Onset and Maintenance of No Evidence of Disease Activity With Ublituximab: Analysis of the Phase 3 ULTIMATE I and II Studies in Participants With Relapsing Multiple Sclerosis

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OBJECTIVE

- To evaluate the timing of no evidence of disease activity (NEDA) onset and proportion of participants maintaining NEDA with ublituximab in pooled post hoc analyses of ULTIMATE I and II

KEY FINDINGS

- 53.4% of ublituximab-treated participants achieved NEDA during Weeks 0-24
- 82.1% of ublituximab-treated participants had NEDA during Weeks 24-96
  - 45.2% of participants achieved NEDA during Weeks 0-24 and maintained NEDA during Weeks 24-96
  - 36.9% of participants had evidence of disease activity (EDA) during Weeks 0-24 but NEDA during Weeks 24-96
- 88.2% of ublituximab-treated participants had NEDA during Weeks 48-96
  - 83.5% of participants achieved NEDA during Weeks 24-48 and maintained NEDA during Weeks 48-96
  - An additional 4.8% of participants had EDA during Weeks 24-48 but achieved NEDA during Weeks 48-96

CONCLUSIONS

- Ublituximab treatment in the Phase 3 ULTIMATE studies resulted in a high proportion of participants achieving and maintaining NEDA
- More than half of participants (53.4%) achieved NEDA by Week 24, which increased to >82% from Week 24 to Week 96 and to >88% from Week 48 to Week 96
- The majority of participants maintained NEDA once achieved

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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 cytolysis (ADCC)[1,2,a]
- In vitro studies demonstrate that ublituximab has 25-30× higher ADCC relative to all other currently approved anti-CD20 therapies used in multiple sclerosis (MS)[3]
- Ublituximab is administered in lower doses and with shorter infusion times compared with other currently infused anti-CD20 therapies[4]
- ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) were identical, Phase 3, randomized, multicenter, double-blind, active-control studies that evaluated the efficacy and safety of ublituximab vs teriflunomide in participants with relapsing multiple sclerosis (RMS)[4]
- 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[4]
- In pooled post hoc analyses, 3-parameter NEDA (NEDA-3) rates for ublituximab vs teriflunomide were 44.6% vs 12.4% at 0-96 weeks, respectively, and 82.1% vs 22.5% at 24-96 weeks (re-baselined; $P<0.0001$ for both)
  - During Weeks 24-96 (re-baselined), 17.9% of ublituximab-treated participants had EDA, and relapse was the most common component (11.4% vs 22.9% with teriflunomide)
  - In contrast, 77.5% of teriflunomide-treated participants had EDA, and the most common component was new/enlarging T2 lesions (71.6% vs 3.1% with ublituximab)[5]

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

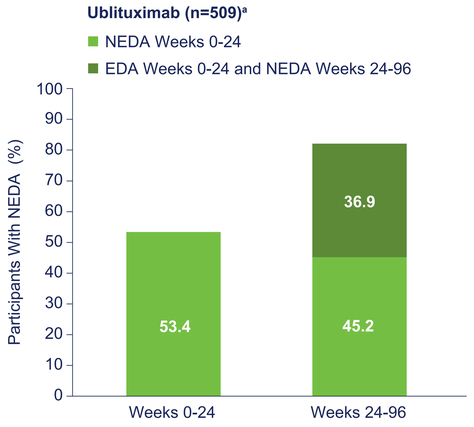
METHODS

- 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[4]
- 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[4]
- Clinical evaluations were performed every 12 weeks, and magnetic resonance imaging (MRI) assessments were performed at Weeks 24, 48, and 96
- NEDA-3 was defined as no confirmed relapses, no Gd+ T1 lesions, no new/enlarging T2 lesions, and no 12-week confirmed disability progression
- Pooled post hoc analyses evaluated the proportion of participants achieving and maintaining NEDA at Weeks 0-24, 24-96, 24-48, and 48-96

RESULTS

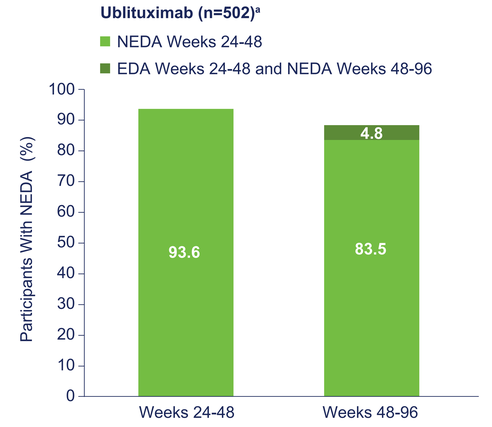
- 53.4% of ublituximab-treated participants achieved NEDA during Weeks 0-24, of which 45.2% of participants maintained NEDA during Weeks 24-96 (re-baselined). In addition, 36.9% of participants had EDA during Weeks 0-24 but then achieved NEDA during Weeks 24-96, bringing the total proportion of participants with NEDA to 82.1% for Weeks 24-96 (re-baselined; **Figure 1**)
- 93.6% of ublituximab-treated participants achieved NEDA during Weeks 24-48, of which 83.5% of participants maintained NEDA during Weeks 48-96. An additional 4.8% of participants had EDA during Weeks 24-48 but then achieved NEDA during Weeks 48-96, for a total of 88.2% of participants with NEDA during Weeks 48-96 (**Figure 2**)
- The leading cause of disease activity during Weeks 0-24 was new/enlarging T2 lesions (occurring in 42.4% of participants); however, this MRI activity decreased in Weeks 24-48 and continued to decrease in Weeks 48-96 (**Figure 3**)

Figure 1. NEDA-3 Rates by Treatment Epoch (Weeks 0-24 vs Weeks 24-96)



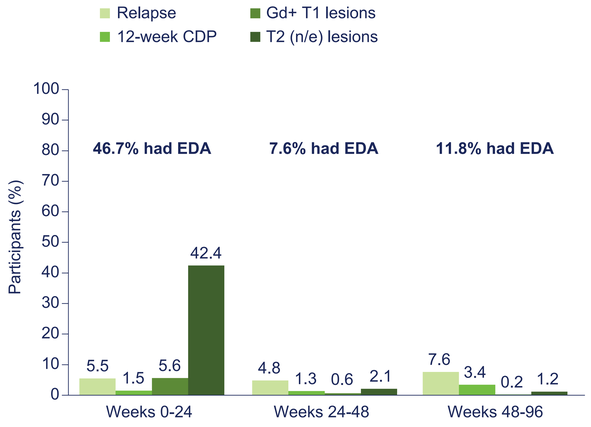
[a]Denominator based on participants in the Weeks 24-96 analysis.
Pooled post hoc analysis. Modified intention-to-treat population.
EDA, evidence of disease activity; NEDA, no evidence of disease activity; NEDA-3, 3-parameter NEDA.

Figure 2. NEDA-3 Rates by Treatment Epoch (Weeks 24-48 vs Weeks 48-96)



[a]Denominator based on participants in the Weeks 48-96 analysis.
Pooled post hoc analysis. Modified intention-to-treat population.
EDA, evidence of disease activity; NEDA, no evidence of disease activity; NEDA-3, 3-parameter NEDA.

Figure 3. Components Driving EDA in Ublituximab-Treated Participants[a]



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