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Ublituximab Is Associated With Significant Improvement in the Multiple Sclerosis Functional Composite (MSFC): Results From the Phase 3 ULTIMATE I & II Studies

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INTRODUCTION

Background

- Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20 **(Figure 1)** and is glycoengineered for enhanced antibody-dependent cellular cytotoxicity[1,2]
- Ublituximab is administered in lower doses with shorter infusion times than other currently available anti-CD20 therapies[3]
- ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) are identical, phase 3, randomized, multicenter, double-blind, active-control studies evaluating the efficacy and safety of ublituximab vs teriflunomide in patients with relapsing multiple sclerosis (RMS)[3]
- ULTIMATE I and II met their primary endpoint, demonstrating a statistically significant reduction in annualized relapse rate for ublituximab compared with teriflunomide. Ublituximab also provided significant improvements in gadolinium-enhancing (Gd+) T1 lesions and new/enlarging T2 lesions, and significantly more patients in the ublituximab arm achieved no evidence of disease activity at 96 weeks than in the teriflunomide arm[3]
- In a prespecified pooled tertiary analysis, ublituximab significantly increased the proportion of patients with 12-week and 24-week confirmed disability improvement (CDI)[3]

Figure 1. CD20-Antigen–Binding Epitope of Ublituximab[4]

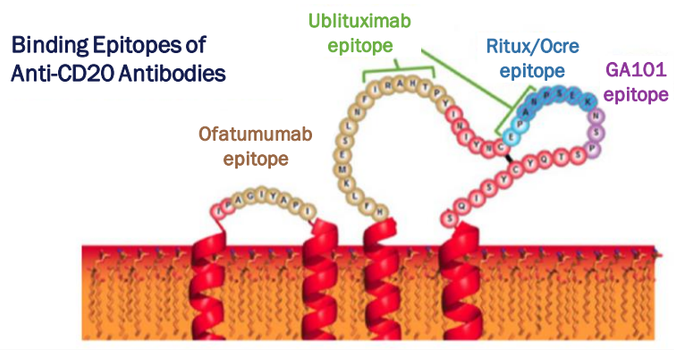


Figure reused with permission under Sage's Sharing Policy for Authors. Fox E, et al. A phase 2 multicenter study of ublituximab, a novel glycoengineered anti-CD20 monoclonal antibody, in patients with relapsing forms of multiple sclerosis. *Mult Scler*. 2021;27(3):420-429; doi: 10.1177/1352458520918375.

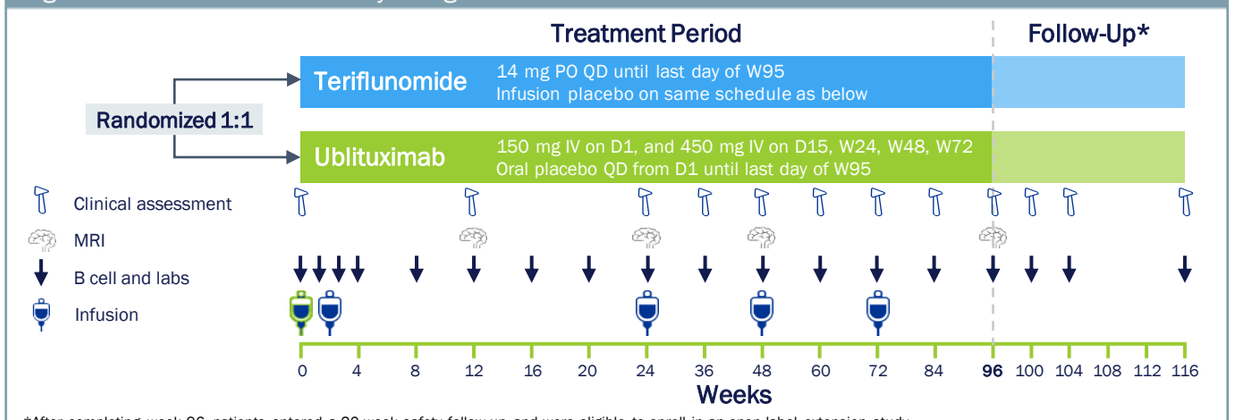
Objectives

- To characterize the effects of ublituximab on the MSFC and its components
  - 9-Hole Peg Test (9-HPT)
  - Timed 25-Foot Walk (T25FW)
  - Paced Auditory Serial Additional Test (PASAT)

Study Design

- ULTIMATE I and II enrolled 1094 RMS patients from 10 countries
- **Key inclusion criteria**
  - Age 18-55 years (inclusive) at screening with RMS diagnosis (2010 revised McDonald criteria): relapsing-remitting or secondary-progressive multiple sclerosis (SPMS) with disease activity
  - Expanded Disability Status Scale (EDSS) score of 0.0-5.5 (inclusive)
  - At least 1 relapse within 1 year prior to screening or ≥2 relapses within 2 years prior to screening and/or a positive Gd+ magnetic resonance imaging scan in the year prior to randomization
- **Key exclusion criteria**
  - Primary-progressive multiple sclerosis or SPMS without disease activity
  - Previous anti-CD20 or other B-cell–directed treatment
  - Disease duration >10 years with an EDSS score ≤2.0
- Patients received ublituximab 450 mg as a 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 **(Figure 2)**
- The MSFC was administered at baseline and every 12 weeks thereafter. The MSFC (tertiary endpoint) and components (9-HPT, T25FW, and PASAT; post hoc analyses) were analyzed using the modified intention-to-treat population
- Change from baseline in MSFC and components were analyzed using a mixed model repeated measures of change from baseline at all postbaseline timepoints
  - The model included treatment, region, baseline EDSS strata, visit, treatment-by-visit interaction, and baseline value as covariates and used an unstructured covariance matrix, restricted maximum likelihood estimation, and the Satterthwaite method for degrees of freedom

Figure 2. ULTIMATE I and II Study Design



*After completing week 96, patients entered a 20-week safety follow-up and were eligible to enroll in an open-label extension study.
D, day; IV, intravenous; MRI, magnetic resonance imaging; PO, by mouth; QD, once daily; W, week.

RESULTS

Baseline Demographics and Disease Characteristics

- Baseline characteristics were well balanced between ULTIMATE I and II and between treatment arms **(Table 1)**[5]

Table 1. Baseline Demographics and Disease Characteristics[5,*]

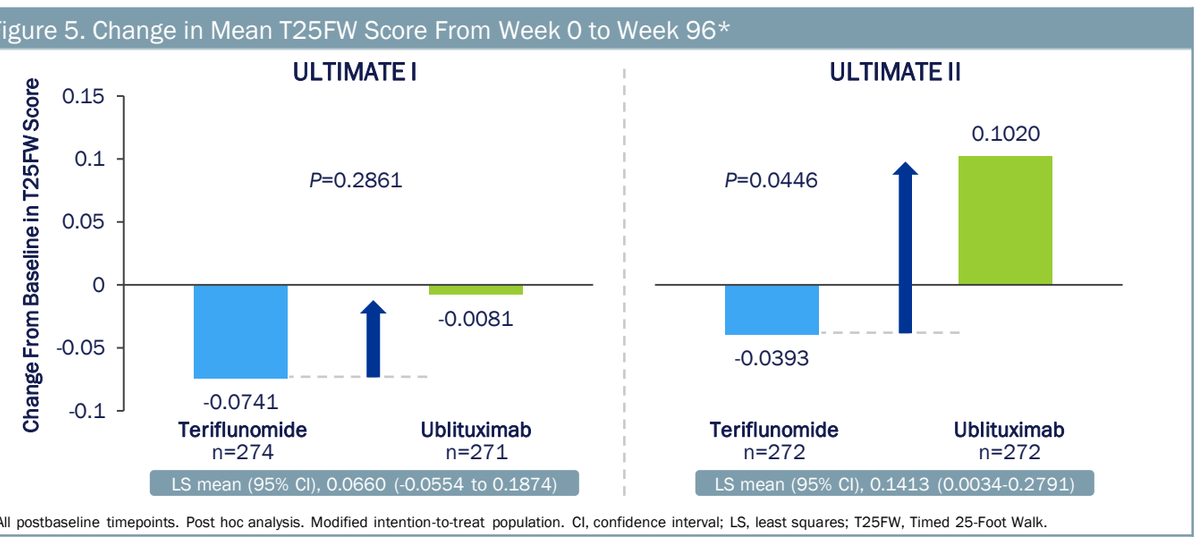
Characteristic, mean ± SD or n (%)	ULTIMATE I N=545		ULTIMATE II N=544	
	Teriflunomide n=274	Ublituximab n=271	Teriflunomide n=272	Ublituximab n=272
Age, years	37.0 ± 9.63	36.2 ± 8.42	36.2 ± 8.96	34.5 ± 8.76
Sex, female, n (%)	179 (65.3)	166 (61.3)	176 (64.7)	178 (65.4)
Race, n (%)				
White	266 (97.1)	264 (97.4)	268 (98.5)	269 (98.9)
Black	6 (2.2)	6 (2.2)	3 (1.1)	2 (0.7)
Type of MS, n (%)				
Relapsing remitting	270 (98.5)	264 (97.4)	267 (98.2)	268 (98.5)
Secondary progressive	4 (1.5)	7 (2.6)	5 (1.8)	4 (1.5)
Duration of MS since first symptoms, years	6.81 ± 5.89	7.52 ± 6.48	7.39 ± 6.26	7.31 ± 6.52
Previously untreated, n (%)†	162 (59.1)	162 (59.8)	155 (57.0)	138 (50.7)
Number of relapses in last 12 months	1.4 ± 0.67	1.3 ± 0.65	1.2 ± 0.65	1.3 ± 0.65
Number of relapses in last 24 months	2.0 ± 1.11	1.8 ± 0.96	1.8 ± 0.92	1.8 ± 0.94
EDSS score at screening	2.89 ± 1.17	2.96 ± 1.21	2.96 ± 1.20	2.80 ± 1.31
T2 lesion volume, cm^3	14.9 ± 15.8	15.9 ± 16.0	15.7 ± 17.5	14.7 ± 13.5
Number of T2 lesions	60.4 ± 37.01	64.1 ± 38.59	64.0 ± 41.23	65.3 ± 41.23
Patients free of Gd+ T1 lesions, n (%)	156 (57.4)‡	153 (56.7)§	135 (50.0)‡	131 (48.2)
Number of Gd+ T1 lesions at baseline	1.6 ± 3.67	2.3 ± 5.47	2.5 ± 5.47	2.6 ± 5.77

*Modified intention-to-treat population. †Untreated with disease-modifying therapy in 5 years prior to study entry. ‡Missing n=2. §Missing n=1.
EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; MS, multiple sclerosis; SD, standard deviation.

T25FW

- In both studies, ublituximab provided significant improvements from baseline to 96 weeks in mean T25FW score vs teriflunomide **(Figure 5)**

Figure 5. Change in Mean T25FW Score From Week 0 to Week 96*

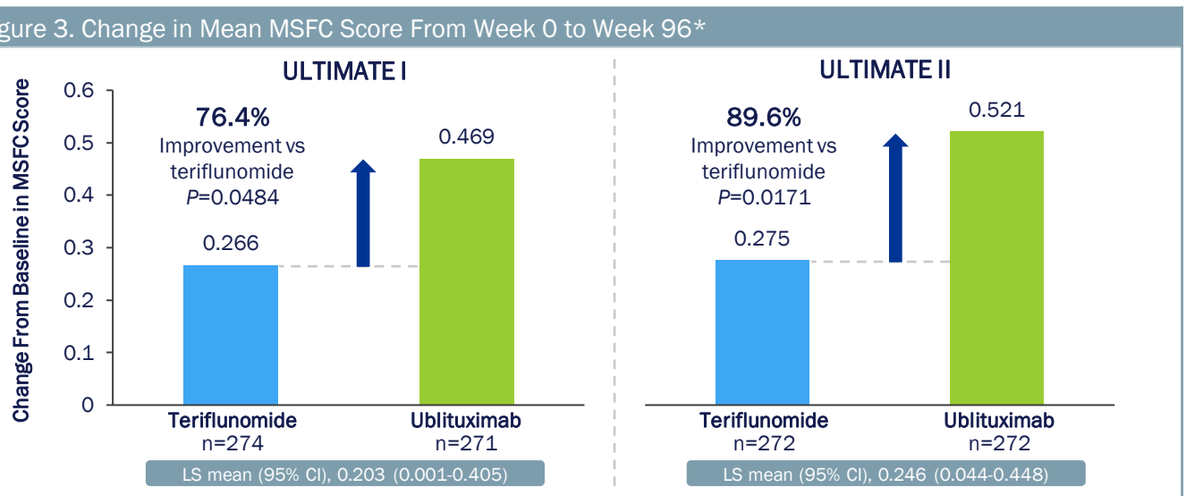


*All postbaseline timepoints. Post hoc analysis. Modified intention-to-treat population. CI, confidence interval; LS, least squares; T25FW, Timed 25-Foot Walk.

MSFC

- Ublituximab demonstrated significantly improved mean MSFC scores from baseline to 96 weeks vs teriflunomide in both ULTIMATE I and II **(Figure 3)**

Figure 3. Change in Mean MSFC Score From Week 0 to Week 96*

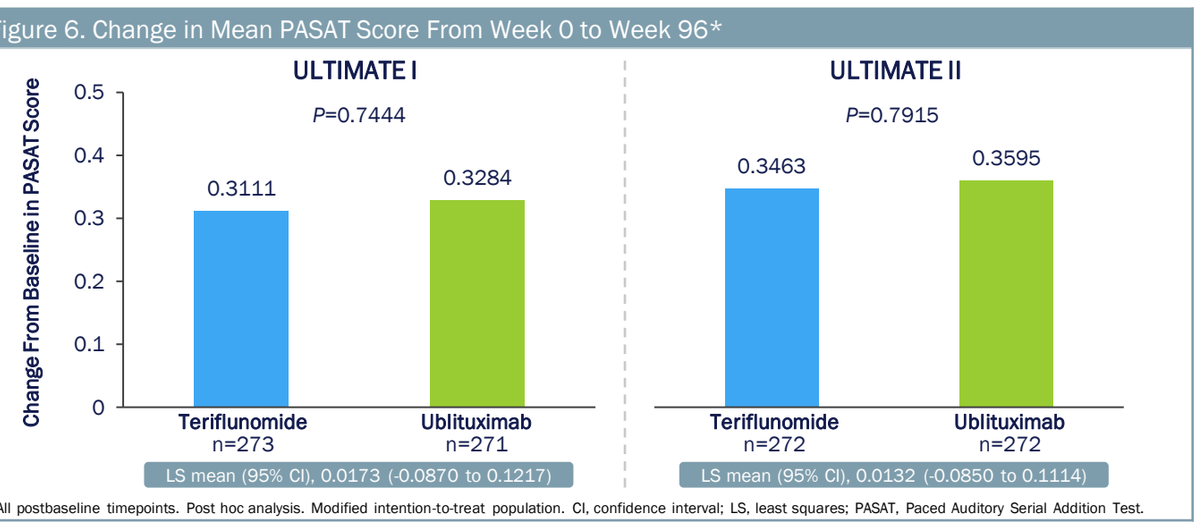


*All postbaseline timepoints. Tertiary endpoint. Modified intention-to-treat population. CI, confidence interval; LS, least squares; MSFC, Multiple Sclerosis Functional Composite.

PASAT

- The change in mean PASAT score from baseline to 96 weeks was similar between treatment groups in both ULTIMATE I and II **(Figure 6)**

Figure 6. Change in Mean PASAT Score From Week 0 to Week 96*

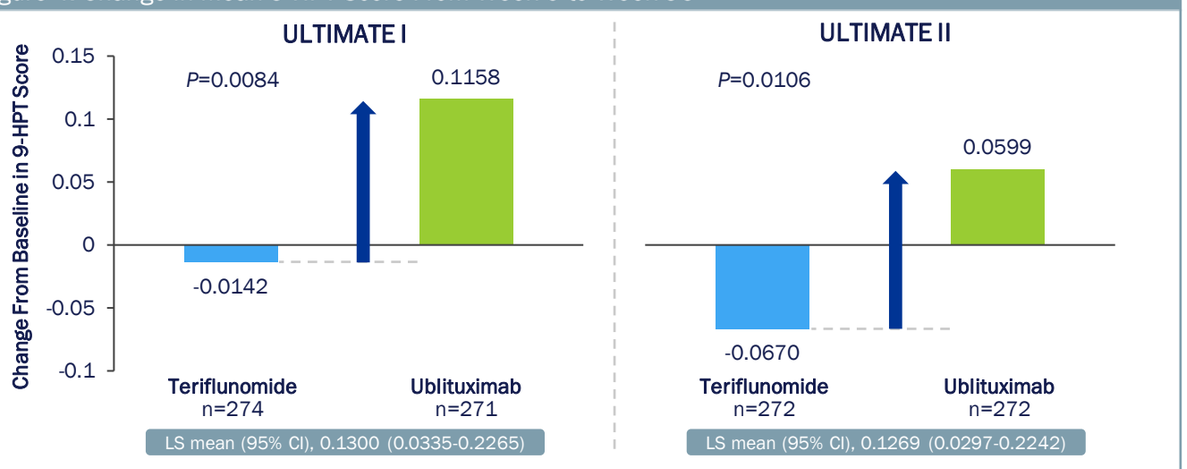


*All postbaseline timepoints. Post hoc analysis. Modified intention-to-treat population. CI, confidence interval; LS, least squares; PASAT, Paced Auditory Serial Addition Test.

9-HPT

- A significant increase in mean 9-HPT score from baseline to 96 weeks was observed with ublituximab vs teriflunomide in both ULTIMATE I and II **(Figure 4)**

Figure 4. Change in Mean 9-HPT Score From Week 0 to Week 96*



*All postbaseline timepoints. Post hoc analysis. Modified intention-to-treat population. 9-HPT, 9-Hole Peg Test; CI, confidence interval; LS, least squares.

CONCLUSIONS

- In the primary analysis of the phase 3 ULTIMATE I and II studies, ublituximab provided superior efficacy vs teriflunomide, with a favorable safety and tolerability profile and no unexpected safety signals[3]
- Improvements in disability were observed with ublituximab in both studies, with significantly more patients achieving 12-week or 24-week CDI vs teriflunomide[3]
- In the analyses reported here, ublituximab treatment was associated with significant improvement in MSFC score vs teriflunomide in both ULTIMATE I and II; this was driven by improvements in disability as measured by the 9-HPT and T25FW
- Further analyses of the effects of ublituximab on disability improvement in patients with RMS are ongoing

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.** Steinman L, et al. Presented at: 7th Congress of EAN—Virtual 2021; June 19-22, 2021. Abstract A-21-00763. **4.** Fox E, et al. *Mult Scler*. 2021;27(3):420-429. **5.** Steinman L, et al. Presented at: AAN 2021 Virtual Annual Meeting; April 17-22, 2021. Poster 9056.

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Scan code to view additional data in presentation 117: Phase 3 Results of the ULTIMATE I & II Global Studies.

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