Diroximel Fumarate Demonstrates Improved Gastrointestinal Tolerability Profile Compared to Dimethyl Fumarate in Patients With Relapsing-Remitting Multiple Sclerosis: Results From the Randomized, Double-blind, Phase 3 EVOLVE-MS-2 Study

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Conclusions

- **In the randomized double-blind EVOLVE-MS-2 study, DRF-treated patients reported less severe GI events and fewer days of GI symptoms when self-assessing GI tolerability, compared with DMF-treated patients.**
- **GI AEs were reported less frequently for DRF-treated patients; treatment discontinuation due to GI AEs was lower with DRF than DMF.**
- **The statistically significant findings using the patient-assessed symptom intensity scales were supported by lower incidences of GI AEs and discontinuations due to GI AEs, suggesting a clinically meaningful improvement in GI tolerability with DRF compared with DMF.**
- **The low rates of treatment discontinuations due to GI AEs in this study are similar to those reported to date (30 March 2018 data cut) in the ongoing, 96-week, open-label, Phase 3, long-term safety study, EVOLVE-MS-1.[5]**
- **These findings indicate that DRF has an improved GI tolerability profile compared with DMF.**

Introduction

- Diroximel fumarate (DRF; ALKS 8700, BIIB098) is a novel oral fumarate for patients with relapsing forms of multiple sclerosis (MS).[1]
- Upon oral administration, DRF is rapidly converted to monomethyl fumarate (MMF) before it reaches systemic circulation. MMF is the same active metabolite as dimethyl fumarate (DMF), an approved treatment for patients with relapsing forms of MS.[2]
- DRF 462 mg and DMF 240 mg produce bioequivalent systemic MMF exposures and are therefore expected to have similar efficacy and safety profiles.
- It is hypothesized that DRF's distinct chemical structure may elicit less gastrointestinal (GI) irritation and lead to an improved GI tolerability profile.[3]
- EVOLVE-MS-2 (NCT03093324) was a Phase 3, randomized, head-to-head, 5-week study to evaluate the GI tolerability of DRF versus DMF in patients with relapsing-remitting MS (RRMS).

Objective

- To compare the GI tolerability of DRF and DMF in patients with RRMS.

Methods

- Adaptive study design: randomized double-blind treatment with DRF or DMF over 5 weeks (Figure 1).
  - Because the study included 2 patient-assessed GI tolerability scales not previously used in a clinical trial setting, a preplanned unblinded analysis of data was conducted after the first 120 patients were randomized (i.e., part A), in which the objectives were to assess the utility of the GI symptom scales; refine the primary endpoint to select the most sensitive measure for detecting a difference between DRF and DMF; and inform the sample size. After the initial 120 patients, the subsequently randomized patients (i.e., part B) were enrolled, bringing the overall planned population to 500 patients.
- Patients were randomized 1:1 to receive either DRF 462 mg twice daily or DMF 240 mg twice daily (titrated dose in Week 1, full dose for Weeks 2–5).
- Key eligibility criteria: aged 18–65 years with a confirmed RRMS diagnosis.[4]
  - No history of GI surgery, clinically significant recurring or active GI symptoms within 3 months of screening, or chronic use of medical therapy to treat GI symptoms within 1 month of screening.
- GI tolerability assessments:
  - Individual Gastrointestinal Symptom and Impact Scale (IGISIS) and Global Gastrointestinal Symptom and Impact Scale (GGISIS).
    - Patients self-assessed duration and severity of 5 GI symptoms (nausea, vomiting, upper abdominal pain, lower abdominal pain, and diarrhea) on an 11-point numerical rating scale by completing eDiary questionnaires once (GGISIS) or twice (IGISIS) daily.
  - Adverse events (AEs) were monitored throughout the study by the Investigator.
- Study endpoints:
  - Primary endpoint: number of days (relative to exposure) with an IGISIS intensity score of ≥ 2 in the overall population.
  - Secondary endpoints: number of days (relative to exposure) with IGISIS intensity scores of ≥ 1 or ≥ 3 in the overall population; IGISIS intensity score of ≥ 2 in patients from Part B only; GGISIS intensity scores of ≥ 1, ≥ 2, or ≥ 3 in the overall population; and worst IGISIS individual symptom score by study week.
  - Summary of AEs and AEs leading to treatment discontinuation.

Results

- Overall, 854 patients underwent screening, 506 were randomized, and 504 (DRF, 253; DMF, 251) received ≥ 1 dose of study drug; 502 patients (DRF, 253; DMF, 249) completed ≥ 1 postbaseline tolerability eDiary assessment and were included in the analysis of patient–assessed GI tolerability (Table 1).
- Baseline demographics and disease characteristics were well balanced between treatment groups (Table 2).

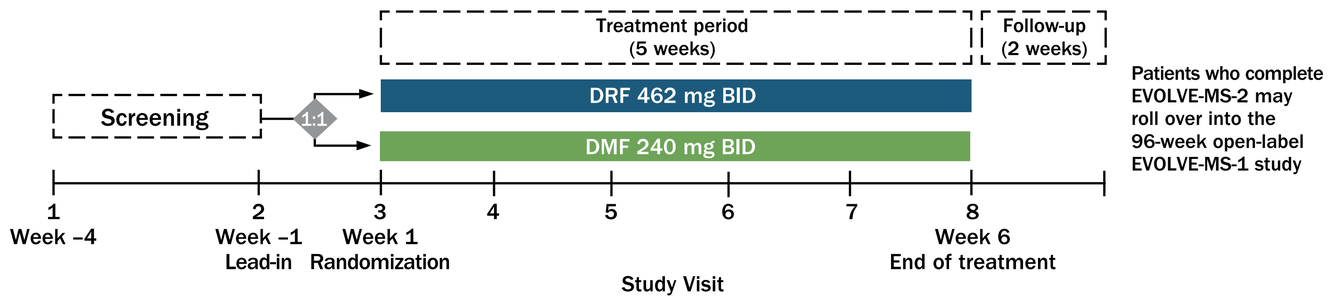
Patient Self-assessed GI Tolerability

- Primary endpoint: number of days (relative to exposure) with an IGISIS intensity score of ≥ 2 was significantly lower with DRF than DMF (adjusted rate ratio, 0.54 [95% CI, 0.39–0.75]; 46% reduction; p = 0.0003; Figure 2).
- Secondary endpoints:
  - Compared with DMF, DRF-treated patients had:
    - Significantly fewer days with IGISIS intensity scores of ≥ 1 and ≥ 3 and GGISIS intensity score of ≥ 1 (Figure 2).
    - Fewer days with GGISIS intensity scores of ≥ 2 and ≥ 3, although the differences were not statistically significant.
    - Significantly fewer days with an IGISIS intensity score of ≥ 2 in an analysis of data collected from part B only (adjusted rate ratio, 0.52 [95% CI, 0.36–0.76]; 48% reduction; p = 0.0007).
      - In an exploratory analysis of this group, there were significantly fewer days with IGISIS intensity scores of ≥ 1 and ≥ 3.
  - Worst IGISIS intensity scores gradually declined over the 5-week treatment period in DRF-treated patients, whereas scores with DMF increased until Week 3 before declining (Figure 3).

AEs

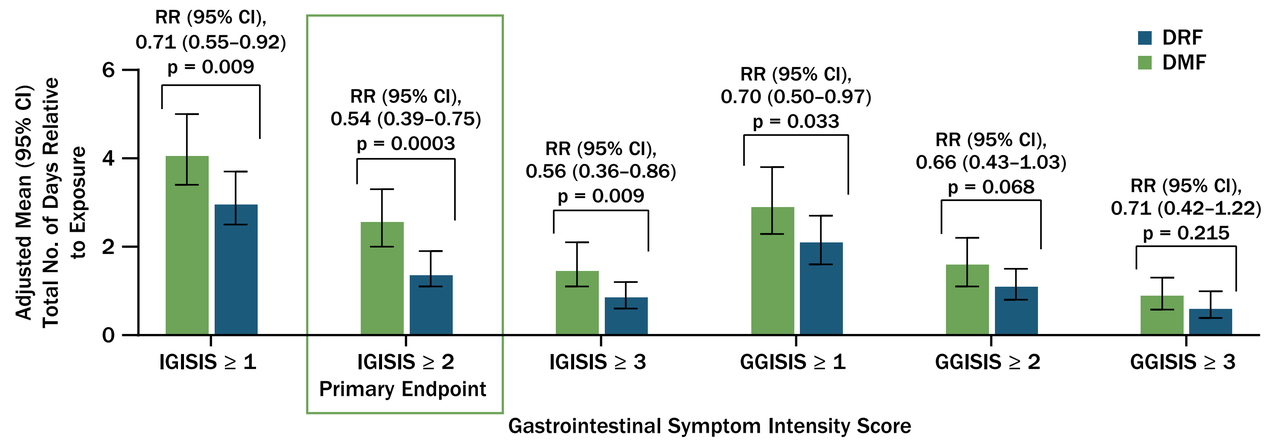
- AEs occurred in 78.3% of patients with DRF and 83.7% with DMF (Table 3).
  - Most AEs were mild or moderate in severity (DRF, 97.5% [193/198]; DMF, 93.3% [196/210]).
- Incidence of GI AEs was lower with DRF than DMF (34.8% vs. 49.0%; Table 3).
- Fewer patients discontinued treatment due to AEs (1.6% vs. 5.6%) and GI AEs (0.8% vs. 4.8%) with DRF than DMF.

Figure 1. EVOLVE-MS-2 Study Design[a]



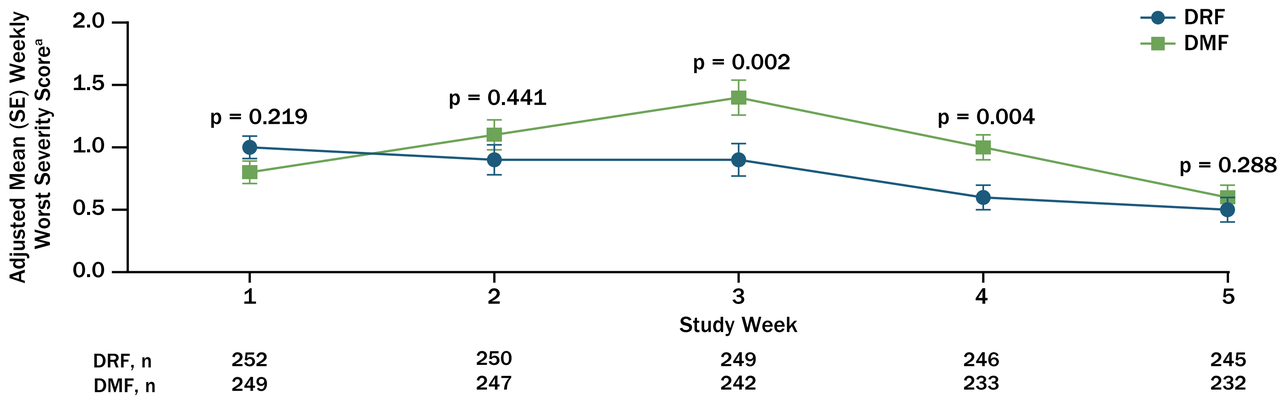
BID = twice daily dosing; DMF = dimethyl fumarate; DRF = diroximel fumarate
[a]EVOLVE-MS-2 utilized an adaptive study design and was conducted in 2 parts (A and B). The first 120 patients randomized were included in part A and subsequent patients were included in part B.

Figure 2. Primary and Secondary Endpoints in the Overall Population



DMF = dimethyl fumarate; DRF = diroximel fumarate; GGISIS = Global Gastrointestinal Symptom and Impact Scale; IGISIS = Individual Gastrointestinal Symptom and Impact Scale; RR = rate ratio

Figure 3. Mean Worst Severity Score for Gastrointestinal Events (IGISIS) by Weekly Interval in the Overall Population



DMF = dimethyl fumarate; DRF = diroximel fumarate; IGISIS = Individual Gastrointestinal Symptom and Impact Scale
[a]Analysis of covariance model; factors include study parts, region (United States and non–United States), age, and body mass index.

Table 1. Disposition of Patients

Patients, n (%)	DRF	DMF
Received ≥ 1 dose of study drug	253 (100)	251 (100)
Completed the treatment period	245 (96.8)	233 (92.8)
Mean (SD) days of treatment exposure, IGISIS[a]	35.2 (4.2)	34.2 (5.9)
Mean (SD) days of treatment exposure, GGISIS[a]	34.2 (4.1)	33.4 (5.1)
Rolled over to EVOLVE-MS-1	239 (94.5)	225 (89.6)
Discontinued the study	8 (3.2)	18 (7.2)
AE leading to discontinuation during the treatment period	4 (1.6)	14 (5.6)
GI AE leading to discontinuation	2 (0.8)	12 (4.8)
Upper abdominal pain	0	5 (2.0)
Diarrhea	1 (0.4)	3 (1.2)
Abdominal pain	0	3 (1.2)
Vomiting	1 (0.4)	2 (0.8)
Abdominal distension	0	1 (0.4)
GI pain	0	1 (0.4)
Nausea	0	1 (0.4)

AE = adverse event; DMF = dimethyl fumarate; DRF = diroximel fumarate; GGISIS = Global Gastrointestinal Symptom and Impact Scale; GI = gastrointestinal; IGISIS = Individual Gastrointestinal Symptom and Impact Scale; TEAE = treatment-emergent adverse event
[a]DRF, n = 253; DMF, n = 249.

Table 2. Baseline Demographics and Disease Characteristics in EVOLVE-MS-2

	DRF n = 253	DMF n = 251
Mean (SD) age, y	43.7 (11.0)	43.7 (9.9)
Female, n (%)	177 (70.0)	190 (75.7)
Mean (SD) BMI, kg/m^2	27.2 (5.9)	27.5 (6.1)
US region,[a] n (%)	135 (53.4)	143 (57.0)
Prior DMT, n (%)		
0	84 (33.2)	85 (33.9)
1	73 (28.9)	72 (28.7)
≥ 2	96 (37.9)	94 (37.4)
Mean (SD) time since diagnosis, y	7.4 (7.8)	7.9 (7.4)
Mean (SD) time since first symptom, y	9.6 (9.0)	10.1 (8.6)
Mean (SD) no. of relapses in previous year	0.6 (0.7)	0.6 (0.7)
Mean (SD) EDSS score	2.7 (1.4)	2.7 (1.4)
Mean (SD) no. of Gd+ lesions[b]	0.9 (2.2)	1.1 (2.8)
Patients with 0 Gd+ lesions, n (%)	180 (71.1)	175 (69.7)

BMI = body mass index; DMF = dimethyl fumarate; DMT = disease-modifying therapy; DRF = diroximel fumarate; EDSS = Expanded Disability Status Scale; Gd+ = gadolinium-enhancing
[a]EVOLVE-MS-2 was conducted in the United States, Poland, and Germany.
[b]DRF, n = 251; DMF, n = 251.

Table 3. GI AEs Experienced in ≥ 5% of Patients (in Either Group)

System Organ Class Preferred Term, n (%)	Treatment Group: DRF n = 253	Treatment Group: DMF n = 251
Any AE	**198 (78.3)**	**210 (83.7)**
GI disorders	**88 (34.8)**	**123 (49.0)**
Diarrhea	39 (15.4)	56 (22.3)
Nausea	37 (14.6)	52 (20.7)
Upper abdominal pain	17 (6.7)	39 (15.5)
Abdominal pain	16 (6.3)	24 (9.6)
Lower abdominal pain	15 (5.9)	17 (6.8)
Vomiting	9 (3.6)	22 (8.8)

AE = adverse event; DMF = dimethyl fumarate; DRF = diroximel fumarate; GI = gastrointestinal

References 1. Vumerity [prescribing information]. Cambridge, MA: Biogen; 2019. 2. Tecfidera [prescribing information]. Cambridge, MA: Biogen; 2019. 3. Palte MJ, et al. *Adv Ther*. 2019;36(11):3154-3165. 4. Polman CH, et al. *Ann Neurol*. 2011;69(2):292-302. 5. Naismith RT, et al. *Mult Scler* [published online 4 November 2019]. doi: 10.1177/1352458519881761.
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