# Lymphocyte Count Reductions in Relapsing-Remitting MS Patients Treated with Delayed-Release Dimethyl Fumarate: Integrated Analysis of the Placebo-Controlled Studies

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# INTRODUCTION

Delayed-release dimethyl fumarate (DMF) is approved in the United States and Australia for the treatment of relapsing forms of multiple sclerosis (MS) and relapsing MS, respectively, and in the European Union and Canada for the treatment of relapsing-remitting MS (RRMS).

Delayed-release DMF demonstrated significant efficacy and an acceptable safety profile in placebo-controlled clinical trials, including a Phase 2b trial<sup>1</sup> and the Phase 3 DEFINE and CONFIRM studies.<sup>2,3</sup> Interim efficacy and safety results of ENDORSE, an ongoing, 5-year extension of DEFINE and CONFIRM, are consistent with those of the parent studies.4-

In clinical trials, the most common adverse events (AEs) associated with delayedrelease DMF treatment were flushing and GI events. Delayed-release DMF was also associated with a decrease in white blood cell (WBC) and lymphocyte counts.

## OBJECTIVE

· To describe the clinical relevance of lymphocyte count reductions in patients treated with delayed-release DMF 240 mg twice (BID) or three times daily (TID), based on an integrated analysis of the placebo-controlled Phase 2b, DEFINE, and CONFIRM

### METHODS

#### Study Design

- · The Phase 2b study, DEFINE, and CONFIRM were multicenter, randomized, double blind, placebo-controlled, parallel-group clinical trials of delayed-release DMF as monotherapy for RRMS. The Phase 2b study was 6 months in duration and DEFINE and CONFIRM were 2 years in duration
- In the Phase 2b study, patients were randomized equally to delayed-release
- DMF 120 mg once daily (QD), 120 mg TID, 240 mg TID, or placebo
- Results for patients in the Phase 2b study randomized to delayed-release DMF 120 mg QD or TID are not presented here, but are generally consistent with those for patients in the delayed-release DMF 240 mg BID and TID groups
- · In DEFINE and CONFIRM, patients were randomized equally to delayed-release DMF 240 mg BID, 240 mg TID, or matching placebo
- One of the Phase 3 studies (CONFIRM) also included glatiramer acetate (GA) as a reference comparator arm
- Results for the GA group are not presented here

#### Key Inclusion Criteria

- Age 18–55 years
- Diagnosis of RRMS (McDonald criteria)<sup>7,8</sup>
- Expanded Disability Status Scale (EDSS)<sup>9</sup> score of 0–5.0

#### Key Exclusion Criteria

- Progressive forms of MS or other significant illness
- Relapse within 50 days prior to randomization
- Corticosteroids within 30 days (Phase 2b) or 50 days (DEFINE, CONFIRM) prior to randomization
- Pre-specified abnormal laboratory parameters including:
- WBC <3.5 x 10<sup>9</sup>/L
- Eosinophils >0.7 x 10<sup>3</sup>/µL or >0.7 GI/L
- · Prior treatment with potent immunosuppressant agents or procedures
- Prior treatment with MS therapies within predefined washout periods, including:
- Interferon β, within 3 months prior to randomization
- Glatiramer acetate, within 3 months prior to randomization (Phase 2b, DEFINE) or at any time (CONFIRM)
- Natalizumab, within 6 months prior to randomization

### Hematology

- Blood was collected every 4 weeks (Phase 2b) or every 4 weeks for the first 3 months and every 12 weeks thereafter (DEFINE and CONFIRM), and within 1 month after study withdrawal or study completion if not continuing in the extension study (Phase 2b, DEFINE, and CONFIRM)
- Hematology included hemoglobin, hematocrit, red blood cell count, WBC count (with differential), and platelet count
- · Lymphocyte counts were graded per Common Terminology Criteria for Adverse Events (CTCAE)<sup>10</sup> (Table 1)

#### Table 1: CTCAE v4.0 grading for lymphocyte counts CTC Grade 2 CTC Grade 3 CTC Grade 0 CTC Grade 1 CTC Grade 4 >LLN<sup>a</sup> <LLN-<0.8-<0.5-<0.2 x 10<sup>9</sup>/L ≥0.8 x 10<sup>9</sup>/L ≥0.5 x 10<sup>9</sup>/L ≥0.2 x 10<sup>9</sup>/L

<sup>a</sup>Lower limit of normal (LLN) = 0.91 x 10<sup>9</sup>/L

#### Stopping Rule for Low WBC Counts

- · Study treatment had to be discontinued in patients with low WBC counts per the following rules:
- Phase 2b: WBC <1.5 x 10<sup>9</sup>/L at any time during the study or WBC counts <2.0 x 10º/L sustained for 4 weeks
- DEFINE and CONFIRM: WBC count <2.0 x 10<sup>9</sup>/L sustained for 4 consecutive weeks after study treatment was withheld for a WBC count <2.0 x10<sup>9</sup>/L confirmed on retesting
- There was no stopping rule based on low lymphocyte counts

# RESULTS

#### Patients

- · A total of 2,428 RRMS patients were randomized and received treatment with placebo (n=836), delayed-release DMF BID (n=769), or delayed-release DMF TID (n=823)
- · Baseline demographic and disease characteristics were similar across the treatment groups (Table 2)

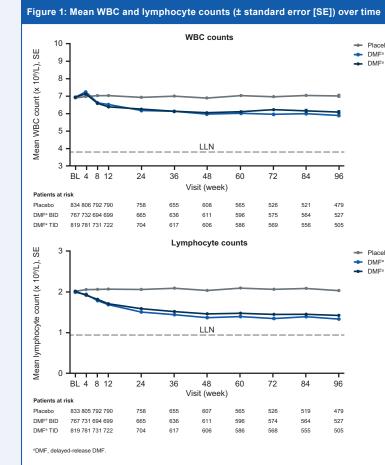
### Table 2: Patient baseline characteristics

Placebo (n=836)	DMF <sup>ь</sup> BID (n=769)	DMF <sup>b</sup> TID (n=823)
		(11=023)
71	70	73
37.6 ± 9.2	37.9 ± 9.2	38.3 ± 9.1
82	81	83
71.8 ± 16.7	71.2 ± 18.2	71.5 ± 17.1
5.3 ± 5.5	5.3 ± 5.3	4.8 ± 5.2
35	34	34
1.3 ± 0.7	1.3 ± 0.7	1.3 ± 0.7
2.5 ± 1.2	2.5 ± 1.3	2.5 ± 1.2
6.897 ± 1.9020	6.926 ± 1.9741	6.940 ± 2.0676
1.995 ± 0.6178	1.970 ± 0.6201	1.994 ± 0.6423
	$37.6 \pm 9.2$ 82 71.8 ± 16.7 5.3 ± 5.5 35 1.3 ± 0.7 2.5 ± 1.2 6.897 ± 1.9020	$37.6 \pm 9.2$ $37.9 \pm 9.2$ $82$ $81$ $71.8 \pm 16.7$ $71.2 \pm 18.2$ $5.3 \pm 5.5$ $5.3 \pm 5.3$ $35$ $34$ $1.3 \pm 0.7$ $1.3 \pm 0.7$ $2.5 \pm 1.2$ $2.5 \pm 1.3$ $6.897 \pm 1.9020$ $6.926 \pm 1.9741$ $1.995 \pm 0.6178$ $1.970 \pm 0.6201$

<sup>d</sup>Lower limit of normal (LLN) for WBC = 3.8 x 10<sup>9</sup>/L

### Hematology

- Mean baseline WBC and lymphocyte counts were similar across the placebo delayed-release DMF BID, and delayed-release DMF TID groups (Table 2)
- In delayed-release DMF-treated patients, mean WBC and lymphocyte counts decreased from baseline by approximately 11% and 30%, respectively, following Week 4 through Week 48, then plateaued, but remained within normal limits throughout the observation period (Figure 1)
- · For the majority of patients, lymphocyte counts were within normal limits at all time points (CTC grade 0). The percentages of patients with worst post-baseline CTC grades 1, 2, or 3 were higher in the delayed-release DMF groups than in the placebo group (Table 3)
- The percentages of patients with more than one grade 3 or 4 lymphocyte count or consecutive grade 3 or 4 lymphocyte counts were increased among delayed-release DMF-treated subjects relative to placebo (Table 4)
- · The incidence of CTC grade 3 or 4 lymphopenia increased over time through Week 48, then stabilized (Figure 2)



### Table 3: Incidence of CTC grades for worst post-baseline lymphocyte counts

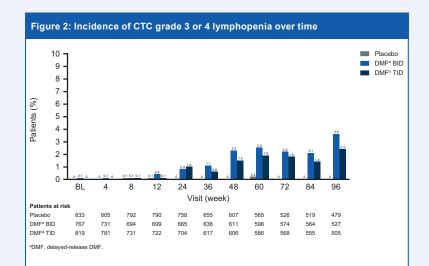
	Placebo (n=830)	DMFª BID (n=757)	DMF <sup>a</sup> TID (n=805)
Category		n (%)	
CTC grade 0	794 (96)	472 (62)	573 (71)
CTC grade 1	14 (2)	76 (10)	62 (8)
CTC grade 2	18 (2)	166 (22)	146 (18)
CTC grade 3	4 (<1)	42 (6)	24 (3)
CTC grade 4	0	1 (<1)	0

Note: Numbers in parentheses are percentages using the number of patients in the safety population with at lepost-baseline lymphocyte value (n=830, 757, and 805 in the placebo, delayed-release DMF BID, and delayed-rele DMF TID groups, respectively) as the denominator.

Table 4: Incidence of at least one, more than one, or consecutive grade 3 or 4lymphocyte counts					
	Placebo (n=830)	DMF <sup>a</sup> BID (n=757)	DMF <sup>a</sup> TID (n=805)		
Characteristic		n (%)			
≥1 grade 3 or 4 lymphocyte count	4 (<1)	43 (6)	24 (3)		
>1 grade 3 or 4 lymphocyte count	0	20 (3)	12 (1)		
Consecutive grade 3 or 4 lymphocyte counts	0	16 (2)	10 (1)		

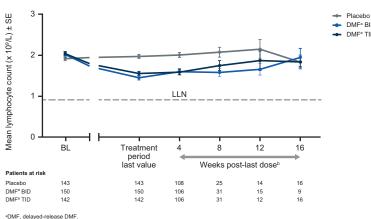
elayed-release DMF. umbers in parentheses are percentages using the number of patients in the safety population with at least one seline lymphocyte value (n=830, 757, and 805 in the placebo, delayed-release DMF BID, and delayed-release groups, respectively) as the denominator.

- Placeb DMF<sup>a</sup> BII 📥 DMFª TI 479 526 521 575 569 556 - Placeb DMF<sup>a</sup> BII 574



Note: Number of patients at risk is the number with a non-missing lymphocyte value at that visit, including those with normal values. The percentage of patients with CTC grade 3 or 4 out of the number of patients at risk at the visit is provided at the top of each bar. Therefore, patier may be counted at more than one visit if they had CTC grade 3 or 4 lymphopenia at more than now visit.

Figure 3: Mean lymphocyte counts (± SE) over time in patients with lymphocyte counts available after the last dose



Note: Patients who either completed or discontinued study treatment and had lymphocyte counts available at baseline, post-baseline during the treatment period, and >2 weeks after the last dose are included in this analysis

# Table 5: Incidence of infections, serious infections, and opportunistic infections

oy worst post-baseline CTC grade	e		
	Placebo (n=830)	DMFª BID (n=757)	DMFª TID (n=805)
Infections, n (%)	469 (57)	462 (61)	492 (61)
CTC grade 0	448/794 (56)	279/472 (59)	335/573 (58)
CTC grade 1	5/14 (36)	52/76 (68)	43/62 (69)
CTC grade 2	14/18 (78)	106/166 (64)	97/146 (66)
CTC grade 3 or 4	2/4 (50)	25/43 (58)	17/24 (71)
Serious infections, n (%)	12 (1.4)	17 (2.2)	15 (1.9)
CTC grade 0	11/794 (1.4)	11/472 (2.3)	10/573 (1.7)
CTC grade 1	0/14	4/76 (5.3)	1/62 (1.6)
CTC grade 2	1/18 (5.6)	2/166 (1.2)	4/146 (2.7)
CTC grade 3 or 4	0/4	0/43	0/24
Opportunistic infections, n (%)	2 (< 1) <sup>b</sup>	0	0
CTC grade 0	2/794 (2.5)	0/472	0/573
CTC grade 1	0/14	0/76	0/62
CTC grade 2	0/18	0/166	0/146
CTC grade 3 or 4	0/4	0/43	0/24

<sup>a</sup> DMF, delayed-release DMF. <sup>⊎</sup>Includes one definite and one possible opportunistic infection. Note: In the first row of each infection category, numbers in par

Note: In the first row of each infection category, numbers in parentheses are percentages using the number of patient in the safety population with at least one post-baseline lymphocyte value (n=830, 757, and 806 in the placebo, delayed release DMF BD, and delayed-release DMF TID groups, respectively) as the denominator. For each CTC grade, numbers in parentheses are percentages based on the number with an infection out of the number with worst post-baseline count in that grade as shown

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- Prior to the 6 month visit window (at or before Day 126), the incidence of CTC grade 3 or 4 lymphopenia was low and similar across treatment groups (Placebo: 3 patients, <1%; BID: 5 patients, <1%; TID: 3 patients, <1%)
- Among delayed-release DMF-treated patients, there was no clear pattern of an increased incidence of infections or serious infections with increasing post-baseline lymphocyte CTC grade
- No opportunistic infections were reported in delayed-release DMF-treated patients. One possible and one definite opportunistic infection were reported in the placebo group
- Across the studies, one patient in the delayed-release DMF TID group discontinued study drug due to an AE associated with leukopenia. No delayed-release DMF-treated patients discontinued study drug due to lymphopenia
- In a subgroup of 292 delayed-release DMF-treated patients with lymphocyte counts available at baseline, post-baseline during the treatment period, and >2 weeks after the last dose (includes both patients who completed treatment and patients who discontinued treatment), mean lymphocyte counts increased after the last dose but did not return to baseline (Figure 3)

# CONCLUSIONS

- In placebo-controlled clinical trials, delayed-release DMF was associated with a decrease in lymphocyte counts
- In delayed-release DMF-treated patients, mean lymphocyte counts were within normal limits at all time points
- There was an increased incidence of lymphopenia categorized as CTC grades 1 2, or 3 in delayed-release DMF-treated patients relative to placebo
- The percentages of patients with at least one, more than one, and consecutive grade 3 or 4 lymphocyte counts were increased among delayed-release DMFreated patients relative to placebo
- Lymphopenia in delayed-release DMF-treated patients was not clearly associated with an overall increased risk of infections, serious infections, or opportunistic infections
- Four weeks after stopping delayed-release DMF, mean lymphocyte counts increased but did not return to baseline

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