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Flushing and Flushing-Related Adverse Events With Diroximel Fumarate in Patients With Relapsing-Remitting Multiple Sclerosis: Results From the Phase 3 EVOLVE-MS-2 Study

Singer BA,[1] Faissner S,[2] Lyons J,[3] Scaramozza M,[3] Woodward C,[3] Wang T,[3] Branco F,[3] Vosoughi R[4]

[1]The MS Center for Innovations in Care, Missouri Baptist Medical Center, St. Louis, MO, USA; [2]Department of Neurology, Ruhr-University Bochum, St. Josef-Hospital, Bochum, Germany; [3]Biogen, Cambridge, MA, USA; [4]Division of Neurology, Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada

OBJECTIVE

- **To present the incidence, severity, and duration of flushing and flushing-related treatment-emergent adverse events (TEAEs) with diroximel fumarate (DRF) versus dimethyl fumarate (DMF) over 5 weeks in EVOLVE-MS-2.**

CONCLUSIONS

- **In the EVOLVE-MS-2 study, the number and duration of flushing AEs were lower for patients treated with DRF compared with DMF.**
  - **EVOLVE-MS-2 was not designed to assess differences in flushing, and previous DMF clinical studies have demonstrated that rates for the TEAE preferred term of "flushing" are variable (24–38%) and not correlated with dose.**
- **Due to the expected variability in rates of flushing, additional real-world data generation is needed to understand the clinical meaningfulness of these findings.**

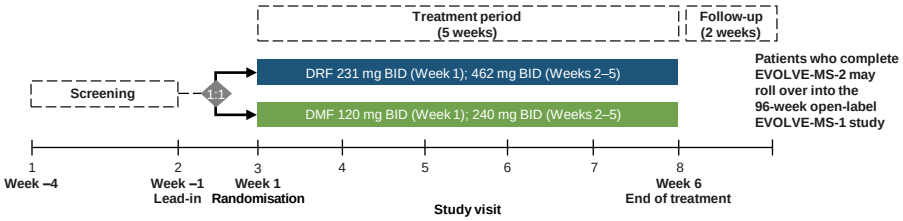
Introduction

- DRF is a next-generation oral fumarate for relapsing multiple sclerosis (MS).
- DRF and DMF produce bioequivalent exposure to the active metabolite monomethyl fumarate.[1-3]
- The mechanism of DMF-induced flushing is not fully elucidated; however, it may be mediated, at least in part, by prostaglandin D_2 (PGD_2). Elevated levels of the PGD_2 metabolite 9α,11β-PGF_2 were seen in some patients following DMF administration. Furthermore, pretreatment with aspirin (which can suppress the production of prostaglandins) decreased the incidence and severity of flushing.[4]
- Flushing incidence was variable across DMF Phase 3 studies (24–38%) and was not correlated with dose.[5-7] DRF has demonstrated improved gastrointestinal tolerability compared with DMF[8]; however, no studies have compared rates of flushing with DRF versus DMF.

Methods

- A post hoc analysis of flushing and flushing-related TEAEs ("flushing") was conducted in patients with relapsing-remitting MS who received DRF or DMF for 5 weeks in the randomised, double-blind, Phase 3 EVOLVE-MS-2 study (NCT03093324). TEAEs were collected by investigators at each study visit (Figure).

Figure. EVOLVE-MS-2 Study Design: Phase 3, Randomised, Double-blind Treatment With DRF or DMF Over 5 Weeks



BID = twice a day; DMF = dimethyl fumarate; DRF = diroximel fumarate

Results

- In EVOLVE-MS-2, 253 and 251 patients received ≥1 dose of DRF or DMF, respectively (Table 1).
- The incidence of flushing was lower with DRF (46%; 116/253) versus DMF (55%; 138/251). All flushing was mild or moderate in severity with DRF; 5 patients (2%) experienced severe flushing events with DMF (Table 2).
- The majority of events occurred in the first week of treatment (DRF 84% [98/116]; DMF 86% [118/138]).
- Median (P10, P90) duration of flushing before resolution was shorter in the DRF group versus the DMF group (1.0 [1, 17] vs. 3.0 [1, 29] days, respectively; Table 3).
- No patients treated with DRF or DMF in EVOLVE-MS-2 discontinued treatment due to flushing. In the ongoing EVOLVE-MS-1, <1% of patients discontinued treatment due to flushing (Table 4).

Table 1. Incidence of Flushing and Flushing-Related TEAEs[a] in EVOLVE-MS-2

Preferred Term, n (%)	Treatment Group: DRF n = 253	Treatment Group: DMF n = 251
Any flushing or flushing-related TEAEs[1]	116 (45.8)	138 (55.0)
Flushing	83 (32.8)	102 (40.6)
Erythema	20 (7.9)	21 (8.4)
Pruritus	18 (7.1)	18 (7.2)
Generalized erythema	4 (1.6)	9 (3.6)
Feeling hot	4 (1.6)	6 (2.4)
Rash	4 (1.6)	6 (2.4)
Pruritus generalized	2 (0.8)	6 (2.4)
Hot flush	4 (1.6)	2 (0.8)
Burning sensation	2 (0.8)	2 (0.8)
Rash pruritic	0	1 (0.4)

DMF = dimethyl fumarate; DRF = diroximel fumarate; TEAE = treatment-emergent adverse event
[a]Flushing and flushing-related TEAEs include flushing, hot flush, erythema, generalized erythema, burning sensation, skin burning sensation, feeling hot, pruritus, pruritus generalized, rash, rash pruritic, rash maculo-papular, rash macular, and rash papular.

Table 2. Severity of Flushing in EVOLVE-MS-2

Preferred Term, n (%)	DRF n = 253	DMF n = 251
Any flushing and flushing-related TEAEs	116 (45.8)	138 (55.0)
Mild	87 (34.4)	105 (41.8)
Moderate	29 (11.5)	28 (11.2)
Severe	0	5 (2.0)

DMF = dimethyl fumarate; DRF = diroximel fumarate; TEAE = treatment-emergent adverse event

Table 3. Duration of Flushing in EVOLVE-MS-2 in Patients With Complete TEAE Start/Stop Dates

	DRF n = 253	DMF n = 251
Participants with treatment-emergent flushing and flushing-related adverse events, n (%)	80 (31.6)	89 (35.5)
Mean (SD)	6.6 (10.74)	8.5 (10.11)
Median	1.0	3.0

DMF = dimethyl fumarate; DRF = diroximel fumarate; TEAE = treatment-emergent adverse event
Duration (day) = TEAE stop date – TEAE start date + 1. If a participant had the same resolved adverse event on multiple occasions during the treatment period, the mean duration was used. Participants with complete TEAE start/stop dates were included.

Table 4. Incidence of Flushing on DRF Leading to Discontinuation From the EVOLVE-MS-1 Study

	DRF
Patients included in the safety population as of 30 September 2020, n (%)	1057 (100)
Participants with flushing leading to discontinuation, n (%)	8 (0.8)

DRF = diroximel fumarate

- In DEFINE/CONFIRM, reports of flushing were higher in DMF-treated patients compared with placebo; flushing led to discontinuations in 4% of DMF-treated patients compared with <1% of placebo-treated patients.[5-7]

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