Ublituximab is Associated With Significant Improvement in Fatigue: Results From ULTIMATE I and II

Enrique Alvarez, MD, PhD,[1] Derrick Robertson, MD,[2] Daniel Wynn, MD,[3] Yihuan Xu, PhD,[4] Lily Lee, PhD,[4] Sibyl Wray, MD[5]

[1]University of Colorado, Aurora, CO; [2]University of South Florida, Tampa, FL; [3]Consultants in Neurology, Northbrook, IL; [4]TG Therapeutics, New York, NY; [5]Hope Neurology, Knoxville, TN

Presented at the Consortium of Multiple Sclerosis Centers (CMSC), May 31 - June 3, 2022, Aurora, CO; Oral XXXXXX.

Disclosures

- EA has received compensation for advisory boards, lectures, and consultancy with Actelion/Janssen, Alexion, Bayer, Biogen, Celgene/BMS, EMD Serono/Merck, Genentech/Roche, Genzyme, Novartis, Sanofi, and TG Therapeutics, and research support from Biogen, Genentech/Roche, Novartis, TG Therapeutics, Patient-Centered Outcomes Research Institute, National Multiple Sclerosis Society, National Institutes of Health, and Rocky Mountain MS Center.
- DR has received grant support from Anokion, Atara Biotherapeutics, Biogen, CorEvitas, EMD Serono, Genentech, GW Pharmaceuticals, Janssen, Novartis, PCORI, PRIME CME, Sanofi, and TG Therapeutics; has received consulting fees from Alexion, Biogen, Bristol Myers Squibb, EMD Serono, Genentech, Greenwich Biosciences, Horizon, Janssen, Mallinckrodt, Novartis, Sanofi, and TG Therapeutics; has received honoraria or speaker fees from Alexion, Biogen, Bristol Myers Squibb, EMD Serono, Genentech, Horizon, Janssen, PRIME CME, Sanofi and TG Therapeutics, all outside the submitted work.
- DW has received compensation from Mylan, Abbvie, Amneal, ANI, EMD Serono, Sanofi, TEVA, Banner Life, Biogen, BMS, Horizon, Immunic, Innocare, GW Therapeutics, Mallinckrodt, TG Therapeutics, Teva, Novartis, Adamas Pharmaceutics and Roche, and as Director, Consultants in Neurology Comprehensive Care Center with National MS Society.
- SW has received honoraria for advisory boards and/or consultants fees from BMS, Biogen, Genentech/Roche, and TG Therapeutics; research support from Biogen, Celgene, EMD Serono, Genentech/Roche, Genzyme/Sanofi, GW Pharmaceuticals, Novartis, TG Therapeutics.

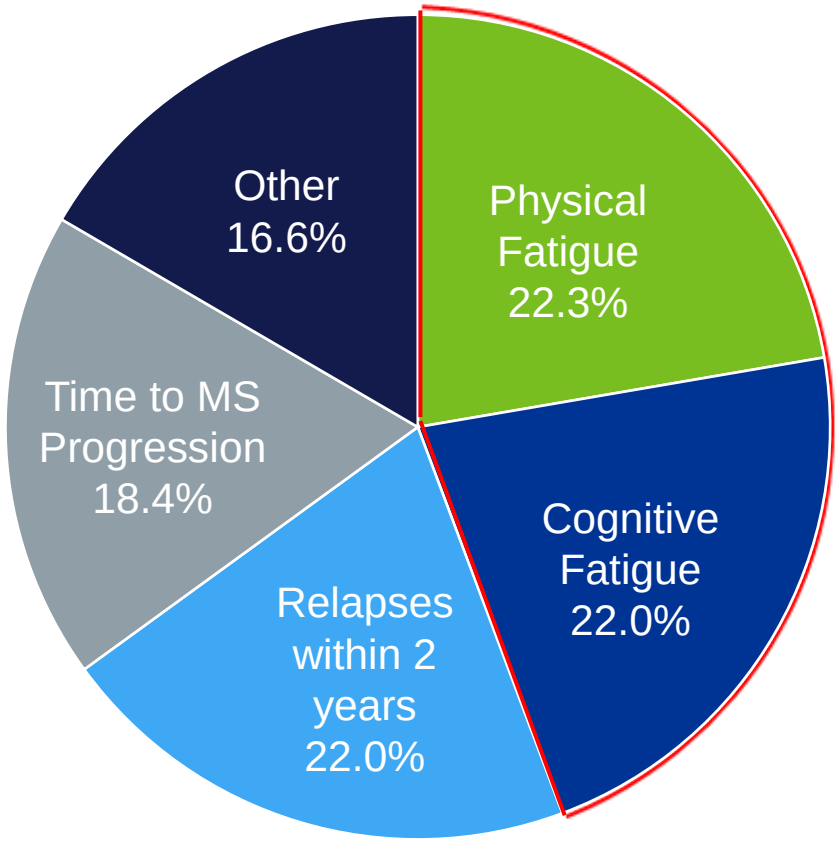
Background

- Fatigue is the most common MS symptom, affecting approximately 80% of patients[1]
- The impact of MS related fatigue is observed in reduced health-related quality of life (HRQoL), daily activities and work productivity[2]
- ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) are identical, Phase 3, randomized, multicenter, double-blind, active-control, double-dummy studies evaluating the efficacy and safety of ublituximab vs teriflunomide in participants with RMS. Ublituximab significantly improved annualized relapse rate and magnetic resonance imaging activity vs teriflunomide.[3]
- The Fatigue Impact Scale (FIS), a 40-question instrument, was used to assess the impact of ublituximab and teriflunomide on cognitive, physical and psychosocial components of fatigue.

1 https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms/Fatigue. 2 Berrigan Neurology 2016; 86: 1417–1424.; Janardhan J Neurol Sci 2002; 205: 51–58. 3. Steinman N Engl J Med 2022;387:704.

Drivers of MS Treatment Preferences[1]

Relative Attribute Importance (RAI)



A recent study exploring treatment preferences for MS patients revealed that

- Patients reported the most valued attributes of MS therapy are the impact on **physical fatigue and cognitive fatigue**
- Patients also reported a willingness to accept 5.5 relapses in 2 years and a decrease of up to 7.4 years in time to MS disease progression to improve their fatigue

[1]Tervonen Mult Scler J Exp Transl Clin. 2023 Jan 23;9(1):20552173221150370. Other includes immune system recovery time (RAI =8.0%), drug interactions (RAI =5.5%), monitoring visits (RAI =3.0%).

OBJECTIVE

- To evaluate changes from baseline in fatigue using the FIS with ublituximab vs teriflunomide in pooled post hoc analyses of ULTIMATE I and II.

ULTIMATE I and II: Study Design

Identical, Phase 3, randomized, multicenter, double-blinded, active-controlled studies conducted in parallel

Study Population

- Age 18-55 years
- RRMS or SPMS (2010 McDonald criteria)
- ≥2 documented relapses within the 2 years prior or ≥1 relapse in the prior year, and/or ≥1 Gd+ lesion in the year prior to screening
- EDSS score 0.0-5.5
- Neurologic stability ≥30 days prior to screening

Treatment (96 Weeks)[a]

Teriflunomide
14 mg PO QD until last day of W95
Infusion placebo on same schedule as below

or (randomized 1:1)

Ublituximab
150 mg IV on D1 over 4 hours, and
450 mg IV over 1 hour on D15, W24, W48, W72
Oral placebo QD from D1 until last day of W95

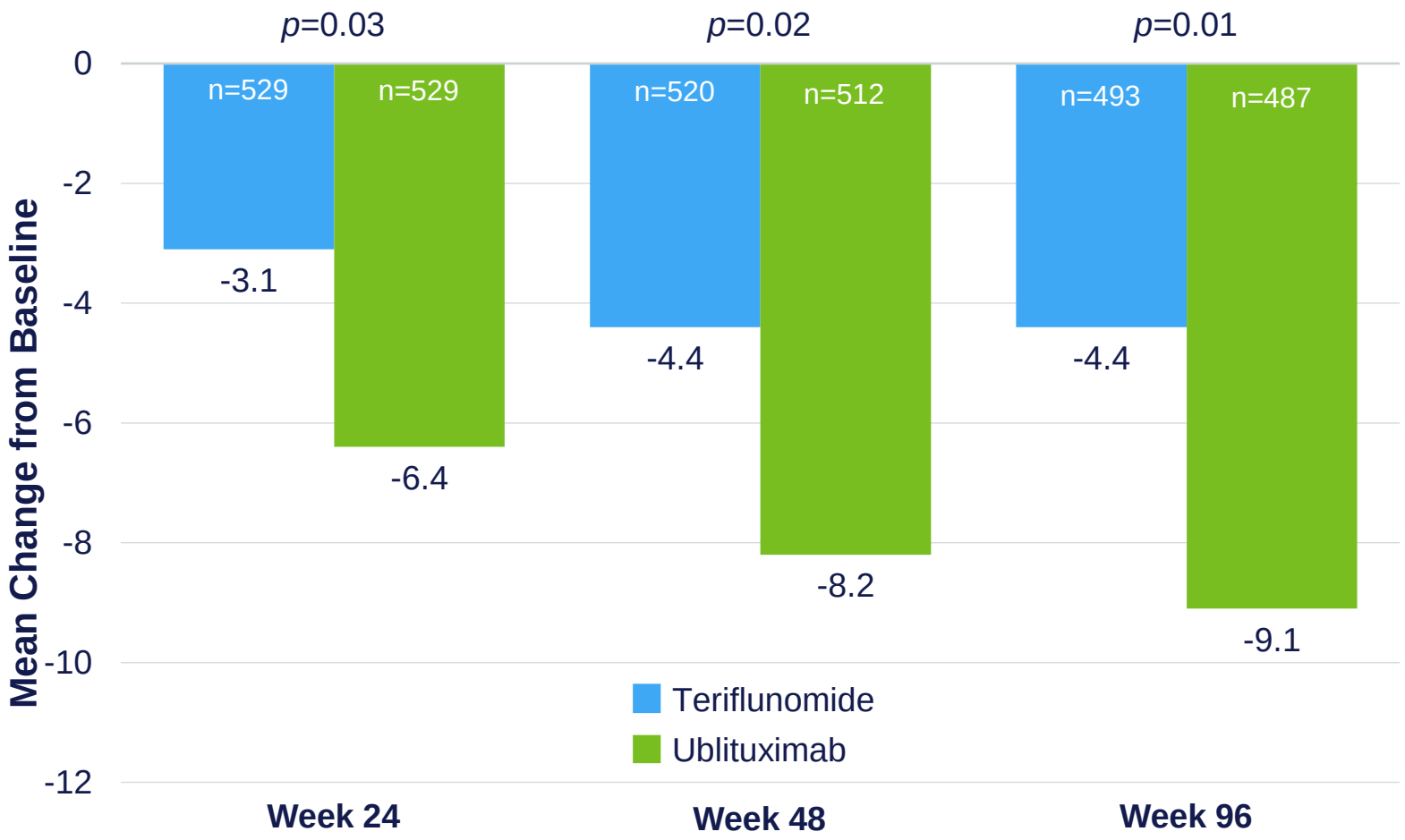
Endpoints (at 96 Weeks)

- **Primary**
  - ARR
- **Key secondary**
  - Total number of Gd+ T1 lesions
  - Total number of new or enlarging T2 hyperintense lesions
  - Proportion of participants with NEDA from Week 24 to Week 96

The FIS was performed at **baseline, Weeks 24, 48 and 96**. Scoring is from 0-160, with higher scores indicating increased functional limitation due to fatigue.

[a]After completing Week 96, participants entered into a 20-week safety follow-up and were eligible to enroll into an OLE study.
ARR, annualized relapse rate; CDI, confirmed disability improvement; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IM, intramuscular; IV, intravenous; NEDA, no evidence of disease activity; PO, by mouth; QD, once daily; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous; SPMS, secondary-progressive multiple sclerosis; W, week.

Change From Baseline in Fatigue Impact Scale (FIS): Total Score

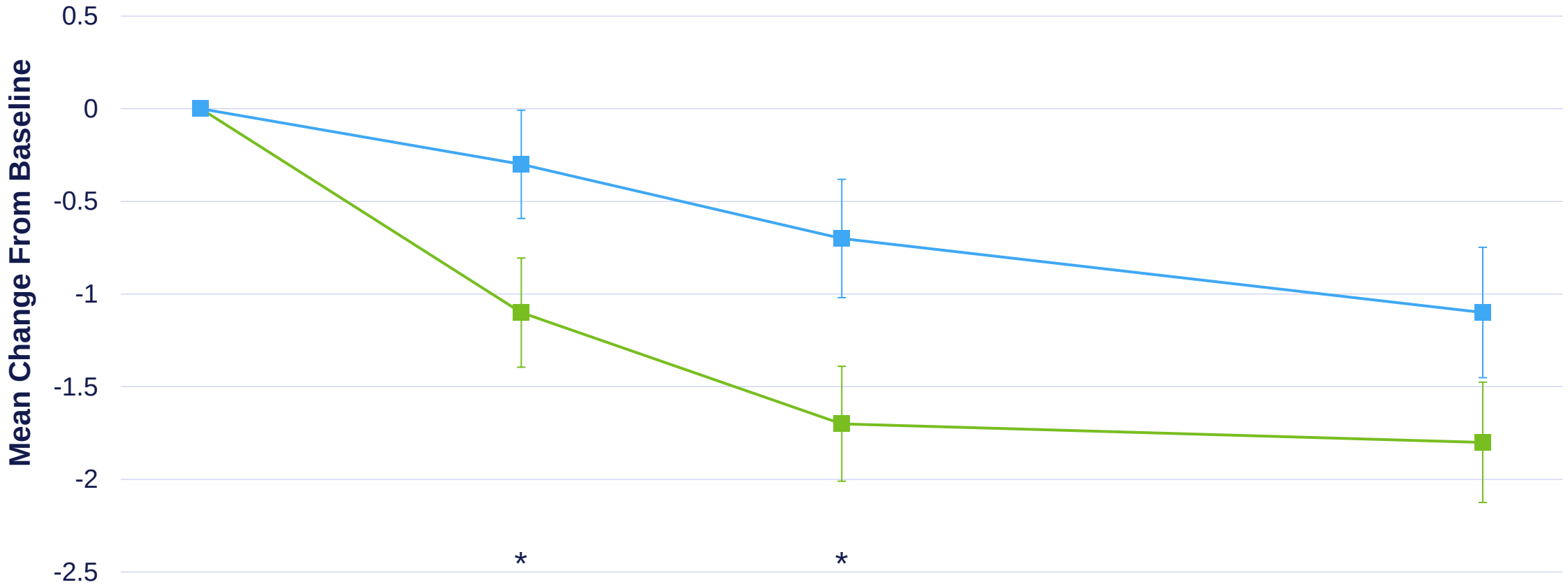


The Minimally Important Difference (MID) for FIS in an MS population is a decrease of 9 points.[1]

p-value based on the t-test of change from baseline.

[1]Rendas-Baum Qual Life Res 2010; 19:1349.

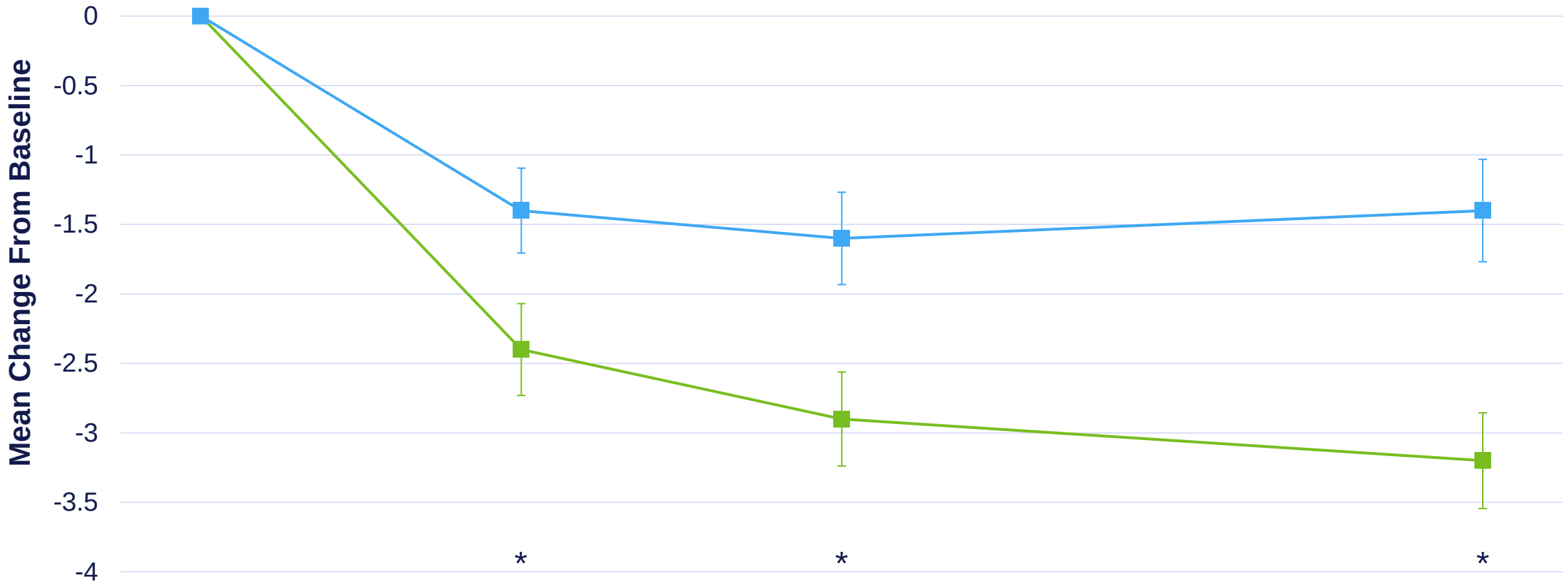
Change From Baseline in Fatigue Impact Scale: Cognitive Dimension Score



Week	BL	24	48	96
Teriflunomide, n	546	529	512	487
Ublituximab, n	540	526	516	491

*p<0.05. Pooled post hoc analysis. Modified intention-to-treat population. p-value based on the t test of change from baseline.
BL, baseline. Error bars represent Standard Error of the Mean

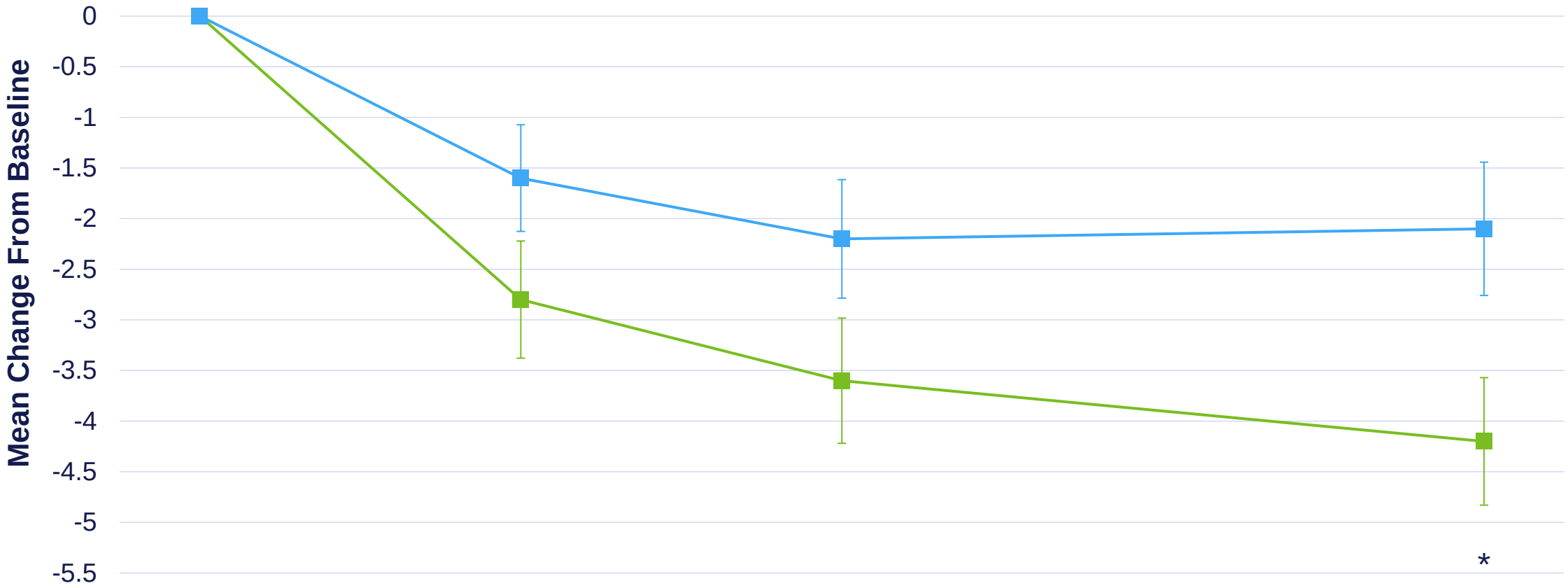
Change From Baseline in Fatigue Impact Scale: Physical Dimension Score



Week	BL	24	48	96
Teriflunomide, n	546	529	512	487
Ublituximab, n	542	529	517	493

*p<0.05. Pooled post hoc analysis. Modified intention-to-treat population. p-value based on the t test of change from baseline.
BL, baseline. Error bars represent Standard Error of the Mean

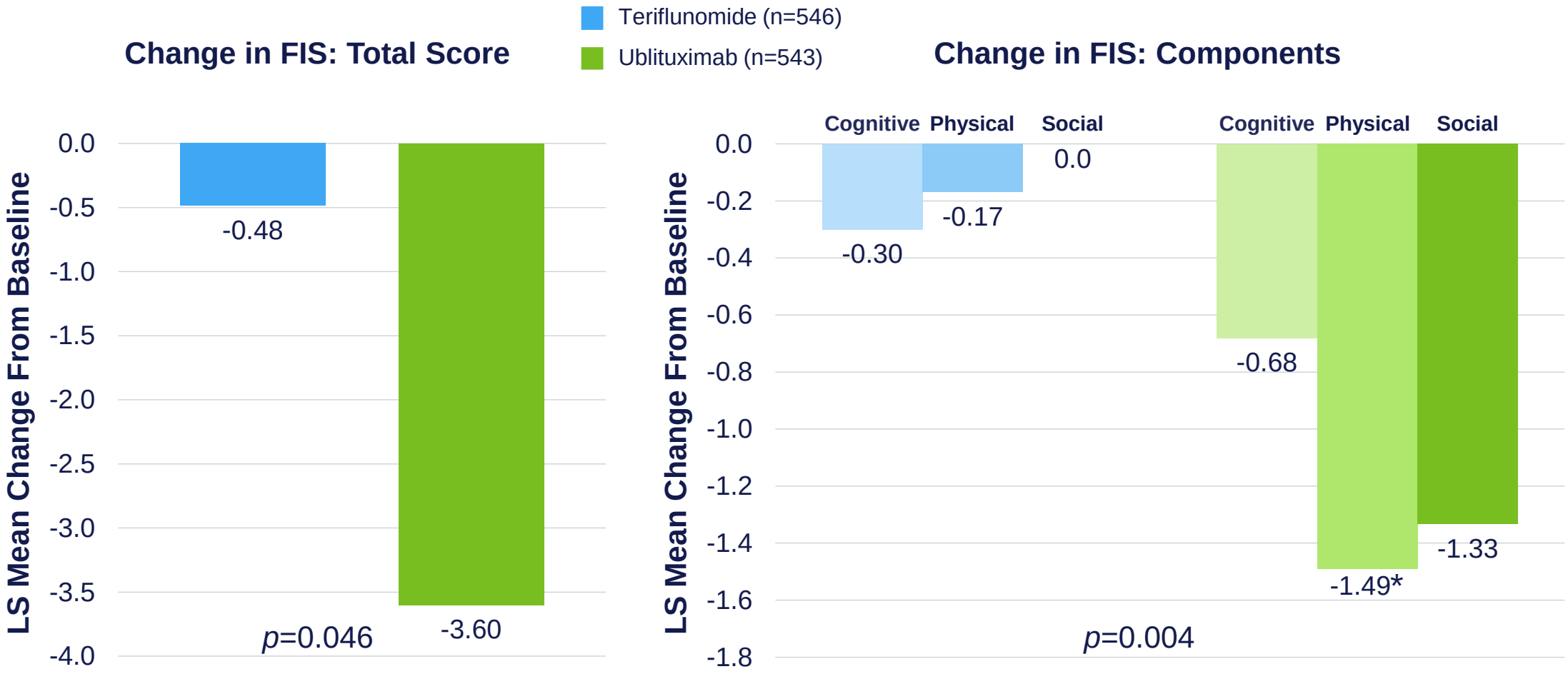
Change From Baseline in Fatigue Impact Scale: Social Dimension Score



Week	BL	24	48	96
Teriflunomide, n	542	523	505	482
Ublituximab, n	534	521	510	484

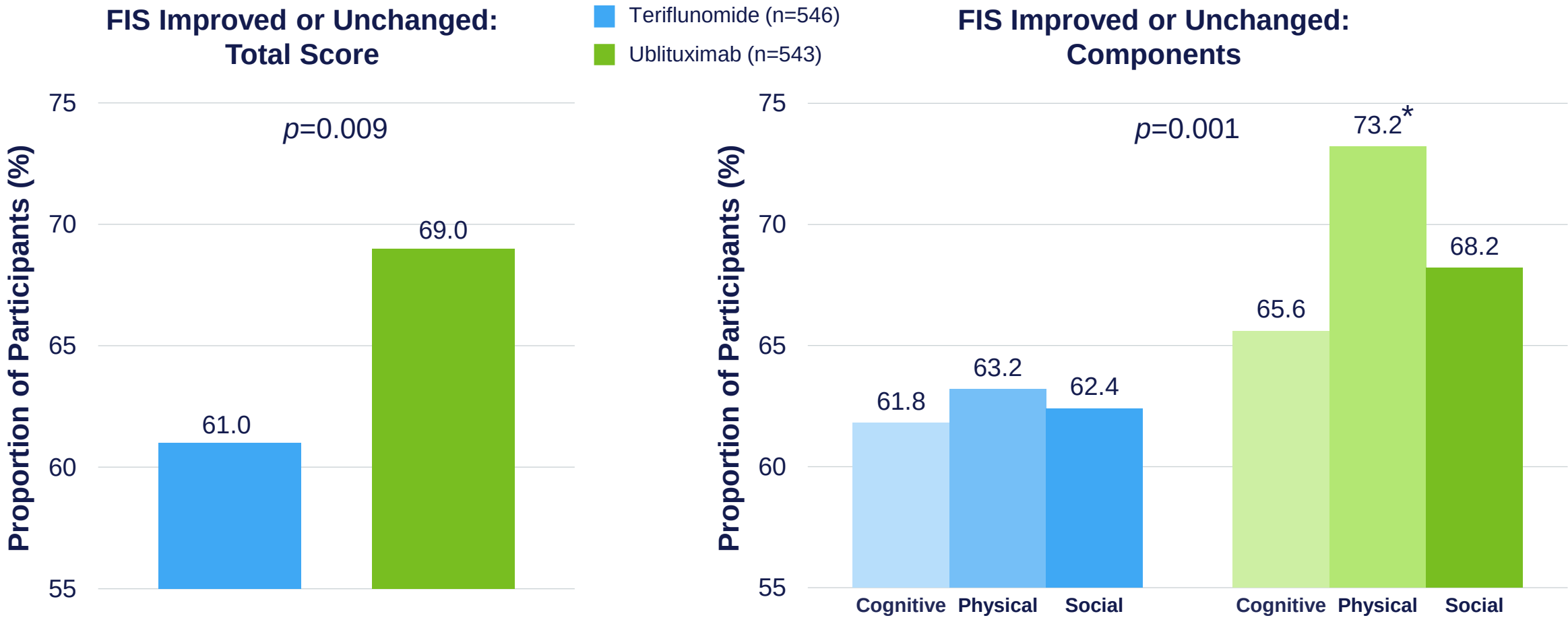
*p<0.05. Pooled post hoc analysis. Modified intention-to-treat population. p-value based on the t test of change from baseline.
BL, baseline. Error bars represent Standard Error of the Mean

Change From Baseline in Fatigue Impact Scale (LS Means)



*p=0.0036. Pooled post hoc analysis. Modified intention-to-treat population. Mixed-model repeated measures of the change from baseline at all postbaseline time points. The model includes treatment, study, region, baseline EDSS strata, visit, treatment-by-visit interaction, and baseline value, and uses an unstructured covariance matrix, restricted maximum likelihood estimation, and the Satterthwaite method for degrees of freedom. FIS, Fatigue Impact Scale.

Proportion of Participants FIS Improved or Unchanged from Baseline to Week 96



Pooled post hoc analysis. Change from Baseline to Week 96. p-value based on chi-square test. Proportion worsened for ubltuximab (31%) vs teriflunomide (39%).
FIS, Fatigue Impact Scale

Conclusions

- In a pooled post-hoc analysis of ULTIMATE I and II, ublituximab was associated with a significant improvement in FIS relative to teriflunomide (p=0.046).
- Ublituximab demonstrated a 9-point improvement at Week 96, previously reported to be the Minimally Important Difference (MID) for FIS in an MS population.
- Across all timepoints, improvement in FIS was observed in all domains (cognitive, physical, social) and was significant in the physical domain.
- A significantly higher proportion of ublituximab participants had FIS scores improved or unchanged at Week 96 compared to baseline.

Acknowledgments

- The authors thank the participants and their families for contributions to the ULTIMATE I and II studies, and to Chris Rowland for editorial support for the presentation. The ULTIMATE I and II studies were sponsored by TG Therapeutics.