significant recurring or active GI symptoms within 3 months of Screening, and neurological stability with no evidence of relapse in the 30 days before Screening. Prior DMT use was permitted.
- The primary endpoint was DRF safety and tolerability.
- Exploratory endpoints included clinical efficacy, as measured by annualized relapse rate (ARR), and radiological efficacy, as measured by number of gadolinium-enhancing (Gd^+) lesions; percentage of patients free from Gd^+ lesions; number of new or enlarging T2 lesions and new T1 hypointense lesions; and no evidence of disease activity-3 (NEDA-3). The following patient-reported outcomes (PROs) were also collected: EuroQol Group Health Outcome Measure 5-Level (EQ-5D-5L) and 12-Item Short Form Health Survey (SF-12).

Assessments and Statistical Analysis

- Safety assessments included number and percentage of treatment-emergent AEs (TEAEs), GI AEs, serious AEs (SAEs), AEs leading to treatment discontinuation, and AEs of special interest.
- Absolute lymphocyte count (ALC) was collected at each study visit; lower limit of normal (LLN) was defined as < 0.91 × 10^9/L.
- MS relapse was defined as new or recurrent neurologic symptoms (not associated with fever/infection) lasting ≥ 24 hours and accompanied by new neurological findings and change in Expanded Disability Status Scale (EDSS) score.
- Baseline ARR values reflect patient-reported relapses in the 12 months before study start.
- NEDA-3 was defined as no relapses, no confirmed disability progression sustained for 12 weeks per EDSS, and no new/newly enlarging T2 hyperintense or Gd^+ lesions.
- Radiological and disability assessments were performed in patients who completed ≥ 1 post-Baseline efficacy assessment.
- Summary statistics were provided for all parameters. Gd^+ lesion count, new/enlarging T2 lesion count, and MS relapse were summarized by timepoint and change from baseline using descriptive statistics. Adjusted ARR was based on a Poisson regression model.

Results

Patients and Baseline Demographics

- As of September 2020, 1057 patients were enrolled and received DRF.
  - Of these, 131 patients were aged 18–29 years.
- At Baseline, mean (SD) age of patients was 25.1 (3.0) years, mean (SD) time since diagnosis was 2.2 (2.7) years, and mean (SD) EDSS score was 1.9 (1.1; Table 1).

Safety and GI Tolerability

- The occurrence of any TEAE in the 18–29 years age group was 87%.
  - The AEs of highest occurrence were flushing, MS relapse, nasopharyngitis, and upper respiratory infection (Table 2).
- No patients discontinued due to GI AEs. One patient discontinued due to flushing.
- SAEs were reported in 22 (16.8%) patients; 1 death due to a fall was reported.
- For AEs of special interest, there were no severe opportunistic infections, malignancies, or premalignant conditions reported.
- Most patients did not experience lymphopenia during the 96-week study (Figure 1A).
- Baseline ALC reduced by ~20% in Year 1, from mean (SD) of 1.85 (0.54) x 10^9/L at Week 0 to 1.48 (0.54) x 10^9/L at Week 48, and remained stable through Week 96 (1.47 [0.49] x 10^9/L; Figure 1B).
  - For comparison, the overall population's baseline ALC was reduced ~29% in Year 1, from mean (SD) 1.81 (0.58) x 10^9/L at Week 0 to 1.29 (0.54) x 10^9/L at Week 48.

Efficacy

- ARR decreased 82% from 0.96 (95% CI, 0.82–1.12) at 12 months prior to study entry to 0.17 (95% CI, 0.11–0.26) after 2 years of DRF treatment (p < 0.0001; Figure 2).
- The number of patients free of Gd^+ lesions increased at Week 96 compared with baseline (80.4% vs. 47.3%, respectively; Figure 3A).
- The number of new T1 hypointense lesions and new/newly enlarging T2 lesions was reduced in the Week 48–Week 96 period compared with the Baseline to Week 48 period (Figures 3B and 3C).
- The estimated proportion of patients who were relapse free was 82.6% at Week 48 and 79.6% at Week 96 (Figure 4).
- The estimated proportion of patients who had no evidence of disease activity at Week 48 was 54.2%; the estimate for Week 96 could not be reliably modeled due to sparse data points.
- 124 (94.7%) did not have 12-week confirmed disability progression during the 96-week study.
- PRO scores remained stable over the course of the study in the overall population as measured by SF-12, EQ-5D-5L, and visual analog scale scores.

Table 1. Baseline Characteristics

Baseline Characteristics	Age 18–29 y n = 131
Age, y, mean (SD)	25.1 (3.0)
Female, n (%)	81 (61.8)
Race, n (%)	
White	119 (90.8)
Black or African American	6 (4.6)
Asian or Other	4 (3.1)
BMI, kg/m^2, mean (SD)	24.5 (6.1)
Time since diagnosis, y, mean (SD)	2.2 (2.7)
No. of prior DMTs, mean (SD)	0.6 (1.0)
No. of relapses in previous year, mean (SD)	1.0 (0.9)
EDSS score, mean (SD)	1.9 (1.1)
No. of Gd^+ lesions, mean (SD)	1.9 (3.5)
Gd^+ lesion free, n (%)	62 (47.3)

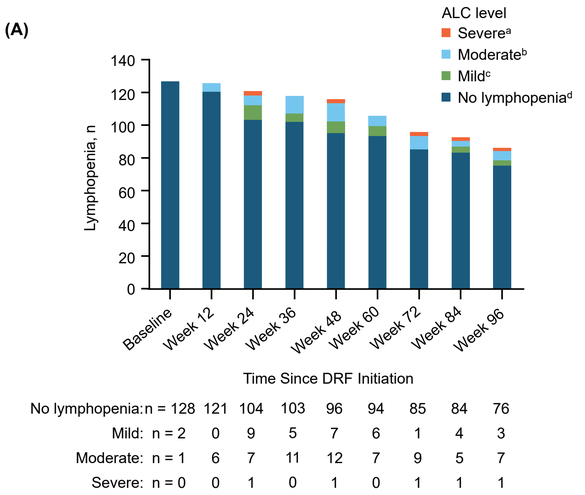
BMI = body mass index; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; Gd^+ = gadolinium-enhancing

Table 2. TEAEs

TEAE	Age 18–29 y n = 131
Any TEAE, n (%)	114 (87.0)
Mild	40 (30.5)
Moderate	60 (45.8)
Severe	14 (10.7)
Most common TEAEs, n (%)	
Flushing	42 (32.1)
MS relapse	28 (21.4)
Nasopharyngitis	26 (19.8)
Upper respiratory infection	18 (13.7)
GI TEAE, n (%)	49 (37.4)
AEs leading to treatment discontinuation[a], n (%)	4 (3.1)
GI AEs leading to treatment discontinuation	0
AEs of special interest, n (%)	
Cardiac disorders[b]	17 (13.0)
Liver Injury	8 (6.1)
Renal Injury	3 (2.3)
SAE, n (%)	22 (16.8)
Death[c]	1 (0.8)

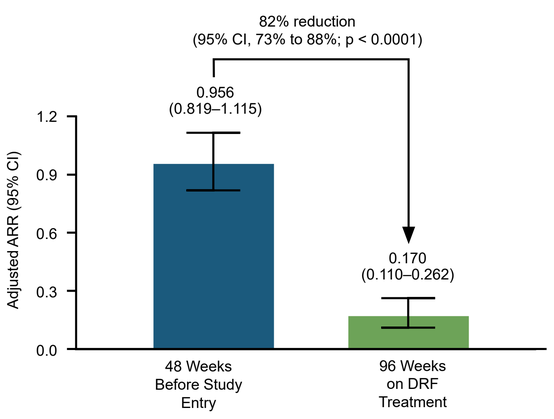
AE = adverse event; GI = gastrointestinal; SAE = serious adverse event; TEAE: treatment-emergent adverse event
[a]AEs leading to discontinuation were as follows, noting patients could have > 1 AE leading to discontinuation: 2 injury, poisoning, and procedural complications; 1 each for fall, road traffic accident, nervous system disorders, central nervous system lesions, vascular disorders, and flushing.
[b]Cardiac disorders included: 10 reports of dizziness; 2 chest pain; 2 dyspnea; and 1 each for chest discomfort, dizziness exertional, palpitations, sinus node dysfunction, and supraventricular tachycardia.
[c]The reason for death was a fall and was deemed by the investigator not related to the study treatment.

Figure 1. (A) Lymphopenia and **(B)** ALC Over Time on Study



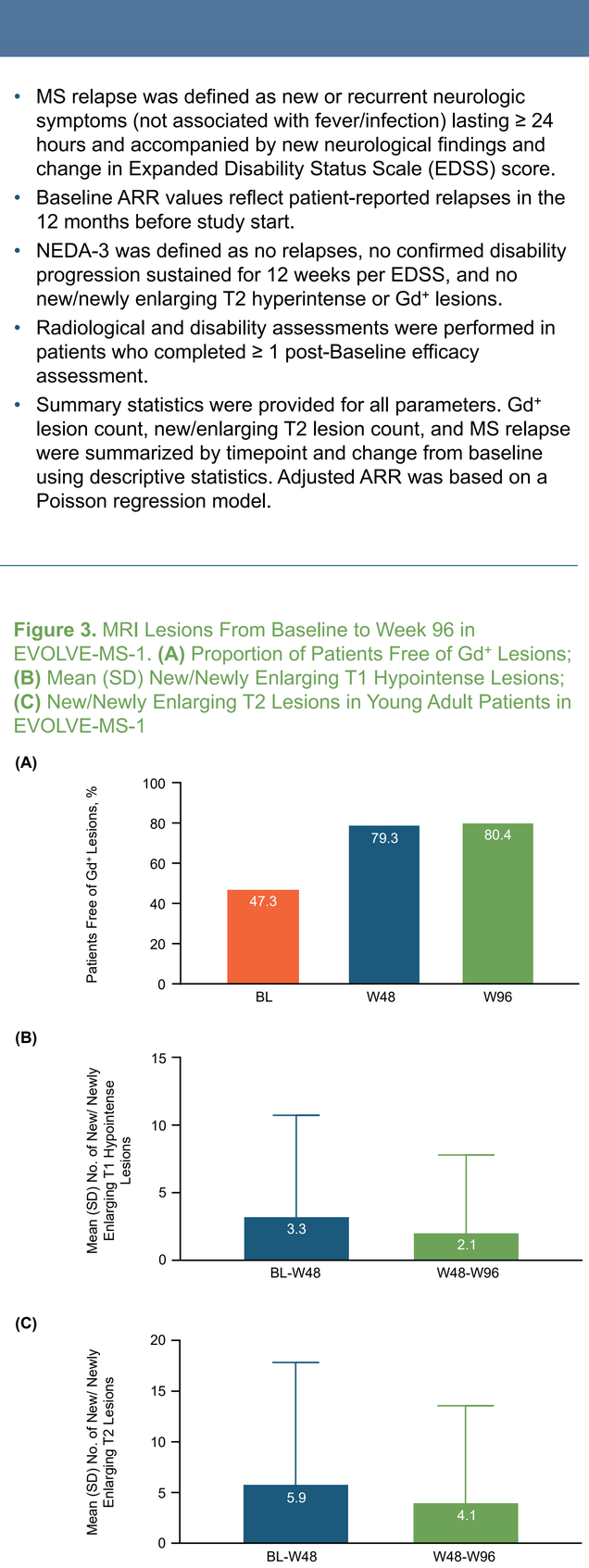
ALC = absolute lymphocyte count; DRF = diroximel fumarate; LLN = lower limit of normal
[a]Severe: ALC ≤ 0.5 x 10^9/L.
[b]Moderate: ALC 0.5–0.8 x 10^9/L.
[c]Mild: ALC ≤ 0.91–0.8 x 10^9/L.
[d]No lymphopenia: ALC ≥ 0.91 x 10^9/L.
Mean (SD) ALC are shown. Sample size ranges from 131 at Week 0 to 88 at Week 96. LLN = 0.91 x 10^9/L.

Figure 2. ARR Was Reduced in the 96 Weeks on DRF Treatment Compared With in the 48 Weeks Prior to Study Entry



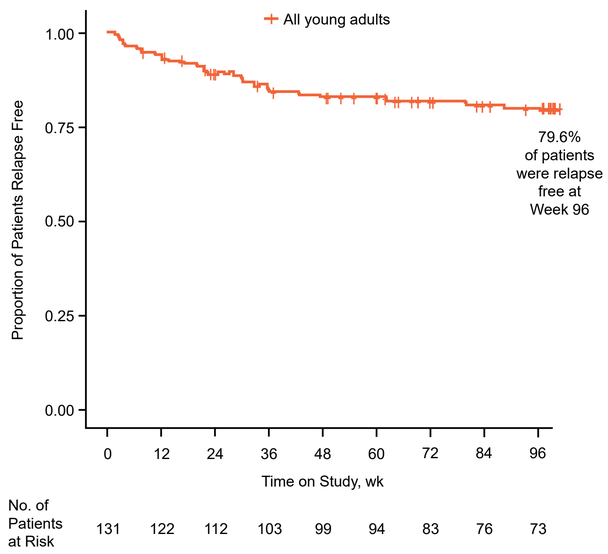
ARR = annualized relapse rate; DRF = diroximel fumarate

Figure 3. MRI Lesions From Baseline to Week 96 in EVOLVE-MS-1. **(A)** Proportion of Patients Free of Gd^+ Lesions; **(B)** Mean (SD) New/Newly Enlarging T1 Hypointense Lesions; **(C)** New/Newly Enlarging T2 Lesions in Young Adult Patients in EVOLVE-MS-1



BL = Baseline; Gd^+ = gadolinium-enhancing; MRI = magnetic resonance imaging

Figure 4. Proportion of Patients Relapse Free Over Time



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