Disability Changes in the Absence of Relapse in the Phase 3 ULTIMATE I and II Studies of Ublituximab Versus Teriflunomide in Participants With Relapsing Multiple Sclerosis

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OBJECTIVE

- To evaluate disability changes in the absence of relapse with ublituximab in the ULTIMATE I and II studies

KEY FINDINGS

- In confirmed relapse-free participants, the mean change from baseline in Expanded Disability Status Scale (EDSS) score was significantly improved with ublituximab versus teriflunomide at Weeks 48 (-0.13 versus -0.06, respectively), 84 (-0.19 versus -0.08), and 96 (-0.19 versus -0.07) (P<0.05 for all)
- In participants without confirmed relapse, the least squares (LS) mean change from baseline at all postbaseline time points up to Week 96 was significantly improved with ublituximab versus teriflunomide, respectively, for:
  - Multiple Sclerosis Functional Composite (MSFC): 0.557 versus 0.359, P=0.0095
  - 9-Hole Peg Test (9-HPT): 0.152 versus 0.025, P=0.0005
  - Timed 25-Foot Walk (T25FW): 0.071 versus -0.025, P=0.0375

CONCLUSIONS

- In pooled post hoc analyses of ULTIMATE I and II, ublituximab was associated with significant improvement versus teriflunomide across multiple disability measures in the subset of participants without confirmed relapses during the study
- These results further support improved disability outcomes with ublituximab versus teriflunomide in participants with relapsing multiple sclerosis (RMS), independent of a reduced risk of relapse

BACKGROUND

- Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20 and is glycoengineered for enhanced antibody-dependent cellular cytotoxicity (ADCC)[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 (MS)[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 studies evaluating the efficacy and safety of ublituximab versus teriflunomide in participants with RMS[5]
- 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 (Gd+) T1 lesions and the number of new/enlarging T2 lesions[5]
- Disability progression in MS has been proposed to occur as a result of both relapses and tissue injury independent of relapse[6]
- Long-term disability progression independent of relapse is common in patients with relapsing-remitting MS[6,7]
- Studies have demonstrated that currently approved anti-CD20 therapies are associated with a reduction in disability progression independent of relapse[8,9]
- Post hoc analyses of the Phase 3 ULTIMATE studies of ublituximab were conducted to evaluate disability progression in participants who did not have confirmed relapse during the studies

METHODS

- ULTIMATE I and II 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]
- Clinical evaluations were performed every 12 weeks[5]
- Pooled post hoc analyses evaluated measures of disease progression in the subset of participants with no Independent Relapse Adjudication Panel (IRAP)-confirmed relapses during the studies

RESULTS

- Baseline characteristics for participants without IRAP-confirmed relapse are shown in **Table 1**

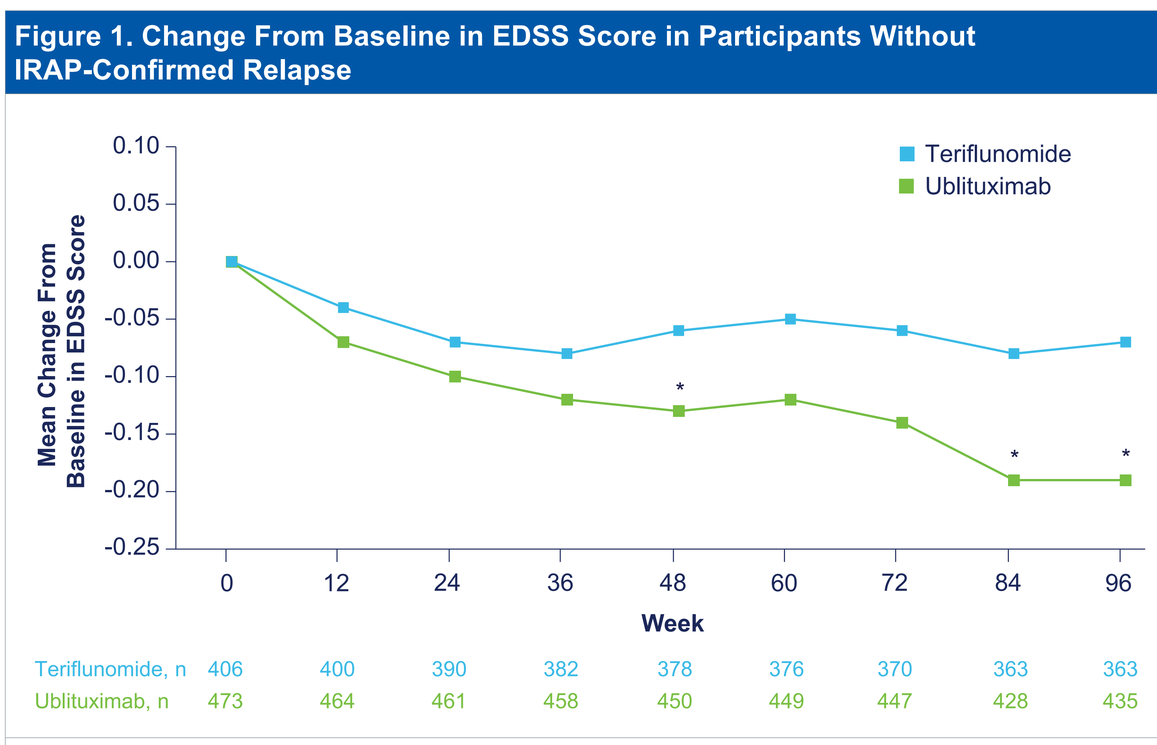
Table 1. Demographics and Baseline Characteristics in Participants Without IRAP-Confirmed Relapse

Mean ± standard deviation or %	Teriflunomide (n=406)	Ublituximab (n=473)
Age, years	37.4±9.2	35.1±8.5
Sex, female, %	66.7	61.7
Time since MS diagnosis, years	4.6±5.0	4.8±5.3
Duration of MS since first symptoms, years	7.0±6.1	7.2±6.3
Number of relapses in last 12 months	1.3±0.7	1.3±0.6
Number of relapses in last 24 months	1.8±1.0	1.8±0.9
Time since most recent relapse, months	6.3±4.6	7.1±8.3
EDSS score at screening	2.8±1.2	2.8±1.2
T2 lesion volume, mL	15.3±17.7	15.1±15.0
Number of T2 lesions	59.3±35.7	64.6±40.4
Participants free of Gd+ T1 lesions, %	55.9	52.4

Safety population.
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IRAP, Independent Relapse Adjudication Panel; MS, multiple sclerosis.

- In confirmed relapse-free participants, the mean change from baseline in EDSS score was significantly improved with ublituximab versus teriflunomide at Weeks 48 (-0.13 versus -0.06), 84 (-0.19 versus -0.08), and 96 (-0.19 versus -0.07) (P<0.05 for all) (**Figure 1**)

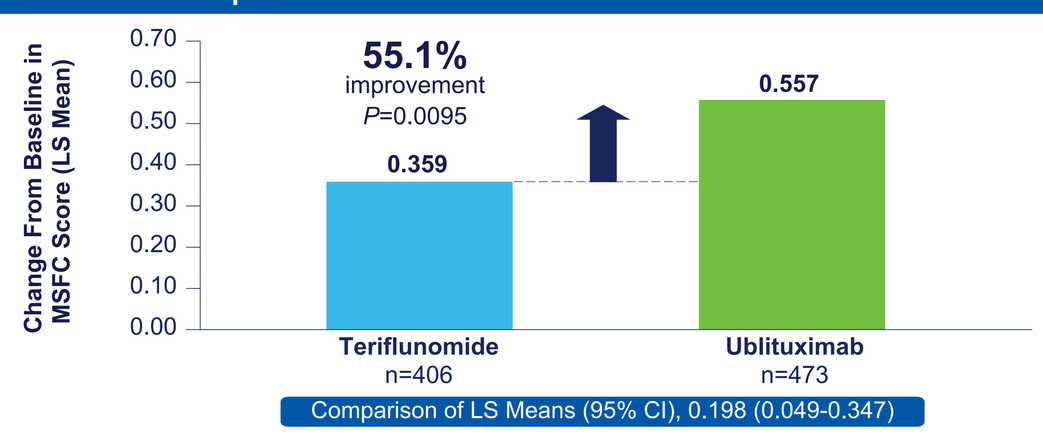
Figure 1. Change From Baseline in EDSS Score in Participants Without IRAP-Confirmed Relapse



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

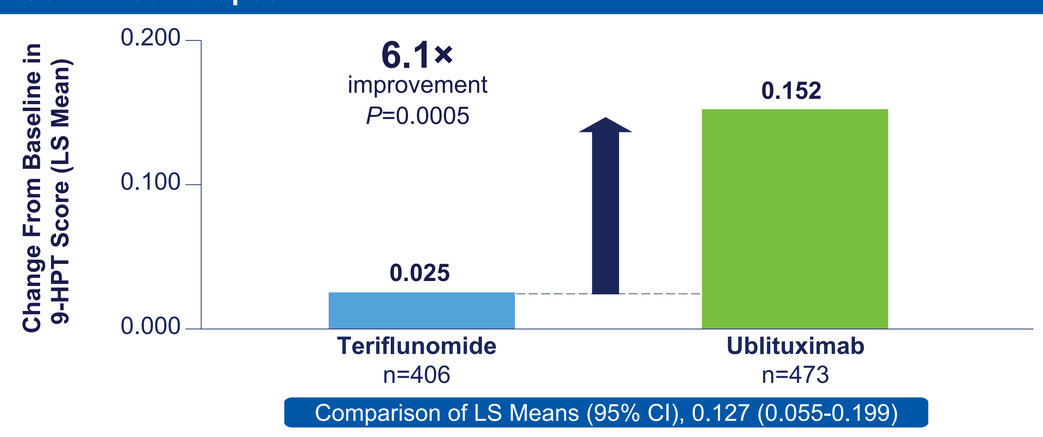
- Other disability measurements also demonstrated improvement with ublituximab versus teriflunomide in confirmed relapse-free participants for all postbaseline time points up to Week 96: MSFC (**Figure 2**), 9-HPT (**Figure 3**), and T25FW (**Figure 4**)

Figure 2. Change From Baseline in MSFC Score in Participants Without IRAP-Confirmed Relapse



Pooled post hoc analysis. Modified intention-to-treat population. 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; IRAP, Independent Relapse Adjudication Panel; LS, least squares; MSFC, Multiple Sclerosis Functional Composite.

Figure 3. Change From Baseline in 9-HPT Score in Participants Without IRAP-Confirmed Relapse



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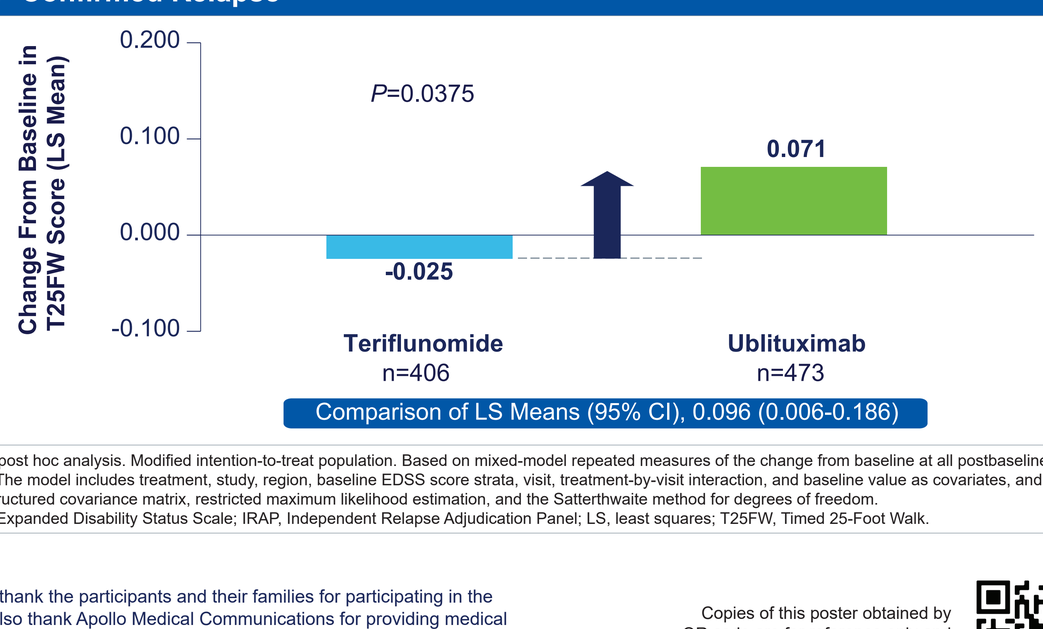
9-HPT, 9-Hole Peg Test; EDSS, Expanded Disability Status Scale; IRAP, Independent Relapse Adjudication Panel; LS, least squares.

Figure 4. Change From Baseline in T25FW Score in Participants Without IRAP-Confirmed Relapse



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EDSS, Expanded Disability Status Scale; IRAP, Independent Relapse Adjudication Panel; LS, least squares; T25FW, Timed 25-Foot Walk.

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; 1-4 June 2022; National Harbor, MD, USA. Oral presentation DMT03. **4.** Steinman L, et al. Presented at: ECTRIMS; 13-15 October 2021; Virtual. Oral presentation 117. **5.** Steinman L, et al. *N Engl J Med*. 2022;387(8):704-714. **6.** Cree BAC, et al. *Ann Neurol*. 2019;85(5):653-666. **7.** Kappos L, et al. *Mult Scler*. 2018;24(7):963-973. **8.** Kappos L, et al. *JAMA Neurol*. 2020;77(9):1132-1140. **9.** Kappos L, et al. Presented at: AAN; 17-21 April 2021; Virtual. Poster P15.087.

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