Ublituximab Efficacy Outcomes in Relapsing Multiple Sclerosis Patient Subgroups in the ULTIMATE I and II Studies

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OBJECTIVE

- To evaluate the efficacy of ublituximab in key subgroups of participants with relapsing multiple sclerosis (RMS) in the Phase 3 ULTIMATE I and II studies

KEY FINDINGS

- At 96 weeks, significant benefits favouring ublituximab vs teriflunomide were observed for nearly all evaluated subgroups, including:
  - Annualised relapse rate (ARR) (P<0.05 for all, except aged ≥38 years or with ≥3 relapses)
  - Number of gadolinium-enhancing (Gd+) T1 lesions (P<0.0001 for all evaluable subgroups)
  - Number of new/enlarging T2 lesions (P<0.0001 for all)
  - Proportion of participants achieving no evidence of disease activity (NEDA) (24-96 weeks re-baselined; P<0.0001 for all)

CONCLUSION

- Ublituximab was superior to teriflunomide in key efficacy measures across multiple demographic and disease characteristic participant subpopulations in ULTIMATE I and II

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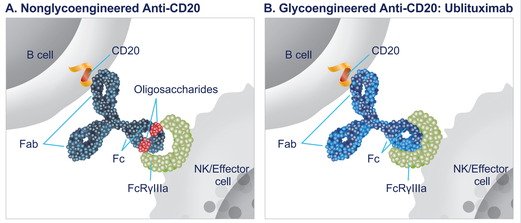
INTRODUCTION

- 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 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[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.

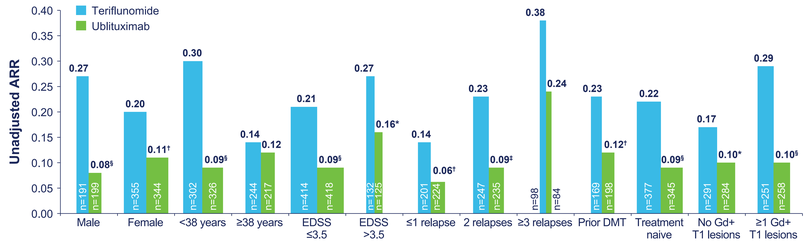
METHODS

- ULTIMATE I and II evaluated 1089 adult participants from 10 countries with a diagnosis of RMS (relapsing-remitting [n=1069] or secondary-progressive [n=20]) 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 every 12 weeks, and magnetic resonance imaging assessments were performed at Weeks 12, 24, 48, and 96
- Pooled post hoc analyses evaluated efficacy at Week 96 based on prespecified subgroups, including sex (male or female), age (<38 or ≥38 years), Expanded Disability Status Scale score (≤3.5 or >3.5), number of relapses in prior 2 years (≤1, 2, or ≥3), prior disease-modifying therapy (yes or no), and baseline number of Gd+ T1 lesions (0 or ≥1)

RESULTS

- ARR at Week 96 by participant subgroup is shown in **Figure 2**
- A statistically significant improvement favouring ublituximab vs teriflunomide was observed for all subgroups, except for participants aged ≥38 years (n=461) or with ≥3 relapses at baseline (n=182)

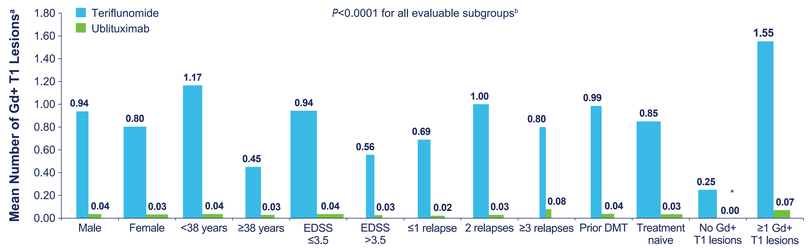
Figure 2. ARR at Week 96 by Participant Subgroup



*P<0.05. †P<0.01. ‡P<0.001. §P<0.0001. Pooled prespecified subgroup analysis. mITT population. Based on negative binomial model (GEE) for the relapse count per participant with logarithmic link function, treatment as covariate 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. Bar widths relative to sample size.
ARR, annualised relapse rate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; mITT, modified intention-to-treat.

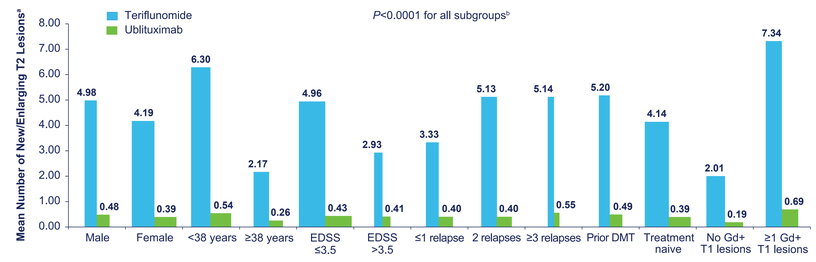
- Ublituximab provided a statistically significant reduction in Gd+ T1 lesions and new/enlarging T2 lesions vs teriflunomide at Week 96 for all evaluable participant subgroups (P<0.0001) **(Figures 3 and 4)**

Figure 3. Gd+ T1 Lesions at Week 96 by Participant Subgroup



*Statistical testing could not be performed. [a]Per MRI scan per participant. Pooled post hoc analysis. mITT-MRI population. [b]Based on negative binomial model (GEE) for the total number of Gd+ T1 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. Bar widths relative to sample size.
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; mITT, modified intention-to-treat; MRI, magnetic resonance imaging.

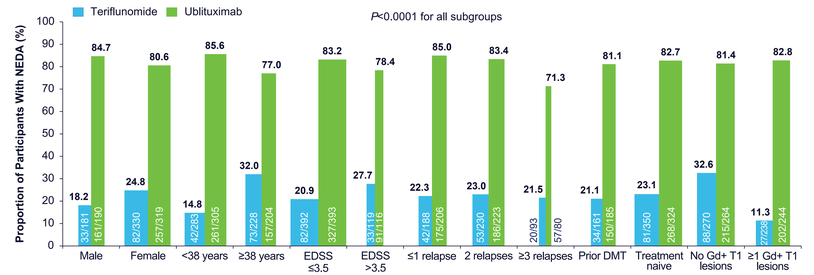
Figure 4. New/Enlarging T2 Lesions at Week 96 by Participant Subgroup



Pooled post hoc analysis. mITT-MRI population. [a]Per MRI scan per participant. [b]Based on negative binomial model (GEE) for the total number of new and 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. Bar widths relative to sample size.
DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; mITT, modified intention-to-treat; MRI, magnetic resonance imaging.

- A significantly higher proportion of ublituximab-treated vs teriflunomide-treated participants achieved NEDA by Week 96 (re-baselined at Week 24) across all subgroups **(Figure 5)**

Figure 5. NEDA at Weeks 24-96 (Re-baselined) by Participant Subgroup



Pooled post hoc analysis. mITT population. NEDA was defined as no confirmed relapses, no Gd+ T1 lesions, no new/enlarging T2 lesions, and no 12-week confirmed disability progression. P value based on logistic regression model with treatment as covariate. Bar widths relative to sample size.
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; mITT, modified intention-to-treat; NEDA, no evidence of disease activity.

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