NICE National Institute for Health and Care Excellence

Diroximel fumarate for treating relapsing-remitting multiple sclerosis [ID1673]

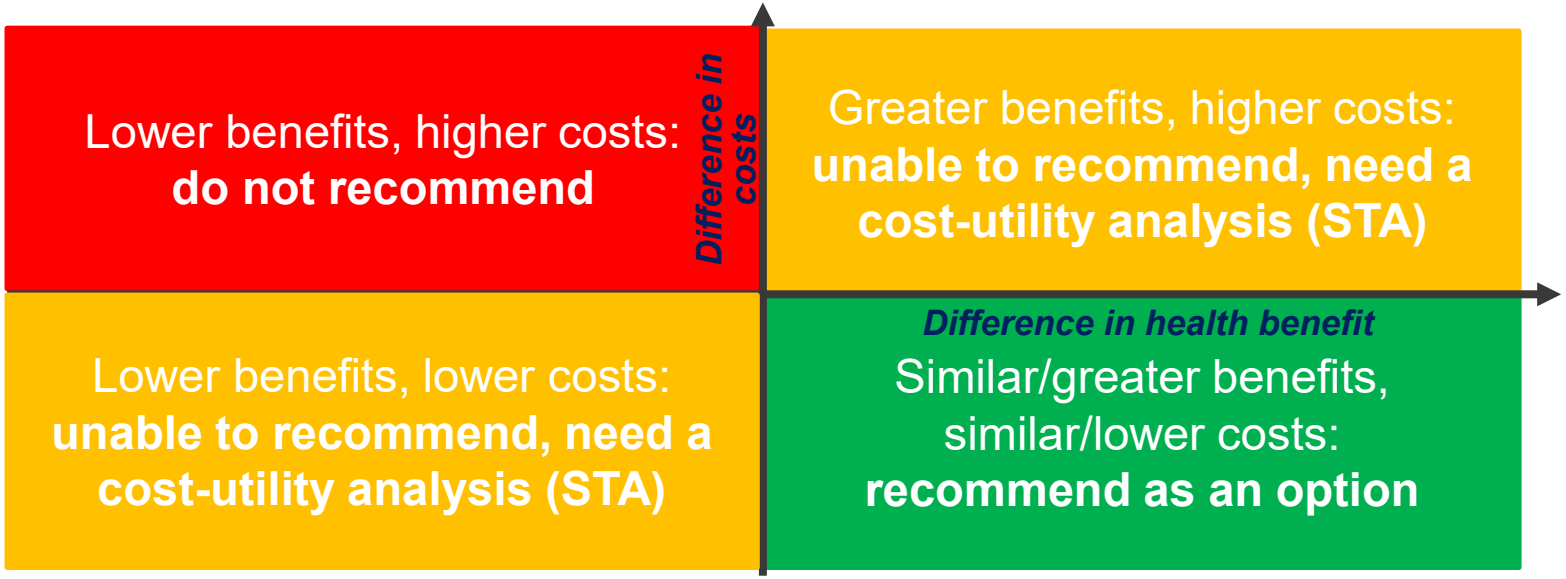
Fast track appraisal

Technology Appraisal Committee B
Lead team: Mary Weatherstone, Nicholas Latimer and Nigel Westwood
ERG: University of Sheffield HTA group
Technical team: Rebecca Thomas, Emma Douch, Yelan Guo and Richard Diaz
Company: Biogen
Committee 17th February 2022

Fast Track Appraisals: Cost comparison

Topic proposed as an fast track appraisal (FTA) using cost comparison methods

- FTAs are appraisals in which less-detailed discussion is sufficient
  - Cost comparison FTA considered if the technology provides **similar/greater benefits** at **similar/lower cost** vs a **NICE-recommended** comparator
- Possible recommendations in an FTA:



  - If a technology is recommended through cost comparison, guidance states:
    - ***"If patients and their clinicians consider both the technology and comparators to be suitable treatments, the least costly should be used"***

Fast Track Appraisal

Diroximel fumarate for treating relapsing-remitting multiple sclerosis meets the criteria for FTA

- Diroximel fumarate has positive opinion by CHMP and EMA on bioequivalence to dimethyl fumarate (TA320, 2014)
- Diroximel fumarate expected to have same clinical efficacy as dimethyl fumarate given bioequivalence
- Diroximel fumarate has improved gastrointestinal tolerability compared with dimethyl fumarate
  - *lower quantities of methanol, a known gastric irritant, are produced upon metabolism of diroximel fumarate compared with dimethyl fumarate*
- [redacted]

EMA: two medicinal products containing the same active substance considered ***bioequivalent*** if they are pharmaceutically equivalent or alternatives…[1]

ERG:
Supports company's case that diroximel fumarate provides similar or greater benefits at a similar or lower overall cost than dimethyl fumarate
There are no issues with the company submission

Abbreviations: FTA: fast track appraisal, TA: technology appraisal

Reference: Dimethyl fumarate for treating relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA320]. Published 2014. Overview | Dimethyl fumarate for treating relapsing-remitting multiple sclerosis | Guidance | NICE; 1. European Medicines Agency. Guideline on the investigation of bioequivalence. 2010. Guideline o the Investigation of Bioequivalence (europa.eu)

Key issues considered by lead team

Key issues considered:

1. Is the clinical efficacy of diroximel fumarate similar/exchangeable to dimethyl fumarate because of the established bioequivalence? Is dimethyl fumarate the appropriate comparator?
2. What is the safety profile of diroximel fumarate compared with dimethyl fumarate?
3. Should diroximel fumarate be recommended at the same point in the treatment pathway as dimethyl fumarate? i.e. first line therapy.
4. If recommending, for what type of relapsing remitting multiple sclerosis:
    - The same as recommended by TA320 for dimethyl fumarate i.e. active relapsing remitting multiple sclerosis defined by 2 significant relapses in last 2 years; excluding highly active or rapidly evolving severe relapsing-remitting multiple sclerosis, as requested by company?

Decision making process for previous fast track appraisals:

Decision making by the lead team and chair has been done for topics:

- which are going through Fast Track Appraisal route;
- where decision making is relatively straight forward;

The decision and resulting recommendation is subsequently presented to the committee for ratification

Patient and carer perspectives

Multiple sclerosis (MS) impacts daily life for people with MS and carers

- Complex and unpredictable condition that impacts all aspects of life
- Can be '*relentless, painful and exhausting*' as associated with '*a wide range of distressing and debilitating symptoms*'
- Relapses have a '*resonating emotional impact*': unpredictable and distressing. Anxiety and frustration caused by loss of independence, impact on employment & disruption to everyday life.
- Extra costs: accessible transport, specialist equipment, medication, help with household activities
- Challenging for families and carers - balancing work, education, health and wellbeing

Balance between effectiveness of treatment and risk of side effects

- Range of treatments provides options for different responses and personal preferences
- "*Bothersome nature of flushing*" sometimes experienced whilst on dimethyl fumarate

Diroximel fumarate provides additional oral treatment option with improved GI toxicity profile

- Significant number of people stop dimethyl fumarate due to gastrointestinal side effects
- Gastrointestinal symptoms less likely to interfere with regular daily activities/work productivity with diroximel fumarate compared to dimethyl fumarate
- Flushing similar to dimethyl fumarate but mostly mild to moderate, reduces after first month of treatment and less likely to result in discontinuation compared to gastrointestinal side effects
- Ease of use: can be given remotely. Oral treatments for MS currently limited
- Positive impact on work productivity, daily activities and number of hospital appointments

NHS England treatment algorithm for multiple sclerosis and company positioning[a]

Company: diroximel fumarate as 1st line treatment alternative to dimethyl fumarate

RRMS: 1 relapse in last 2 years & radiological activity	RRMS: 2 significant relapses in last 2 years	Rapidly evolving severe MS (RES)
1st line therapy (and *alternatives for intolerance to first-line therapy in italics*)		
• *Interferon beta-1a* • *Glatiramer acetate* • Ocrelizumab [b] • Peginterferon beta-1a • Ofatumumab • Ponesimod	• *Beta interferons (1a and 1b)* • *Dimethyl fumarate (TA320)* • *Glatiramer acetate* • Ocrelizumab [b] • Peginterferon beta-1a • *Teriflunomide* • Ofatumumab • Ponesimod	• *Alemtuzumab* • *Cladribine* • Natalizumab • *Ocrelizumab* [b] • *[Fingolimod, only as alternative to natalizumab]* • Ofatumumab

ERG:

- Company's overview of current treatment pathway for people with RRMS acceptable
- Positioning of DRF as alternative to DMF, other parts of pathway unchanged

[a] N.B Peginterferon beta-1a and ofatumumab on slide but not in algorithm because recommended after algorithm published; [b] Only if alemtuzumab contraindicated or otherwise unsuitable.

NHS England is commissioning dimethyl fumarate as an option for people who have had 1 relapse in last 12 months due to impact of COVID-19

Abbreviations: RRMS, relapsing remitting multiple sclerosis; MS, multiple sclerosis; RES, rapidly evolving severe; DRF, diroximel fumarate; DMF, dimethyl fumarate; TA, technology appraisal. **Source**: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/03/Treatment-Algorithm-for-Multiple-Sclerosis-Disease-Modifying-Therapies-08-03-2019-1.pdf

Diroximel fumarate (Vumerity)

EMA: diroximel fumarate shown to be bioequivalent to the authorised dimethyl fumarate at recommended doses. Efficacy and safety expected to be similar between the two

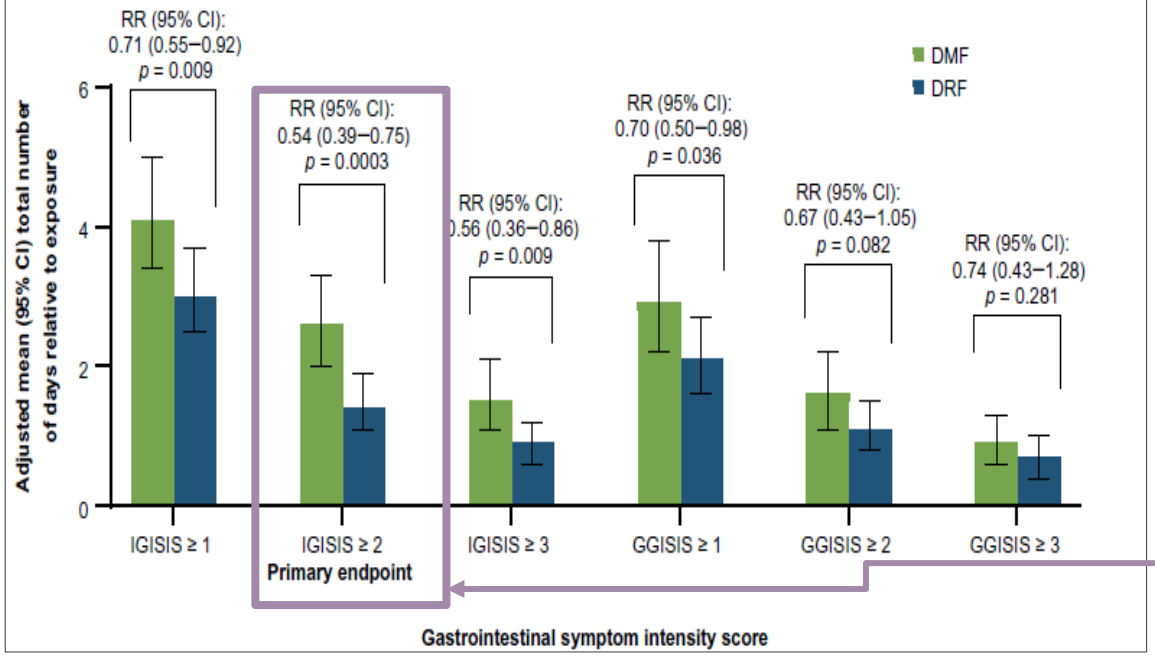
Diroximel fumarate	Dimethyl fumarate
The treatment of adult patients with relapsing-remitting multiple sclerosis	Treatment of adult patients with relapsing remitting multiple sclerosis
Oral administration Starting dose: 231mg twice a day for 7 days Maintenance dose: 462mg twice a day thereafter Lifetime course of treatment	Oral administration Starting dose: 120mg twice a day for 7 days Maintenance dose: 240mg twice a day thereafter Lifetime course of treatment
• List price: £1,471.07 per 120-capsule pack (231mg). Annual cost £17,849. • Separate Patient Access Scheme (PAS discount) approved	• List price: £1,373 per 56-capsule pack (240mg). Annual cost £17,849. • PAS discount approved
With approved PAS, diroximel fumarate saves [redacted] per patient annually compared with dimethyl fumarate	

Abbreviations: EMA: European Medicine Agency; **Source**: company submission, table 20 and ERG report.

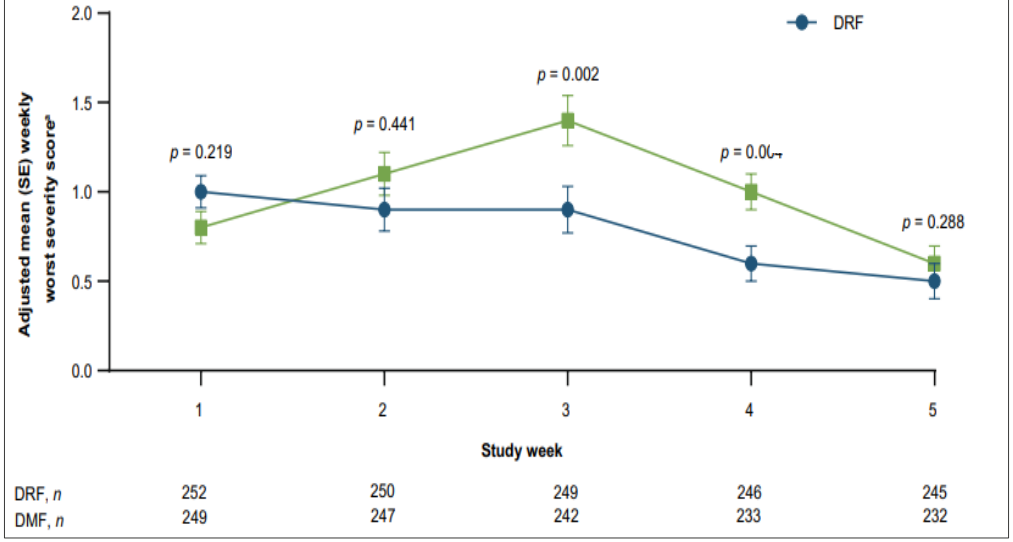
EVOLVE-MS-2 (pivotal trial) results: GI symptoms

Diroximel fumarate improves gastrointestinal symptoms compared with dimethyl fumarate (5 week treatment duration), based on two symptom scales

Adjusted mean number of days at different symptom intensity scores as measured by IGISIS & GGISIS in the FAS



Mean worst IGISIS severity score



Statistically significant reduction in number of days with symptom intensity score ≥ 2 (primary endpoint)

GI symptoms primary outcome: measurement

- 2 patient self-reported GI symptom scales (IGISIS & GGISIS) uniquely developed for EVOLVE-MS-2 evaluating duration and severity of GI symptoms; both adapted from the Global Flushing Severity Scale (validated measure)
  - range from 0 (no GI symptoms) to 10 (extreme GI symptoms) over past 12 hours (IGISIS) or 24 hours (GGISIS)
- Pre-planned unblinded data analysis: modifications to scale allowed after 1st 120 patients enrolled

Abbreviations: CI, confidence interval; DMF, dimethyl fumarate; DRF, diroximel fumarate; FAS, full analysis set; GI, gastrointestinal symptoms; GGISIS, Global Gastrointestinal Symptom and Impact Scale; IGISIS, Individual Gastrointestinal Symptoms and Impact Scale; SE, standard error; RR, rate ratio. **Source**: Company submission, figures 4 and 5.

EVOLVE-MS-2: adverse events

ERG: *safety profile of DRF aligned with DMF on AEs assessed; overall safety and tolerability of DRF appeared better than DMF*

	DRF (n = 253)	DMF (n = 251)
Any TEAE, n (%)	198 (78)	210 (84)
GI disorders	88 (35)	123 (49)
Diarrhoea	39 (15)	56 (22)
Nausea	37 (15)	52 (21)
Upper abdominal pain	17 (7)	39 (16)
Abdominal pain	16 (6)	24 (10)
Lower abdominal pain	15 (6)	17 (7)
Vomiting	9 (4)	22 (9)
General disorders and administration site conditions	16 (6)	30 (12)
Fatigue	6 (2)	13 (5)
Infections and infestations	43 (17)	35 (14)
Nasopharyngitis	15 (6)	11 (4)
Investigations	27 (11)	24 (10)
ALT increased	14 (6)	9 (4)
Nervous system disorders	37 (15)	34 (14)
Headache	10 (4)	14 (6)
Skin and subcutaneous tissue disorders	49 (19)	58 (23)
Erythema	20 (8)	21 (8)
Pruritus	18 (7)	18 (7)
Vascular disorders	88 (35)	107 (43)
Flushing	83 (33)	102 (41)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; DMF, dimethyl fumarate; DRF, diroximel fumarate; GI, gastrointestinal; TEAE, treatment emergent adverse event. Source: Company submission, Table 17

Lead team's considerations

1. Company's proposed population for DRF is consistent with TA 320 (DMF for treating RRMS)
2. DMF is the appropriate comparator for this FTA
3. The clinical efficacy of DRF is similar/exchangeable to DMF because of the established bioequivalence
4. The gastrointestinal toxicity profile of DRF may be preferable to DMF for patients; safety profiles of 2 drugs aligned and overall safety and tolerability of DRF appeared better than DMF although AEs such as flushing continued
5. DRF is cost saving to the NHS compared with DMF
6. DRF is proposed as a direct replacement for DMF therefore could be recommended:
    - at the same point in the treatment pathway as DMF i.e. first line therapy
    - for the same population as DMF
        - active relapsing remitting multiple sclerosis defined by 2 significant relapses in last 2 years (although the definition of 'active' relapsing remitting multiple sclerosis has evolved since the appraisal of dimethyl fumarate, it is appropriate to be in line with the recommendation of dimethyl fumarate, and as requested by company)
        - excluding highly active or rapidly evolving severe relapsing-remitting multiple sclerosis

Abbreviations: DMF: Dimethyl fumarate ; DRF: diroximel fumarate; FTA: fast track appraisal, RRMS: relapsing-remitting multiple sclerosis; TA: technology appraisal

Reference: TA320, 2014: Dimethyl fumarate for treating relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA320]. Overview | Dimethyl fumarate for treating relapsing-remitting multiple sclerosis | Guidance | NICE;

Recommendation

Lead team's recommendation for ratification

- Diroximel fumarate is ***recommended as an option*** for treating adults with active relapsing-remitting multiple sclerosis (normally defined as 2 clinically significant relapses in the previous 2 years), only if:
  - *they do not have highly active or rapidly evolving severe relapsing-remitting multiple sclerosis*
  - *the company provides diroximel fumarate according to the commercial arrangement*
- If patients and their clinicians consider diroximel fumarate to be one of a range of suitable treatments, including dimethyl fumarate, choose the least expensive (taking into account administration costs and commercial arrangements).

PMB slides

The following slides were presented to the lead team at the PMB to inform decision making. They are included in the committee slides for information only.

NICE National Institute for Health and Care Excellence

Diroximel fumarate for treating relapsing-remitting multiple sclerosis [ID1673]

Fast track appraisal

Technology Appraisal Committee B
Lead team: Mary Weatherstone, Nicholas Latimer and Nigel Westwood
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Company: Biogen
Pre-meeting briefing 27th January 2022

Disease background: multiple sclerosis (MS)

- Chronic, lifelong, neurological disease with no cure, resulting in progressive, irreversible disability
- Affects central nervous system:
  - immune system mistakenly attacks myelin sheath (layer that surrounds and protects nerves), disrupting signals travelling along the nerves
- 85% of multiple sclerosis is relapsing-remitting (RRMS): episodes of relapses (neurological worsening) separated by remission (periods of stability)
- Associated with pain, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment
- Diagnosis generally between 30 - 60 years of age
- Approximately 130,000 people in the UK have multiple sclerosis, and about 7,000 people are newly diagnosed each year
- Treatment (disease-modifying therapies): decrease frequency and severity of relapses, reduce accumulation of lesions, slow accumulation of physical and mental disability, maintain or improve patient quality of life

Types of multiple sclerosis

Primary progressive multiple sclerosis
- Gradual disability progression from onset with no obvious relapses or remission

Relapsing-remitting multiple sclerosis (RRMS)
- 85% of people at diagnosis
- Treatment strategy: patient choice, number of relapses, MRI activity and response to previous treatment

50% to 60% in 15 to 20 years

One-way

Secondary progressive multiple sclerosis (SPMS)
- Steady progression of neurological damage with or without relapses
- Treatment might be restricted to secondary progressive disease *with relapses*

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MRI, magnetic resonance imaging.

Patient and carer perspectives

Multiple sclerosis (MS) impacts daily life for people with MS and carers

- Complex and unpredictable condition that impacts all aspects of life
- Can be '*relentless, painful and exhausting*' as associated with '*a wide range of distressing and debilitating symptoms*'
- Relapses have a '*resonating emotional impact*': unpredictable and distressing. Anxiety and frustration caused by loss of independence, impact on employment & disruption to everyday life.
- Extra costs: accessible transport, specialist equipment, medication, help with household activities
- Challenging for families and carers - balancing work, education and taking care of one's own health and wellbeing difficult

Balance between effectiveness of treatment and risk of side effects

- Range of treatments provides options for different responses and personal preferences
- Common to switch treatments multiple times due to side effects of current options: unmet need for treatments with more tolerable toxicity profiles.
- Important to start treatment soon after diagnosis

Diroximel fumarate provides additional oral treatment option with improved toxicity profile

- Significant number of people stop dimethyl fumarate due to gastrointestinal side effects: these are improved with diroximel fumarate
- Ease of use: can be given remotely. Oral treatments for MS currently limited
- Positive impact on work productivity, daily activities and number of hospital appointments

NHS England treatment algorithm and company positioning[a]

Company: diroximel fumarate as 1st line treatment alternative to dimethyl fumarate

RRMS: 1 relapse in last 2 years & radiological activity	RRMS: 2 significant relapses in last 2 years	Rapidly evolving severe MS (RES)
1st line therapy (and *alternatives for intolerance to first-line therapy in italics*)		
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ERG:

- Company's overview of current treatment pathway for people with RRMS acceptable
- Positioning of DRF as alternative to DMF, other parts of pathway unchanged

◉ *Does the committee consider company's proposed positioning appropriate?*

[a] N.B Peginterferon beta-1a and ofatumumab on slide but not in algorithm because recommended after algorithm published; [b] Only if alemtuzumab contraindicated or otherwise unsuitable.

Abbreviations: RRMS, relapsing remitting multiple sclerosis; MS, multiple sclerosis**;** RES, rapidly evolving severe; DRF, diroximel fumarate; DMF, dimethyl fumarate; TA, technology appraisal. **Source**: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/03/Treatment-Algorithm-for-Multiple-Sclerosis-Disease-Modifying-Therapies-08-03-2019-1.pdf

Diroximel fumarate (Vumerity)

EMA: diroximel fumarate shown to be bioequivalent to the authorised dimethyl fumarate at recommended doses. Efficacy and safety expected to be similar between the two.

Marketing authorisation	Adults with relapsing–remitting multiple sclerosis
Mechanism of action	Not fully understood but thought to activate nuclear factor (erythroid derived 2)-like 2 (Nrf2) transcriptional pathway to increase production of antioxidants and control immune system.
Administration and dose	Oral administration Starting dose: 231mg twice a day for 7 days Maintenance dose: 462mg twice a day thereafter Lifetime course of treatment
Cost of treatment	• List price: £1,471.07 per 120-capsule pack (231mg). Annual cost £17,849. PAS approved.

Abbreviations: EMA: European Medicine Agency; DRF, diroximel fumarate; DMF, dimethyl fumarate; PAS: Patient Access Scheme; **Source:** company submission, table 2.

Bioequivalence

EMA: two medicinal products containing the same active substance considered ***bioequivalent*** if they are:

- pharmaceutically equivalent or alternatives, and
- their bioavailabilities lie within acceptable predefined limits, ensuring similarity in terms of safety and efficacy[1]

CHMP: "the benefits of Vumerity [DRF] are expected to be the same as those of Tecfidera [DMF], including the reduction of the risk of the appearance of relapses and inflammatory lesions in the central nervous system"[2]

EMA: "Since comparative exposure to the common active metabolite MMF [monomethyl fumarate] from 240 mg of DMF and 462 mg of DRF has been shown, *the efficacy results from the DMF clinical programme can be used to support efficacy claims for DRF"*[3]

ERG:
Positive opinions provided by regulatory bodies, content to accept that diroximel fumarate and dimethyl fumarate are bioequivalent.

◉ *Does the committee agree that the clinical treatment effects of dimethyl fumarate and diroximel fumarate are similar given the established bioequivalence?*

Abbreviations: EMA: European Medicine Agency; CHMP, Committee on Human Medicinal Products; DMF, dimethyl fumarate, DRF, diroximel fumarate

[1] European Medicines Agency. Guideline on the investigation of bioequivalence. 2010. Guideline o the Investigation of Bioequivalence (europa.eu)

[2] European Medicines Agency. Summary of opinion (initial authorisation). 2021. Vumerity, INN-diroximel fumarate (europa.eu)

[3] European Medicines Agency. Assessment report. Vumerity. 2021. Vumerity, INN-diroximel fumarate (europa.eu)

Fast Track Appraisal

Diroximel fumarate meet the criteria for fast-track appraisal

Company has proposed this appraisal follows the FTA process based on:

- Diroximel fumarate having bioequivalence to dimethyl fumarate (TA320) and thus the same clinical efficacy
- Diroximel fumarate has an improved side effect profile compared with dimethyl fumarate
- [redacted]

ERG:

- Supports company's case that diroximel fumarate provides similar or greater benefits at a similar or lower overall cost than dimethyl fumarate
- There are no issues with the company submission

Abbreviations: FTA: fast track appraisal, TA: technology appraisal

Reference: Dimethyl fumarate for treating relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA320]. Published 2014. Overview | Dimethyl fumarate for treating relapsing-remitting multiple sclerosis | Guidance | NICE

Decision problem.

ERG: deviations appropriate

	NICE final scope	Deviation from the scope	ERG assessment
Population	People with relapsing-remitting multiple sclerosis	Not including those who have highly active or rapidly evolving severe forms of the condition	Deviation appropriate
Intervention	Diroximel fumarate	None	N/A
Comparators	Beta interferon Dimethyl fumarate Glatiramer acetate Ocrelizumab Ofatumumab Peginterferon beta-1a Ponesimod Teriflunomide	Dimethyl fumarate only	Appropriate given cost-comparison against dimethyl fumarate
Outcomes	Relapse rate, relapse severity, disability, disease progression, MS symptoms, subclinical disease activity, mortality, adverse events	Proportion with relapse, annualised relapse rate, disability, disease progression, freedom from disease activity, subclinical disease activity, adverse events, health-related quality of life	Deviations appropriate; no difference in clinical outcomes expected between DMF and DRF
Subgroups?	People who could not tolerate previous treatment	Clinical trials did not generate evidence for this subgroup	Omitting subgroup appropriate

Abbreviations: MS, multiple sclerosis; DMF, dimethyl fumarate; DRF, diroximel fumarate. **Source**: ERG report, table 1

Decision problem: population

Company: population aligned with TA320

Company:

- Seeking reimbursement for diroximel fumarate aligned with comparator *dimethyl fumarate (TA320)* i.e. for people with RRMS who do not have highly active or rapidly evolving severe RRMS
- Evidence base on diroximel fumarate limited to this population

TA320 (2014): dimethyl fumarate as an option for treating:

- ***active*** relapsing-remitting multiple sclerosis (normally defined as 2 clinically significant relapses in the previous 2 years) in adults, only if:
  - ➢ they do not have highly active or rapidly evolving severe relapsing-remitting multiple sclerosis

***Considerations of population in TA320*:**

- "*Active*" defined according to Association of British Neurologists (ABN) guidelines *(2009)*: 2 relapses in 2 years[a]
- ERG: trial populations more closely reflected people with RRMS who met the ABN's prescribing criteria for disease-modifying therapy (2 or more relapses in 2 years) than people with RRMS in general
- Committee: insufficient evidence to recommend dimethyl fumarate in rapidly evolving severe, and highly active, RRMS

ABN guidelines (2015): clinicians starting disease modifying therapies earlier, when disease judged 'active' due to single recent relapse, radiological evidence, being newly diagnosed, or established disease with new MRI lesions without relapse[b]

◉ *Would diroximel fumarate be recommended for the same population as dimethyl fumarate?*

[a]ERG report for TA320. [b]Scolding et al., 2015. **Abbreviations**: TA, Technology Appraisal; ABN, Association of British Neurologists; RRMS, relapsing remitting multiple sclerosis

Decision problem: comparator

ERG and company agree diroximel fumarate the only comparator

Company's rationale:

- Dimethyl fumarate:
  - the most widely prescribed disease modifying therapy for relapsing remitting multiple sclerosis in NHS England; estimates of market share:
    - [redacted]% of the active relapsing-remitting multiple sclerosis market and [redacted]% of the total market in all forms of multiple sclerosis combined
  - predominant treatment diroximel fumarate would displace, validated in company's medical advisory board; *and*
- Diroximel fumarate:
  - is to be recommended for the population of relevance, as in TA320 (2014):
  - has demonstrated bioequivalence to dimethyl fumarate

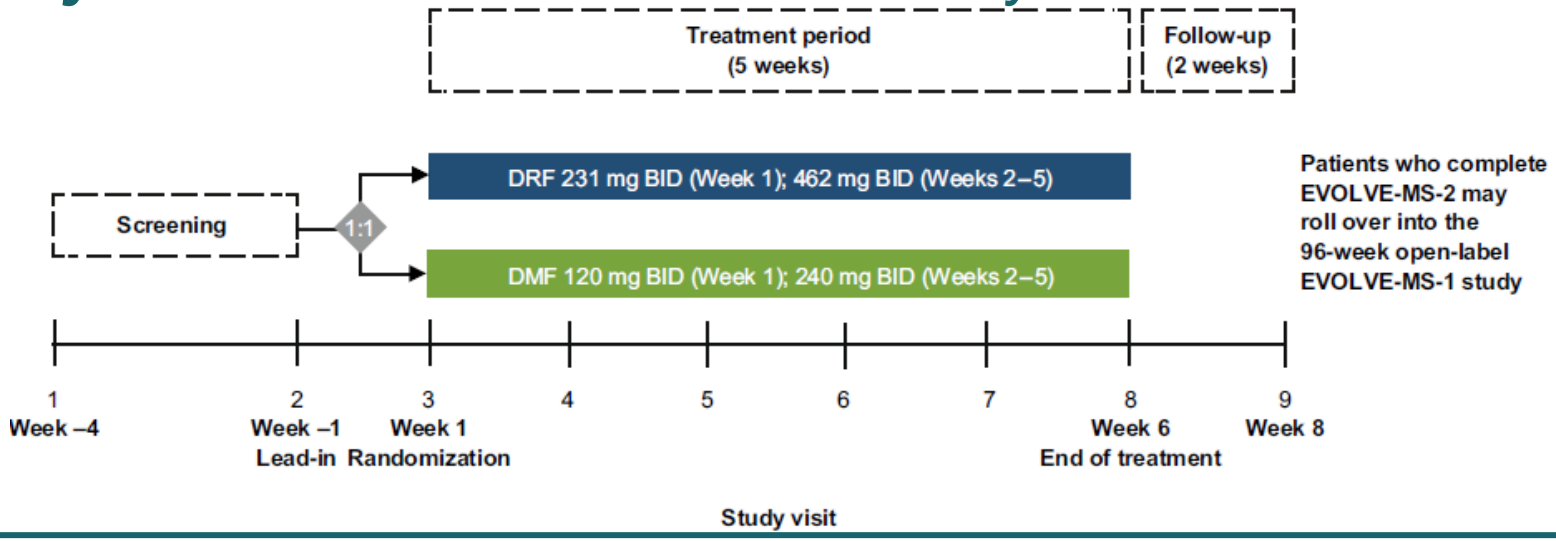
◉ *Does the committee consider dimethyl fumarate the appropriate comparator?*

Abbreviations: TA, Technology Appraisal

Clinical effectiveness

EVOLVE-MS-2 study design

*Randomised, double-blind, phase 3 trial **assessing gastrointestinal tolerability** of diroximel fumarate vs dimethyl fumarate*



Company:

- baseline demographics and disease characteristics between treatment arms well balanced
- Findings generalisable to UK practice as naïve comparison to real-world experience of dimethyl fumarate in UK cohort showed similar patient characteristics and clinical outcomes

Company: lower quantities of methanol, a known gastric irritant, are produced upon metabolism of DRF compared with DMF. Consequently, DRF is believed to elicit less localised irritation in the gastrointestinal tract than DMF.

ERG comments on clinical trials:

- no concerns with quality of company's trials
- **agrees with company** that baseline demographics and disease characteristics are generally well balanced

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Abbreviations: DRF, diroximel fumarate; DMF, dimethyl fumarate; BID, twice a day. **Source**: company submission, figure 2

Baseline characteristics: EVOLVE-MS-2 study

Population baseline characteristics well balanced

	Diroximel fumarate (n = 253)	Dimethyl fumarate (n = 251)
Mean age (SD), years	43.7 (11)	43.7 (10)
Female, n (%)	177 (70)	190 (76)
Race, n (%)		
White	232 (92)	227 (90)
Black or African American	20 (8)	20 (8)
Other	1 (0)	4 (2)
Mean weight (SD), kg	78.0 (19)	78.2 (20)
Mean body mass index (SD), kg/m^2	27.2 (6)	27.5 (6)
Prior disease-modifying therapy, n (%)		
0	84 (33)	85 (34)
1	73 (29)	72 (29)
2	60 (24)	43 (17)
≥ 3	36 (14)	51 (20)
Mean time since diagnosis (SD), years	7.4 (8)	7.9 (7)
Mean time since first symptom (SD), years	9.6 (9)	10.1 (9)
Mean no. of relapses in previous year (SD)	0.6 (1)	0.6 (1)
Mean Expanded Disability Status Scale score (SD)	2.70 (1)	2.72 (1)
Mean no. of gadolinium-enhancing lesions (SD)	0.9 (2)	1.1 (3)
Patients with 0 gadolinium-enhancing lesions, n (%)	180 (71)	175 (70)

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Abbreviations: SD, standard deviation. **Source**: company submission, table 6

Measures of gastrointestinal tolerability used in EVOLVE-MS-2

Measures are unique to this trial, but based on a validated measure

Primary outcome: number of days with Individual Gastrointestinal Symptom and Impact Scale (IGISIS) individual symptom intensity score ≥ 2 relative to exposure days

Secondary outcomes: IGISIS scores (≥1, ≥3), Global Gastrointestinal Symptom and Impact Scare (GGISIS) scores (≥1, ≥2, ≥3)

Individual GI Symptom and Impact Scale (IGISIS)

Assessment of intensity of each of the 5 GI symptoms over the **last 12 hours**

- Nausea
- Vomiting
- Upper abdominal pain
- Lower abdominal pain
- Diarrhea

Interference of GI symptoms with daily activities

Administered **twice daily** (at the time of each dose)

Global GI Symptom and Impact Scale (GGISIS)

Assessment of intensity of each of the 5 GI symptoms over the last **24 hours**

- Nausea
- Vomiting
- Upper abdominal pain
- Lower abdominal pain
- Diarrhea

Interference of GI symptoms with daily activities and work

Administered **once daily** (with AM dose)

- Two electronic diary symptom scales to evaluate duration and severity of gastrointestinal symptoms
- Designed for EVOLVE-MS-2, adapted from the Global Flushing Severity Scale (validated measure)
- Pre-planned unblinded data analysis:
  - After randomisation of first 120 patients, modifications to the scales were permitted.

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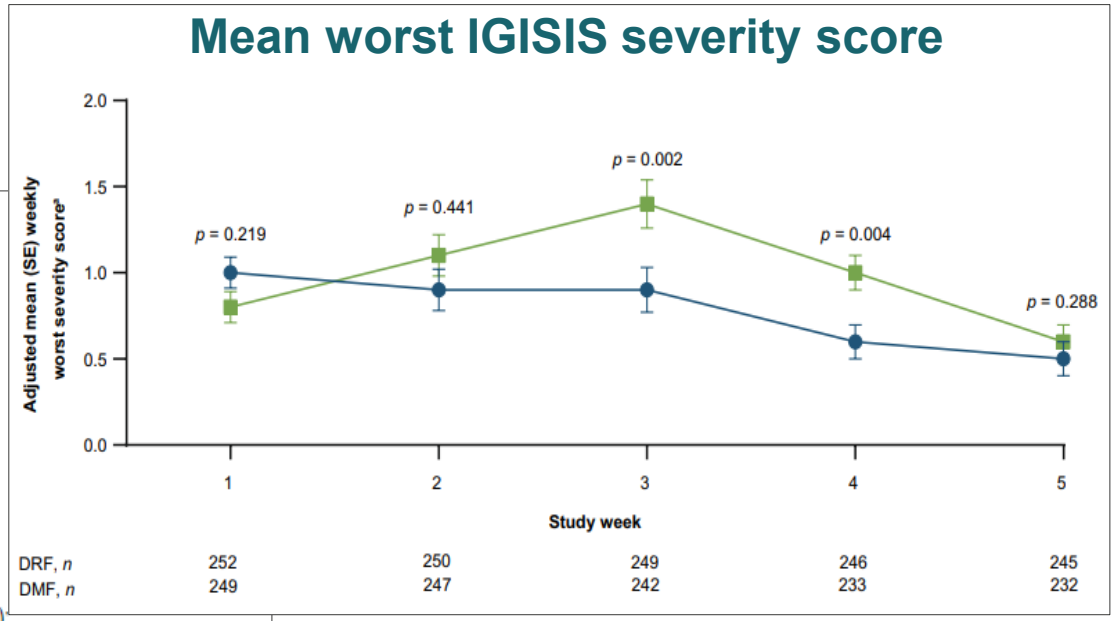
Abbreviations: AE, adverse event; GI. Gastrointestinal. **Source**: company submission, figure 1

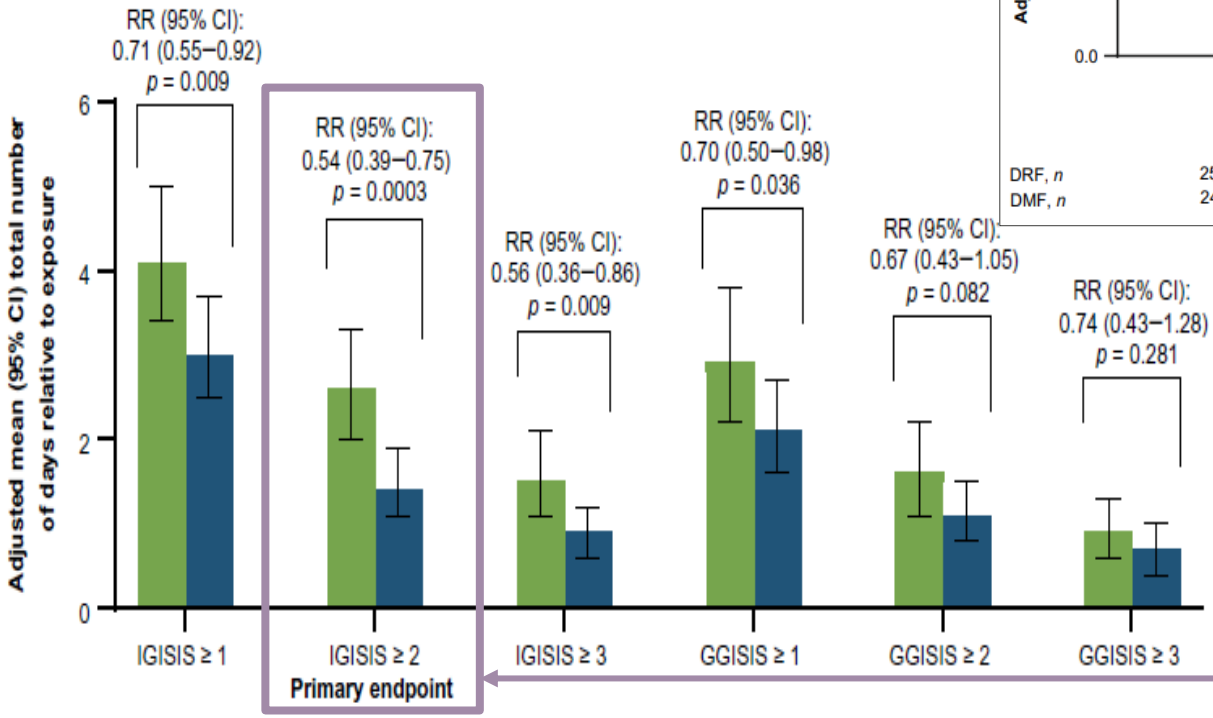
EVOLVE-MS-2 results: gastrointestinal symptoms

Diroximel fumarate improves gastrointestinal symptoms compared with dimethyl fumarate (5 week treatment duration)

Mean worst IGISIS severity score



Adjusted mean number of days at different symptom intensity scores as measured by IGISIS & GGISIS in the FAS



Key:
- DRF
- DMF

Statistically significant reduction in number of days with symptom intensity score ≥ 2 (primary endpoint)

Abbreviations: CI, confidence interval; DMF, dimethyl fumarate; DRF, diroximel fumarate; FAS, full analysis set; GGISIS, Global Gastrointestinal Symptom and Impact Scale; IGISIS, Individual Gastrointestinal Symptoms and Impact Scale; **both scales from 0 (no GI symptoms) to 10 (extreme GI symptoms).** SE, standard error; RR, rate ratio. **Source:** Company submission, figures 4 and 5.

EVOLVE-MS-1 results: interim analyses

Diroximel fumarate improves multiple sclerosis health outcomes (Feb 2020 data cut, follow up 96 weeks, median exposure 59.9 weeks)

Number of multiple sclerosis relapses, safety population	**Total (n = 1,057)**
0, n (%)	[redacted]
1 to ≥ 4, n (%)	[redacted]
EDSS scores, full analysis set population	**Total (n = 1,057)**
Mean EDSS score (SD)	[redacted]
Mean change in EDSS score from baseline (SD)	[redacted]
Disability progression, full analysis set population	**Total (n = 1,041)**
Confirmed disability progression, n (%)	[redacted]
Timed 25-foot walk, full analysis set population	**Total (n = 1,041)**
Mean score	[redacted]
Change from baseline	[redacted]
MRI outcomes, full analysis set population	**Total (n = 1,041)**
Mean number of Gd+ lesions (SD)	[redacted]
Mean change from baseline in Gd+ lesions (SD)	[redacted]
Mean change from baseline to week 48 in new/enlarging T2 lesions (SD)	[redacted]
Mean change from week 48 to week 96 in new/enlarging T2 lesions (SD)	[redacted]
Health related Quality of Life (EQ-5D-5L) , full analysis set population	**Total (n = 612)**
Mean decrease in index score	[redacted]

Abbreviations: EDSS, expanded disability status scale; Gd+, gadolinium-enhancing. ***Change from baseline = baseline from EVOLVE-MS-1***. EDSS scores range from 0 to 10 with lower scores indicating better outcome. EQ-5D-5L index scores range from 0 to 1 with lower scores indicating worse outcomes. Final data expected [redacted]. **Source**: company submission, table 10, 11, 12, 13 and pages 54, 55.

Five clinical experts representing different UK geographies confirmed patients in the EVOLVE-MS-1 study were representative of the clinical cohort seen in their practice.

Cost comparison

Company cost-comparison

Diroximel fumarate would give *incremental cost savings* of [redacted] per patient annually

ERG, satisfied that:

- diroximel fumarate and dimethyl fumarate are bioequivalent
- safety and tolerability of diroximel fumarate appears to be better than of dimethyl fumarate
- [redacted]

NICE

Abbreviations: PAS, patient access scheme. **Source**: company submission, table 20

Considerations for recommendation

1. Does the committee consider the clinical efficacy of diroximel fumarate to be similar/exchangeable to dimethyl fumarate because of the established bioequivalence?
2. Should diroximel fumarate be recommended at the same point in the treatment pathway as dimethyl fumarate? i.e. first line therapy.
3. If recommending, for what type of relapsing remitting multiple sclerosis:
   - The same as recommended by TA320 for dimethyl fumarate i.e. active relapsing remitting multiple sclerosis defined by 2 significant relapses in last 2 years. Excluding highly active or rapidly evolving severe relapsing-remitting multiple sclerosis?

NB: NHS England is commissioning dimethyl fumarate as an option for people who have had 1 relapse in last 12 months due to considerations around the impact of COVID-19

Potential recommendation?

- Diroximel fumarate is recommended as an option for treating adults with active relapsing-remitting multiple sclerosis (normally defined as 2 clinically significant relapses in the previous 2 years), only if:
  - *they do not have highly active or rapidly evolving severe relapsing-remitting multiple sclerosis*
  - *the company provides diroximel fumarate according to the commercial arrangement*
- If patients and their clinicians consider diroximel fumarate to be one of a range of suitable treatments, including dimethyl fumarate, choose the least expensive (taking into account administration costs and commercial arrangements).

Back-up information for PMB slides

Info: comparison with TA320 (dimethyl fumarate) (1)

	TA320: dimethyl fumarate: recommended in 2014	ID1673: diroximel fumarate
MA wording	The treatment of adult patients with relapsing-remitting multiple sclerosis	Treatment of adult patients with relapsing remitting multiple sclerosis
NICE recommendation	Recommended as an option for treating adults with ***active*** relapsing-remitting multiple sclerosis (***normally defined as 2 clinically significant relapses in the previous 2 years****), only if: • they do not have highly active or rapidly evolving severe relapsing-remitting multiple sclerosis and • the manufacturer provides dimethyl fumarate with the discount agreed in the patient access scheme.	N/A
Pivotal trial(s)	DEFINE CONFIRM	EVOLVE-MS-1 EVOLVE-MS-2
Study design	DEFINE, international, multicentre, double-blind phase III RCT. CONFIRM, international, multicentre, double-blind phase III RCT.	EVOLVE-MS-1, phase III, open-label, single-arm EVOLVE-MS-2, phase III, randomised, double-blind
Population (n)	DEFINE n=1234 CONFIRM n=1417 Confirmed diagnosis of relapsing-remitting multiple sclerosis according to McDonald criteria	EVOLVE-MS-2 n=504 EVOLVE-MS-1 n=1,057 Confirmed diagnosis of relapsing-remitting multiple sclerosis according to revised McDonald 2010 criteria

*Dimethyl fumarate is only recommended by NICE for people who have had 2 relapses in 24 months. However, NHS England is commissioning dimethyl fumarate as an option for people in this category who have had 1 relapse in last 12 months due to considerations around the impact of COVID-19.

Info: comparison with TA320 (dimethyl fumarate) (2)

	TA320: dimethyl fumarate: recommended in 2014	ID1673: diroximel fumarate
Inclusion criteria	Both trials: 18 – 55 years old, diagnosis of RRMS confirmed by McDonald criteria, EDSS score of 0 – 5, 1 relapse in last year and MRI scan showing lesions consistent with MS or gadolinium-enhancing lesions on MRI scans within 6 weeks of randomisation	Both trials: Adults aged 18–65 years, confirmed diagnosis of relapsing-remitting multiple sclerosis, neurologically stable, no evidence of relapse 30 days before screening
Intervention (dosing)	Licensed dose 240mg twice daily	Starting dose: 231 mg twice daily Maintenance dose: 462 mg twice daily
Comparator (n)	DEFINE, 3 arms: DMF 240mg twice daily (n=410), DMF 240mg 3 times daily (n=416) and placebo (n=408) CONFIRM, 4 arms: DMF 240mg twice daily (n=359), DMF 240mg 3 times daily (n=345), glatiramer acetate (n=350) and placebo (n=363).	EVOLVE-MS-1: NA EVOLVE-MS-2: dimethyl fumarate (n=252)
Primary outcomes assessed	DEFINE, proportion of patients with a relapse at 2 years CONFIRM, annualised relapse rate at 2 years	EVOLVE-MS-1: safety and tolerability. EVOLVE-MS-2: number of days with Individual Gastrointestinal Symptom and Impact Scale (IGISIS) individual symptom intensity score ≥ 2 relative to exposure days.
Follow up:	Treated for 96 weeks, follow up visit at 100 weeks if completed treatment	EVOLVE-MS-1: 96 weeks on treatment, 2 week follow up. EVOLVE-MS-2: 5-weeks on treatment, 2 week follow-up.

Abbreviations: DMF, dimethyl fumarate; DRF, diroximel fumarate