Ublituximab Significantly Reduces Radiological Disease Activity at 12 Weeks: Post-hoc analysis of Participants with Highly Active Disease in the ULTIMATE I & II Phase 3 Studies

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OBJECTIVE

- To evaluate the impact of ublituximab on radiologic outcomes and NEDA at 12 weeks in participants with highly active disease at baseline in the phase 3 ULTIMATE I and II studies.

KEY FINDINGS

- In a subgroup of participants with highly active disease, ublituximab treatment resulted in significant improvements at 12 weeks vs. teriflunomide, including:
  - 83% reduction in Gd+T1 lesions (least squares mean per scan = 0.114 vs. 0.683) with 88% of participants free from Gd+T1 lesions (both $p<0.0001$) at this early timepoint
  - 58% reduction in new/enlarging T2 lesions (least squares mean per scan = 1.754 vs. 4.127) ($p<0.0001$)
  - 30% of participants in the ublituximab group achieved NEDA vs.10% in the teriflunomide group ($p=0.0012$)

CONCLUSION

- Ublituximab significantly reduced key MRI measures of disease activity at 12 weeks in a subgroup of participants with highly active disease at baseline, with 30% of people achieving NEDA. These results could be beneficial in managing disease and limiting future accumulation of disability in this population

BACKGROUND

- Ublituximab is a novel monoclonal antibody targeting CD20 and is glycoengineered for enhanced antibody-dependent cellular cytolysis.[1-5]

- ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) are identical, Phase 3, randomized, multicenter, double-blind, active-control studies that evaluated the efficacy and safety of ublituximab versus teriflunomide in participants with relapsing multiple sclerosis (RMS).[6]

- In the ULTIMATE I and II studies, ublituximab significantly reduced annualized relapse rate and radiologic disease activity compared to teriflunomide.[6]

- High efficacy therapies, including anti-CD20 mAbs, that impact disease activity early in people with highly active disease could play a crucial role in limiting neurologic damage and slowing disease progression.[7]

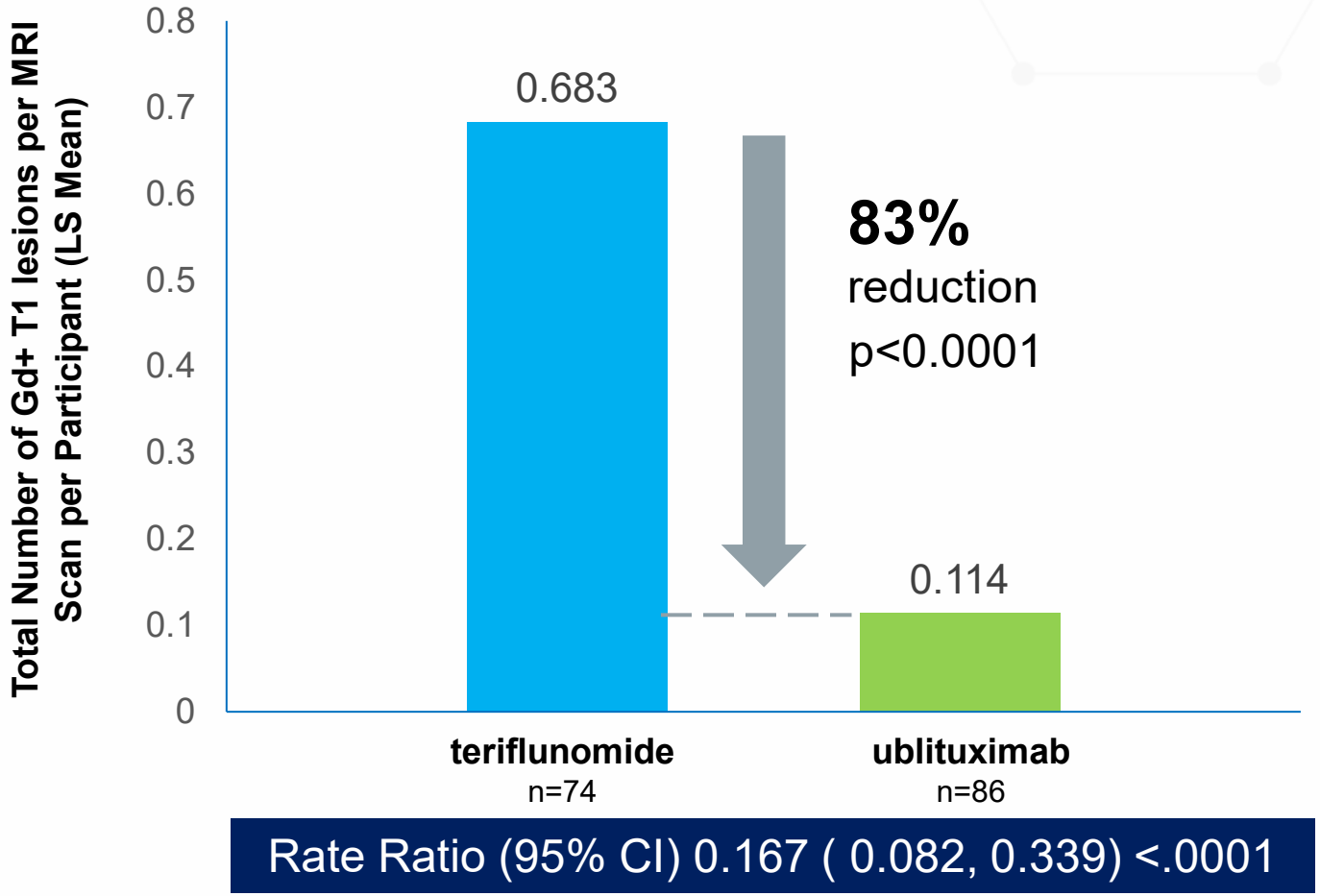
METHODS

- The ULTIMATE I (N=549) and II (N=545) studies evaluated ublituximab 450mg IV infusion every 24 weeks vs. 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 specific timepoints throughout the study, including at week 12.[6]
- Pooled post hoc analyses at week 12 were performed to evaluate the number of Gd+ T1 lesion counts, n/e T2 lesion counts and NEDA in a subgroup of people with highly active disease at baseline, defined as ≥2 relapses in the year prior and ≥1 Gd+ T1 lesion at baseline.[7]

RESULTS

- Ublituximab treatment resulted in an 83% reduction in Gd+ T1 lesions compared with teriflunomide at week 12 (least squares [LS] mean (95% CI) = 0.114 vs 0.683 for ublituximab vs teriflunomide, respectively [p<0.0001]).

Figure 1. Number of Gd+ T1 lesions in participants with highly active disease at week 12



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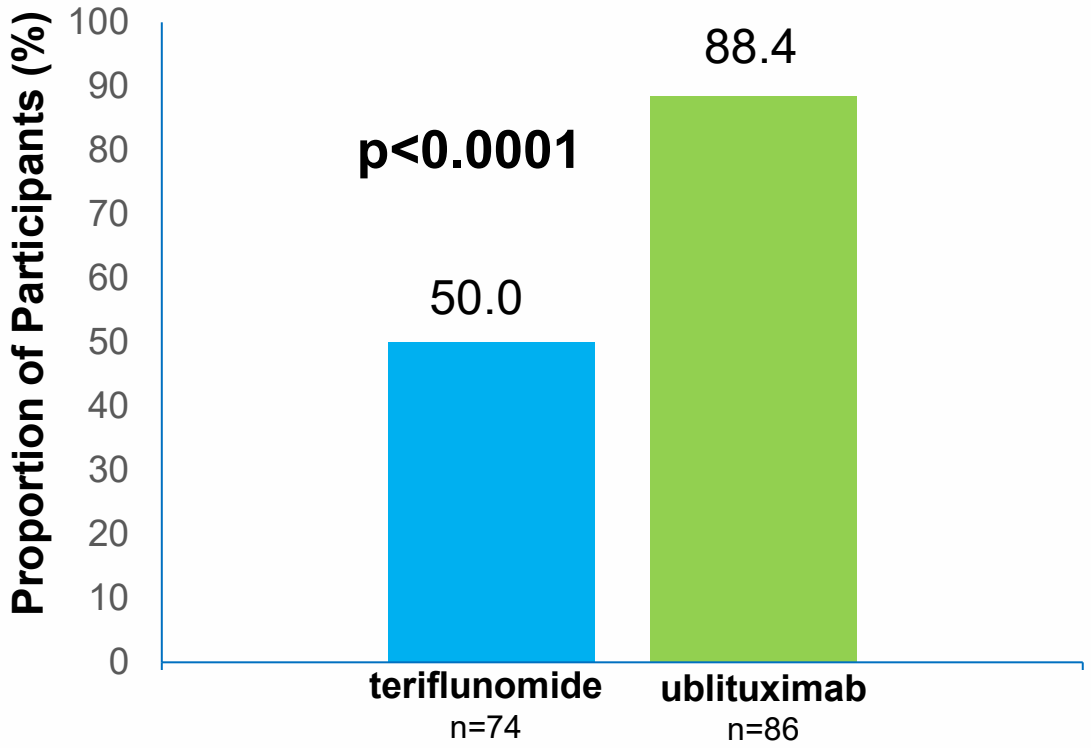
Pooled post hoc analysis. Modified intent to treat MRI population. EMA definition: highly active disease (HAD) was defined as >=2 Relapses in prior year and >=1 Gd+ Lesion at baseline.*GEE (Generalized Estimating Equation) model with covariates treatment, region, baseline EDSS strata, baseline number of lesions (0/>=1). P value based on Fisher exact test.

RESULTS (continued)

- 88% of participants were free from Gd^{+} lesions in the ublituximab treated group compared to 50% of those in the teriflunomide group ($p<0.0001$).

Figure 2. Proportion of participants with highly active disease free from Gd+ T1 lesions at week 12



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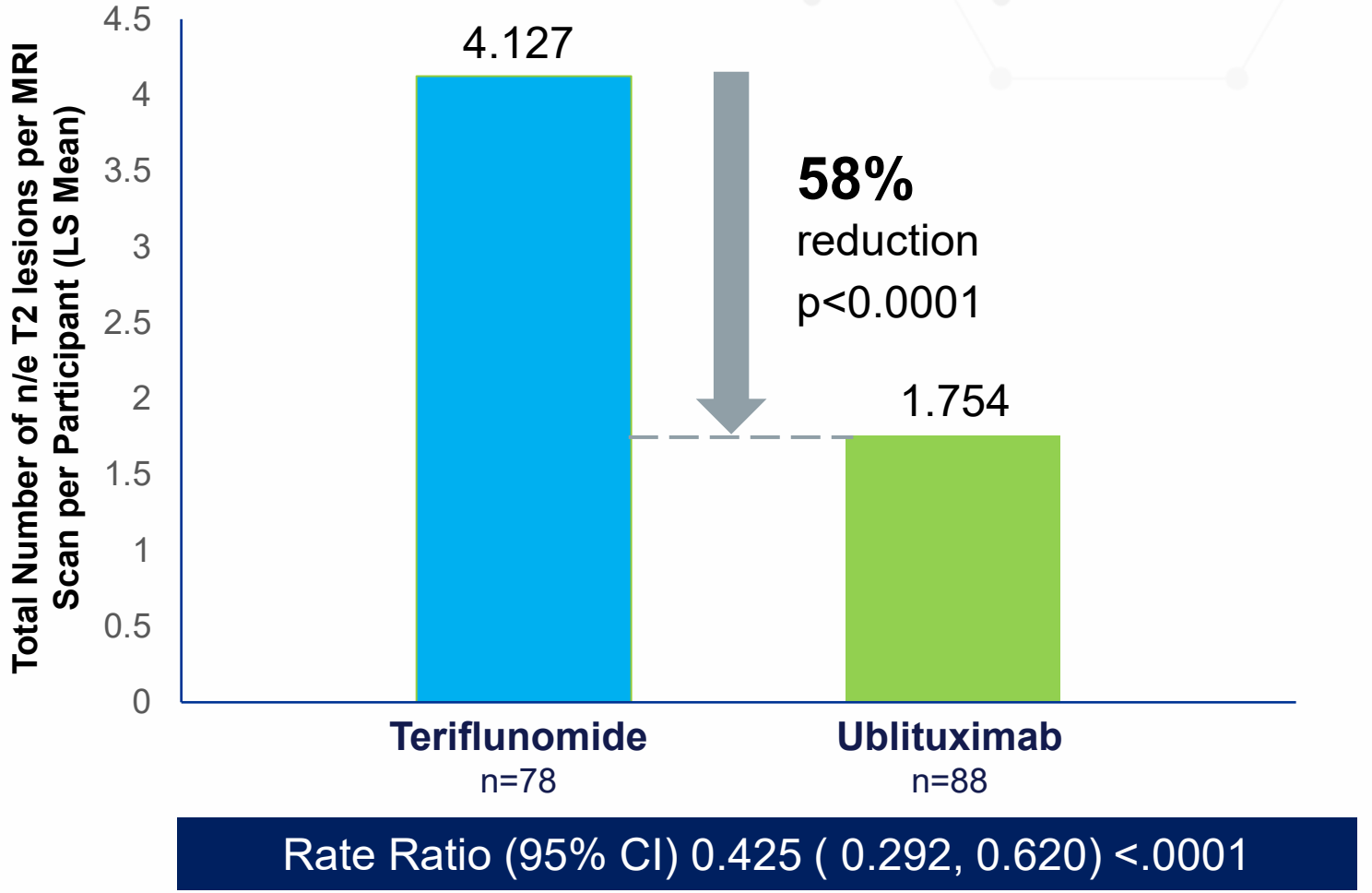
Pooled post hoc analysis. Modified intent-to-treat MRI population. EMA definition: highly active disease (HAD) was defined as >=2 Relapses in prior year and >=1 Gd+ Lesion at baseline. Note: p-value was based on Fisher exact test.

RESULTS (continued)

- The number of n/e T2 lesions at 12 weeks was also significantly reduced in this population (58% reduction; LS mean = 1.754 vs 4.127 for ublituximab and teriflunomide, $p<0.0001$, respectively).

Figure 3. New/Enlarging T2 lesions in participants with highly active disease at week 12

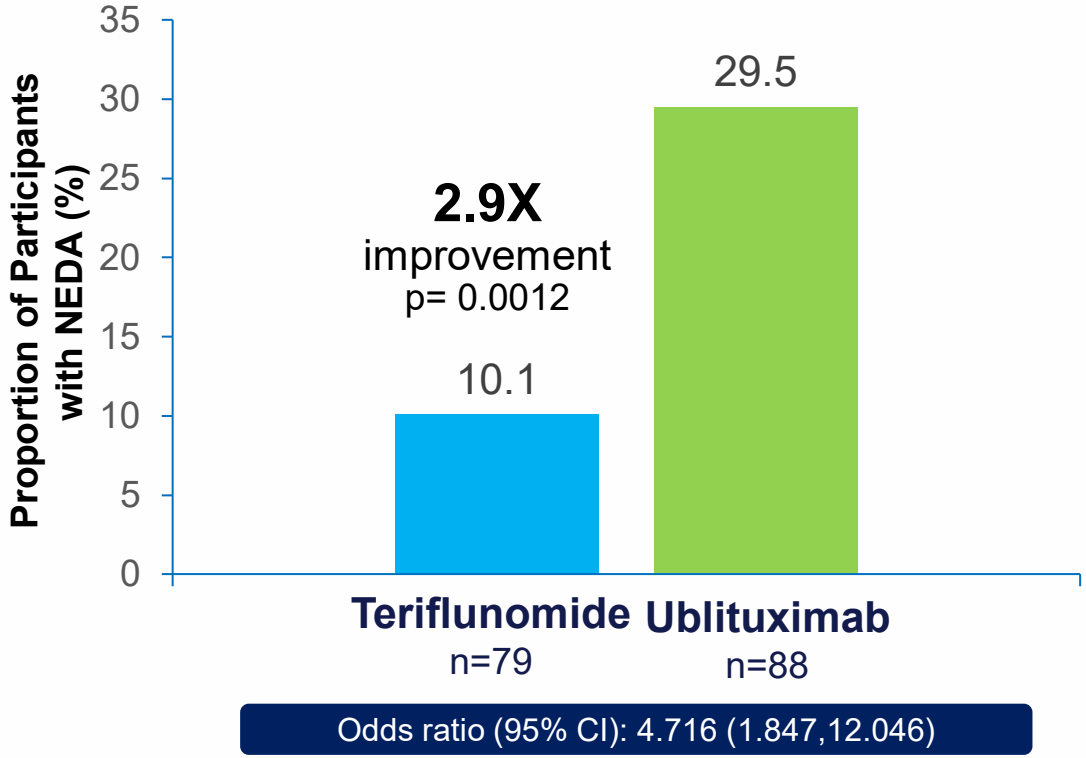


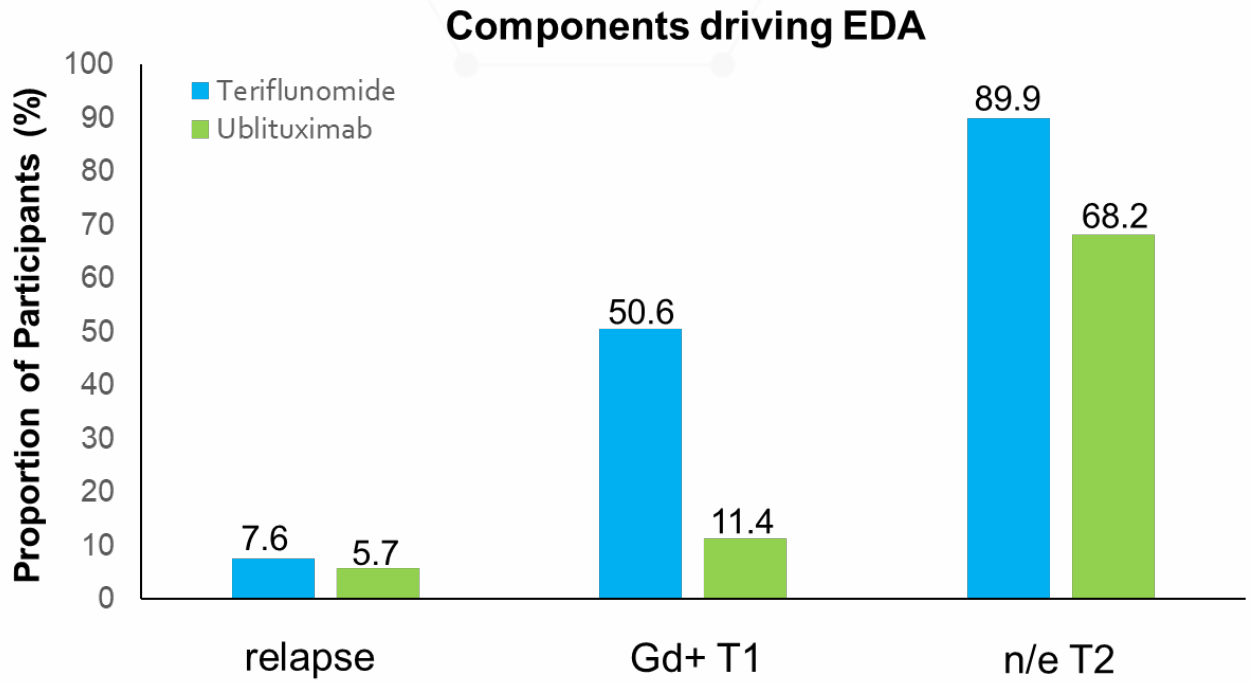
*GEE (Generalized Estimating Equation model with logarithmic link function, covariates treatment, baseline EDSS, region, baseline number of lesions, and an offset based on the log-transformed number of MRI scans for specific visit and study.) Pooled post hoc analysis. Modified intent-to-treat MRI population.

RESULTS (continued)

- A significantly higher proportion of ublituximab treated participants with highly active disease at baseline achieved NEDA compared to teriflunomide at week 12 (30% vs. 10%; *P*=0.0012). Disease activity in participants not achieving NEDA was largely driven by T2 lesions in both groups, with a significantly higher number of participants in the ublituximab treated group demonstrating a reduction in Gd+T1 lesions compared to the teriflunomide treated participants.

Figure 4. Proportion of patients with highly active disease achieving NEDA at week 12





* NEDA rate is the proportion of subject with no evidence of disease activity excluding patients who discontinued treatment early due to reasons other than death and lack of efficacy during the analysis time frame.

** Logistic regression model with baseline adjustments, treatment, study (for pooled analysis), region, baseline EDSS strata, plus log transformed baseline MRI lesion counts (T1unenhancing,T2, Gad enhancing).

Pooled post hoc analysis. Modified intent to treat MRI population. EMA definition: highly active disease (HAD) was defined as >=2 Relapses in prior year and >=1 Gd+ Lesion at baseline.

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