Ublituximab Treatment Is Associated With a Significant Proportion of Patients Achieving No Evidence of Disease Activity (NEDA): Results From the ULTIMATE I and ULTIMATE II Phase 3 Studies of Ublituximab vs Teriflunomide in Relapsing Multiple Sclerosis (RMS)

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Presented at the 2022 American Academy of Neurology (AAN), April 2-7, Seattle, WA; April 24-26, Virtual. Poster P6.005.

OBJECTIVE

- To characterize the effects of ublituximab on 3-parameter NEDA (NEDA-3)

KEY FINDINGS

- In pooled post hoc analyses evaluating NEDA-3 by treatment epoch and patient subtype:
  - NEDA-3 rates for ublituximab vs teriflunomide cohorts by treatment epoch at 0-96 weeks were 44.6% vs 12.4%, respectively, and at 24-96 weeks (re-baselined) were 82.1% vs 22.5% ($P<0.0001$ for both)
  - NEDA-3 at 24-96 weeks (re-baselined) was achieved in 82.7% vs 23.1% of treatment-naive, 81.1% vs 21.1% of previously treated (prior disease-modifying therapy [DMT]), 82.4% vs 18.6% of early-disease, and 81.9% vs 26.5% of late-disease patients in ublituximab- vs teriflunomide-treated cohorts, respectively ($P<0.0001$ for all)
  - The leading cause of disease activity during Weeks 24-96 (re-baselined) was new/enlarging T2 lesions for teriflunomide (occurring in 71.6% of patients) and relapse for ublituximab (occurring in 11.4% of patients)

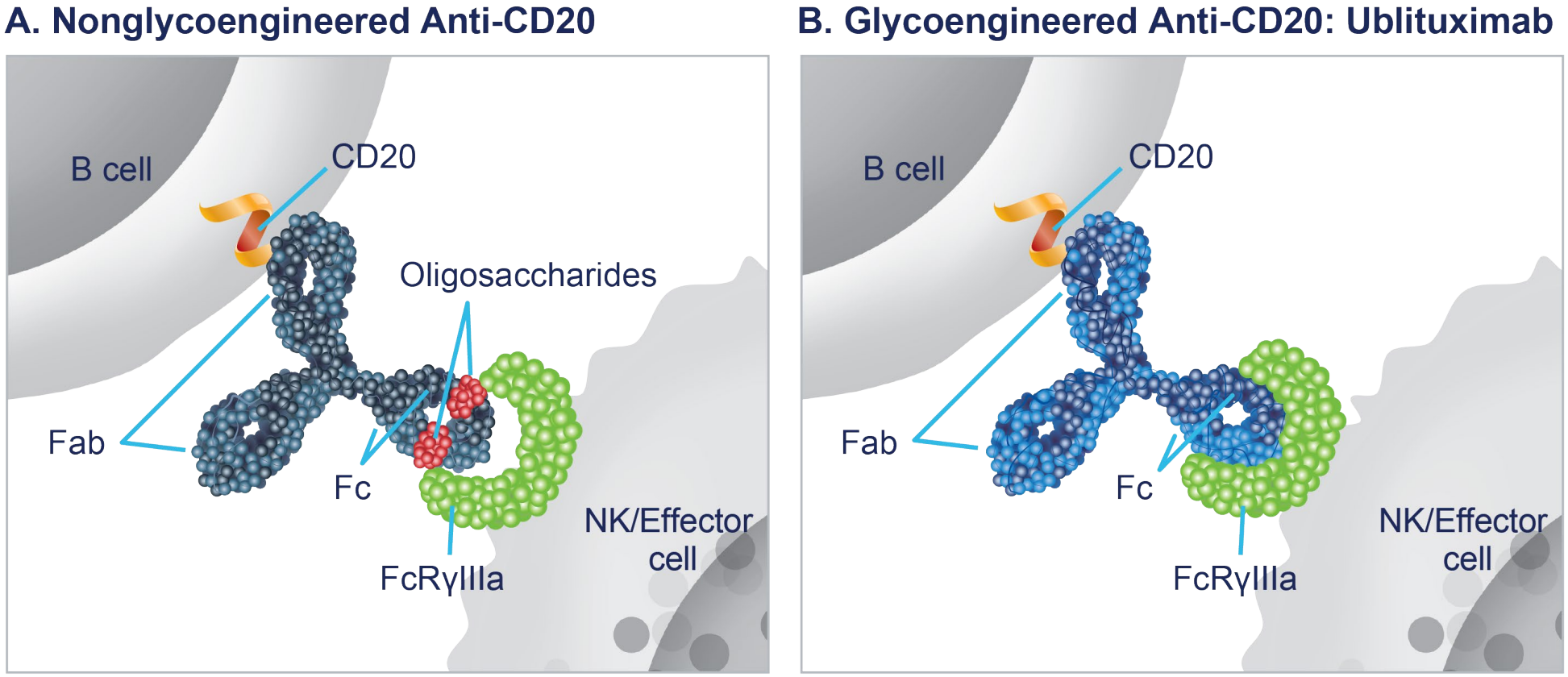
CONCLUSION

- ULTIMATE I and II post hoc pooled analyses demonstrated a consistent NEDA benefit for ublituximab-treated patients across treatment epochs and key patient subpopulations

BACKGROUND

- Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20 and is glycoengineered for enhanced antibody-dependent cellular cytotoxicity **(Figure 1)**[1,2]
- Ublituximab is administered in lower doses and with shorter infusion times compared with other currently infused anti-CD20 therapies[3]
- ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) are identical, Phase 3, randomized, multicenter, double-blind, active-control studies evaluating the efficacy and safety of ublituximab vs teriflunomide in patients with RMS[3]
- ULTIMATE I and II met their primary endpoint, demonstrating a statistically significant reduction in annualized relapse rate for ublituximab compared with teriflunomide as well as significant improvements in the number of gadolinium-enhancing (Gd+) T1 lesions and the number of new/enlarging T2 lesions[3]

Figure 1. Ublituximab Is Glycoengineered to Enhance ADCC



(A) In nonglycoengineered anti-CD20 antibodies, the core fucose of Fc-linked oligosaccharides sterically blocks interaction with FcγRIIIa, reducing affinity.[4,5] **(B)** Ublituximab is glycoengineered to have a low fucose content in the Fc region, which allows for closer interaction and enhanced affinity for all variants of FcγRIIIa.[5-7]

ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer.

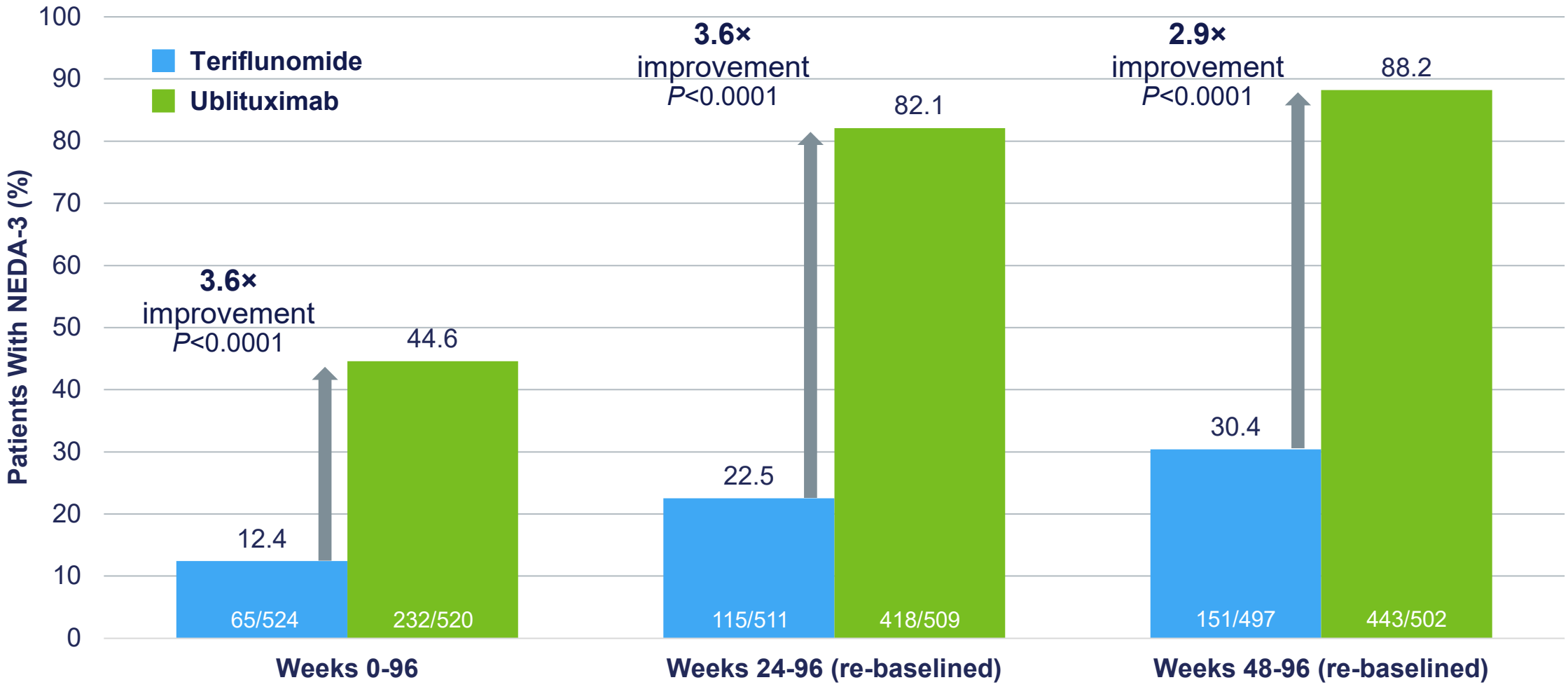
METHODS

- ULTIMATE I and II enrolled a total of 1094 adult patients from 10 countries with a diagnosis of RMS (relapsing-remitting or secondary-progressive) with disease activity[3]
- Patients received ublituximab 450 mg administered by 1-hour intravenous infusion every 24 weeks (following Day 1 infusion of 150 mg and Day 15 infusion of 450 mg) or teriflunomide 14 mg oral once daily for 96 weeks[3]
- Clinical evaluations were performed every 12 weeks, and magnetic resonance imaging (MRI) assessments were performed at Weeks 12, 24, 48, and 96
- NEDA-3 was defined as no confirmed relapses, no T1 Gd+ lesions, no new/enlarging T2 lesions, and no 12-week confirmed disability progression
- Pooled post hoc analyses evaluated NEDA-3 by treatment epoch and patient subtype: treatment-naive, prior DMT, and early- and late-disease (≤3 and >3 years following diagnosis, respectively)
- NEDA rate is the proportion of patients with NEDA, excluding patients who discontinued treatment early due to reasons other than death and lack of efficacy during the analysis time frame
- *P* values were derived from a logistic regression model with baseline adjustments, treatment, study (for pooled analysis), region, baseline Expanded Disability Status Scale strata, and log transformed baseline MRI lesion counts (T1 nonenhancing, T2, and T1 Gd+ lesions)

RESULTS

- NEDA-3 rates were improved with ublituximab vs teriflunomide for the overall treatment period (Weeks 0-96) and for re-baselined epochs, Weeks 24-96 and Weeks 48-96 (*P*<0.0001 for all) **(Figure 2)**

Figure 2. NEDA-3 Rates by Treatment Epoch

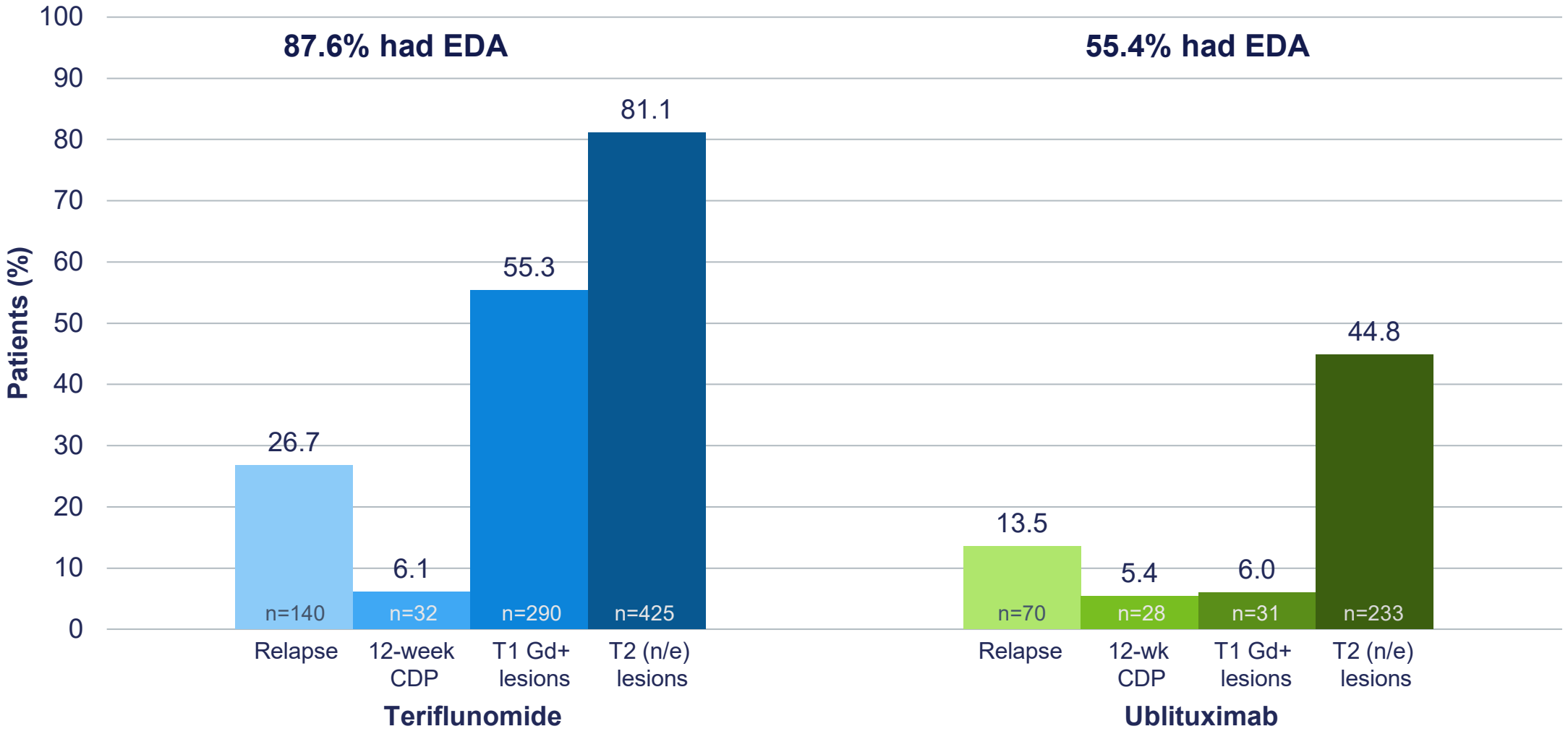


NEDA-3 was defined as no confirmed relapses, no T1 Gd+ lesions, no new/enlarging T2 lesions, and no 12-week confirmed disability progression. Pooled post hoc analysis. Modified intention-to-treat population.
Gd+, gadolinium-enhancing; NEDA, no evidence of disease activity.

RESULTS (continued)

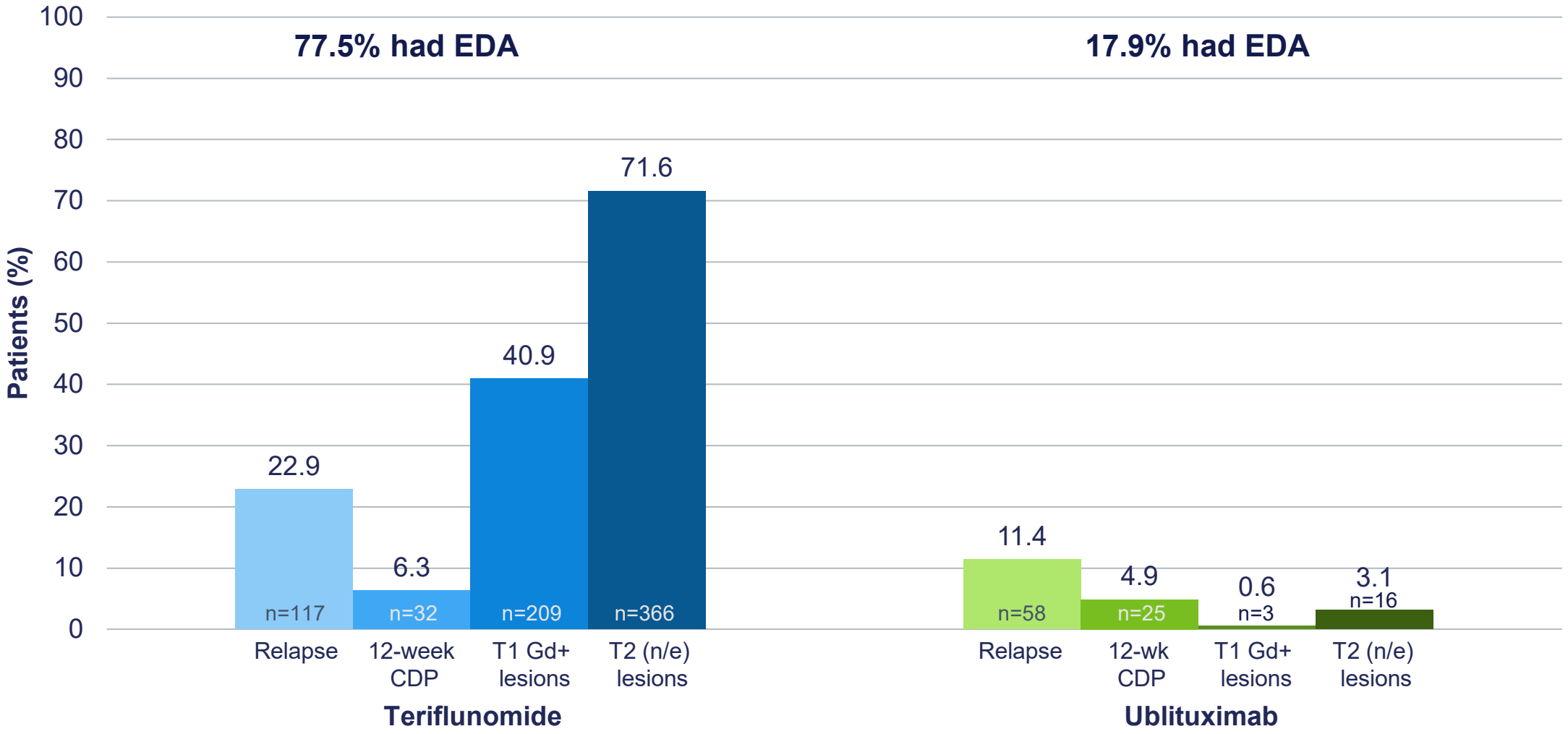
- The components of disease activity during the Weeks 0-96 and Weeks 24-96 (re-baselined) epochs are shown in **Figures 3 and 4**

Figure 3. Components Driving Evidence of Disease Activity at Weeks 0-96[a]



[a]Patients may have >1 component of EDA. Pooled post hoc analysis. Modified intention-to-treat population. Teriflunomide n=524; ublituximab n=520.
CDP, confirmed disease progression; EDA, evidence of disease activity; Gd+, gadolinium-enhancing; n/e, new/enlarging.

Figure 4. Components Driving Evidence of Disease Activity at Weeks 24-96 (Re-baselined)[a]

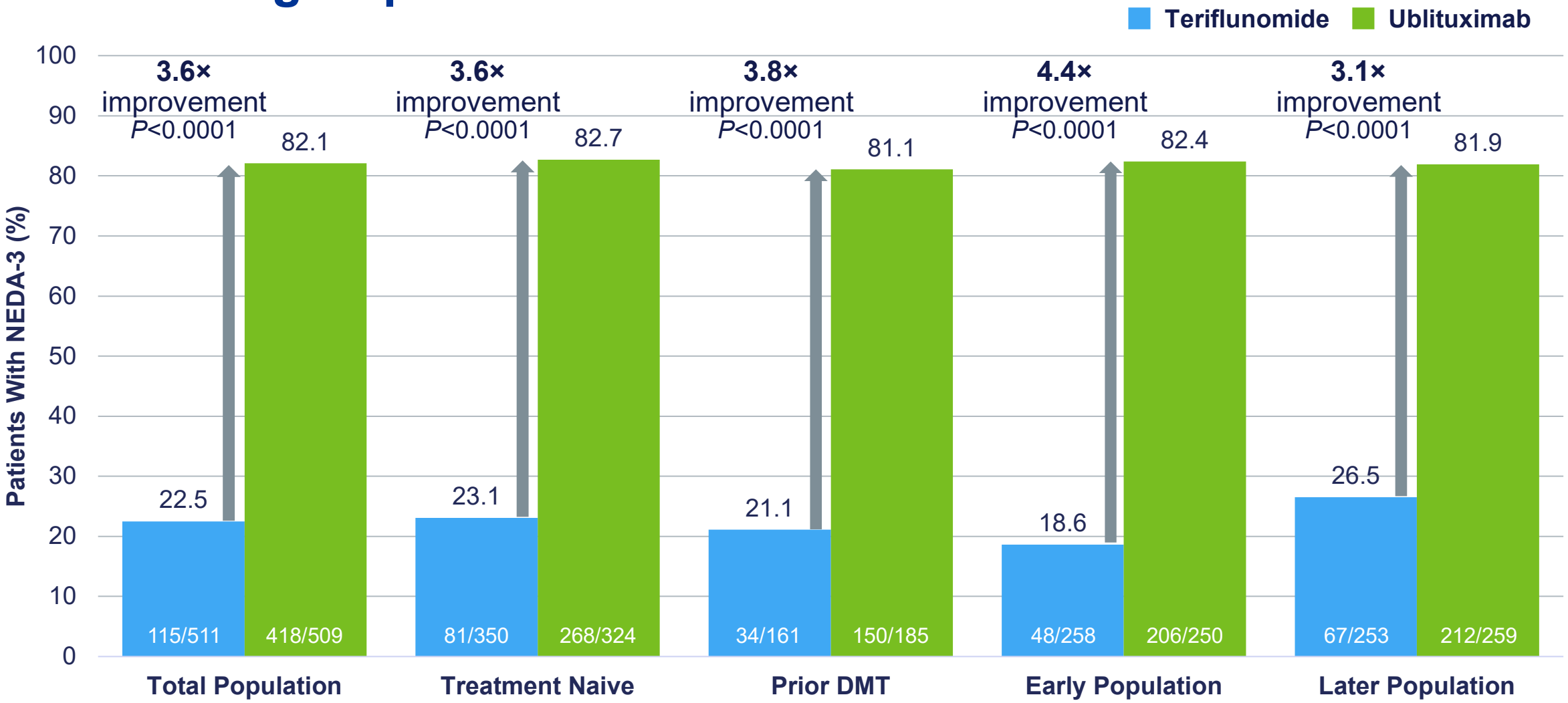


[a]Patients may have >1 component of EDA. Pooled post hoc analysis. Modified intention-to-treat population. Teriflunomide n=511; ublituximab n=509.
CDP, confirmed disease progression; EDA, evidence of disease activity; Gd+, gadolinium-enhancing; n/e, new/enlarging.

RESULTS (continued)

- NEDA-3 at Weeks 24-96 (re-baselined) was improved with ublituximab vs teriflunomide for the subgroups of treatment-naive, previously treated, early-disease, and late-disease patients (*P*<0.0001 for all) **(Figure 5)**

Figure 5. NEDA at Weeks 24-96 (Re-baselined) in Patient Subgroups



NEDA-3 was defined as no confirmed relapses, no T1 Gd+ lesions, no new/enlarging T2 lesions, and no 12-week confirmed disability progression. Early population vs later population defined as < or ≥ median time from diagnosis to randomization, approximately 3 years. Pooled post hoc analysis. Modified intention-to-treat population.
DMT, disease-modifying therapy; Gd+, gadolinium-enhancing; NEDA, no evidence of disease activity.

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ACKNOWLEDGMENTS

- The authors thank the patients and their families for participating in the ULTIMATE I and II studies. The authors also thank Apollo Medical Communications for providing medical writing and editorial support, which was funded by TG Therapeutics. The ULTIMATE I and II studies were sponsored by TG Therapeutics.

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