Disability Improvements With Ublituximab in Relapsing Multiple Sclerosis: Pooled Post Hoc Analyses of the ULTIMATE I and II Studies

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OBJECTIVE

- To evaluate sustained confirmed disability improvement (CDI) and clinically meaningful improvements in Expanded Disability Status Scale (EDSS) score with ublituximab in participants with relapsing multiple sclerosis (RMS) in the ULTIMATE I and II studies

KEY FINDINGS

- Among ublituximab participants who demonstrated 12-week CDI, 95.4% (62/65) sustained the improvement through the end of the study
- The time to 12-week CDI was significantly improved with ublituximab vs teriflunomide, regardless of treatment history: treatment naive (*P*=0.0095); previously treated (*P*=0.0076)
- A higher proportion of ublituximab-treated participants had >1 EDSS score improvement events than teriflunomide-treated participants (12.9% vs 7.0%; *P*<0.01)
- Among participants with a baseline EDSS score ≥2.0, significantly more ublituximab-treated than teriflunomide-treated participants had EDSS score improvements of 1.0 step at Weeks 60-96 and 1.5 steps at Weeks 36-96

CONCLUSIONS

- Evaluations of EDSS score improvements during treatment showed a consistent and significant benefit with ublituximab vs teriflunomide
- Along with prespecified 12- and 24-week CDI analyses, pooled post hoc evaluations of sustained 12-week CDI and EDSS score provide further evidence of clinically meaningful disability improvement with ublituximab in ULTIMATE I and II

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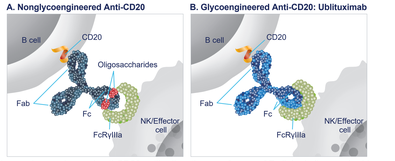
INTRODUCTION

- Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20 and is glycoengineered for enhanced antibody-dependent cellular cytotoxicity (ADCC) **(Figure 1)**[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[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, double-dummy studies evaluating the efficacy and safety of ublituximab vs teriflunomide in participants with RMS[4]
- 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 T1 lesions and the number of new/enlarging T2 lesions[4]
- In a prespecified pooled tertiary analysis, improvements with ublituximab vs teriflunomide were seen in both 12-week CDI (12.0% vs 6.0%, respectively; *P*=0.0003) and 24-week CDI (9.6% vs 5.1%, respectively; *P*=0.0026)[4]

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.[5,6]
(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.[6-8]

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

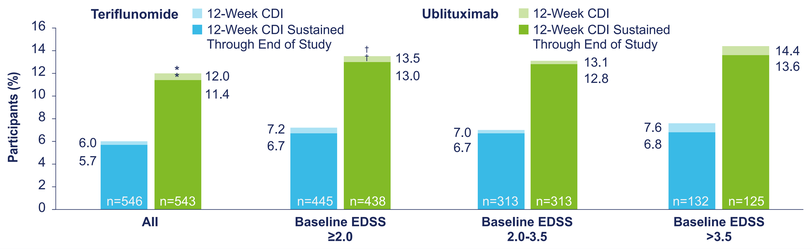
METHODS

- 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 oral once daily for 96 weeks[4]
- Clinical evaluations were performed at baseline and every 12 weeks, and magnetic resonance imaging assessments were performed at Weeks 12, 24, 48, and 96
- CDI was defined as a reduction from the baseline EDSS score of ≥1.0 point (or 0.5 point if the baseline EDSS score was >5.5) that was sustained and confirmed at the next scheduled visit(s) ≥12 or ≥24 weeks after the initial documentation of neurological improvement
- Pooled data from both studies were evaluated in post hoc analyses

RESULTS

- The proportion of participants achieving 12-week CDI and, of those, the proportion who had sustained CDI through the end of the study are shown in **Figure 2**
- Higher rates of 12-week CDI occurred with ublituximab vs teriflunomide for all participants (12.0% vs 6.0%, respectively; *P*=0.0005) regardless of baseline EDSS score
- A higher proportion of ublituximab-treated participants had sustained CDI compared with teriflunomide-treated participants (all participants: 11.4% vs 5.7%, respectively; *P*=0.0005)
- 95.4% (62/65) of ublituximab-treated participants who had 12-week CDI sustained the improvement through the end of the study

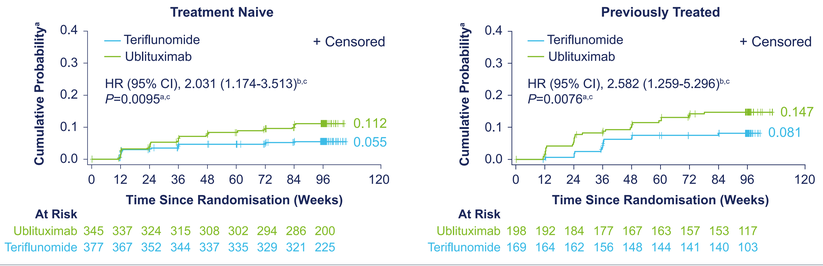
Figure 2. Sustained CDI Through End of Study



*P=0.0005 for all participants and †P<0.01 for participants with baseline EDSS score ≥2.0 for 12-week CDI and for 12-week CDI sustained through end of study for all participants (ublituximab vs teriflunomide). *P* value by Cochran-Mantel-Haenszel test. Statistics were not performed for other comparisons. Pooled post hoc analysis. Modified intention-to-treat population. Sustained CDI requires that end of study EDSS score is not higher than baseline score.
CDI, confirmed disability improvement; EDSS, Expanded Disability Status Scale.

- The time to 12-week CDI was significantly improved with ublituximab vs teriflunomide regardless of treatment history: treatment naive (*P*=0.0095); previously treated (*P*=0.0076) **(Figure 3)**

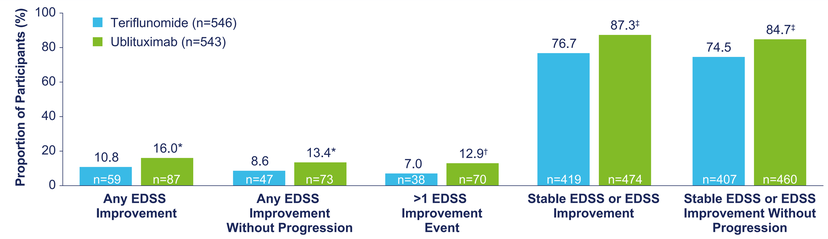
Figure 3. Time to 12-Week CDI by Prior Treatment



aEstimated by Kaplan-Meier method. bHR estimated using Cox regression model with treatment group as covariate. cStratification factors included region, baseline EDSS score, and study. *P* value by stratified log-rank test. Pooled post hoc analysis. Modified intention-to-treat population. CDI, confirmed disability improvement; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio.

- Evaluation of EDSS score changes during the trial showed significant improvements with ublituximab vs teriflunomide for all analyses in **Figure 4,** as follows:
  - Any EDSS improvement (≥1 EDSS score decrease; may have had an EDSS score increase during the trial)
  - Any EDSS improvement without progression (≥1 EDSS score decrease with no EDSS score increase during the trial)
  - >1 EDSS improvement event (>1 EDSS score decrease; may have had an EDSS score increase during the trial)
  - Stable EDSS (did not meet criteria for EDSS improvement or progression) or any EDSS improvement (as above)
  - Stable EDSS (as above) or EDSS improvement without progression (as above)
- Of note, participants receiving ublituximab were more likely to have >1 EDSS score improvement event than participants on teriflunomide (12.9% vs 7.0%, respectively) (*P*<0.01)

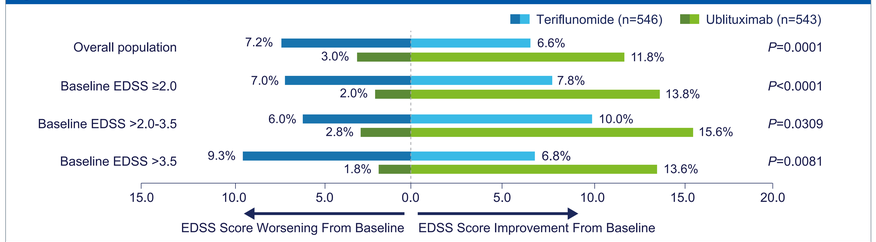
Figure 4. Participants With EDSS Improvement[a]



*P<0.05. †P<0.01. ‡P<0.0001. [a]No improvement or progression events were confirmed. *P* value by chi-square test.
Pooled post hoc analysis. Modified intention-to-treat population. EDSS, Expanded Disability Status Scale.

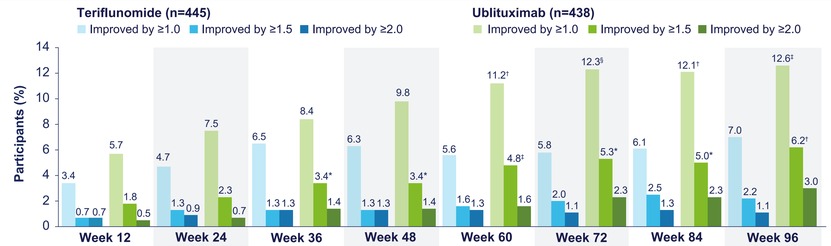
- The proportions of participants with EDSS score worsening or improvement from baseline at Week 96 is shown in **Figure 5**
- Among participants with a baseline EDSS score ≥2.0, significantly more ublituximab-treated than teriflunomide-treated participants had EDSS score improvements of 1.0 step at Weeks 60-96 and 1.5 steps at Weeks 36-96 **(Figure 6)**

Figure 5. EDSS Score Change From Baseline at Week 96



Percentage based on the number of participants who had both baseline and Week 96 EDSS assessment in each analysis set. EDSS score decrease ≥1.0 is categorised as improvement; EDSS score increase ≥1.0 as worsening; others as stable (not shown). *P* value based on ordinal logistic regression model. Pooled post hoc analysis. Modified intention-to-treat population.
EDSS, Expanded Disability Status Scale.

Figure 6. EDSS Improvement (Baseline EDSS Score ≥2.0)[a]



Percentage based on the number of participants who had baseline EDSS assessment in the analysis population.
*P<0.05. †P<0.005. ‡P<0.01. §P<0.001 for comparisons of each category at every timepoint (ublituximab vs teriflunomide). [a]No improvement events were confirmed. *P* value by chi-square test.
Pooled post hoc analysis. Modified intention-to-treat population. EDSS, Expanded Disability Status Scale.