Disease Outcomes With Ublituximab in Participants With Highly Active Disease: Subpopulation Analyses of the Phase 3 ULTIMATE I and II Studies in Participants With Relapsing Multiple Sclerosis

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The 75th American Academy of Neurology (AAN) Annual Meeting, April 22-27, 2023, Boston, Massachusetts. Poster P6.002.

OBJECTIVE

- To evaluate efficacy of ublituximab in participants enrolled in ULTIMATE I and II with highly active disease at baseline

KEY FINDINGS

- In the highly active disease population, significant improvements with ublituximab (n=88) were observed at Week 96 versus teriflunomide (n=80), including:
  - An unadjusted annualized relapse rate (ARR) of 0.145 and 0.496, respectively ($P<0.0001$)
  - The least squares (LS) means of gadolinium-enhancing (Gd+) T1 lesions and new/enlarging T2 lesions per scan was 0.038 versus 0.875 and 0.568 versus 6.367 for ublituximab versus teriflunomide (both $P<0.0001$)
  - Higher rates of no evidence of disease activity (NEDA) (Weeks 24-96, re-baselined): 77.9% versus 16.4% ($P<0.0001$)

CONCLUSION

- In pooled post hoc analyses of ULTIMATE I and II, ublituximab was associated with significant treatment benefit across multiple efficacy measures at Week 96 versus teriflunomide in participants with highly active disease at baseline

BACKGROUND

- Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20 and is glycoengineered to exhibit a low fucose content in its fragment crystallizable (Fc) region[1-3,a]
- The exclusion of specific fucose molecules on the Fc region enhances its affinity for all variants of FcγRIIIa receptors, thereby increasing engagement of natural killer (NK) cells and resulting in increased antibody-dependent cellular cytolysis relative to other approved anti-CD20 antibodies[1,4,5]
- Ublituximab is administered in lower doses and with shorter infusion times compared with other currently infused anti-CD20 therapies[6]
- 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 versus teriflunomide in participants with relapsing multiple sclerosis (RMS)[6]
- ULTIMATE I and II met their primary endpoint, demonstrating a statistically significant reduction in ARR for ublituximab compared with teriflunomide as well as significant improvements in the number of Gd+ T1 lesions and the number of new/enlarging T2 lesions[6]
- The therapeutic window for patients experiencing highly active disease, characterized by increased and more severe relapses, may be narrow. Identification of this population and treatment with highly efficacious therapy are important in managing disease and limiting future disability accumulation[7]

[a]Ublituximab was approved by the U.S. Food and Drug Administration for the treatment of relapsing forms of multiple sclerosis in December 2022.

METHODS

- ULTIMATE I and II enrolled a total of 1094 adult participants from 10 countries with a diagnosis of RMS (relapsing-remitting or secondary-progressive) with disease activity[6]
- Participants 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 orally once daily for 96 weeks[6]
- Clinical evaluations were performed every 12 weeks, and magnetic resonance imaging (MRI) assessments were performed at Weeks 24, 48, and 96[6]
- Pooled post hoc subpopulation analyses evaluated efficacy measures at Week 96 in participants with highly active disease, defined as ≥2 relapses in the year prior and ≥1 Gd+ T1 lesion at baseline[7]

RESULTS

Participant Demographics and Baseline Characteristics

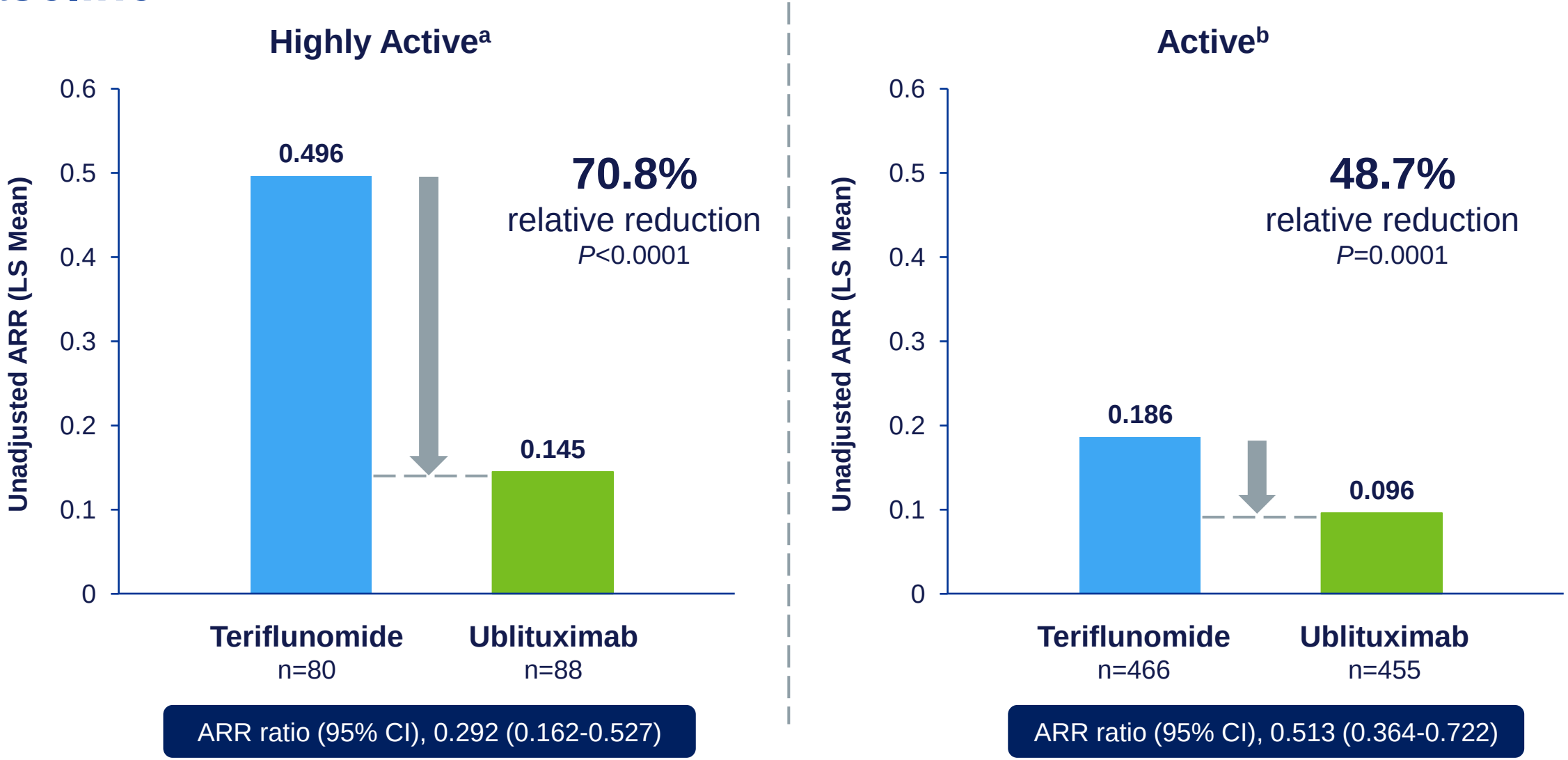
Characteristic *Mean ± standard deviation or %*	Highly Active Participants[a]		Active Participants[b]	
	Teriflunomide (n=80)	Ublituximab (n=88)	Teriflunomide (n=466)	Ublituximab (n=455)
Age, years	32.6±8.6	32.2±8.3	37.3±9.3	35.9±8.6
Gender, female, %	71.3	68.2	63.9	62.4
Time since first MS symptoms, years	6.1±4.8	5.4±4.9	7.3±6.3	7.8±6.7
Time since diagnosis, years	3.6±3.7	3.4±4.1	4.9±5.3	5.3±5.6
Time since most recent relapse, months	3.8±1.5	4.2±2.0	6.7±5.1	7.6±9.1
Number of relapses in the year prior to screening	2.2±0.5	2.2±0.4	1.2±0.6	1.1±0.5
Number of relapses in the 2 years prior to screening	2.7±1.0	2.8±1.1	1.8±1.0	1.6±0.8
Baseline EDSS score	2.9±0.9	3.1±1.2	2.9±1.2	2.8±1.3
Number of baseline Gd+ T1 lesions	5.1±5.8	5.6±7.4	1.5±4.2	1.8±5.0
Baseline T2 lesions count	73.4±43.5	72.2±41.8	60.3±38.1	63.3±39.4
Baseline T2 lesion volume, mL	19.7±19.8	17.6±15.3	14.5±15.9	14.9±14.7

[a]Defined as ≥2 relapses in the prior year and ≥1 Gd+ T1 lesion at baseline. [b]Defined as the entire population from ULTIMATE I and II, excluding those participants who met the criteria for highly active.
Modified intention-to-treat population. Pooled post hoc analysis.
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis.

RESULTS (continued)

- In the highly active population, ublituximab was associated with a 70.8% decrease in unadjusted ARR compared with teriflunomide: 0.145 versus 0.496, respectively (*P*<0.0001; **Figure 1**)

Figure 1. ARR in Participants With Highly Active Disease at Baseline[a]

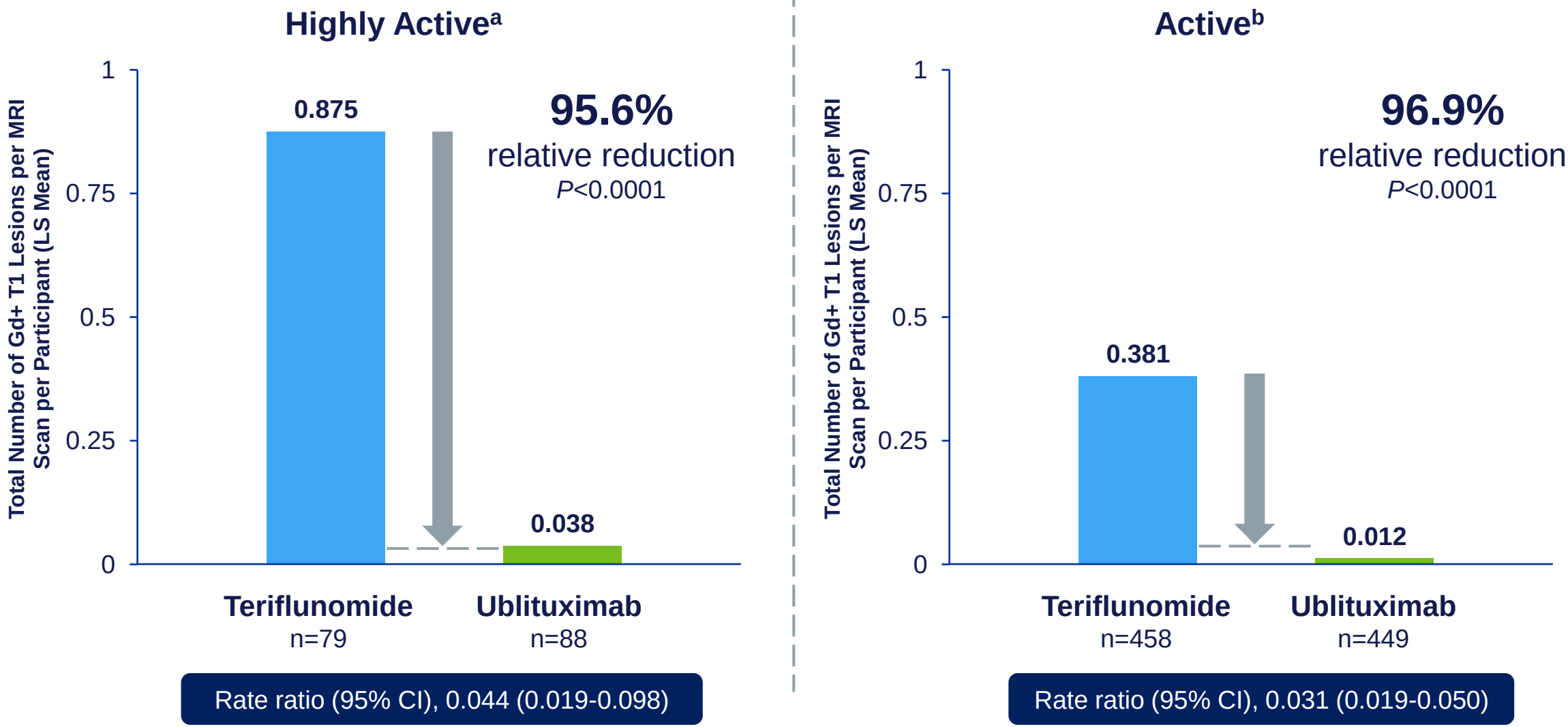


[a]Defined as ≥2 relapses in the prior year and ≥1 Gd+ T1 lesion at baseline. mITT population. Pooled post hoc analysis. [b]Defined as the entire population from ULTIMATE I and II, excluding those participants who met the criteria for highly active. Based on negative binomial model (GEE) for the relapse count per participant with logarithmic link function, treatment as covariate, and log(years of treatment) as offset within each subgroup, and an overall model adding subgroup and treatment by subgroup interaction for the interaction *P* value.
ARR, annualized relapse rate; Gd+, gadolinium-enhancing; GEE, general estimating equation; LS, least squares, mITT, modified intention-to-treat.

RESULTS (continued)

- There was a statistically significant 95.6% reduction in Gd+ T1 lesions with ublituximab versus teriflunomide in the highly active participants (total number LS means: 0.038 versus 0.875, *P*<0.0001) (**Figure 2**)

Figure 2. Gd+ T1 Lesions in Participants With Highly Active Disease at Baseline[a]

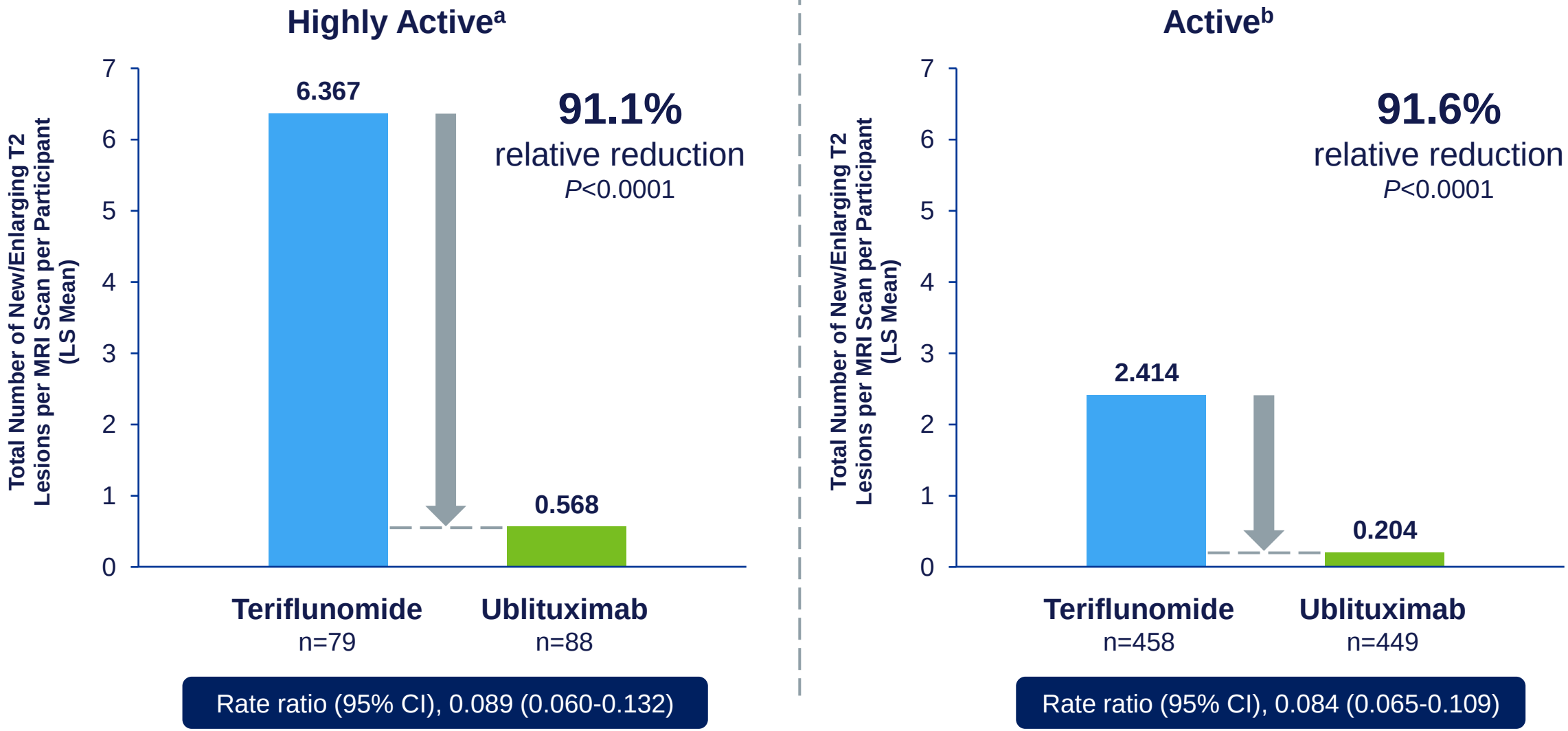


[a]Defined as ≥2 relapses in the prior year and ≥1 Gd+ T1 lesion at baseline. [b]Defined as the entire population from ULTIMATE I and II, excluding those participants who met the criteria for highly active.
mITT-MRI population. Pooled post hoc analysis. Based on negative binomial model (GEE) for the total number of Gd+ T1 lesions per MRI scan with logarithmic link function, region, treatment, baseline EDSS score, baseline number of lesions (0/≥1), and study as covariates, and an offset based on the log-transformed number of postbaseline MRI scans.
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; GEE, general estimating equation; LS, least squares; mITT, modified intention-to-treat; MRI, magnetic resonance imaging.

RESULTS (continued)

- The LS mean number of new/enlarging T2 lesions per scan was significantly lower with ublituximab compared with teriflunomide in highly active participants (0.568 versus 6.367, *P*<0.0001) (**Figure 3**)

Figure 3. New/Enlarging T2 Lesions in Participants With Highly Active Disease at Baseline[a]

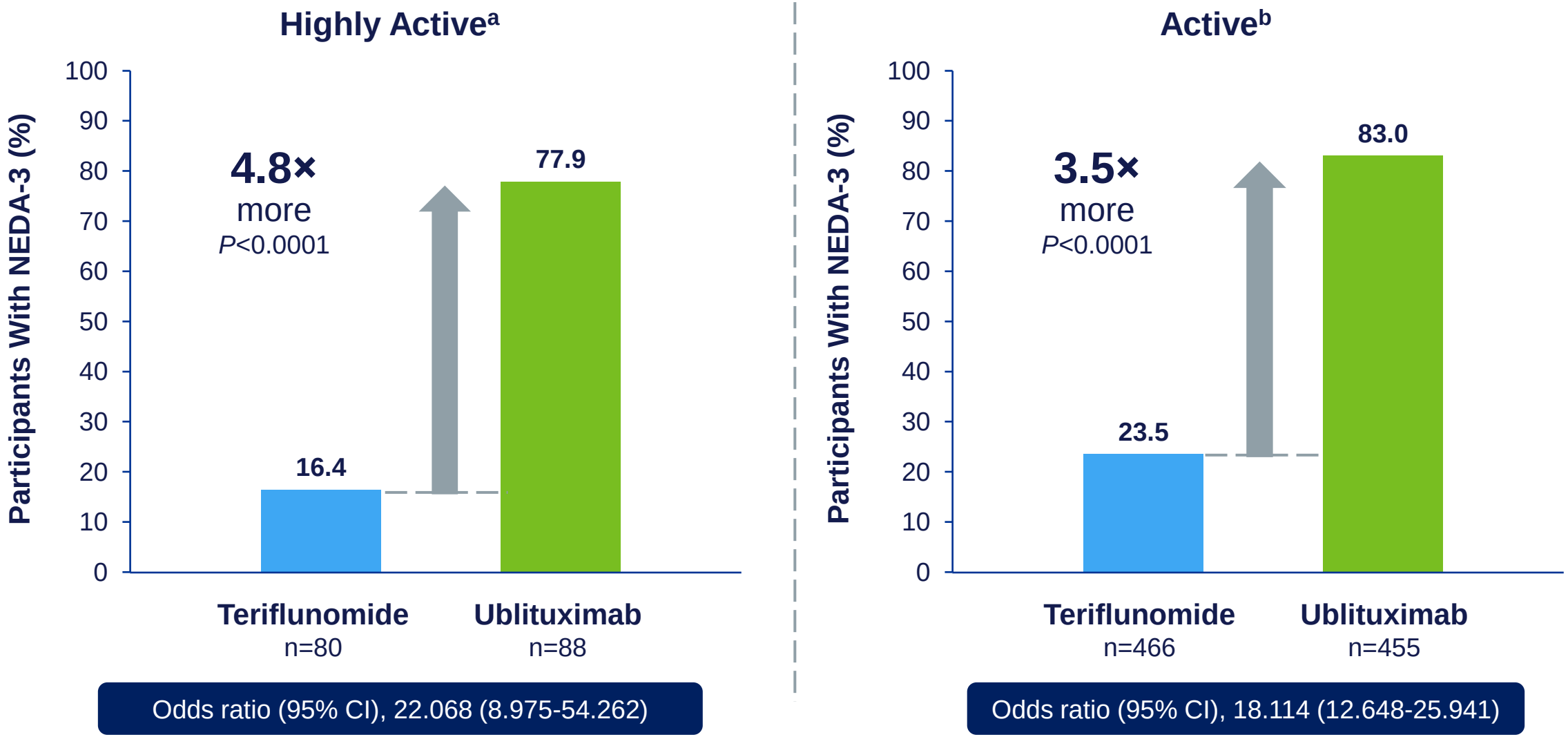


[a]Defined as ≥2 relapses in the prior year and ≥1 Gd+ T1 lesion at baseline. [b]Defined as the entire population from ULTIMATE I and II, excluding those participants who met the criteria for highly active. mITT-MRI population. Pooled post hoc analysis. Based on negative binomial model (GEE) for the total number of new and enlarging T2 lesions per MRI scan with logarithmic link function, region, treatment, baseline EDSS score, baseline number of lesions, and study as covariates, and an offset based on the log-transformed number of postbaseline MRI scans.
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; GEE, general estimating equation; LS, least squares; mITT, modified intention-to-treat; MRI, magnetic resonance imaging.

RESULTS (continued)

- NEDA rates at Weeks 24-96 (re-baselined) in the highly active subpopulation were significantly higher with ublituximab (77.9%) than with teriflunomide (16.4%), *P*<0.0001 (**Figure 4**)

Figure 4. NEDA-3 at Weeks 24-96 (Re-baselined) in Participants With Highly Active Disease at Baseline[a]



[a]Defined as ≥2 relapses in the prior year and ≥1 Gd+ T1 lesion at baseline. [b]Defined as the entire population from ULTIMATE I and II, excluding those participants who met the criteria for highly active. mITT population. NEDA-3 was defined as no confirmed relapses, no Gd+ T1 lesions, no new/enlarging T2 lesions, and no 12-week confirmed disability progression. Logistic regression model with treatment, study, region, baseline EDSS score, and log-transformed baseline MRI lesion counts (T1 nonenhancing, T2, Gd+) as covariates.
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; mITT, modified intention-to-treat; MRI, magnetic resonance imaging; NEDA, no evidence of disease activity; NEDA-3, 3-parameter NEDA.

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ACKNOWLEDGMENTS

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

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