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Efficacy of Delayed-release Dimethyl Fumarate in Newly Diagnosed Patients With Relapsing-remitting Multiple Sclerosis Using a Composite Measure of Disability: Integrated Analysis of the Phase 3 DEFINE and CONFIRM Studies

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- **Disclosures**
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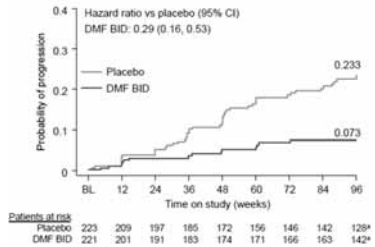
Introduction

- Newly diagnosed patients with RRMS may have better long-term outcomes if treated early with a therapy that controls their disease activity[1]
- As previously reported,[1] the estimated proportion of newly diagnosed patients in DEFINE/CONFIRM with 12-week confirmed EDSS progression at 2 years was 23% in the PBO group and 7% in the DMF 240 mg BID group, representing a relative risk reduction of 71% (*P*<.0001 vs. PBO)



Estimated proportion of patients with disability progression at Week 96 was derived using Kaplan-Meier analysis. Hazard ratio, 95% CI, and *P* values were based on a stratified Cox proportional hazards model with study as the stratifying variable, adjusted for baseline Expanded Disability Status Scale (EDSS) score (as a continuous variable), baseline age (<40 vs. ≥40 years), and region; BID = twice daily; DMF = delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF); PBO = placebo; RRMS = relapsing-remitting multiple sclerosis; 1. Gold R, *et al*. *Mult Scler*. 2015;21(1):57–66.

Rationale and Objective

Rationale

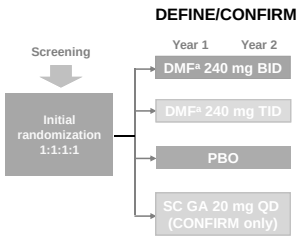
- EDSS scores and MSFC *z* scores present limitations in determining clinically meaningful changes in disease progression[1]
- A potentially more reliable approach is to use a composite outcome measure, where worsening is defined as a prespecified change in any component score, and to show worsening in the same component at ≥2 subsequent time points[1]

Objective

- To assess the clinical effect of DMF on multicomponent composite measures of disability progression in newly diagnosed patients with RRMS from the DEFINE/CONFIRM studies

MSFC = Multiple Sclerosis Functional Composite; 1. Cohen JA, *et al*.; International Advisory Committee on Clinical Trials in Multiple Sclerosis. *Lancet Neurol*. 2012;11(5):467–476.

Study Design



- Inclusion criteria included:
  - Age: 18–55 years
  - Diagnosis of RRMS (McDonald criteria)[1]
  - EDSS score of 0–5.0
  - ≥1 relapse in the 12 months before randomization OR ≥1 Gd^+ lesion in the 6 weeks before randomization
- Exclusion criteria included:
  - Prior treatment with GA within the past 3 months (DEFINE) or at any time (CONFIRM)

- **Newly diagnosed** patients were defined as:
  - RRMS diagnosed within 1 year before the study entry **AND**
  - Naïve to MS disease-modifying therapy or previously treated with corticosteroids alone

[a]DMF, delayed-release DMF (also known as gastro-resistant DMF); GA = glatiramer acetate; Gd^+ = gadolinium-enhancing; MS = multiple sclerosis; QD = once daily; SC = subcutaneous; TID = three times daily; 1. Polman CH, *et al*. *Ann Neurol*. 2005;58(6):840–846.

Methods

- Composite-confirmed disability progression (CDP) was defined as the first occurrence of sustained worsening from baseline of any of the following components:
  - EDSS
  - Timed 25-Foot Walk (T25FW)
  - 9-Hole Peg Test (9HPT)
  - Paced Auditory Serial Addition Test (PASAT)
  - Visual Function Test (VFT)
- Assessments were performed at baseline and at 12-week intervals thereafter
- Composite-CDP was confirmed for 12 or 24 weeks by assessing any of the functional outcomes
- Statistical analysis comparisons were based on a Cox proportional hazards model adjusted for baseline covariates
- Results are reported for PBO and DMF 240 mg BID (the approved dosage)
- The GA arm was excluded from the analysis of newly diagnosed patients in DEFINE/CONFIRM (and from all other integrated analyses of DEFINE/CONFIRM), as it was a reference arm and was included in CONFIRM only

Components of the Composite-CDP Outcome Measures

Component	Disability directly measured	Scores and units of measurement	Definition of disability progression
EDSS	Overall disability	Scores are calculated based on disability in 8 functional systems	≥1.0- or ≥1.5-point increase from baseline EDSS score (>0 or 0, respectively)
T25FW	Walking speed	Time to completion (seconds)	≥20% worsening from baseline[a,1,2]
9HPT	Upper extremity function and dexterity	Time to completion (seconds)	≥20% worsening from baseline[a,1,2]
PASAT	Cognitive function	Number of correct responses (total of 60)	≥20% worsening from baseline[a,1]
VFT	Visual loss	Number of correct responses (total of 60)	≥10-letter worsening from baseline[a,3]

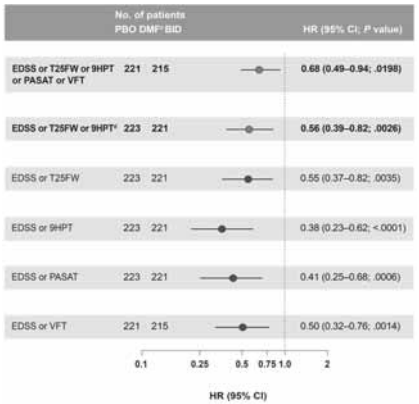
[a]These disability progression threshold criteria were based on previously established standards and published data;[1-3] 1. Rudick RA, *et al*. *Mult Scler*. 2009;15(8):984–997; 2. Schwid SR, *et al*. *Neurology*. 2002;58(8):1294–1296; 3. Balcer LJ, *et al*. *Neurology*. 2007;68(16):1299–1304.

Baseline Demographics and Disease Characteristics

Characteristic[a,1]	Placebo n=223	DMF[b] BID n=221
Age, y	36.5 (9.4)	35.3 (9.4)
Female, %	70	73
Time since first MS symptoms, y	4.3 (5.3)	4.3 (5.8)
Median (min, max)	2.0 (0, 31)	2.0 (0, 42)
Time since diagnosis, y	0.5 (0.5)	0.5 (0.5)
Median (min, max)	1.0 (0, 1.0)	1.0 (0, 1.0)
Relapses in prior year	1.4 (0.6)	1.4 (0.6)
Prior treatment with steroids, %	7	10
EDSS score	2.2 (1.1)	2.1 (1.1)

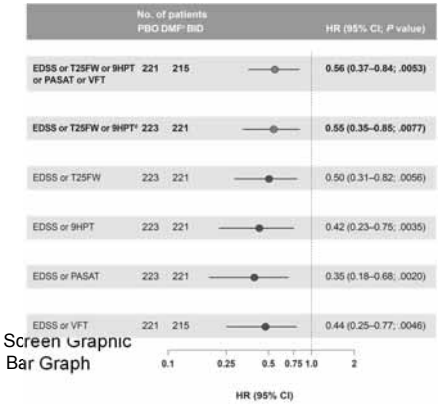
[a]Values are mean (SD) unless stated otherwise; [b]DMF, delayed-release DMF (also known as gastro-resistant DMF); max = maximum; min = minimum; 1. Gold R, *et al*. *Mult Scler*. 2015;21(1):57–66.

HR of 12-Week Composite-CDP Outcomes and Functional Subcomponents[a,b]



[a]Stratified by study, adjusted for baseline age, region, and baseline PASAT, EDSS, T25FW, 9HPT, or VFT according to model outcome; [b]Patients were classified as having progression if they demonstrated the defined worsening in any one of the components; [c]DMF, delayed-release DMF (also known as gastro-resistant DMF); HR = hazard ratio; Cadavid D, *et al. Mult Scler*. 2016. doi: 10.1177/1352458516638941.

HR of 24-Week Composite-CDP Outcomes and Functional Subcomponents[a,b]



Half Screen Graphic
Bar Graph

[a]Stratified by study, adjusted for baseline age, region, and baseline PASAT, EDSS, T25FW, 9HPT, or VFT according to model outcome; [b]Patients were classified as having progression if they demonstrated the defined worsening in any one of the components; [c]DMF, delayed-release DMF (also known as gastro-resistant DMF); Cadavid D, *et al. Mult Scler*. 2016. doi: 10.1177/1352458516638941

Conclusions

- DMF 240 mg BID significantly reduced the risk of CDP in newly diagnosed patients with RRMS compared with PBO as measured using functional composite endpoints
  - Statistically significant reductions for DMF vs. PBO also were observed across all combinations of the EDSS plus each of the other individual components
- These findings are consistent with previously published data suggesting the potential for greater clinical benefits in patients with RRMS who receive DMF treatment early in their disease course
- Although this analysis presents its own limitations (e.g. patients with worsening in one component were treated the same as those with worsening in multiple components), the composite CDP measure proposed here may be more reliable than assessing its individual components alone, capturing clinically meaningful changes in disability progression across multiple neuro-performance components