

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.<sup>4,6</sup>

In clinical trials, the most common adverse events (AEs) associated with delayed-release 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 (TID) or three times daily (D), based on an integrated analysis of the placebo-controlled Phase 2b, DEFINE, and CONFIRM studies

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>9</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

Table with 5 columns: CTC Grade 0 to 4. Rows: Definitions for LLN, <LLN, and ≥LLN. 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 10<sup>9</sup>/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 x 10<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

Table with 4 columns: Characteristic, Placebo (n=836), DMF BID (n=769), DMF TID (n=823). Rows: Female, Age, Race, Body weight, Time since MS diagnosis, Any prior approved MS treatment, Relapses in prior year, EDSS score, Mean WBC count, Mean lymphocyte count.

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)

Figure 1: Mean WBC and lymphocyte counts (± standard error [SE]) over time

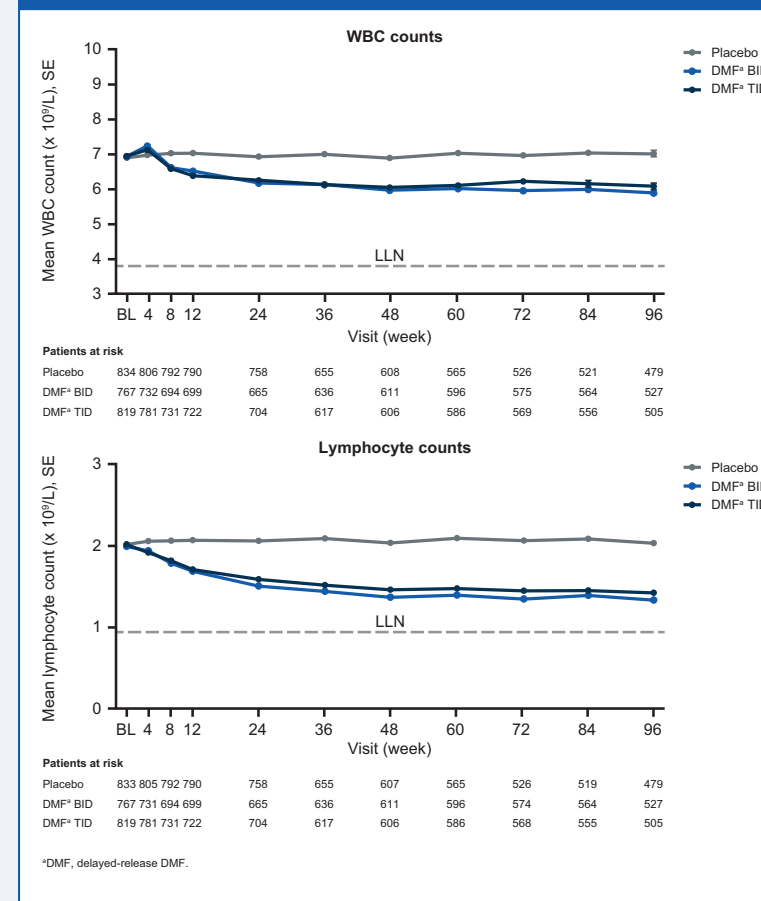


Table 3: Incidence of CTC grades for worst post-baseline lymphocyte counts

Table with 3 columns: Category, Placebo (n=830), DMF BID (n=757), DMF TID (n=805). Rows: CTC grade 0, 1, 2, 3, 4.

Table 4: Incidence of at least one, more than one, or consecutive grade 3 or 4 lymphocyte counts

Table with 3 columns: Characteristic, Placebo (n=830), DMF BID (n=757), DMF TID (n=805). Rows: ≥1 grade 3 or 4 lymphocyte count, >1 grade 3 or 4 lymphocyte count, Consecutive grade 3 or 4 lymphocyte counts.

Figure 2: Incidence of CTC grade 3 or 4 lymphopenia over time

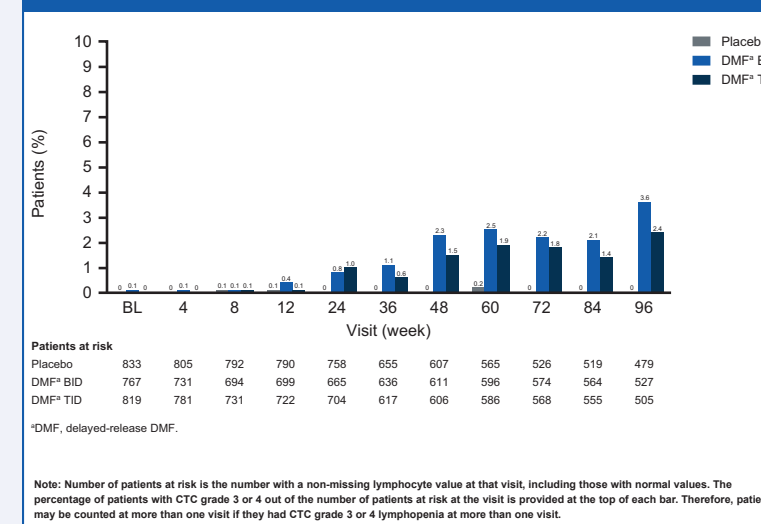


Figure 3: Mean lymphocyte counts (± SE) over time in patients with lymphocyte counts available after the last dose

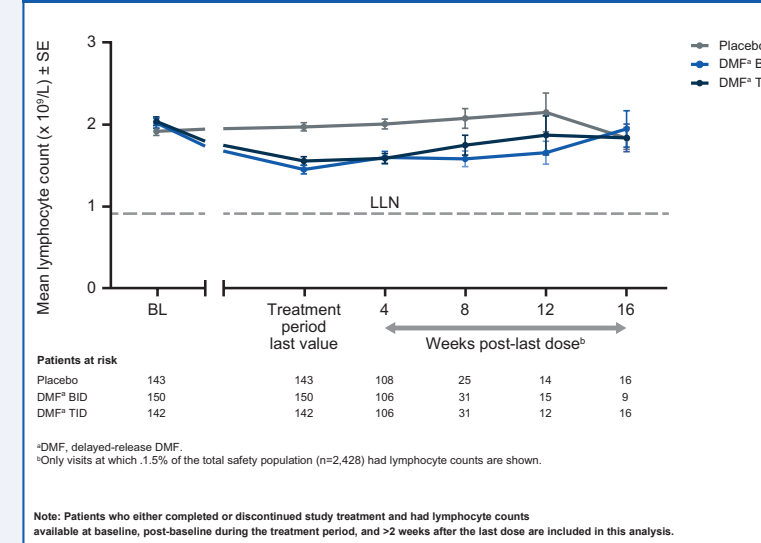


Table 5: Incidence of infections, serious infections, and opportunistic infections by worst post-baseline CTC grade

Table with 3 columns: Infections/Infections, Placebo (n=830), DMF BID (n=757), DMF TID (n=805). Rows: Infections, n (%); Serious infections, n (%); Opportunistic infections, n (%).

- 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 DMF-treated 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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