Disease Outcomes With Ublituximab in Treatment-Naive Participants: Subpopulation Analyses of the Phase 3 ULTIMATE I and II Studies in Participants With Relapsing Multiple Sclerosis

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OBJECTIVE

- To evaluate efficacy with ublituximab in treatment-naive participants enrolled in the ULTIMATE I and II studies

KEY FINDINGS

- In the treatment-naive subpopulation, significant improvements with ublituximab versus teriflunomide were observed at Week 96, including:
  - An adjusted annualised relapse rate (ARR) of 0.081 and 0.188, respectively (*P*<0.0001)
  - Estimated rates of 12-week confirmed disability improvement (CDI) were 11.2% versus 5.5%, hazard ratio (95% CI), 2.031 (1.174-3.513; *P*=0.0095)
  - The least squares (LS) means of gadolinium-enhancing (Gd+) T1 lesions and new/enlarging T2 lesions per scan was 0.031 versus 0.791 and 0.390 versus 4.144 for ublituximab versus teriflunomide (*P*<0.0001 for both)
  - Higher rates of no evidence of disease activity (NEDA) (re-baselined at Week 24): 82.7% versus 23.1% (*P*<0.0001)
  - 89.9% relative improvement with ublituximab in Multiple Sclerosis Functional Composite (MSFC) score from baseline (*P*=0.0047)

CONCLUSION

- In pooled post hoc analyses of participants who had not received a prior disease-modifying therapy (DMT) in ULTIMATE I and II, ublituximab was associated with significant treatment benefit across multiple efficacy measures at Week 96 versus teriflunomide, and similar or improved benefit versus the overall ublituximab population, as previously reported[1]

BACKGROUND

- Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20 and is glycoengineered for enhanced antibody-dependent cellular cytotoxicity (ADCC)[2,3]
- In vitro studies demonstrate that ublituximab has 25-30× higher ADCC relative to all other currently approved anti-CD20 therapies used in multiple sclerosis[4]
- Ublituximab is administered in lower doses and with shorter infusion times compared with other currently infused anti-CD20 therapies[1]
- 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 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 lesions[5]
- As evidence suggests that initial treatment with a more efficacious DMT is superior to an escalating approach at reducing disability progression and relapse rate,[6,7] post hoc analyses were evaluated to assess ublituximab's efficacy in treatment-naive participants

METHODS

- The Phase 3 ULTIMATE I and II studies 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]
- Pooled post hoc subpopulation analyses evaluated efficacy measures at Week 96 in participants who had or had not received prior approved DMT in the 5 years prior to study enrolment

RESULTS

- Baseline characteristics for the treatment-naive and previously treated populations are shown in **Table 1**

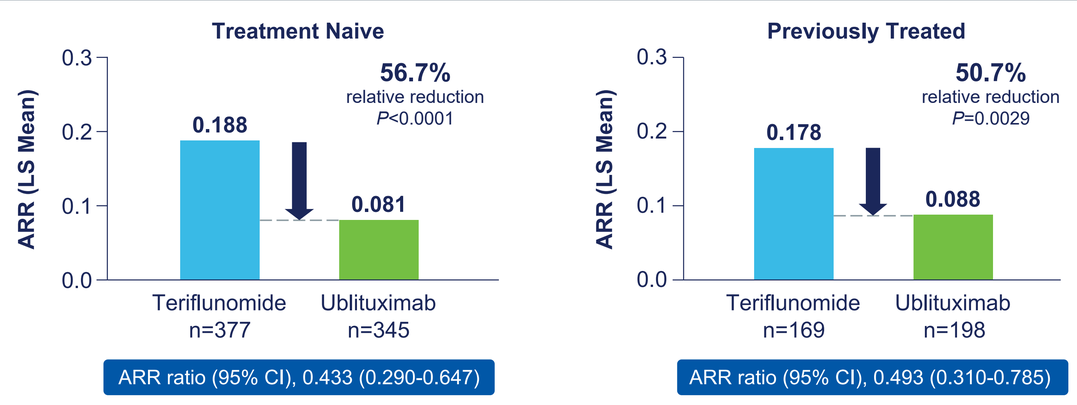
Table 1. Participant Demographics and Baseline Characteristics in Treatment-Naive Participants

Characteristic *Mean ± standard deviation or %*	Treatment Naive		Previously Treated	
	Teriflunomide (n=377)	Ublituximab (n=345)	Teriflunomide (n=169)	Ublituximab (n=198)
Age, years	35.7±9.2	35.2±8.6	38.5±9.3	35.7±8.6
Sex, female, %	63.7	61.4	68.0	66.7
Duration of MS since first symptoms, years	6.2±5.7	6.4±6.3	9.1±6.4	9.2±6.4
Time since diagnosis, years	3.9±4.8	3.8±5.0	6.5±5.2	7.1±5.5
Number of relapses in last 12 months	1.3±0.7	1.3±0.6	1.3±0.7	1.3±0.7
Number of relapses in last 24 months	1.8±0.9	1.8±0.8	2.1±1.2	1.9±1.2
Time since most recent relapse, months	6.0±4.3	6.3±3.8	6.8±5.8	8.4±13.0
EDSS score at screening	2.8±1.2	2.8±1.2	3.2±1.2	3.1±1.3
T2 lesion volume, cm^3	14.4±15.5	14.7±14.7	17.3±18.9	16.4±15.0
Number of T2 lesions	62.5±39.6	63.9±39.5	61.4±38.3	66.2±40.6
Participants free of Gd+ T1 lesions, %	52.0	50.7	56.2	55.1

Modified intention-to-treat population.
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis.

- In the treatment-naive population, ublituximab was associated with a 56.7% decrease in adjusted ARR compared with teriflunomide: 0.081 versus 0.188, respectively (*P*<0.0001) (**Figure 1**)

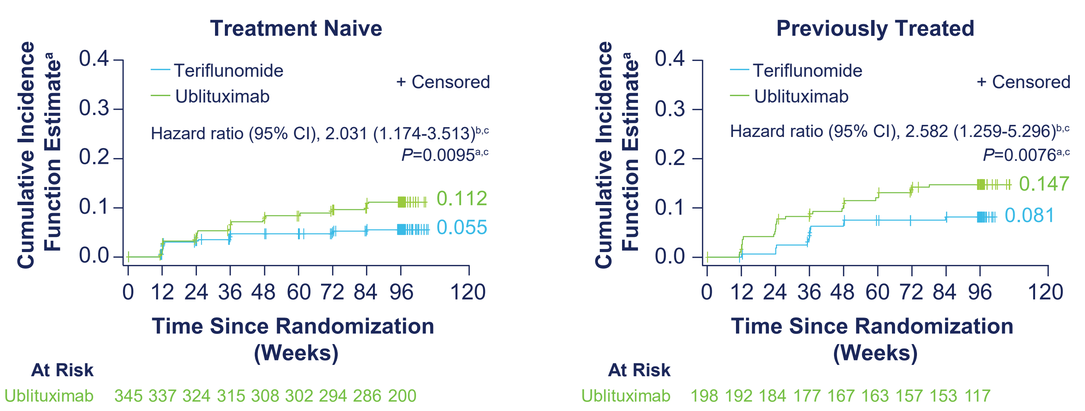
Figure 1. ARR (Adjusted)[a] at Week 96 in Treatment-Naive Participants



[a]Unadjusted ARR: teriflunomide, 0.095; ublituximab, 0.223 (*P*<0.0001). Modified intention-to-treat population. Pooled post hoc analysis. Based on negative binomial model (GEE) for the relapse count per participant with logarithmic link function, treatment, region, and baseline EDSS score as covariates and log (years of treatment) as offset within each subgroup, and an overall model adding subgroup and treatment by subgroup interaction for the interaction *P* value.
ARR, annualised relapse rate; EDSS, Expanded Disability Status Scale; GEE, general estimating equation; LS, least squares.

- By Kaplan-Meier estimate at Week 96, significantly more ublituximab-treated (11.2%) than teriflunomide-treated (5.5%) participants in the treatment-naive subgroup achieved 12-week CDI (*P*=0.0095) (**Figure 2**)
- Benefit in time to 12-week CDI was similar in the treatment-naive and overall ublituximab-treated populations (data not shown)

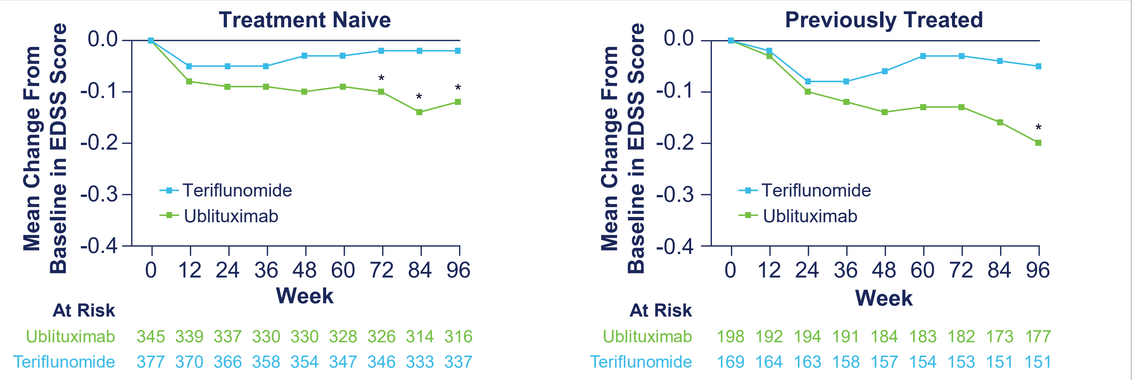
Figure 2. Time to 12-Week CDI in Treatment-Naive Participants



[a]Estimated by Kaplan-Meier method. [b]Hazard ratio is estimated using Cox regression model with treatment group as covariate. [c]Stratification factors included region, baseline EDSS score, and study. Modified intention-to-treat population. Pooled post hoc analysis. *P* value from Kaplan-Meier analysis.
CDI, confirmed disability improvement; EDSS, Expanded Disability Status Scale.

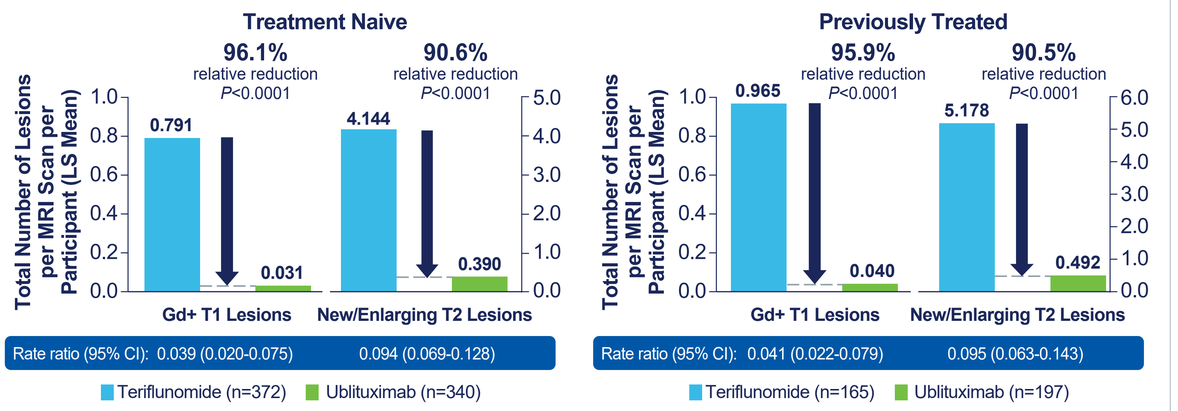
- Estimated 12-week confirmed disability progression was low in both groups of the treatment-naive cohort, hazard ratio (95% CI), 0.698 (0.351-1.386; *P*=0.2973)
- In the treatment-naive cohort, significant improvements from baseline in EDSS score were observed for ublituximab versus teriflunomide at Weeks 72, 84, and 96 (**Figure 3**)
- There was a statistically significant 96.1% reduction in Gd+ T1 lesions with ublituximab versus teriflunomide in treatment-naive participants (total number LS mean: 0.031 versus 0.791, *P*<0.0001) (**Figure 4**)
- The LS mean number of new/enlarging T2 lesions per scan was significantly lower with ublituximab compared with teriflunomide in treatment-naive participants (0.390 versus 4.144, *P*<0.0001) (**Figure 4**)

Figure 3. Mean EDSS Score Change From Baseline in Treatment-Naive Participants



*P<0.05. Modified intention-to-treat population. Pooled post hoc analysis. *P* value based on *t* test.
EDSS, Expanded Disability Status Scale.

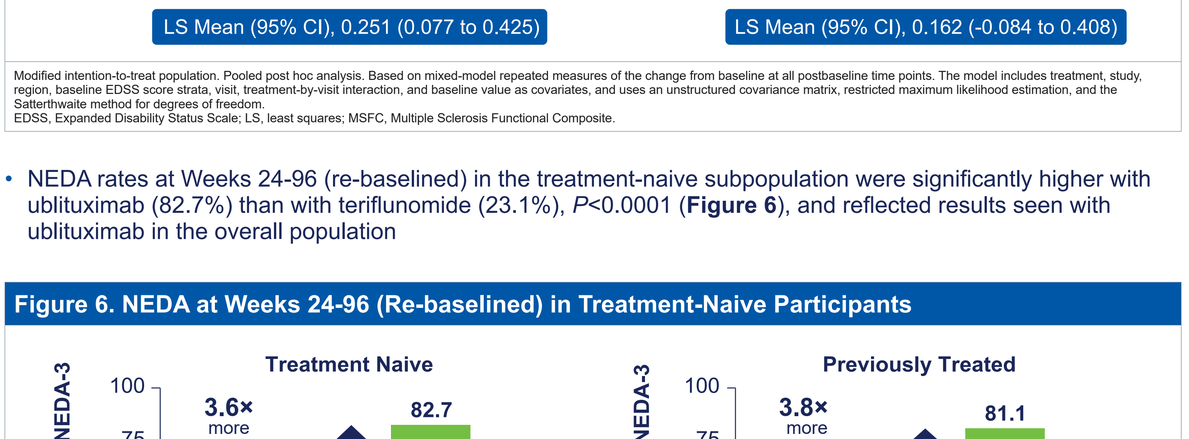
Figure 4. Gd+ T1 Lesions and New/Enlarging T2 Lesions in Treatment-Naive Participants



mITT-MRI population. Pooled post hoc analysis. Based on negative binomial model (GEE) for the total number of Gd+ T1 lesions and new/enlarging T2 lesions per MRI scan with logarithmic link function, treatment as covariate and an offset based on the log-transformed number of postbaseline MRI scans within each subgroup, and an overall model adding subgroup and treatment by subgroup interaction for the interaction *P* value.
Gd+, gadolinium-enhancing; GEE, general estimating equation; LS, least squares; mITT, modified intention-to-treat; MRI, magnetic resonance imaging.

- Among treatment-naive participants, there was an 89.9% relative improvement in change from baseline in MSFC score with ublituximab versus teriflunomide (*P*=0.0047) (**Figure 5**)

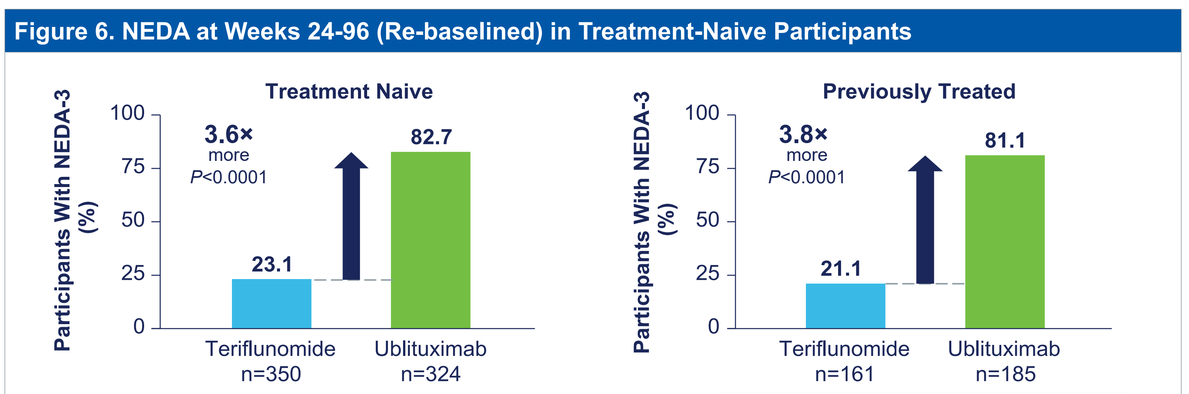
Figure 5. Change From Baseline in MSFC Score in Treatment-Naive Participants



Modified intention-to-treat population. Pooled post hoc analysis. Based on mixed-model repeated measures of the change from baseline at all postbaseline time points. The model includes treatment, study, region, baseline EDSS score strata, visit, treatment-by-visit interaction, and baseline value as covariates, and uses an unstructured covariance matrix, restricted maximum likelihood estimation, and the Satterthwaite method for degrees of freedom.
EDSS, Expanded Disability Status Scale; LS, least squares; MSFC, Multiple Sclerosis Functional Composite.

- NEDA rates at Weeks 24-96 (re-baselined) in the treatment-naive subpopulation were significantly higher with ublituximab (82.7%) than with teriflunomide (23.1%), *P*<0.0001 (**Figure 6**), and reflected results seen with ublituximab in the overall population

Figure 6. NEDA at Weeks 24-96 (Re-baselined) in Treatment-Naive Participants



Modified intention-to-treat population. NEDA-3 was defined as no confirmed relapses, no Gd+ T1 lesions, no new/enlarging T2 lesions, and no disability progression confirmed for at least 12 weeks. NEDA-3 rate is the proportion of participants with NEDA, excluding participants 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 score strata, plus log-transformed baseline MRI lesion counts (T1 nonenhancing, T2, Gd+).
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; NEDA-3, 3-parameter no evidence of disease activity.

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