Reduced Disease Progression With Ublituximab vs Teriflunomide in the Phase 3 ULTIMATE I and II Studies in Relapsing Multiple Sclerosis

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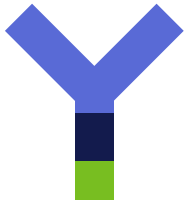
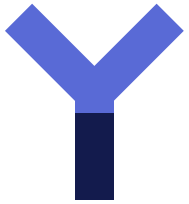
Presented at the Consortium of Multiple Sclerosis Centers (CMSC), June 1-4, 2022, National Harbor, MD; Oral DMT03.

Disclosures

- Enrique Alvarez 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.

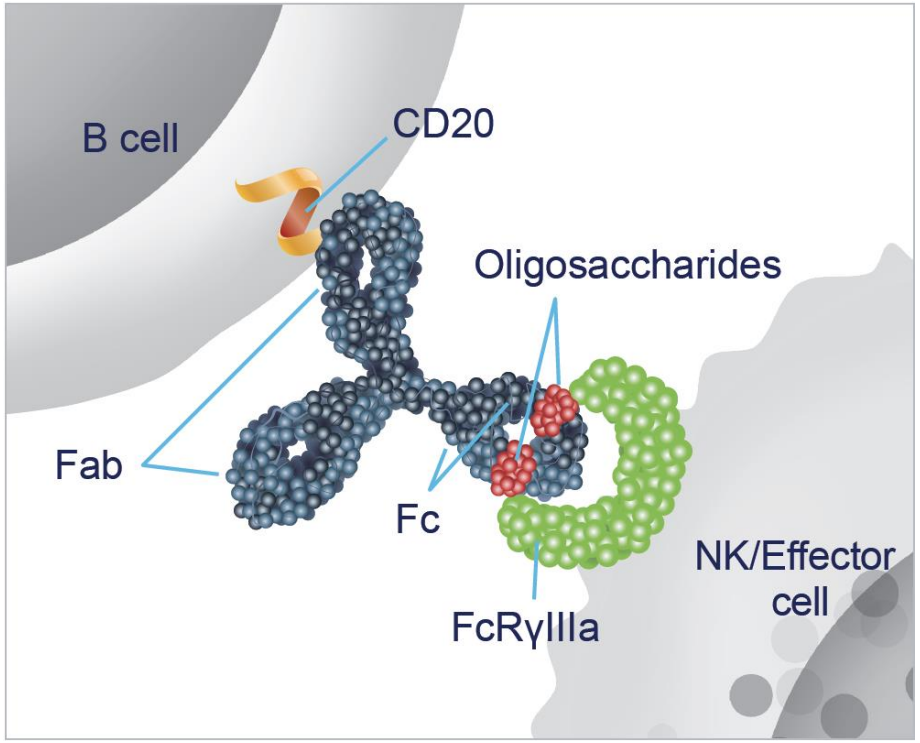
Ublituximab Is a Novel, Next-Generation Glycoengineered Anti-CD20 mAb

	Ublituximab	Rituximab	Ocrelizumab	Ofatumumab
Mouse Human Glycoengineered				
Structure	Glycoengineered chimeric IgG1	Chimeric IgG1	Humanized IgG1	Recombinant fully human IgG1
Regimen	150 mg D1, 450 mg D15, then 450 mg every 24 wk	1 g D1 and D15, then 1 g every 24 wk	300 mg D1 and D15, then 600 mg every 24 wk	20 mg every 4 wk
Route	Intravenous	Intravenous	Intravenous	Subcutaneous
Infusion time[a]	1 h[b]	Not approved for MS	2 h[c]	-
Primary MOA	ADCC	CDC	ADCC	CDC
ADCC	+++++[1]	+[2]	++[3]	++[4]
CDC	++[2]	+++[2]	+[3]	+++++[2]

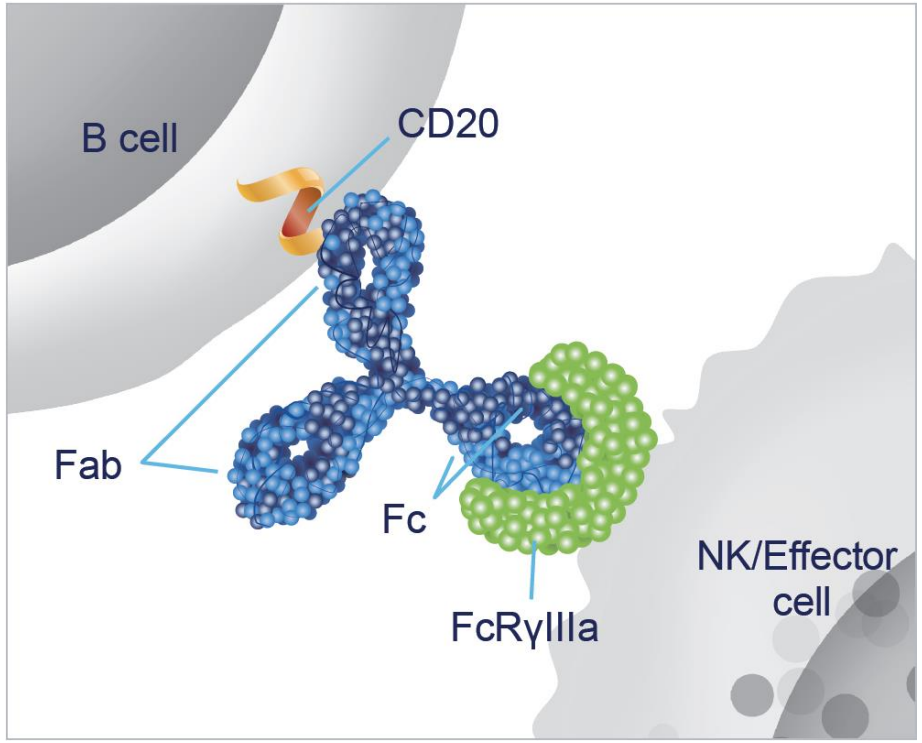
[a]After initial dose. [b]Initial infusion time over 4 hours. [c]Initial infusion time over 2.5 hours.
ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; D, day; Ig, immunoglobulin; mAb, monoclonal antibody; MOA, mechanism of action; MS, multiple sclerosis.
Adapted from Ancau M, et al. *Expert Opin Biol Ther*. 2019;19(8):829-843 and Sellebjerg F, et al. *CNS Drugs*. 2020;34(3):269-280.
1. de Romeuf C, et al. *Br J Haematol*. 2008;140(6):635-643. 2. Bellon A, et al. *Blood*. 2011;118(21):3913. 3. Bennett J. 2011 North American Neuro-Ophthalmology Society Annual Meeting Syllabus; pages 319-326. 4. Teeling JL, et al. *J Immunol*. 2006;177(1):362-371.

Ublituximab Is Glycoengineered to Enhance ADCC

In nonglycoengineered anti-CD20 antibodies, the core fucose of Fc-linked oligosaccharides sterically blocks interaction with FcγRIIIa on effector cells, reducing affinity[1,2]



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[2-4]

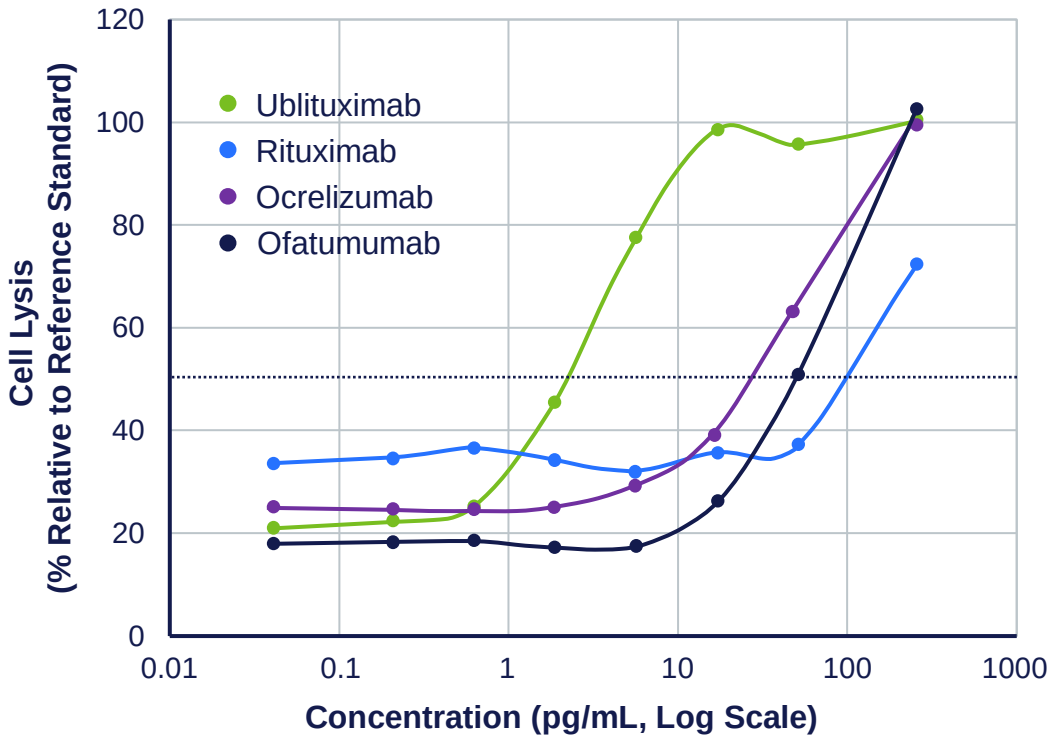


Fab, fragment antigen-binding; Fc, fragment crystallizable; FcγR, Fc gamma receptor; NK, natural killer.

1. Ferrara C, et al. *Proc Natl Acad Sci U S A*. 2011;108(31):12669-12674. 2. Sun Y, et al. *J Biol Chem*. 2021;297(1):100826. 3. de Romeuf C, et al. *Br J Haematol*. 2008;140(6):635-643.
4. Fox E, et al. *Mult Scler*. 2021;27(3):420-429.

Ublituximab Has the Highest ADCC Activity Compared With Other Anti-CD20s

ADCC Dose Response Curve[1]



- ADCC activity was measured using CD20-expressing Raji cells in the presence of KILR® (CD16+) effector cells and human serum samples diluted to 250-fold
- Cell viability was measured using CytoTox-Glo™

ADCC Activity[1]

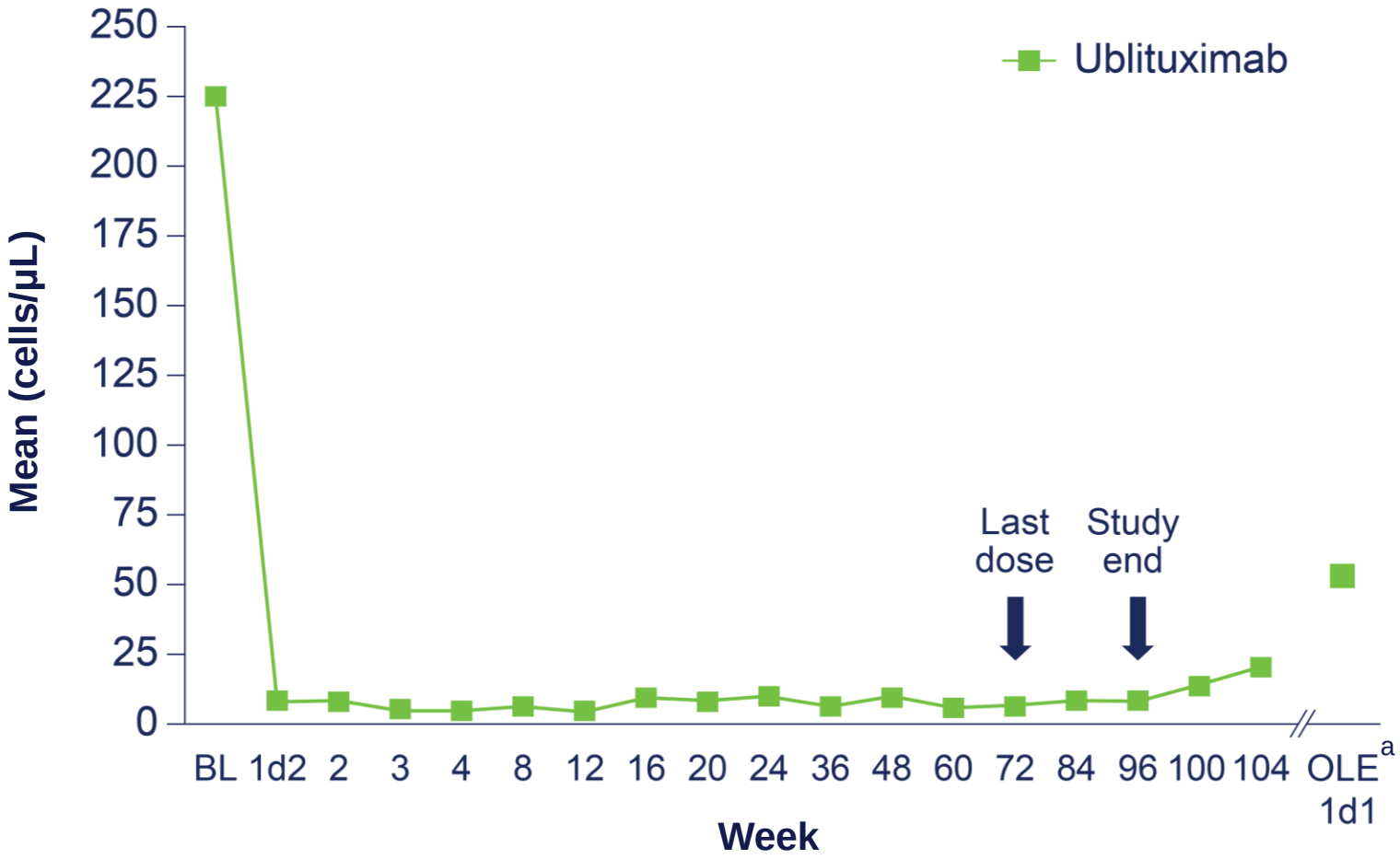
	EC_{50}[a] (pg/mL)
Ublituximab	2.42
Rituximab	5457.0
Ocrelizumab	60.8
Ofatumumab	74.1

[a]The EC_{50} is the concentration (or dose) effective in producing 50% of the maximal response and allows for comparison of drug potencies.[2]

KILR CD16+, single donor-derived human CD8+ T-lymphocytes engineered to express CD16 (FcγRIII) on their plasma membrane surface.

1. TG Therapeutics. Data on file. 2. Science Direct. Accessed February 10, 2022. https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/ec50.

B-Cell Depletion With Ublituximab in ULTIMATE I and II: Pooled Analysis



[a]Mean time since last dose was 54.8 weeks for participants with B-cell counts at OLE 1d1. Pooled post hoc analysis. Modified intention-to-treat (mITT) population. Data presented as the mean B-cell count among participants evaluable at each timepoint.
1d1, Week 1 Day 1; 1d2, Week 1 Day 2; BL, baseline; OLE, open-label extension.
Fox E, et al. Presented at: ACTRIMS 2022, February 24-26; West Palm Beach, FL. Poster P105.

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

Premedication[b]

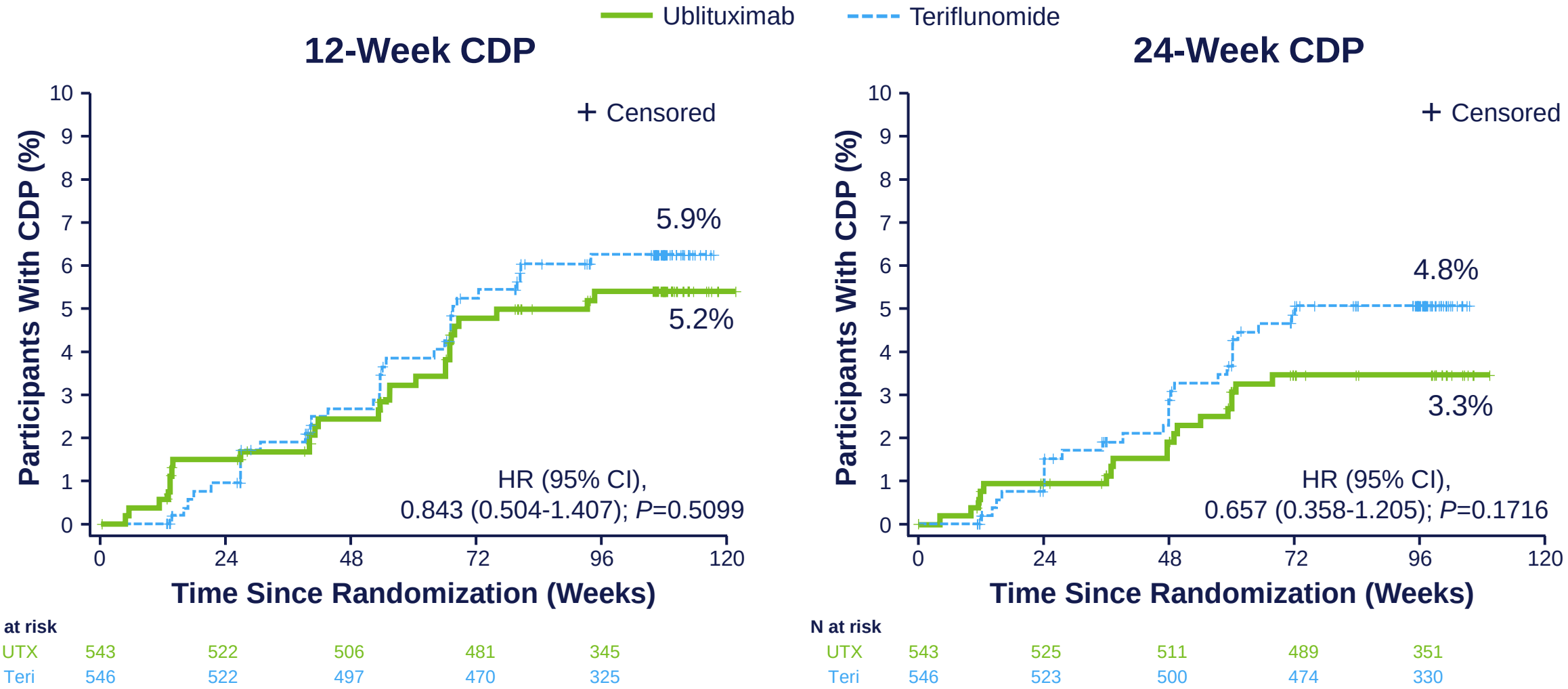
30-60 minutes prior to each dose of ublituximab or IV placebo: antihistamine (diphenhydramine 50 mg or equivalent) and corticosteroid (dexamethasone 10-20 mg or equivalent): oral, IV, IM, and/or SC (investigator discretion)

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
- **Prespecified pooled analyses**
  - 12- and 24-week CDP
  - 12- and 24-week CDI
- **Safety and tolerability**

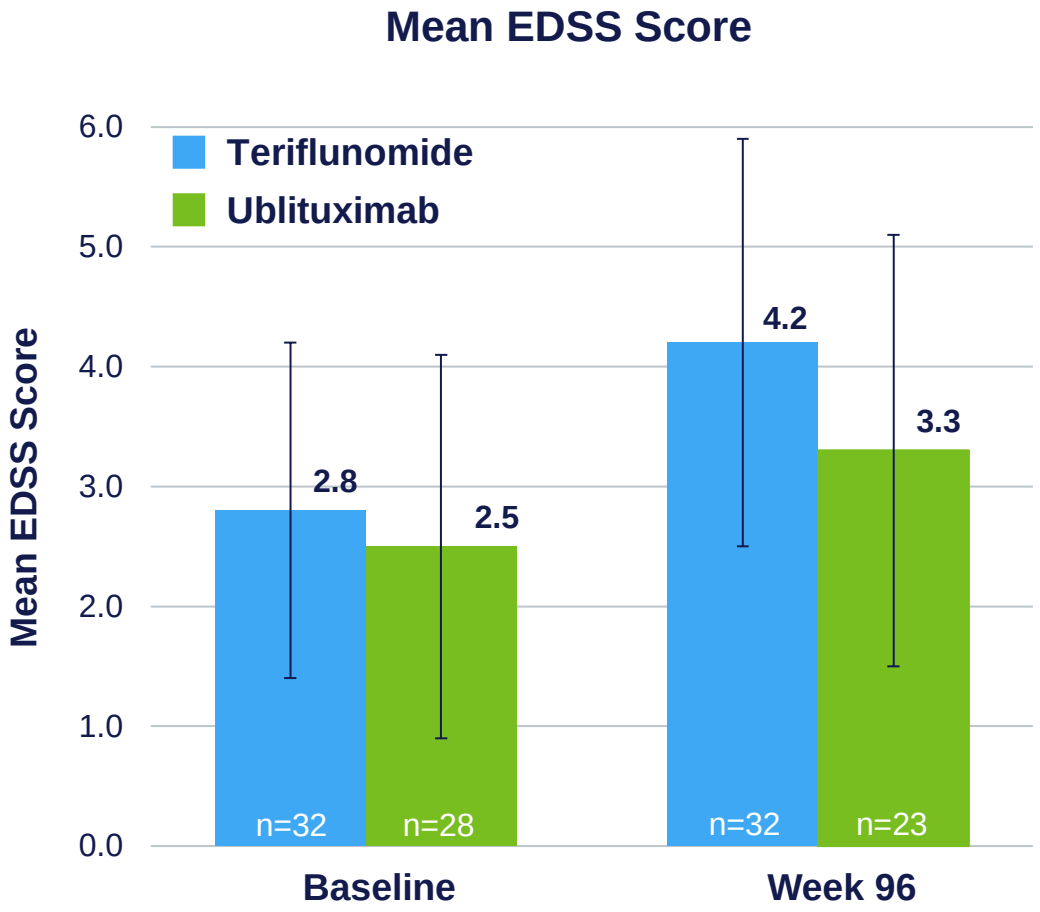
[a]After completing Week 96, participants entered into a 20-week safety follow-up and were eligible to enroll into an OLE study.
[b]Acetaminophen (650 mg or equivalent; only used for intervention) was restricted to participants who experienced fever or pyrexia after the first dose, or as clinically warranted.
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.

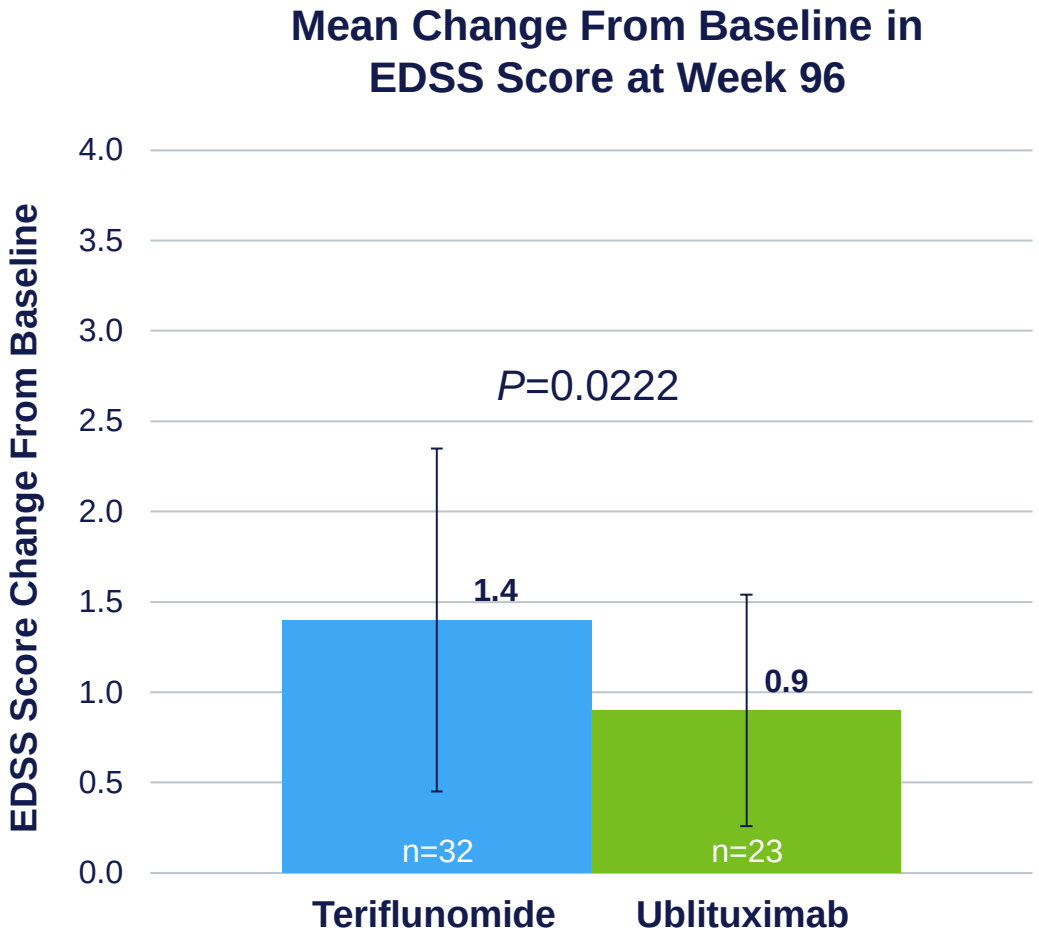
Confirmed Disability Progression
Prespecified Pooled Analysis



mITT population. Hazard ratio estimated using Cox regression model with treatment group as covariate stratified by region, baseline EDSS, and study. *P* value from stratified log-rank test.
CI, confidence interval; HR, hazard ratio; Teri, teriflunomide; UTX, ublituximab.
Steinman L, et al. Presented at: ECTRIMS 2021, October 13-15; Virtual. Abstract 2021-00630.

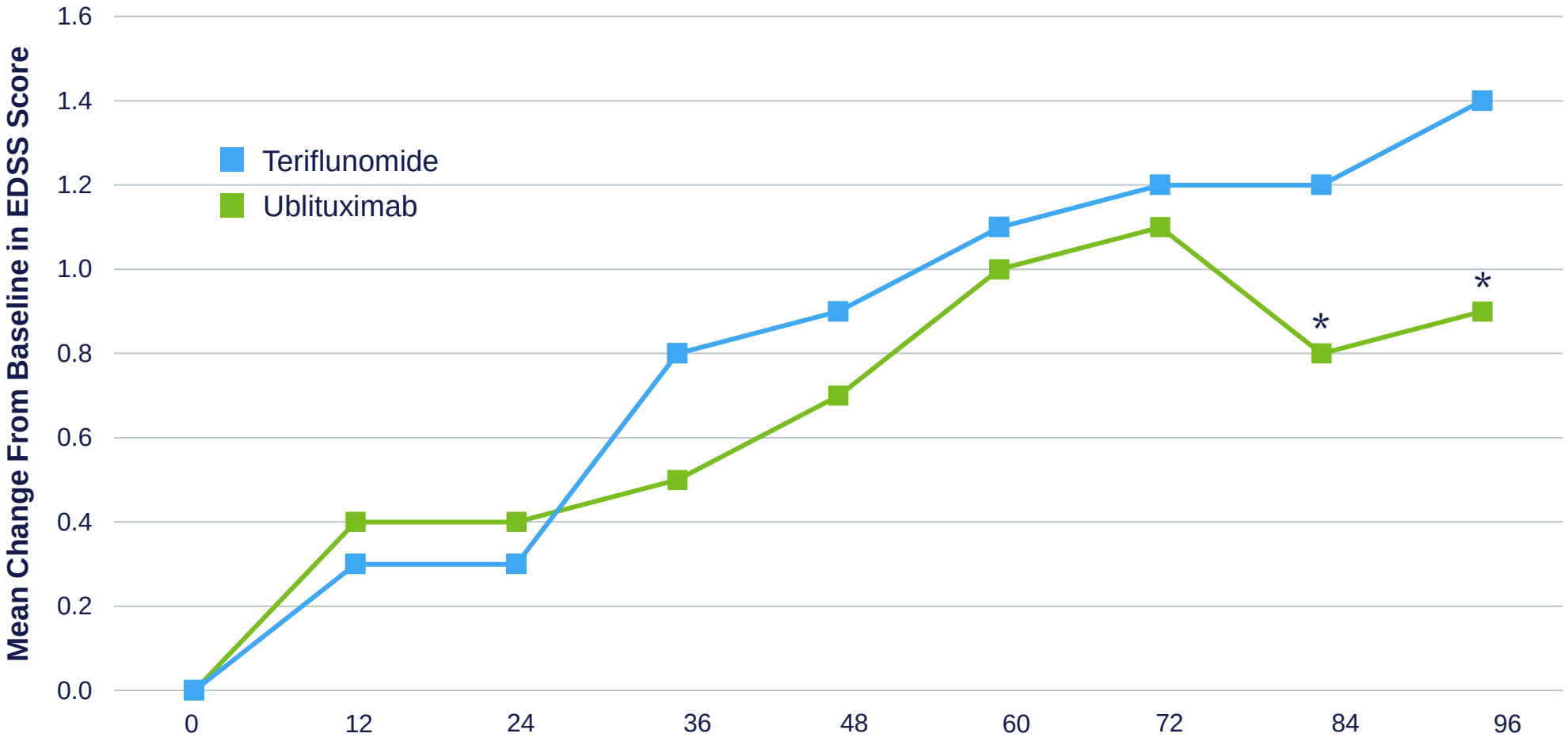
EDSS Values for Participants With 12-Week Confirmed Disability Progression





mITT population. Pooled post hoc analysis. *P* value from *t* test.
SD, standard deviation.

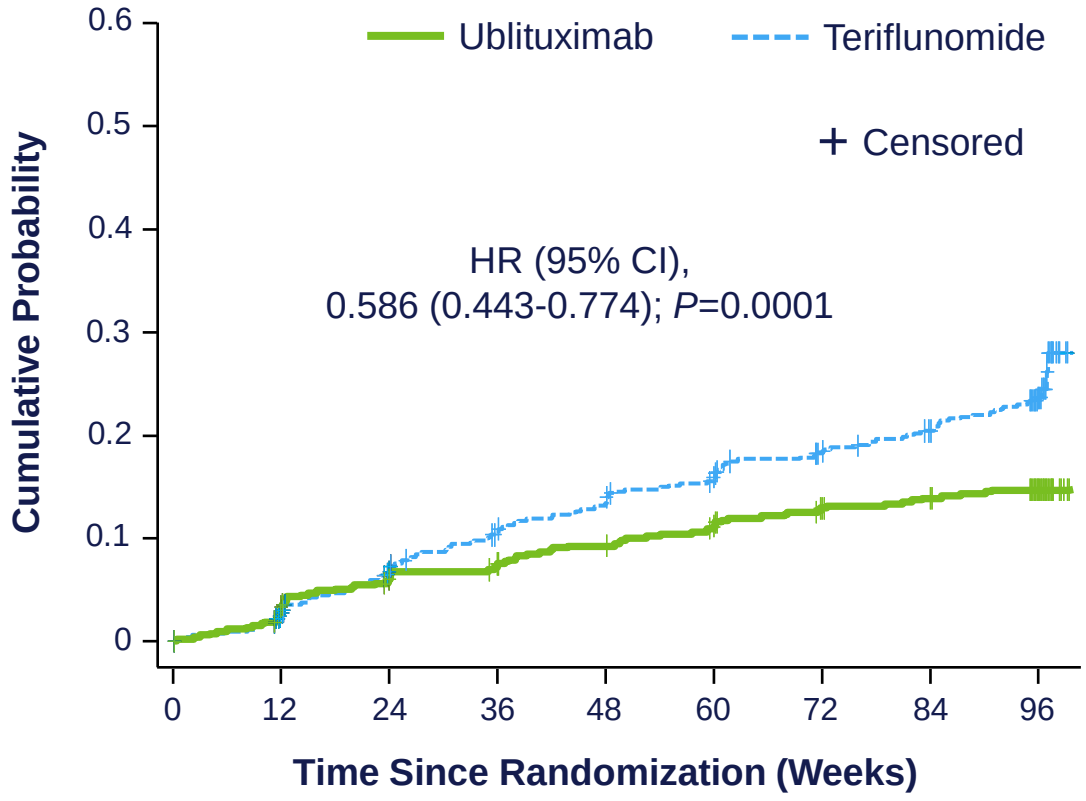
Mean EDSS Score Change From Baseline
(Participants With 12-Week Confirmed Disability Progression)



Week	0	12	24	36	48	60	72	84	96
Teriflunomide, n	32	32	32	29	31	28	31	29	32
Ublituximab, n	28	26	28	26	26	28	27	20	23

mITT population. Pooled post hoc analysis. *P<0.05.

Time to Disability Progression
(Confirmed and Unconfirmed)



N at risk

Ublituximab	543	520	500	491	476	463	446	436	315
Teriflunomide	546	523	496	469	452	437	416	401	276

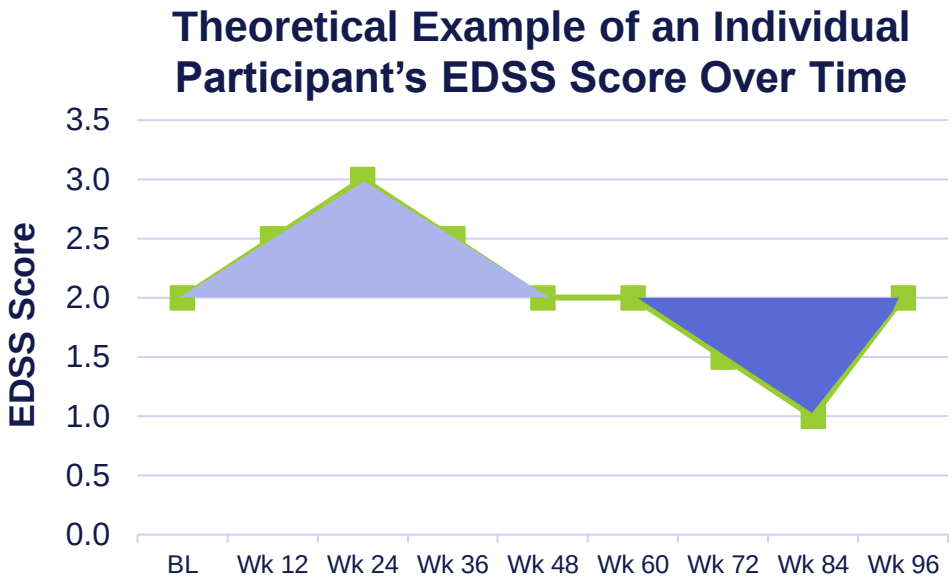
Participants free of disability progression (confirmed and unconfirmed)[a] at Week 96, % (95% CI)[b]

- Ublituximab: 85.3% (82.0-88.1)
- Teriflunomide: 76.3% (72.4-79.8)

[a]Confirmed disability progression required a subsequent confirmation of the increase in EDSS score at a regular scheduled visit ≥12 weeks after the initial documentation of an increase from baseline in EDSS score. Unconfirmed disability progression was an increase in EDSS score from baseline that was not confirmed at a subsequent visit. [b]Estimated by Kaplan-Meier method. mITT population. Pooled post hoc analysis. *P* value from Kaplan-Meier analysis. Hazard ratio estimated using Cox regression model with treatment groups as covariates. Stratification factors included region, baseline EDSS, and study.

AUC Change in EDSS Score[1,2]

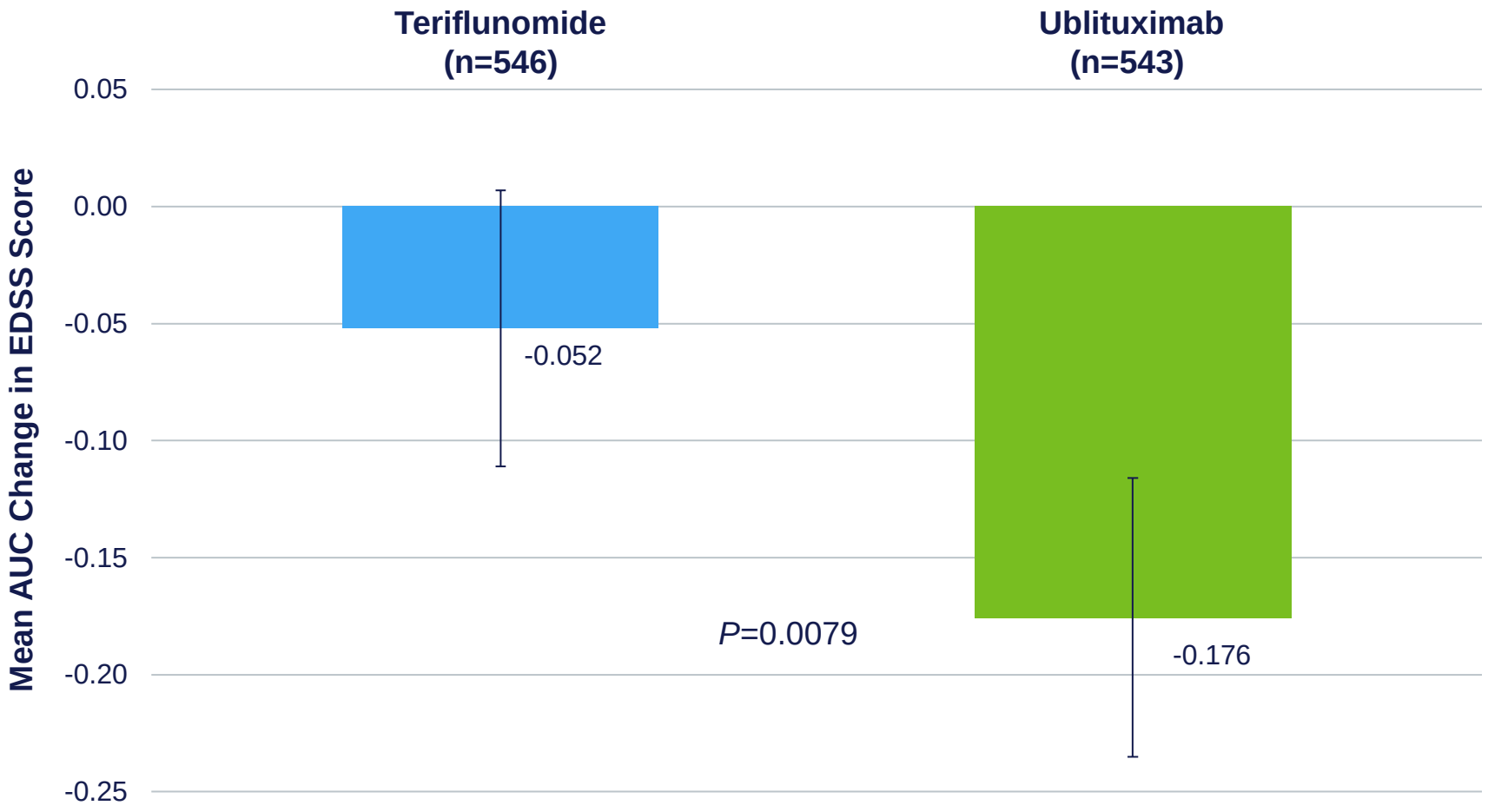
- People with MS can have fluctuating disease courses. As CDP and CDI events may revert in individuals, these measures may not capture net relevant changes in disability during a trial
- AUC change in EDSS integrates both confirmed and unconfirmed disability progression and improvement events, and may better represent changes in disability than CDP or CDI analyses
- Methodology:
  - EDSS scores are plotted over time for each participant
  - AUC is calculated using a trapezoidal or rectangular method and normalized to baseline EDSS
  - Result is defined as AUC change in EDSS
- Positive AUC change in EDSS indicates a net worsening from baseline
- Negative AUC change in EDSS indicates a net improvement from baseline



AUC, area under the curve; Wk, week.

1. Liu C, et al. *J Neurol Neurosurg Psychiatry.*1998;64(6):726-729. 2. Rudick R, et al. Presented at: Joint ACTRIMS-ECTRIMS Meeting, September 10-13, 2014; Boston, MA. Poster P073.

Mean AUC Change in EDSS Score From Week 0 to Week 96 (mITT Population)



mITT population. Pooled post hoc analysis. ANCOVA on rank test was used to compare the least squares means AUC between treatment group, adjusted for baseline EDSS.
ANCOVA, analysis of covariance.

Conclusions

- A low rate of 12-week and 24-week confirmed disability progression was observed with ublituximab and teriflunomide in prespecified pooled analyses, and the difference did not meet statistical significance[1]
  - In participants with 12-week confirmed disability progression, the change in EDSS score from baseline with ublituximab was significantly lower than with teriflunomide at Weeks 84 and 96
- In exploratory analyses, compared with teriflunomide, ublituximab demonstrated:
  - A lower risk of combined confirmed and unconfirmed disability progression
  - A greater reduction in mean AUC change in EDSS score from baseline to Week 96
- An extension study is ongoing and will continue to assess changes in disability progression over longer periods of time

1. Steinman L, et al. Presented at: ECTRIMS 2021; October 13-15; Virtual. Abstract 2021-00630.

Acknowledgments

- The authors thank the participants and their families for participating in the ULTIMATE I and II studies. The authors also thank Apollo Medical Communications for providing medical writing and editorial support, which was funded by TG Therapeutics. The ULTIMATE I and II studies were sponsored by TG Therapeutics.