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ORIGINAL RESEARCH

Real-World Safety and Effectiveness of Dimethyl Fumarate in Patients with MS: Results from the ESTEEM Phase 4 and PROCLAIM Phase 3 Studies with a Focus on Older Patients

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ABSTRACT

Introduction: Real-world studies in the USA report that 41–56% of patients with multiple sclerosis (MS) are ≥ 50 years old, yet data on their response to disease-modifying therapies (DMTs) is limited. Dimethyl fumarate (DMF) is an oral DMT approved for treating relapsing MS. This analysis evaluated the safety, efficacy, and immunophenotype changes of DMF in patients ≥ 50 years compared with patients < 50 years.

Methods: ESTEEM, a 5-year, real-world, observational phase 4 study, assessed the safety and effectiveness of DMF, including treatment-emergent serious adverse events (SAEs) and adverse events (AEs) leading to treatment discontinuation. Absolute lymphocyte counts (ALCs) were recorded from a subset of patients. The PROCLAIM study, a phase 3b interventional study, reported safety outcomes and lymphocyte subset changes in patients with relapsing–remitting MS (RRMS) treated with DMF. The study evaluated safety outcomes by analyzing the incidence of SAEs and detailed changes in $CD4^+$ and $CD8^+$

Prior Presentation: Some of these data have been previously presented at the 72nd American Academy of Neurology Annual Meeting, April 25–May 1, 2020, virtual and 2019 CMSC Annual Meeting, May 28–June 1, 2019, Seattle, Washington.

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T cell compartments over 96 weeks of DMF treatment.

Results: ESTEEM included 4020 patients aged < 50 years and 1069 aged ≥ 50 years. AEs leading to discontinuation were reported by 19.6% patients < 50 years and 29.6% of patients ≥ 50 years, with gastrointestinal disorders being the most common. SAEs were reported by 5.2% of patients < 50 years and 8.9% those ≥ 50 years. In PROCLAIM, SAEs were reported in 13% of patients < 50 years and 10% of those ≥ 50 years. Median ALC decreased by 35% in patients < 50 years and 50% in those ≥ 50 years in ESTEEM, with similar patterns observed in PROCLAIM.

Conclusions: ESTEEM found no unexpected safety signals in older patients and annualized relapse rates (ARRs) were significantly reduced in both age groups. Both studies indicated that DMF is efficacious and has a favorable safety profile in patients with RRMS aged ≥ 50 years.

Clinical Trial Registration: ESTEEM (NCT02047097), PROCLAIM (NCT02525874).

Keywords: Dimethyl fumarate; Effectiveness; Real-world evidence; Relapsing multiple sclerosis; Safety

Key Summary Points

Why carry out this study?

The population of patients with multiple sclerosis (MS) aged ≥ 50 years has been underrepresented in clinical trials.

As this older population grows, there is a critical need to understand how disease-modifying therapies (DMTs), including dimethyl fumarate (DMF), perform in this age group.

Given the age-related changes in immune function, this study aims to evaluate whether older patients with MS respond differently to DMF in terms of safety, efficacy, and immune profile changes compared to those aged < 50 years.

What was learned from the study?

The study found that DMF was similarly effective in reducing annualized relapse rates in patients aged < 50 and ≥ 50, and showed no unexpected safety signals in older patients, despite a greater decrease in absolute lymphocyte counts in the older age group.

The study found that DMF is a viable treatment option for older patients with MS.

The safety and efficacy profiles of DMF in older patients are consistent with those in younger patients. This could influence future treatment guidelines and encourage the inclusion of older patients in MS clinical trials.

INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated chronic inflammatory demyelinating disease of the central nervous system and the most common cause of neurological disability in young adults [1]. Life expectancy of people with MS (pwMS) is minimally affected [2, 3]; however, MS-related morbidity impacts patients

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throughout their life. Clinical symptoms of MS often begin in a patient's mid-20s to 30s, although there is a wide spectrum of clinical onset [4], and as the general population ages and treatment for MS improves, the prevalence of MS in older people increases [5]. Although the average age of pwMS in western countries has increased (currently mid-50s) [6], relatively little is known about the clinical characteristics of older (>50 years old) pwMS and their response to treatment.

As a result of aging, there are qualitative and quantitative changes to the innate and adaptive compartments of the immune system (immunosenescence), and these changes may have implications for differences in disease course in older pwMS versus their younger counterparts [7], with MS showing a more inflammatory phenotype in younger patients versus older patients [8, 9]. Additionally, older patients may have increased risk of infections and infection-related mortality [10], with clinically significant changes to the immune system occurring in patients over the age of 50 [11, 12]. Because of these differences in the aging immune system, there is also the possibility that older pwMS may respond differently to disease-modifying therapies (DMTs) or have a different benefit/risk profile [7].

Typically, phase 3 clinical trials conducted in adult populations with relapsing MS have an upper age limit as part of their inclusion criteria and therefore few clinical trials include patients >55 years old [13]. In the DISCOMS study, which was a multicenter, randomized, controlled, non-inferiority trial, discontinuation of MS DMT in patients older than 55 with stable disease was not found to be non-inferior to continuation of DMT, as there was a small increased risk of new magnetic resonance imaging (MRI) activity in patients who discontinued DMT; however, the risk of relapse was similar between patients who discontinued and those who continued on their original DMT [14]. Therefore there remains a need to better understand this understudied, older population with MS. Based on real-world and phase 4 studies in the USA, the number of pwMS ≥ 50 years old ranged from 41% to 56% [15, 16].

Dimethyl fumarate (DMF) is an oral DMT approved for treating relapsing forms of MS in adults. DMF has demonstrated significant, clinically meaningful, sustained efficacy and a favorable benefit–risk profile in the pivotal phase 3 studies DEFINE and CONFIRM, and in real-world studies of patients with relapsing–remitting MS (RRMS) [15, 17–19]. The safety profile of DMF is well understood to be acceptable, with flushing and gastrointestinal (GI) events being commonly reported adverse events (AEs) in clinical trials and real-world studies. A key observation in DMF-treated patients is a decline in absolute lymphocyte count (ALC), which generally is observed in the first year of DMF treatment, followed by a plateau over time [20]. In a study characterizing ALC profiles of DMF-treated patients in phase 2b and phase 3 trials, ALC levels typically remained above the lower limit of normal; however, 2.2% of patients treated with DMF for ≥ 6 months developed prolonged, severe lymphopenia (grade 3; ALC $< 0.5 \times 10^9$/L, lasting ≥ 6 months) [20], and lymphopenia increases the risk of developing progressive multifocal leukoencephalopathy (PML) [21]. PML in patients treated with DMF is rare, with an incidence of 0.90 per 100,000 person-years of exposure [22]. There was no association between lymphopenia and serious infections or malignancies in patients treated with DMF for up to 13 years in the ENDORSE study [19].

Additionally, DMF treatment is associated with shifts in circulating immune cells, which generally adopt a more naive/anti-inflammatory phenotype in treated patients [23]. $CD8^+$ cells are found to be reduced to a greater extent than $CD4^+$ cells within the T cell compartment [24]. However, changes in circulating immune cells have not been specifically explored in older patients. Preliminary real-world evidence suggests no notable differences in safety, effectiveness, or patient-reported outcomes between patients aged ≥ 55 years and those < 55 years old who are treated with DMF [25].

More than 595,000 patients have been treated with DMF, representing > 1,391,820 patient-years of exposure as of 30 June 2023. On the basis of recent study estimates, between 241,000 and 329,000 of these patients are ≥ 50 years old [15,

16]. Moreover, on average, patients treated with DMF in real-world studies are older than those in clinical trials, reinforcing the need for data on patients ≥ 50 years of age. For example, in the US North American Research Committee on Multiple Sclerosis (NARCOMS) Registry, the median age of patients with RRMS reporting DMF initiation was 53 years, with a range of 46–59 years [26]. In a number of real-world comparative drug studies, patients treated with DMF are older than their counterparts on other DMTs [27–29]. Therefore, more clinical information on the effects of DMF in older patients is needed.

In order to evaluate safety and efficacy of DMF in a patient population ≥ 50 years old, the phase 4 study ESTEEM (NCT02047097) [30–32] and the phase 3b study PROCLAIM (NCT02525874) [24] were reviewed. The objective was to provide information on both DMF safety and effectiveness, as well as changes in the immune cell compartment observed in patients aged ≥ 50 years compared with those aged < 50 years.

METHODS

Study Design and Participants

ESTEEM Study Design and Analysis

ESTEEM (NCT02047097) is a phase 4, multinational, prospective, noninterventional study evaluating the long-term safety and effectiveness of DMF in patients with RRMS treated in real-world clinical practice. Patients with RRMS could remain in ESTEEM for up to 5 years. In this analysis of the ESTEEM data, we investigated DMF safety and effectiveness in an older cohort of patients with MS, aged ≥ 50 years ($n = 1069$) versus < 50 years ($n = 4020$). This interim analysis of ESTEEM (data cut 7 April 2020) includes patients newly prescribed DMF in routine practice at 393 sites globally. The age inclusion criterion for ESTEEM was ≥ 18 years.

The primary endpoint evaluated was the incidence rate and type/pattern of treatment-emergent serious AEs (SAEs) and AEs leading to treatment discontinuation. Secondary endpoints include effectiveness of DMF on MS relapse activity and patient-reported outcomes (PROs). Relapse data were collected with the aim of assessing clinical effectiveness over the 12 months before and after initiation of DMF. Relapses were defined as new or recurrent neurologic symptoms not associated with fever lasting at least 24 h. New or recurrent neurologic symptoms that evolved gradually over months were considered disease progression, not an acute relapse. New or recurrent neurologic symptoms that occurred within 30 days following the onset of a relapse as defined above were considered part of the same relapse. While MS relapses resulting in hospitalization are considered SAEs, they were not reported as SAEs in the study unless, in the opinion of the physician, a relapse is complicated by other SAEs. ALCs were recorded from a subset of patients. PROs were reported before DMF initiation (baseline) and at 4 years after initiation of DMF.

PROCLAIM Study Design and Analysis

PROCLAIM (NCT02525874), an open-label, multicenter, 96-week, phase 3b study, assessed change in lymphocyte subsets and immunoglobulin levels during 48 and 96 weeks of DMF treatment (240 mg twice-daily) in patients aged 18–65 years with a confirmed diagnosis of RRMS [24]. The study objectives were to evaluate the effect of DMF on lymphocyte subset counts (primary) and the pharmacodynamic effect of DMF on ALCs and immunoglobulin (Ig) isotypes (secondary) in patients with RRMS during the first 48 weeks of treatment. Other exploratory study objectives included safety, tolerability, and MS disease activity (measured by clinical relapse, annualized relapse rate [ARR]) or sustained clinical disease progression (measured by the Expanded Disability Status Scale [EDSS]), as well neurofilament light chain (NfL). The study details and exclusion criteria have previously been described [24].

This post hoc analysis of PROCLAIM is designed to complement and add to those data from the ESTEEM study. PROCLAIM investigated changes to the immune cell compartment for patients aged < 50 ($n = 159$) and ≥ 50 ($n = 59$) years

at baseline and also assessed safety outcomes in these patient age groups.

ALC and immune cell phenotyping lab data: ALC was measured using complete blood cell differential. Changes in lymphocyte subsets were assessed by flow cytometry utilizing cell surface markers (Supplementary Table S1). In PROCLAIM, DMF was temporarily withheld if ALC reached a confirmed level of $< 0.5 \times 10^9$/L persisting for > 24 weeks. Study treatment could then be resumed after lymphocyte counts recover. If the patient developed a lymphocyte count $< 0.5 \times 10^9$/L on one occasion on resumption of study treatment, or if a patient's lymphocyte count remained less than the lower limit of normal for 24 consecutive weeks after resumption of treatment, the patient was then permanently discontinued from the study.

Statistical Analysis

In ESTEEM, ARRs were obtained by fitting a repeated-measure negative binomial model (ARR = total number of relapses during the study for all patients/total number of patient-years followed in the study). Mean change in PROs from baseline to 48 months was assessed using a Wilcoxon signed-rank test; only patients with no missing data were included. The lymphocyte data presented here from the PROCLAIM study were not designed or powered to test the effect of age on the lymphocyte compartment; therefore, the relationship between age and peripheral immune cell compartments changes after DMF treatment was explored as a post hoc analysis.

Ethical Approval

The ESTEEM and PROCLAIM studies were conducted in accordance with the International Conference on Harmonization Guidelines on Good Clinical Practice, the ethical principles outlined in the Declaration of Helsinki, and all applicable local laws and regulations. ESTEEM was approved by local ethics committees at each of the 393 sites, which were overseen by the ESTEEM Study Contract Research Organization ethics committee. PROCLAIM investigators were required to obtain approval of the protocol, informed consent form, and other required study documents from the local ethics committee, overseen by the PROCLAIM Study Contract Research Organization. In both studies, written assent and consent forms were obtained from each patient or their parent or legal guardian.

RESULTS

Study Population

In total, for ESTEEM, 4020 and 1069 patients aged < 50 and ≥ 50 years old, respectively, received ≥ 1 DMF dose and were included in the analysis (Table 1). The mean (SD) age of the older patient cohort was 56 (5) years, with an age range of 50–83 years of age, and the mean (SD) age of the < 50 years cohort was 36 (8) years, with an age range of 18–49. The ≥ 50 years patient cohort had a higher mean baseline EDSS compared with the < 50 years patient cohort. A greater proportion of patients ≥ 50 years old had received a prior DMT, with older patients having a longer mean time since MS diagnosis. The mean duration in ESTEEM was similar between groups: 34.2 (17.5) months for patients < 50 years old and 35.0 (18.5) months for patients ≥ 50 years old.

In the PROCLAIM analysis, 218 patients were included in the analysis; 27% ($n = 59$) of PROCLAIM patients were ≥ 50 years of age (Table 1), with 39/59 (66%) completing the 2-year study. The mean (SD) age of the older patient cohort in PROCLAIM was 56 (4) years, with an age range of 50–65 years, and the mean (SD) age in the < 50 cohort was 37 (8) years, with an age range of 19–49 years of age. The ≥ 50 patient cohort had a higher mean baseline EDSS compared with the < 50 patient cohort. A similar proportion of patients ≥ 50 and < 50 years old had received a

Table 1 Baseline characteristics among patients aged < 50 and ≥ 50 years in the ESTEEM and PROCLAIM populations

Characteristic	ESTEEM patients		PROCLAIM patients	
	Aged < 50 years *n* = 4020	Aged ≥ 50 years *n* = 1069	Aged < 50 years *n* = 159	Aged ≥ 50 years *n* = 59
Mean (SD) age at enrollment, years	36 (8)	56 (5)	37 (8)	56 (4)
Min–max	18–49	50–83	19–49	50–65
Female, *n* (%)	2983 (74)	780 (73)	102 (64)	49 (83)
Median baseline ALC level ($\times 10^9$/L)[a]	1.9	1.8	1.8	1.8
Mean (SD) no. of relapses in prior year	0.9 (0.8)	0.6 (0.8)	0.8 (0.9)	0.7 (0.8)
Median (range) baseline EDSS score[b]	1.5 (0.0–8.0)	2.5 (0.0–7.0)	2.0 (0.0–7.0)	3.5 (0.0–7.0)
Mean (SD) duration of DMF treatment, months	27.3 (18.5)	26.5 (19.9)	21.0 (6.5)	19.2 (7.7)
Mean (SD) duration in study, months	34.2 (17.5)	35.0 (18.5)	22.3 (6.2)	21.5 (7.1)
Any prior DMT, *n* (%)	2478 (62)	782 (73)	108 (68)	41 (69)
Interferon beta-1a	715 (29)	271 (35)	50 (31)	18 (31)
Glatiramer acetate	986 (40)	306 (39)	39 (25)	18 (31)
Interferon beta-1b	443 (18)	171 (22)	22 (14)	8 (14)
Natalizumab	204 (8)	89 (11)	4 (3)	4 (7)
Other prior DMT	55 (2)	25 (3)	49 (31)[c]	16 (27)[c]

ALC absolute lymphocyte count, *DMT* disease-modifying therapy, *EDSS* Expanded Disability Status Scale, *SD* standard deviation

[a]Median baseline ALC level in ESTEEM recorded for 2793 patients aged < 50 years and 720 patients aged ≥ 50 years

[b]EDSS assessment at enrollment

[c]Other prior DMT in PROCLAIM includes fingolimod hydrochloride, investigational drug, methylprednisolone, blinded therapy, dimethyl fumarate, interferon beta, fampridine, peginterferon beta-1A, teriflunomide, daclizumab, fingolimod, laquinimod, methylprednisolone sodium succinate, peginterferon, baclofen, calcium monoethylfumarate, magnesium monoethylfumarate, zinc ethyl fumarate, plovamer acetate, prednisone, steroids

prior DMT. Older patients had a longer mean time since MS diagnosis.

Safety and Discontinuations

In the ESTEEM study, a total of 19.6% (*n* = 786) of patients aged < 50 years and 29.6% (*n* = 316) of patients aged ≥ 50 years reported any AE leading to treatment discontinuation (Table 2), with GI disorders being the most reported. Of patients in the < 50 years old group, 5.2% (*n* = 209) reported SAEs versus 8.9% (*n* = 95) in the ≥ 50 years old group (Table 2). Infections were the most common SAEs in both age groups (< 50 years old, 1.3% [*n* = 51]; ≥ 50 years old, 2.3% [*n* = 25]) (Table 2), with urinary tract infection being the most common type of serious infection in the < 50 years group (15.7%), while pneumonia was the most common serious infection in the ≥ 50 years

Table 2 SAEs and most common AEs leading to DMF discontinuation in ESTEEM and PROCLAIM patient populations (incidence of ≥ 1%)

Category, *n* (%)	ESTEEM		PROCLAIM	
	Aged < 50 years *n* = 4020	Aged ≥ 50 years *n* = 1069	Aged < 50 years *n* = 159	Aged ≥ 50 years *n* = 59
Any SAE[a]	209 (5)	95 (9)	20 (13)	6 (10)
Infections and infestations[b]	51 (1)	25 (2)	2 (1)	0
Injury, poisoning, and procedural complications	23 (< 1)	12 (1)	0	0
GI disorders	20 (< 1)	11 (1)	0	0
Neoplasms: benign, malignant, and unspecified (including cysts and polyps)	26 (< 1)	14 (1)	0	1 (2)
Nervous system disorders	27 (< 1)	10 (< 1)	11 (7)	5 (8)
MS relapse	7 (< 1)	1 (< 1)	11 (7)	5 (8)
Any AE leading to treatment discontinuation	786 (20)	316 (30)	15 (9)	13 (22)
GI disorders	319 (8)	106 (10)	3 (2)	3 (5)
Diarrhea	89 (2)	34 (3)	2 (1)	1 (2)
Nausea	76 (2)	39 (4)	0	0
Abdominal pain, upper	75 (2)	14 (1)	0	0
Abdominal pain	62 (2)	11 (1)	0	1 (2)
Vomiting	51 (1)	16 (1)	1 (< 1)	0
Abdominal discomfort	17 (< 1)	4 (< 1)	0	1 (2)
Lip edema	0	1 (< 1)	0	1 (2)
Vascular disorders	142 (4)	30 (3)	1 (< 1)	1 (2)
Flushing	130 (3)	25 (2)	1 (< 1)	1 (2)
Blood and lymphatic system disorders	111 (3)	74 (7)	4 (3)	2 (3)
Lymphopenia	95 (2)	68 (6)	4 (3)	2 (3)
Skin and subcutaneous tissue disorders	87 (2)	30 (3)	3 (2)	1 (2)
Generalized erythema	9 (< 1)	1 (< 1)	1 (< 1)	1 (2)
Nervous system disorders	86 (2)	29 (3)	4 (3)	3 (5)
Burning sensation	1 (< 1)	2 (< 1)	0	1 (2)
MS	22 (< 1)	4 (< 1)	0	1 (2)
MS relapse	21 (< 1)	1 (< 1)	4 (3)	1 (2)
Investigations	72 (2)	40 (4)	1 (< 1)	4 (7)
Lymphocyte count decreased	39 (1)	26 (2)	0	4 (7)

Table 2 continued

Category, *n* (%)	ESTEEM		PROCLAIM	
	Aged < 50 years *n* = 4020	Aged ≥ 50 years *n* = 1069	Aged < 50 years *n* = 159	Aged ≥ 50 years *n* = 59
General disorders and administration site conditions	47 (1)	29 (3)	0	0
Immune system disorders	16 (< 1)	7 (< 1)	0	1 (2)
Hypersensitivity	14 (< 1)	6 (< 1)	0	1 (2)

AE adverse event, *DMF* dimethyl fumarate, *GI* gastrointestinal, *MS* multiple sclerosis, *SAE* serious adverse event

[a]In the ESTEEM group, death occurred in 1 patient aged < 50 years and in 2 patients age ≥ 50 years. In the PROCLAIM group, there were no deaths

[b]Infections and infestations include abscess jaw, abscess limb, acute sinusitis, appendiceal abscess, appendicitis, appendicitis perforated, bacteremia, bacterial infection, bronchitis, bronchitis bacterial, cellulitis, cholangitis infective, coxsackie viral infection, diverticulitis, *Escherichia* pyelonephritis, *Escherichia* sepsis, gastroenteritis, gastroenteritis viral, herpes simplex, herpes zoster, infection, infection parasitic, influenza, klebsiella bacteremia, large intestine infection, liver abscess, nasopharyngitis, parainfluenza virus infection, pelvic inflammatory disease, periorbital cellulitis, peritonitis, pneumonia, pyelonephritis, pyelonephritis acute, sepsis, subcutaneous abscess, tonsilitis, upper respiratory tract infection, urinary tract infection, urosepsis, varicella, viral infection, viral upper respiratory tract infection

population (28.0%). In the PROCLAIM analysis, SAEs occurred in 13% of patients < 50 years old and 10% of those ≥ 50 years old (Table 2), with MS relapse being the most common SAE, affecting 7% and 8% of patients in each age group, respectively.

Lymphocytes

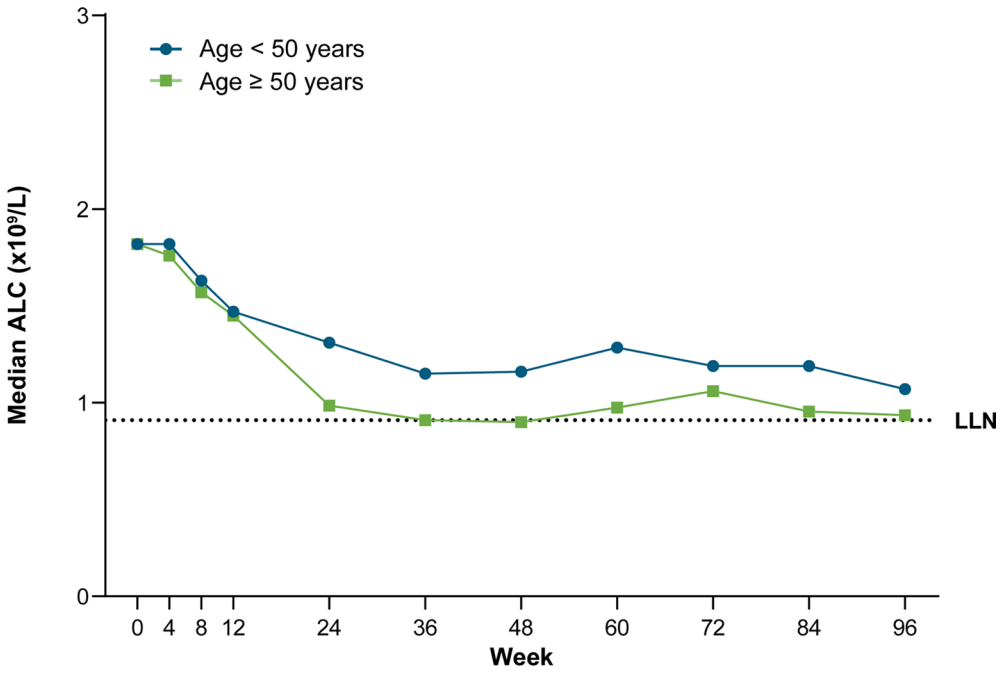
ALC

Of the patients participating in the ESTEEM study, 1063 patients had ALCs recorded at baseline and after 96 weeks of DMF initiation. In these patients, the median percentage change in lymphocyte counts from baseline to week 96 was a decrease of 35% ($n = 877$) in patients aged < 50 years and a decrease of 50% ($n = 186$) for patients aged ≥ 50 years. A numerically lower proportion of patients < 50 years (2%) discontinued DMF as a result of lymphopenia compared with those ≥ 50 years (6%). There was also a numerically lower proportion of discontinuations due to "lymphocyte count decreased" in patients < 50 years (1.0%) compared with patients ≥ 50 years (2.4%). Among patients participating in PROCLAIM, median decline in ALC followed a similar pattern between patients aged ≥ 50 years and < 50 years over 96 weeks with DMF treatment (Fig. 1).

Lymphocyte Subsets

In PROCLAIM, mean total $CD4^+$ and $CD8^+$ cell values were similar between the < 50 and ≥ 50 years age groups at baseline (Fig. 2). Both total $CD4^+$ and $CD8^+$ cells decreased on DMF treatment in patients < 50 and ≥ 50 years old, with mean total $CD4^+$ cells decreasing to a greater extent in patients ≥ 50 years old (Fig. 2). Baseline $CD4^+$ T cell compartment composition was similar for patients in both the < 50 and ≥ 50 years age groups (Fig. 3b). In contrast, baseline $CD8^+$ T cell compartment composition differed for patients < 50 and ≥ 50 years old (Fig. 3b), with a lower proportion of naive and higher proportion of central memory and effector $CD8^+$ cells in older patients. Regardless of age, the relative proportion of naive $CD4^+$ and $CD8^+$ T cells increased and central and effector memory $CD4^+$ and $CD8^+$ T cells decreased with DMF treatment (Fig. 3).

The relative proportion of naive B cells and transitional B cells increased from baseline to week 96 (Fig. 3c). The relative proportion



Age < 50 years, *n*	159	156	156	153	151	145	134	132	134	129	129
Age ≥ 50 years, *n*	59	57	55	57	54	51	51	48	49	46	42

Fig. 1 Median ALC with DMF treatment over 96 weeks in patients < 50 and ≥ 50 years old in PROCLAIM. *ALC* absolute lymphocyte count, *DMF* dimethyl fumarate, *LLN* lower limit of normal. LLN = 0.91×10^9/L

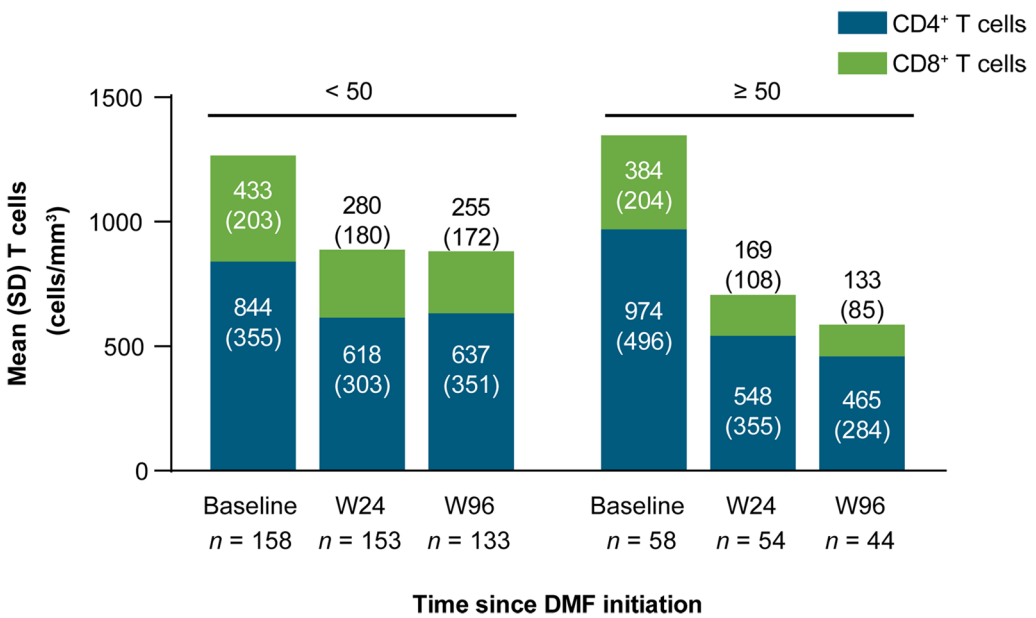
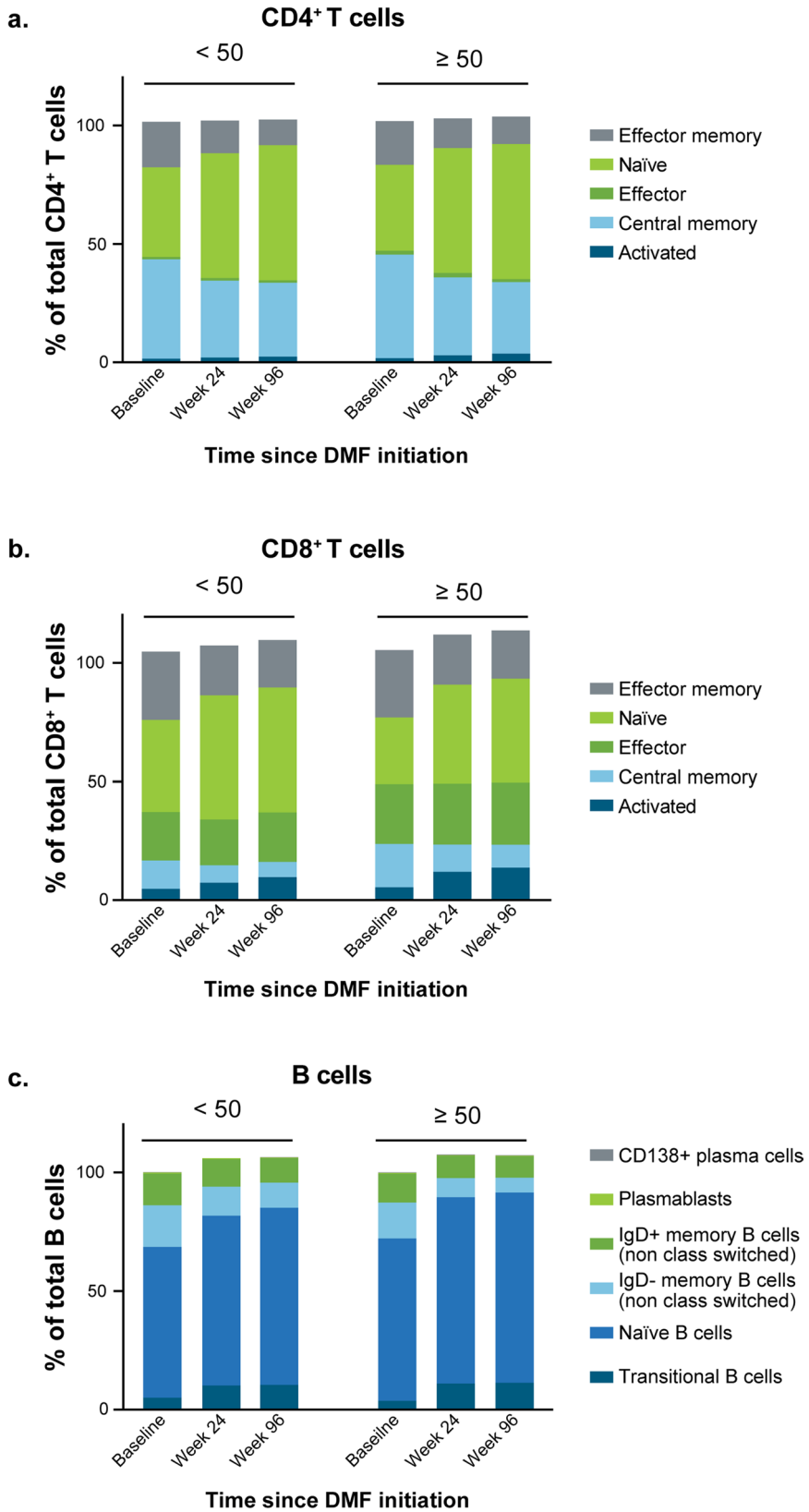


Fig. 2 Mean total $CD4^+$ and $CD8^+$ T cells for patients < 50 and ≥ 50 years old at baseline in PROCLAIM. *DMF* dimethyl fumarate, *SD* standard deviation, *W* week


a.
CD4⁺ T cells
< 50
≥ 50
% of total CD4⁺ T cells
100
50
0
Baseline
Week 24
Week 96
Time since DMF initiation
Effector memory
Naïve
Effector
Central memory
Activated
b.
CD8⁺ T cells
< 50
≥ 50
% of total CD8⁺ T cells
Time since DMF initiation
Effector memory
Naïve
Effector
Central memory
Activated
c.
B cells
< 50
≥ 50
% of total B cells
Time since DMF initiation
CD138+ plasma cells
Plasmablasts
IgD+ memory B cells (non class switched)
IgD- memory B cells (non class switched)
Naïve B cells
Transitional B cells

◂**Fig. 3** Mean T cell and B cell compartment composition at baseline, week 24, and week 96 in PROCLAIM. *DMF* dimethyl fumarate, *Ig* immunoglobulin. Plasmablasts and $CD138^+$ plasma cells < 1% at all timepoints. As a result of the nature of the analysis, total cells may add up to > 100%

of IgD^- memory B cells decreased in both age groups following DMF treatment.

Serum Neurofilament Light Chain Levels

In PROCLAIM, median serum neurofilament light chain (sNfL) levels tended to be higher in older patients than younger patients at all timepoints with wide range (Fig. 4). Data also showed that DMF treatment lowered sNfL levels in both age groups, though the ranges overlapped. In patients < 50 years old, median (min–max) sNfL levels were 9.5 (2.7–60.5) pg/mL at baseline and decreased to 7.0 (1.4–28.2) pg/mL at 96 weeks ($p < 0.0001$), while in patients ≥ 50 years old, sNfL levels were 12.9 (5.1–59.0) pg/mL at baseline and decreased to 11.3 (5.2–35.2) pg/mL at 96 weeks ($p = 0.02$).

ARR and Relapses in ESTEEM

Among patients < 50 years old, ARR 1 year before DMF initiation was 0.88 compared with 0.10 over 4 years of DMF treatment, a decrease of 88.4% (87.6–89.3%; $p < 0.0001$) (Fig. 5). Similarly, among patients ≥ 50 years old, ARR 1 year before DMF initiation was 0.61 compared with 0.06 over 4 years of DMF treatment, a decrease of 90.2% (88.1–91.9%; $p < 0.0001$) (Fig. 5). The estimated proportion of patients without a relapse at 4 years was 69.7% among patients < 50 years of age and 80.9% in the ≥ 50 years age group.

PROs

After 4 years of DMF treatment, most PRO scores were stable or improved in both the younger and older patient age groups (Table 3).

DISCUSSION

Life expectancy of the general population is increasing, and advances in MS treatment have led to an increase in the average age of people with MS [5]; clinicians are treating people with MS into later decades of their life and, therefore, evidence around MS management in people with MS in their 50s and beyond is of great importance [13]. Our findings from these two studies in patients with RRMS show that the use of DMF in older patients (≥ 50 years of age) is generally efficacious and the safety profile is consistent with the overall DMF experience, with the profiles of SAEs and AEs leading to treatment discontinuation being similar to what is already known for DMF use in MS. The incidence of SAEs was similar across age groups; while the percentage of SAEs was slightly higher in the ≥ 50 age group in ESTEEM, it was slightly lower in PROCLAIM, suggesting there is no meaningful difference between groups. Moreover, in ESTEEM, DMF was effective in patients both < 50 years and ≥ 50 years as shown by ARR being significantly reduced in the 4 years after DMF initiation compared with the 12 months before DMF treatment initiation and also the estimated proportion of patients relapse free.

Immunosenescence, or age-related changes in the immune system, affects both innate and adaptive immunity [10]. As a result of the increasing age of the population of patients with MS being treated with DMTs, there is a need to understand the implications of immunosenescence on the long-term efficacy and safety of treatments, especially those known to decrease lymphocyte count such as DMF. Our analyses of ALC data from ESTEEM and PROCLAIM both show a numerically higher percentage decrease in ALC from baseline to week 96 of DMF treatment in older patients than younger patients, though both groups remained at or above a median ALC of 0.9×10^9/L, and hence management approaches would not change. These data are limited by virtue of being a secondary analysis, but similar findings were shown in a smaller patient study, where the decline in ALC following 12 months of DMF treatment was significantly greater in patients aged > 50 years than

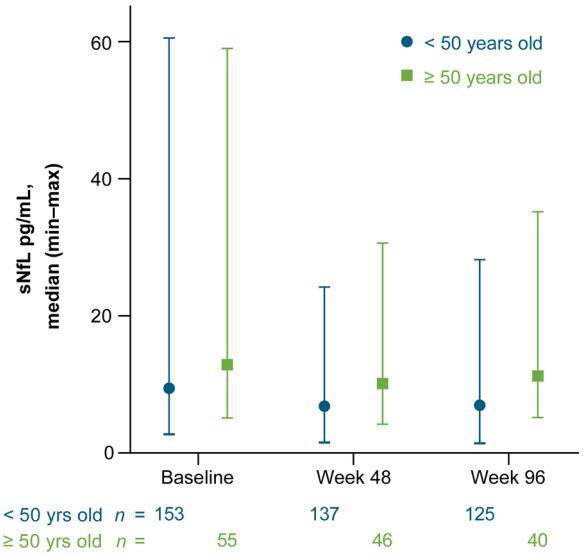


Fig. 4 Median sNfL levels by age group over 96 weeks of DMF treatment. *DMF* dimethyl fumarate, *sNfL* serum neurofilament light chain

those aged ≤ 50 years (−55.7% versus −40.0%; $p = 0.01$) [33]. In our study, despite the greater on-treatment declines in ALC in older patients, the infection rates were similarly low between age groups; while the rate of infections was slightly higher in the ≥ 50 age group in ESTEEM, it was slightly lower in PROCLAIM, suggesting there is likely no meaningful difference between age groups. Absolute rate of infection in pwMS increases with age [7]; however, this may be due to increased infection rates in the general older population overall, as the relative risk of serious infections is higher in younger patients with MS compared with the general population [34].

Understanding DMF-associated lymphopenia in older patients is key, as lymphopenia is the risk factor for patients developing PML on DMF treatment. All reported cases of PML on DMF occurred in patients with lymphopenia, and, as of 21 July 2021, nine out of 12 patients with PML had prolonged moderate-to-severe lymphopenia [22]. In the lymphocyte subset analysis of PROCLAIM, the ALC decrease due to DMF did not appear to be driven by any particular lymphocyte subset(s) for either group. Naive and transitional B cell populations have also been shown to increase following DMF treatment [23]. Our data show the pattern of lymphocyte

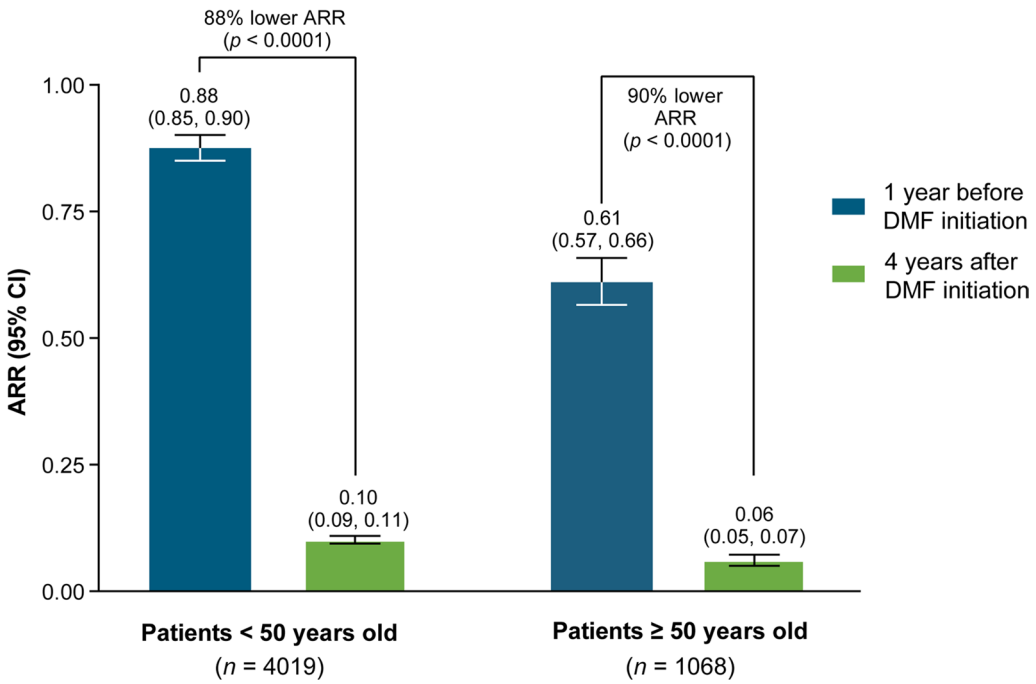


Fig. 5 ARR in the 1 year before and up to 4 years after DMF initiation for patients aged < 50 and ≥ 50 years from ESTEEM. *ARR* annualized relapse rate, *CI* confidence interval, *DMF* dimethyl fumarate

Table 3 Change in patient-reported outcomes from baseline to 4 years in ESTEEM

Measure	Description	Component	ESTEEM	
			Aged < 50 years *n* = 4020	Aged ≥ 50 years *n* = 1069
			Mean (SD) change from baseline to 48 months	
MSIS-29[a]	20 items assess physical impact of MS in terms of mobility and self-care; nine items assess psychological impact of MS	Physical impact	0.5 (11.8)[c]	0.9 (11.2)[d]
		Psychological impact	− 0.6 (6.4)[e]	− 0.8 (5.4)[d]
MFIS-5[a]	Five items assess how fatigue impacts subjects' lives		0.0 (4.7)[f]	− 0.4 (4.2)[g]
EQ-5D-5L Index Score[b]	Five items assess mobility, self-care, usual activities, pain and discomfort, anxiety and depression		− 0.006 (0.188)[h]	− 0.010 (0.177)[i]
EQ-VAS[b]	Patients' own global rating of their overall health using a VAS		1.9 (19.2)[j]	2.6 (21.7)[k]
WPAI-MS[a]	Six items assess the number of work hours missed, impact on productivity, and daily activities during past 7 days	Absenteeism	− 0.07 (0.36)[l]	− 0.05 (0.30)[m]
		Presenteeism	− 0.01 (0.28)[n]	− 0.06 (0.28)[o]
		Overall work impairment	− 0.05 (0.32)[p]	− 0.04 (0.28)[q]
		Activity impairment due to problem	− 0.01 (0.25)[r]	− 0.01 (0.24)[s]

EQ-5D-5L five-item EuroQol 5 Dimensions Index Score, *EQ-VAS* EQ-5D visual analog scale, *MS* multiple sclerosis, *MSIS* Multiple Sclerosis Impact Scale, *MFIS* Modified Fatigue Impact Scale, *SD* standard deviation, *VAS* visual analog scale, *WPAI* work productivity and impairment

[a]Higher values indicate greater impact of MS

[b]Higher values indicate better health status

At 48 months: [c]*n* = 367, [d]*n* = 102, [e]*n* = 361, [f]*n* = 290, [g]*n* = 90, [h]*n* = 319, [i]*n* = 97, [j]*n* = 319, [k]*n* = 98, [l]*n* = 156, [m]*n* = 32, [n]*n* = 200, [o]*n* = 42, [p]*n* = 145, [q]*n* = 31, [r]*n* = 320, [s]*n* = 95

subset changes with DMF treatment in older patients is consistent with these findings. We further expand on these findings by showing that the increase in naive and transitional B cells, increase in naive T cells, and decrease in memory T cells were similar in patients < 50 years and those ≥ 50 years. This suggests that there is no major difference in the way DMF affects the lymphocyte subsets across the age groups.

Research into the innate immune system in aging patients with MS may help elucidate MS disease pathology [35]. Studies point to age as a factor that alters the transcriptome of microglia from homeostatic/regulatory toward a degeneration-associated state, making these cells less phagocytic while elevating their production of pro-inflammatory cytokines [36, 37]. Another component of the innate immune system—nucleotide-binding domain leucine-rich repeat-containing NOD-like receptor (NLR) family pyrin domain-containing 3 (NLRP3) inflammasome—also appears to play a key role in MS pathogenesis [35]. NLRP3 regulates pro-inflammatory cytokine production and induces pyroptotic cell death. With aging, there is higher

potential for mitochondrial dysfunction, which is one of the main triggers of NLRP3 inflammasome activation leading to inflammation and axonal damage.

NfL is a neuronal protein that is released upon neuroaxonal damage, independent of underlying etiology. Like NLRP3 inflammasome-related components, NfL can be used to monitor disease activity in neurological conditions [38]. NfL is emerging as a non-specific biomarker of MS disease activity, with elevated sNfL associated with clinical and MRI measures of increased disease activity [39–41]. We show that sNfL levels were higher in older patients than younger patients at baseline, week 48, and week 96, in line with what has previously been observed for older populations [42]. Although baseline sNfL levels differed, there was a decrease in sNfL levels with DMF treatment in both younger and older patients, consistent with the findings from a prospective, phase 4 study showing that 1 year of treatment with DMF decreased sNfL by 69% from baseline [43].

There were limitations to this study. AEs were differently reported in PROCLAIM versus ESTEEM: PROCLAIM reported all AEs and SAEs, while ESTEEM only reported treatment-emergent SAEs and AEs leading to treatment discontinuation, limiting the conclusions that can be drawn about overall safety in this population. Furthermore, many of the ESTEEM ALC data were not able to be utilized for this analysis. In the current analysis, only direct measurements of lymphocytes were used. Prior interim analyses of ESTEEM have utilized two data sources for lymphocyte data: one source with direct measurements and another source with measurements converted from white blood cells. However, as a result of issues related to white blood cell conversion factors, the second data source is no longer being utilized; therefore, only 1063 patients had ALC data at baseline and after 96 weeks.

Nonetheless, we conducted our analysis by comparing patients in two age groups (< 50 years versus ≥ 50) to gain an understanding of age impact. The cutoff age of 50 years was chosen to ensure analysis of a reasonable group size, as a higher cutoff would result in a smaller group of older patients with limited data to draw meaningful conclusions. Despite these limitations, this is one of the few robust databases to analyze patients at ≥ 50 years old, and analysis of both sets of results provided consistent outcomes.

Taken together, these data, focused on patients aged ≥ 50 years, were consistent across two studies. Although not directly comparable, these findings increase confidence in the results, and together indicate that DMF is efficacious and has a favorable safety profile in patients with RRMS aged ≥ 50 years in routine clinical practice.

CONCLUSION

Although almost half of patients with MS in the USA are ≥ 50 years of age, data on older people's response to DMTs are limited. This analysis examined the safety, efficacy, and immunophenotype changes in DMF-treated patients ≥ 50 years compared to younger patients. Data across these populations from the ESTEEM and PROCLAIM studies showed no new safety signals in older patients with MS. Overall, SAEs and AEs leading to discontinuation in older patients were similar to those already associated with DMF in patients with MS. Importantly, older age did not appear to affect changes in lymphocyte subsets in patients with MS treated with DMF. Efficacy outcomes were also comparable, with ARRs significantly reduced in both age groups. Data from this study provide necessary information on the use of DMF in the treatment of patients ≥ 50 years of age with RRMS. Additional research in this older population of patients with MS is needed to further optimize clinical practices and outcomes in this growing cohort.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. Biogen commits to share patient-level data, trial-level data, CSRs, and protocols with qualified scientific researchers. Biogen has established a process for researchers to request access to such data from Biogen-sponsored interventional clinical trials conducted in patients (phase I–IV) for products and indications submitted to and approved in both the United States and the European Union, since 2004. For information on the process for submitting a scientific or medical research proposal that includes a request for access to data from Biogen-sponsored clinical research, please visit https://vivli.org/. For general enquiries, please contact datasharing@biogen.com.

Declarations

Conflict of Interest. Yang Mao-Draayer: consulting fees from Biogen, Celgene, EMD Serono, Genzyme, Novartis, and Roche-Genentech; contracted research for Biogen, Chugai, NIAID Autoimmune Center of Excellence UM1-AI110557, NIH NINDS R01-NS080821, Novartis, and Sanofi-Genzyme; speaker bureaus for Biogen and Teva. Amit Bar-Or: speaker/consulting fees and/or grant support from Atara Biotherapeutics, Biogen, Celgene/Receptos, Genentech/Roche, GlaxoSmithKline, Medimmune, Merck/EMD Serono, Novartis, and Sanofi-Genzyme. Konstantin Balashov: grant/research support from Biogen; consultant for Genentech/Roche. John Foley: nothing to disclose. Kyle Smoot: received research support from AbbVie, Biogen, EMD Serono, Genentech, IMS Health, MedDay, and Novartis; and consulting fees from Biogen, Celgene, EMD Serono, Genzyme, Genentech, and

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Ethical Approval. The ESTEEM and PROCLAIM studies were conducted in accordance with the International Conference on Harmonization Guidelines on Good Clinical Practice, the ethical principles outlined in the Declaration of Helsinki, and all applicable local laws and regulations. ESTEEM was approved by local ethics committees at each of the 393 sites, which were overseen by the ESTEEM Study Contract Research Organization ethics committee. PROCLAIM investigators were required to obtain approval of the protocol, informed consent form, and other required study documents from the local ethics committee, overseen by the PROCLAIM Study Contract Research Organization. In both studies, written assent and consent forms were obtained from each patient or their parent or legal guardian.

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