Improved Quality of Life With Ublituximab in the ULTIMATE I and II Studies in Relapsing Multiple Sclerosis

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OBJECTIVE

- To evaluate the effects of ublituximab on quality of life (QOL) in participants with relapsing multiple sclerosis (RMS) in the ULTIMATE I and II studies

KEY FINDINGS

- Statistically significant improvements favouring ublituximab vs teriflunomide were seen in multiple components of the Multiple Sclerosis Quality of Life-54 (MSQOL-54) at all postbaseline timepoints, including overall QOL, physical and mental health composites, role limitations (physical), physical health, changes in health, and energy
- In the Short Form-36 (SF-36), significant improvements were observed for ublituximab vs teriflunomide in the physical component summary, physical functioning, and role-physical

CONCLUSION

- Ublituximab provided significant improvement over teriflunomide in multiple measures of QOL and physical functioning at 96 weeks in pooled post hoc analyses of ULTIMATE I and II

REFERENCES 1. Le Garff-Tavernier M, et al. *Leukemia*. 2014;28(1):230-233. **2.** Babiker HM, et al. *Expert Opin Investig Drugs*. 2018;27(4):407-412. **3.** Alvarez E, et al. Presented at: CMSC; June 1-4, 2022; National Harbor, MD. Oral presentation DMT03. **4.** Steinman L, et al. Presented at: ECTRIMS; October 13-15, 2021; Virtual. Oral presentation 117. **5.** Ferrara C, et al. *Proc Natl Acad Sci U S A*. 2011;108(31):12669-12674. **6.** Sun Y, et al. *J Biol Chem*. 2021;297(1):100826. **7.** de Romeuf C, et al. *Br J Haematol*. 2008;140(6):635-643. **8.** Fox E, et al. *Mult Scler*. 2021;27(3):420-429.

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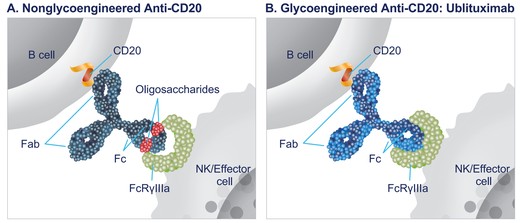
INTRODUCTION

- 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]

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]
- MSQOL-54 assessments, inclusive of SF-36, were tertiary endpoints of the individual studies
- Pooled post hoc analyses of the change from baseline in MSQOL-54 and SF-36 were conducted for Weeks 24, 48, and 96, and were evaluated based on all postbaseline timepoints using mixed-model repeated measures
  - The model included treatment, study, region, baseline Expanded Disability Status Scale score strata, visit, treatment-by-visit interaction, and baseline value, and used an unstructured covariance matrix, restricted maximum likelihood estimation, and the Satterthwaite method for degrees of freedom
- The change from baseline at Week 96 only was also evaluated for MSQOL-54 and SF-36

RESULTS

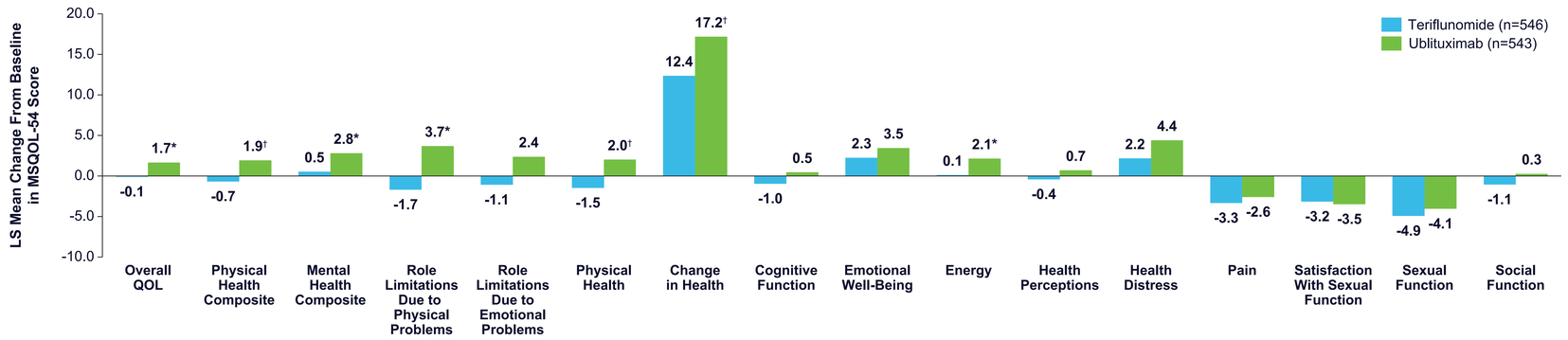
- Change from baseline in MSQOL-54 for all postbaseline timepoints is shown in **Figure 2**
- Statistically significant improvements favouring ublituximab vs teriflunomide were seen in the components of overall QOL, physical health composite, mental health composite, role limitations (physical), physical health, changes in health, and energy
- When evaluating the change from baseline in MSQOL-54 at Week 96 only, improvements were seen for ublituximab vs teriflunomide for all components. Formal statistical testing was not performed for this analysis (data not shown)
- Change from baseline in SF-36 for all postbaseline timepoints is shown in **Table 1**
- Statistically significant improvements favouring ublituximab vs teriflunomide were seen in physical component summary, physical functioning, and role-physical
- When evaluating the change from baseline in SF-36 at Week 96 only, improvements were seen for ublituximab vs teriflunomide for all components. Formal statistical testing was not performed for this analysis (data not shown)

Table 1. Change in SF-36 Scores From Baseline to Week 96 (All Postbaseline Timepoints)

Component[a]	Teriflunomide (n=546)	Ublituximab (n=543)	*P* Value
Physical Component Summary	**-1.0**	**0.1**	**0.01**
Mental Component Summary	1.0	1.6	0.28
Bodily Pain	-1.5	-1.1	0.43
General Health	-0.1	0.4	0.23
Mental Health	1.3	2.0	0.22
Physical Functioning	**-0.6**	**0.8**	**0.001**
Role-Emotional	-0.3	0.8	0.12
Role-Physical	**-0.5**	**1.0**	**0.01**
Social Functioning	0.2	0.6	0.42
Vitality	0.3	1.2	0.06

[a]Norm-based scoring for all components except Physical Component Summary and Mental Component Summary. Mixed-model repeated measures of the change from baseline at all postbaseline timepoints (LS means). Pooled post hoc analysis. Modified intention-to-treat population.
LS, least squares; SF-36, Short Form-36.

Figure 2. Change in MSQOL-54 Scores From Baseline to Week 96 (All Postbaseline Timepoints)



*$P<0.05$. †$P<0.01$. Mixed-model repeated measures of the change from baseline at all postbaseline timepoints. Pooled post hoc analysis. Modified intention-to-treat population.
LS, least squares; MSQOL-54, Multiple Sclerosis Quality of Life-54; QOL, quality of life.

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