Pharmacodynamics of B-Cell Depletion and Pharmacokinetics of the Novel Anti-CD20 Monoclonal Antibody Ublituximab in Patients With Relapsing Multiple Sclerosis

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OBJECTIVES

- To evaluate the pharmacodynamics (PD) of B-cell depletion with ublituximab in the Phase 3 ULTIMATE I and II studies and the pharmacokinetics (PK) of ublituximab treatment

KEY FINDINGS

- Starting at Week 1 Day 2, patients had a notable decrease from baseline in the mean number of CD19+ B cells (96.2% reduction), which remained consistent through Week 96 (97.6% reduction)
- Prior to the first open-label extension (OLE) infusion, an average of 55 weeks after the last infusion, mean B-cell numbers had increased to 23.8% of baseline

CONCLUSION

- In ULTIMATE I and II, peripheral B-cell numbers declined rapidly after the first ublituximab infusion and remained low during treatment, which is consistent with ublituximab's mechanism of action

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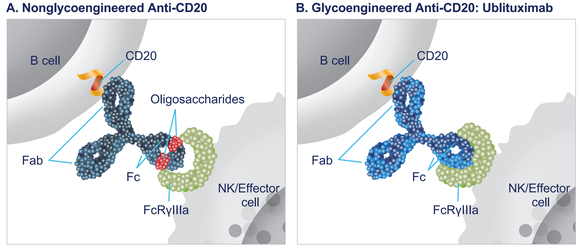
BACKGROUND

- Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20[1]
- Ublituximab is glycoengineered to exclude certain sugar molecules normally expressed on the antibody. Removal of these sugar molecules enhances affinity for all variants of FcγRIIIa receptors, which confers greater antibody-dependent cellular cytotoxicity (ADCC) and enhances the potency of ublituximab **(Figure 1)**[1,2]

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.[3,4] **(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.[4-6]

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

- Ublituximab demonstrated 100 times greater natural killer cell–mediated ADCC in vitro than rituximab[1]
- Ublituximab is administered in lower doses and with shorter infusion times compared with other currently infused anti-CD20 therapies[7]
- ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) were identical, Phase 3, randomized, multicenter, double-blind, active-control studies that evaluated the efficacy and safety of ublituximab vs teriflunomide in patients with relapsing multiple sclerosis (RMS)[7]
- ULTIMATE I and II met their primary endpoint, demonstrating a statistically significant reduction in annualized relapse rate for ublituximab compared with teriflunomide[7]
- Ublituximab also provided significant improvements in the number of gadolinium-enhancing T1 lesions and the number of new/enlarging T2 lesions, and improvements in the proportion of patients with no evidence of disease activity vs teriflunomide at 96 weeks[7]

METHODS

- ULTIMATE I and II enrolled a total of 1094 adult patients from 10 countries with a diagnosis of RMS (relapsing-remitting or secondary-progressive) with disease activity[7]
- Patients received ublituximab 450 mg administered by 1-hour intravenous (IV) 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[7]
- The last dose of ublituximab was given at Week 72, with retreatment starting on average (mean) 54-55 weeks later for patients enrolling in the OLE
- PD analyses were performed in the modified intention-to-treat population at prespecified intervals
- PK data were evaluated in patients enrolled in the Phase 2 and Phase 3 studies who received ≥1 ublituximab dose
- Ublituximab data were combined with a previous analysis set including two Phase 1 studies and one Phase 3 study in patients with hematologic malignancies, primarily chronic lymphocytic leukemia, for the population PK (PopPK) analysis of ublituximab
  - The PopPK dataset included 5624 quantifiable ublituximab serum concentrations from 591 patients with RMS. The combined dataset included a total of 7485 quantifiable ublituximab serum concentrations from 895 patients
- The individual post hoc estimates from the final PopPK model were used to compute steady-state exposure metrics (maximum serum ublituximab concentration [C_{max}]) over a 24-week interval. Steady state was assumed to be achieved following the Week 48 dose. C_{max} for Day 1 was also derived. The individual terminal half-life of ublituximab was calculated and summarized using descriptive statistics

RESULTS

B-Cell Depletion by Study

- Mean B-cell levels for the individual ULTIMATE I and ULTIMATE II studies are shown in **Figure 2**
- Both studies showed a consistent reduction in B cells starting at Day 2 that was maintained throughout the studies

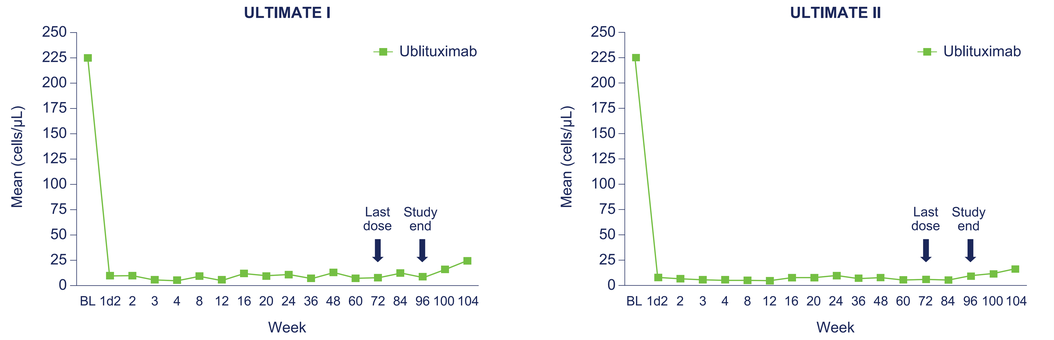
B-Cell Depletion: Pooled Analysis

- In a pooled post hoc analysis of ULTIMATE I and II (N=543), the mean number of CD19+ B cells at baseline in patients receiving ublituximab was 225.0 cells/μL
- Starting at Week 1 Day 2, ublituximab patients had a notable decrease from baseline in the mean number of CD19+ B cells (-216.4 cells/μL [96.2% reduction]), which remained consistent through Week 96 (-219.6 cells/μL [97.6% reduction]), 24 weeks after the last infusion **(Figure 3, Table 1)**
- 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
- The proportion of ublituximab-treated patients with B-cell counts remaining suppressed to ≥95% of baseline levels by Week 55 (entry into OLE) was 34.5%

Pharmacokinetics

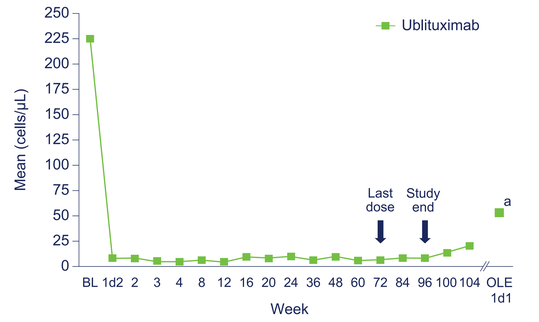
- The PK of ublituximab following repeated IV infusions was adequately described by a 2-compartment model with first-order elimination. Ublituximab exposures increased in a dose-proportional manner (ie, linear PK) over the dose range of 150-600 mg in patients with RMS
- Clearance (interindividual variability) was 11.3 mL/h (38.1%)
- Half-life (90% confidence interval) was 21.8 (21.4-22.1) days
- Median time to reach steady state was 15.5 weeks
- Median C_{max} ratio of Week 24 to Day 1 was 3.04 (range, 3.00-3.42), consistent with the 3-fold increase in the amount of the dose and indicative of no accumulation. Similarly, the C_{max} ratio of Week 48 to Week 24 was 1, indicative of no accumulation

Figure 2. Mean CD19+ B-Cell Levels



Absolute B-lymphocyte (B-cell) count of CD19+ B cells. Data cutoff November 23, 2020. Modified intention-to-treat population. Data presented as mean B-cell count among patients evaluable at each timepoint.
1d2, Week 1 Day 2; BL, baseline.

Figure 3. Mean CD19+ B-Cell Levels: Pooled Analysis



[a]Mean time since last dose was 54.8 weeks for patients with B-cell counts at OLE Week 1 Day 1. Pooled post hoc analysis. Data cutoff May 1, 2021. Modified intention-to-treat population. Data presented as the mean B-cell count among patients evaluable at each timepoint.
1d1, Week 1 Day 1; 1d2, Week 1 Day 2; BL, baseline; OLE, open-label extension.

Table 1. B-Cell Levels Over Time

CD19+ B Cells (cells/μL)	Mean	Min/Max
Baseline	225.0	16/882
Week 1 Day 2	8.6	1/183
Week 2	8.2	1/553
Week 12	4.6	0/68
Week 24	10.1	1/159
Week 48	10.2	1/269
Week 72	6.5	1/199
Week 96	8.4	1/571
OLE Week 1 Day 1[a]	53.5	0/552

[a]Mean time since last dose was 54.8 weeks for patients with B-cell counts at Week 1 Day 1 of the OLE. Pooled post hoc analysis. Data cutoff May 1, 2021. Modified intention-to-treat population. Data presented as the absolute B-cell count among patients evaluable at each timepoint.
Max, maximum; Min, minimum; OLE, open-label extension.