

Ublituximab Reduces Thalamic Volume Loss and New Lesion Formation in Participants of the ULTIMATE I & II Phase 3 Studies

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OBJECTIVE

- To evaluate the impact of ublituximab on thalamic volume and new lesion formation in ULTIMATE I and II during and after Year 1.

KEY FINDINGS

- In the mITT MRI population, significant improvements with ublituximab versus teriflunomide were observed at Week 96, as detailed below:
 - Ublituximab treatment significantly reduced thalamic volume loss relative to teriflunomide by 22% over 2 years.
 - Ublituximab treatment significantly reduced total number of new and enlarging T2 hyperintense lesions relative to teriflunomide by 75.8%, 99.2%, 99.7% from 0-24, 24-48, and 48-96 weeks, respectively.
 - Ublituximab treatment significantly reduced the number of new non-enhancing T1 lesions relative to teriflunomide by 40.1%, 98.1%, and 99.7% from 0-24, 24-48, and 48-96 weeks, respectively.
 - Reduction in non-enhancing T1 lesion volume was more pronounced in Year 2 of Ublituximab treatment (85.5%) than in Year 1 (63%), compared to Teriflunomide.

CONCLUSIONS

- Ublituximab reduced thalamic volume loss and T1/T2 lesions compared with teriflunomide. New T1 and T2 lesion formation was almost completely suppressed after 6 months and throughout Year 2 of Ublituximab treatment.

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BACKGROUND

- Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20 and is glycoengineered for enhanced antibody-dependent cellular cytotoxicity (ADCC)¹
- Ublituximab has greater ADCC potential and increased Fcγ-receptor binding affinity relative to all other currently approved anti-CD20 therapies used in multiple sclerosis^{2,3}
- Ublituximab is administered in lower doses and with shorter infusion times compared with other currently infused anti-CD20 therapies,¹ (450 mg in 1-hour infusions after the first infusion of 150 mg over 4 hours)⁴
- ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) were 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)⁵
- 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 lesions⁴.

RESULTS

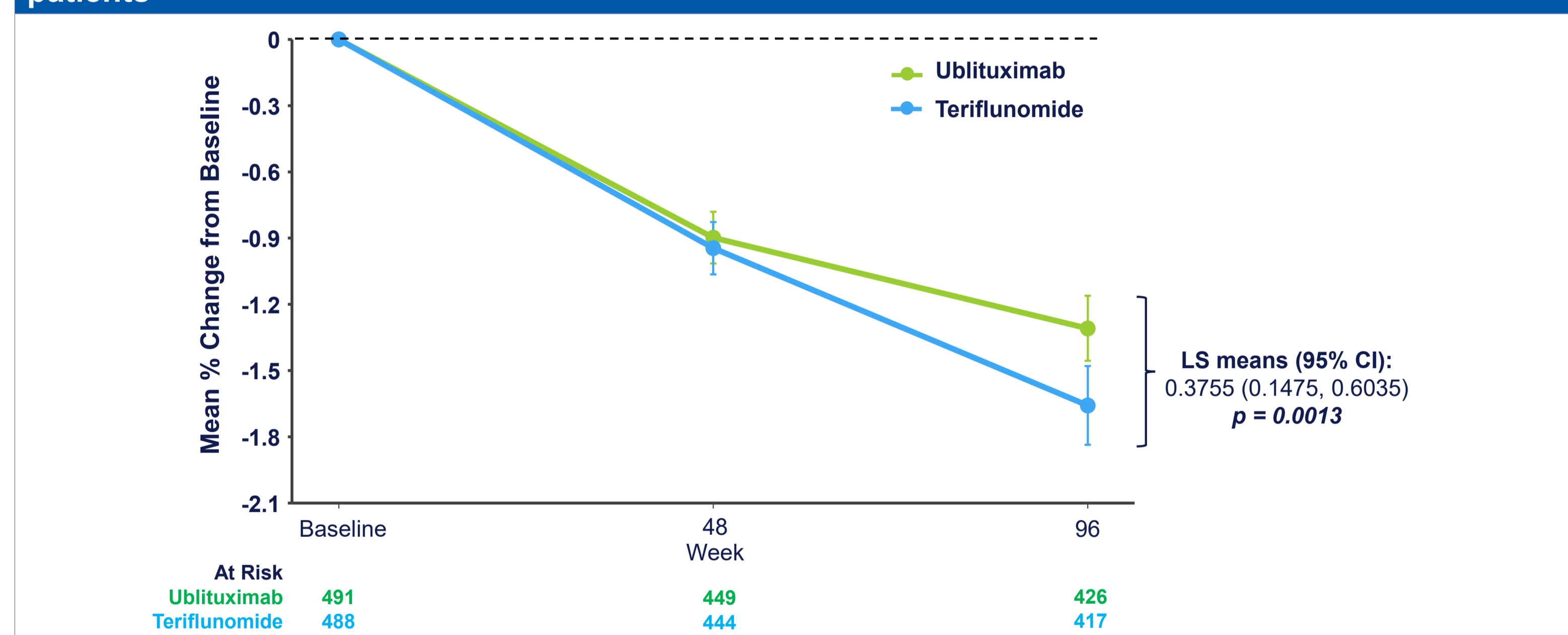
- Baseline characteristics for the modified Intention to treat MRI populations are shown in Table 1

Table 1. Participant Demographics and Baseline Characteristics in the modified ITT MRI population

Characteristic	Teriflunomide N = 537	Ublituximab N = 537
Age (years)	36.5±9.30	35.4±8.65
Gender, Female, n (%)	352 (65.5%)	338 (62.9)
Race, n (%)		
White	525 (97.8%)	527 (98.1%)
Black	9 (1.7%)	8 (1.5%)
Other	3 (0.6%)	2 (0.4%)
Time since MS diagnosis (years)	4.7±4.9	4.9±5.4
Number of relapses in the previous 12 months	1.3±0.7	1.3±0.6
Number of relapses in the previous 24 months	1.9±1.0	1.8±0.9
EDSS Score at baseline	2.9±1.2	2.9±1.3
Number of baseline Gadolinium (Gd+) lesions, n (%)		
0	290 (54.0%)	281 (52.3)
≥ 1	247 (46.0%)	256 (47.7)
Number of T2 Lesions at baseline	62.1±39.29	64.6±39.74
Baseline T2 lesion volume (cm ³)	15.29±14.78	15.10±16.54
Baseline brain volume (cm ³)	1669.36±104.90	1666.97±106.16
Baseline Thalamic volume (cm ³)	15.65±1.99	15.63±2.05

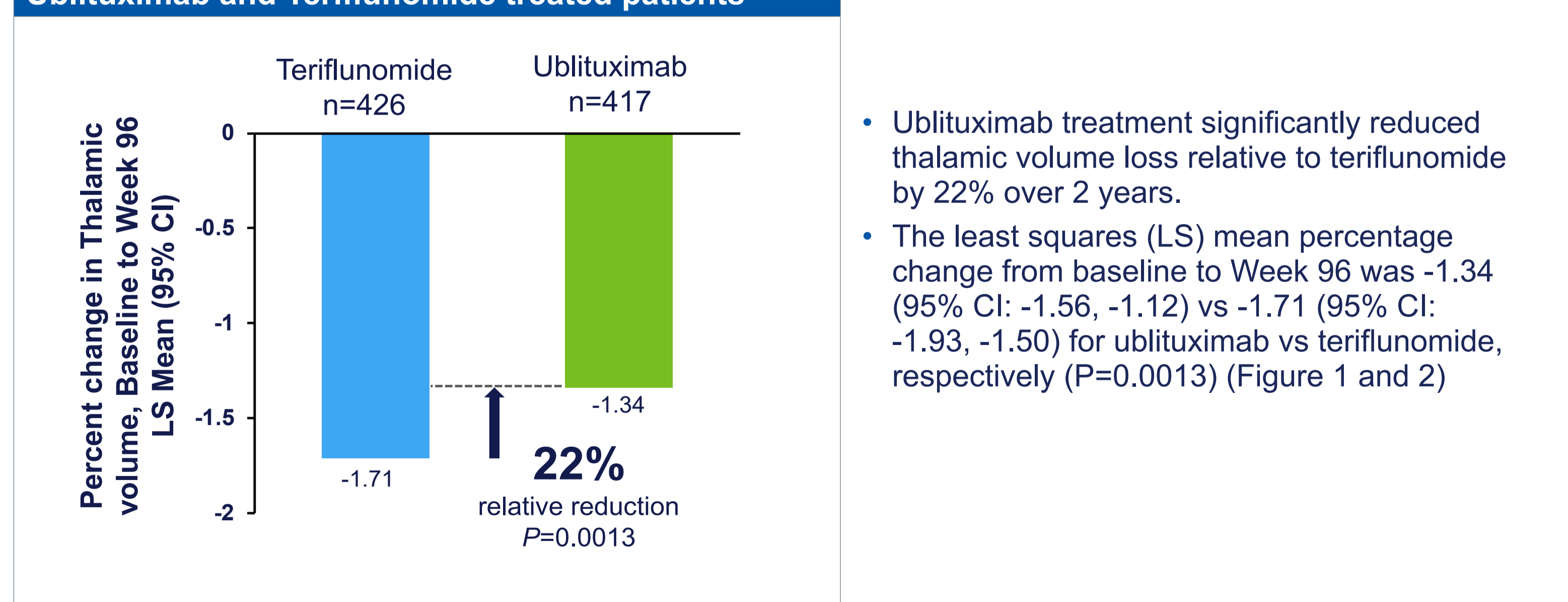
The modified Intention-to-Treat MRI (mITT-MRI) population consists of all subjects in the ITT population who received at least one dose of study medication, had at least one baseline and post-baseline efficacy assessment, and had at least one baseline and post-baseline MRI efficacy assessment. EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis.

Figure 1. Thalamic volume loss at weeks 48 and 96 in Ublituximab and Teriflunomide treated patients



Post-hoc analysis. CI = Confidence Interval, LS Means = Least Square Means; MMR (Mixed Model Repeated Measures) of the percentage change from baseline at week 48 and 96. The model includes treatment, region, baseline EDSS strata, visit, treatment-by-visit interaction, and baseline value as covariates and uses an unstructured covariance matrix. p-value based on Least Square Means at week 96.

Figure 2. Thalamic volume loss at week 96 in Ublituximab and Teriflunomide treated patients



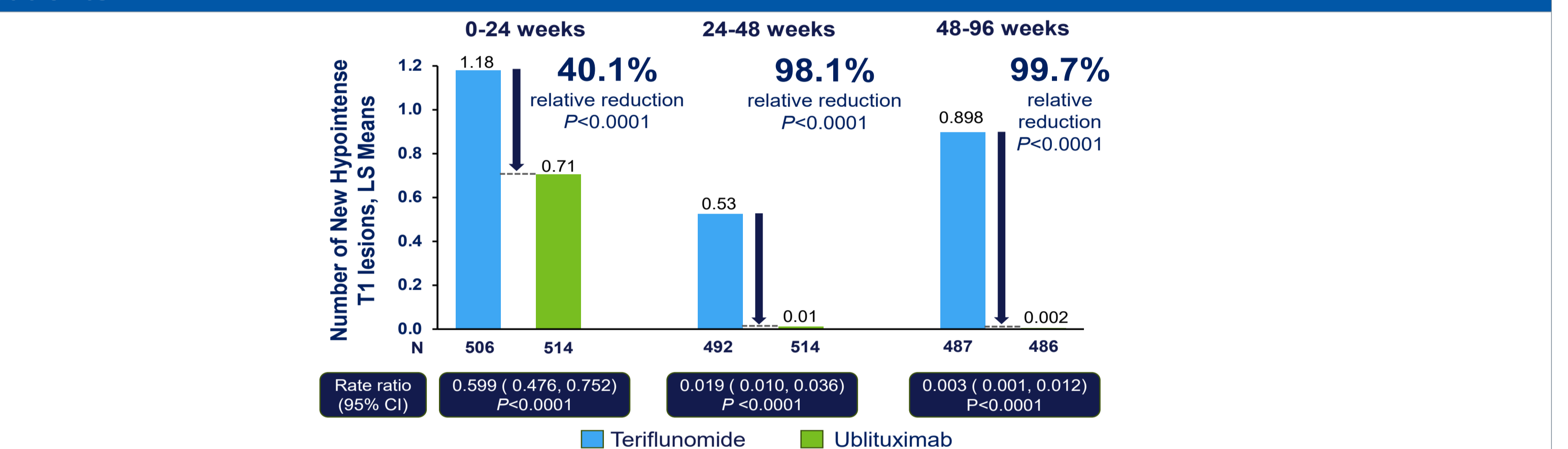
- Ublituximab treatment significantly reduced the number of new non-enhancing T1 lesions relative to teriflunomide by 40.1%, 98.1%, and 99.7% from baseline-24, 24-48, and 48-96 weeks respectively (Figure 3).
- LS mean counts of new non-enhancing T1 lesions from baseline to Week 24 for ublituximab was 0.71 (95% CI: 0.54, 0.92) vs 1.18 (95% CI: 0.90, 1.54) for teriflunomide (P<0.0001) (Figure 3)
- LS mean counts of new non-enhancing T1 lesions from Week 24 to Week 48 for ublituximab was 0.01 (95% CI: 0.01, 0.02) vs 0.53 (95% CI: 0.34, 0.82) for teriflunomide (P<0.0001) (Figure 3)
- LS mean counts of new non-enhancing T1 lesions from Week 48 to Week 96 for ublituximab was 0.002 (95% CI: 0.001, 0.011) vs 0.898 (95% CI: 0.574, 1.406) for teriflunomide (P<0.0001) (Figure 3)

DISCLOSURES DA has received personal compensation for serving as a consultant for Alexion, Biogen, Celgene, Eli Lilly, EMD Serono, Frequency Therapeutics, Genentech, Merck, Novartis, Roche, Sanofi, and Shionogi, and holds an equity interest in NeuroRx. LS has received compensation for consulting from TG Therapeutics. HPH has received honoraria for serving on steering or data monitoring committees or speaker fees from Bayer, Biogen, Celgene, BMS, Cellego, Merck, Novartis, TG Therapeutics, and Roche with approval by the Rector of Heinrich-Heine-Universität. KS has received honoraria for speaking, consulting, and serving on advisory boards from Merck, Novartis, Roche, Biogen, Celgene, BMS, and TG Therapeutics. LL, DC, KB, KM are employed by TG Therapeutics. BACC has received personal compensation for consulting from Alexion, Atara, Autobahn, Avotres, Biogen, EMD Serono, Gossamer Bio, Horizon, Neuron23, Novartis, Sanofi, TG Therapeutics, and Therni, and research support from Genentech.

METHODS

- The active-controlled ULTIMATE I (N=549) and II (N=545) studies evaluated ublituximab 450 mg intravenous infusion every 24 weeks (following Day 1 infusion of 150 mg and Day 15 infusion of 450 mg) vs teriflunomide 14 mg orally once daily for 96 weeks⁵
- In the pooled modified intention-to-treat population (N=537 in each group), the percentage thalamic volume change was measured from baseline to Week 96 and in yearly epochs using paired Jacobian integration.
- Post hoc analyses of changes over 0-24, 24-48, and 48-96-week epochs were performed for number of new T1 non-enhancing lesions and total number of new and enlarging T2 hyperintense lesions. In addition, the volume of hypointense T1 lesions was assessed over 2 years and at yearly epochs.

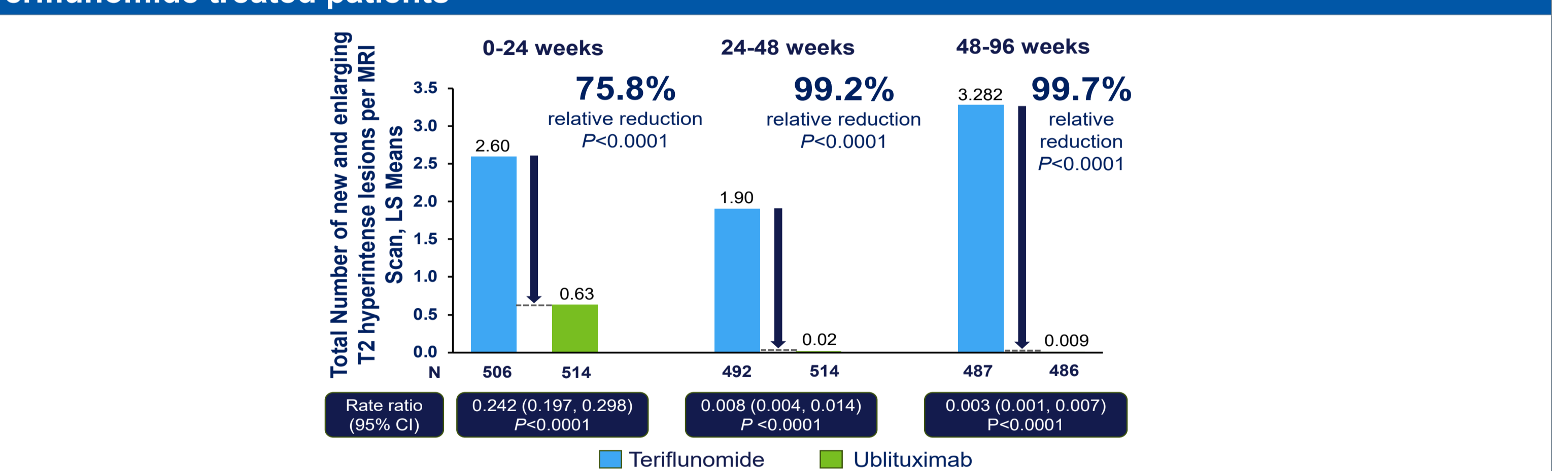
Figure 3. Number of new T1 non-enhancing lesions in Ublituximab and Teriflunomide treated patients



GEE (Generalized Estimating Equation) model with logarithmic link function, covariates region, risk treatment, baseline EDSS strata, baseline T1 non-enhancing lesion count, and an offset based on the log-transformed number of post-baseline MRI scans during analysis epoch. Rate ratio derived as Ublituximab/Teriflunomide.

- Ublituximab treatment significantly reduced total number of new and enlarging T2 hyperintense lesions relative to teriflunomide by 75.8%, 99.2%, 99.7% from 0-24, 24-48, and 48-96 weeks respectively (Figure 4)
- LS mean of total number of new and enlarging T2 hyperintense lesions from baseline to Week 24 for ublituximab was 0.63 (95% CI: 0.50, 0.80) vs 2.60 (95% CI: 2.07, 3.27) for teriflunomide (P<0.0001) (Figure 4)
- LS mean of total number of new and enlarging T2 hyperintense lesions from Week 24 to Week 48 for ublituximab was 0.02 (95% CI: 0.01, 0.03) vs 1.90 (95% CI: 1.37, 2.65) for teriflunomide (P<0.0001) (Figure 4)
- LS mean of total number of new and enlarging T2 hyperintense lesions from Week 48 to Week 96 for ublituximab was 0.009 (95% CI: 0.004, 0.022) vs 3.282 (95% CI: 2.439, 4.418) for teriflunomide (P<0.0001) (Figure 4)

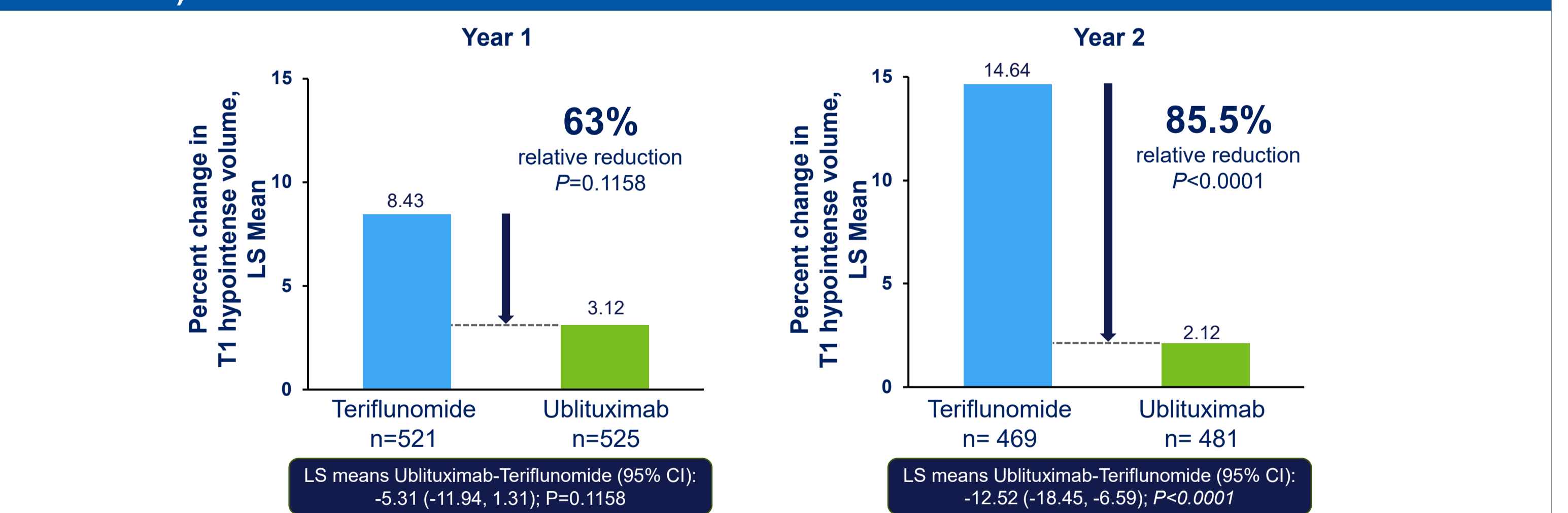
Figure 4. Total Number of new and enlarging T2 hyperintense lesions in Ublituximab and Teriflunomide treated patients



GEE (Generalized Estimating Equation) model with logarithmic link function, covariates treatment, baseline number of lesions, and an offset based on the log-transformed number of MRI scans for specific visit and study. Rate Ratio derived as Ublituximab/Teriflunomide.

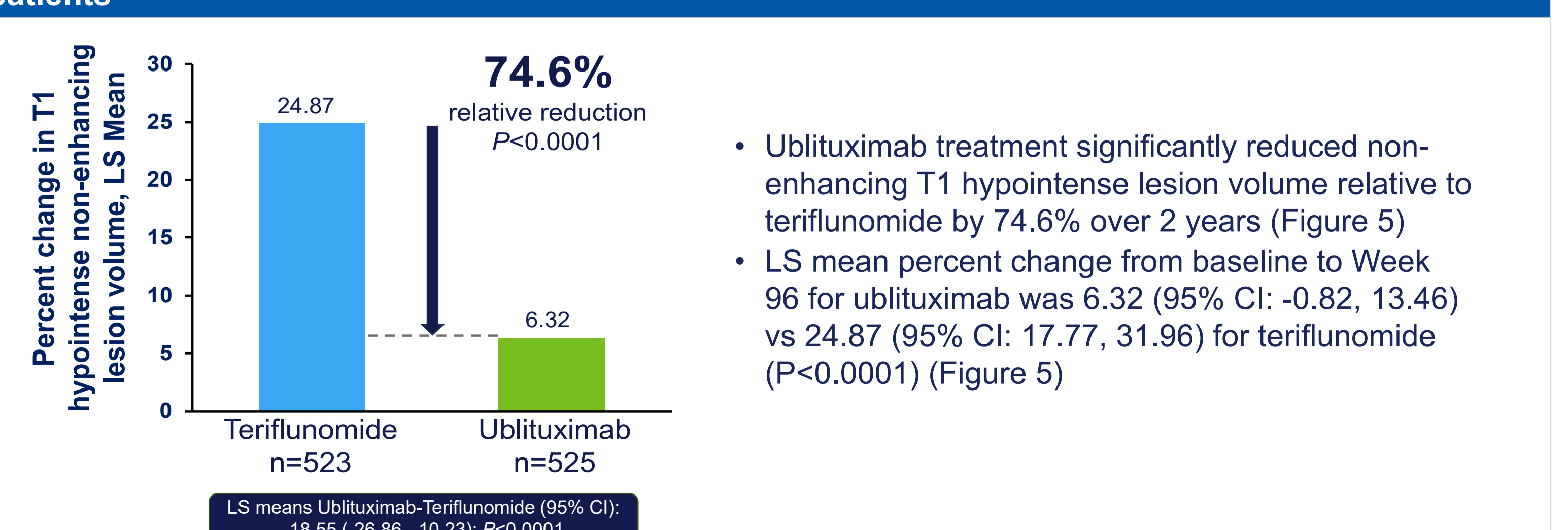
- Reduction in T1 hypointense lesion volume was more pronounced in Year 2 of ublituximab treatment (85.5%) than in Year 1 (63%), compared to teriflunomide (Figure 5)
- LS mean percent change in Year 1 for ublituximab was 3.12 (95% CI: -3.05, 9.29) vs 8.43 (95% CI: 2.22, 14.64) for teriflunomide (P=0.1158) (Figure 5)
- LS mean percent change in Year 2 was 2.12 (95% CI: -4.59, 8.83) vs 14.64 (95% CI: 8.06, 21.22) for teriflunomide (P<0.0001) (Figure 5)

Figure 5. Volume of hypointense T1 lesions in Ublituximab and Teriflunomide treated patients (Year 1 and Year 2)



MMRM (Mixed Model Repeated Measures) of the percentage change from baseline to week 96. The model includes treatment, region, baseline EDSS strata, studies, baseline value of Hypointense T1 volume, visit, interaction of treatment and visit as covariates.

Figure 6. Volume of hypointense T1 lesions at week 96 in Ublituximab and Teriflunomide treated patients



MMRM (Mixed Model Repeated Measures) of the percentage change from baseline to week 96. The model includes treatment, region, baseline EDSS strata, studies, baseline value of Hypointense T1 volume, visit, interaction of treatment and visit as covariates.