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Comparing the Impact of Dose Titration on Gastrointestinal Tolerability: Diroximel Fumarate Versus Dimethyl Fumarate in Patients With Relapsing-Remitting Multiple Sclerosis

Naismith RT,[1] Badwan R,[2] Chen H,[3] Lyons J,[3] Miller C,[3] Scaramozza M,[3] Shankar SL,[3] Antezana A[4]

[1]Washington University School of Medicine, St. Louis, MO, USA; [2]Biogen, Research Triangle Park, NC, USA; [3]Biogen, Cambridge, MA, USA; [4]Neuromedical Clinic of Central Louisiana, Alexandria, LA, USA

OBJECTIVE

- **To investigate the impact of dose titration on gastrointestinal (GI) tolerability with diroximel fumarate (DRF) versus dimethyl fumarate (DMF).**

CONCLUSIONS

- **GI events were less frequent and less severe with DRF versus DMF.**
- **GI adverse event (AE) incidence/severity were highest with DMF in Weeks 3 and 4, after 1-week titration.**
  - **Results are consistent with DMF real-world experience. To improve GI tolerability, some health care providers have employed extended titration schedules for DMF.**
- **The pattern of GI events peaking at Weeks 3 and 4 was not observed with DRF, which simplifies initiation of therapy and may prevent delays to reaching maintenance dose by eliminating the need for extended titration schedules.[1,2]**

Introduction

- DRF is a next-generation oral fumarate approved in the United Kingdom for patients with relapsing forms of multiple sclerosis (MS).[3]
- Orally administered DRF 462 mg and DMF 240 mg produce bioequivalent exposure of the active metabolite monomethyl fumarate and are therefore expected to exhibit comparable efficacy and safety profiles.[4,5]
- In EVOLVE-MS-2, a 5-week, Phase 3, head-to-head randomised controlled trial DRF (462 mg twice daily) demonstrated an improved GI tolerability profile compared with DMF (240 mg twice daily).
  - DRF had fewer days of self-assessed GI symptoms on the Individual Gastrointestinal Symptom and Impact Scale (IGISIS): 46% reduction in the number of days with an IGISIS symptom intensity score ≥2 versus DMF (rate ratio [95% CI], 0.54 [0.39–0.75]; *P* = 0.0003).
    - The primary endpoint of EVOLVE-MS-2 was the number of days with an IGISIS intensity score ≥2 relative to exposure.
  - Fewer GI AEs: 34.8% for DRF versus 49.0% for DMF.
  - Lower discontinuation rates due to GI AEs: 0.8% for DRF versus 4.8% for DMF.[6]
- Approved dosing of DRF and DMF includes a 1-week titration period; we evaluated the impact of dose titration on GI tolerability to determine if DRF tolerability appeared to be dose dependent.

Methods

Study Design

- In EVOLVE-MS-2, twice-daily dosing was titrated (DRF 231 mg; DMF 120 mg) for 1 week, followed by maintenance dosing (DRF 462 mg; DMF 240 mg) for Weeks 2–5 (Figure 1).
- Key eligibility criteria: aged 18–65 years with a confirmed diagnosis of relapsing-remitting MS.[7]
  - 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.
- Patients self-assessed incidence and severity of GI symptoms (nausea, vomiting, upper abdominal pain, lower abdominal pain, and diarrhoea) on an 11-point numerical rating scale (IGISIS) twice daily using eDiaries.
- GI tolerability was assessed in weekly intervals.

Figure 1. EVOLVE-MS-2 Study Design

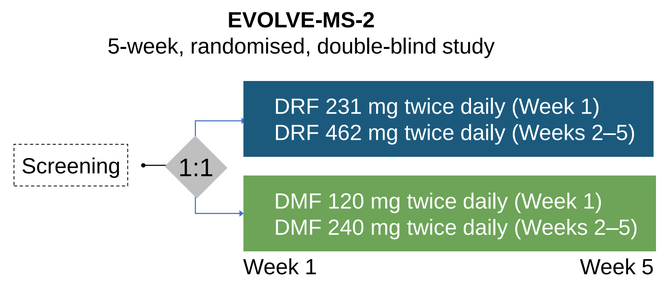


Figure adapted from Naismith et al., *CNS Drugs*, 2020;34(2):185-196. To view a copy of the Creative Commons license, visit http://creativecommons.org/licenses/by-nc/4.0/.

Results

Patients

- Overall, 253 and 251 patients received ≥1 dose of DRF or DMF, respectively. Baseline demographics and disease characteristics are shown in Table 1.

Table 1. Baseline Demographics and Disease Characteristics in EVOLVE-MS-2

	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)	190 (76)
Race/ethnicity, n (%)		
White	232 (92)	227 (90)
Black or African American	20 (8)	20 (8)
Other	1 (< 1)	4 (2)
Mean (SD) BMI, kg/m^2	27.2 (5.9)	27.5 (6.1)
US region, n (%)	135 (53)	143 (57)
Prior DMT, n (%)[a]	169 (67)	166 (66)
Mean (SD) time since diagnosis, y	7.4 (7.8)	7.9 (7.4)
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	0.9 (2.2)[b]	1.1 (2.8)
Gd$^+$ lesion free, n (%)	180 (71)	175 (70)

BMI = body mass index; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; Gd$^+$ = gadolinium-enhancing; SD = standard deviation
[a]Prior DMT includes immunomodulatory and immunosuppressant (investigational or approved).
[b]n = 251.

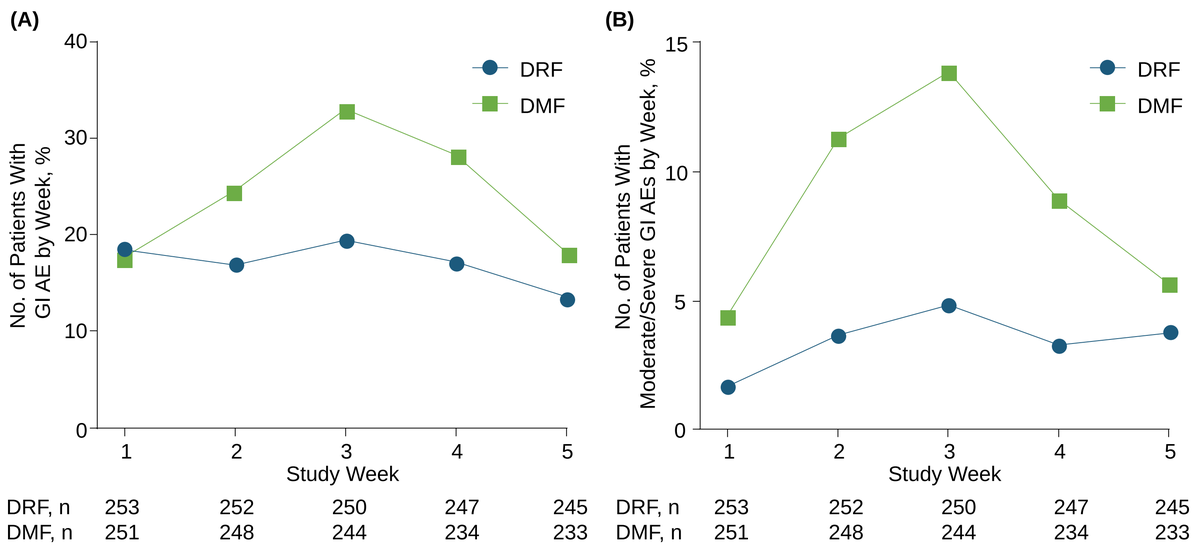
GI Event Severity

- GI event severity, measured by mean (standard error [SE]) worst IGISIS score, was generally constant across all weeks for DRF (range, 0.5 [0.1] to 1 [0.1]); however, with DMF, scores increased from Week 1 (0.8 [0.1]) to Week 2 (1.1 [0.1]), peaked during Week 3 (1.4 [0.1]), and then declined during Weeks 4 (1 [0.1]) and 5 (0.6 [0.1]; Figure 2).
- GI severity was significantly higher with DMF versus DRF in Weeks 3 and 4 (*P* <0.05).

Incidence of GI AEs

- Incidence of GI AEs followed a similar pattern to GI AE severity (Figure 3).
  - Weekly incidence of GI AEs ranged from 12.8–18.8% for DRF and from 11.6–32.0% for DMF, remaining generally constant for DRF but peaking for DMF in Weeks 3 and 4 (Figure 3A).
  - Moderate/severe GI AEs were less likely with DRF (range, 1.6–4.8%) versus DMF (range, 4.4–13.9%; Figure 3B).

Figure 3. **(A)** Mean GI AE[a] Overall Incidence and **(B)** Incidence of Moderate/Severe AEs[b] by Weekly Interval

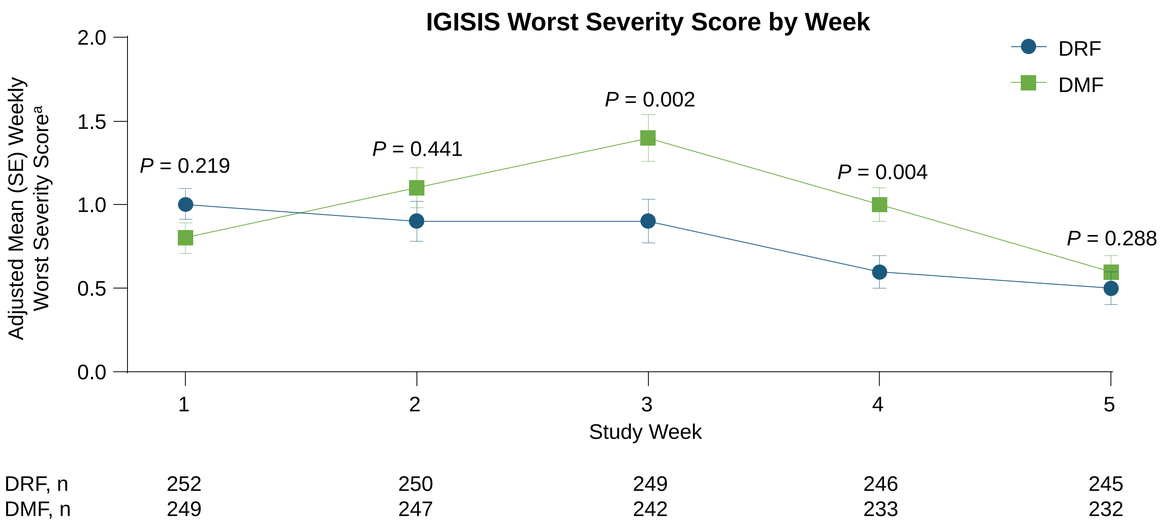


[a]GI tolerability events were defined as those Preferred Terms in the Level 2 subordinate Standardised MedDRA Queries "Gastrointestinal nonspecific inflammations," "Gastrointestinal nonspecific symptoms and therapeutic procedures," or "Gastrointestinal nonspecific dysfunction" (under the Level 1 Standardised MedDRA Query "Gastrointestinal nonspecific inflammation and dysfunctional conditions").
[b]If a patient experienced > 1 AE in a category, the patient was counted only once, according to the highest severity.

GI-Related Discontinuations

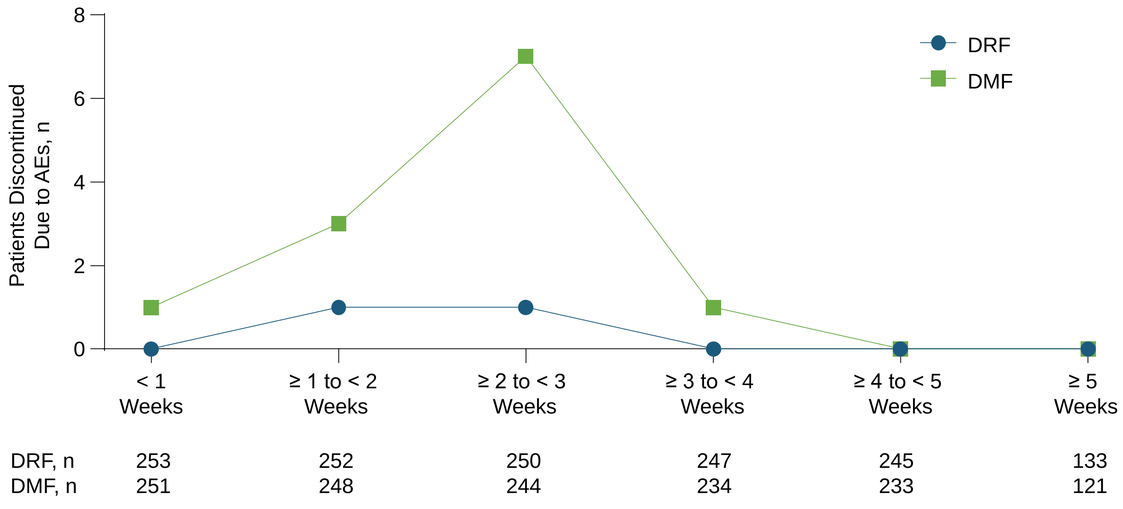
- Discontinuations due to GI AEs occurred in 2 (0.8%) DRF and 12 (4.8%) DMF patients; most DMF discontinuations occurred in Week 3 (7/12 patients; 58.3%; Figure 4).

Figure 2. Mean Worst Severity Score for GI Events by Weekly Interval in the Overall Population



[a]Analysis of covariance model; factors include study parts, region (USA and non-USA), age, and body mass index.

Figure 4. Mean GI-Related Discontinuations by Weekly Interval



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