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Ph3 results of the ULTIMATEI&II global studies: Ublituximab v. teriflunomide in RMS

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INTRODUCTION

Background and Objectives

- Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20 (**Figure 1**) and is glycoengineered for enhanced antibody-dependent cellular cytotoxicity
- Ublituximab is administered in lower doses with shorter infusion times than other currently available anti-CD20 therapies

Primary Objective

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

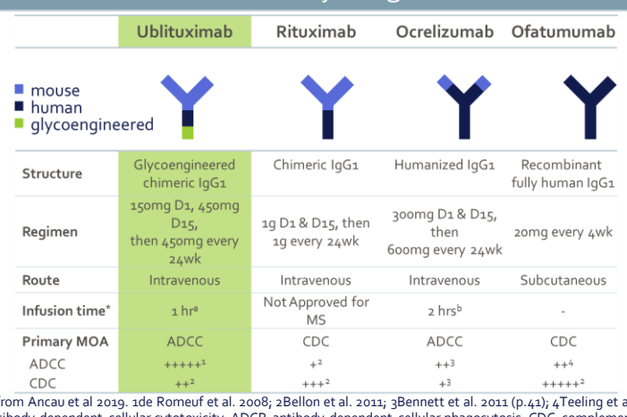
Primary Endpoint (by individual study):

ARR at 96 wks *(number of confirmed MS relapses in a year)*

Pre-specified Pooled Analysis:

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

Figure 1. Ublituximab Is a Novel Glycoengineered Anti-CD20 mAb

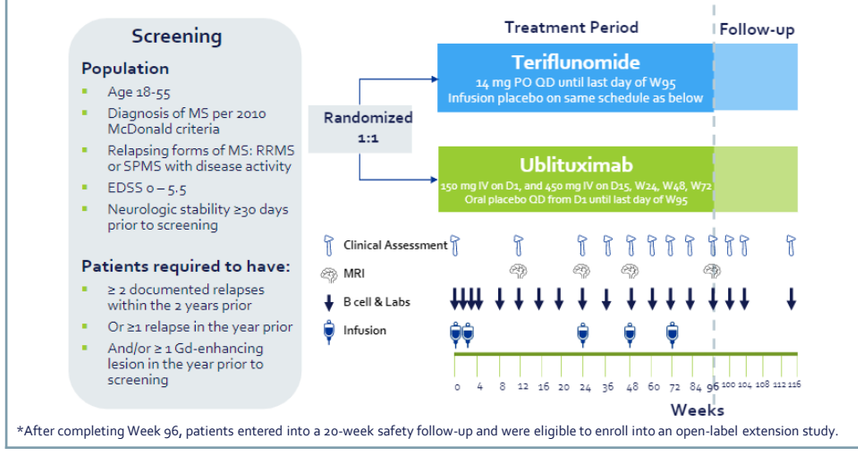


	Ublituximab	Rituximab	Ocrelizumab	Ofatumumab
Structure	Glycoengineered chimeric IgG1	Chimeric IgG1	Humanized IgG1	Recombinant fully human IgG1
Regimen	150mg D1, 450mg D15, then 450mg every 24wk	1g D1 & D15, then 1g every 24wk	300mg D1 & D15, then 600mg every 24wk	20mg every 4wk
Route	Intravenous	Intravenous	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. 1de Romeuf et al. 2008; 2Bellon et al. 2011; 3Bennett et al. 2011 (p.41); 4Teeling 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

Study Design

Figure 2. ULTIMATE I and II Study Design

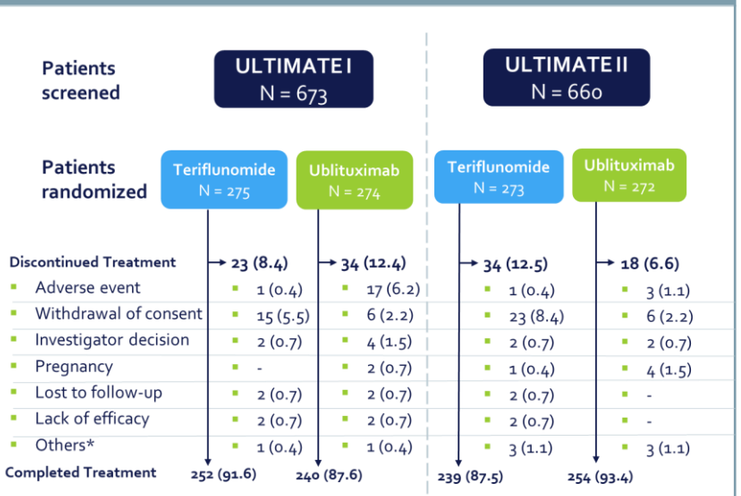


*After completing Week 96, patients entered into a 20-week safety follow-up and were eligible to enroll into an open-label extension study.

RESULTS

Patient Disposition & Analysis Population

Figure 3. Patient Disposition and Analysis Population



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

Demographics and Disease Characteristics

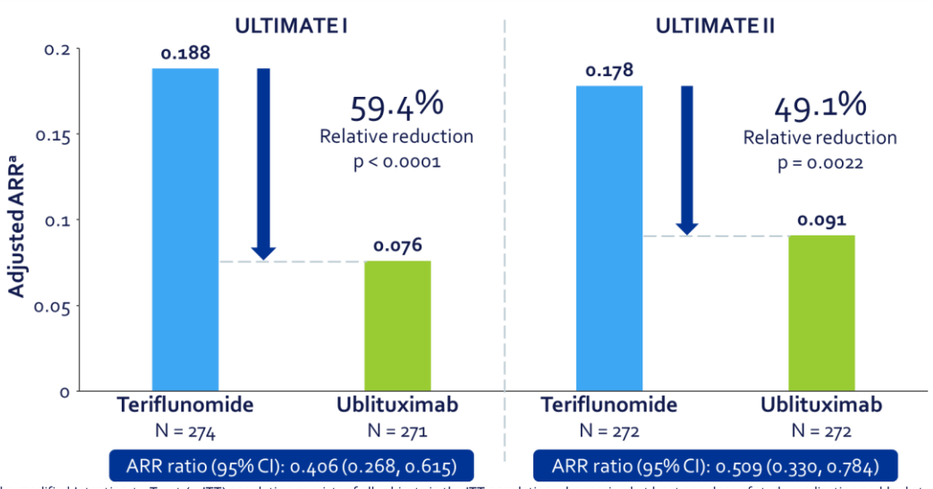
Table 1. Baseline Demographics and Disease Characteristics

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

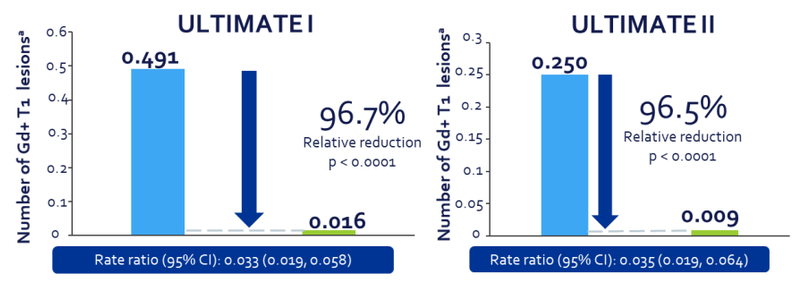
Figure 4. **Annualized Relapse Rate (ARR)**



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.

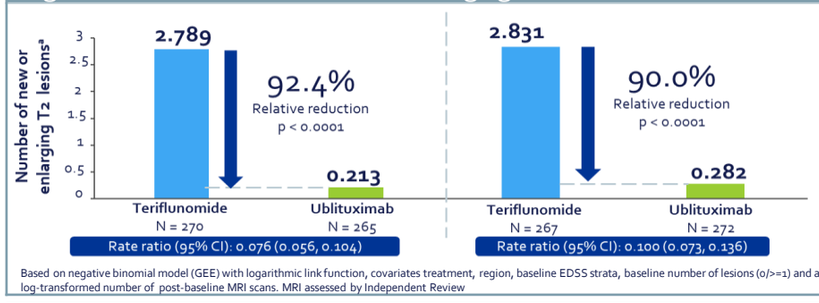
MRI: T1 and T2 Lesions

Figure 5a. MRI: Total Number of Gd+ T1 Lesions



- Modified Intention-to-Treat MRI (mITT-MRI) population: all subjects in the ITT population with at least one dose and one baseline and post-baseline efficacy and MRI efficacy assessments

Figure 5b. MRI: Number of New or Enlarging T2 Lesions

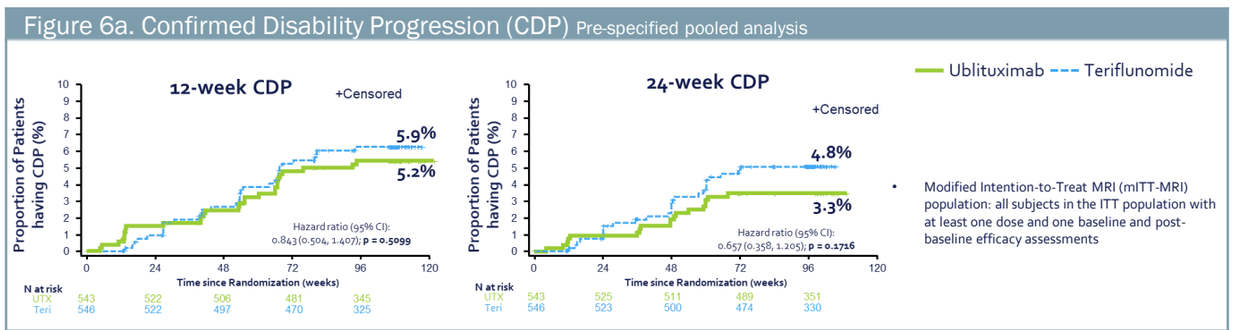


- Modified Intention-to-Treat MRI (mITT-MRI) population: all subjects in the ITT population with at least one dose and one baseline and post-baseline efficacy and MRI efficacy assessments

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

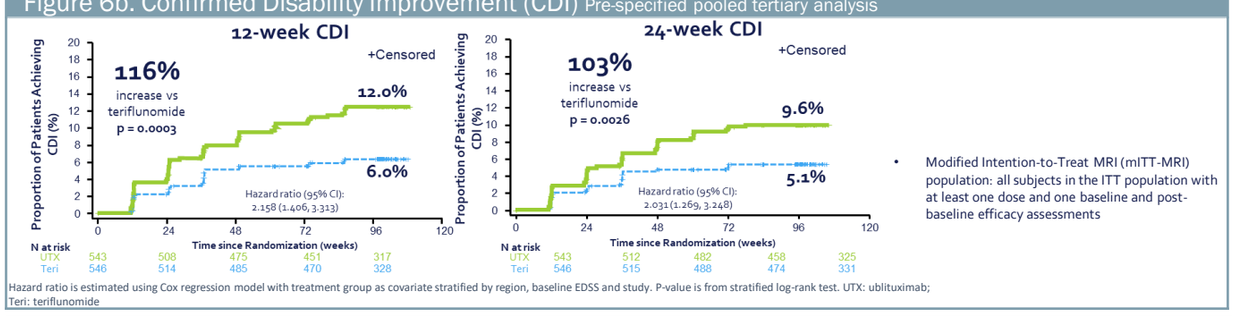
Disability

Figure 6a. Confirmed Disability Progression (CDP) Pre-specified pooled analysis



- Modified Intention-to-Treat MRI (mITT-MRI) population: all subjects in the ITT population with at least one dose and one baseline and post-baseline efficacy assessments

Figure 6b. Confirmed Disability Improvement (CDI) Pre-specified pooled tertiary analysis

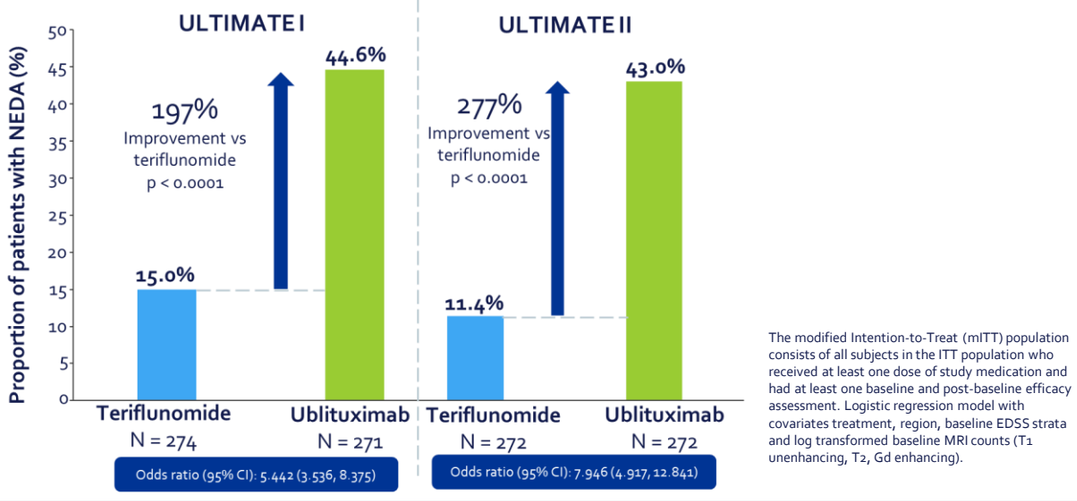


- Modified Intention-to-Treat MRI (mITT-MRI) population: all subjects in the ITT population with at least one dose and one baseline and post-baseline efficacy assessments

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)

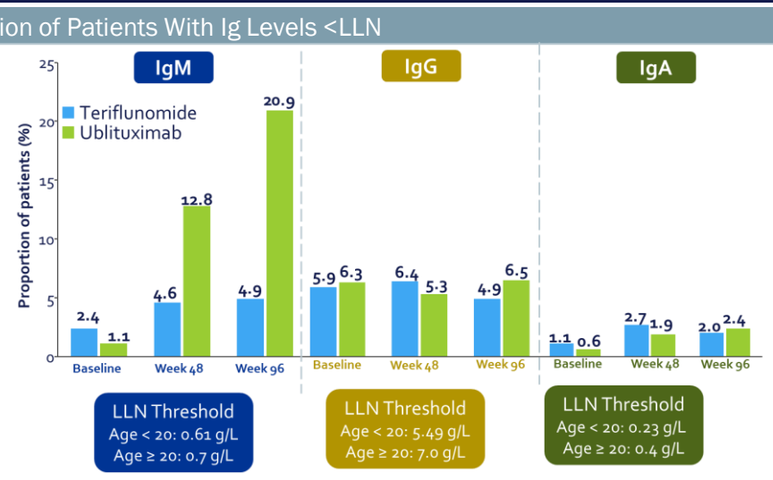
Figure 7. NEDA



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).

Immunoglobulins

Figure 8. Proportion of Patients With Ig Levels <LLN



LLN: Lower Limit of Normal

Safety

Table 2a: Most Common 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

- 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)

Table 2b. 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)

SAE: serious adverse event; SOC: system organ class

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 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

Acknowledgements: We thank the patients and their families for participating in the ULTIMATE I and II studies.

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