Phase 3 Results of the ULTIMATE I & II Global Studies: Ublituximab Versus Teriflunomide in Relapsing Multiple Sclerosis

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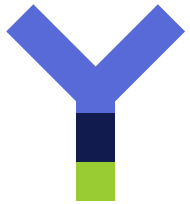
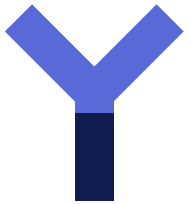
Disclosures

- Lawrence Steinman has received compensation from TG Therapeutics, Inc.

Ublituximab Is a Novel Glycoengineered Anti-CD20 mAb

	Ublituximab	Rituximab	Ocrelizumab	Ofatumumab
mouse human glycoengineered				
Structure	Glycoengineered chimeric IgG1	Chimeric IgG1	Humanized IgG1	Recombinant fully human IgG1
Regimen	150mg D1, 450mg D15, then 450mg every 24wk	1g D1 & D15, then 1g every 24wk	300mg D1 & D15, then 600mg every 24wk	20mg every 4wk
Route	Intravenous	Intravenous	Intravenous	Subcutaneous
Infusion time*	1 hr[a]	Not Approved for MS	2 hrs[b]	-
Primary MOA	ADCC	CDC	ADCC	CDC
ADCC	+++++[1]	+[2]	++[3]	++[4]
CDC	++[2]	+++[2]	+[3]	+++++[2]

Adapted from Ancau et al 2019. [1]de Romeuf et al. 2008; [2]Bellon et al. 2011; [3]Bennett et al. 2011 (p.41); [4]Teeling et al. 2006. ADCC: antibody-dependent cellular cytotoxicity; ADCP: antibody-dependent cellular phagocytosis; CDC: complement-dependent cytotoxicity; D: day; MS: multiple sclerosis; wk: week. [a] Initial infusion time over 4 hours; [b] Initial infusion time over 2.5 hours ; *after initial dose

ULTIMATE I & II: Study Design

Identical phase 3, randomized, multi-center, double-blinded, active-controlled studies that were conducted in parallel

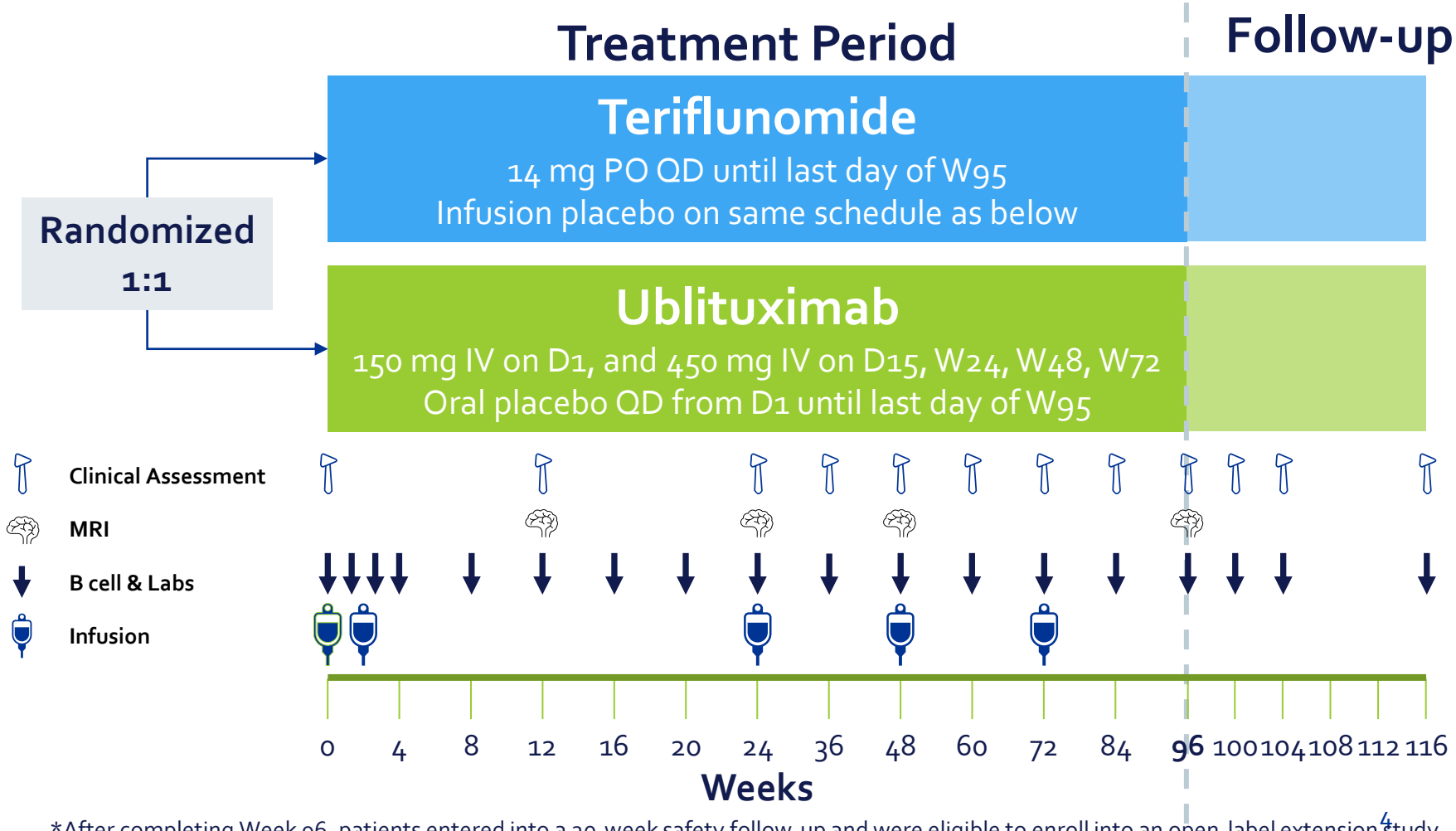
Screening

Population

- Age 18-55
- Diagnosis of MS per 2010 McDonald criteria
- Relapsing forms of MS: RRMS or SPMS with disease activity
- EDSS 0 – 5.5
- Neurologic stability ≥30 days prior to screening

Patients required to have:

- ≥ 2 documented relapses within the 2 years prior
- Or ≥1 relapse in the year prior
- And/or ≥ 1 Gd-enhancing lesion in the year prior to screening



*After completing Week 96, patients entered into a 20-week safety follow-up and were eligible to enroll into an open-label extension study.

SPMS: Secondary Progressive Multiple Sclerosis; RRMS: Relapsing Remitting Multiple Sclerosis

ULTIMATE I & II: Study Objective and Key Endpoints

Objective: To evaluate the efficacy and safety of ublituximab compared with teriflunomide in patients with relapsing multiple sclerosis

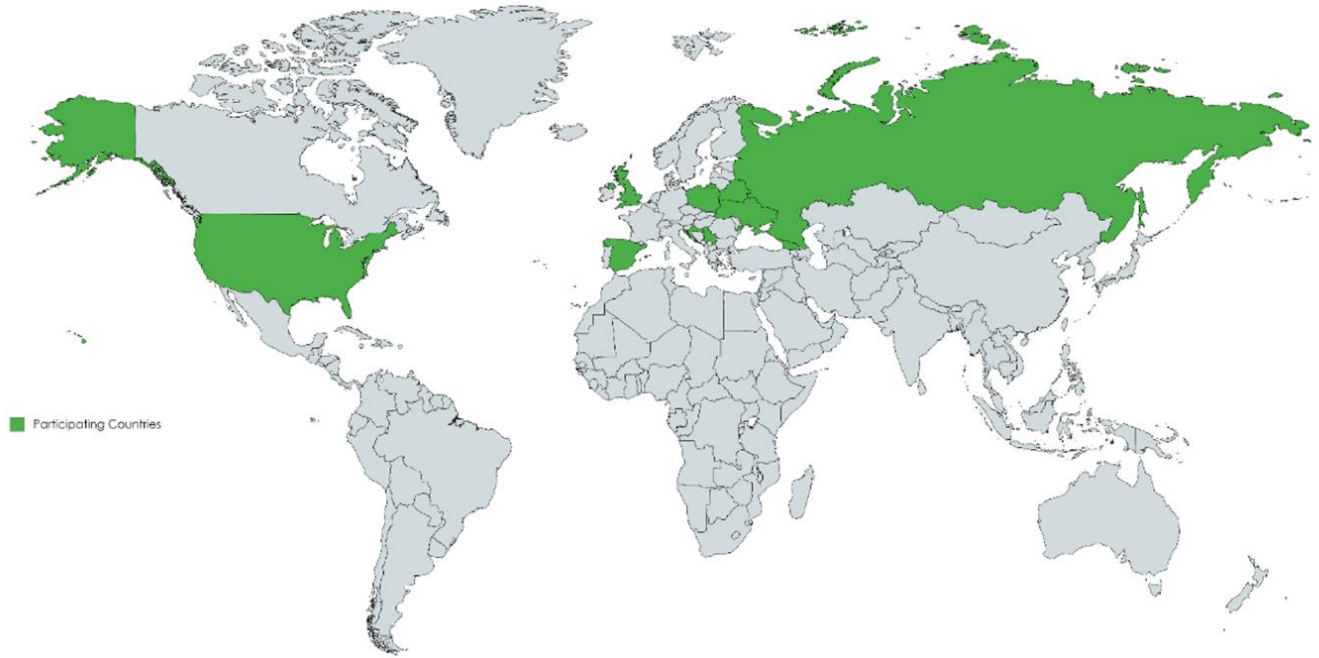
By individual study	
Primary endpoint	Annualized relapse rate at 96 weeks *(number of confirmed multiple sclerosis relapses in a year)*
Key secondary endpoints	▪ Total number of Gd-enhancing T1 lesions by Week 96 ▪ Total number of new or enlarging T2 hyperintense lesions by Week 96 ▪ Proportion of subjects with NEDA from Week 24 to Week 96
Pre-specified pooled analysis	
Key secondary endpoints	▪ Time to CDP for at least 12 weeks
Tertiary analyses	▪ Time to CDP for at least 24 weeks ▪ Time to CDI for at least 12 weeks ▪ Time to CDI for at least 24 weeks

ARR: annualized relapse rate; CDP: confirmed disability progression; CDI: confirmed disability improvement; Gd: gadolinium; NEDA: no evidence of disease activity.

ULTIMATE I & II: Independent Global Studies

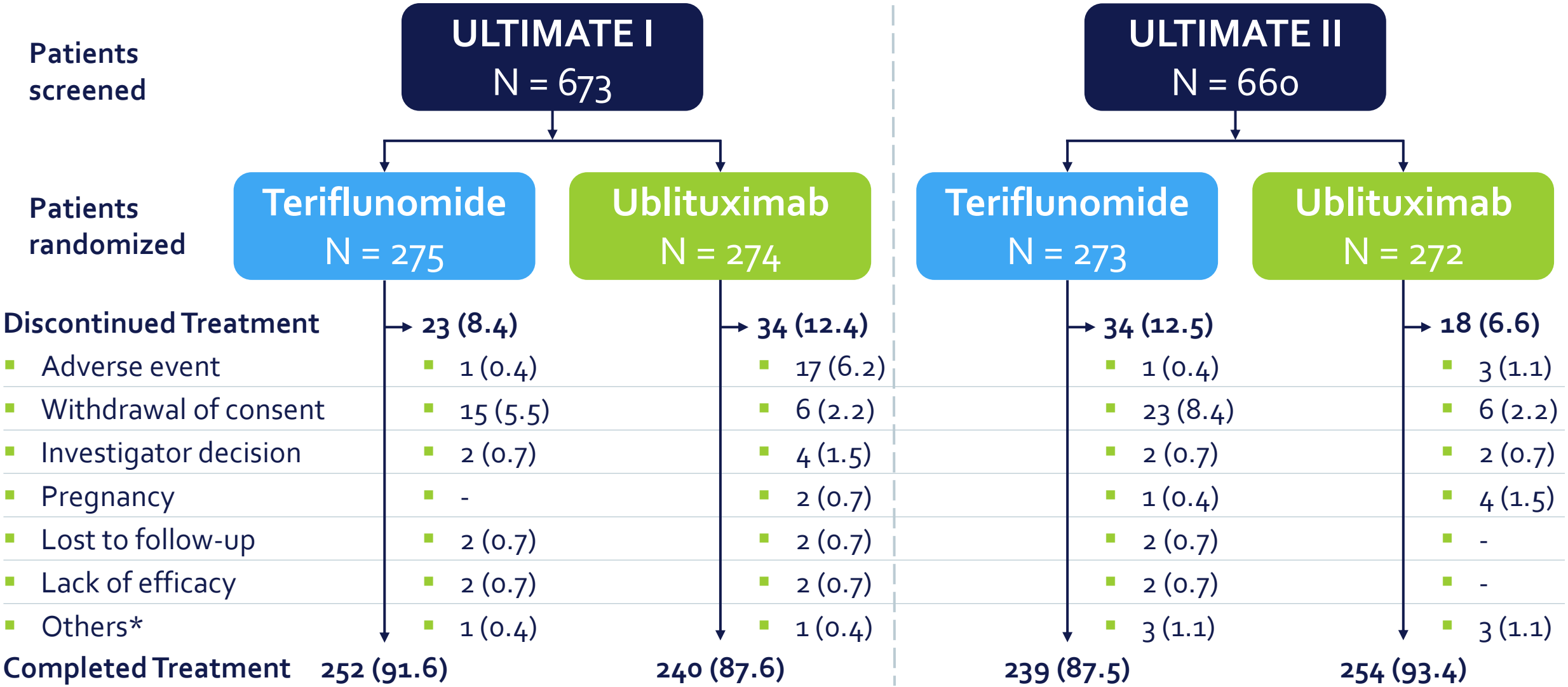
- First patient first infusion: 22 September 2017
- Last patient first infusion: 04 October 2018
- 1094 patients were randomized across 106 sites in 10 countries

Country, n (%)	ULTIMATE I	ULTIMATE II
Belarus	64 (11.7)	64 (11.7)
Croatia	-	49 (9.0)
Georgia	83 (15.1)	-
Poland	41 (7.5)	77 (14.1)
Russia	133 (24.2)	163 (29.9)
Serbia	64 (11.7)	-
Spain	5 (0.9)	8 (1.5)
UK	4 (0.7)	5 (0.9)
Ukraine	107 (19.5)	143 (26.2)
USA	48 (8.7)	36 (6.6)
Total	**549**	**545**



UK: United Kingdom; USA: United States of America

Patient Disposition & Analysis Population



Data represented as n (%). *Others include: alternative treatment and COVID-19.

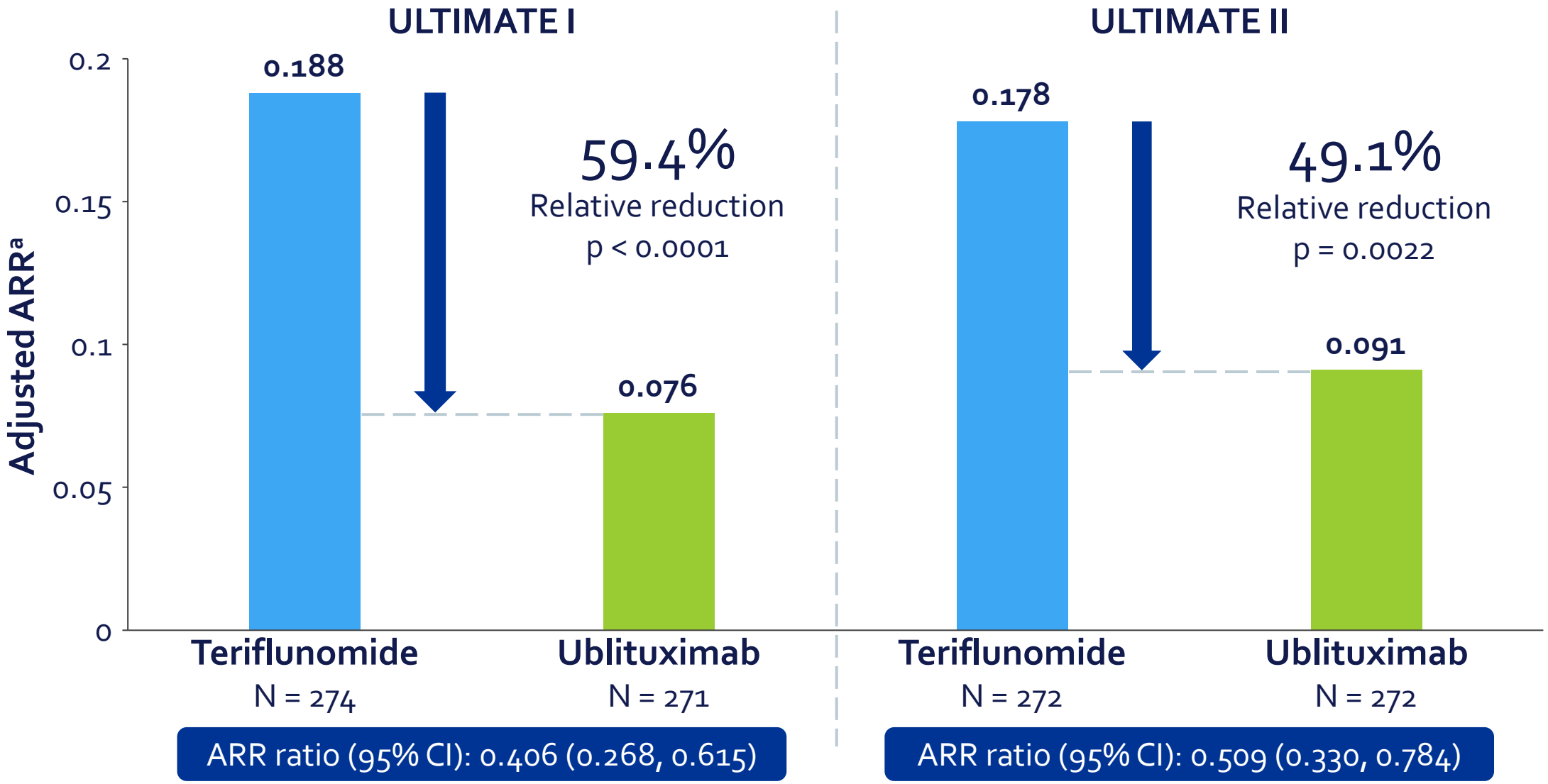
Patient Demographics & Baseline Characteristics

ULTIMATE I & II populations are consistent and poolable

Characteristic	ULTIMATE I (N = 545)		ULTIMATE II (N = 544)	
Mean ± standard deviation or n (%)	Teriflunomide N = 274	Ublituximab N = 271	Teriflunomide N = 272	Ublituximab N = 272
Age, years	37.0 ± 9.63	36.2 ± 8.24	36.2 ± 8.96	34.5 ± 8.76
Sex, Female, n (%)	179 (65.3)	166 (61.3)	176 (64.7)	178 (65.4)
Race, %				
Caucasian	266 (97.1)	264 (97.4)	268 (98.5)	269 (98.9)
African American	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 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

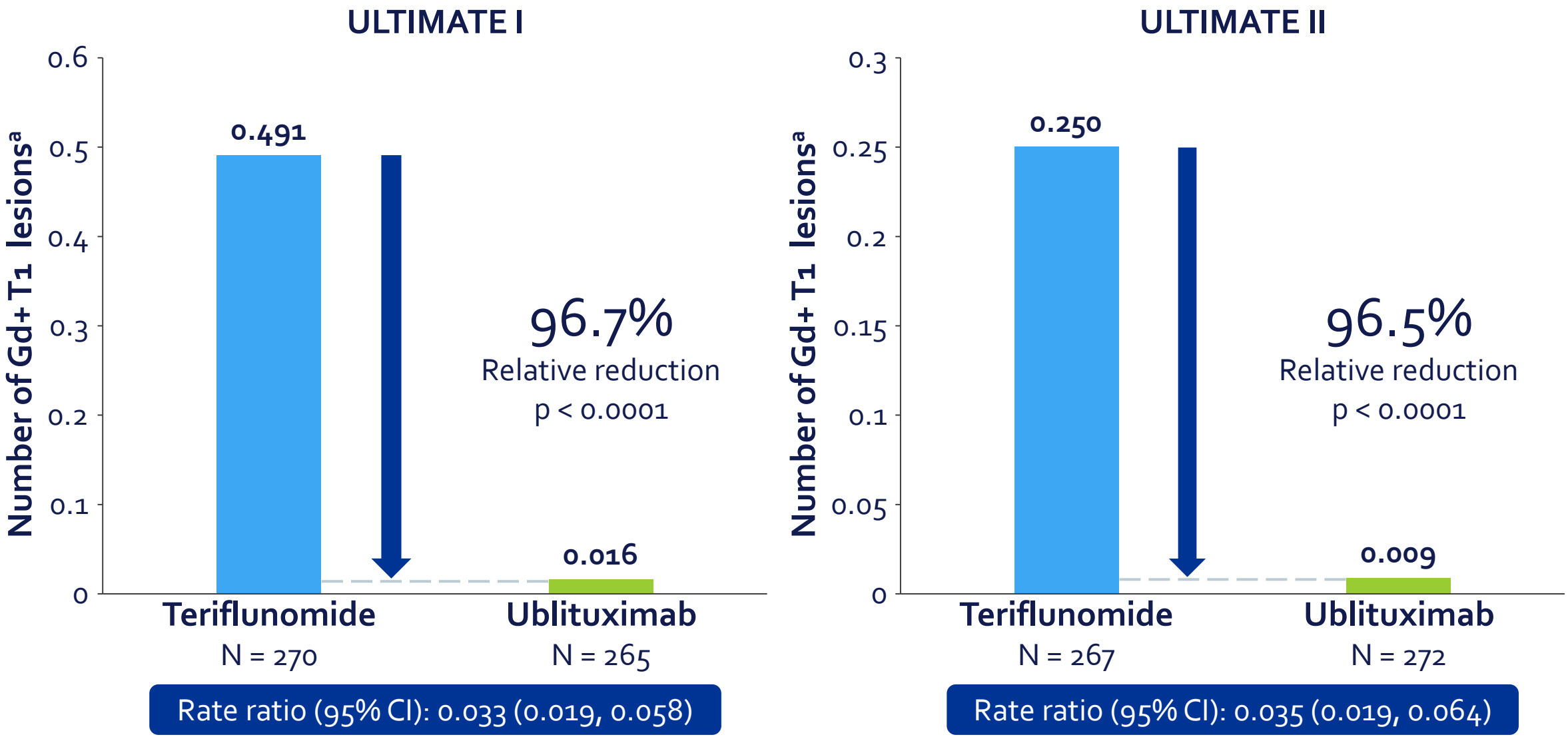
Modified Intent-to-Treat population: All patients in the ITT population who received at least one dose of study drug and had at least one baseline and post-baseline efficacy assessment. *Untreated with disease-modifying therapy in 5 years prior to study entry. DMT: disease-modifying therapy; EDSS: expanded disability status scale; Gd+: gadolinium-enhancing; MS: multiple sclerosis.

Primary Endpoint: Annualized Relapse Rate (ARR)



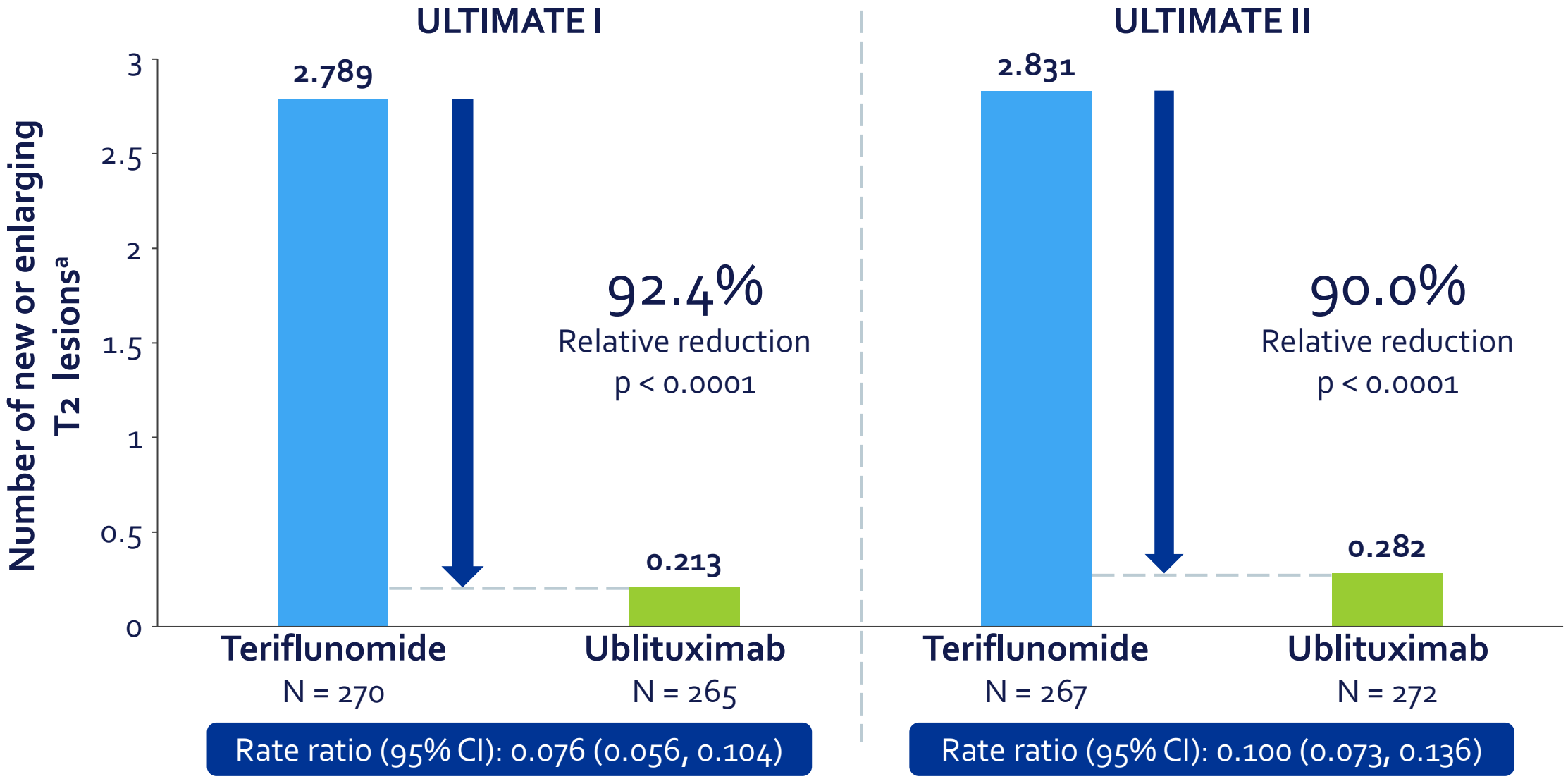
The modified Intention-to-Treat (mITT) population consists of all subjects in the ITT population who received at least one dose of study medication and had at least one baseline and post-baseline efficacy assessment. Based on negative binomial model (GEE) for the relapse count per subject with logarithmic link function, treatment, region, and baseline EDSS strata as covariates and log (years of treatment) as offset.
CI: confidence interval.

MRI: Total Number of Gd+ T1 Lesions



The modified Intention-to-Treat MRI (mITT-MRI) population consists of all subjects in the ITT population who received at least one dose of study medication, had at least one baseline and post-baseline efficacy assessment, and had at least one baseline and post-baseline MRI efficacy assessment. Based on negative binomial model (GEE) with logarithmic link function, covariates treatment, region, baseline EDSS strata, baseline number of lesions (o/>=1) and an offset based on the log-transformed number of post-baseline MRI scans. MRI assessed by Independent Review

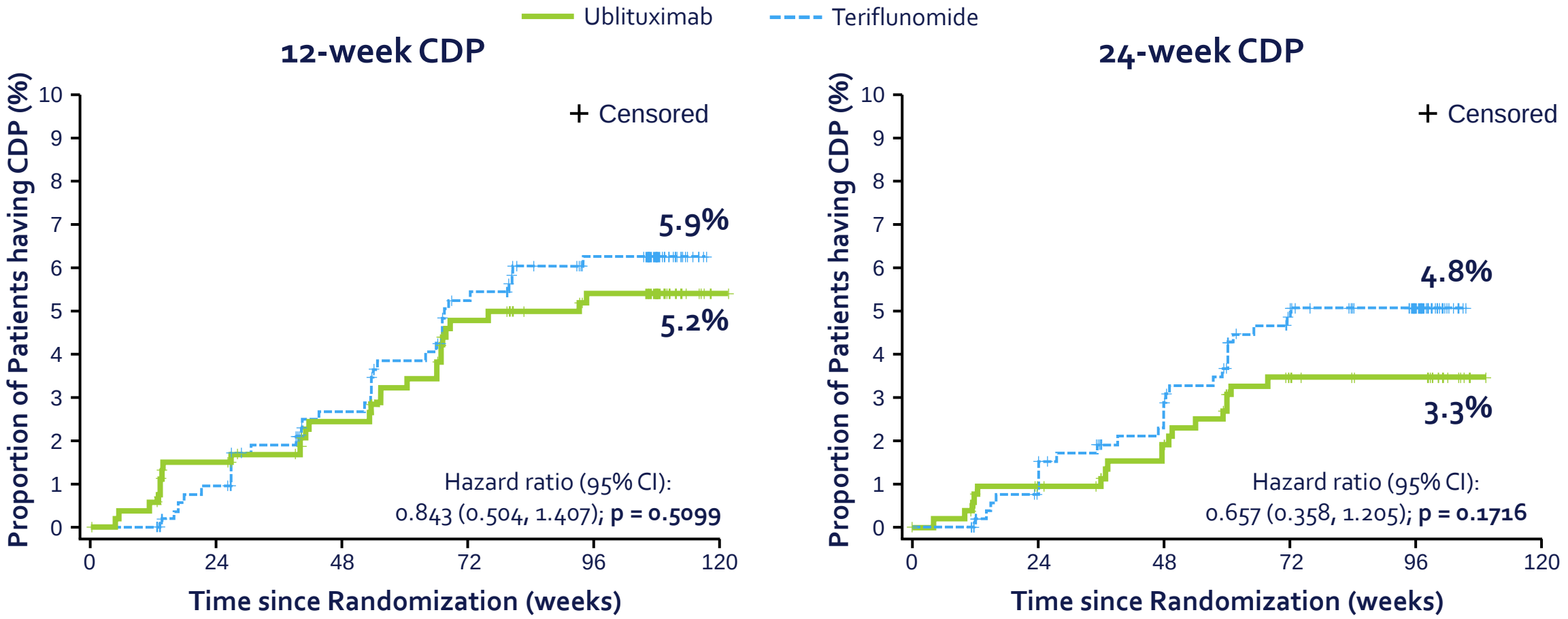
MRI: Number of New or Enlarging T2 Lesions



The modified Intention-to-Treat MRI (mITT-MRI) population consists of all subjects in the ITT population who received at least one dose of study medication, had at least one baseline and post-baseline efficacy assessment, and had at least one baseline and post-baseline MRI efficacy assessment. Based on negative binomial model (GEE) with logarithmic link function, covariates treatment, region, baseline EDSS strata, baseline number of lesions (0/>=1) and an offset based on the log-transformed number of post-baseline MRI scans. MRI assessed by Independent Review

Confirmed Disability Progression (CDP)

Pre-specified pooled analysis



N at risk

UTX	543	522	506	481	345
Teri	546	522	497	470	325

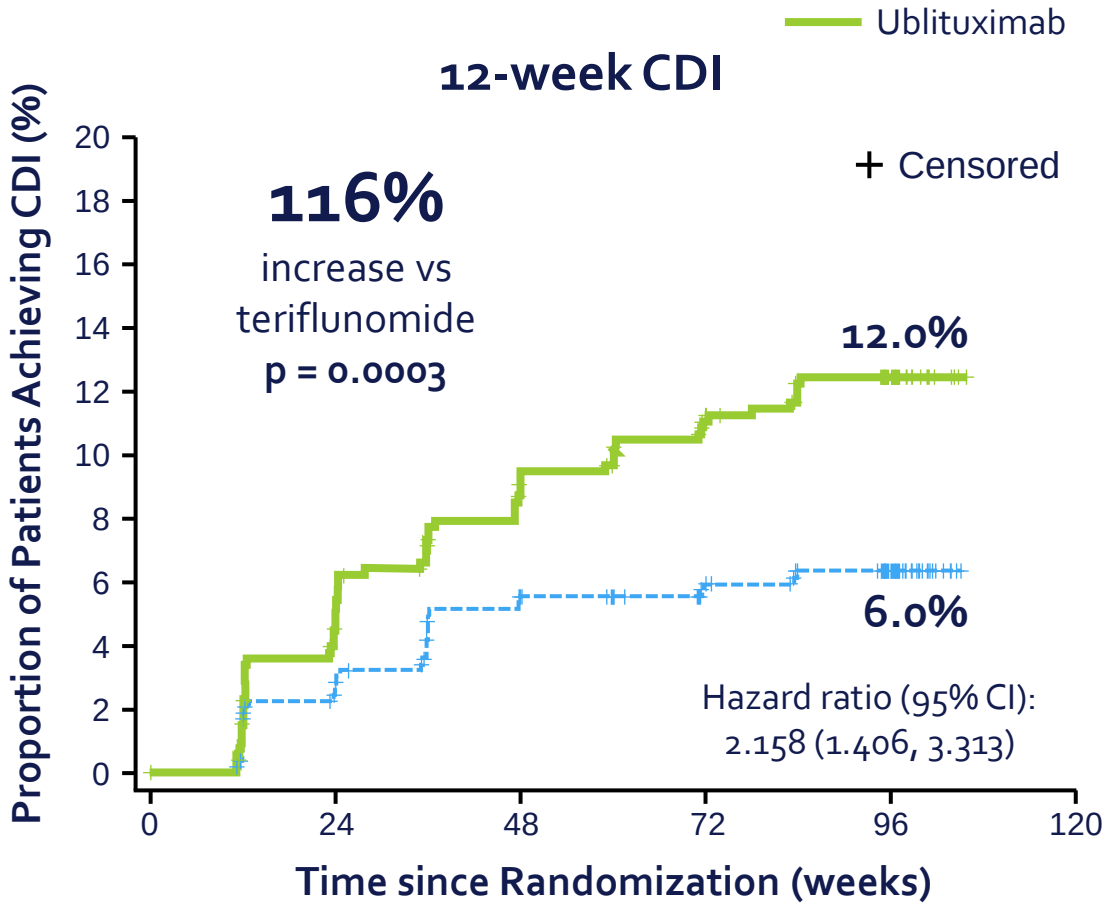
N at risk

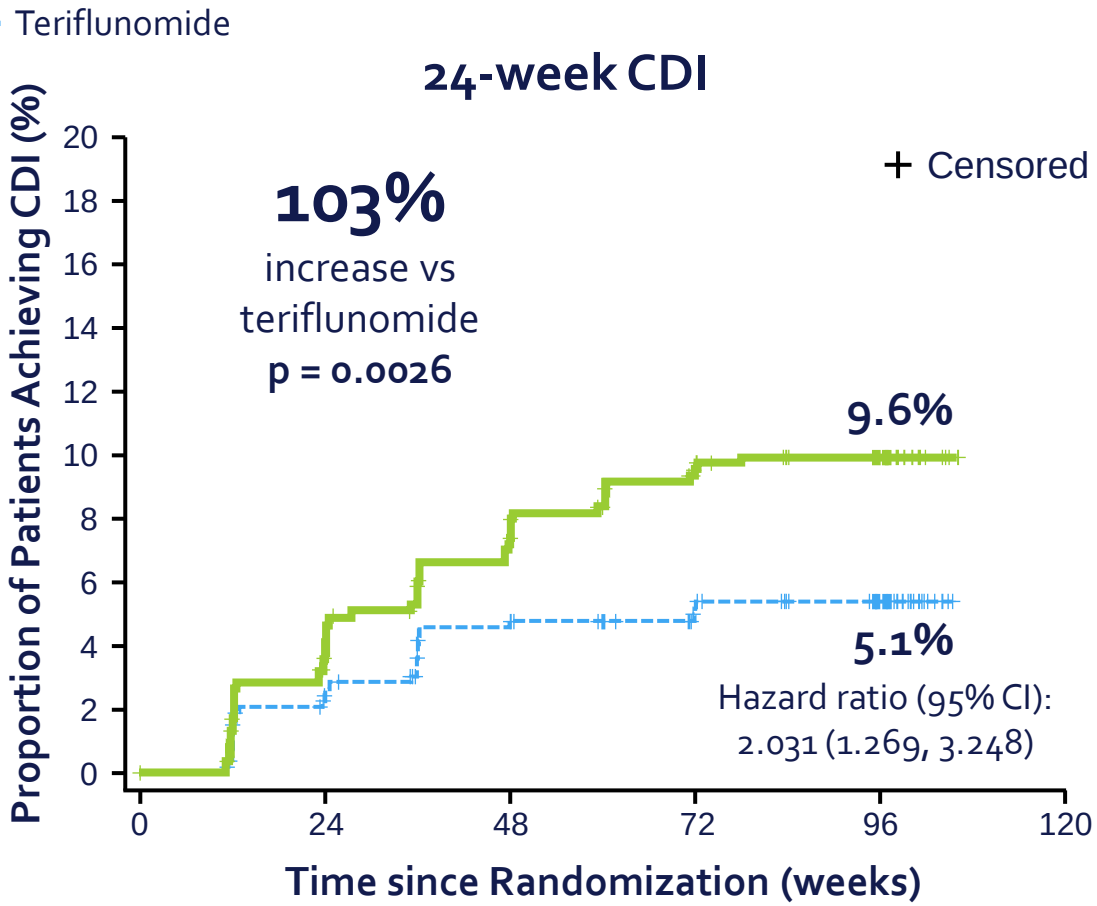
UTX	543	525	511	489	351
Teri	546	523	500	474	330

The modified Intention-to-Treat (mITT) population consists of all subjects in the ITT population who received at least one dose of study medication and had at least one baseline and post-baseline efficacy assessment. Hazard ratio is estimated using Cox regression model with treatment group as covariate stratified by region, baseline EDSS and study. P-value is from stratified log-rank test. UTX: ublituximab; Teri: teriflunomide

Confirmed Disability Improvement (CDI)

Pre-specified pooled tertiary analysis



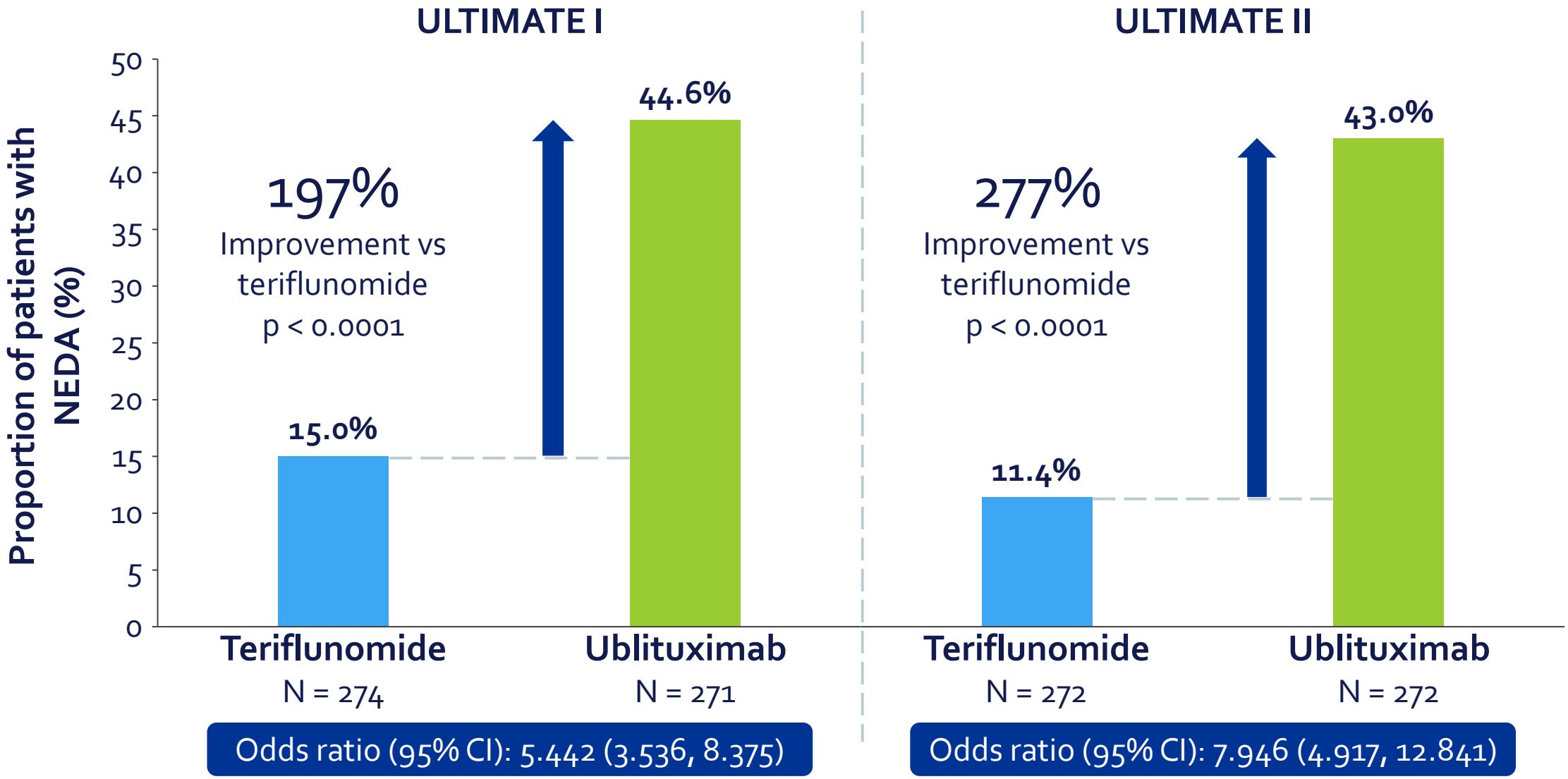


N at risk					
UTX	543	508	475	451	317
Teri	546	514	485	470	328

N at risk					
UTX	543	512	482	458	325
Teri	546	515	488	474	331

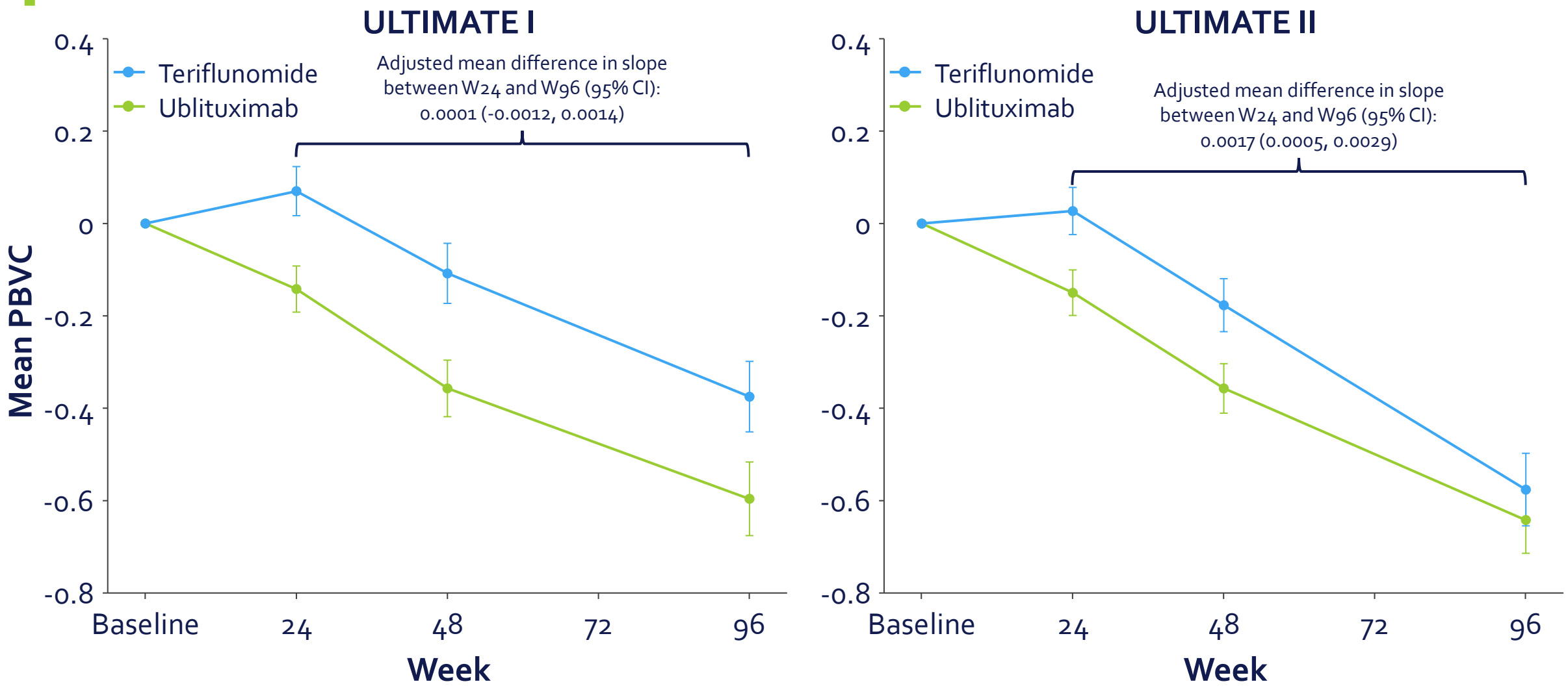
The modified Intention-to-Treat (mITT) population consists of all subjects in the ITT population who received at least one dose of study medication and had at least one baseline and post-baseline efficacy assessment. Hazard ratio is estimated using Cox regression model with treatment group as covariate stratified by region, baseline EDSS and study. P-value is from stratified log-rank test. UTX: ublituximab; Teri: teriflunomide

No Evidence of Disease Activity (NEDA)



The modified Intention-to-Treat (mITT) population consists of all subjects in the ITT population who received at least one dose of study medication and had at least one baseline and post-baseline efficacy assessment. Logistic regression model with covariates treatment, region, baseline EDSS strata and log transformed baseline MRI counts (T_1 unenhancing, T_2, Gd enhancing).

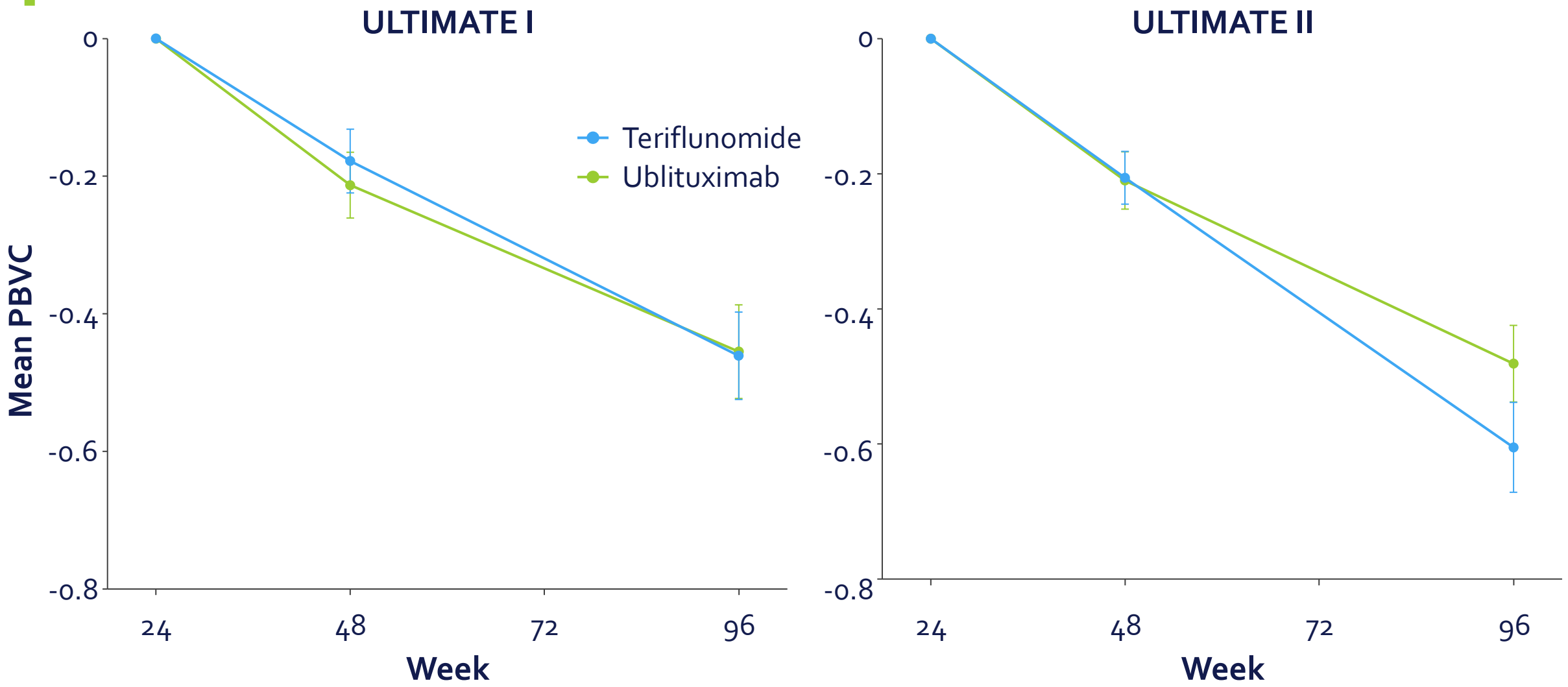
MRI: Brain Volume Change
Baseline to Week 96



Secondary endpoint. MRI modified Intent-to-Treat population (mITT-MRI) . PBVC: percent brain volume change from baseline to W96. Analysis of slope between W24 and W96 was post-hoc.

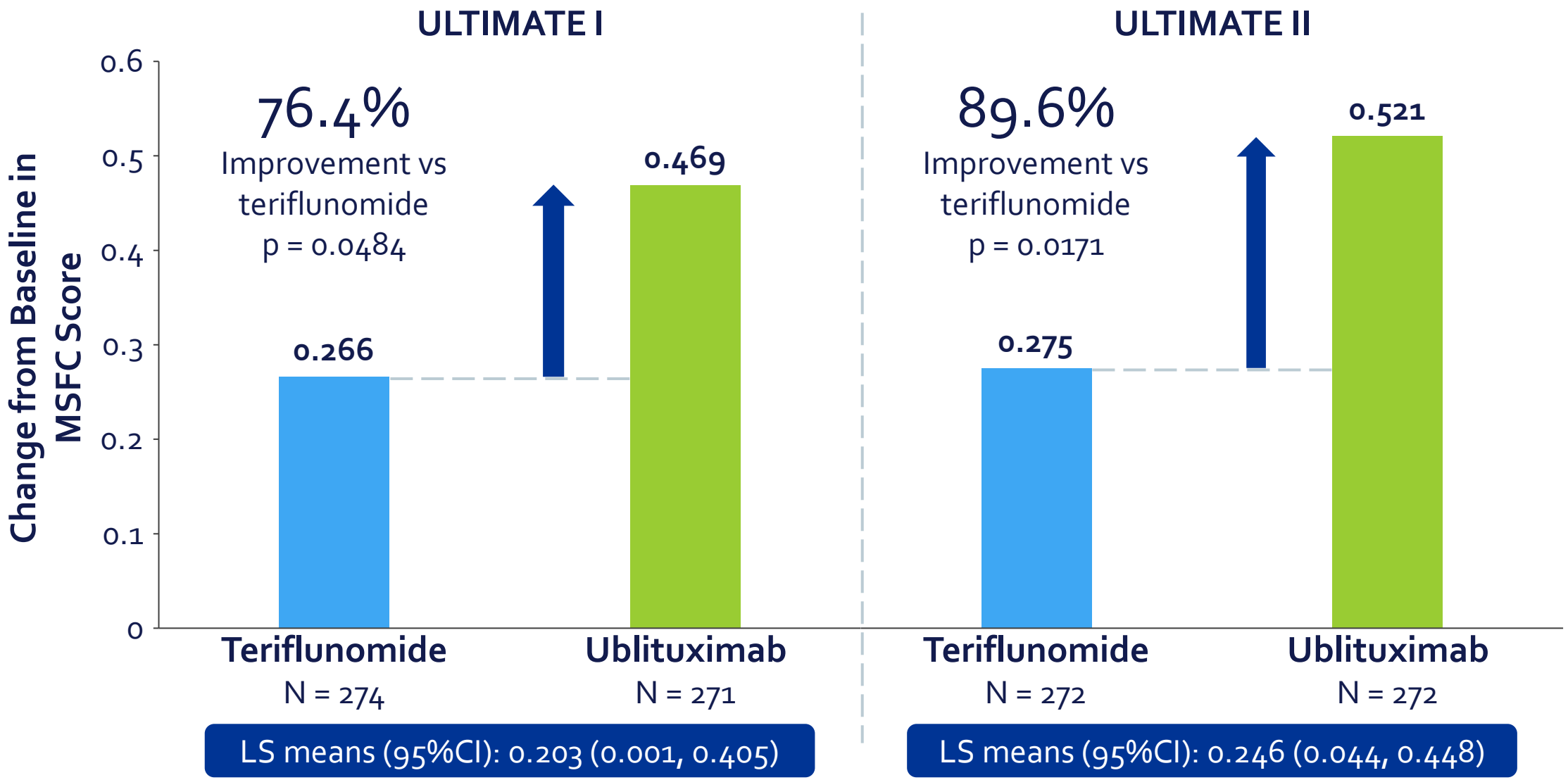
MRI: Brain Volume Change

Week 24 to Week 96 (post-hoc analysis)



MRI modified Intent-to-Treat population (mITT-MRI) . PBVC: percent brain volume change from W24 to W96.

Multiple Sclerosis Functional Composite (MSFC)



Tertiary endpoint. Modified Intent-to-Treat population. LS Means = Least Square Means *MMRM (Mixed Model Repeated Measures) of the change from baseline at all post-baseline time points. MSFC: Multiple Sclerosis Functional Composite ; CI: confidence interval

Adverse Events

Most common AEs, n (%) *≥5% in any treatment group*	**Teriflunomide** N=548	**Ublituximab** N=545
Any AE	**486 (88.7)**	**483 (88.6)**
IRR	67 (12.2)	260 (47.7)
Headache	138 (25.2)	165 (30.3)
Nasopharyngitis	96 (17.5)	97 (17.8)
Lymphopenia	5 (0.9)	51 (9.4)
Back pain	53 (9.7)	48 (8.8)
Respiratory tract infection viral	31 (5.7)	41 (7.5)
Respiratory tract infection	38 (6.9)	40 (7.3)
Upper respiratory tract infection	33 (6.0)	39 (7.2)
Diarrhea	53 (9.7)	36 (6.6)
Lymphocyte count decreased	9 (1.6)	34 (6.2)
Abdominal pain	17 (3.1)	32 (5.9)
Pharyngitis	11 (2.0)	31 (5.7)
Pyrexia	23 (4.2)	30 (5.5)
Insomnia	16 (2.9)	28 (5.1)
Nausea	26 (4.7)	28 (5.1)
Hypertension	35 (6.4)	19 (3.5)
Alopecia	84 (15.3)	18 (3.3)

AE: adverse event. IRR: Infusion-related reaction. IRR includes AEs designated as IRR in the CRF. AEs included within IRR are not included in individual preferred terms

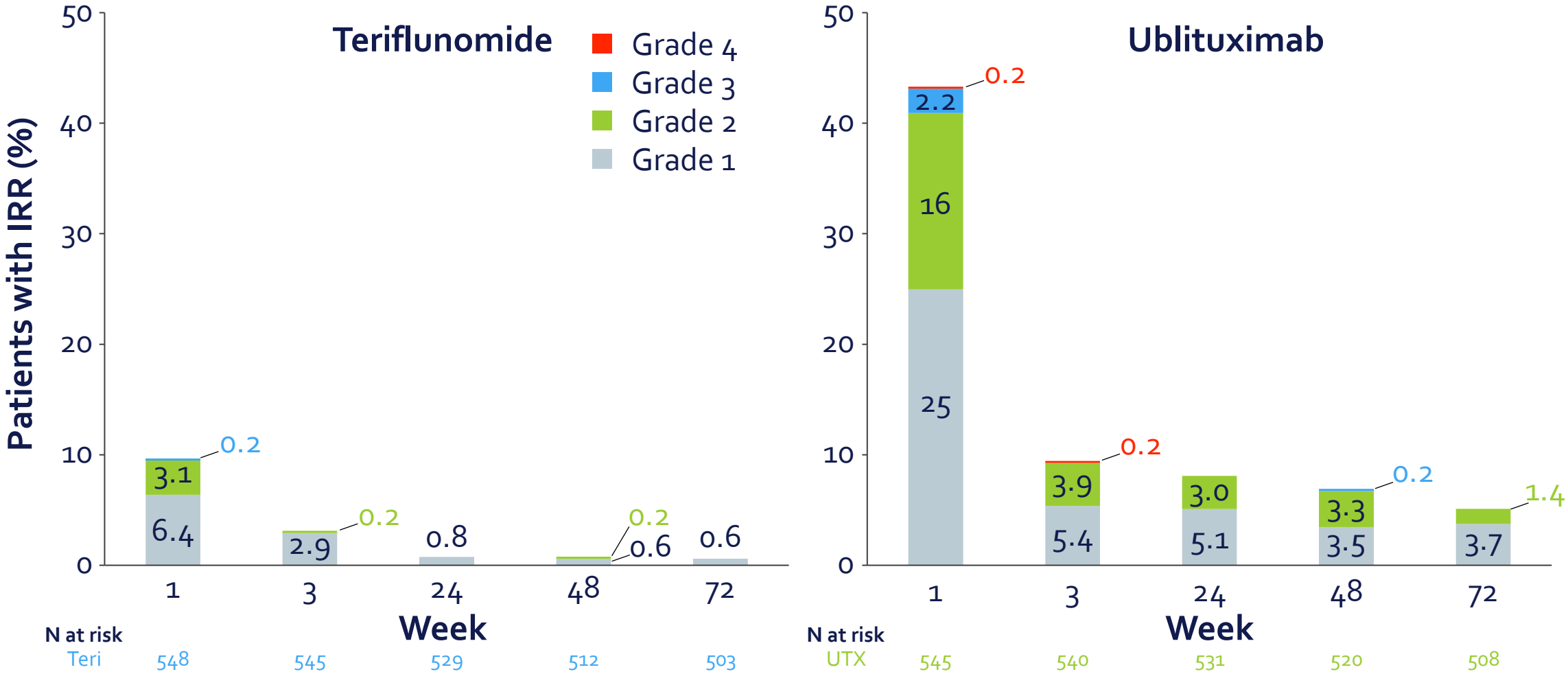
Serious Adverse Events

SAEs, n (%)	Teriflunomide N = 548	Ublituximab N = 545
Any serious AEs	34 (6.2)	52 (9.5)
Most common SAEs by SOC *≥1% in any treatment group*		
Infections and infestations	14 (2.6)	22 (4.0)
Nervous system disorders	7 (1.3)	5 (0.9)

- Three total malignancies were reported
  - 2 ublituximab (endometrial, uterine) versus 1 teriflunomide (tongue)
- Three total deaths occurred
  - Ublituximab: pneumonia, encephalitis (post-measles), salpingitis
  - 1 death was deemed possibly related to treatment (pneumonia)
- No cases of progressive multifocal leukoencephalopathy (PML)

SAE: serious adverse event; SOC: system organ class

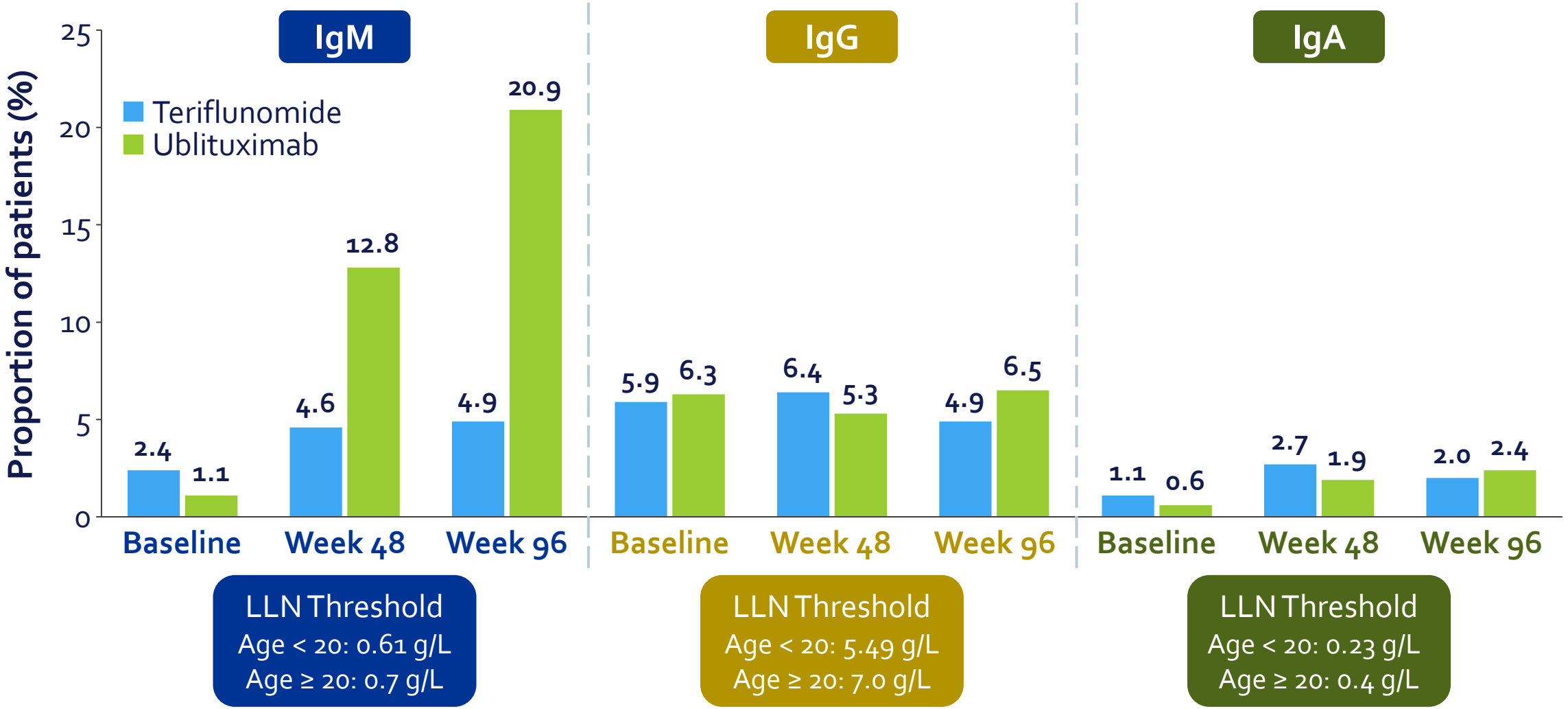
Infusion Related Reactions by Dose & Severity



- IRRs were most frequent on the 1st dose: 43% in the ublituximab group and 9.7% in the teriflunomide group (placebo infusion) reported an IRR on Day 1
- Most IRRs were mild to moderate and decreased in frequency with subsequent dosing
- Three subjects (0.6%) discontinued ublituximab due to an IRR following the first dose, which included a myocardial ischemia deemed unrelated to treatment

IRR: infusion related reaction; Teri: teriflunomide; UTX: ublituximab.

Proportion of Patients With Ig Levels <LLN



LLN: Lower Limit of Normal

Conclusions

- In the Phase III ULTIMATE I & II studies ublituximab met its primary endpoint of ARR and reduced MRI parameters compared with teriflunomide
- A very low rate of disability progression was observed with ublituximab, with >94% of patients showing no 12-week CDP, and >96% of patients showing no 24-week CDP, although neither was statistically different from teriflunomide
- In a pre-specified pooled tertiary analysis, ublituximab increased the proportion of patients with 12-week CDI and 24-week CDI
- A significantly higher percentage of patients treated with ublituximab achieved NEDA and displayed improved MSFC scores compared with teriflunomide
- Ublituximab exhibited a favorable safety and tolerability profile with no unexpected safety signals
- These data are being prepared for marketing authorization application submissions in the US and EU

In ULTIMATE I & ULTIMATE II, ublituximab, a one-hour infusion, demonstrated robust efficacy and a favorable safety profile that benefited RMS patients