Flushing and Gastrointestinal Adverse Event Analysis From the Phase 3 EVOLVE-MS-1 Study of Diroximel Fumarate in Patients With Relapsing-Remitting Multiple Sclerosis

Faissner S,[1] Antezana AO,[2] Hernández Pérez MA,[3] de Seze J,[4] Adair H,[5] Branco F,[5] Chen H,[5] Levin S,[5] England SM,[5] Chuang M,[5] Naismith R[6]

[1]Ruhr-University Bochum, St Josef-Hospital, Bochum, Germany; [2]Neuromedical Clinic of Central Louisiana, Alexandria, LA, USA; [3]Hospital Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain; [4]Strasbourg University Hospital and Clinical Investigation Center, Strasbourg, France; [5]Biogen, Cambridge, MA, USA; [6]Washington University School of Medicine, St Louis, MO, USA

OBJECTIVE

- To evaluate flushing and flushing-related adverse events (AEs) and gastrointestinal (GI) AEs in participants treated with diroximel fumarate (DRF) in EVOLVE-MS-1.

CONCLUSIONS

- Flushing, flushing-related AEs, and GI AEs were most common in the first month of treatment with DRF.
  - These AEs were mostly mild to moderate in severity and resolved in the majority of participants.
- Among rollover groups, overall flushing, flushing-related AEs, and GI AE incidence was low, and few participants reported these AEs after 5 months of treatment.
- Flushing, flushing-related AEs, and GI AEs led to treatment discontinuation in < 1% of participants in all subgroups.
- These data are consistent with the known safety profile of DRF.

Introduction

- DRF is a next-generation oral fumarate for treatment of relapsing forms of multiple sclerosis (MS).[1,2]
- Oral administration of DRF 462 mg and dimethyl fumarate (DMF) 240 mg produce bioequivalent exposure of the active metabolite monomethyl fumarate; therefore, DRF is expected to exhibit comparable efficacy and safety profiles to DMF.[3,4]
- Flushing, flushing-related AEs, and GI AEs are commonly reported AEs with DMF treatment.[5]
- Phase 3 clinical trials of DRF have demonstrated favorable GI tolerability and a low rate (< 1%) of treatment discontinuation due to GI AEs.[4,6]
- The aim of this analysis is to characterize incidence and impact of flushing, flushing-related AEs, and GI AEs in EVOLVE-MS-1.

Methods

Study Design

- EVOLVE-MS-1 (NCT02634307), an open-label, 96-week, Phase 3 study, assessed safety, tolerability, and efficacy of DRF in adults with relapsing-remitting MS between 10 December 2015 and 11 November 2021.
- Participants either newly initiated DRF (de novo) or rolled over from completing EVOLVE-MS-2 (NCT03093324), a randomized, blinded, Phase 3 study of DRF or DMF over 5 weeks.
  - Participants who took DRF during EVOLVE-MS-2 formed the DRF rollover group.
  - Participants who took DMF during EVOLVE-MS-2 formed the DMF rollover group.
- From the final data of EVOLVE-MS-1, we report outcomes for treatment-emergent flushing, flushing-related AEs, and treatment-emergent GI AEs in the overall study population and in the de novo, DRF rollover, and DMF rollover subgroups.
  - Flushing and flushing-related AEs included: flushing, pruritus, erythema, rash, feeling hot, burning sensation, generalized pruritus, generalized erythema, skin burning sensation, hot flush, pruritic rash, maculo-papular rash, papular rash, and macular rash.

Results

Participants

- Overall, 1057 participants were enrolled in EVOLVE-MS-1. Four hundred sixty-four participants had completed EVOLVE-MS-2: 239 in the DRF rollover group and 225 in the DMF rollover group. Five hundred ninety-three participants were newly initiated on DRF (de novo; Table 1).
- Mean (SD) age of participants in the overall population was 42.5 (10.8) years with a mean (SD) time since MS onset of 9.8 (8.3) years.
- Median (range) DRF exposure was 1.84 (0–1.96) years.

Safety Summary

- AEs were reported in 938 (89%) participants: 88% (519/593) in the de novo group, 89% (212/239) in the DRF rollover group, and 92% (207/225) in the DMF rollover group.
  - Most AEs were mild or moderate in severity (Table 2).
- AEs led to discontinuation of DRF in 8.0% (85/1057) of participants in the overall population, 8.3% (49/593) in the de novo population, 9.6% (23/239) of the DRF rollover group, and 5.8% (13/225) of the DMF rollover group.

Flushing and Flushing-Related AEs

- Flushing and flushing-related AEs were reported in 36.7% (388/1057) of patients.
  - Incidence of flushing and flushing-related AEs were highest in the de novo group: 49.2% (292/593) versus 22.2% (53/239) in the DRF rollover group and 21.8% (49/225) in the DMF rollover group.
  - Flushing and flushing-related AEs led to treatment discontinuation in 0.8% (8/1057) of participants in the overall population.
- Among participants with flushing and flushing-related AEs with complete start dates, the majority (71.9% [279/388]) had events within the first month of treatment.
  - Flushing and flushing-related AEs in the first month were highest in the de novo group (40.8%) compared with the DRF rollover (8.8%) and DMF rollover (7.1%) groups (Figure 1).
  - Overall, < 2% of participants per month reported flushing AEs from ≥ 5 months to 24 months.
- Flushing and flushing-related AEs resolved in 84.5% (328/388) of participants.
- Of participants with flushing and flushing-related AEs, 17% were concomitantly taking aspirin, which is used to reduce occurrence and severity of flushing.

GI AEs

- Overall, 31.9% (337/1057) of participants reported GI AEs: 33.7% (200/593) of de novo participants, 29.7% (71/239) of DRF rollover participants, and 29.3% (66/225) of DMF rollover participants.
  - GI AEs led to discontinuation of treatment in 0.7% (7/1057) of the overall population, 0.4% (1/239) of the DRF rollover group, and 0.4% (1/225) of the DMF rollover group.
- Median duration of GI AEs that resolved was 10.0 days for participants in the overall population, 10.5 days for de novo participants, 13.0 days for DRF rollover participants, and 8.0 days for DMF rollover participants.
- Months 1 and 2 had the highest frequency of GI AEs with 15.0% and 4.5% of patients, respectively.
  - Data were available for the 336 participants for whom complete start dates for GI AEs were recorded.
  - Incidence of GI AEs in the first month was highest in the de novo group (19.7%) compared with the DRF rollover (9.2%) and DMF rollover (8.9%) groups (Figure 2).
- GI AEs resolved in 91.7% (309/337) of participants.
- Of participants with GI AEs, 155/337 (46.0%) received transient concomitant therapy for GI symptoms.
- Overall, 94.4% of GI AEs were mild or moderate, with 9 severe cases in the de novo group, and 5 severe cases in both the DRF and DMF rollover groups (Table 3).

Table 1. Baseline Demographics

Demographics	De Novo n = 593	DRF Rollover n = 239	DMF Rollover n = 225	Overall n = 1057
Mean (SD) age, y	41.5 (11.0)	44.0 (11.0)	43.7 (9.8)	42.5 (10.8)
Female, n (%)	427 (72.0)	165 (69.0)	170 (75.6)	762 (72.1)
Mean (SD) BMI, kg/m^2	26.2 (6.1)	27.0 (5.9)	27.6 (6.2)	26.6 (6.1)
Race, n (%)				
White	547 (92.2)	220 (92.1)	205 (91.1)	972 (92.0)
Black or African American	37 (6.2)	19 (7.9)	16 (7.1)	72 (6.8)
Asian	4 (0.7)	0	1 (0.4)	5 (0.5)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.4)	1 (<0.1)
Other	5 (0.8)	0	2 (0.9)	7 (0.7)
Prior DMT, n (%)[a]	379 (63.9)	159 (66.5)	143 (63.6)	681 (64.4)
Time since MS onset, y, mean (SD)	9.8 (8.0)	9.6 (8.9)	9.9 (8.5)	9.8 (8.3)
No. of relapses in previous year, mean (SD)	0.8 (0.8)	0.6 (0.7)	0.6 (0.7)	0.7 (0.8)
EDSS score, mean (SD)	2.7 (1.5)	2.6 (1.5)	2.7 (1.4)	2.7 (1.5)
No. of Gd+ lesions, mean (SD)	1.3 (4.2)	0.8 (2.2)	0.9 (2.6)	1.1 (3.5)
Gd+ lesion free, n (%)	406 (68.5)	176 (73.6)	159 (70.7)	741 (70.1)

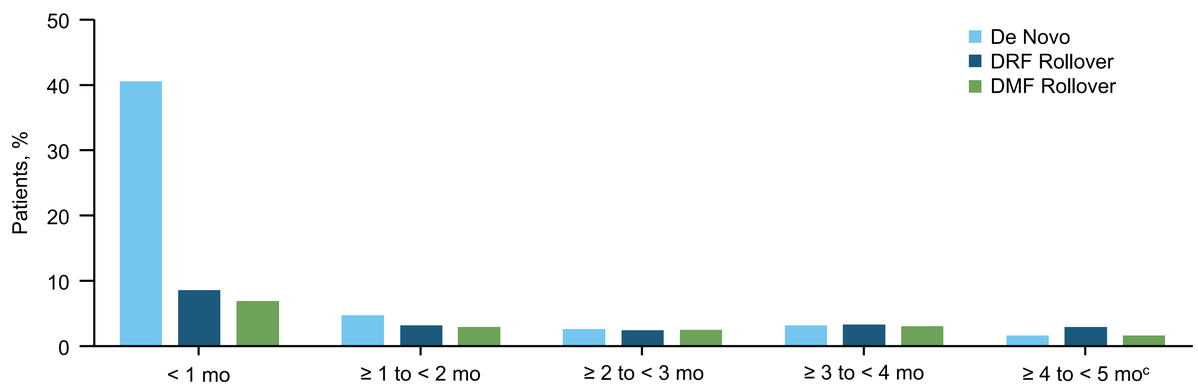
BMI = body mass index; DMF = dimethyl fumarate; DMT = disease-modifying therapy; DRF = diroximel fumarate; EDSS = Expanded Disability Status Scale; Gd+ = gadolinium-enhancing; MS = multiple sclerosis
[a]Prior DMT includes immunomodulatory and immunosuppressant (investigational or approved).

Table 2. Safety Summary

AE[a], n (%)	De Novo n = 593	DRF Rollover n = 239	DMF Rollover n = 225	Overall n = 1057
Any AE	519 (87.5)	212 (88.7)	207 (92)	938 (88.7)
Mild	170 (28.7)	66 (27.6)	70 (31.1)	306 (28.9)
Moderate	297 (50.1)	123 (51.5)	112 (49.8)	532 (50.3)
Severe	52 (8.8)	23 (9.6)	25 (11.1)	100 (9.5)
SAE[a]	69 (11.6)	29 (12.1)	25 (11.1)	123 (11.6)
AEs leading to discontinuation	49 (8.3)	23 (9.6)	13 (5.8)	85 (8.0)
GI AE	200 (33.7)	71 (29.7)	66 (29.3)	337 (31.9)
GI AEs leading to discontinuation	5 (0.8)	1 (0.4)	1 (0.4)	7 (0.7)
Flushing, flushing-related AE[b]	288 (48.6)	51 (21.3)	49 (21.8)	388 (36.7)
Flushing, flushing-related AE leading to treatment discontinuation	4 (0.7)	3 (1.3)	1 (0.4)	8 (0.8)
Death[c]	3 (0.5)	1 (0.4)	0	4 (0.4)
Most common AEs (occurring in ≥ 10% of participants):				
Flushing	226 (38.1)	33 (13.8)	29 (12.9)	288 (27.2)
MS relapse	113 (19.1)	48 (20.1)	45 (20.0)	206 (19.5)
URTI	76 (12.8)	42 (17.6)	35 (15.6)	153 (14.5)
Nasopharyngitis	86 (14.5)	24 (10.0)	27 (12.0)	137 (13.0)
Lymphopenia	51 (8.6)	35 (14.6)	38 (16.9)	124 (11.7)
Diarrhea	66 (11.1)	18 (7.5)	25 (11.1)	109 (10.3)
UTI	55 (9.3)	25 (10.5)	24 (10.7)	104 (9.8)
Headache	49 (8.3)	23 (9.6)	24 (10.7)	96 (9.1)
Fatigue	39 (6.6)	26 (10.9)	22 (9.8)	87 (8.2)

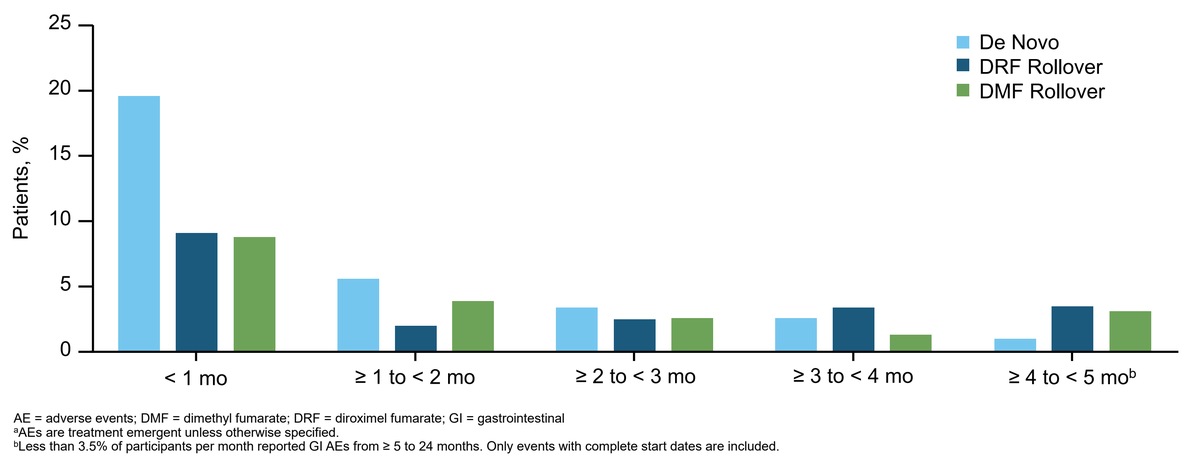
AE = adverse event; DMF = dimethyl fumarate; DRF = diroximel fumarate; GI = gastrointestinal; MS = multiple sclerosis; SAE = serious adverse event; URTI = upper respiratory tract infection; UTI = urinary tract infection
[a]AEs are treatment-emergent unless otherwise indicated.
[b]Flushing, flushing-related AEs included: flushing, pruritus, erythema, rash, feeling hot, burning sensation, pruritus generalized, generalized erythema, skin burning sensation, hot flush, pruritic rash, maculo-papular rash, papular rash, and macular rash.
[c]Accidental fall, bacterial pneumonia, hypertensive heart disease, and cardiac arrest; none of the deaths were considered related to study drug by the Investigator.

Figure 1. Percentage of Participants Reporting Flushing and Flushing-Related[a] AEs[b] Over 24 Months



AE = adverse event; DMF = dimethyl fumarate; DRF = diroximel fumarate
[a]Flushing, flushing-related AEs included: flushing, pruritus, erythema, rash, feeling hot, burning sensation, pruritus generalized, generalized erythema, skin burning sensation, hot flush, pruritic rash, maculo-papular rash, papular rash, and macular rash.
[b]AEs are treatment-emergent unless otherwise specified.
[c]Less than 2% of participants per month reported flushing from ≥ 5 to 24 months.
Only events with complete start dates are included.

Figure 2. Percentage of Participants Reporting GI AEs[a] Over 24 Months



AE = adverse events; DMF = dimethyl fumarate; DRF = diroximel fumarate; GI = gastrointestinal
[a]AEs are treatment emergent unless otherwise specified.
[b]Less than 3.5% of participants per month reported GI AEs from ≥ 5 to 24 months. Only events with complete start dates are included.

Table 3. Severity of Flushing and Flushing-Related AEs[a] and GI AEs[b]

	De Novo n = 593	DRF Rollover n = 239	DMF Rollover n = 225	Overall n = 1057
Flushing and flushing-related AE severity in participants with flushing and flushing-related AEs	n = 292	n = 53	n = 49	n = 394
Mild, n (%)	224 (76.7)	36 (67.9)	40 (81.6)	300 (76.1)
Moderate, n (%)	63 (21.6)	13 (24.5)	8 (16.3)	84 (21.3)
Severe, n (%)	5 (1.7)	4 (7.5)	1 (2.0)	10 (2.5)
GI AEs severity in participants with GI AE	n = 200	n = 71	n = 66	n = 337
Mild, n (%)	132 (66.0)	40 (56.3)	33 (50.0)	205 (60.8)
Moderate, n (%)	59 (29.5)	26 (36.6)	28 (42.4)	113 (33.5)
Severe, n (%)	9 (4.5)	5 (7.0)	5 (7.6)	19 (5.6)

AE = adverse event; GI = gastrointestinal; DMF = dimethyl fumarate; DRF = diroximel fumarate
If a participant experiences > 1 adverse event in a category, the participant is counted only once according to the greatest severity.
[a]Flushing, flushing-related AEs included: flushing, pruritus, erythema, rash, feeling hot, burning sensation, pruritus generalized, generalized erythema, skin burning sensation, hot flush, pruritic rash, maculo-papular rash, papular rash, and macular rash.
[b]AEs are treatment emergent unless otherwise specified.

References 1. Vumerity [summary of product characteristics]. Netherlands B.V.: Biogen; 2022. 2. Vumerity [prescribing information]. Cambridge, MA: Biogen; 2022. 3. Tecfidera [prescribing information]. Cambridge, MA: Biogen; 2022. 4 Naismith RT, et al. *Mult Scler*. 2020;26(13):1729-1739. 5. Gold R, et al. *Mult Scler*. 2022;28(5):801-816. 6. Naismith RT, et al. *CNS Drugs*. 2020;34(2):185-196. Disclosures SF: speaker/scientific board honoraria from Biogen, BMS, Celgene, Genesis Pharma, Novartis, and Roche; grant support from Ruhr-University Bochum, DMSG, Stiftung für therapeutische Forschung, Lead Discovery Center GmbH, and Novartis; AA: consultant for TG Therapeutics; speaker for Biogen, Bristol Myers Squibb, and EMD Serono; MAHP and JdS: nothing to disclose; HA, FB, HC, SL, SE, and MC: employees of and hold stocks/stock options in Biogen; RN: consultant for Abata Therapeutics, Banner Life Sciences, BeiGene, Biogen, Bristol Myers Squibb, Genentech, Genzyme, GW Therapeutics, Janssen, Horizon Therapeutics, Lundbeck, NervGen, and TG Therapeutics. Acknowledgments This study was sponsored by Biogen (Cambridge, MA, USA). Writing and editorial support for the preparation of this poster was provided by Excel Scientific Solutions (Fairfield, CT, USA): funding was provided by Biogen.