Supplementary Appendix

Supplement to: Naismith RT, Wolinsky JS, Wundes A, et al. Diroximel Fumarate (DRF) in Patients with Relapsing-Remitting Multiple Sclerosis: Interim Safety and Efficacy Results from the Phase 3 EVOLVE-MS-1 Study

Table of Contents

Supplementary Methods

Inclusion criteria

Patients who rolled over from the EVOLVE-MS-2 study were eligible to participate in EVOLVE-MS-1 if they met the following inclusion criteria: (1) willing and able to provide informed consent, (2) capable of understanding and complying with the protocol, (3) willing to use an acceptable method of contraception for the duration of the study, and (4) completed the full treatment period of EVOLVE-MS-2 within 7 days of EVOLVE-MS-1 Study Visit 2.

Newly enrolled patients were eligible to participate in EVOLVE-MS-1 if they met the first three conditions above plus the following: (1) adult aged 18–65 at screening, (2) confirmed diagnosis of relapsing-remitting multiple sclerosis according to the revised McDonald criteria,[1] (3) Expanded Disability Status Scale score of 0.0–6.0 at screening and Visit 2, and (4) neurologically stable with no evidence of relapse within the 30 days prior to Visit 2.

Exclusion criteria

Patients who rolled over from EVOLVE-MS-2 were not eligible to participate if they met the following: (1) any findings that would compromise the safety of the patient or his/her ability to adhere to the study protocol in the opinion of the investigator, and (2) pregnant or breastfeeding, or planned to become pregnant or breastfeed during or within 30 days after the study.

Newly enrolled patients were not eligible if they met above conditions plus: (1) a diagnosis of primary progressive, secondary progressive, or progressing relapsing MS, (2) clinically significant medical condition or disease (cardiovascular, gastrointestinal, pulmonary, endocrine, renal, malignancy), medical history (suicidal ideation, drug or alcohol abuse), or laboratory abnormality (elevated aminotransferases, lymphocytes, thyroid stimulating hormone, urine test) that precluded participation in the opinion of the investigator, (3) clinically significant recurring or

active gastrointestinal symptoms within 3 months of screening, (4) history of prior dimethyl fumarate discontinuation due to tolerability or lack of efficacy, (5) positive serology test for hepatitis B, hepatitis C, or human immunodeficiency virus, (6) has received total lymphoid irradiation or stem cell transplant at any time; immunosuppressive agents within 2 years of Visit 2; teriflunomide within 2 years of Visit 2; natalizumab within 2 months of Visit 2; prior use of alemtuzumab; fingolimod within 90 days of Visit 2; daclizumab within 6 months of Visit 2; B cell–targeted therapies for the treatment of MS within 12 months of screening; orsteroids, with the exception of topical or inhaled steroids, within 30 days of Visit 2.

Supplementary Results

Timed 25-foot walk (T25-FW) scores and patient-reported outcomes (PROs)

Patient performance on the T25-FW test remained generally stable over the first year of treatment: mean (standard deviation [SD]) score was 7.0 (4.6), *n* = 675 at baseline and 7.2 (6.7), *n* = 498 at Week 48, where a score range of 6.0–7.9 indicates the patient requires some help performing activities of daily living and a >20% change in score is considered clinically meaningful.[2] Similar stability was observed for PROs: 12-Item Short Form Health Survey (mean [SD] physical score: baseline, 42.7 [10.8], *n* = 671; Week 48, 43.4 [10.6], *n* = 508; scores are compared with the mean [SD] score in the general US population, which is 50 [10])[3] and EQ-5D-5L (mean [SD] visual analogue scale score: baseline, 74.1 [17.5], *n* = 618; Week 48, 74.4 [18.1], *n* = 505; scores range 0–100, with 100 being best health imaginable).[4] However, longer-term follow-up is warranted.

Supplemental Table 1. Adverse Events Leading to Treatment Discontinuation

TEAE, *n* (%)	Overall population (*n* = 696)
Any TEAE	44 (6.3)
Blood and lymphatic system disorders	5 (0.7)
Lymphopenia	4 (0.6)
Leukopenia	1 (0.1)
Cardiac disorders	1 (0.1)
Hypertensive heart disease	1 (0.1)
Gastrointestinal disorders	5 (0.7)
Anal incontinence	1 (0.1)
Diarrhoea	1 (0.1)
Dyspepsia	1 (0.1)
Irritable bowel syndrome	1 (0.1)
Peptic ulcer	1 (0.1)
General disorders and administration site conditions	2 (0.3)
Fatigue	1 (0.1)
Feeling abnormal	1 (0.1)
Immune system disorders	2 (0.3)
Drug hypersensitivity	1 (0.1)
Hypersensitivity	1 (0.1)
Infections and infestations	1 (0.1)
Cystitis	1 (0.1)
Injury, poisoning and procedural complications	2 (0.3)
Fall	1 (0.1)
Road traffic accident	1 (0.1)
Investigations	7 (1.0)
Liver function test increased	2 (0.3)
Alanine aminotransferase increased	1 (0.1)
Blood alkaline phosphatase increased	1 (0.1)
Blood pressure abnormal	1 (0.1)
Lymphocyte count decreased	1 (0.1)
Urine albumin/creatinine ratio increased	1 (0.1)
Metabolism and nutrition disorders	1 (0.1)
Decreased appetite	1 (0.1)
Neoplasms benign, malignant and unspecified	1 (0.1)
Invasive ductal breast carcinoma	1 (0.1)
Nervous system disorders	9 (1.3)
Multiple sclerosis relapse	7 (1.0)
Hemiparesis	1 (0.1)
Migraine	1 (0.1)
Psychiatric disorders	3 (0.4)
Drug abuse	1 (0.1)
Emotional disorder	1 (0.1)
Suicidal ideation	1 (0.1)

Suicide attempt	1 (0.1)
Skin and subcutaneous tissue disorders	3 (0.4)
Urticaria	2 (0.3)
Pruritus	1 (0.1
Vascular disorders	2 (0.3)
Flushing	2 (0.3)

TEAE: treatment-emergent adverse event

Supplemental Figures

Supplemental Figure 1. Mean plasma MMF concentration over time following dosing of DRF or DMF. A single oral dose of DRF 462 mg or DMF 240 mg was administered to healthy adults, ages 18 to 55 years, while fasting. MMF was quantified in serum samples collected for pharmacokinetic evaluation following administration of study drug predose and at 0.25, 0.5, 1, 1.5, 2. 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours postdose. Mean absorption lag time was 1 hour for both treatments. For DRF and DMF, the median time to maximal concentration was 2.5 and 3.0 hours, respectively. Mean MMF concentrations were less than the lower limit of quantification by 8 hours postdose for both treatments.

DMF: dimethyl fumarate; DRF: diroximel fumarate

Supplemental Figure 2. Individual lymphocyte counts on and off treatment in the six patients who entered mandatory lymphocyte monitoring. Patients who completed or discontinued the study with a last measured ALC $<0.8 \times 10^9$/L were required to continue on study for lymphocyte reconstitution assessment (three visits over a 6-month period). Individual patient lymphocyte counts by study visit on DRF treatment, at end of treatment, and in the lymphocyte monitoring period are shown.

DRF: diroximel fumarate; ET: end of treatment visit; FU: follow-up visit; LM: lymphocyte monitoring visit

References

1. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; 69: 292-302.
2. Goldman MD, Motl RW, Scagnelli J, et al. Clinically meaningful performance benchmarks in MS: timed 25-foot walk and the real world. *Neurology* 2013; 81: 1856-1863.
3. Ware JE, Kosinski M and Keller SD. *SF-12: How to Score the SF-12 Physical and Mental Health Summary Scales*. 2nd ed. Boston, MA: The Health Institute, New England Medical Center, 1995.
4. Group E. EQ-5D-5L user guide: Basic information on how to use the EQ-5D-5L instrument, https://eurogol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf (2015, accessed 13 March 2019).