Relapse Rate and Time to First Relapse Were Improved With Ublituximab vs Teriflunomide in the Phase 3 ULTIMATE I and ULTIMATE II Studies in Patients With Relapsing Multiple Sclerosis (RMS)

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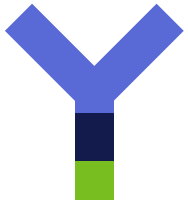
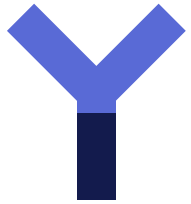
Disclosures

- Lawrence Steinman has received compensation for consulting from TG Therapeutics

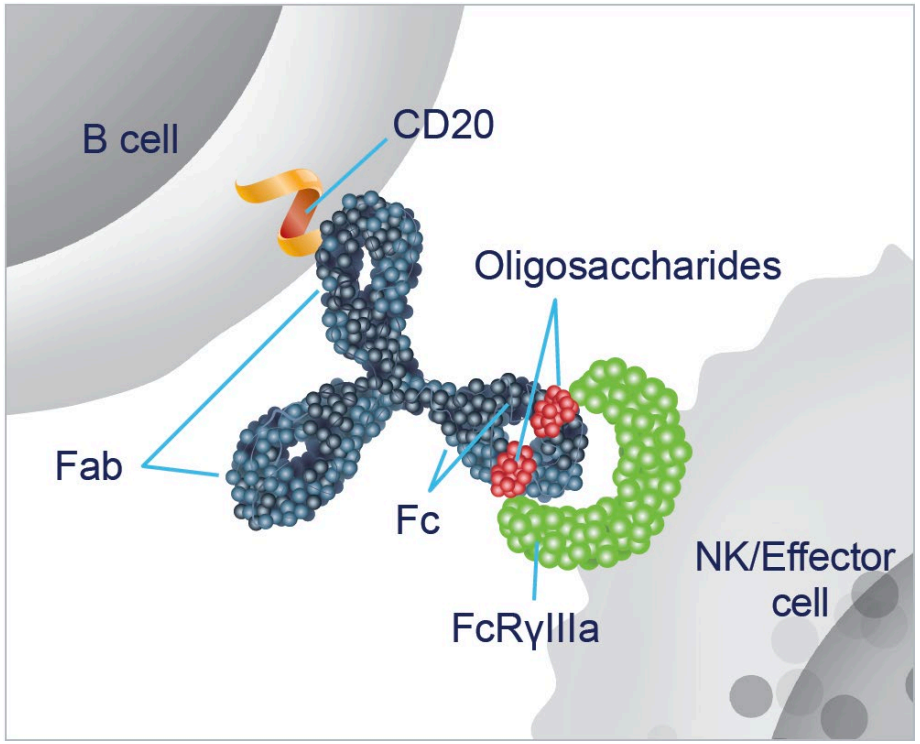
Ublituximab Is a Novel, Next-Generation Glycoengineered Anti-CD20 mAb

	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]

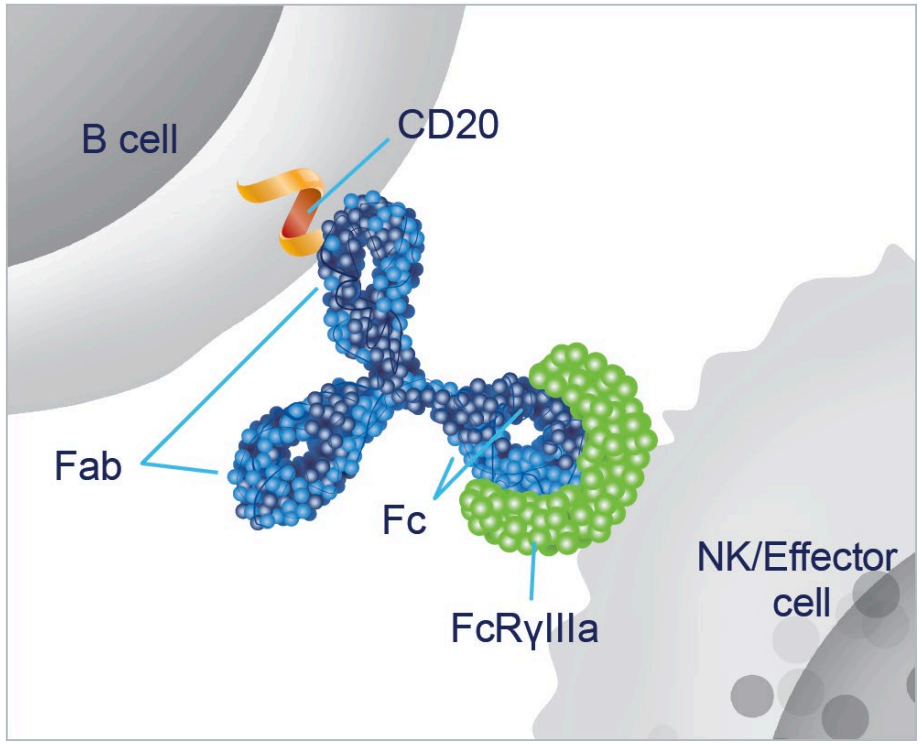
[a]After initial dose. [b]Initial infusion time over 4 hours. [c]Initial infusion time over 2.5 hours.
ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; D, day; Ig, immunoglobulin; mAb, monoclonal antibody; MOA, mechanism of action; MS, multiple sclerosis.
Adapted 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]



In vitro studies demonstrate that ublituximab has higher ADCC relative to all other anti-CD20 therapies used in MS[5,6]

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. 5. Bellon A, et al. Presented at ASH; December 10-13, 2011. 6. TG Therapeutics. Data on file.

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]

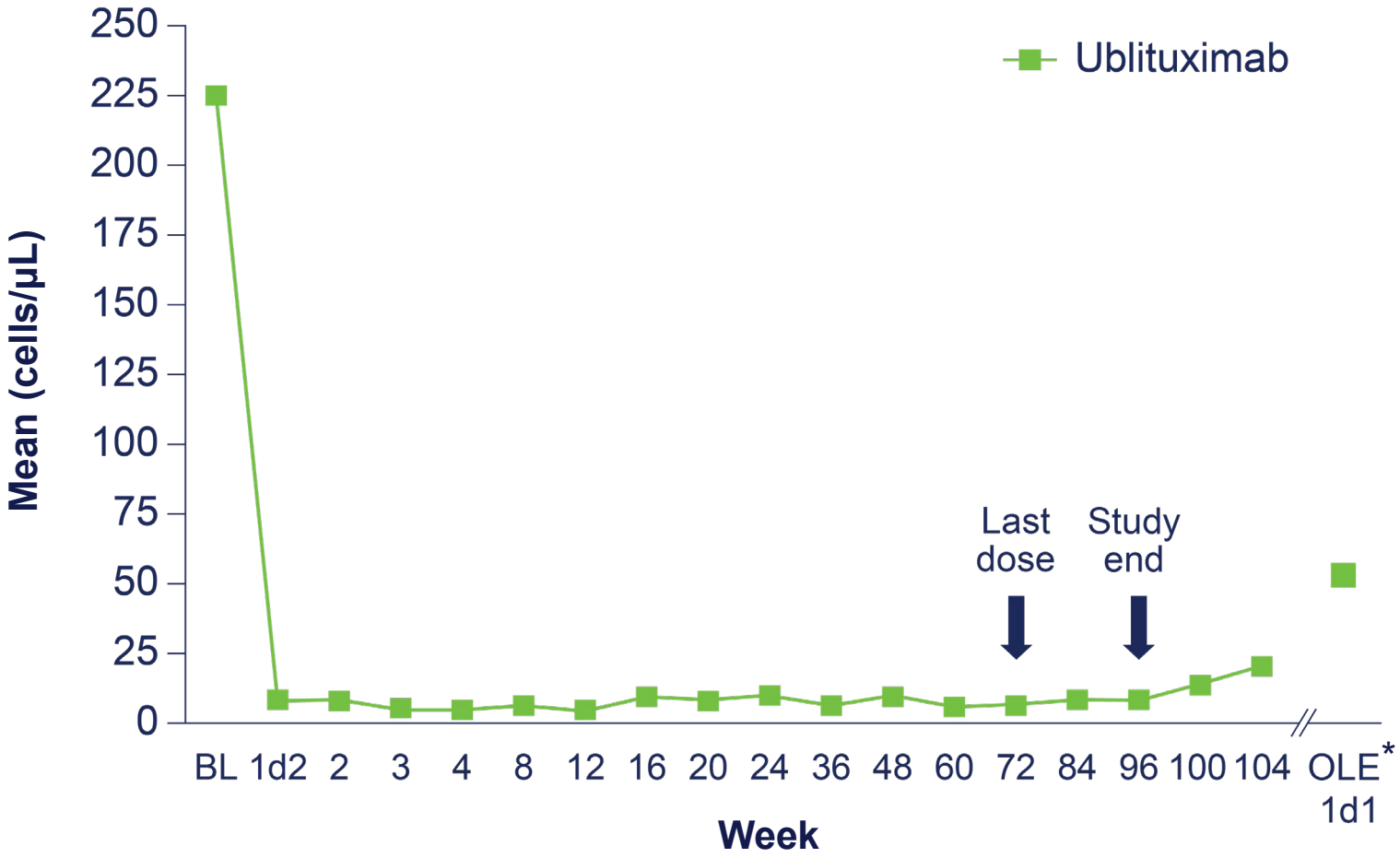
30-60 minutes prior to each dose of ublituximab or IV placebo: antihistamine (diphenhydramine 50 mg or equivalent) and corticosteroid (dexamethasone 10-20 mg or equivalent): oral, IV, IM, and/or SC (investigator discretion)

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 patients with NEDA from Week 24 to Week 96
- **Prespecified pooled analyses**
  - 12- and 24-week CDP
  - 12- and 24-week CDI
- **Safety and tolerability**

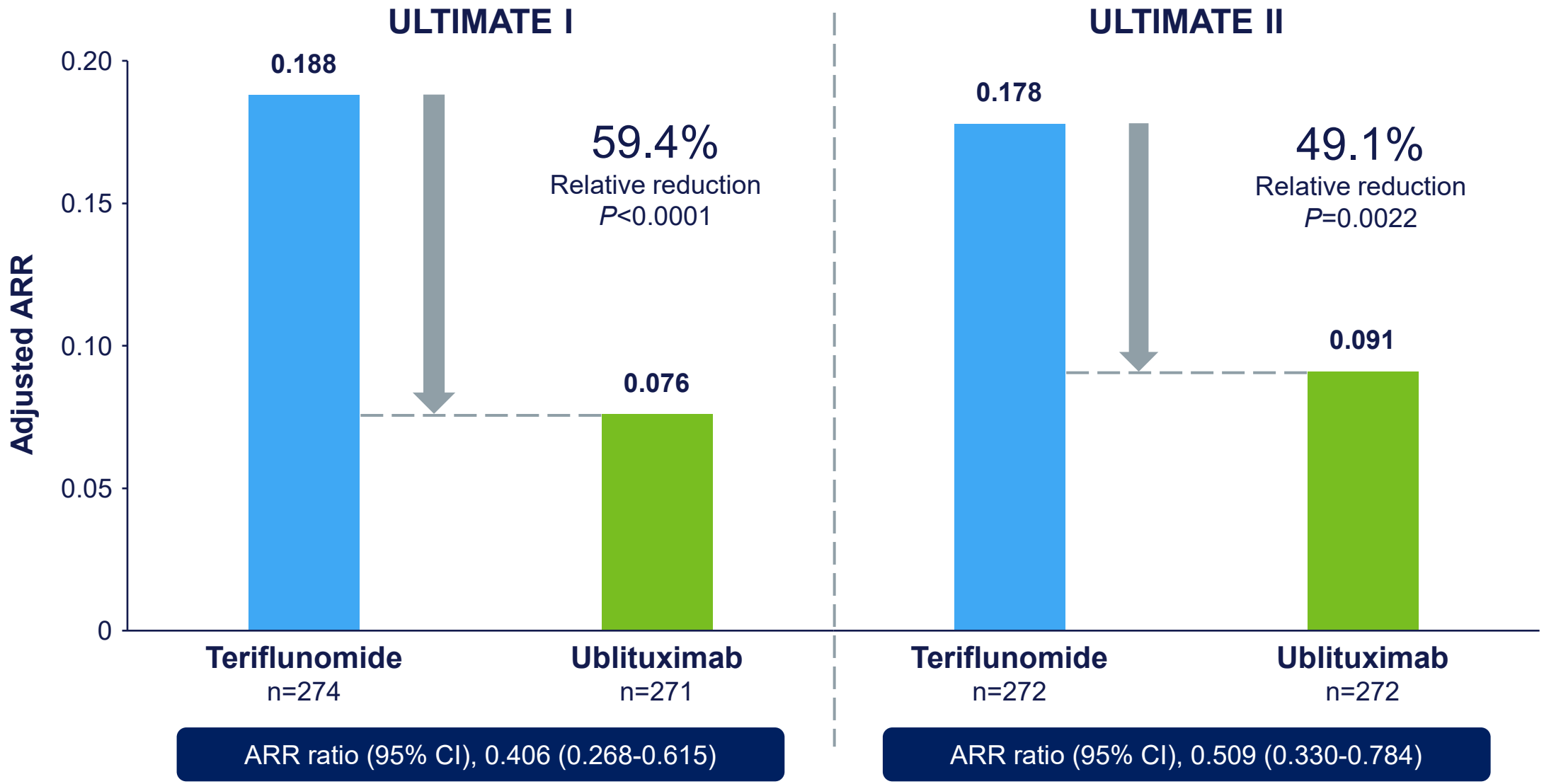
[a]After completing Week 96, patients entered into a 20-week safety follow-up and were eligible to enroll into an open-label extension study.
[b]Acetaminophen (650 mg or equivalent; only used for intervention) was restricted to patients who experienced fever or pyrexia after the first dose, or as clinically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

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



*Mean time since last dose was 54.8 weeks for patients with B-cell counts at OLE Week 1 Day 1. Pooled post hoc analysis. Modified intention-to-treat (ITT) population. Data presented as the mean B-cell count among patients 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. Poster P105.

Primary Endpoint: ARR

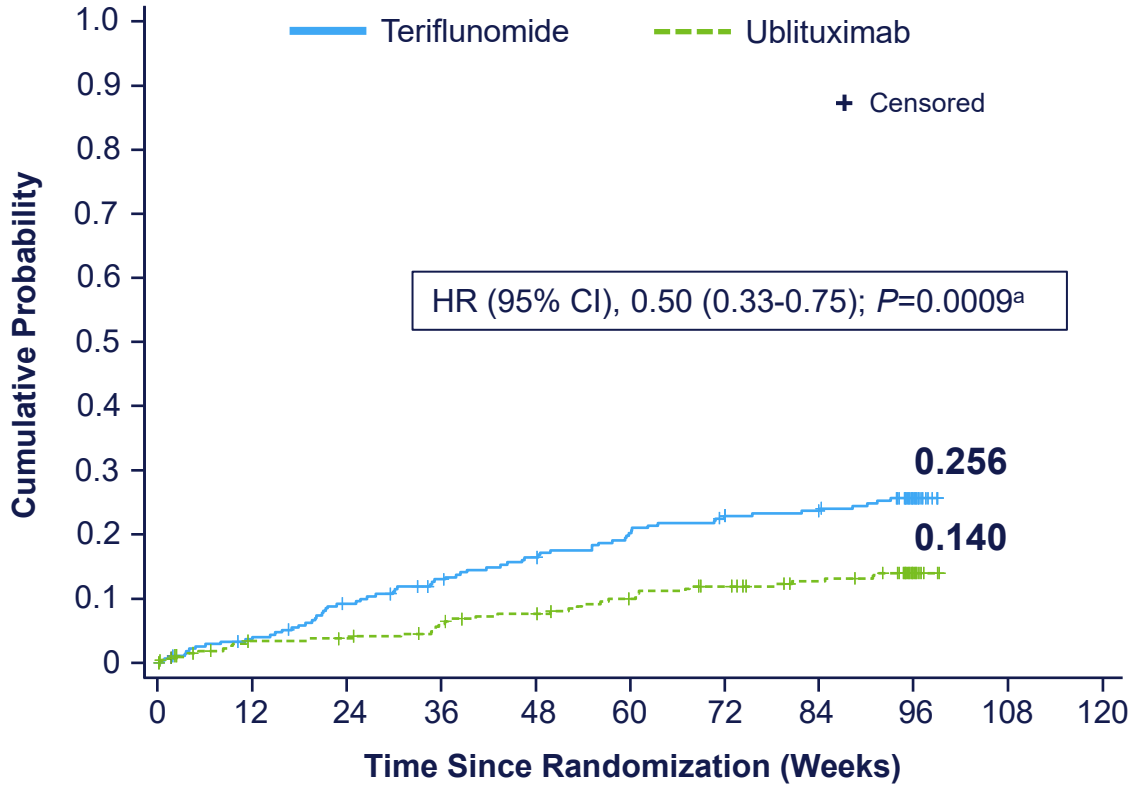


Modified ITT population. Based on negative binomial model (GEE) for the relapse count per patient with logarithmic link function, treatment, region, and baseline EDSS strata as covariates and log (years of treatment) as offset. CI, confidence interval.

Steinman L, et al. Presented at ECTRIMS 2021. Abstract 2021-00630.

Time to First Confirmed Relapse

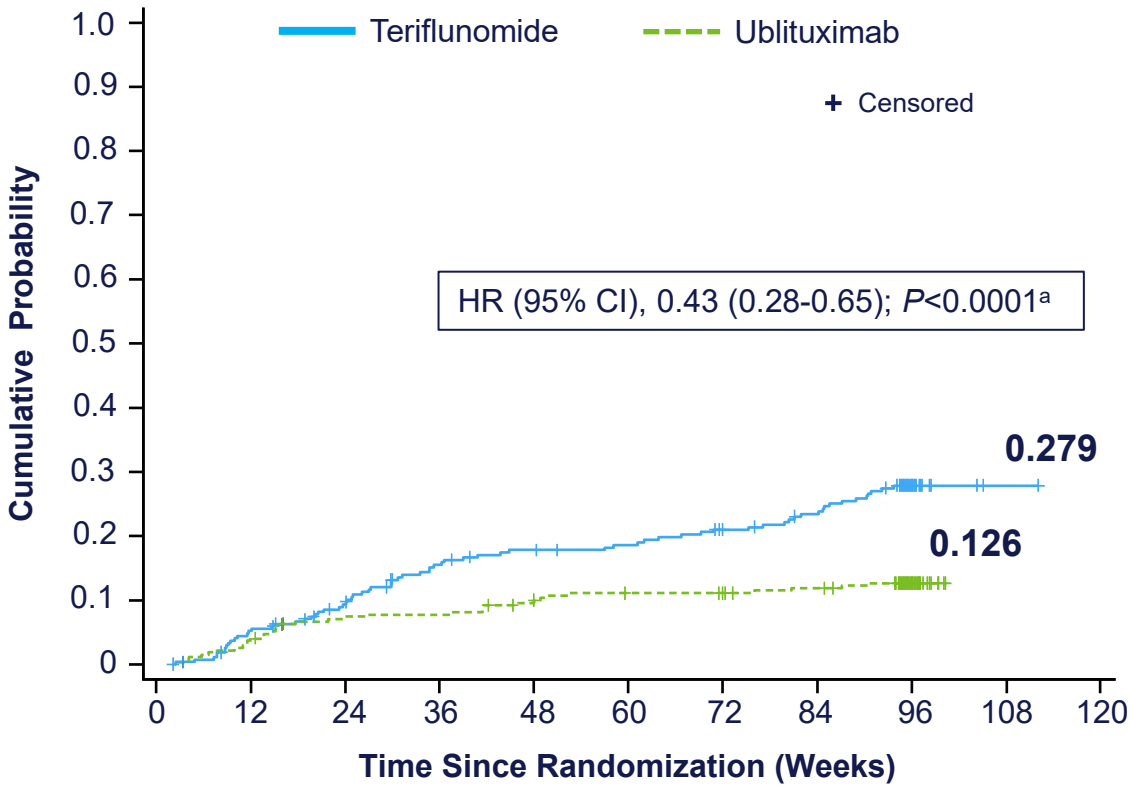
ULTIMATE I



N at risk

Ublituximab	271	254	252	244	238	229	222	214	49
Teriflunomide	274	261	243	230	220	209	202	197	42

ULTIMATE II

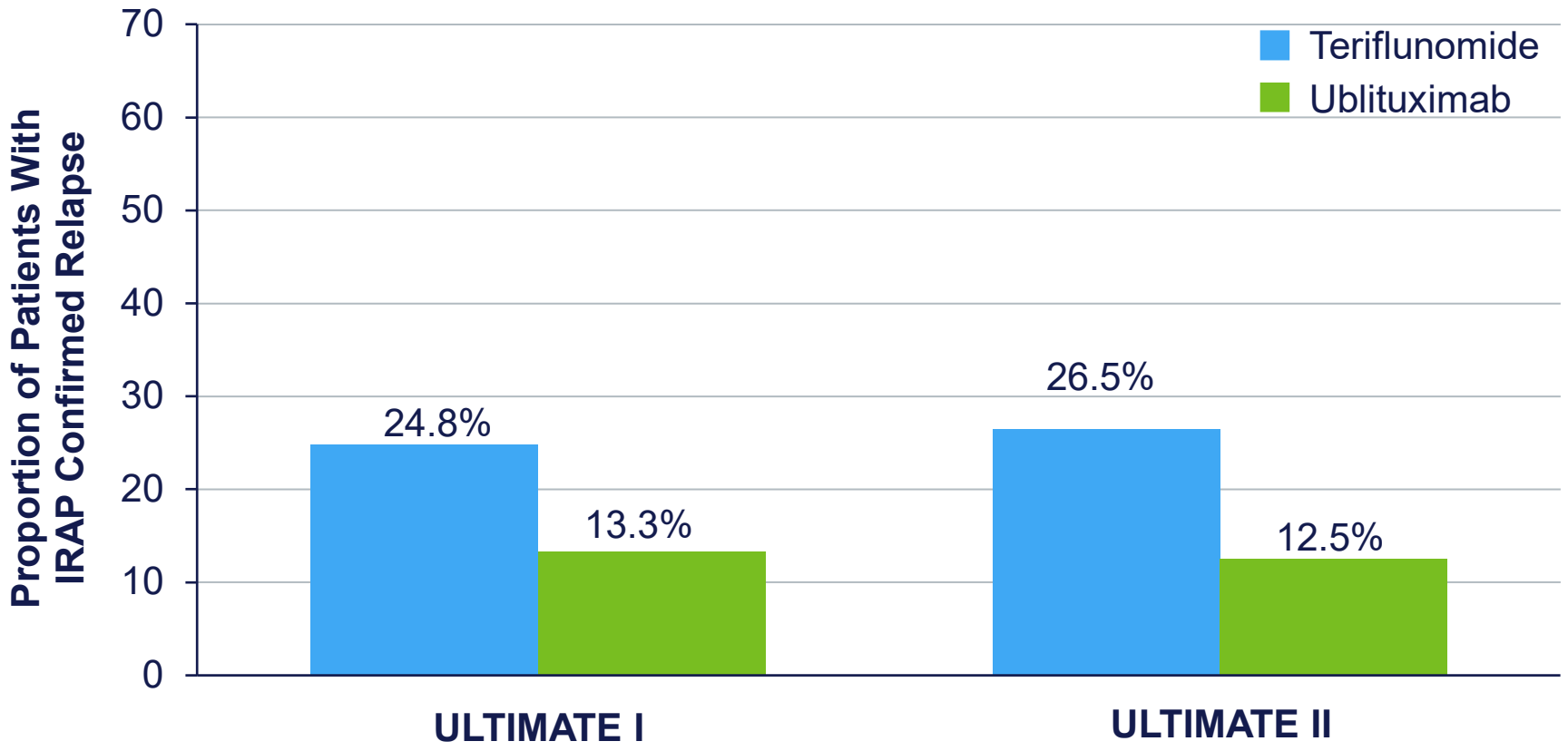


N at risk

Ublituximab	272	262	250	249	242	236	235	230	58
Teriflunomide	272	255	238	218	210	206	198	189	41

Modified ITT population. Post hoc analysis. [a]Cox proportional hazards model with treatment, region, number of relapses in previous year, baseline EDSS strata (<3.5, ≥3.5), baseline number of T1 Gd+ lesions, sex, and the patient's age at baseline as covariates.
HR, hazard ratio.

Patients With Confirmed Relapse During Treatment



Treatment history (treatment naive vs prior DMT) and Gd+ T1 lesion count at baseline (0 vs ≥1) were not associated with relapse occurrence

Modified ITT population.
DMT, disease-modifying therapy; IRAP, Independent Relapse Adjudication Panel.

Conclusions

- In ULTIMATE I and II, peripheral B-cell numbers declined rapidly after the first ublituximab infusion and remained low during treatment, which is consistent with ublituximab's mechanism of action
- In the Phase 3 ULTIMATE I and II trials, the primary endpoint of ARR was significantly improved at 96 weeks for patients treated with ublituximab vs teriflunomide
- Both the time to first confirmed relapse and the proportion of patients with a confirmed relapse during treatment were reduced with ublituximab vs teriflunomide in both studies
- The prevention of relapses represents an important goal of DMT, with the potential for a marked impact on the accumulation of disability[1]
- Ublituximab exhibited a favorable safety and tolerability profile with no unexpected safety signals[2]

1. Kalincik T. *Neuroepidemiology*. 2015;44(4):199-214. 2. Steinman L, et al. Presented at: ECTRIMS; October 13-15, 2021; Virtual. Oral presentation 117.

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