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

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## OBJECTIVE

- To report interim safety, tolerability, and efficacy outcomes in patients with relapsing-remitting multiple sclerosis (RRMS) from EVOLVE-MS-1 who received diroximel fumarate (DRF) for up to 2 years.

## CONCLUSIONS

- Safety and efficacy results from the ongoing EVOLVE-MS-1 study were consistent with previous findings of DRF and the known benefit-risk profile for dimethyl fumarate (DMF).
- The low rate (<1%) of gastrointestinal (GI)–related treatment discontinuation over the 2-year study period suggests DRF is a well-tolerated option from a GI perspective.
- At 2 years, clinical and radiological measures were reduced from baseline, supporting DRF as an effective treatment option in patients with RRMS and in patients who are newly diagnosed with RRMS.

## Introduction

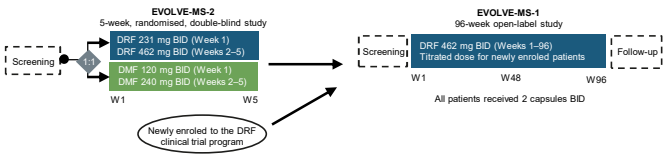
- DRF is an oral fumarate approved in the United States and Europe for patients with relapsing forms of multiple sclerosis (MS).[1]
- Oral administration of DRF 462 mg and DMF 240 mg produce bioequivalent exposure of the active metabolite monomethyl fumarate and are therefore expected to exhibit comparable efficacy and safety profiles.[2,3]
- DRF has an improved GI tolerability profile compared with DMF.[4]

## Methods

### Study Design

- EVOLVE-MS-1 (NCT02634307) is an ongoing open-label study evaluating DRF safety, tolerability, and efficacy over 96 weeks in adults with RRMS (Figure 1).
- Safety and efficacy outcomes were evaluated in the EVOLVE-MS-1 overall study population and newly diagnosed patients (≤1 year since diagnosis and treatment naive).

**Figure 1.** EVOLVE-MS-1 Study Design




BID=twice a day; DMT=disease-modifying therapy; DRF=diroximel fumarate; GI=gastrointestinal; RRMS=relapsing-remitting multiple sclerosis.
EVOLVE-MS-1 data cut: 01 September 2020.
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/.

**EVOLVE-MS-1 key eligibility criteria**

- 18–65 years old
- Confirmed RRMS diagnosis[5]
- 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

## Results

### Patients

- As of 01 September 2020, 1057 patients were enrolled, 464 of whom had completed EVOLVE-MS-2.
- Median DRF exposure was 2.0 (range, 0.0–2.1) years.
- The study included 109 newly diagnosed patients.
- Baseline characteristics are shown in Table 1.
- In the overall population, 62.3% of patients completed the study and 23.3% discontinued treatment; 8% discontinued due to adverse events (AEs) and <1% due to GI AEs.
- Rates of treatment discontinuation were 17.4% in newly diagnosed patients; discontinuation due to AEs was 6% (Figure 2) and <1% due to GI AEs.

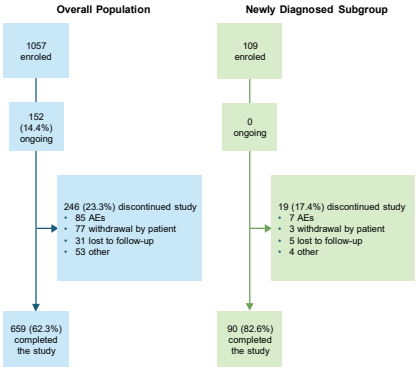
### Safety Summary

- AEs were reported in 88% (932/1057) of patients; most (89% [834/932]) were mild or moderate in severity.
- GI AEs were reported in 32% (334/1057) of patients.
- AEs and GI AEs led to treatment discontinuation in 8% and <1% of patients, respectively (Table 2).

### Efficacy Outcomes

- Annualised relapse rate was significantly reduced on treatment compared with the 12 months before study entry for both populations (Figure 3).
- Estimated proportion of patients who were:
  - Free from confirmed disability progression: 93.4% by Week 48 and 90.0% by Week 96 overall, with similar rates in the new diagnosed subgroup (Figure 4A)
  - Relapse free: 87.7% by Week 48 and 82.4% by Week 96 overall; 88.6% at Week 48 and 84.5% by Week 96 overall in newly diagnosed patients (Figure 4B)
  - No evidence of Disease Activity-3: 64.9% by Week 48 and 38.4% by Week 96 overall; 43.3% by Week 48 in newly diagnosed patients.
- Gadolinium-enhancing (Gd$^+$) lesion counts were significantly reduced at Week 96 compared with baseline for the overall population and newly diagnosed patient subgroup (Figure 5).
- The percentage of patients who were Gd$^+$ lesion free at Week 96 was 91.2% in the overall population, 85.9% in newly diagnosed patients, compared with 69.0%, and 55.4%, respectively, at baseline.
- Mean (SE) number of new/newly enlarging T2 lesions remained stable or declined slightly from Year 1 to Year 2 (Figure 6).

**Figure 2.** EVOLVE-MS-1 Patient Disposition



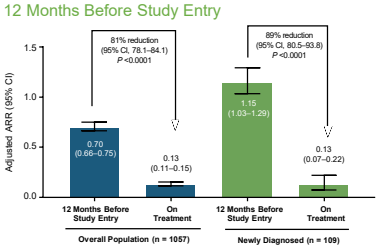

AE=adverse event.
EVOLVE-MS-1 data cut: 01 September 2020.

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

| Characteristics | Overall Population n = 1057 | Newly Diagnosed Subgroup n = 109 |
|---|---|---|
| Age, y, mean (SD) | 42.5 (10.8) | 36.0 (10.8) |
| Female, n (%) | 762 (72) | 78 (72) |
| Race, n (%) | | |
| White | 972 (92) | 104 (95) |
| Black or African American | 72 (7) | 5 (5) |
| Other | 13 (1) | 0 |
| BMI, kg/m$^2$, mean (SD) | 26.6 (6.1) | 25.4 (6.2) |
| US region, n (%) | 453 (43) | 31 (28) |
| Prior DMT[a], n (%) | 681 (64) | 0 (0) |
| Time since diagnosis, y, mean (SD) | 7.6 (7.3)[b] | 0.4 (0.5) |
| No. of relapses in previous year, mean (SD) | 0.7 (0.8) | 1.2 (0.7) |
| EDSS score, mean (SD) | 2.7 (1.5) | 2.0 (1.1) |
| No. of Gd$^+$ lesions, mean (SD) | 1.1 (3.5)[c] | 1.9 (5.1) |
| Gd$^+$ lesion free, n (%) | 741 (70) | 61 (56) |

BMI=body mass index; DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; Gd$^+$=gadolinium-enhancing.
EVOLVE-MS-1 data cut: 01 September 2020.
[a]Prior DMT includes immunomodulatory and immunosuppressant (investigational or approved). [b]n=1056. [c]n=1053.

**Figure 3.** ARR[a] on Treatment Compared With the 12 Months Before Study Entry



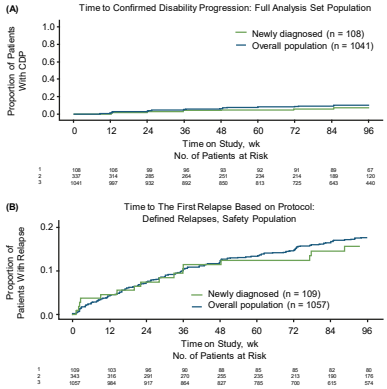

ARR = annualised relapse rate.
[a]Calculation of ARR was based on patient-reported relapses in the 12 months before study entry compared with protocol-defined relapses during the study period.

**Table 2.** Safety Summary in the Overall Population

| AE, n (%) | Overall Population n = 1057 |
|---|---|
| Any AE | 932 (88) |
| Mild | 307 (29) |
| Moderate | 527 (50) |
| Severe | 98 (9) |
| GI AE | 334 (32) |
| AEs leading to discontinuation during the treatment period | 85 (8) |
| GI AEs leading to discontinuation during the treatment period | 7 (< 1) |
| SAE | 120 (11) |
| Death[a] | 4 (< 1) |
| Most common AEs (occurring in ≥10% of patients cumulatively) | |
| Flushing | 288 (27) |
| MS relapse | 201 (19) |
| Upper respiratory tract infection | 151 (14) |
| Nasopharyngitis | 136 (13) |
| Diarrhoea | 109 (10) |
| Lymphopenia | 118 (11) |
| AEs of special interest (SOC) | |
| Cardiac disorders | 44 (4) |
| Liver injury | 76 (7.2) |
| Renal injury | 36 (3.4) |
| Infections[b] | 9 (< 1) |
| Malignancies[c] | 5 (< 1) |

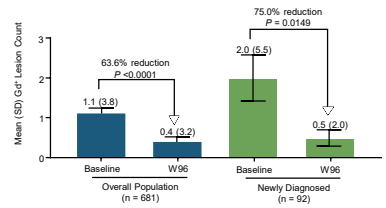
AE=adverse event; GI=gastrointestinal; MS=multiple sclerosis; SAE=serious adverse event; SOC=System Organ Class.
EVOLVE-MS-1 data cut: 01 September 2020. [a]Accidental fall, bacterial pneumonia, hypertensive heart disease, and cardiac arrest; none of the deaths were considered related to study drug by the Investigator. [b]Includes opportunistic infections (AEs and SAEs) and all serious infections (including serious opportunistic infections). [c]Includes malignancies and premalignant conditions.

**Figure 4.** Time to **(A)** CDP[a] and **(B)** First Relapse



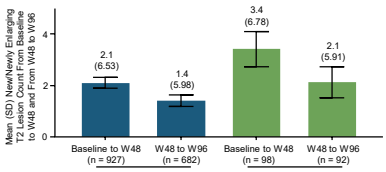

CDP was defined as progression of disability, sustained for ≥12 weeks, assessed as EDSS score increase of ≥1.5 points from a baseline score of 0, an EDSS score increase of ≥1.0 point from a baseline score between 1.0 and 5.5 (inclusive), or an EDSS score increase of ≥0.5 point from a baseline score ≥6.0.
CDP=confirmed disability progression; EDSS=Expanded Disability Status Scale.

**Figure 5.** Mean Number of Gd$^+$ Lesions




Gd$^+$=gadolinium-enhancing.
EVOLVE-MS-1 data cut: 01 September 2020.

**Figure 6.** Change From Baseline in Number of New/Newly Enlarging T2 Lesions




References 1. Vumerity (diroximel fumarate) [summary of product characteristics]. Badhoevedorp, The Netherlands: Biogen Netherlands B.V.; 2021. 2. Tecfidera (dimethyl fumarate) [summary of product characteristics]. Badhoevedorp, The Netherlands: Biogen Netherlands B.V.; 2022. 3. Wehr A, et al. Presented at: American Academy of Neurology Annual Meeting; April 21–27, 2018; Los Angeles, CA: P403. 4. Naismith RT, et al. *CNS Drugs*. 2020;34(2):185-196. 5. 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; BAS: AbbVie, Alexion, Biogen, Bristol Myers Squibb, Cigna, EMD Serono, Janssen, Genentech, Greenwich Biosciences, Horizon, Novartis, Octave Bioscience, Roche, Sanofi Genzyme and TG Therapeutics; research grant support from AbbVie, Alkermes, Biogen, Greenwich Biosciences, MedImmune, Novartis, Roche, and Sanofi Genzyme; JD: advisory boards for Bayer, Biogen, Janssen, Medis, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva; speaker bureaus for Bayer, Hemofarm, Medis, Medtronic, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva; HC, JL, and SK: employees of and hold stocks/stock options in Biogen; FTB: speaker fees/research support from and advisory boards for Bayer, Biogen, Janssen, Medis, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva; speaker bureaus for Bayer, Hemofarm, Medis, Medtronic, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva; 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, Novartis, and Sanofi-Genzyme. **Acknowledgements** This study was sponsored by Biogen (Cambridge, MA, USA). Writing and editorial support for the preparation of this poster was provided by Ashfield MedComms, an Ashfield Health company; funding was provided by Biogen.