



# Efficacy of Ublituximab in People with Highly Active Relapsing Multiple Sclerosis

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## ABSTRACT

**Introduction:** People with highly active multiple sclerosis benefit from early treatment with highly efficacious disease-modifying therapies. Here we present data on the efficacy of ublituximab versus teriflunomide in a subgroup

**Prior Presentation:** Data were previously presented by (1) Alvarez E, et al. at the 75th American Academy of Neurology (AAN) Annual Meeting, April 22–27, 2023, Boston, Massachusetts. Poster P6.002 and (2) Robertson D, et al. at the 76th American Academy of Neurology (AAN) Annual Meeting, April 13–18, 2024, Denver, Colorado. Poster P9.017.

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of participants with highly active disease at baseline.

**Methods:** Pooled post hoc analyses of the phase 3 ULTIMATE I ( $N=549$ ) and II ( $N=545$ ) studies evaluated efficacy measures at weeks 12 and 96 in participants with highly active disease, defined as  $\geq 2$  relapses in the year prior and  $\geq 1$  gadolinium-enhancing (Gd+) T1 lesion at baseline.

**Results:** In the highly active disease population, the unadjusted annualized relapse rates (ARR) at week 96 were 0.145 and 0.496 for the ublituximab ( $n=88$ ) and teriflunomide ( $n=80$ ) groups, respectively (70.8% relative reduction,  $P<0.001$ ). The number (least squares means) of

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gadolinium-enhancing T1 lesions per scan for ublituximab versus teriflunomide was 0.114 versus 0.683 at week 12 (83.3% relative reduction) and 0.038 versus 0.875 at week 96 (95.6% relative reduction; both  $P < 0.001$ ). Corresponding values for new/enlarging T2 lesions (ublituximab versus teriflunomide) were 1.754 versus 4.127 at week 12 (57.5% relative reduction) and 0.568 versus 6.367 at week 96 (91.1% relative reduction, both  $P < 0.001$ ). No evidence of disease activity-3 (NEDA-3) rates with ublituximab versus teriflunomide were 29.5% versus 10.1% ( $P = 0.001$ ) at week 12 and 77.9% versus 16.4% ( $P < 0.001$ ) at week 96 (weeks 24–96, re-baselined).

**Conclusion:** Ublituximab was associated with significant treatment benefits across multiple efficacy measures versus teriflunomide in participants with highly active disease at baseline.

**Trial Registration:** Clinical trial registry: ULTIMATE I and II ClinicalTrials.gov numbers, NCT03277261 (registration date September 7, 2017) and NCT03277248 (registration date September 7, 2017).

**Keywords:** Annualized relapse rate; Anti-CD20; Highly active disease; Multiple sclerosis; No evidence of disease activity; Radiologic disease; Ublituximab

### Key Summary Points

#### *Why carry out this study?*

Multiple sclerosis is a heterogeneous disease with a progressive nature that varies from person to person. Earlier treatment with highly efficacious disease-modifying therapies may be beneficial in people with more frequent relapses and radiological disease activity.

Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20 on B cells and is glycoengineered to enhance antibody-dependent cellular cytotoxicity. Ublituximab showed superiority vs teriflunomide in reducing disease activity in the phase 3 ULTIMATE I and II studies in participants with relapsing multiple sclerosis.

Pooled post hoc analyses of the ULTIMATE studies were conducted to evaluate the efficacy of ublituximab vs teriflunomide in the subpopulation of participants with highly active relapsing multiple sclerosis.

#### *What was learned from the study?*

Treatment with ublituximab resulted in significantly fewer relapses, gadolinium-enhancing T1 lesions, and T2 lesions, and significantly higher rates of no evidence of disease activity-3 at 2 years compared with teriflunomide.

These results highlight the potential for ublituximab to reduce disease activity in people with more active multiple sclerosis.

## INTRODUCTION

Multiple sclerosis (MS) is a neurodegenerative, inflammatory disease of the central nervous system (CNS) [1]. Aberrant responses to CNS autoantigens play a fundamental role in MS pathogenesis [1, 2], and as a result, the disease-modifying therapies (DMTs) that have been approved for treatment are directed at different immunological targets [3]. On the basis of clinical data, these DMTs are often categorized according to efficacy in reducing relapse rates along a continuum of moderate to very high efficacy. Most recently, anti-CD20 monoclonal antibodies (mAbs) have emerged as a highly effective treatment option for people with MS [2, 4–6]. Anti-CD20 antibody-mediated depletion of B cells may contribute to therapeutic effects by reducing antigen presentation and activation of T cells, decreasing inflammatory cytokine production by B and T cells and promoting a shift

toward a less activated inflammatory immune environment [7–9].

Currently available anti-CD20 mAbs bind to and deplete B cells via various effector functions, including antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity [10]. The molecular and biological characteristics that contribute to the mechanisms of action of anti-CD20 mAbs may confer differences between these agents in efficacy, safety, tolerability, and administration requirements. Ublituximab targets a unique epitope of CD20 and is glycoengineered to have low fucose content in its fragment crystallizable (Fc) region, enabling closer interactions with and greater affinity for all Fc gamma receptor IIIa variants while enhancing ADCC [11–13]. Ublituximab is administered at lower doses and with shorter infusion times after the first infusion relative to other infused anti-CD20 therapies [14, 15]. How these differences in antibody structure and function might translate into improved clinical outcomes is not yet fully understood; however, it has been hypothesized that highly efficient B-cell depletion, as has been reported with ublituximab treatment, could correlate with rapid reduction in inflammation and decreased accumulation of disability [10].

The phase 3 ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) trials compared ublituximab with orally administered teriflunomide in participants with relapsing MS (RMS) [16]. Over 2 years of treatment, ublituximab significantly reduced the annualized relapse rate (ARR) versus teriflunomide (primary endpoint; relative reduction, 59% [ $P < 0.001$ ] in ULTIMATE I and 49% [ $P = 0.002$ ] in ULTIMATE II) and also significantly improved both the mean number of gadolinium-enhancing (Gd+) T1 lesions (relative reduction, 97% and 96%, respectively;  $P < 0.001$  for both studies) and the number of new or enlarging T2 lesions (relative reduction, 92% and 90%, respectively;  $P < 0.001$  for both studies). On the basis of a post hoc analysis of pooled data from the ULTIMATE I and II trials, participants receiving ublituximab were 3.6-fold more likely than those treated with teriflunomide to achieve no evidence of disease activity (NEDA)-3, defined as an absence of relapses and

Gd+ T1 or new/enlarging T2 lesions on magnetic resonance imaging (MRI) as well as by a lack of sustained disease progression, during the clinical trials [17].

A subset of people with MS experience highly active disease, characterized by a high relapse frequency and/or an increased burden of brain MRI lesions [18–20]. Even among those with clinically stable disease, a high burden of ongoing MRI activity is associated with poor prognosis and cumulative disability [18]. Given the better response to DMTs earlier in the disease course and the potential for rapid accumulation of neurological damage and disability in highly active MS, people with this phenotype have a relatively narrow window of opportunity during which DMTs may prevent irreversible damage [18, 21–25]. Treatment early in the disease course with high-efficacy therapies, including anti-CD20 mAbs, could thus play a crucial role in limiting neurologic damage and slowing disease progression in people with highly active disease [21, 22, 26]. The current analyses were performed to evaluate the efficacy of ublituximab in participants enrolled in ULTIMATE I and II with highly active disease at baseline.

## METHODS

### Study Design and Participants

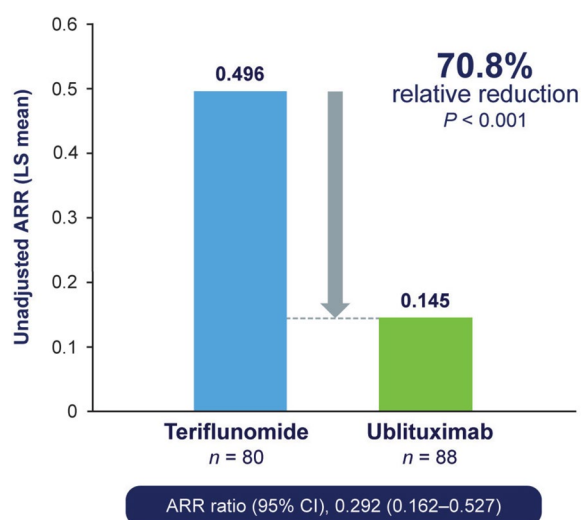
Post hoc subpopulation analyses characterized the efficacy of ublituximab among participants with highly active MS in the pooled population of two identical, phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled trials (ULTIMATE I and ULTIMATE II) conducted between September 2017 and October 2018 at 104 sites across 10 countries. The trial protocols were approved by the institutional review board or ethics committee at each study center (US central IRB approval reference numbers ULTIMATE I Pro00021474, ULTIMATE II Pro00021820), and the trials were conducted in accordance with Good Clinical Practice guidelines and the principles of the

**Table 1** Demographics and baseline characteristics for participants with highly active disease

Characteristic	Teriflunomide ( <i>n</i> = 80)	Ublituximab ( <i>n</i> = 88)
Age, years	32.6 ± 8.6	32.2 ± 8.3
Gender, %		
Female	71.3	68.2
Male	28.8	31.8
Region, %		
USA & Western Europe	6.3	8.0
Eastern Europe	93.8	92.0
Time since first MS symptoms, years	6.1 ± 4.8	5.4 ± 4.9
Time since diagnosis, years	3.6 ± 3.7	3.4 ± 4.1
Time since most recent relapse, months	3.8 ± 1.5	4.2 ± 2.0
Number of relapses in the year prior to screening	2.2 ± 0.5	2.2 ± 0.4
Number of relapses in the 2 years prior to screening	2.7 ± 1.0	2.8 ± 1.1
Baseline EDSS score	2.9 ± 0.9	3.1 ± 1.2
Number of baseline Gd+ T1 lesions	5.1 ± 5.8	5.6 ± 7.4
Baseline T2 lesion count	73.4 ± 43.5	72.2 ± 41.8
Baseline T2 lesion volume, mL	19.7 ± 19.8	17.6 ± 15.3

Data are presented as mean ± standard deviation or %

EDSS Expanded Disability Status Scale, Gd+ gadolinium-enhancing, MS multiple sclerosis



**Fig. 1** ARR at week 96 in participants with highly active disease at baseline. ARR annualized relapse rate, CI confidence interval, LS least squares

Declaration of Helsinki. All participants provided written informed consent.

Methodological details have previously been reported [16]. Briefly, the studies enrolled neurologically stable people 18–55 years of age with RMS (2010 revised McDonald criteria) who had at least two relapses in the previous 2 years or one relapse and/or at least one Gd+ T1 lesion in the year before screening, brain MRI abnormalities consistent with MS, and an Expanded Disability Status Scale (EDSS) score of 0–5.5 at screening. Key exclusion criteria included a diagnosis of primary progressive MS, disease duration ≥ 10 years with an EDSS score ≤ 2.0 at screening, and previous treatment with stem cell transplantation, alemtuzumab, natalizumab, teriflunomide, leflunomide, or an anti-CD20 mAb or other B cell-directed therapy.

Participants were randomly assigned in a 1:1 ratio to receive intravenously administered (IV)

ublituximab (150 mg infused over 4 h on day 1; 450 mg infused for a 1-h duration on day 15 and at weeks 24, 48, and 72) plus orally administered placebo or teriflunomide 14 mg once daily for 96 weeks plus IV placebo.

### Clinical and MRI Endpoints

Clinical evaluations including EDSS were conducted at baseline and every 12 weeks, and brain MRI scans were obtained at weeks 12, 24, 48, and 96 (Gd+ T1 lesions and T2 lesions). The ARR was defined as the number of confirmed, protocol-defined relapses of MS per participant-year, with protocol-defined relapses including new or worsening neurological symptoms attributable to MS in the absence of fever or infection persisting for more than 24 h, immediately preceded by  $\geq 30$  days of stability or improvement in neurological condition and accompanied by objective neurological worsening corresponding to an increase of at least half a point on the EDSS, 2.0 points in a single EDSS functional system score, or 1.0 point in each of at least two EDSS functional system scores. An independent panel adjudicated each suspected relapse to centrally confirm a protocol-defined relapse.

Confirmed disability progression (CDP) was defined as a sustained and confirmed ( $\geq 12$  weeks) increase from baseline of  $\geq 1$  point in EDSS score not attributable to a different etiology (e.g., fever, concurrent illness, or concomitant medication) when the baseline score was  $\leq 5.5$  and an increase of  $\geq 0.5$  points when the baseline score was  $> 5.5$ .

NEDA-3 rate is the proportion of participants with no evidence of disease activity, excluding those who discontinued treatment early due to reasons other than death and lack of efficacy during the analysis time frame. NEDA-3 was defined as having no confirmed relapses, no MRI activity (Gd+ T1 lesions/new or enlarging T2 lesions), and no 12-week CDP. For week 12 NEDA-3, CDP was defined as a sustained increase from baseline of  $> 1$  point in EDSS score when baseline was  $< 5.5$  and an increase of  $> 0.5$  points when baseline was  $> 5.5$  that occurred during the first 12 weeks of treatment and was confirmed at week 24. Participants who had an increase in

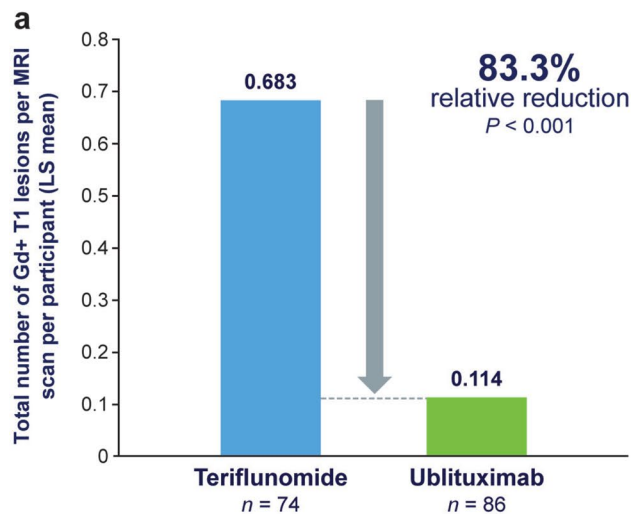
EDSS score at week 12 that was not confirmed at week 24 were considered to have achieved NEDA-3 at week 12 if they also met the other NEDA-3 criteria. NEDA-3 analyses at week 12 did not include re-baselined MRI data; week 96 NEDA-3 analyses used re-baselined MRI data. For re-baselined periods, all components of NEDA-3 were re-baselined to week 24, and EDSS progression events occurring at the last scheduled visit (week 96) were not considered to represent 12-week CDP since these events could not be confirmed 12 weeks later.

### Statistical Analyses

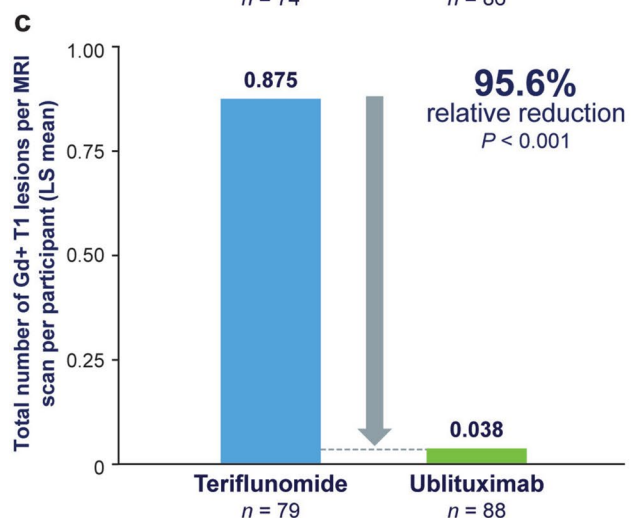
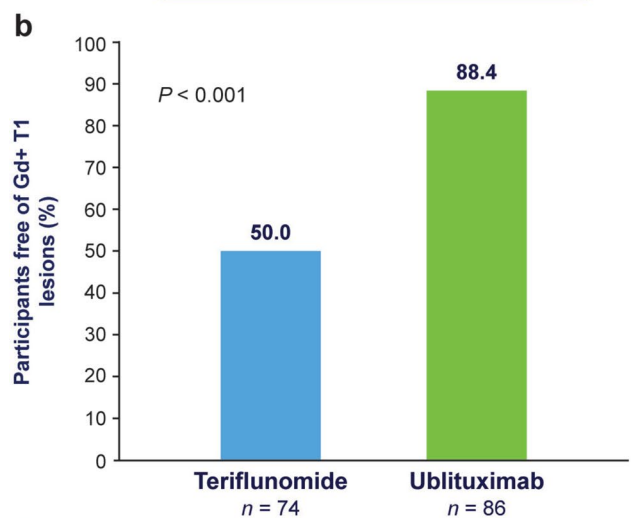
Pooled post hoc analyses were performed to evaluate the ARR (at week 96), Gd+ T1 lesion counts (at weeks 12 and 96), new or enlarging T2 lesion counts (at weeks 12 and 96), and NEDA-3 (at weeks 12 and 96) in the subgroup of participants with highly active disease at baseline, defined as  $\geq 2$  relapses in the previous year and at least one Gd+ T1 lesion at baseline.

Baseline characteristics, ARR, and NEDA-3 data were analyzed in the modified intention-to-treat (mITT) population, which included all participants who received at least one dose of trial drug and completed a baseline and at least one postbaseline efficacy assessment. Analyses of MRI endpoints were based on the mITT-MRI population of participants who received at least one dose of trial drug and had a baseline and at least one postbaseline efficacy and MRI assessment. Baseline demographic and clinical characteristics were summarized using descriptive statistics. ARRs were analyzed based on a negative binomial model (generalized estimating equation [GEE]) for relapse count per participant with logarithmic link function, treatment as covariate, and log (years of treatment) as offset and were expressed as least squares (LS) means. Rate ratios and corresponding 95% confidence intervals (CIs) were provided for the comparisons of ublituximab versus teriflunomide.

Analyses of Gd+ T1 and new or enlarging T2 lesions were based on negative binomial models (GEE) for the total number of Gd+ T1 lesions or new or enlarging T2 lesions per MRI scan with logarithmic link function, region, treatment,



Rate ratio (95% CI), 0.167 (0.082–0.339)



Rate ratio (95% CI), 0.044 (0.019–0.098)

◀**Fig. 2** Gd+ T1 lesions in participants with highly active disease at baseline: **a** total number at week 12, **b** participants free of Gd+ T1 lesions at week 12, and **c** total number at weeks 0–96. *CI* confidence interval, *Gd+* gadolinium-enhancing, *LS* least squares, *MRI* magnetic resonance imaging

baseline EDSS score, baseline number of lesions (0 or  $\geq 1$  for Gd+ T1 lesions), and study as covariates and an offset based on the log-transformed number of postbaseline MRI scans. For NEDA-3, odds ratios (ORs) and corresponding 95% CIs were determined based on logistic regression model with treatment, study, region, baseline EDSS score, and log-transformed baseline MRI lesion counts (T1 nonenhancing, T2, Gd+) as covariates. *P* values for analyses of the proportion of participants free of Gd+ T1 lesions at week 12 were based on Fisher's exact test.

## RESULTS

### Participant Demographics and Baseline Characteristics

Among 1094 participants (ublituximab,  $n=546$ ; teriflunomide,  $n=548$ ) enrolled in ULTIMATE I and ULTIMATE II, 1089 were included in the mITT population. Of these, 168 had highly active disease at baseline (ublituximab,  $n=88$ ; teriflunomide,  $n=80$ ). Demographic and clinical characteristics were well balanced across treatment arms in the highly active disease subgroup (Table 1). Participants in the highly active disease subgroup tended to be younger with a shorter time since symptom onset and diagnosis than those not meeting highly active criteria in the overall ULTIMATE study population (Table 1). Consistent with the criteria for highly active disease, the time since the most recent relapse was shorter, and the number of relapses in the previous 1 or 2 years, the number of baseline Gd+ T1 lesions, and the baseline T2

lesion count were higher in the highly active disease subgroup.

### ARR

In the highly active disease subgroup, ublituximab was associated with a 70.8% decrease in unadjusted ARR over 96 weeks compared with teriflunomide: 0.145 versus 0.496, respectively ( $P<0.001$ ; Fig. 1).

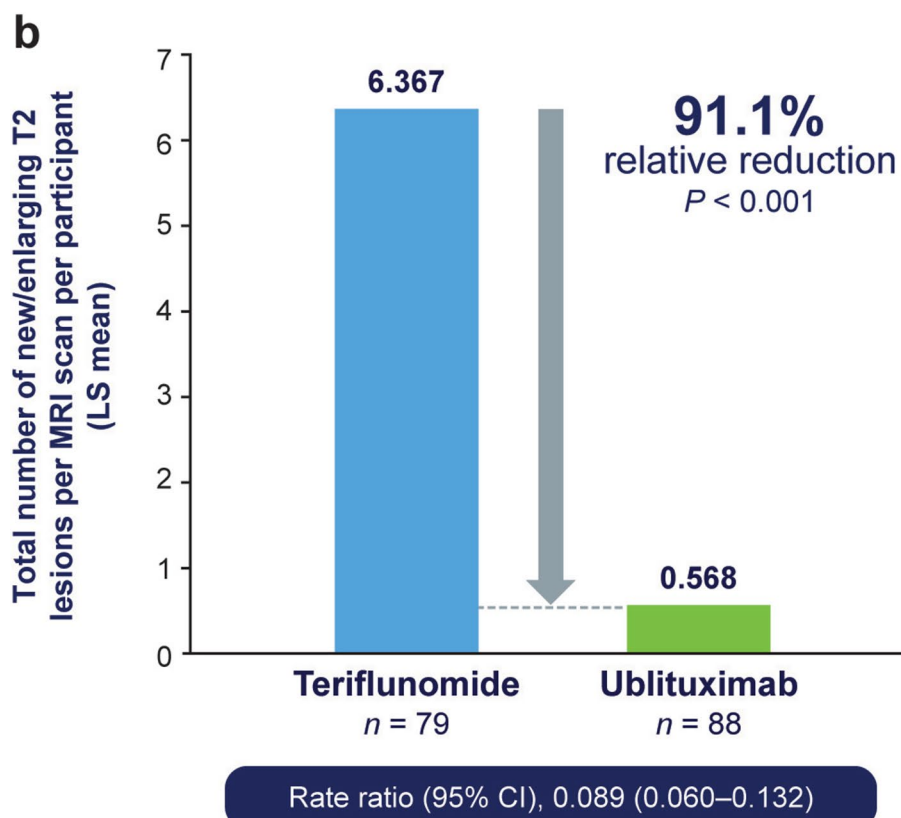
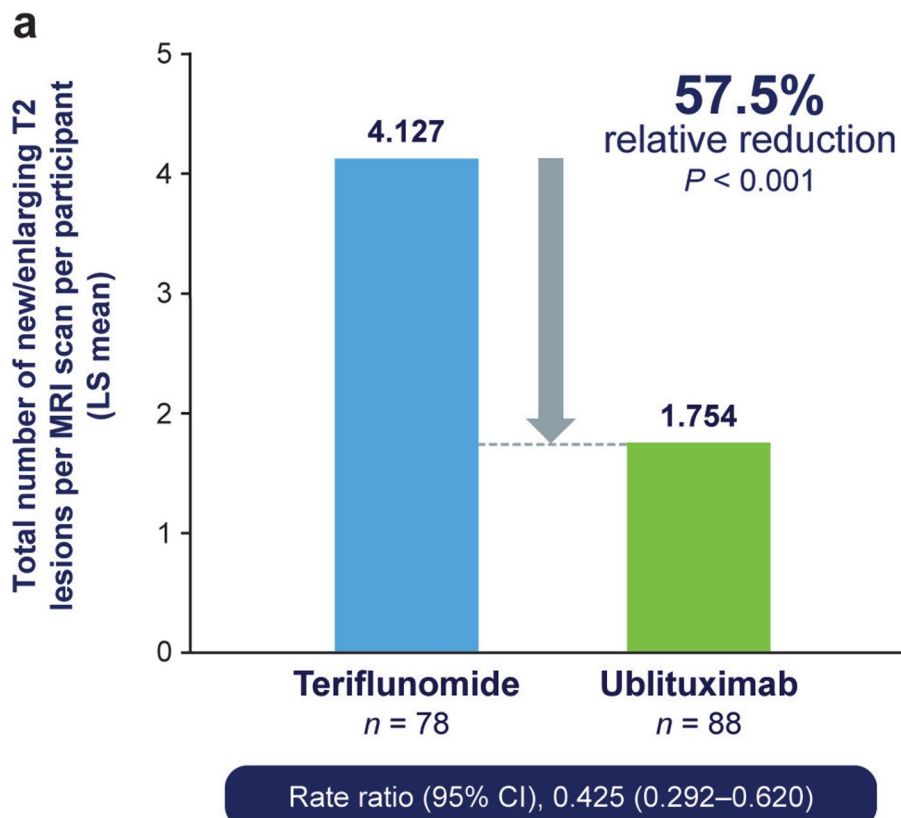
### MRI Activity

Among participants with highly active disease, at week 12, there was an 83.3% reduction in Gd+ T1 lesions with ublituximab treatment compared with teriflunomide (LS mean 0.114 for ublituximab versus 0.683 for teriflunomide;  $P<0.001$ ) (Fig. 2a). Overall, 88.4% ( $n=86$ ) were free from Gd+ T1 lesions in the ublituximab-treated group versus 50.0% ( $n=74$ ) in the teriflunomide group ( $P<0.001$ ) at week 12 (Fig. 2b). During weeks 0 to 96, the overall treatment period, there was a 95.6% reduction in Gd+ T1 lesions with ublituximab treatment compared with teriflunomide treatment in the highly active disease subgroup (total number LS means 0.038 versus 0.875, respectively;  $P<0.001$ ) (Fig. 2c).

There was a significant reduction in the number of new or enlarging T2 lesions at week 12 with ublituximab versus teriflunomide in the highly active disease subgroup (57.5% relative reduction; LS mean 1.754 versus 4.127 for ublituximab and teriflunomide,  $P<0.001$ , respectively) (Fig. 3a). Furthermore, in this subpopulation of participants with highly active disease, the LS mean number of new or enlarging T2 lesions per scan during weeks 0 to 96 was significantly lower with ublituximab compared with teriflunomide (91.1% relative reduction; 0.568 versus 6.367, respectively;  $P<0.001$ ) (Fig. 3b).

### NEDA-3 Outcomes

A significantly higher proportion of ublituximab-treated participants with highly active disease at baseline achieved NEDA-3 compared



◀**Fig. 3** Total number of new or enlarging T2 lesions in participants with highly active disease at baseline at a week 12 and **b** weeks 0–96. *CI* confidence interval, *Gd+* gadolinium-enhancing, *LS* least squares, *MRI* magnetic resonance imaging

with teriflunomide at week 12 (29.5% versus 10.1%; OR [95% CI] 4.716 [1.847–12.046];  $P=0.001$ ) (Fig. 4a). Disease activity in participants not achieving NEDA-3 at week 12 was largely driven by T2 lesions in both treatment groups (Fig. 4b). Among participants with highly active disease who did not achieve NEDA-3 at week 12, the number of participants demonstrating a reduction in Gd+ T1 lesions was significantly higher in the ublituximab-treated group compared with the teriflunomide-treated group (Fig. 4b).

NEDA-3 rates at weeks 24–96 (re-baselined) in the highly active disease subgroup were 4.8-fold higher with ublituximab (77.9%) than with teriflunomide (16.4%; OR [95% CI] 22.068 [8.975–54.262];  $P<0.001$ ) (Fig. 5a). Drivers of disease activity in participants not achieving NEDA-3 at weeks 24–96 were primarily relapse and CDP in the ublituximab group and MRI activity in the teriflunomide group (Fig. 5b).

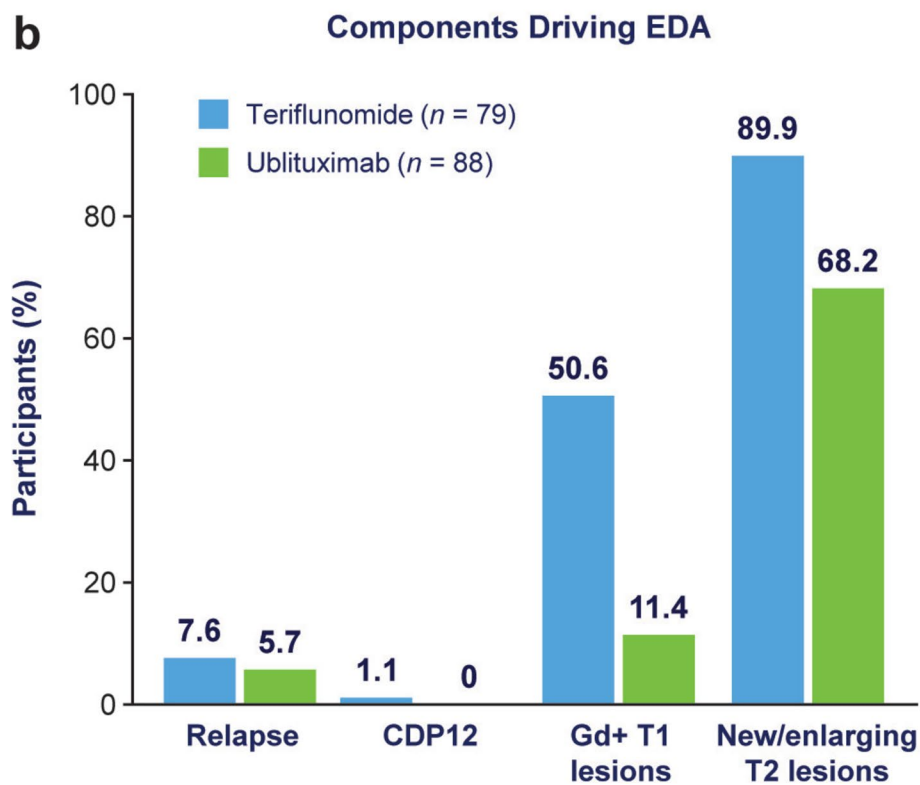
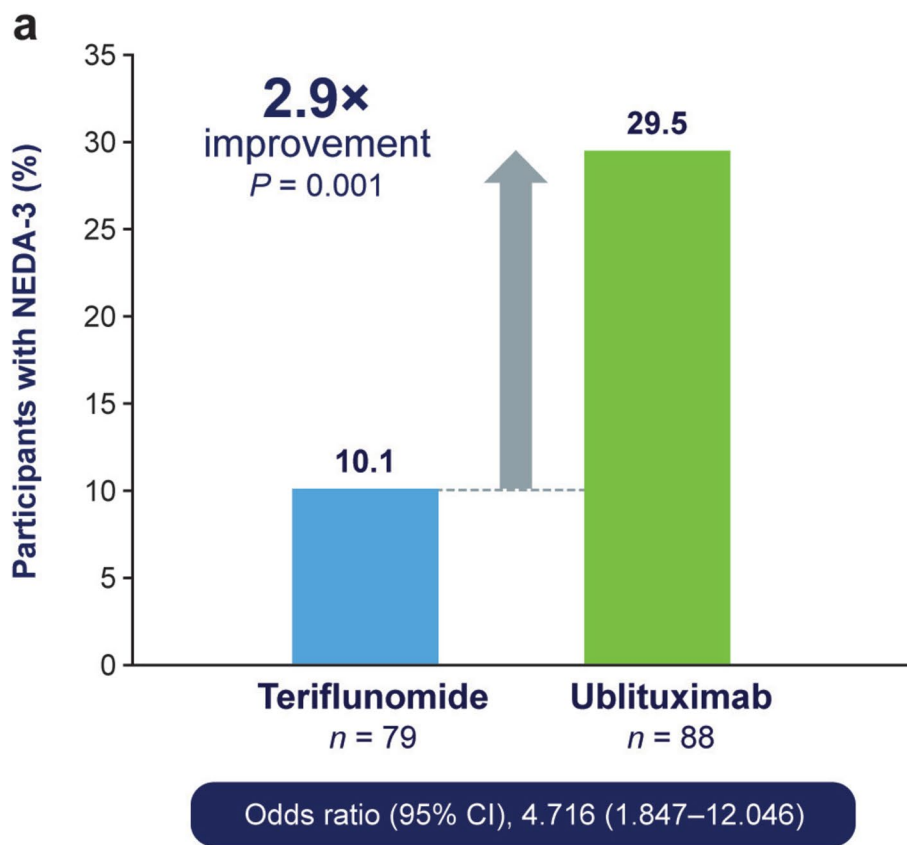
## DISCUSSION

In the ULTIMATE I and II studies, 168 of 1094 (15.4%) participants had highly active disease at baseline, falling within the range noted in previous studies [16, 22, 27–30]. People with highly active MS have an increased risk of rapid accumulation of disability and faster disease progression, resulting in a higher disease burden [24, 31]. Disability accrual can occur in the setting of relapse-associated worsening or progression independent of relapse activity (PIRA), indicating that disability may accumulate even in people with a seemingly stable clinical course [18]. Highly active disease may also be associated with worse health-related quality of life and greater levels of fatigue than in less active disease [32, 33], although additional research is needed to

evaluate the relationship between disease activity and patient burden.

Early disease progression in MS is driven primarily by relapses occurring during the first 2 years of disease, with later relapses contributing to a lesser degree [24, 31]. Currently available DMTs target the early inflammatory process and thus are most effective during the early stages of disease [28]. In relapsing MS, the period after the first demyelinating attack is characterized by peak central nervous system inflammation and is believed to constitute a window of opportunity for effective treatment with DMTs. Consistent with this hypothesis, studies have shown that early implementation of high-efficacy DMTs, including anti-CD20 mAbs, is associated with better long-term outcomes than escalation therapy or delayed initiation of high-efficacy DMTs, both in overall populations with MS [23, 25, 34–37] and in those with highly active MS [26]. People with breakthrough disease on a first-line DMT may benefit from switching to a highly active DMT at the beginning of new disease activity, providing a second window of opportunity for preventing disability [18, 38]. However, considering the faster progression of highly active disease, the window of opportunity for preventing accumulation of disability and disease progression in this subpopulation is relatively narrow [18, 21, 22, 24].

In this post hoc analysis of pooled data from ULTIMATE I and II, ublituximab was associated with significant treatment benefits across multiple efficacy measures versus teriflunomide in participants with highly active disease at baseline. Benefits were observed as early as week 12, at which time point ublituximab significantly reduced key MRI measures of disease activity compared with teriflunomide and was associated with a 30% rate of NEDA-3 (versus 10% with teriflunomide). Relative reductions in Gd+ T1 lesions and new/enlarging T2 lesions observed with ublituximab versus teriflunomide exceeded 90% in participants with highly active disease. Further, ublituximab-treated participants with highly active disease achieved NEDA-3 at weeks 24–96 (re-baselined) at a 4.8-fold higher rate than those treated with teriflunomide. ULTIMATE I and II were the first pivotal phase 3



◀**Fig. 4 a** Proportion of participants with highly active disease at baseline achieving NEDA-3 at week 12 and **b** components driving disease activity in participants not achieving NEDA-3 at week 12. There was only one person in total who experienced confirmed disability progression in the first 12 weeks. *CDPI2* 12-week confirmed disability progression, *CI* confidence interval, *EDA* evidence of disease activity, *Gd+* gadolinium-enhancing, *NEDA-3* 3-parameter no evidence of disease activity

studies of a high-efficacy therapy in RMS to evaluate a 12-week time point, and they demonstrated a rapid reduction in acute inflammation with ublituximab, as evidenced by significant reduction in Gd+ MRI lesions at 3 months. These observations highlight the potent efficacy of ublituximab among people with highly active MS.

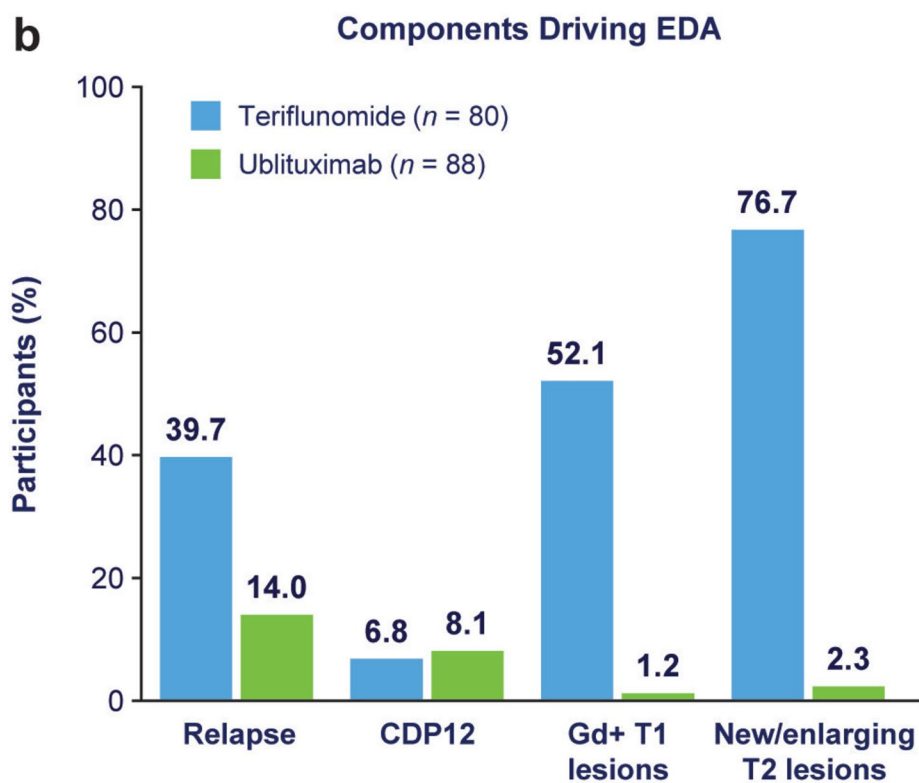
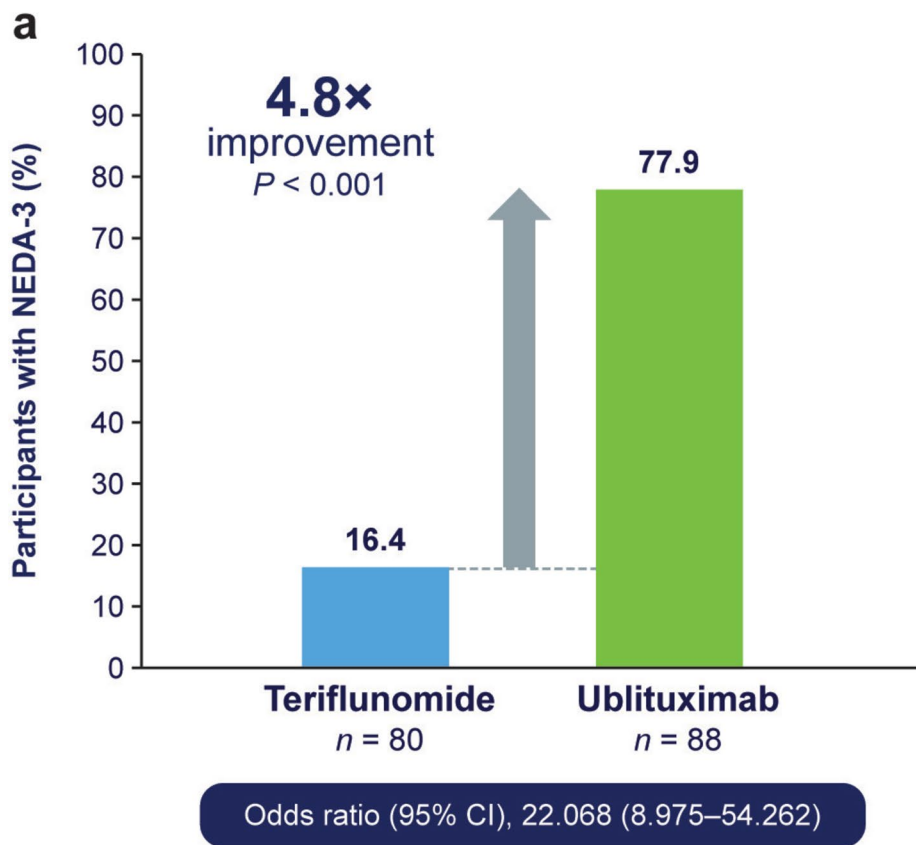
Achievement of NEDA-3 is an important clinical endpoint given that it has been significantly associated with improved long-term outcomes among people with RMS [39–41]. Among participants not achieving NEDA-3 at week 12 during treatment with ublituximab, disease activity in both treatment groups was largely driven by new or enlarging T2 lesions. This finding is consistent with results of a post hoc analysis of NEDA-3 in the overall pooled ULTIMATE I and II population, which found that new or enlarging T2 lesions were the primary driver of disease activity during weeks 0–96 among both teriflunomide- and ublituximab-treated participants [17]. In that analysis, new or enlarging T2 lesions were a key driver of disease activity among teriflunomide-treated but not among ublituximab-treated participants not achieving NEDA-3 during weeks 24–96 (re-baselined) or 48–96 (re-baselined) [17], likely reflecting the weeks to months required for the potent anti-inflammatory effects of anti-CD20 mAbs to become fully apparent [42–44].

The clinical practice guidelines of both the American Academy of Neurology and the European Committee for Treatment and Research in Multiple Sclerosis/European Academy of Neurology recommend that people with highly active MS be treated with high-efficacy DMTs due to their demonstrated efficacy in this patient population and the superiority of high-efficacy DMTs over interferon (IFN)- $\beta$  in clinical trials [45, 46].

The current findings with ublituximab in people with highly active MS are largely consistent with previous findings from subgroup analyses of clinical trials that have demonstrated benefits of high-efficacy DMTs in people with highly active MS [30, 47]. In a post hoc analysis of data from the phase 3 OPERA I and II studies, ocrelizumab showed comparable efficacy over 96 weeks of treatment in previously treated participants with active ( $n=301$ ) or highly active ( $n=283$ ) MS with respect to relative reductions (versus IFN- $\beta$ 1a) in ARR (65% and 68%, respectively), Gd+ T1 lesions (98% in both subgroups), new/enlarging T2 lesions (80% relative reduction in both subgroups), and 12-week CDP (54% and 53%, respectively) [48]. A subgroup analysis in 180 treatment-naïve participants with highly active MS from ENSEMBLE, an open-label, single-arm, phase 3b trial of ocrelizumab in early stage (duration  $\leq 3$  years) relapsing-remitting MS (RRMS), demonstrated high efficacy of ocrelizumab, with 64.4% of participants achieving NEDA-3, 90.6% having no relapses, 83.9% having no MRI activity, and 82.2% having no 24-week CDP at 4 years. Results in this subgroup were comparable with those seen in the overall study population [49].

Data from retrospective cohort studies in people with highly active MS have also demonstrated comparable effectiveness of different high-efficacy DMTs, including anti-CD20 mAbs, in this clinical population [26, 50, 51].

Limitations of the current analyses of pooled data from ULTIMATE I and II include the post hoc nature of the analyses and the possibility that individuals enrolled in the controlled trials may differ from the real-world clinical population. Additionally, the number of participants with highly active disease in the ULTIMATE I and II trials was relatively small (approximately 80 for each treatment group), and for NEDA-3 analyses, overall follow-up was limited and radiologic examinations were performed per protocol; thus, data for more frequent time points were not available. While the benefits observed with ublituximab in people with highly active MS in these analyses are similar to those reported with other high-efficacy DMTs in this population, prospective head-to-head comparative efficacy trials are needed to establish the relative



◀**Fig. 5** **a** Proportion of participants with highly active disease at baseline achieving NEDA-3 at weeks 24–96 (re-baselined) and **b** components driving disease activity in participants not achieving NEDA-3 at weeks 24–96. *CDPI2* 12-week confirmed disability progression, *CI* confidence interval, *EDA* evidence of disease activity, *Gd+* gadolinium-enhancing, *NEDA-3* 3-parameter no evidence of disease activity

efficacy and safety of individual high-efficacy DMTs in people with highly active disease.

## CONCLUSIONS

In this post hoc analysis of pooled data from the phase 3 ULTIMATE I and II trials, ublituximab produced statistically significant improvements in key clinical and MRI measures in participants with highly active disease at baseline. These results suggest that ublituximab could be beneficial in managing disease and limiting future accumulation of disability to improve outcomes in this population of people with highly active MS.

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**Data Availability.** Data may be provided on reasonable request to the following email: TGPublications@tgtxinc.com.

## Declarations

**Conflict of Interest.** Enrique Alvarez has received compensation for advisory boards, lectures, and consultancy with Biogen, Celgene/BMS, Cionic, EMD Serono/Merck, Genentech/Roche, Genzyme, Horizon/Amgen, Novartis, Sanofi, and TG Therapeutics, and research support from Biogen, Genentech/Roche, Novartis, TG Therapeutics, Patient-Centered Outcomes Research Institute, National Multiple Sclerosis Society, National Institutes of Health, and Rocky Mountain MS Center. Hans-Peter Hartung has received honoraria for serving on steering and data monitoring committees, consulting, and speaking at symposia from Aurinia Pharma, Bayer Pharma AG, Biogen Idec, BMS Celgene, Merck KG Darmstadt, Neuraxpharm, Novartis, Roche, Sanofi, and TG Therapeutics, with approval by the rector of Heinrich-Heine University. Hans-Peter Hartung is an Editorial Board member of *Neurology and Therapy*. Hans-Peter Hartung was not involved in the selection of peer reviewers nor any of the subsequent editorial decisions. Lawrence Steinman has received research support and honoraria from BMS, Roche, and TG Therapeutics. Dr. Steinman

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**Ethical Approval.** Each study site's institutional review board or ethics committee approved the trials (US central IRB approval reference numbers ULTIMATE I Pro00021474, ULTIMATE II Pro00021820), which adhered

to Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

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## REFERENCES

1. Riedhammer C, Weissert R. Antigen presentation, autoantigens, and immune regulation in multiple sclerosis and other autoimmune diseases. *Front Immunol.* 2015;6:322. <https://doi.org/10.3389/fimmu.2015.00322>.
2. Furman MJ, Meuth SG, Albrecht P, et al. B cell targeted therapies in inflammatory autoimmune disease of the central nervous system. *Front Immunol.* 2023;14:1129906. <https://doi.org/10.3389/fimmu.2023.1129906>.
3. Dobson R, Giovannoni G. Multiple sclerosis - a review. *Eur J Neurol.* 2019;26(1):27–40. <https://doi.org/10.1111/ene.13819>.
4. Carlson AK, Amin M, Cohen JA. Drugs targeting CD20 in multiple sclerosis: pharmacology, efficacy, safety, and tolerability. *Drugs.* 2024;84(3):285–304. <https://doi.org/10.1007/s40265-024-02011-w>.
5. Comi G, Bar-Or A, Lassmann H, et al. Role of B cells in multiple sclerosis and related disorders. *Ann Neurol.* 2021;89(1):13–23. <https://doi.org/10.1002/ana.25927>.

6. Greenfield AL, Hauser SL. B-cell therapy for multiple sclerosis: entering an era. *Ann Neurol*. 2018;83(1):13–26. <https://doi.org/10.1002/ana.25119>.
7. Palanichamy A, Jahn S, Nickles D, et al. Rituximab efficiently depletes increased CD20-expressing T cells in multiple sclerosis patients. *J Immunol*. 2014;193(2):580–6. <https://doi.org/10.4049/jimmunol.1400118>.
8. Shinoda K, Li R, Rezk A, et al. Differential effects of anti-CD20 therapy on CD4 and CD8 T cells and implication of CD20-expressing CD8 T cells in MS disease activity. *Proc Natl Acad Sci U S A*. 2023;120(3):e2207291120. <https://doi.org/10.1073/pnas.2207291120>.
9. von Essen MR, Hansen RH, Hojgaard C, Ammitz-boll C, Wiendl H, Sellebjerg F. Ofatumumab modulates inflammatory T cell responses and migratory potential in patients with multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(4):e200004. <https://doi.org/10.1212/NXI.000000000200004>.
10. Cree BAC, Berger JR, Greenberg B. The evolution of anti-CD20 treatment for multiple sclerosis: optimization of antibody characteristics and function. *CNS Drugs*. 2025;39(6):545–64. <https://doi.org/10.1007/s40263-025-01182-8>.
11. Babiker HM, Glode AE, Cooke LS, Mahadevan D. Ublituximab for the treatment of CD20 positive B-cell malignancies. *Expert Opin Investig Drugs*. 2018;27(4):407–12. <https://doi.org/10.1080/13543784.2018.1459560>.
12. Fox E, Lovett-Racke AE, Gormley M, et al. A phase 2 multicenter study of ublituximab, a novel glycoengineered anti-CD20 monoclonal antibody, in patients with relapsing forms of multiple sclerosis. *Mult Scler*. 2021;27(3):420–9. <https://doi.org/10.1177/1352458520918375>.
13. Le Garff-Tavernier M, Decocq J, de Romeuf C, et al. Analysis of CD16+CD56dim NK cells from CLL patients: evidence supporting a therapeutic strategy with optimized anti-CD20 monoclonal antibodies. *Leukemia*. 2011;25(1):101–9. <https://doi.org/10.1038/leu.2010.240>.
14. BRIUMVI (ublituximab-xiiv). Prescribing information. TG Therapeutics; 2022. <https://www.tgtherapeutics.com/label-prescribing-info/uspi-briumvi.pdf>. Accessed 1 Oct 2024.
15. Alvarez A, Steinman L, Fox EJ, et al. Reduced disease progression with ublituximab vs teriflunomide in the phase 3 ULTIMATE I and II studies in relapsing multiple sclerosis. In: Consortium of Multiple Sclerosis Centers; June 1–4 2022; National Harbor, MD.
16. Steinman L, Fox E, Hartung HP, et al. Ublituximab versus teriflunomide in relapsing multiple sclerosis. *N Engl J Med*. 2022;387(8):704–14. <https://doi.org/10.1056/NEJMoa2201904>.
17. Alvarez E, Steinman L, Fox EJ, et al. Improvements in no evidence of disease activity with ublituximab vs. teriflunomide in the ULTIMATE phase 3 studies in relapsing multiple sclerosis. *Front Neurol*. 2024;15:1473284. <https://doi.org/10.3389/fneur.2024.1473284>.
18. Correale J, Rush CA, Barboza A. Are highly active and aggressive multiple sclerosis the same entity? *Front Neurol*. 2023;14:1132170. <https://doi.org/10.3389/fneur.2023.1132170>.
19. Sørensen PS, Centonze D, Giovannoni G, et al. Expert opinion on the use of cladribine tablets in clinical practice. *Ther Adv Neurol Disord*. 2020;13:1756286420935019. <https://doi.org/10.1177/1756286420935019>.
20. Wiendl H, Gold R, Berger T, et al. Multiple Sclerosis Therapy Consensus Group (MSTCG): position statement on disease-modifying therapies for multiple sclerosis (white paper). *Ther Adv Neurol Disord*. 2021;14:17562864211039648. <https://doi.org/10.1177/17562864211039648>.
21. Arrambide G, Iacobaeus E, Amato MP, et al. Aggressive multiple sclerosis (2): treatment. *Mult Scler*. 2020;26(9):1045–63. <https://doi.org/10.1177/1352458520924595>.
22. Fernández Ó. Is there a change of paradigm towards more effective treatment early in the course of apparent high-risk MS? *Mult Scler Relat Disord*. 2017;17:75–83. <https://doi.org/10.1016/j.msard.2017.07.003>.
23. Iaffaldano P, Lucisano G, Guerra T, et al. Early intensive versus escalation approach: ten-year impact on disability in relapsing multiple sclerosis. *Ann Clin Transl Neurol*. 2025. <https://doi.org/10.1002/acn3.70131>.
24. Rush CA, MacLean HJ, Freedman MS. Aggressive multiple sclerosis: proposed definition and treatment algorithm. *Nat Rev Neurol*. 2015;11(7):379–89. <https://doi.org/10.1038/nrneurol.2015.85>.
25. Selmaj K, Cree BAC, Barnett M, Thompson A, Hartung HP. Multiple sclerosis: time for early treatment with high-efficacy drugs. *J Neurol*. 2024;271(1):105–15. <https://doi.org/10.1007/s00415-023-11969-8>.

26. Alonso R, Casas M, Lazaro L, et al. Achieving no evidence of disease activity-3 in highly active multiple sclerosis patients treated with cladribine and monoclonal antibodies. *Mult Scler J Exp Transl Clin.* 2023;9(1):20552173231154712. <https://doi.org/10.1177/20552173231154712>.
27. Cellierino M, Boffa G, Lapucci C, et al. Predictors of ocrelizumab effectiveness in patients with multiple sclerosis. *Neurotherapeutics.* 2021;18(4):2579–88. <https://doi.org/10.1007/s13311-021-01104-8>.
28. Díaz C, Zarco LA, Rivera DM. Highly active multiple sclerosis: an update. *Mult Scler Relat Disord.* 2019;30:215–24. <https://doi.org/10.1016/j.msard.2019.01.039>.
29. Ellenberger D, Flachenecker P, Fneish F, et al. Aggressive multiple sclerosis: a matter of measurement and timing. *Brain.* 2020;143(11):e97. <https://doi.org/10.1093/brain/awaa306>.
30. Ziemssen T, Bass AD, Berkovich R, et al. Efficacy and safety of alemtuzumab through 9 years of follow-up in patients with highly active disease: post hoc analysis of CARE-MS I and II patients in the TOPAZ extension study. *CNS Drugs.* 2020;34(9):973–88. <https://doi.org/10.1007/s40263-020-00749-x>.
31. Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. *Brain.* 2010;133(7):1914–29. <https://doi.org/10.1093/brain/awq118>.
32. Ahvenjärvi H, Niiranen M, Simula S, et al. Fatigue and health-related quality of life depend on the disability status and clinical course in RRMS. *Mult Scler Relat Disord.* 2023;77:104861. <https://doi.org/10.1016/j.msard.2023.104861>.
33. Spelman T, Geale K, Anell B, Hillert J, Wong SL. The association between disease activity and health-related quality of life in RRMS patients. *Value Health.* 2017;20(9):A728. <https://doi.org/10.1016/j.jval.2017.08.1975>.
34. Guger M, Enzinger C, Leutmezer F, et al. Early intensive versus escalation treatment in patients with relapsing-remitting multiple sclerosis in Austria. *J Neurol.* 2024;271(6):3142–52. <https://doi.org/10.1007/s00415-024-12256-w>.
35. Popiel M, Bartosik-Psujek H. Clinical and radiological consequences of delayed therapy escalation in patients with relapsing-remitting multiple sclerosis. *Neurol Neurochir Pol.* 2024;58(1):84–93. <https://doi.org/10.5603/pjnns.97040>.
36. Simonsen CS, Flemmen H, Broch L, et al. Early high efficacy treatment in multiple sclerosis is the best predictor of future disease activity over 1 and 2 years in a Norwegian population-based registry. *Front Neurol.* 2021;12:693017. <https://doi.org/10.3389/fneur.2021.693017>.
37. Spelman T, Magyari M, Piehl F, et al. Treatment escalation vs immediate initiation of highly effective treatment for patients with relapsing-remitting multiple sclerosis: data from 2 different national strategies. *JAMA Neurol.* 2021;78(10):1197–204. <https://doi.org/10.1001/jamaneurol.2021.2738>.
38. Castillo-Trivino T, Mowry EM, Gajofatto A, et al. Switching multiple sclerosis patients with breakthrough disease to second-line therapy. *PLoS ONE.* 2011;6(2):e16664. <https://doi.org/10.1371/journal.pone.0016664>.
39. Prosperini L, Ruggieri S, Haggiag S, Tortorella C, Pozzilli C, Gasperini C. Prognostic accuracy of NEDA-3 in long-term outcomes of multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm.* 2021. <https://doi.org/10.1212/nxi.0000000000001059>.
40. Rotstein D, Solomon JM, Sormani MP, et al. Association of no evidence of disease activity with no long-term disability progression in multiple sclerosis: a systematic review and meta-analysis. *Neurology.* 2022;99(2):e209–20. <https://doi.org/10.1212/wnl.000000000000200549>.
41. Simonsen CS, Flemmen H, Broch L, et al. Rebaseline no evidence of disease activity (NEDA-3) as a predictor of long-term disease course in a Norwegian multiple sclerosis population. *Front Neurol.* 2022;13:1034056. <https://doi.org/10.3389/fneur.2022.1034056>.
42. Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab versus teriflunomide in multiple sclerosis. *N Engl J Med.* 2020;383(6):546–57. <https://doi.org/10.1056/NEJMoa1917246>.
43. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med.* 2017;376(3):221–34. <https://doi.org/10.1056/NEJMoa1601277>.
44. Margoni M, Preziosa P, Filippi M, Rocca MA. Anti-CD20 therapies for multiple sclerosis: current status and future perspectives. *J Neurol.* 2022;269(3):1316–34. <https://doi.org/10.1007/s00415-021-10744-x>.
45. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of

- the American Academy of Neurology. *Neurology*. 2018;90(17):777–88. <https://doi.org/10.1212/wnl.0000000000005347>.
46. Montalban X, Gold R, Thompson AJ, et al.ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler*. 2018;24(2):96–120. <https://doi.org/10.1177/1352458517751049>.
  47. Derfuss T, Bergvall NK, Sfikas N, Tomic DL. Efficacy of fingolimod in patients with highly active relapsing-remitting multiple sclerosis. *Curr Med Res Opin*. 2015;31(9):1687–91. <https://doi.org/10.1185/03007995.2015.1067191>.
  48. Turner B, Cree BAC, Kappos L, et al. Ocrelizumab efficacy in subgroups of patients with relapsing multiple sclerosis. *J Neurol*. 2019;266(5):1182–93. <https://doi.org/10.1007/s00415-019-09248-6>.
  49. Hartung HP, Benedict RHB, Berger T, et al. Ocrelizumab in early-stage relapsing-remitting multiple sclerosis: the phase IIIb ENSEMBLE 4-year, single-arm, open-label trial. *Neurology*. 2024;103(12):e210049. <https://doi.org/10.1212/wnl.0000000000210049>.
  50. Rollot F, Couturier J, Casey R, et al. Comparative effectiveness of natalizumab versus anti-CD20 in highly active relapsing-remitting multiple sclerosis after fingolimod withdrawal. *Neurotherapeutics*. 2022;19(2):476–90. <https://doi.org/10.1007/s13311-022-01202-1>.
  51. Signoriello E, Signori A, Lus G, et al. NEDA-3 achievement in early highly active relapsing remitting multiple sclerosis patients treated with ocrelizumab or natalizumab. *Mult Scler Relat Disord*. 2024;87:105594. <https://doi.org/10.1016/j.msard.2024.105594>.