B-Cell Depletion and Return in Participant Subgroups of the Phase 3 ULTIMATE I and II Studies of Ublituximab Versus Teriflunomide in Participants With Relapsing Multiple Sclerosis

Edward J. Fox, MD, PhD,[1] Lawrence Steinman, MD,[2] Hans-Peter Hartung, MD,[3-6] Enrique Alvarez, MD, PhD,[7] Peiqing Qian, MD,[8] Sibyl Wray, MD,[9] Derrick Robertson, MD,[10] DeRen Huang, MD, PhD,[11] Krzysztof Selmaj, MD, PhD,[12,13] Daniel Wynn, MD,[14] Jenna A. Bosco,[15] Lily Lee, PhD,[15] Bruce A. C. Cree, MD, PhD, MAS[16]

[1]Central Texas Neurology Consultants, Round Rock, TX, USA; [2]Stanford University, Stanford, CA, USA; [3]Heinrich Heine University Düsseldorf, Düsseldorf, Germany; [4]Brain and Mind Centre, University of Sydney, Sydney, Australia; [5]Department of Neurology, Medical University of Vienna, Vienna, Austria; [6]Department of Neurology, Palacký University Olomouc, Olomouc, Czech Republic; [7]University of Colorado, Aurora, CO, USA; [8]Swedish Medical Center, Seattle, WA, USA; [9]Hope Neurology, Knoxville, TN, USA; [10]University of South Florida, Tampa, FL, USA; [11]Columbus Neuroscience, Westerville, OH, USA; [12]Center of Neurology, Lodz, Poland; [13]Department of Neurology, University of Warmia and Mazury, Olsztyn, Poland; [14]Consultants in Neurology, Northbrook, IL, USA; [15]TG Therapeutics, New York, NY, USA; [16]UCSF Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA, USA

OBJECTIVE

- To evaluate B-cell depletion and return with ublituximab in participant subgroups in ULTIMATE I and II

KEY FINDINGS

- In the overall ublituximab-treated pooled population, participants had a 96.2% reduction from baseline in the mean number of CD19+ B cells starting at Week 1 Day 2, which remained consistent through Week 96
- Prior to the first open-label extension (OLE) infusion, mean B-cell numbers had increased to 23.8% of baseline
- The kinetics and extent of B-cell depletion were similar for all evaluated subgroups: age (<38 years versus ≥38 years), gender (female versus male), and body mass index (BMI) (<30 kg/m^2 versus ≥30 kg/m^2)
- Mean B-cell levels (cells/µL) at the first OLE visit (mean 50-55 weeks after last infusion) were slightly higher for the subgroups aged <38 years (63.5 versus 37.7 for ≥38 years) and males (57.3 versus 51.0 for females)
- B-cell return prior to 1 or more subsequent ublituximab infusions during treatment was associated with higher mean age, BMI, and B-cell count, and fewer gadolinium-enhancing (Gd+) T1 lesions at baseline
- Infusion-related reactions (IRRs) were more common in participants with residual B cells at Weeks 24, 48, and 72 than in participants with sustained B-cell depletion

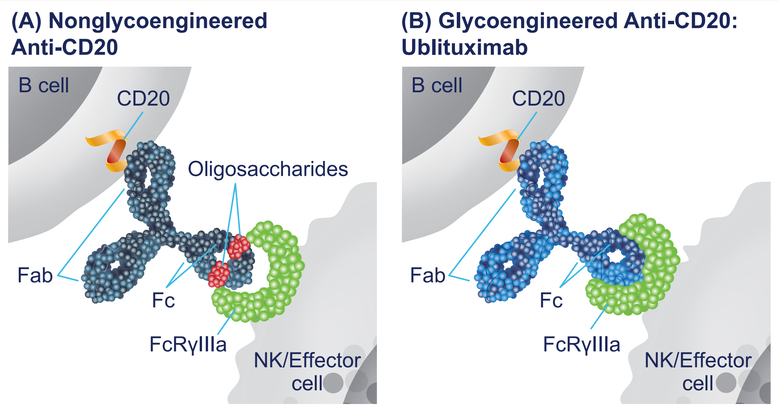
CONCLUSIONS

- In ULTIMATE I and II, peripheral B-cell numbers declined rapidly after the first ublituximab infusion and remained low during treatment, as expected with ublituximab's mechanism of action
- In pooled post hoc analyses, B-cell depletion with ublituximab was consistent across evaluated subgroups

BACKGROUND

- Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20 and is glycoengineered for enhanced antibody-dependent cellular cytotoxicity (ADCC) (**Figure 1**)[1,2]
- In vitro studies demonstrate that ublituximab has 25-30× higher ADCC relative to all other currently approved anti-CD20 therapies used in multiple sclerosis[3]
- Ublituximab is administered in lower doses and with shorter infusion times compared with other currently infused anti-CD20 therapies[4]
- ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) are identical, Phase 3, randomised, multicentre, double-blind, active-control studies evaluating the efficacy and safety of ublituximab versus teriflunomide in participants with relapsing multiple sclerosis (RMS)[5]
- ULTIMATE I and II met their primary endpoint, demonstrating a statistically significant reduction in annualised relapse rate for ublituximab compared with teriflunomide as well as significant improvements in the number of Gd+ T1 lesions and the number of new/enlarging T2 lesions[5]
- As B-cell return with anti-CD20 therapy can differ across patient types,[6-8] post hoc subgroup analyses were performed to evaluate B-cell depletion and return kinetics with ublituximab treatment in in ULTIMATE I and II

Figure 1. Ublituximab Is Glycoengineered to Enhance ADCC



(A) In nonglycoengineered anti-CD20 antibodies, the core fucose of Fc-linked oligosaccharides sterically blocks interaction with FcγRIIIa, reducing affinity.[9,10] **(B)** 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.[10-12]

ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer.

METHODS

- The Phase 3 ULTIMATE I and II studies enrolled a total of 1094 adults from 10 countries with a diagnosis of RMS (relapsing-remitting or secondary-progressive) with disease activity[5]
- Participants received ublituximab 450 mg administered by 1-hour intravenous infusion every 24 weeks (following Day 1 infusion of 150 mg and Day 15 infusion of 450 mg) or teriflunomide 14 mg oral once daily for 96 weeks[5]
- Pooled post hoc analyses evaluated the kinetics of B-cell depletion and return in ublituximab-treated subgroups: age (<38 years versus ≥38 years), gender (females versus males), and BMI (<30 kg/m^2 versus ≥30 kg/m^2)
- B-cell return, defined as ≥10 cells/µL, was also evaluated at each time point

RESULTS

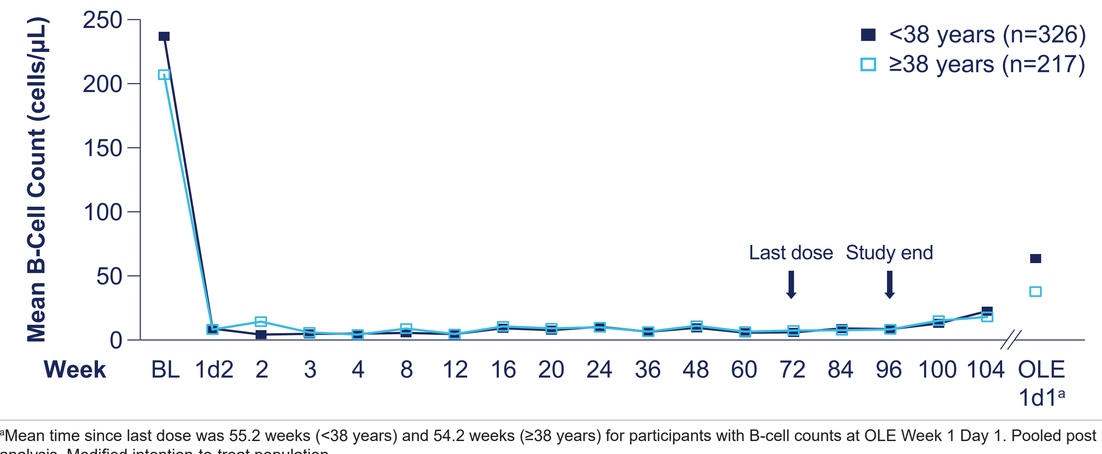
B-Cell Depletion and Return: Pooled ULTIMATE I and II Studies

- In the overall ublituximab-treated ULTIMATE I and II population, participants had a notable decrease from baseline in the mean number of CD19+ B cells (-216.4 cells/µL [96.2% reduction]) starting at Week 1 Day 2, which remained consistent through Week 96 (-219.6 cells/µL [97.6% reduction])[13]
- Prior to the first OLE infusion, an average of 55 weeks after the last infusion, mean B-cell numbers had increased to 23.8% of baseline[13]

B-Cell Depletion and Return: Pooled Post Hoc Subgroup Analyses

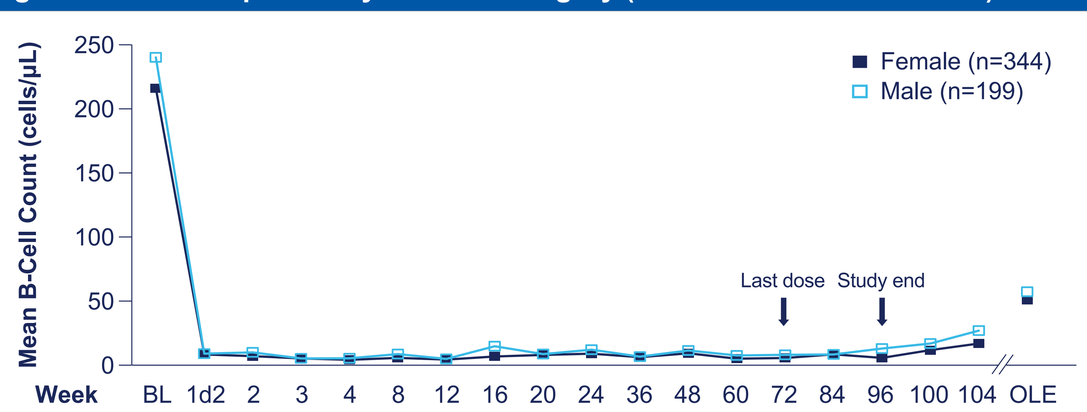
- The kinetics and extent of CD19+ B-cell depletion from baseline starting at Week 1 Day 2 were similar across and within pooled ULTIMATE I and II age, gender, and BMI subgroups
- Mean CD19+ B-cell decrease stayed consisted through Week 96 for all subgroups
- For study participants <38 and ≥38 years of age, the decrease in mean number of B cells from baseline starting at Week 1 Day 2 was 96.2% (-228.1 cells/µL) and 95.9% (-198.7 cells/µL), respectively (**Figure 2**)
- In females and males, the decrease in mean number of B cells from baseline starting at Week 1 Day 2 was 96.2% (-207.9 cells/µL) and 96.2% (-231.0 cells/µL), respectively (**Figure 3**)
- Mean B-cell levels (cells/µL) at the first OLE visit (mean 50-55 weeks after last infusion) were slightly higher for the subgroups aged <38 years (63.5 versus 37.7 for ≥38 years) and males (57.3 versus 51.0 for females)

Figure 2. B-Cell Depletion by Age Category (Mean CD19+ B-Cell Count)



[a]Mean time since last dose was 55.2 weeks (<38 years) and 54.2 weeks (≥38 years) for participants with B-cell counts at OLE Week 1 Day 1. Pooled post hoc analysis. Modified intention-to-treat population.
1d1, Week 1 Day 1; 1d2, Week 1 Day 2; BL, baseline; OLE, open-label extension.

Figure 3. B-Cell Depletion by Gender Category (Mean CD19+ B-Cell Count)



[a]Mean time since last dose was 55.3 weeks (female) and 54.0 weeks (male) for participants with B-cell counts at OLE Week 1 Day 1. Pooled post hoc analysis. Modified intention-to-treat population.
1d1, Week 1 Day 1; 1d2, Week 1 Day 2; BL, baseline; OLE, open-label extension.

- The decrease in mean number of B cells from baseline starting at Week 1 Day 2 in participants with BMI <30 kg/m^2 and ≥30 kg/m^2 was 96.3% (-213.5 cells/µL) and 95.2% (-230.3 cells/µL), respectively (data not shown)
  - The number of participants with BMI ≥30 kg/m^2 was small (n=61), limiting comparisons for the BMI subgroup
- Baseline characteristics for participants with or without B-cell return prior to 1 or more subsequent ublituximab infusions during treatment are shown in **Table 1**. B-cell return was associated with higher mean age, BMI, and B-cell count, and fewer Gd+ T1 lesions at baseline

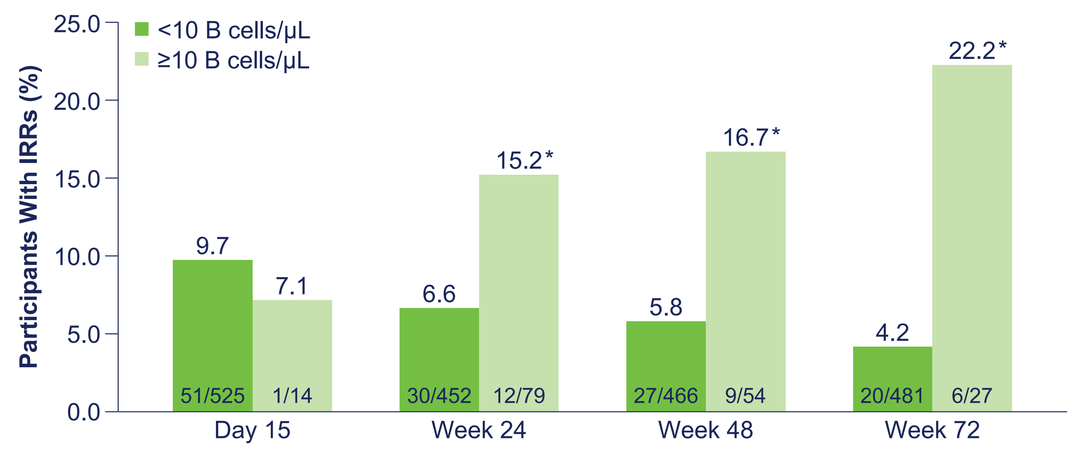
Table 1. Baseline Characteristics for Participants With or Without B-Cell Return[a] Prior to Subsequent Ublituximab Infusions

Characteristic *Mean ± standard deviation or %*	B-Cell Return[a] (n=107)	No B-Cell Return (n=433)	*P* Value
Age, years	36.9±8.91	34.9±8.54	0.0341
Gender, %			
Female	55.1	65.1	0.0580
Male	44.9	34.9	
BMI, kg/m^2	26.3±6.50	23.9±4.67	<0.0001
Race, %			
White	95.3	98.8	0.0522
Black or African American[b]	3.7	0.9	
Other	0.9	0.2	
Gd+ T1 lesions, number	1.4±2.91	2.7±6.10	0.0348
CD19+ B cells, cells/µL	249.7±135.20	219.3±114.15	0.0180

[a]Participants with B-cell return were those with a nadir (predose) CD19+ B-cell count of ≥10 cells/µL at any infusion at Weeks 3, 24, 48, or 72. Pooled post hoc analysis. [b]n=4 participants in each group. Safety population (participants in the ublituximab arm with postbaseline, predose CD19+ B-cell counts).
BMI, body mass index; Gd+, gadolinium-enhancing.

- IRRs occurred more frequently in ublituximab-treated participants with B-cell return at Weeks 24, 48, and 72 versus participants with sustained B-cell depletion (**Figure 4**). Increased IRRs in participants with B-cell return were not observed at Day 15, 2 weeks after the first ublituximab loading dose of 150 mg
- No difference in relapse rates were observed for ublituximab-treated participants with B-cell return versus those with sustained B-cell depletion (data not shown)

Figure 4. IRRs in Ublituximab-Treated Participants by B-Cell Level (Nadir)



*P<0.05. Pooled post hoc analysis. Safety population.
IRRs, infusion-related reactions.

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