Improving the Gastrointestinal Tolerability of Fumaric Acid Esters: Early Findings on Gastrointestinal Events with Diroximel Fumarate in Patients with Relapsing-Remitting Multiple Sclerosis from the Phase 3, Open-Label EVOLVE-MS-1 Study

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ABSTRACT

Introduction: Diroximel fumarate (DRF) is a novel oral fumarate in development for patients with relapsing forms of multiple sclerosis (MS). Clinical findings from the DRF development program suggest that rates of gastrointestinal (GI) treatment-emergent adverse events (TEAEs) and discontinuation due to GI TEAEs are low, based on clinical and real-world observations of other fumaric acid esters, including dimethyl fumarate (DMF). The incidence of GI TEAEs varies from 40 to 88% in clinical and real-world studies of DMF. The objective of this study is to present GI tolerability findings from the EVOLVE-MS-1 study and present biologic hypotheses for the improved GI properties of DRF.

Methods: GI TEAEs and treatment discontinuation because of GI TEAEs were assessed in DRF-treated patients with relapsing-remitting MS who were participating in the ongoing, 96-week, open-label, phase 3 EVOLVE-MS-1 study.

Results: As of March 30, 2018, a total of 696 patients were enrolled in EVOLVE-MS-1. GI TEAEs were reported in 30.9% (215/696) of patients; the vast majority (96%; 207/215) experienced events that were mild or moderate in severity. When GI AEs did occur, they occurred early in treatment, resolved (88.8%; 191/215), and were of short duration [median 7.5 (range 1–87) days] in most patients. GI TEAEs led to < 1% of patients discontinuing treatment.

Conclusions: We suggest that the distinct chemical structure of DRF contributes to the observed low rates of GI TEAEs and GI-associated treatment discontinuations, possibly due to a combination of several factors. We hypothesize that these factors may include less reactivity with off-target proteins and/or lower production of a methanol leaving group that may contribute to GI irritation. A direct
comparison of GI tolerability with DRF versus DMF is being evaluated in the EVOLVE-MS-2 study.

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**Keywords:** Dimethyl fumarate; Diroximel fumarate; Fumaric acid ester; Gastrointestinal; Multiple sclerosis; Neurology; Relapsing-remitting multiple sclerosis; Tolerability

**INTRODUCTION**

Delayed-release dimethyl fumarate (DMF) is a fumaric acid ester (FAE) approved as an oral therapy for relapsing forms of multiple sclerosis (MS). DMF has been shown to be effective in significantly reducing clinical and radiologic measures of disease activity in patients with relapsing-remitting MS (RRMS) in clinical trials as well as in patients with MS treated in real-world studies [1–5]. DMF undergoes esterase cleavage to monomethyl fumarate (MMF) prior to reaching systemic circulation in the blood (Fig. 1a). DMF therapy is thought to act by modulating cell-signal pathways that produce neuroprotective and immunomodulatory effects [6–8].

Through clinical trial and real-world experience, the benefits of DMF treatment for patients with relapsing MS and its safety profile have been well established [1–5]. Gastrointestinal (GI) side effects are commonly reported in patients receiving DMF therapy, including nausea, vomiting, diarrhea, and upper abdominal pain [9–11]. During phase 3 trials, GI adverse events (AEs) were reported in 40% of patients treated with DMF compared with 30% of patients treated with placebo [1, 2]. The incidence of GI AEs was 88% in a real-world study in which patients self-reported symptoms using eDiaries [10]. Although GI events are generally mild in severity and typically resolve within the first 2 months of treatment, these issues may impact patient quality of life and ultimately medication adherence. GI AEs are a common cause of discontinued DMF treatment [1, 2, 10, 12, 13].

![Fig. 1 Fumaric acid ester metabolism.](image)

a) Upon oral administration, DMF undergoes esterase cleavage before systemic circulation to produce the major metabolites MMF and methanol. b) DRF undergoes esterase cleavage to produce the major metabolites MMF and HES and the minor metabolites RDC-8439 and methanol. DMF dimethyl fumarate, DRF diroximel fumarate, HES 2-hydroxyethyl succinimide, MMF monomethyl fumarate.
Diroximel fumarate (DRF) is a novel oral fumarate in development for patients with relapsing forms of MS. Like DMF, DRF is metabolized to MMF, but with the methanol leaving group substituted with an inert leaving group, 2-hydroxyethyl succinimide (HES; Fig. 1b) [14]. At therapeutic doses, DRF and DMF produce bioequivalent systemic exposure of MMF, which is thought to drive efficacy in patients with MS. However, the other metabolite profiles of DMF and DRF are different. The first step of DRF metabolism produces two major metabolites, MMF and HES, and two minor metabolites, RDC-8439 and methanol (Fig. 1b). This is in contrast to DMF, where the first step of metabolism produces MMF and methanol as the major metabolites (Fig. 1a). Because of its chemical structure and corresponding metabolites, DRF is expected to confer an efficacy and safety profile consistent with the experience of DMF, but with an improved GI tolerability profile.

The effects of DRF, including its GI tolerability profile, are being assessed as part of the DRF clinical development program, which comprises ten completed phase 1 studies (nine conducted in healthy volunteers; one conducted in healthy volunteers and patients with varying degrees of renal impairment) and two phase 3 studies in patients with RRMS; EVOLVE-MS-1 and EVOLVE-MS-2. Over 1500 participants have received DRF as part of the clinical development program, including 696 patients (representing 685 patient-years of exposure) enrolled in the ongoing EVOLVE-MS-1 study as of March 2018. Clinical findings from the DRF development program suggest that rates of GI events and discontinuation due to GI events are low. The objective of this article is to present GI tolerability findings from the phase 3 EVOLVE-MS-1 study and to present biologic hypotheses for why rates of GI AEs with DRF appear low.

METHODS

EVOLVE-MS-1 Study

Two phase 3 studies are assessing patients with RRMS treated with DRF. EVOLVE-MS-1 (NCT02634307) is an ongoing, global, open-label, single-arm, phase 3 study assessing long-term safety, tolerability, and treatment effects of DRF 462 mg twice daily over 96 weeks. The EVOLVE-MS-1 study design, end points, and analysis populations have been described previously (R.T. Naismith et al., Multiple Sclerosis Journal, accepted, 2019). EVOLVE-MS-1 enrollment is ongoing, with 800–1000 patients planned for this study. The EVOLVE-MS-1 study population includes patients who rolled over from the 5-week EVOLVE-MS-2 (NCT03093324) study and those who were newly enrolled in the DRF clinical development program. EVOLVE-MS-2 is a randomized, double-blind, phase 3 study to evaluate the tolerability of DRF versus DMF over 5 weeks.

EVOLVE-MS-1 Patients and Dosing

DRF 462 mg was administered twice daily by oral capsules. Patients receiving DRF for the first time were given a titrated dose of DRF 231 mg twice daily for the first study week followed by 462 mg twice daily thereafter; all other patients received DRF 462 mg twice daily over the entire 96-week study period.

The EVOLVE-MS-1 study protocol did not include specific instructions on management strategies for patients with GI TEAEs. However, dose reduction to 231 mg twice daily was permitted at the investigator’s discretion starting on day 8 of treatment for patients unable to tolerate the 462 mg twice-daily dose. If a patient continued to be unable to tolerate the 462 mg twice-daily dose after 1 month of treatment, further dose reduction was not permitted and that patient was discontinued from the study. Concomitant medications for treating GI symptoms were not prohibited.

Patients participating in the phase 3 EVOLVE-MS-1 study were 18–65 years of age, with a confirmed diagnosis of RRMS [15] and no evidence of relapse within 30 days of screening. Patients were not eligible if they had significant recurring or active GI symptoms within 3 months of screening, including symptoms that required the initiation of or change in symptomatic medical treatment; clinically
significant gastrointestinal and/or other major
disease that would preclude participation in a
clinical trial, prior history of DMF discontinua-
tion because of tolerability issues or lack of
efficacy; or a clinically significant medical con-
dition that prevented participation in the
opinion of the investigator.

The EVOLVE-MS-1 study protocol was
approved by the institutional review board at
each study site. The study was conducted in
accordance with the Declaration of Helsinki and
International Council of Harmonisation Good
Clinical Practice guidelines. All study partici-
pants provided written, informed consent.

Assessments and Analysis Populations

Safety was evaluated based on the incidence of
treatment-emergent AEs (TEAEs), incidence of
serious AEs, and AEs leading to discontinued
treatment. TEAEs were reported and coded
according to medical dictionary for regulatory
activities (MedDRA) system organ class (SOC).
GI TEAEs were coded according to the MedDRA
preferred terms within the SOC for GI disorders,
which included nausea, diarrhea, upper
abdominal pain, vomiting, constipation,
abdominal pain, flatulence, gastroesophageal
reflux disease, abdominal discomfort, and 34
other GI-related events. As patients with prior
history of significant GI disease were excluded
from the study, herein we report GI events that
occurred during the treatment period (GI
TEAEs). Safety analyses were performed using
the safety population, which was defined as all
patients who received at least one dose of study
drug. Summary statistics were provided for
safety data.

RESULTS

Patients

As of March 30, 2018, a total of 696 patients
were enrolled in the ongoing phase 3 EVOLVE-
MS-1 study and received at least one dose of
DRF. Enrolled patients were mean (SD) 41.9
(11.0) years of age; 72.6% were female, 91.7%
were white, 40.7% were enrolled in the United
States, and 64.9% had received prior disease-
modifying therapy. Mean (SD) time since diag-
nosis was 7.6 (7.3) years.

GI TEAEs and Treatment Discontinuation
Because of GI TEAEs

At the time of the data cut (March 30, 2018),
patients had received DRF for a median of 59.9
(range, 0.1–98.9) weeks. Of the 696 enrolled
patients, 83.2% were on treatment with DRF, 1.9%
completed the study, and 14.9% discontinued
treatment; 6.3% discontinued DRF
because of AEs. Less than 1% of patients discon-
tinued DRF specifically because of GI TEAEs
(0.7%; 5/696; one patient each with anal
incontinence, diarrhea, dyspepsia, irritable
bowel syndrome, and peptic ulcer).

GI TEAEs were reported in 30.9% (215/696)
of the overall population, the most common
(occurring in at least 2% of patients) of which
were diarrhea (10.8%; 75/696), nausea (6.8%;
47/696), upper abdominal pain (4.5%; 31/696),
vomiting (3.6%; 25/696), constipation (3.4%;
24/696), abdominal pain (2.4%; 17/696), flatu-
lence (2.2%; 15/696), and gastroesophageal
reflux disease (2.0%; 14/696; Table 1). Among
patients with GI TEAEs, the vast majority, 96%
(207/215), had events that were mild or mod-
erate in severity; the severity of specific GI
events is shown in Table 1. Serious GI AEs
were reported in 0.4% (3/696) of patients (Table 1).

GI TEAEs occurred early in treatment, typi-
cally within 1 month of initiating DRF. Among
the 214 patients with GI TEAEs with complete
start and end dates recorded, 60.3% (129/214)
experienced their first event at < 1 month,
9.8% (21/214) had first events from ≥ 1
to < 2 months, 5.1% (11/214) had events
from ≥ 2 to < 3 months, 9.3% (20/214) had
events from ≥ 3 to < 6 months, 7.5% (16/214)
had events from ≥ 6 to < 9 months, 3.7%
(8/214) had events from ≥ 9 to < 12 months,
and 4.2% (9/214) had events at ≥ 12 months.
Median (25th–75th percentile) time to onset for
first GI TEAE was 19 (5–83) days. Incidence of
overall and key individual GI events by time
interval is shown in Fig. 2. Of patients who
experienced GI TEAEs, events resolved in 88.8% (191/215) of patients with a median (10th–90th percentile) duration of 7.5 (1–87) days; median (10th–90th percentile) duration of diarrhea was 5 (1–63) days, nausea was 4 (1–86) days, upper abdominal pain 5 (1–94) days, and vomiting 1 (1–14) day. Durations of additional individual GI events are shown in Table 2 and Fig. 3.

**Patient Management**

Patients who experienced GI TEAEs with DRF treatment were allowed to reduce their DRF dose temporarily and/or receive concomitant therapy to manage GI symptoms. GI TEAEs led to dose reduction in 1.9% (13/696) patients. Thirty-nine percent (84/215) of patients who experienced GI TEAEs received transient concomitant therapy to treat GI symptoms.

**DISCUSSION**

Interim findings from the ongoing, 96-week, open-label EVOLVE-MS-1 study suggest that DRF is a well-tolerated treatment option for patients with RRMS. Patients in EVOLVE-MS-1

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**Table 1** Incidence and severity of gastrointestinal TEAEs and serious gastrointestinal events occurring in patients in EVOLVE-MS-1

| TEAE, n (%) | Phase 3 EVOLVE-MS-1, N = 696 |
|-------------|-------------------------------|
|             | Mild | Moderate | Severe | Total |
| Gastrointestinal disorders<sup>a</sup> | 147 (21.1) | 60 (8.6) | 8 (1.1) | 215 (30.9) |
| Diarrhea | 48 (6.9) | 24 (3.4) | 3 (0.4) | 75 (10.8) |
| Nausea | 39 (5.6) | 8 (1.1) | 0 | 47 (6.8) |
| Upper abdominal pain | 27 (3.9) | 4 (0.6) | 0 | 31 (4.5) |
| Vomiting | 14 (2.0) | 10 (1.4) | 1 (0.1) | 25 (3.6) |
| Constipation | 21 (3.0) | 2 (0.3) | 1 (0.1) | 24 (3.4) |
| Abdominal pain | 6 (0.9) | 10 (1.4) | 1 (0.1) | 17 (2.4) |
| Flatulence | 14 (2.0) | 1 (0.1) | 0 | 15 (2.2) |
| Gastroesophageal reflux disease | 9 (1.3) | 5 (0.7) | 0 | 14 (2.0) |
| Abdominal discomfort | 13 (1.9) | 0 | 0 | 13 (1.9) |
| Dyspepsia | 10 (1.4) | 1 (0.1) | 1 (0.1) | 12 (1.7) |
| Dental caries | 2 (0.3) | 3 (0.4) | 1 (0.1) | 6 (0.9) |
| Dysphagia | 4 (0.6) | 2 (0.3) | 0 | 6 (0.9) |
| Dry mouth | 4 (0.6) | 1 (0.1) | 0 | 5 (0.7) |
| Gastrointestinal disorders, serious events | 3 (0.4) |
| Abdominal pain | – | – | – | 1 (0.1) |
| Inguinal hernia | – | – | – | 1 (0.1) |
| Peptic ulcer | – | – | – | 1 (0.1) |

Data cutoff date is March 30, 2018. *–* indicates not applicable

**TEAE** treatment-emergent adverse event

<sup>a</sup> Events occurring in at least five patients; data are based on the Medical Dictionary for Regulatory Activities system organ class and preferred terms
who reported GI TEAEs typically experienced events that were mild, transient (89% resolved), and of short duration (median, 7.5 days). Most events occurred within 1 month of treatment initiation. The timing and severity of GI TEAEs with DRF are similar to patterns observed in clinical trials of DMF [1, 2, 10]. However, the overall proportion of patients experiencing GI

![Graph](image)

**Fig. 2** GI TEAEs occurred early in treatment. Incidence of all GI TEAEs, diarrhea, nausea, and vomiting were reported by time interval. Patients with multiple events in a time interval were counted only once for that interval. Patients who experienced events in multiple time intervals were counted with each interval. DRF diroximel fumarate, GI gastrointestinal, TEAE treatment-emergent adverse event

**Table 2** Summary of duration of gastrointestinal TEAEs that resolved in patients in EVOLVE-MS-1

| TEAEs occurring in at least 2% of patients | Overall population, N = 696 |
|-------------------------------------------|-----------------------------|
|                                           | All events, n (%) | Events that resolved\(^a\), n (%) | Duration in days, median (10th–90th percentile) |
| Gastrointestinal TEAEs, all events        | 215 (30.9) | 191 (88.8) | 7.5 (1–87) |
| Diarrhea                                  | 75 (10.8)  | 68 (90.7)  | 5.0 (1–63) |
| Nausea                                    | 47 (6.8)   | 43 (91.5)  | 4.0 (1–86) |
| Upper abdominal pain                      | 31 (4.5)   | 24 (77.4)  | 5.0 (1–94) |
| Vomiting                                  | 25 (3.6)   | 24 (96.0)  | 1.0 (1–14) |
| Constipation                              | 24 (3.4)   | 14 (58.3)  | 16.0 (3–120) |
| Abdominal pain                            | 17 (2.4)   | 14 (82.4)  | 8.0 (1–52) |
| Flatulence                                | 15 (2.2)   | 9 (60.0)   | 19.0 (1–120) |
| Gastroesophageal reflux disease           | 14 (2.0)   | 7 (50.0)   | 86.0 (1–167) |

Data cutoff date March 30, 2018

*TEAE* treatment-emergent adverse event

\(^a\) Of events with complete start and end dates

|graphic|
TEAEs (approximately 31%) and the extremely low discontinuation rate due to GI TEAEs (<1%) over the 96-week treatment period in EVOLVE-MS-1 suggest that this novel oral fumarate has improved GI tolerability compared with DMF. The EVOLVE-MS-2 study will allow for a more complete evaluation of the GI tolerability profiles of DRF versus DMF.

Although the mechanisms driving GI tolerability of FAEs are unclear, there is evidence to suggest that subtle differences in FAEs could greatly affect tolerability. For example, recent studies have demonstrated that FAEs have differing irritant capacities based upon their chemical structure [16]. Lammintausta et al. further explored the irritant nature of FAEs by conducting skin patch testing [17]. Although the compounds tested in this series (including DMF) were all very similar in chemical structure, they observed a wide range of irritation associated with exposure to the compounds, providing evidence that the irritant nature of these compounds can be altered based upon minor changes to the fumarate ester structure. From a scientific rationale standpoint, DRF is well positioned to have an improved GI tolerability profile compared to DMF.

**Release of a Less Irritating Promoiety: HES Versus Methanol**

The first step in DMF metabolism, esterase hydrolysis, generates stoichiometric quantities of MMF and methanol in a 1:1 ratio. In contrast, in the first step of DRF metabolism, MMF and methanol are generated in approximately a 9:1 ratio, causing a significantly lower exposure of methanol with DRF treatment compared with DMF treatment (Fig. 1a, b). The release of methanol upon the first step of DMF...
metabolism may be a contributing factor to DMF-associated tolerability issues. At high systemic concentrations, methanol consumption is known to cause GI AEs [14, 18]. Formic acid is the main driver of methanol side effects and is generated by the enzymes alcohol dehydrogenase (ADH) and formaldehyde dehydrogenase during methanol metabolism [19, 20]. ADHs, depending upon the isoform, are exclusively expressed within the duodenum, small intestine, and liver (e.g., ADH1A or ADH4), or expressed in numerous tissues (ADH1C), whereas aldehyde dehydrogenases are highly expressed throughout most human tissues [21]. Therefore, locally elevated levels of methanol and the GI-irritating metabolite formic acid within the small intestine may subsequently play a role in the mechanism of GI issues and contribute to GI events (Fig. 4a). Because DRF generates significantly less methanol, this potential mechanism of irritation would be mitigated.

To put the systemic exposure of methanol after taking DMF or DRF into context, pharmacokinetic studies have demonstrated that blood levels of methanol and formic acid in patients taking DMF or DRF were either undetectable or significantly below the levels known to cause any systemic adverse effects. Consumption of compounds containing methyl esters is common in many diets. For example, one of the most frequently consumed molecules containing a methyl ester is aspartame, the artificial sweetener in soft drinks and other food items. The US Food and Drug Administration has set the acceptable maximal daily intake of aspartame at 50 mg/kg [22]. For a 70-kg person, that would be the equivalent of approximately 18–22 cans of 12-oz diet soft drinks. The total amount of methanol generated from a 240 mg dose of DMF is equivalent to that generated after consumption of approximately five to six cans of aspartame-containing 12-oz diet soft drinks [23]. In summary, even though a local elevated concentration of methanol within the GI tract may be causing GI tolerability issues, the overall exposure of methanol from DMF treatment is well below the acceptable safe limits for methanol ingestion and does not cause any systemic issues in patients.

DRF Is Less Reactive Toward Pre-Systemic Off-Target Proteins Compared with DMF

The small molecular weight (144.1 g/mol) of DMF and therefore small physical size allow it to access numerous receptors and proteins within the GI tract and GI wall [11, 24–26]. These interactions are beneficial when they are on target, thereby contributing to the efficacy of the drug. Alternatively, if they are off target, they could cause GI issues such as diarrhea, nausea, and vomiting. There is ambiguity surrounding which cell type or receptor is driving the GI events associated with FAE treatment. DMF could be reacting with the microbiota, analogous to how antibiotics cause GI events, or it could be reacting with pre-systemic proteins/receptors, analogous to how acarbose or opioids modulate GI function [27, 28]. It is hypothesized that DRF will have fewer off-target interactions with GI receptors/proteins (located either in the microbiota or GI tract) compared with DMF because of potential differences in molecular size, electrophilicity, and/or the half-life of the molecules (Fig. 4b–d).

A key determinant of whether a molecule can interact with a protein or receptor is its ability to physically fit into a binding cleft; this is governed by the van der Waals radii of the molecule (which are directly proportional to the size and number of atoms in the compound) and whether the filled chemical space bumps into and has steric clashes with the structure of the protein or receptor. DRF is almost double the molecular weight of DMF and occupies a significantly larger molecular volume; therefore, it is likely that DRF occupies fewer proteins/receptors (including off-target proteins/receptors) than DMF because of steric clashes. In addition to the increase in volume, DRF has significantly more molecular complexity than DMF because the methyl group of DMF is substituted with HES for DRF. This substitution adds five carbons and three heteroatoms (one nitrogen and two oxygen atoms) to DRF, significantly altering the hydrophobic and hydrophilic requirements for an energetically favorable binding to a target. Consequently, DRF has more restraints on the proteins with which it can form complexes compared with
DMF and therefore likely reacts with fewer off-target proteins (Fig. 4b).

The putative mechanism of action for fumarate esters is through a Michael addition of a protein nucleophile, typically a cysteine thiol functional group, to the alpha-beta unsaturated ester of the fumarate ester (DRF, DMF, or MMF). The reactivity of the alkene (carbon–carbon double bond) dictates which thiols within the proteome it will covalently modify. This is governed by the interplay between the chemical structure of the fumarate ester and the protein microenvironment to which it binds. Based on the chemical structure differences between DRF and DMF, it is possible that DRF is less electrophilic (i.e., has a less reactive alkene) and therefore would react with fewer off-target proteins compared with DMF. DMF dimethyl fumarate, DRF diroximel fumarate, GI gastrointestinal, HES 2-hydroxyethyl succinimide, MMF monomethyl fumarate

Fig. 4 Hypotheses for enhanced GI tolerability of DRF. Diester fumarates, such as DMF and DRF, are small-molecular-weight drugs capable of modifying the function of several proteins. These interactions can be considered on target when contributing to the efficacy of the drug and off target when contributing to the unwanted side effects, such as GI events. a DMF hydrolyzes to MMF and methanol (a known GI irritant). This localized methanol production within the GI tract may contribute to DMF GI tolerability issues. In contrast, DRF mainly hydrolyzes to HES (a biologically inert metabolite) and MMF. b DRF is a larger molecule than DMF; therefore, DRF may not fit into as many protein-binding pockets as DMF because of steric clashes between DRF and off-target proteins. c DRF could be less electrophilic; therefore, DRF may not react with certain off-target proteins compared with DMF. d The rate of hydrolysis to MMF may be slightly faster for DRF compared with DMF, thereby lowering the amount of DRF exposure to the GI tract and causing less covalent binding to off-target proteins compared with DMF. DMF dimethyl fumarate, DRF diroximel fumarate, GI gastrointestinal, HES 2-hydroxyethyl succinimide, MMF monomethyl fumarate
biologic effects of DMF are established within the first minutes of exposure. The systemic pharmacokinetic profiles of DMF and DRF are well established and have demonstrated bioequivalent exposure of MMF following hydrolysis. However, if the pre-systemic rate of hydrolysis to MMF is slightly faster for DRF compared with DMF, this may reduce the time of exposure of DRF to off-target proteins compared with DMF and possibly mitigate GI side effects (Fig. 4d). In summary, DRF may have fewer off-target interactions with GI receptors/proteins (located either in the microbiota or GI tract) compared with DMF because of potential differences in molecular size, electrophilicity, and/or half-life of the molecules.

CONCLUSIONS

DRF is a novel oral fumarate with a distinct chemical structure in development for patients with relapsing forms of MS. It is hypothesized that DRF may produce a differentiated GI tolerability profile through less direct irritation within the GI tract (due to formation of less methanol) and possibly because of less reactivity with off-target receptors as a result of its distinct chemical structure. Clinical implications of these hypotheses are unknown; however, clinical data to date suggest DRF has favorable GI tolerability, particularly when considering the tolerability profiles of other FAEs such as DMF. Importantly, the GI tolerability of DRF compared with DMF is being evaluated in the head-to-head EVOLVE-MS-2 trial; in addition to real-world data, this will further inform the GI tolerability profile of DRF.

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Compliance with Ethics Guidelines. The EVOLVE-MS-1 study protocol was approved by central and local ethics committees at each study site (see supplementary material for full details) and is being conducted in accordance with the International Council on Harmonization guidelines for Good Clinical Practice and
the Declaration of Helsinki. All patients provided written, informed consent.

**Data Availability.** EVOLVE-MS-1 was registered with ClinicalTrials.gov (NCT02634307). Study data will be shared in accordance with applicable regulations and laws.

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