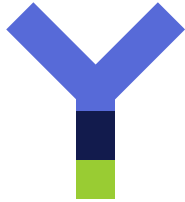





Ublituximab versus Teriflunomide in Relapsing Multiple Sclerosis: Results of the Phase 3 ULTIMATE I and II Trials

Lawrence Steinman, MD¹; Edward Fox, MD, PhD²; Hans-Peter Hartung, MD^{3,4,5}; Enrique Alvarez, MD, PhD⁶; Peiqing Qian, MD⁷; Sibyl Wray, MD⁸; Derrick Robertson, MD⁹; DeRen Huang, MD, PhD¹⁰; Krzysztof Selmaj, MD, PhD^{11, 12}; Daniel Wynn, MD¹³; Michael S. Weiss¹⁴, Jenna A. Bosco¹⁴, Sean A. Power¹⁴, Koby Mok, PhD¹⁴; Bruce Cree, MD, PhD, MAS¹⁵

¹Stanford University, Stanford, CA, USA ²Central Texas Neurology Consultants, Round Rock, TX, USA ³Heinrich Heine University, Dusseldorf, Germany, ⁴Brain and Mind Centre, University of Sydney, Australia, ⁵Department of Neurology, Medical University of Vienna, Austria ⁶University of Colorado, Aurora, CO, USA ⁷Swedish Medical Center, Seattle, WA, USA ⁸Hope Neurology, Knoxville, TN, USA ⁹University of South Florida, Tampa, FL, USA ¹⁰Center for Multiple Sclerosis, Mount Carmel Health System, Westerville, OH, USA, ¹¹Center of Neurology, Lodz, Poland, ¹²University of Warmia & Mazury, Olsztyn, Poland ¹³Consultants in Neurology, Northbrook, IL, USA ¹⁴TG Therapeutics, New York, NY, USA ¹⁵UCSF Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA, USA

Ublituximab Is a Novel Glycoengineered Anti-CD20 mAb

	Ublituximab	Rituximab	Ocrelizumab	Ofatumumab
<ul style="list-style-type: none"> ■ 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	++++	++	+++	++
CDC	+	++	++	+++

Adapted from Ancau et al 2019 and Sellebjerg et al. 2020. 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

ULTIMATE I & II: Study Design

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

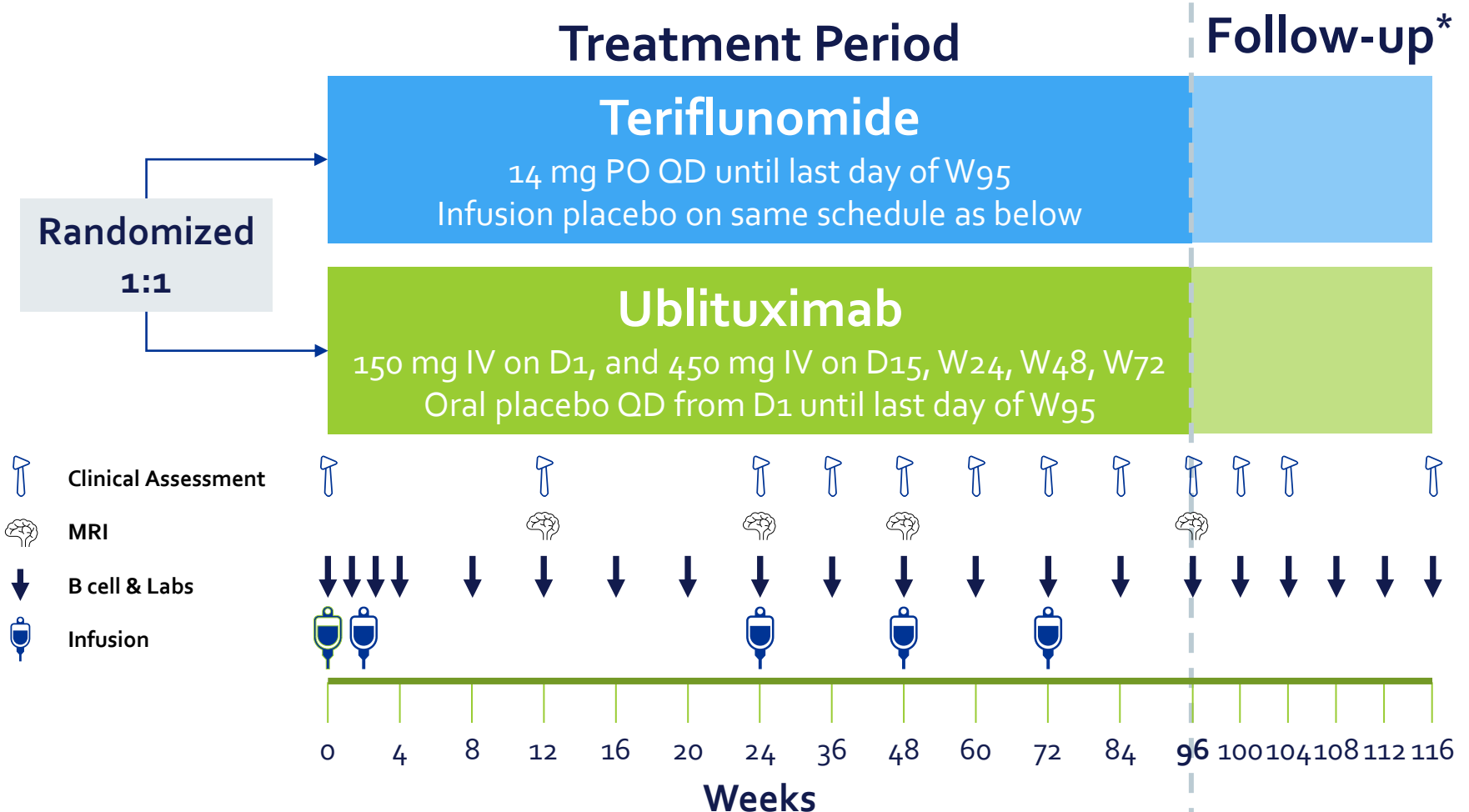
Screening

Population

- Age 18-55 years
- 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. ³

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

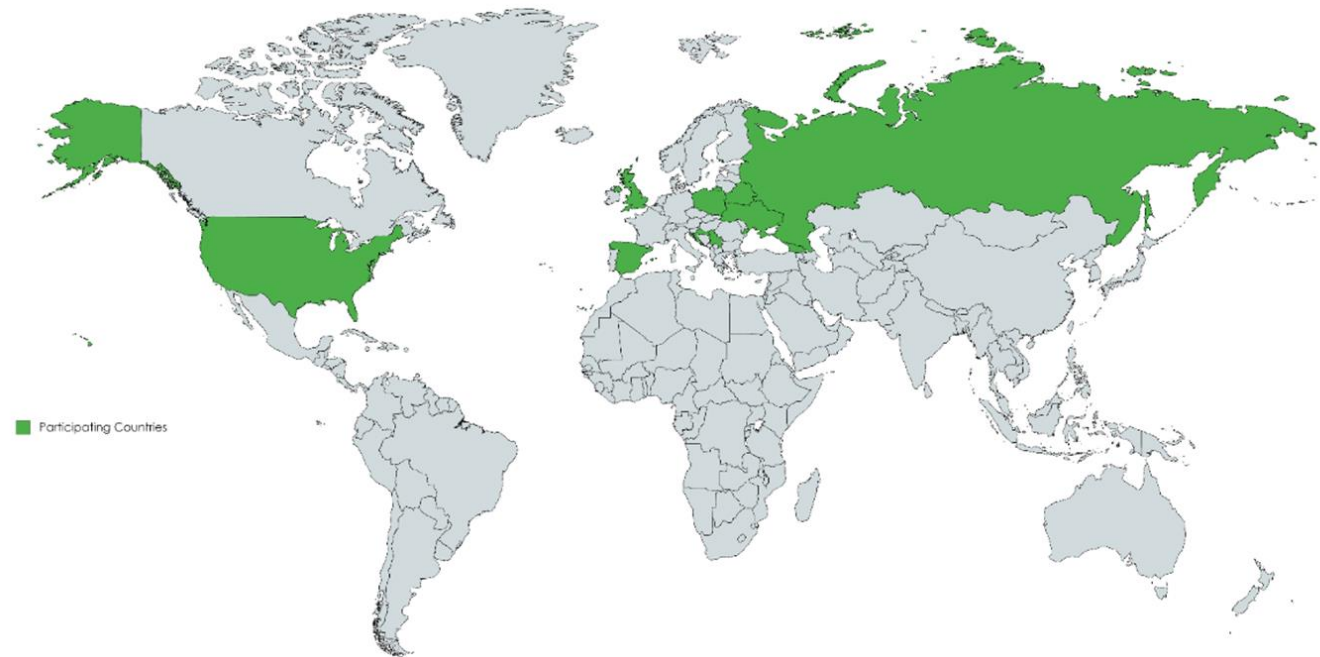
Tertiary analyses

- Time to CDP for at least 24 weeks
- Time to CDI for at least 12 weeks
- Time to CDI for at least 24 weeks

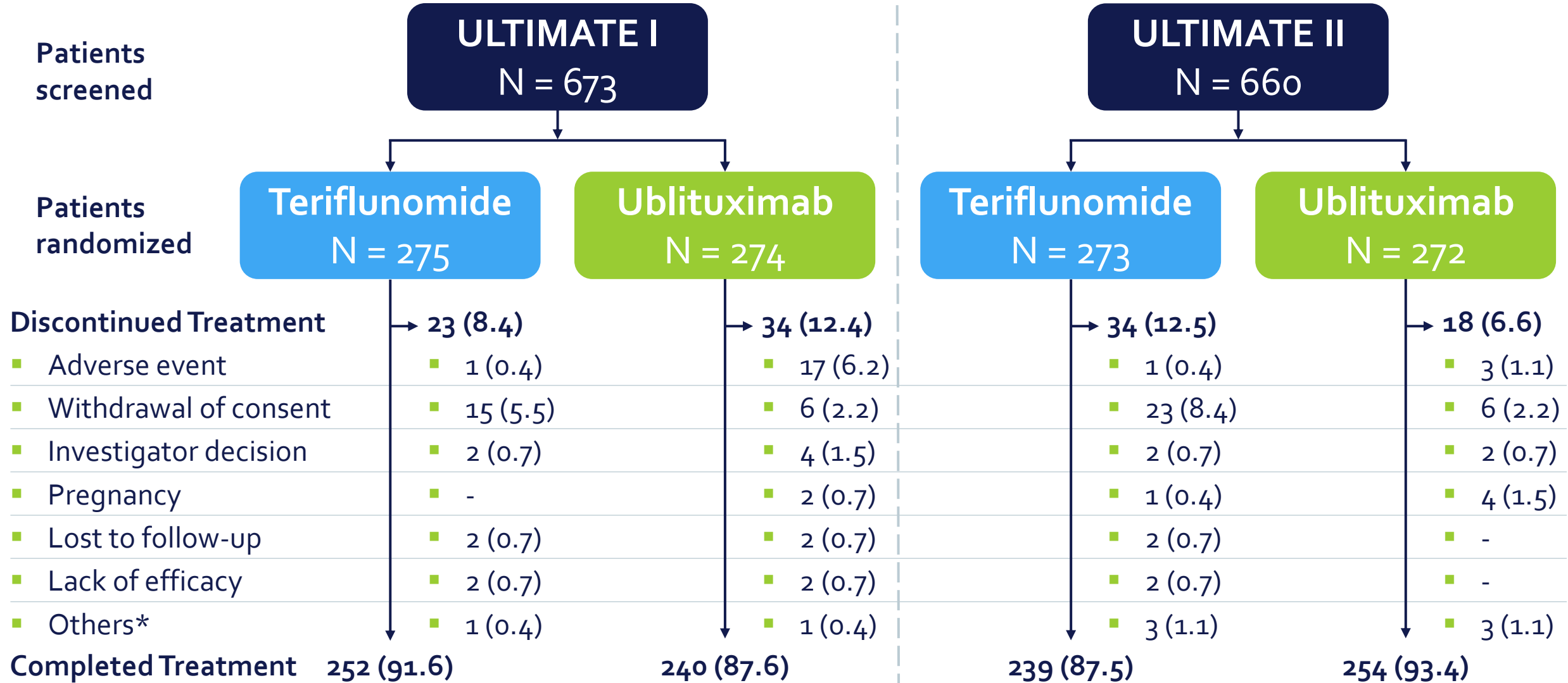
ULTIMATE I & II: Independent Global Studies

- 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



Patient Disposition & Analysis Population



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

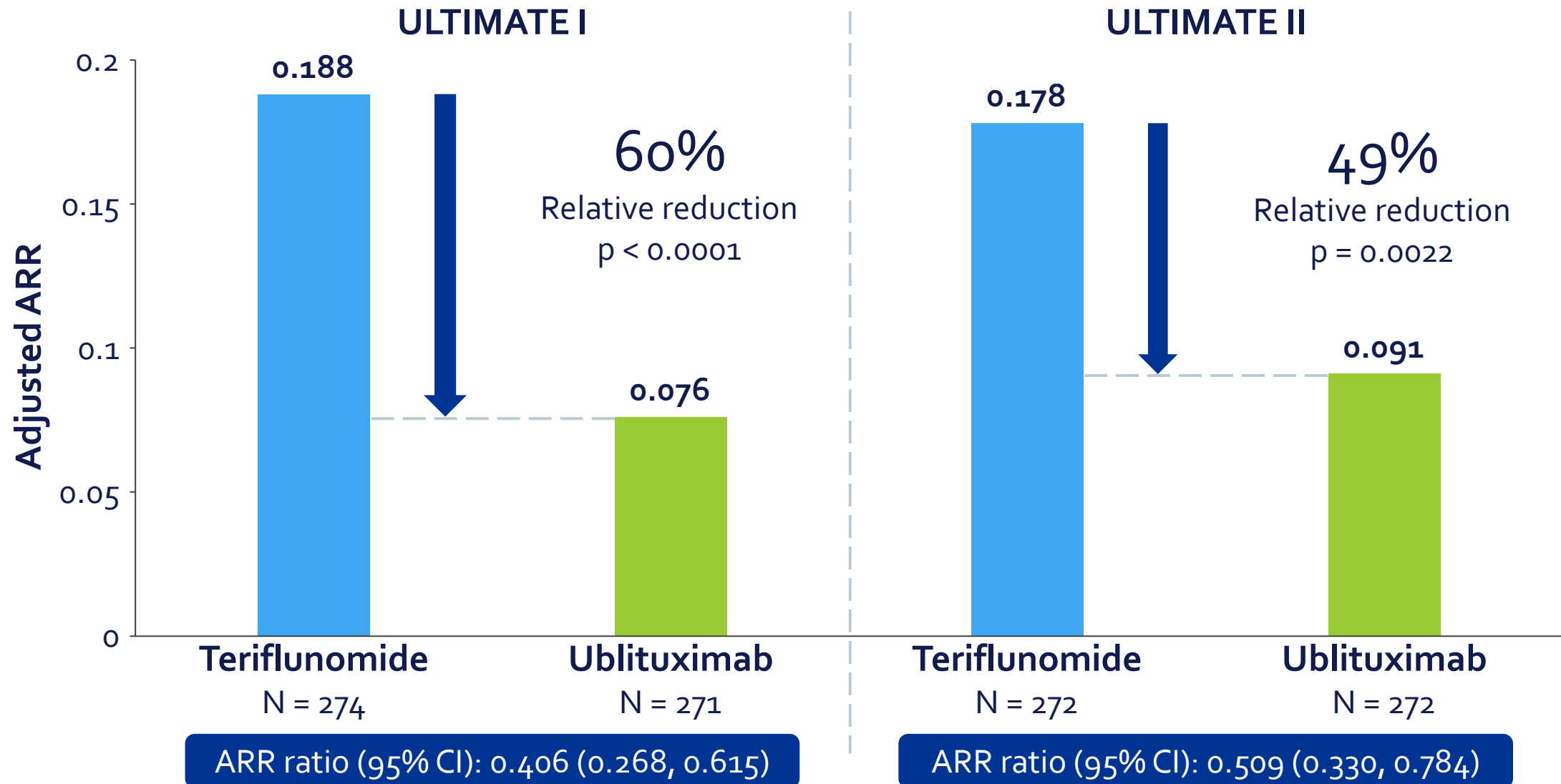
Patient Demographics & Baseline Characteristics

ULTIMATE I & II populations are consistent and poolable

Characteristic	ULTIMATE I (N = 545)		ULTIMATE II (N = 544)	
	Teriflunomide N = 274	Ublituximab N = 271	Teriflunomide N = 272	Ublituximab N = 272
<i>Mean ± standard deviation or n (%)</i>				
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, cm³	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

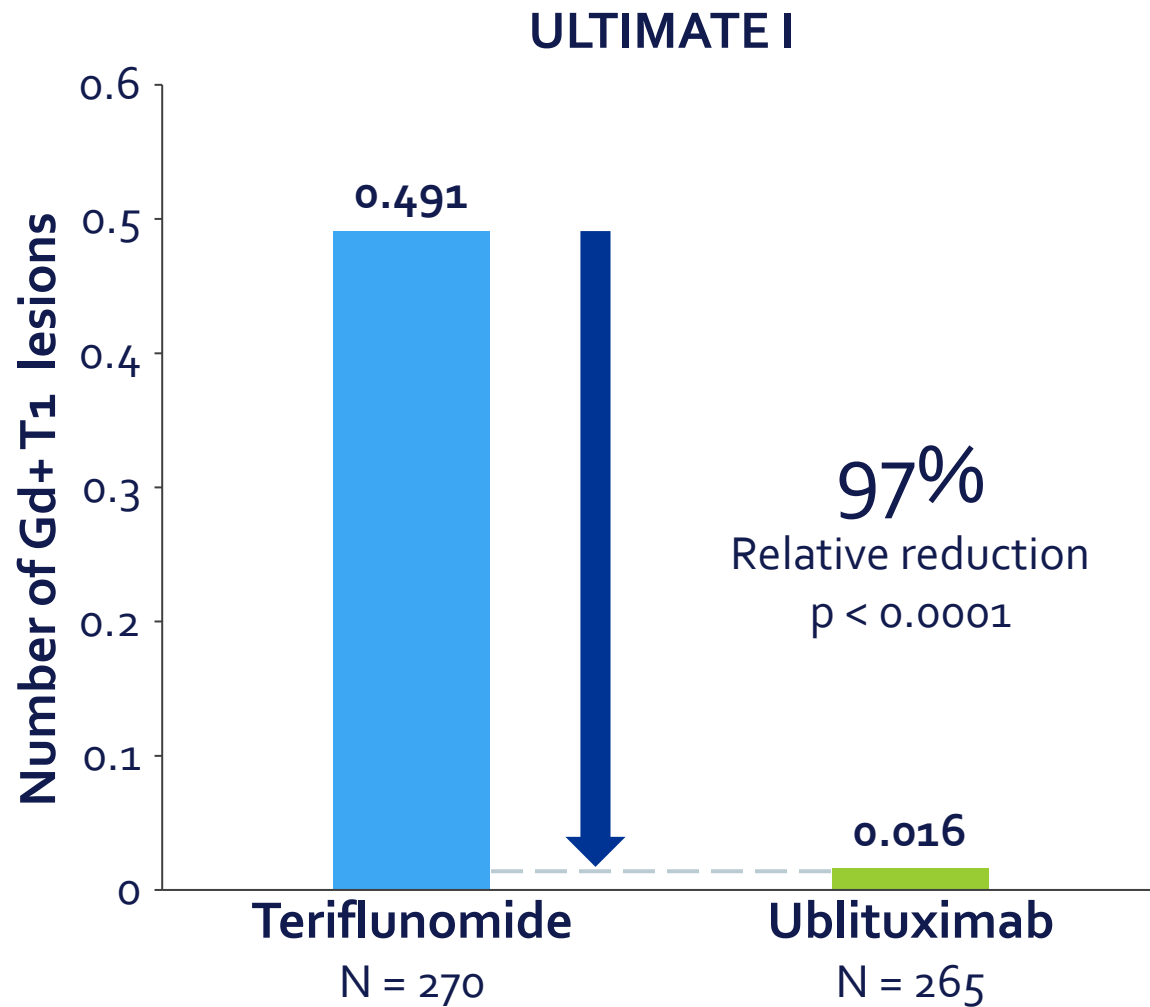
Modified Intent-to-Treat population: All patients in the ITT population who received at least one dose of study drug and had at least one baseline and post-baseline efficacy assessment. *Untreated with disease-modifying therapy in 5 years prior to study entry. DMT: disease-modifying therapy; EDSS: expanded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

Primary Endpoint: Annualized Relapse Rate (ARR)

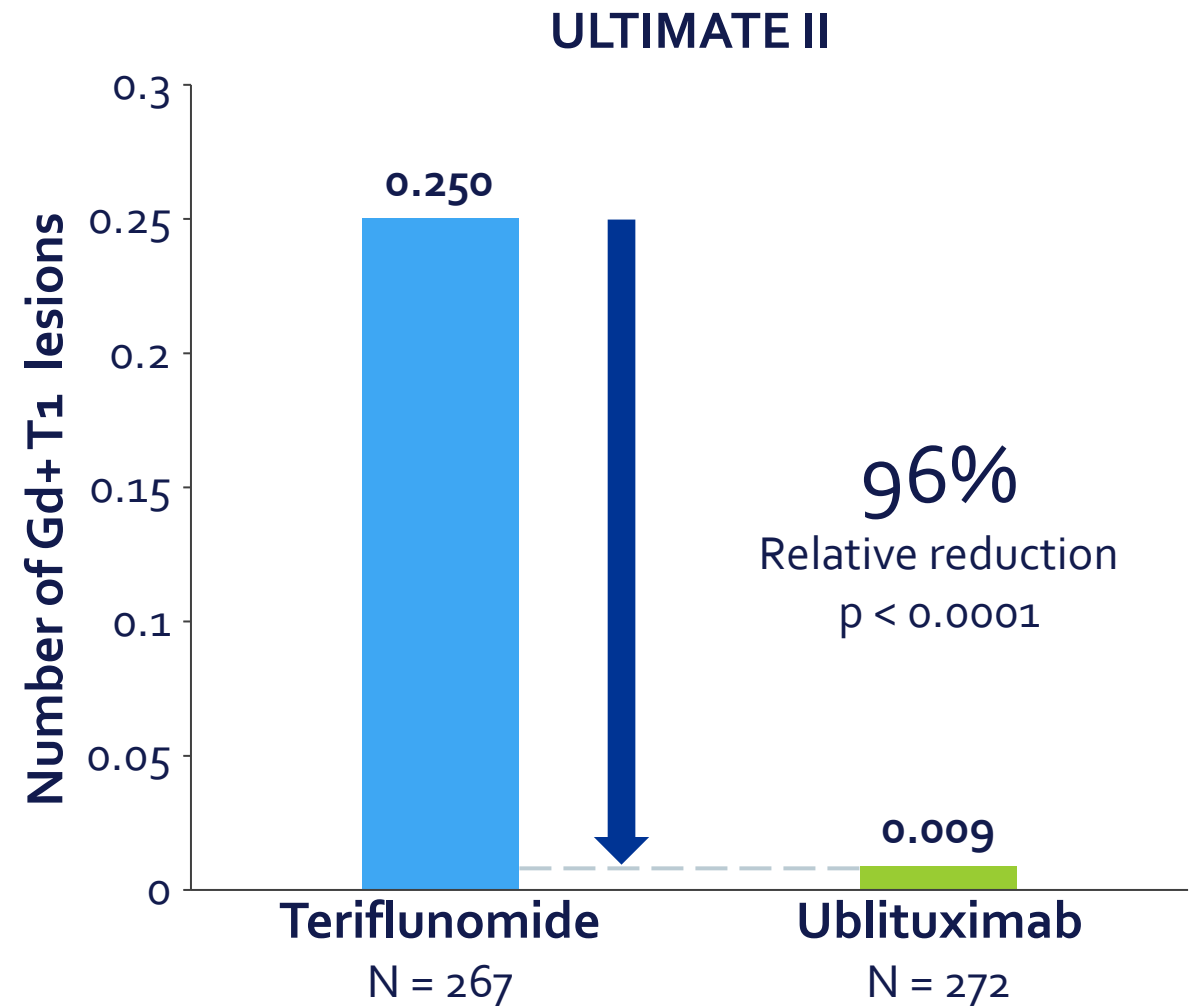


The modified Intention-to-Treat (mITT) population consists of all subjects in the ITT population who received at least one dose of study medication and had at least one baseline and post-baseline efficacy assessment. Based on negative binomial model (GEE) for the relapse count per subject with logarithmic 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



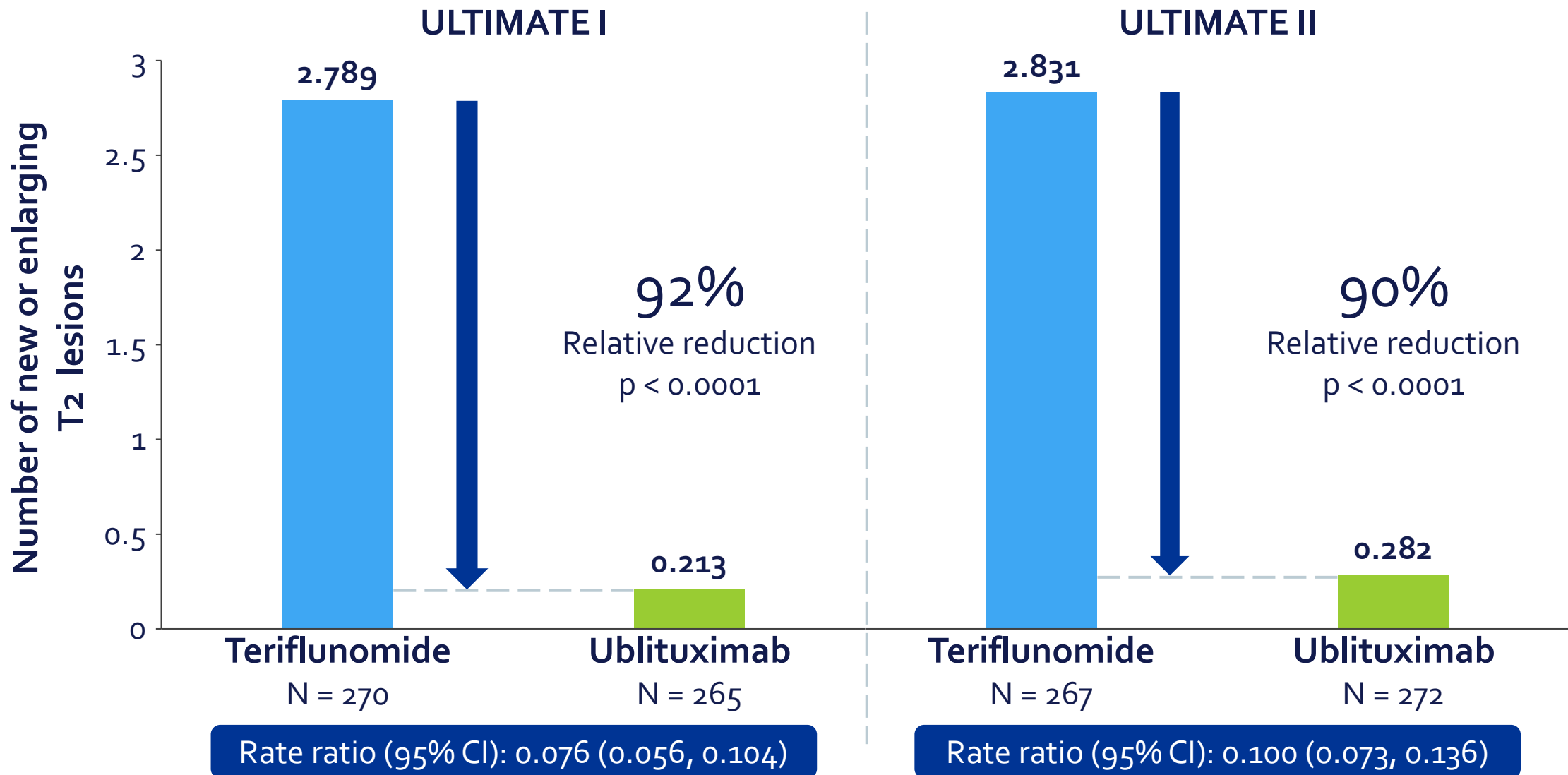
Rate ratio (95% CI): 0.033 (0.019, 0.058)



Rate ratio (95% CI): 0.035 (0.019, 0.064)

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 ($0 \geq 1$) and an offset based on the log-transformed number of post-baseline MRI scans. MRI assessed by Independent Review

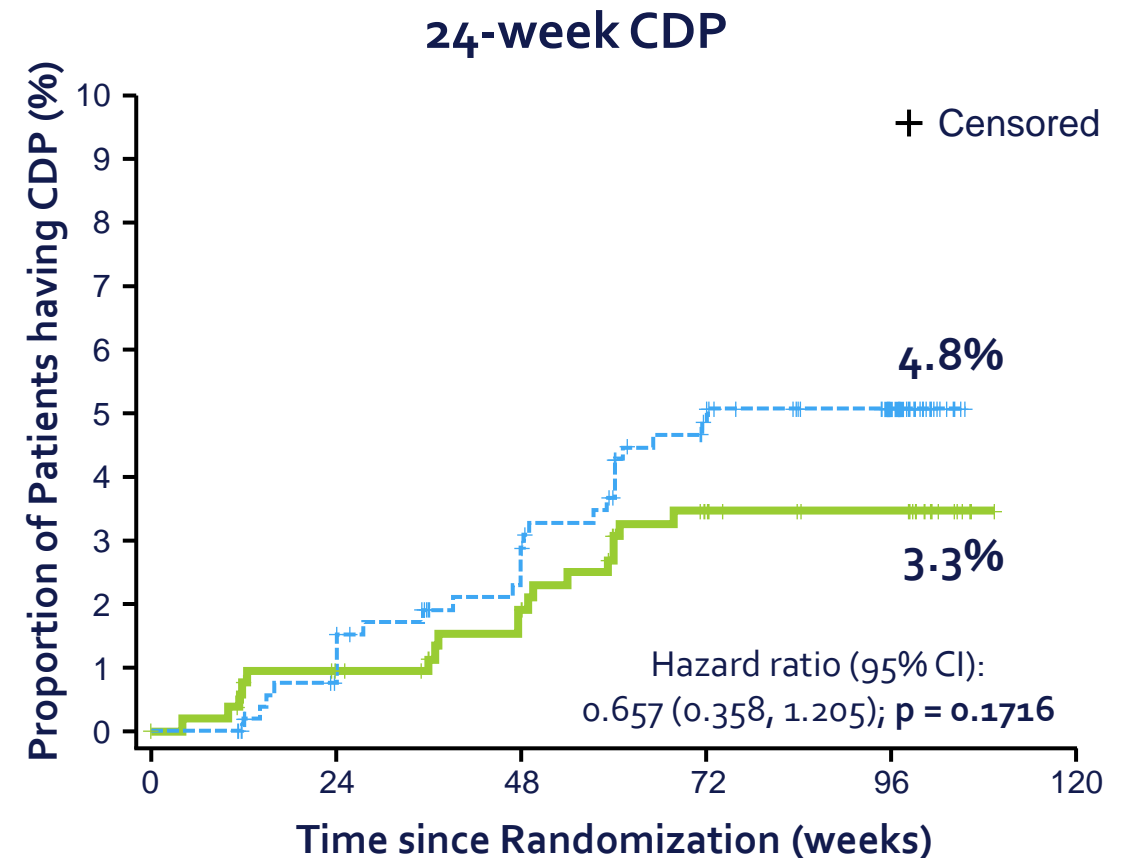
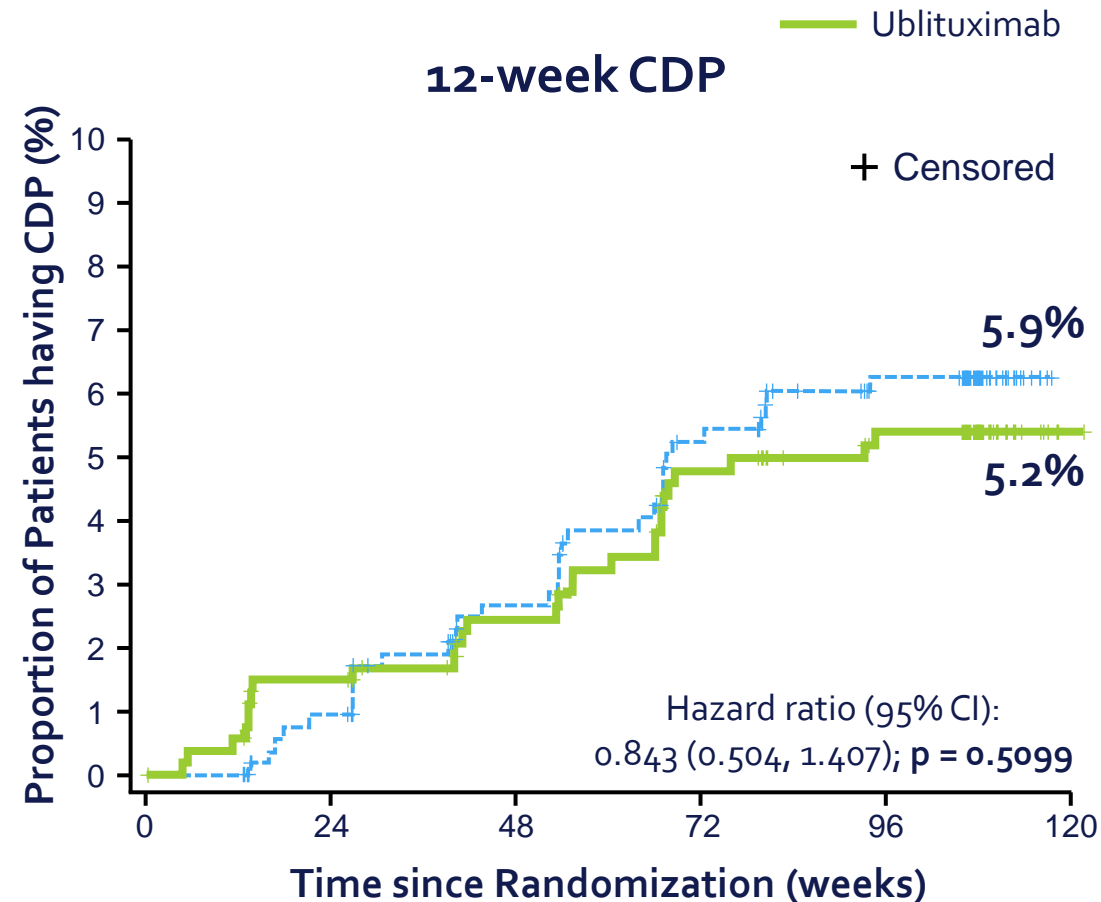
MRI: Number of New or Enlarging T2 Lesions



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 ($0 \geq 1$) 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

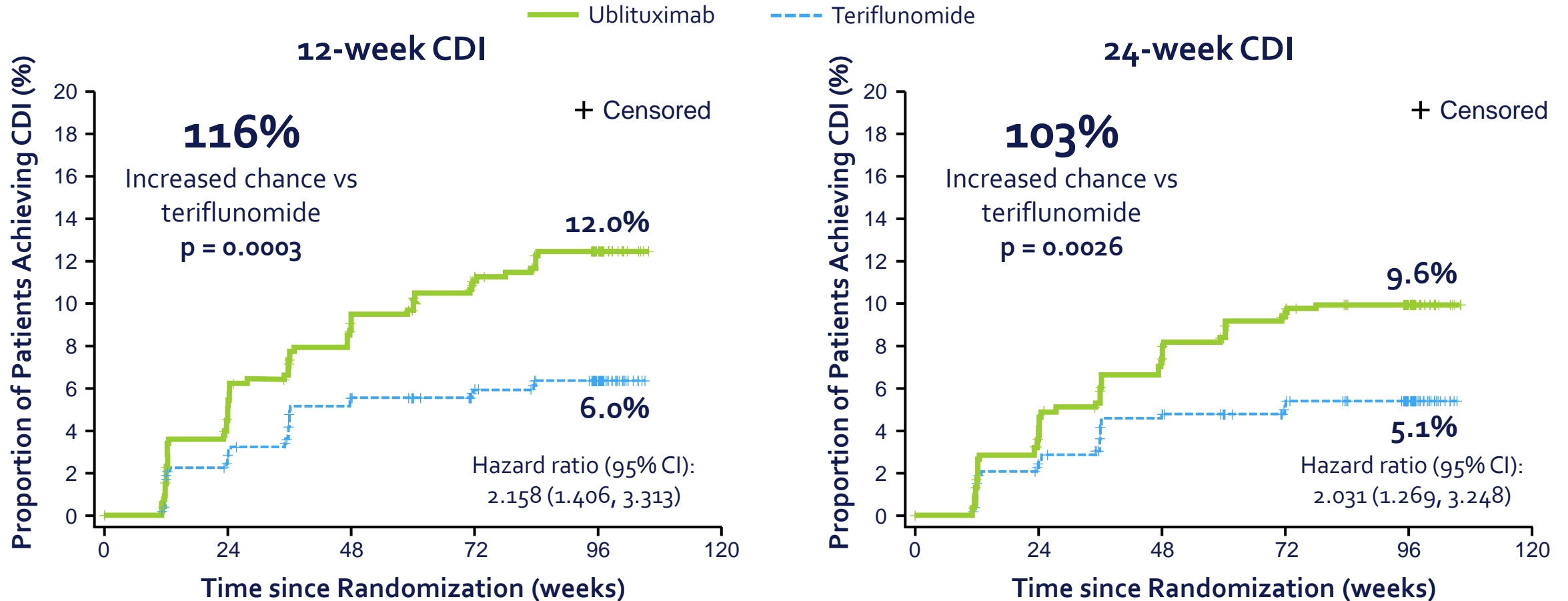
N at risk

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

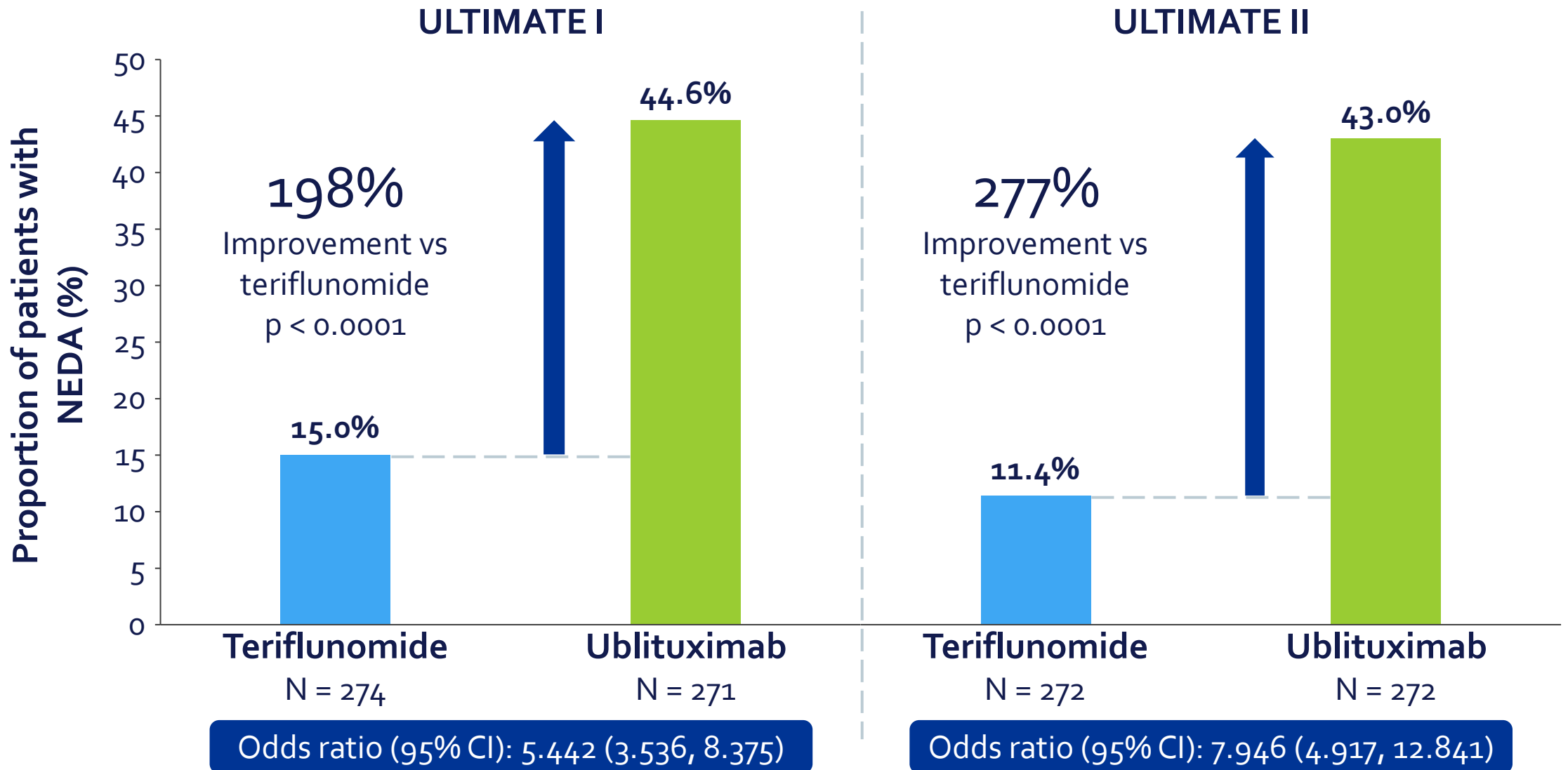
N at risk

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

Percent increased chance based on hazard ratio

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 (T1 unenhancing, T2, Gd enhancing).

Adverse Events

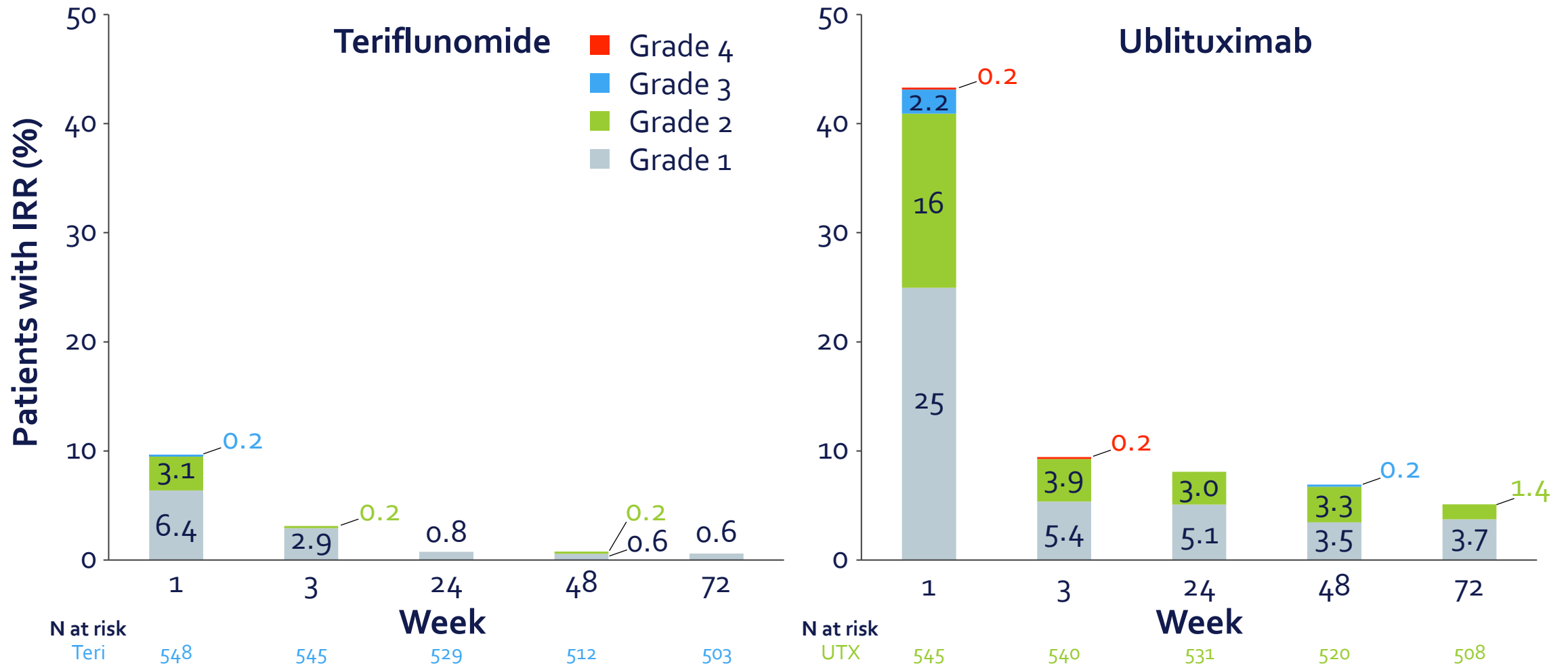
Most common AEs, n (%) ≥5% in any treatment group	Teriflunomide N=548	Ublituximab N=545
Any AE	486 (88.7)	483 (88.6)
IRR	67 (12.2)	260 (47.7)
Headache	138 (25.2)	165 (30.3)
Nasopharyngitis	96 (17.5)	97 (17.8)
Lymphopenia	5 (0.9)	51 (9.4)
Back pain	53 (9.7)	48 (8.8)
Respiratory tract infection viral	31 (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)

Serious Adverse Events

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

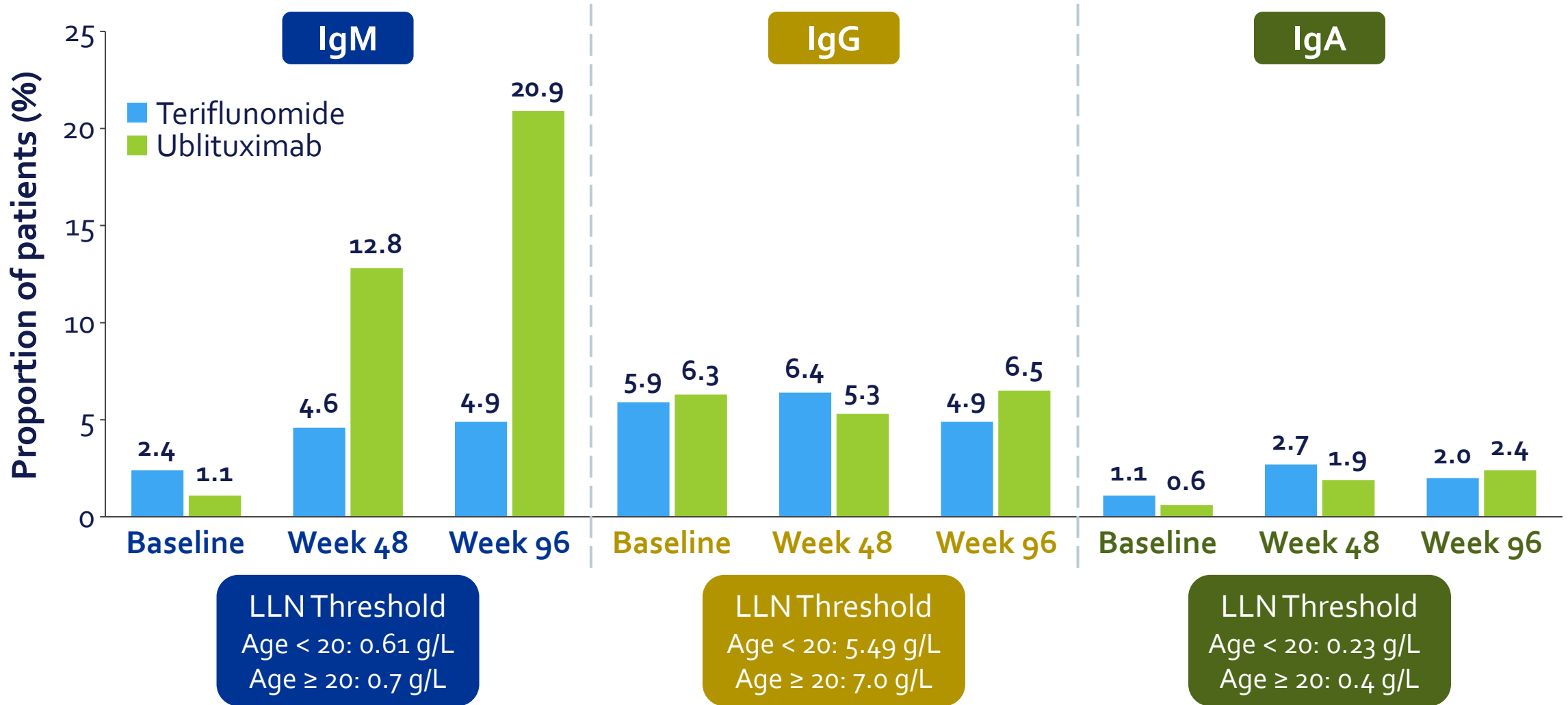
- Three total malignancies were reported
 - 2 ublituximab (endometrial, uterine) versus teriflunomide 1 (tongue)
- Three total deaths occurred
 - Ublituximab: pneumonia, encephalitis (post-measles), salpingitis
 - 1 death was deemed possibly related to treatment (pneumonia)
- No cases of progressive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

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

Proportion of Patients With Ig Levels <LLN



Conclusions

- In the Phase III ULTIMATE I & II studies, ublituximab significantly reduced ARR and 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 compared with teriflunomide achieved NEDA
- Ublituximab exhibited a favorable safety and tolerability profile with no unexpected safety signals
- These data are being prepared for a Biological License Application

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