

Supplementary Material

Diroximel Fumarate Demonstrates an Improved Gastrointestinal Tolerability Profile Compared with Dimethyl Fumarate in Patients with Relapsing-Remitting Multiple Sclerosis: Results from the Randomized, Double-Blind, Phase III EVOLVE-MS-2 Study

CNS Drugs

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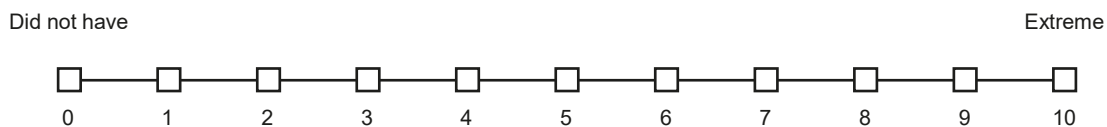
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Fig. S1 a IGISIS and **b** GGISIS symptom and impact scales. The IGISIS and GGISIS questionnaires allowed patients to self-assess duration and severity of nausea, vomiting, upper abdominal pain, lower abdominal pain, and diarrhea. *GGISIS* Global Gastrointestinal Symptom and Impact Scale, *GI* gastrointestinal, *IGISIS* Individual Gastrointestinal Symptom and Impact Scale

a

1. How intense has your **NAUSEA** been on a scale (shown below) from 0 (did not have) to 10 (extreme)?

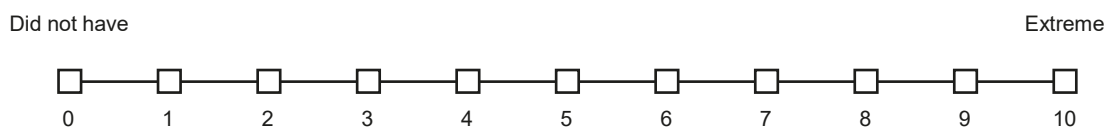


- When did your nausea start? _____
- When did your nausea stop? _____
- How much has your nausea INTERFERED with your ability to accomplish your regular daily activities? (choose one):

Regular daily activities refer to the things you usually do, such as shopping, household work, taking care of a child or family member, exercising, etc.

- Not at all
- Slightly
- Moderately
- Quite a bit
- Extremely

2. How intense has your **VOMITING** been on a scale (shown below) from 0 (did not have) to 10 (extreme)?

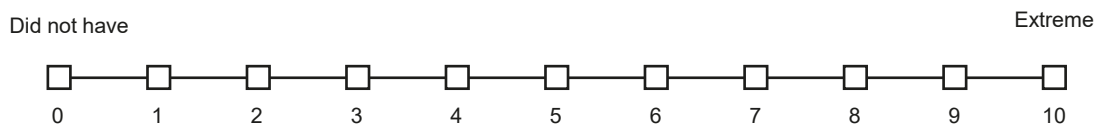


- When did your vomiting start? _____
- When did your vomiting stop? _____
- How much has your vomiting INTERFERED with your ability to accomplish your regular daily activities? (choose one):

Regular daily activities refer to the things you usually do, such as shopping, household work, taking care of a child or family member, exercising, etc.

- Not at all
- Slightly
- Moderately
- Quite a bit
- Extremely

3. How intense has your **UPPER ABDOMINAL PAIN** been on a scale (shown below) from 0 (did not have) to 10 (extreme)?

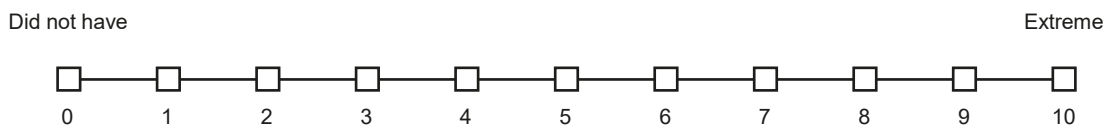


- When did your upper abdominal pain start? _____
- When did your upper abdominal pain stop? _____
- How much has your upper abdominal pain INTERFERED with your ability to accomplish your regular daily activities? (choose one):

Regular daily activities refer to the things you usually do, such as shopping, household work, taking care of a child or family member, exercising, etc.

- Not at all
- Slightly
- Moderately
- Quite a bit
- Extremely

4. How intense has your **LOWER ABDOMINAL PAIN** been on a scale (shown below) from 0 (did not have) to 10 (extreme)?

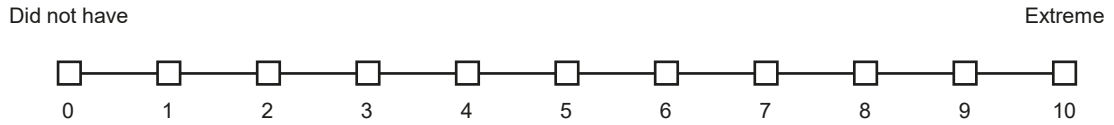


- When did your lower abdominal pain start? _____
- When did your lower abdominal pain stop? _____
- How much has your lower abdominal pain INTERFERED with your ability to accomplish your regular daily activities? (choose one):

Regular daily activities refer to the things you usually do, such as shopping, household work, taking care of a child or family member, exercising, etc.

- Not at all
- Slightly
- Moderately
- Quite a bit
- Extremely

5. How intense has your **DIARRHEA** been on a scale (shown below) from 0 (did not have) to 10 (extreme)?



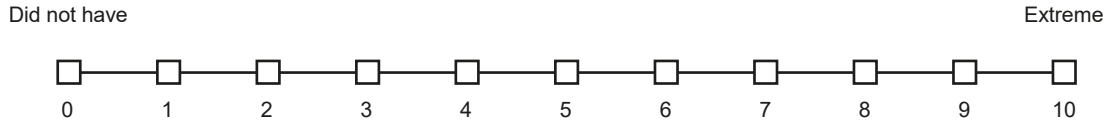
- a. When did your diarrhea start? _____
- b. When did your diarrhea stop? _____
- c. How much has your diarrhea **INTERFERED** with your ability to accomplish your regular daily activities? (choose one):

Regular daily activities refer to the things you usually do, such as shopping, household work, taking care of a child or family member, exercising, etc.

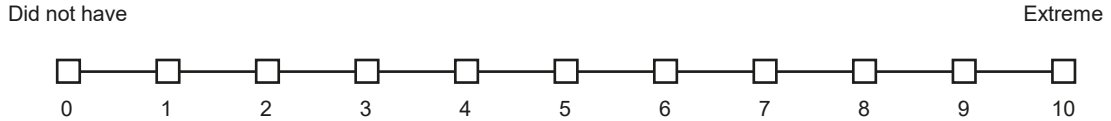
- i. Not at all
- ii. Slightly
- iii. Moderately
- iv. Quite a bit
- v. Extremely

b

1. Rate the **intensity** of your GI symptoms in general over the past 24 hours on a scale from 0 (did not have) to 10 (extreme) as shown below.



2. Rate how **bothersome** your GI symptoms have been in general over the past 24 hours on a scale from 0 (did not have) to 10 (extreme) as shown below.



3. How much have your GI symptoms **interfered** with your ability to accomplish your regular daily activities over the past 24 hours? (choose one):

Regular daily activities refer to the things you usually do, such as shopping, household work, taking care of a child or family member, exercising, etc.

- a. Not at all
- b. Slightly
- c. Moderately
- d. Quite a bit
- e. Extremely

4. Are you currently employed (working for pay)?

If NO, check "NO" below and you have completed this questionnaire.

If YES, check "YES" below and please answer questions 5 and 6.

NO
 YES

5. During the past 24 hours, how many hours of work did you miss because of your GI symptoms?

How many hours that you were supposed to work or were scheduled to work did you miss because of your GI symptoms? If you didn't miss any work, indicate "0" hours below. Do not include time you missed to participate in this study.

If you weren't scheduled to work during the past 24 hours, check "Not applicable" below.

HOURS
 Not applicable

6. How much have your GI symptoms affected your productivity while you were working over the past 24 hours? (choose one)

Was there time during the past 24 hours when you were limited in the amount or kind of work you could do or you accomplished less than you usually do because of your GI symptoms?

- a. Not at all
- b. Slightly
- c. Moderately
- d. Quite a bit
- e. Extremely

Fig. S2 CONSORT diagram. *AE* adverse event, *DMF* dimethyl fumarate, *DRF* diroximel fumarate. ^aReasons for screening failures included abnormal blood tests ($n = 53$), significant medical condition or abnormality ($n = 33$), unwillingness to comply with protocol ($n = 29$), patient safety and adherence to protocol ($n = 22$), lack of confirmed diagnosis of relapsing-remitting multiple sclerosis ($n = 20$), gastrointestinal symptoms ($n = 17$), lack of protocol compliance ($n = 17$), history of prohibited treatment ($n = 16$), lack of informed consent ($n = 16$), positive serology test for hepatitis C or B, or human immunodeficiency virus at screening ($n = 15$), long-term use of gastrointestinal therapy ($n = 15$), dairy exclusion compliance ($n = 15$), abnormal urine tests ($n = 13$), history of major disease ($n = 12$), relapse within 30 days ($n = 12$), dairy exclusion gastrointestinal symptoms ($n = 9$), current or prior participation in a clinical trial within 3 months of screening ($n = 8$), history of gastrointestinal surgery or disease ($n = 7$), clinically significant history of suicidal ideation or suicidal behavior in the last 12 months as assessed by the Columbia Suicide Severity Rating Scale at screening ($n = 5$), history of malignancy ($n = 4$), baseline Expanded Disability Status Scale score > 6.0 at screening and randomization ($n = 3$), history of myocardial infarction ($n = 2$), lack of contraception compliance ($n = 2$), drug/alcohol abuse ($n = 1$), pregnancy ($n = 1$), confirmed diagnosis of progressive relapsing multiple sclerosis ($n = 1$)

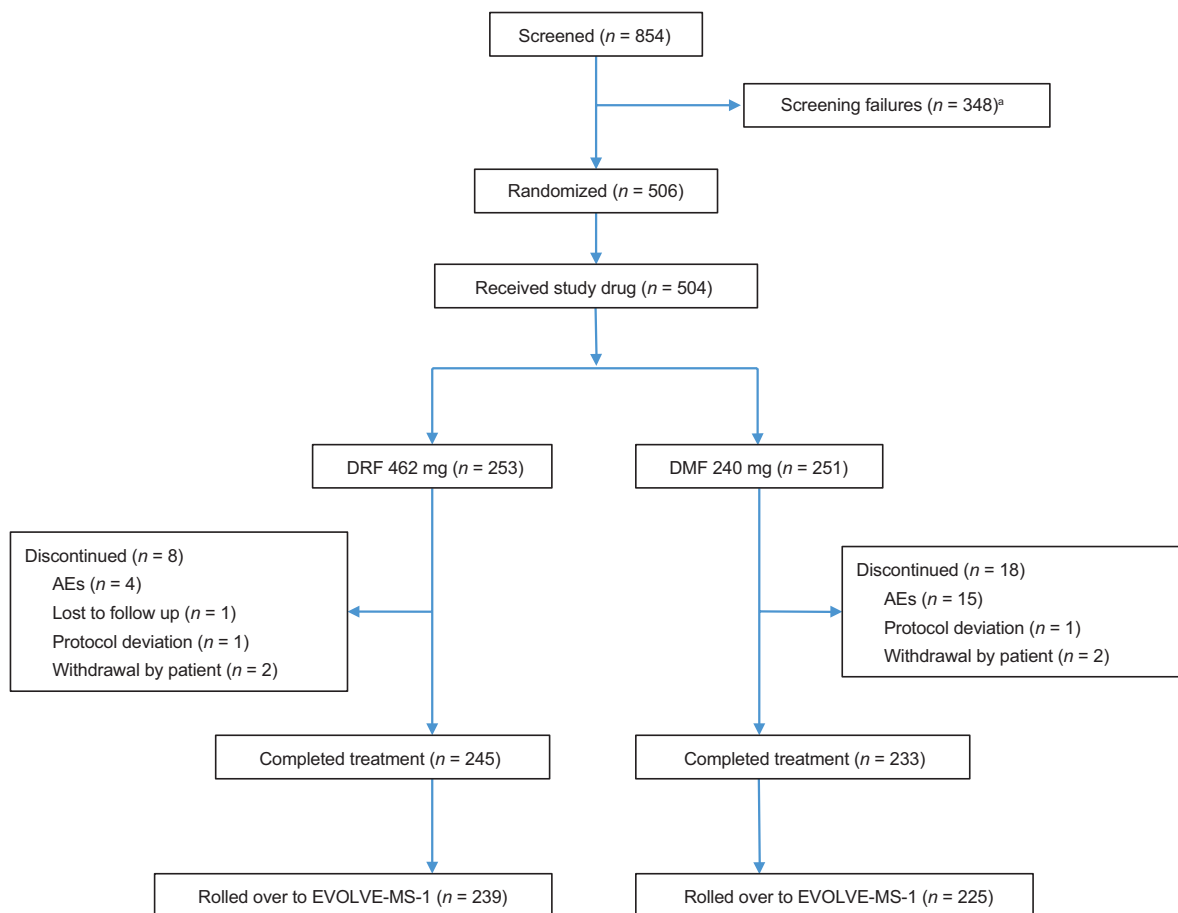


Fig. S3 Exploratory endpoints: analyses of IGISIS and GGISIS in the part B-only population. *CI* confidence interval, *DMF* dimethyl fumarate, *DRF* diroximel fumarate, *GGISIS* Global Gastrointestinal Symptom and Impact Scale, *IGISIS* Individual Gastrointestinal Symptom and Impact Scale, *RR* rate ratio

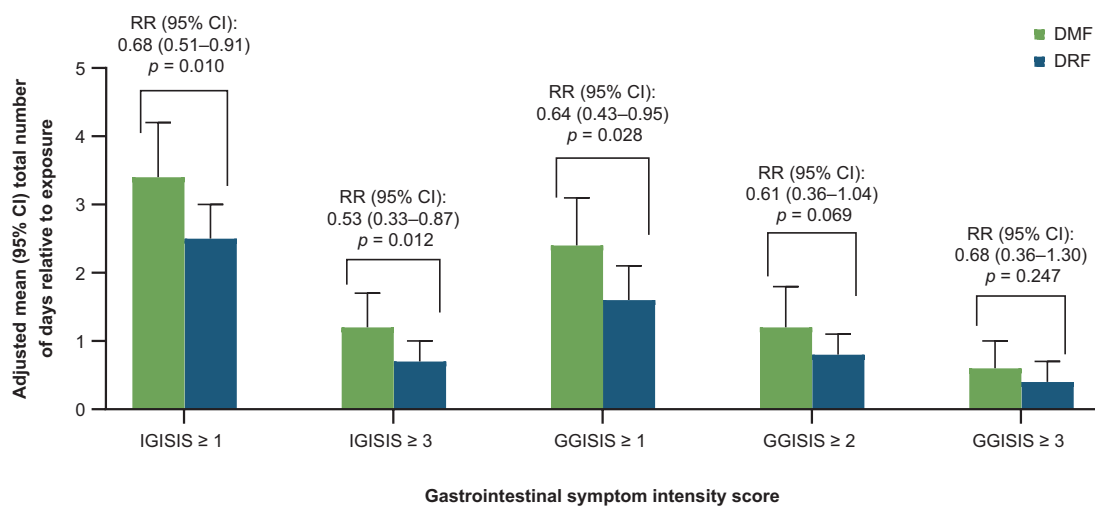


Table S1 Patient-assessed interference of gastrointestinal symptoms with ability to accomplish regular daily activities

Worst patient-assessed symptom interference level during treatment, ^a <i>n</i> (%)	DRF 462 mg (<i>n</i> = 253)	DMF 240 mg (<i>n</i> = 249)
IGISIS		
Nausea		
Not reported	160 (63.2)	142 (57.0)
Not at all	31 (12.3)	39 (15.7)
Slightly/moderately	56 (22.1)	51 (20.5)
Quite a bit/extremely	6 (2.4)	17 (6.8)
Vomiting		
Not reported	234 (92.5)	214 (85.9)
Not at all	7 (2.8)	4 (1.6)
Slightly/moderately	9 (3.6)	17 (6.8)
Quite a bit/extremely	3 (1.2)	14 (5.6)
Upper abdominal pain		
Not reported	177 (70.0)	142 (57.0)
Not at all	35 (13.8)	35 (14.1)
Slightly/moderately	38 (15.0)	55 (22.1)
Quite a bit/extremely	3 (1.2)	17 (6.8)
Lower abdominal pain		
Not reported	175 (69.2)	165 (66.3)
Not at all	30 (11.9)	20 (8.0)
Slightly/moderately	45 (17.8)	56 (22.5)
Quite a bit/extremely	3 (1.2)	8 (3.2)
Diarrhea		
Not reported	169 (66.8)	145 (58.2)
Not at all	29 (11.5)	31 (12.4)
Slightly/moderately	46 (18.2)	57 (22.9)
Quite a bit/extremely	9 (3.6)	16 (6.4)
GGISIS		
Not reported	0	0
Not at all	171 (67.6)	143 (57.4)
Slightly/moderately	61 (24.1)	77 (30.9)
Quite a bit/extremely	20 (7.9)	27 (10.8)

DMF dimethyl fumarate, DRF diroximel fumarate, GGISIS Global Gastrointestinal Symptom and Impact Scale, IGISIS Individual Gastrointestinal Symptom and Impact Scale

^aPatients were asked to indicate how much each symptom interfered with their ability to accomplish their regular daily activities