Abstract # 4494

Efficacy and Safety of Ublituximab vs Teriflunomide in Patients with Relapsing Multiple Sclerosis: Results from Two Phase 3 Studies ULTIMATE I & ULTIMATE II

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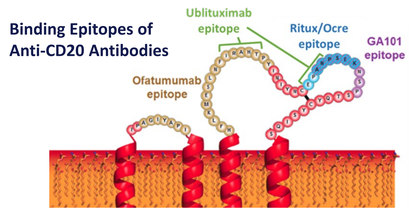
BACKGROUND

Ublituximab

- Ublituximab (UTX; TG-1101) is a novel chimeric monoclonal antibody (mAb) that targets a unique epitope on the CD20 antigen (**Figure 1**). It is glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, thereby conferring greater antibody-dependent cellular cytotoxicity (ADCC).
- In *in vitro* studies, ublituximab demonstrated 100 times greater natural killer (NK)-cell-mediated ADCC than rituximab in patient-donor CLL cells[1].
- To date, over 2100 patients with various B-cell mediated diseases have been treated with ublituximab. Completed oncology studies have demonstrated robust activity, with excellent safety and tolerability.
- The ublituximab phase 2 RMS study showed >99% B-cell depletion by week 4 and benefits on MRI and clinical parameters[2]

Figure 1. CD20 Antigen Binding Epitope of Ublituximab



[3]*Adapted from Klein et al, 2013*

STUDY DESIGN

Study Objectives

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

Study Endpoints

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

STUDY DESIGN

- ULTIMATE I (NCT03277261) & ULTIMATE II (NCT03277248) are two, identical phase 3, randomized, multi-center, double-blinded, double dummy, active controlled trials, evaluating a **one-hour** 450mg infusion of ublituximab vs teriflunomide in RMS (**Figure 2**).

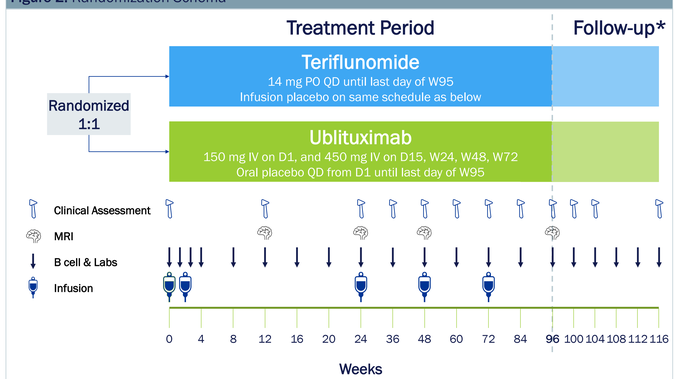
Key Inclusion Criteria

- Patients aged 18–55 years (inclusive) at screening
- Diagnosis of MS per 2010 Revised McDonald criteria
- Relapsing MS: relapsing-remitting course, or secondary progressive course with disease activity
- EDSS score of 0–5.5 (inclusive)
- Documentation of ≥1 relapse within 1 year prior to screening or ≥2 relapses within 2 years prior to screening or a positive Gd+ MRI scan during the year prior to randomization
- Neurologically stable within 1 month prior to randomization

Key Exclusion Criteria

- Primary progressive MS or SPMS without disease activity
- Previous Anti-CD20 or other B cell directed treatment
- Disease duration >10 years with an EDSS score of ≤2.0
- Active chronic disease of the immune system other than MS or immunodeficiency syndrome
- Neurological findings consistent or confirmed with progressive multifocal leukoencephalopathy

Figure 2. Randomization Schema



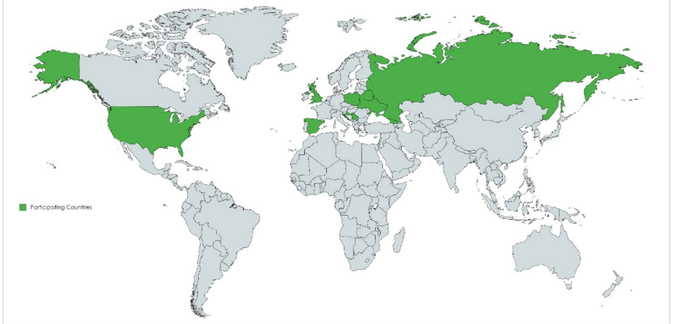
*After completing Week 96, patients entered into a 20-week safety follow-up and were eligible to enroll into an open-label extension study.

RESULTS

Study Enrollment

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

Figure 3. Participating 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**

Abbreviations: UK: United Kingdom; USA: United States of America.

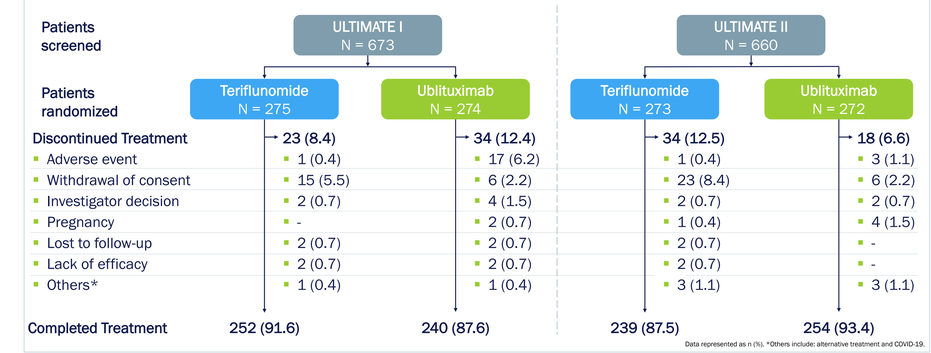
Abbreviations: ARR: annualized relapse rate; CDP: confirmed disability progression; CDI: confirmed disability improvement; Gd: gadolinium; NEDA: no evidence of disease activity.

References: 1. Le Garff-Tavernier M, et al. Leukemia 2011; 2. Fox E, et al. *Mult Scler J* 2020; 3. Klein C, et al. *Mabs* 2013.

RESULTS

Disposition

Figure 4. Disposition



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

Baseline Demographics & Disease Characteristics

- Baseline characteristics were well balanced between ULTIMATE I and ULTIMATE II studies, and between treatment arms (**Table 1**)

Table 1. Baseline demographics and disease characteristics

Characteristic *Mean ± standard deviation or n (%)*	ULTIMATE I N = 545		ULTIMATE II N = 544	
	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. *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.

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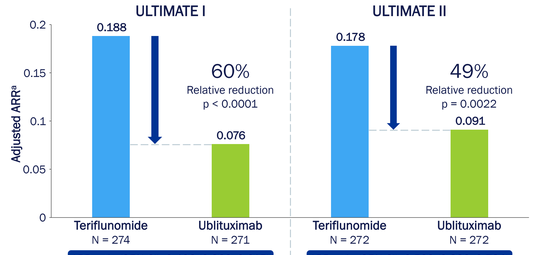
PRIMARY ENDPOINT: ANNUALIZED RELAPSE RATE

- Ublituximab significantly reduced protocol-defined ARR by 60% in ULTIMATE I and by 49% in ULTIMATE II, compared with teriflunomide (**Figure 5**)

Figure 5. Protocol-defined ARR by 96 weeks



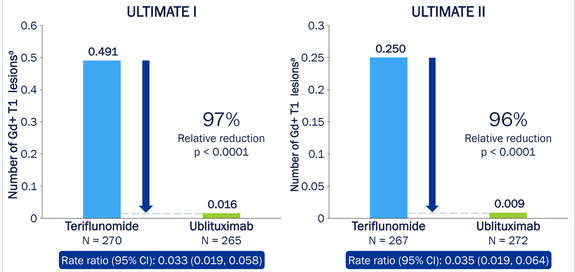
The modified Intention-to-Treat (mITT) population consists of all subjects in the ITT population who received at least one dose of study medication and had at least one baseline and post-baseline efficacy assessment. Based on negative binomial model (GEE) for the relapse count per subject with logarithmic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

BRAIN MRI

MRI: Gd+ T1 Lesions

- Compared with teriflunomide, ublituximab significantly reduced the mean number of T1 gadolinium-enhancing lesions (**Figure 6**) and the mean number of new or enlarging T2 hyperintense lesions (**Figure 7**) through the 96-week treatment period

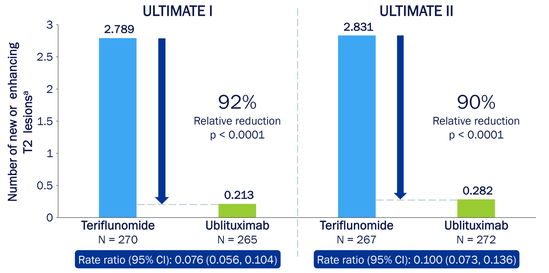
Figure 6. Total Number of Gd+ T1 Lesions by Independent Review



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: New or Enlarging T2 Lesions

Figure 7. Number of New or Enlarging T2 Lesions by Independent Review



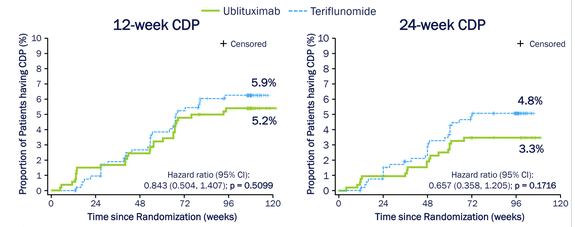
The modified Intention-to-Treat MRI (mITT-MRI) population consists of all subjects in the ITT population who received at least one dose of study medication, had at least one baseline and post-baseline efficacy assessment, and had at least one baseline and post-baseline MRI efficacy assessment. Based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

DISABILITY

Confirmed Disability Progression (CDP)

- In prespecified pooled analysis of ULTIMATE I and ULTIMATE II, 12-week CDP and 24-week CDP are shown in **Figure 8**

Figure 8. Confirmed Disability Progression (CDP) Pre-specified pooled analysis

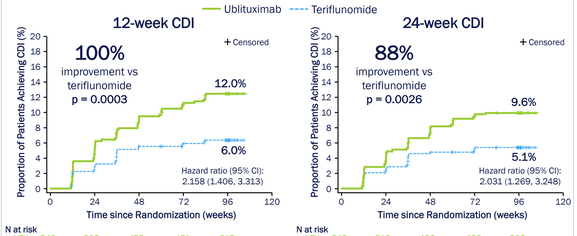


The modified Intention-to-Treat (mITT) population consists of all subjects in the ITT population who received at least one dose of study medication and had at least one baseline and post-baseline efficacy assessment. Hazard ratio is estimated using Cox regression model with treatment group as covariate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

Confirmed Disability Improvement (CDI)

- In prespecified pooled tertiary analysis of ULTIMATE I and ULTIMATE II, compared with teriflunomide, ublituximab improved 12-week CDI by 100% (p=0.0003) and 24-week CDI by 88% (p=0.0026; **Figure 9**)

Figure 9. Confirmed Disability Improvement (CDI) Pre-specified pooled tertiary analysis

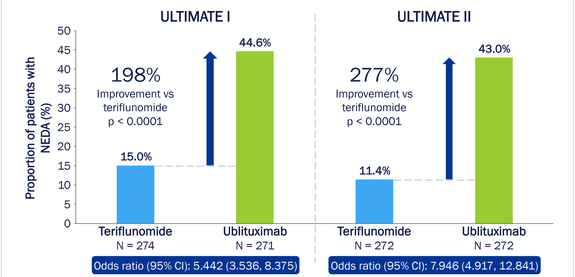


The modified Intention-to-Treat (mITT) population consists of all subjects in the ITT population who received at least one dose of study medication and had at least one baseline and post-baseline efficacy assessment. Hazard ratio is estimated using Cox regression model with treatment group as covariate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

NO EVIDENCE OF DISEASE ACTIVITY

- Ublituximab increased the proportion of patients that achieved NEDA vs teriflunomide in ULTIMATE I and ULTIMATE II by 198% and 277%, respectively, through Week 96 (p<0.0001 for both; **Figure 10**)

Figure 10. No Evidence of Disease Activity (NEDA) from Week 24 – Week 96



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, Gad enhancing).

SAFETY

Most Common Adverse Events (AEs)

- The proportion of patients reporting AEs was 88.7% for teriflunomide and 88.6% for ublituximab groups across ULTIMATE I and ULTIMATE II studies (**Table 2**)
- The most commonly reported AEs were infusion-related reactions (IRRs) and headache in the ublituximab group, and headache and nasopharyngitis in the teriflunomide group
- 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)

Table 2. AEs over the 96-week treatment period

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

- Serious AEs were reported in 6.2% of teriflunomide-treated patients and 9.5% of ublituximab-treated patients across ULTIMATE I and ULTIMATE II (**Table 3**)

Table 3. SAEs over the 96-week treatment period

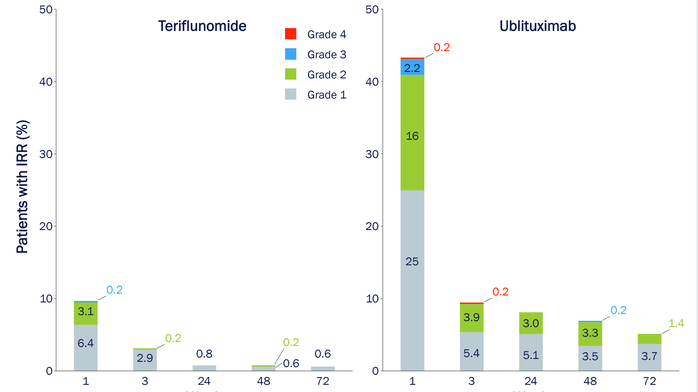
SAEs, n (%)	Teriflunomide N = 548	Ublituximab N = 545
Any serious AEs	34 (6.2)	52 (9.5)
Most common SAEs by SOC *≥1% in any treatment group*		
Infections and infestations	14 (2.6)	22 (4.0)
Nervous system disorders	7 (1.3)	5 (0.9)

SAE: serious adverse event; SOC: System Organ Class.

Infusion Related Reactions

- 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 (**Figure 11**)
- 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

Figure 11. IRRs by Infusion



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

CONCLUSIONS

- In the Phase III UTMATE I & II studies ublituximab, compared with teriflunomide, significantly reduced ARR and MRI parameters
- 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
- 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

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