Ublituximab Treatment Is Associated With a Significant Proportion of Participants Achieving NEDA-4

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OBJECTIVE

- To evaluate 4-parameter no evidence of disease activity (NEDA-4) with ublituximab versus teriflunomide in pooled post hoc analyses of ULTIMATE I and II using different annual brain volume loss (BVL) thresholds

KEY FINDINGS

- A significantly higher proportion of ublituximab- versus teriflunomide-treated participants achieved NEDA-4 (Weeks 24-96, re-baselined) at the evaluated annual BVL thresholds
  - 0.4%: 44.2% versus 13.5% (odds ratio [OR], 5.48 [95% CI, 4.03-7.46]); *P*<0.0001
  - 0.8%: 68.0% versus 19.0% (OR, 10.10 [95% CI, 7.50-13.60]); *P*<0.0001
  - 1.2%: 71.9% versus 19.6% (OR, 11.69 [95% CI, 8.64-15.81]); *P*<0.0001
- Lower rates of BVL with ublituximab versus teriflunomide were observed for each annual BVL threshold (Weeks 24-96, re-baselined): 0.4%, 49.5% versus 54.0%; 0.8%, 21.2% versus 25.8%; and 1.2%, 16.1% versus 18.8%, respectively

CONCLUSIONS

- Because BVL is predictive of long-term disability progression and cognitive decline, inclusion of BVL in NEDA analyses may provide a more comprehensive evaluation of disease activity and progression and might be predictive of long-term disability
- In pooled post hoc analyses across a range of annual BVL thresholds, significantly more participants achieved NEDA-4 with ublituximab versus teriflunomide in ULTIMATE I and II

BACKGROUND

- Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20 and is glycoengineered for enhanced antibody-dependent cellular cytotoxicity (ADCC)[1,2]
- 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) are identical, Phase 3, randomised, multicentre, 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 annualised 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[5]
- In pooled post hoc analyses, 3-parameter NEDA rates for ublituximab versus teriflunomide were 44.6% versus 12.4% at 0-96 weeks, respectively, and 82.1% versus 22.5% at 24-96 weeks (re-baselined) (*P*<0.0001 for both)[6]
- As brain atrophy is associated with both cognitive dysfunction[7] and poorer outcomes, including long-term disability progression,[8-11] an expanded definition of NEDA that incorporates brain atrophy (NEDA-4) has been proposed[12,13]
- A BVL of ≥0.4% per year has been suggested as a cutoff value to define pathological brain atrophy in people with MS[11]

METHODS

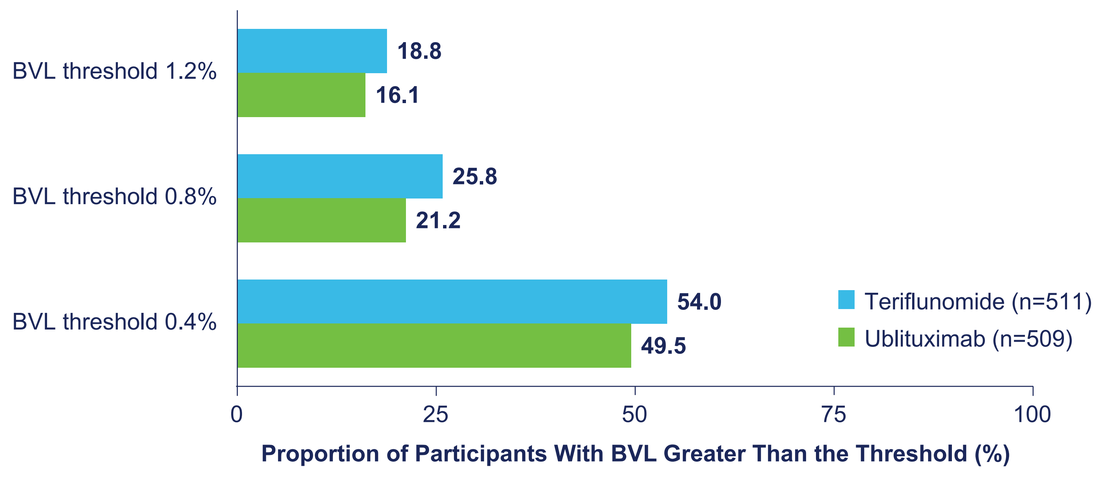
- ULTIMATE I and II enrolled a total of 1094 adults from 10 countries with a diagnosis of RMS (relapsing-remitting or secondary-progressive) with disease activity[5]
- Participants received ublituximab 450 mg administered by 1-hour intravenous infusion every 24 weeks (following Day 1 infusion of 150 mg and Day 15 infusion of 450 mg) or teriflunomide 14 mg oral once daily for 96 weeks[5]
- Clinical evaluations were performed every 12 weeks, and magnetic resonance imaging (MRI) assessments were performed at Weeks 12 (Gd+ T1 lesions only), 24, 48, and 96
- NEDA-4 was defined as no confirmed relapses, no Gd+ T1 lesions, no new/enlarging T2 lesions, no disability progression confirmed for at least 12 weeks (12-week confirmed disability progression), and BVL less than the defined threshold
- BVL was analysed using the Jacobian integration method and evaluated using 0.4%, 0.8%, and 1.2% annual thresholds
- Pooled post hoc analyses evaluated the proportion of participants achieving NEDA-4 at Week 96, re-baselined at Week 24
- NEDA-4 rate is the proportion of participants with NEDA-4, excluding participants who discontinued treatment early due to reasons other than death and lack of efficacy during the analysis time frame
- *P* values were derived from a logistic regression model with baseline adjustments for treatment, study, region, baseline Expanded Disability Status Scale strata, and log-transformed baseline MRI lesion counts (T1 nonenhancing, T2, and Gd+ T1 lesions)

RESULTS

BVL

- In the overall population, a lower proportion of ublituximab-treated than teriflunomide-treated participants had BVL exceeding each annual BVL threshold (Weeks 24-96, re-baselined) (**Figure 1**)

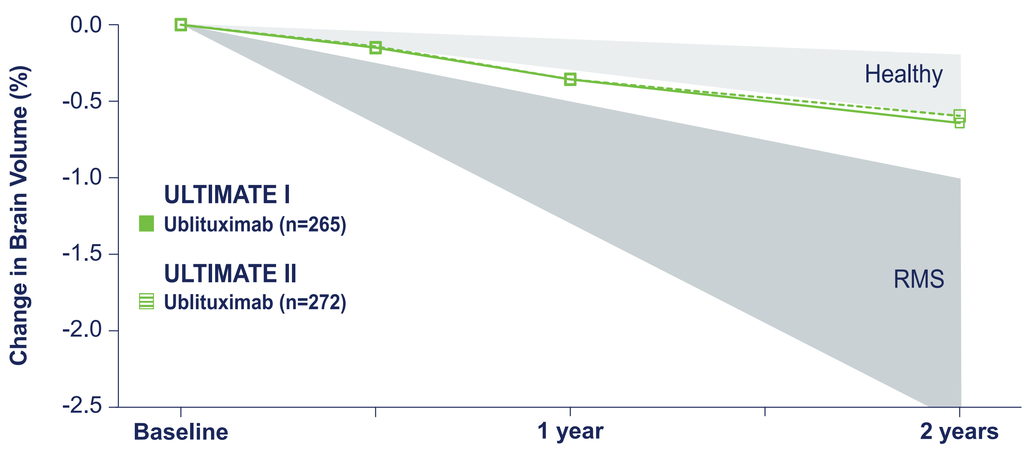
Figure 1. BVL at Weeks 24-96 (Re-baselined)



P values were not significant. Pooled post hoc analysis. mITT-MRI population.
BVL, brain volume loss; mITT, modified intention-to-treat; MRI, magnetic resonance imaging.

- BVL over time for participants in the individual ULTIMATE studies is shown in **Figure 2**, in context with expected rates of BVL based on historical data for healthy individuals and people with RMS. The rate of BVL among those receiving ublituximab was similar to that expected for healthy individuals[14]

Figure 2. BVL in ULTIMATE Studies and Historical BVL for Healthy Individuals and People With RMS



Data from ULTIMATE I and ULTIMATE II (mITT-MRI population) are superimposed over shaded areas, indicating ranges of BVL data for healthy individuals and people with RMS.[14] Shaded areas are based on historical data and are illustrative only.
BVL, brain volume loss; mITT, modified intention-to-treat; MRI, magnetic resonance imaging; RMS, relapsing multiple sclerosis.

NEDA-4

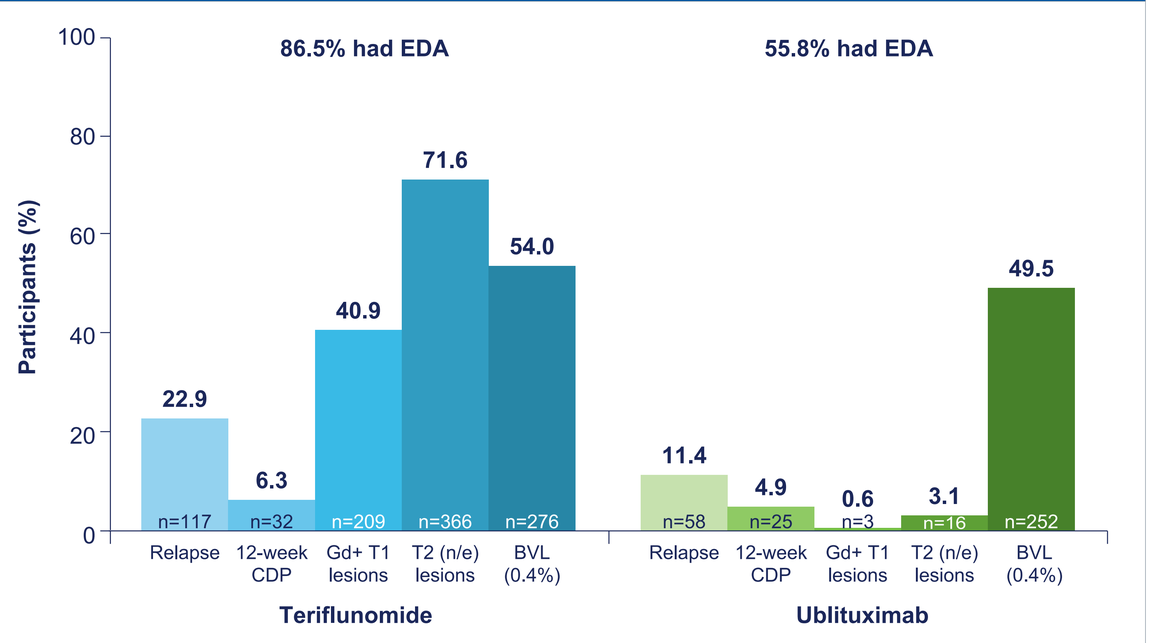
- A significantly higher proportion of ublituximab- versus teriflunomide-treated participants achieved NEDA-4 (Weeks 24-96, re-baselined) at the evaluated annual BVL thresholds (**Figure 3**)
  - 0.4%: 44.2% versus 13.5% (OR, 5.48 [95% CI, 4.03-7.46]); *P*<0.0001
  - 0.8%: 68.0% versus 19.0% (OR, 10.10 [95% CI, 7.50-13.60]); *P*<0.0001
  - 1.2%: 71.9% versus 19.6% (OR, 11.69 [95% CI, 8.64-15.81]); *P*<0.0001

Figure 3. NEDA-4 Rates by BVL Threshold (Weeks 24-96 Re-baselined)

NEDA-4 was defined as no confirmed relapses, no Gd+ T1 lesions, no new/enlarging T2 lesions, no 12-week confirmed disability progression, and no BVL per specified annual threshold. Pooled post hoc analysis. Modified intention-to-treat population.
BVL, brain volume loss; Gd+, gadolinium-enhancing; NEDA-4, 4-parameter no evidence of disease activity.

- In participants who did not achieve NEDA-4 at Weeks 24-96 (re-baselined) using the 0.4% annual BVL threshold, the main driver of disease activity was BVL in the ublituximab group and new/enlarging T2 lesions in the teriflunomide group (**Figure 4**)
- Using the 0.8% and 1.2% annual BVL thresholds, these trends persisted, albeit with the proportion of participants with BVL reduced at each threshold (0.8%: ublituximab, 21.2%, teriflunomide, 25.8%; 1.2%: ublituximab, 16.1%, teriflunomide, 18.8%; data not shown)

Figure 4. Components Driving EDA at Weeks 24-96 (Re-baselined)[a]: BVL Threshold 0.4%



[a]Participants may have >1 component of EDA. Pooled post hoc analysis. Modified intention-to-treat population. Teriflunomide, n=511; ublituximab, n=509.
BVL, brain volume loss; CDP, confirmed disability progression; EDA, evidence of disease activity; Gd+, gadolinium-enhancing; n/e, new/enlarging.

- Baseline characteristics for ublituximab participants with or without NEDA-4 are shown in **Table 1**
- On average, ublituximab-treated participants who achieved NEDA-4 had less MRI disease activity at baseline than participants who did not achieve NEDA-4

Table 1. Demographics and Baseline Characteristics in Ublituximab-Treated Participants With or Without NEDA-4 (BVL Threshold 0.4%) at Weeks 24-96 (Re-baselined)[a]

Characteristic	Evaluated Ublituximab-Treated Population	
Mean ± standard deviation or %	With NEDA-4 (n=225)	Without NEDA-4 (n=284)
Age, years	35.2±8.5	35.4±8.9
Sex, female, %	61.8	63.4
Time since MS diagnosis, years	5.1±5.4	4.8±5.2
Duration of MS since first symptoms, years	7.7±6.5	7.2±6.4
Number of relapses in last 12 months	1.2±0.5	1.4±0.7
Number of relapses in last 24 months	1.7±0.8	1.9±1.1
Time since most recent relapse, months	7.2±7.5	7.1±9.5
EDSS score at screening	2.8±1.3	3.0±1.2
T2 lesion volume, mL	14.1±15.0	15.9±14.2
Number of T2 lesions	59.6±36.4	68.3±41.9
Participants free of Gd+ T1 lesions, %	58.2	46.8
Brain volume, mm^3	1,679,690±106,768	1,657,323±101,440

[a]Participants included in NEDA-4 analysis using 0.4% BVL threshold.
BVL, brain volume loss; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; NEDA-4, 4-parameter no evidence of disease activity.

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