Reduction in T1 Hypointense Lesions With Ublituximab vs Teriflunomide in the Phase 3 ULTIMATE I and II Studies in Relapsing Multiple Sclerosis

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OBJECTIVE

- To evaluate the impact of ublituximab on T1 hypointense lesions in the Phase 3 ULTIMATE I and II studies

KEY FINDINGS

- In pooled post hoc analyses:
  - Mean change from baseline at 96 weeks (across all postbaseline timepoints) in T1 hypointense lesion volume was 0.0101 for ublituximab and 0.0491 for teriflunomide, a difference of -0.0390 (95% confidence interval, -0.0585 to -0.0195; *P*<0.0001)
  - Mean number±standard deviation of new T1 hypointense lesions at 96 weeks was significantly reduced with ublituximab vs teriflunomide (1.5±3.55 vs 5.4±10.67, respectively; *P*<0.0001)

CONCLUSIONS

- In pooled post hoc analyses, significant reductions in both the volume and number of new T1 hypointense lesions were seen with ublituximab vs teriflunomide at 96 weeks
- These radiological findings support the clinical benefits of ublituximab in patients with relapsing multiple sclerosis (RMS)

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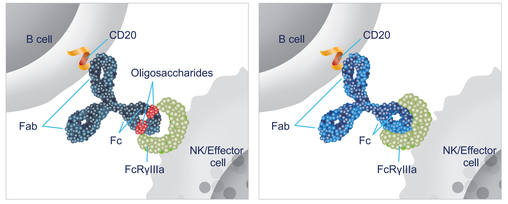
BACKGROUND

- Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20 and is glycoengineered for enhanced antibody-dependent cellular cytotoxicity **(Figure 1)**[1,2]

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.[3,4] **(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.[4-6]

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

- Ublituximab is administered in lower doses and with shorter infusion times compared with other currently infused anti-CD20 therapies[7]
- 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[7]
- ULTIMATE I and II studies met their primary endpoint, demonstrating a statistically significant reduction in annualized relapse rate for ublituximab compared with teriflunomide (0.076 vs 0.188; *P*<0.0001 [ULTIMATE I]; 0.091 vs 0.178; *P*=0.0022 [ULTIMATE II])[7]
- Ublituximab also provided significant improvements in the number of gadolinium-enhancing T1 lesions and the number of new/enlarging T2 lesions, and improvements in the proportion of patients with no evidence of disease activity vs teriflunomide at 96 weeks[7]
- T1 black holes are hypointense lesions commonly seen on T1-weighted images in patients with multiple sclerosis and are indicative of chronic stage disease associated with white matter destruction, axonal loss, and irreversible clinical outcome[8]

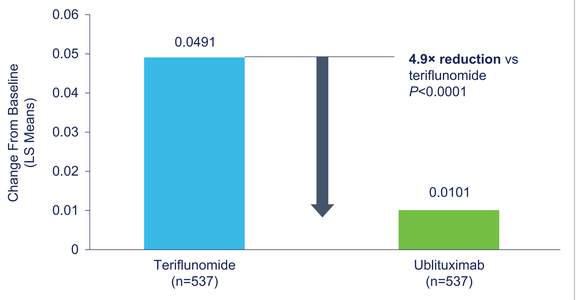
METHODS

- ULTIMATE I and II studies enrolled a total of 1094 adult patients from 10 countries with a diagnosis of RMS (relapsing-remitting or secondary-progressive) with disease activity[7]
- 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[7]
- Clinical evaluations were performed every 12 weeks, and magnetic resonance imaging (MRI) assessments were performed at Weeks 24, 48, and 96
- Volume of T1 hypointense lesions was a tertiary endpoint in the individual studies. Pooled analyses of T1 hypointense lesions were performed post hoc for patients who received ≥1 dose of study drug and had baseline and postbaseline MRI efficacy assessments
- T1 hypointense lesion volume (least squares [LS] means) was assessed using mixed model repeated measures of the change in cubic root transformed volume from baseline at scheduled visits up to 96 weeks. The model includes treatment, study, region, baseline Expanded Disability Status Scale (EDSS) strata, visit, treatment-by-visit interaction, and baseline volume (cube root transformed) as covariates and uses an unstructured covariance matrix
- T1 hypointense lesion counts (LS means) were evaluated using a generalized estimating equation model with logarithmic link function, covariates (region, treatment, baseline EDSS strata, baseline T1 nonenhancing lesion count), and an offset based on the log-transformed number of postbaseline MRI scans

RESULTS

- Baseline volume of T1 hypointense lesions was 3.28 mL and 3.34 mL in the pooled ublituximab and teriflunomide groups, respectively
- Ublituximab provided a statistically significant reduction in T1 hypointense lesion volume at Week 96 (across all postbaseline timepoints) vs teriflunomide in the pooled analysis **(Figure 2)**

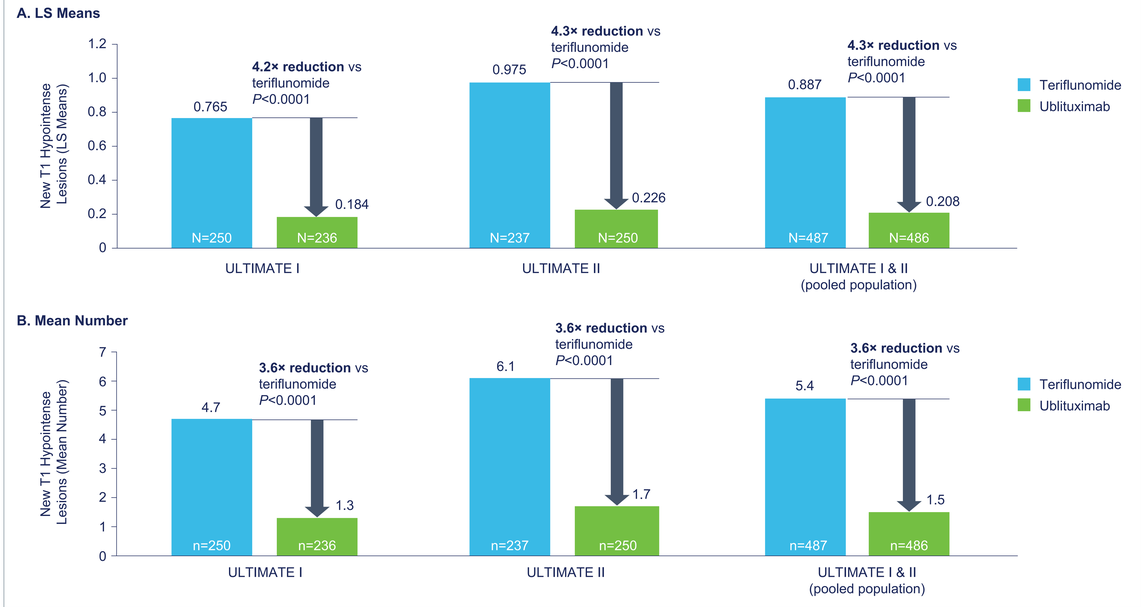
Figure 2. ULTIMATE I and II: LS Means Change in T1 Hypointense Lesion Volume From Week 0 to Week 96



LS means of the change in cube root transformed volume across all postbaseline timepoints. Pooled post hoc analysis.
CI, confidence interval; LS, least squares.

- Mean number of T1 hypointense lesions at baseline was:
  - ULTIMATE I: ublituximab, 35.9; teriflunomide, 33.3
  - ULTIMATE II: ublituximab, 38.6; teriflunomide, 38.6
  - Pooled ULTIMATE I and II: ublituximab, 37.3; teriflunomide, 35.9
- There was a significant reduction in new T1 hypointense lesions with ublituximab vs teriflunomide in the individual studies and in the pooled analysis **(Figure 3)**

Figure 3. New T1 Hypointense Lesions From Baseline to Week 96: (A) LS Means and (B) Mean Number[a]



The LS means estimate the number of new T1 hypointense lesions per scan adjusted by other covariates. The mean number is the observed number of new T1 hypointense lesions up to Week 96 (cumulative) without adjustment.
[a]Only including patients with Week 96 visit. LS, least squares.