*Original Research Paper*

# A phase 2 multicenter study of ublituximab, a novel glycoengineered anti-CD20 monoclonal antibody, in patients with relapsing forms of multiple sclerosis

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## Abstract

**Background:** Ublituximab, a novel monoclonal antibody (mAb) targeting a unique epitope on the CD20 antigen, is glycoengineered for enhanced B-cell targeting through antibody-dependent cellular cytotoxicity (ADCC). Greater ADCC may allow lower doses and shorter infusion times versus other anti-CD20 mAbs.

**Objective:** The objective was to determine optimal dose, infusion time, and activity of ublituximab in relapsing multiple sclerosis.

**Methods:** This is a phase 2, placebo-controlled study. Patients received three ublituximab infusions (150 mg over 1–4 hours on day 1 and 450–600 mg over 1–3 hours on day 15 and week 24) in six dosing cohorts. The primary endpoint was B-cell depletion.

**Results:** In all cohorts ($N=48$), median B-cell depletion was >99% by week 4, maintained at weeks 24 and 48. Most common adverse events (AEs) were infusion-related reactions (all grade 1–2), with no apparent increased incidence at shorter infusion times. There were no AE-related discontinuations. At weeks 24 and 48, no T1 gadolinium-enhancing lesions ($p=0.003$) and a 10.6% decrease in T2 lesion volume ($p=0.002$) were detected. The annualized relapse rate was 0.07; 93% remained relapse free on study. Overall, 74% of patients had no evidence of disease activity (NEDA).

**Conclusion:** Ublituximab was safely infused as rapid as 1 hour, producing robust B-cell depletion and profound reductions in magnetic resonance imaging (MRI) activity and relapses.

*Keywords:* Ublituximab, TG-1101, multiple sclerosis, relapse, magnetic resonance imaging, gadolinium-enhancing lesions

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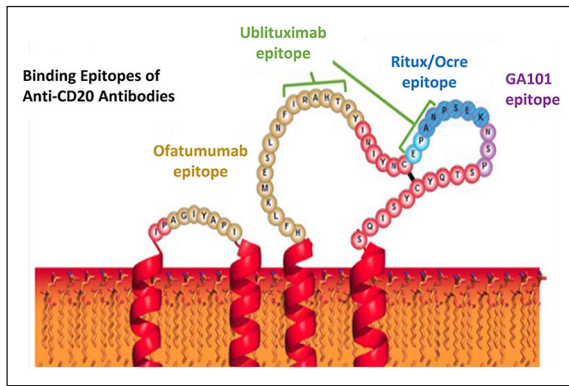
## Introduction

While long recognized as primarily a T-cell-mediated disease, recent research suggests B-cells play an active role in the pathogenesis of multiple sclerosis (MS) via a variety of mechanisms. These include antigen presentation and activation of proinflammatory T-cells, inflammatory cytokine release, production of auto-reactive antibodies that can travel across the blood-brain barrier into the central nervous system (CNS) to cause complement-mediated attack on the myelin sheath, and, in later stages, formation of lymphoid aggregates resembling germinal centers in the meninges that may lead to demyelination and neurodegeneration.[1,2]

The role of B-cells in MS pathogenesis is strongly supported by results of trials of B-cell-depleting monoclonal antibodies (mAbs).[3–5] These mAbs target the CD20 trans-membrane antigen expressed on pre-B-cells and throughout the lifecycle of both naïve and memory B-cells. Anti-CD20 mAbs are capable of eliciting direct cell death, complement activation, and Fc-gamma receptor (FcγR)–mediated phagocytosis through immune effectors such as natural killer

**Figure 1.** Ublituximab binds to a unique epitope on the CD20 molecule.

(NK) cells and macrophages.[6] Because CD20 is not expressed on hematopoietic stem cells or plasma cells, treatment with anti-CD20 mAbs retains immunoglobulin G (IgG) levels, sustains existing humoral protection, and allows repopulation of the B-cell compartment after treatment cessation.[1,2] Early clinical testing with the anti-CD20 mAb, rituximab (Rituxan®), showed promising activity in patients with relapsing multiple sclerosis (RMS).[7–9] And recently, the anti-CD20 mAb ocrelizumab (Ocrevus®) was approved for treatment of RMS after demonstrating superiority over subcutaneous interferon beta (IFNβ)-1a in phase 3 clinical trials.[3]

Ublituximab (TG-1101; TG Therapeutics, New York, NY) is a novel, type I chimeric, immunoglobulin G1 (IgG1) anti-CD20 mAb glycoengineered with a low fucose content in its fragment crystallizable (Fc) region to enhance affinity for all variants of FcγRIIIa receptors, thereby producing potent antibody-dependent cellular cytotoxicity (ADCC).[10,11] Ublituximab demonstrated 100 times greater NK cell–mediated ADCC in vitro than rituximab in cells from patient donors with chronic lymphocytic leukemia (CLL).[10] The difference between rituximab and ublituximab was more pronounced when target cells expressed lower levels of CD20 molecules.[10,12] Ublituximab targets a unique epitope on CD20 not targeted by other anti-CD20 mAbs (Figure 1).[11]

More than 1500 patients with B-cell malignancies have been treated with ublituximab in completed or ongoing clinical trials.[11] Oncology studies of ublituximab have demonstrated robust clinical activity at the phase 2/3 dose of 900 mg, with acceptable safety and tolerability.[11] This study was conducted to determine whether the enhanced ADCC potency of ublituximab can benefit patients with RMS at lower doses than those used in oncology and whether it can be tolerably administered in more rapid infusion times than those of other anti-CD20 infused mAb therapies.

## Methods

This phase 2, 48-week, placebo-controlled, multicenter trial evaluated the safety and efficacy of ublituximab in patients with RMS (ClinicalTrials.gov NCT02738775) and was designed to determine the optimal ublituximab dose and infusion time in this patient population. The trial was conducted at eight sites throughout the United States. The study protocol was approved by all participating institutional review boards or independent ethics committees, and all patients provided written informed consent before study participation.

### Patients

Eligible patients were aged 18–55 years with a confirmed diagnosis of RMS per 2010 McDonald Criteria[13] and had an Expanded Disability Status Scale (EDSS) score of 0–5.5 at screening. Patients must have been neurologically stable for at least 30 days before screening but had to have experienced ≥2 relapses in the previous 2 years or 1 relapse within 1 year before screening, and/or had ≥1 gadolinium-enhancing lesion on brain magnetic resonance imaging (MRI).

Key exclusion criteria included prior treatment with an anti-CD20 or other B-cell-directed therapy, or with alemtuzumab, within 1 year before screening; use of fingolimod or natalizumab within 90 days; use of glatiramer acetate, IFNβ, dimethyl fumarate, or glucocorticoids within 30 days; disease duration of more than 10 years with an EDSS score ≤2; and absolute lymphocyte counts <1000/μL.

### Study procedures

Patients were enrolled sequentially into six consecutive treatment cohorts and randomized to receive ublituximab or placebo in a 3:1 ratio. Study drug was administered via intravenous (IV) infusion at the doses and infusion times shown in Table 1. Each cohort received infusions at a higher dose and/or at a faster rate than the preceding cohort. An independent Data Safety Monitoring Board (DSMB) reviewed laboratory and clinical safety data from the first two patients in each cohort (one patient each in the ublituximab and placebo arms) before the subsequent cohort could enroll. Placebo administration was designed to assess the safety and tolerability of the excipients in the drug product. At study day 28, the identity of patients randomized to placebo was

**Table 1.** Randomization to cohorts with varying doses and infusion times.

| Cohort | Treatments | Day 1/infusion time | Day 15/infusion time | Week 24/infusion time |
|---|---|---|---|---|
| 1 | Placebo (*n*=2) | Placebo/4 h | Placebo/3 h | – |
|   | Ublituximab (*n*=6) | 150 mg/4 h | 450 mg/3 h | 450 mg/1.5 h |
| 2 | Placebo (*n*=2) | Placebo/4 h | Placebo/1.5 h | – |
|   | Ublituximab (*n*=6) | 150 mg/4 h | 450 mg/1.5 h | 450 mg/1 h |
| 3 | Placebo (*n*=2) | Placebo/4 h | Placebo/1 h | – |
|   | Ublituximab (*n*=6) | 150 mg/4 h | 450 mg/1 h | 600 mg/1 h |
| 4 | Placebo (*n*=2) | Placebo/3 h | Placebo/1 h | – |
|   | Ublituximab (*n*=6) | 150 mg/3 h | 600 mg/1 h | 600 mg/1 h |
| 5 | Placebo (*n*=2) | Placebo/2 h | Placebo/1 h | – |
|   | Ublituximab (*n*=6) | 150 mg/2 h | 600 mg/1 h | 600 mg/1 h |
| 6 | Placebo (*n*=2) | Placebo/1 h | Placebo/1 h | – |
|   | Ublituximab (*n*=6) | 150 mg/1 h | 600 mg/1 h | 600 mg/1 h |

h: hour.
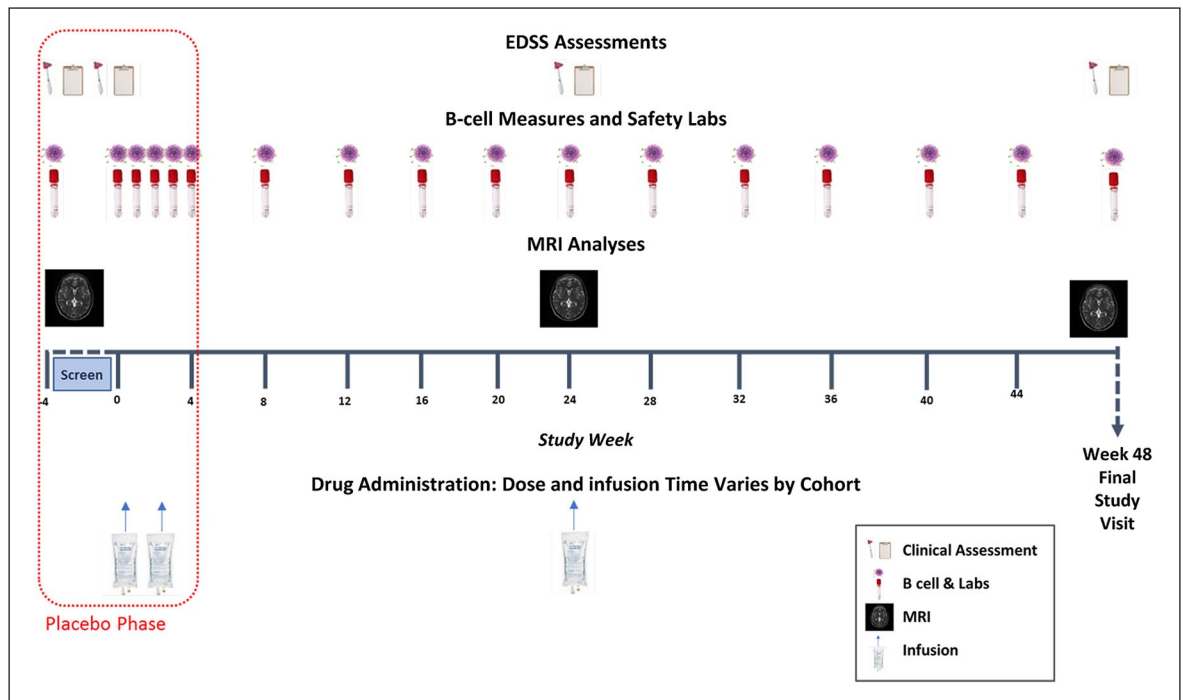


**Figure 2.** Timeline of study assessments and procedures.

unblinded, they were rescreened, and then they crossed-over to receive ublituximab at the dose and schedule of their respective cohort.

All patients were to receive three IV ublituximab infusions, administered on days 1 and 15, and at week 24, and were followed for a total of 48 weeks (Figure 2). Patients received an initial dose of ublituximab 150 mg on day 1 at infusion times ranging from 1 to 4 hours and then 450 or 600 mg on day 15 and week 24 at infusion times ranging from 1 to 3 hours. Patients received premedication with an oral antihistamine and an oral corticosteroid ~30 minutes before ublituximab dosing.

B-lymphocytes were measured from peripheral blood samples taken at intervals shown in Figure 2. Samples were collected pre-dose on day 15 and at week 24. Flow cytometric analysis was utilized to identify the
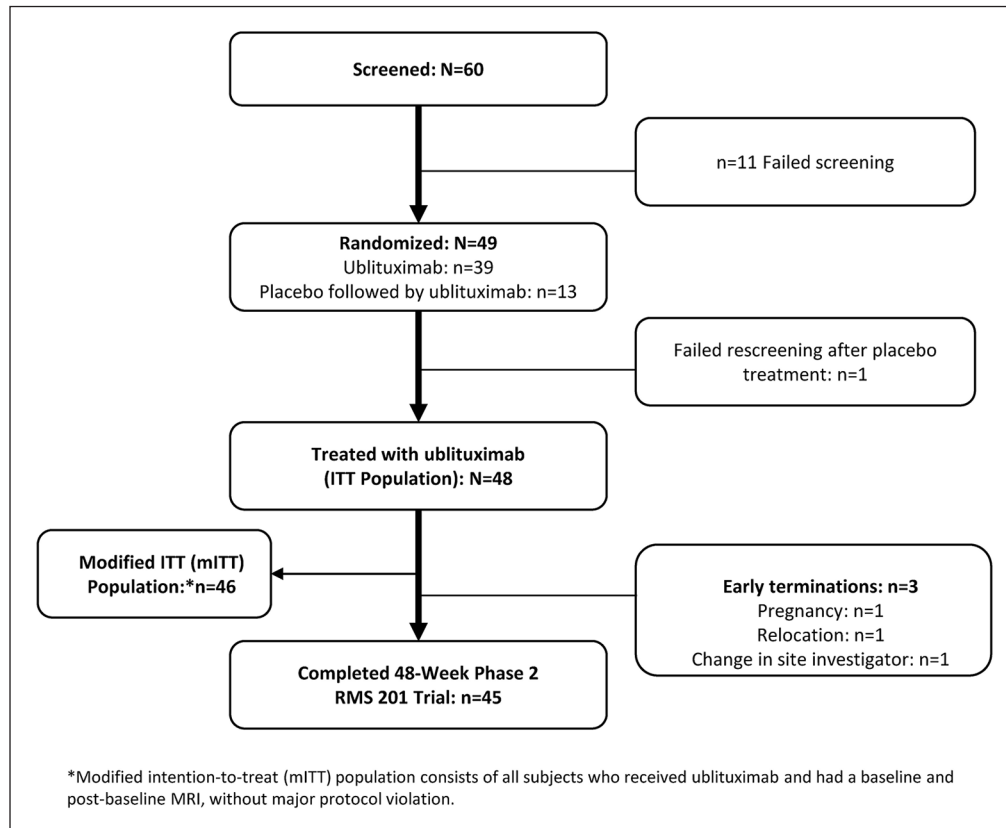
**Figure 3.** Patient disposition.

B-cell (CD3-CD19+) population within the peripheral blood mononuclear cells over time.

MRI acquisition was performed at individual sites at baseline, week 24, and week 48 using existing MRI equipment operating at field strengths of 1.5 and 3.0 Tesla, with commercially available (multi-channel) head coils. The following sequences were obtained using 3-mm slices (no gap) and whole brain coverage: T2-weighted two-dimensional (2D) multi-slide turbo spin echo (TSE), T2-weighed 2D fluid-attenuated inversion recovery (FLAIR), and pre- and post-gadolinium injection (typically 0.1 mmol/kg) T1-weighted images.

All MRI data were transferred to the Ichan School of Medicine at Mt Sinai, New York, NY and analyzed by two experienced operators blinded to subjects' identity. T1 gadolinium-enhancing and T2-hyperintense lesion count and volume were measured on the post-gadolinium T1-weighted images and T2-weighted images, respectively. To be counted, lesions had to be at least three voxels in maximum size. Lesion volumes were computed using a semi-automated segmentation technique based on user-supervised local thresholding (Xinapse Systems, Northants, England).

*Study endpoints*

The primary endpoint was the responder rate, defined as the proportion of ublituximab-treated patients with ≥95% peripheral CD19+ B-cell depletion from baseline within 2 weeks after the second ublituximab infusion (i.e. at week 4).

Secondary endpoints included the effects of ublituximab on gadolinium-enhancing T1-weighted lesions, T2-weighted lesion volume and number of new or enlarging T2 lesions on brain MRI, annualized relapse rate (ARR), and proportion of relapse-free patients. MS relapse was defined as the occurrence of new or worsening neurological symptoms immediately preceded by a stable or improving neurological state of ≥30 days, with symptoms that persisted for >24 hours in the absence of fever, accompanied by objective neurological worsening consistent with an EDSS score increase of ≥0.5 point for patients with a baseline EDSS score of >1.0, or of ≥1.0 point for patients with a baseline EDSS score of 0. Patients experiencing a relapse on study could receive rescue therapy with IV methylprednisolone 1 g/day for up to 5 consecutive days.

Also assessed as an exploratory endpoint was the proportion of patients with confirmed disability progression at week 48. Confirmed disability progression was defined as an initial increase of ≥1.0 point from the baseline EDSS score (not attributable to another etiology, concurrent illness, or concomitant medication) when the baseline score was ≤5.5, and of ≥0.5 point when the baseline score was >5.5, confirmed in a subsequent EDSS assessment 24 weeks later. Confirmed disability improvement followed the same criteria, but with a sustained *decrease* of ≥1.0 EDSS point from baseline. No evidence of disease activity (NEDA) was defined as no evidence of clinical (relapse, confirmed disability progression) or MRI (T1-weighted gadolinium-enhancing or new/enlarging T2 lesions) disease activity.

The safety and tolerability of ublituximab was determined by investigator-reported adverse events (AEs), including the number and severity of infusion-related reactions (IRRs) that occurred during or within 24 hours of an infusion. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

The optimal ublituximab dose and infusion time was determined by comparing the efficacy of B-cell depletion and safety and tolerability among the six dosing cohorts.

### Statistical analyses

Patient characteristics at baseline and study endpoints are reported descriptively. A modified intention-to-treat (mITT) population comprised all patients who received ublituximab and had at least one baseline and one post-baseline MRI, without a major protocol deviation.

For the primary endpoint, the percentage of B-cells at week 4 was compared to the screening/baseline percentages for each patient. The mean and median B-cell percentages for the study population were compared using a Mixed Model for Repeated Measures (IBM SPSS v.25). ARR was calculated as the number of relapses per patient year during the 48-week active treatment period, annualized to 1 year.

Hypothesis testing was conducted at a two-sided significance level of 0.05, with p values generated using a two-tailed t test.

### Results

#### Patient disposition

Of 60 patients screened, 49 patients were randomized to treatment (36 ublituximab, 13 placebo)

**Table 2.** Patient demographic and disease characteristics at baseline.

| | All patients (*N*=48) |
|---|---|
| Age (years), mean (SD) | 40 (10) |
| Female sex, *n* (%) | 31 (65) |
| Disease duration (years), mean (SD) | 7.7 (8.1) |
| Prior disease-modifying therapy, *n* (%) | 32 (67) |
| Interferon beta | 23 (48) |
| Glatiramer acetate | 19 (40) |
| Natalizumab | 12 (25) |
| Fingolimod | 12 (25) |
| Dimethyl fumarate | 17 (35) |
| Teriflunomide | 2 (4) |
| Other | 8 (17) |
| EDSS score, mean (SD) | 2.44 (1.36) |
| Number of gadolinium-enhancing lesions, mean (SD) | 3.63 (7.80) |
| T2-weighted lesion volume (cm$^3$), mean (SD) | 14.87 (20.45) |
| Number of relapses in the previous 12 months, mean (SD) | 1.45 (1.05) |

EDSS: Expanded Disability Status Scale; SD: standard deviation.

across the six treatment cohorts (Figure 3). One patient in cohort 4 initially randomized to placebo failed the day 28 rescreening and was discontinued before receiving ublituximab; all other patients initially randomized to placebo received ublituximab upon completion of the placebo phase. Thus, 48 patients received ublituximab on-study (ITT population). Mean ublituximab treatment duration was 47 weeks.

In all, 46 of the 48 patients (96%) had a baseline and at least one post-baseline MRI assessment and comprise the mITT population. Forty-five patients (94%) received all doses of ublituximab and completed the 48-week study assessment; of the three ublituximab-treated patients who discontinued early, one patient stopped due to pregnancy but continued to be monitored for safety (the patient later gave birth to a healthy infant), one patient relocated during the study, and one patient discontinued when the treating investigator left the study site. All 45 patients who completed the 48-week study entered the long-term extension phase of the trial.

At study entry, mean (±standard deviation (SD)) age was 40 (±10) years and the majority of patients were female (65%; Table 2). Mean disease duration was 7.7 (±8.1) years; disease duration was <5 years for 22
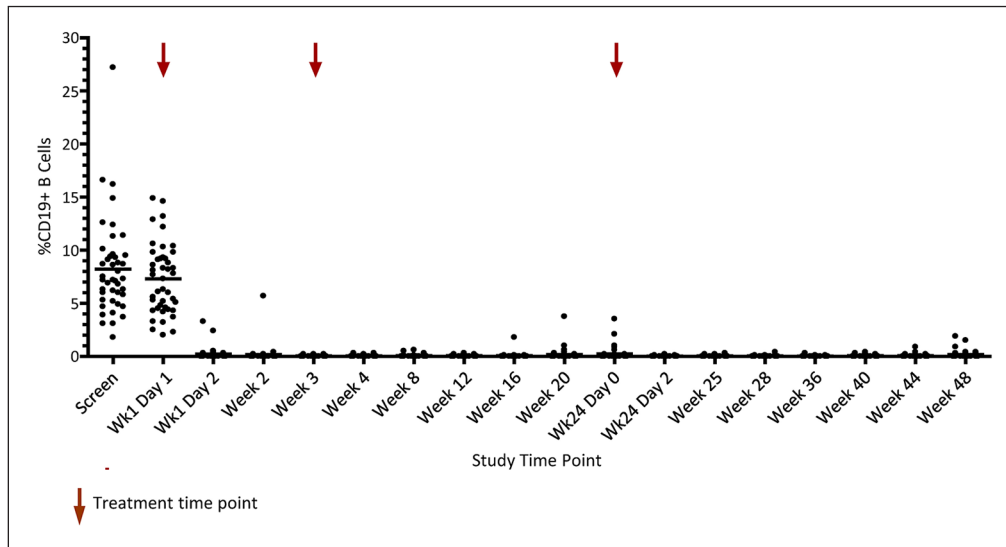
**Figure 4.** B-cell depletion with ublituximab.
All ublituximab-treated patients showed >95% B-cell depletion by week 4 (>99% median reduction; *p* < 0.001). B-cells were analyzed prior to treatment. Reductions were maintained before dosing at week 24 and at week 48.

patients (46%) and >10 years for 16 patients (33%). Two thirds (67%) of all patients had received prior disease-modifying therapies for RMS.

*Efficacy*
*B-cell depletion.* The responder rate (proportion of patients with ≥95% peripheral CD19+ B-cell depletion from baseline within 2 weeks after the second ublituximab infusion) was 100%. CD19+ B-cells were efficiently depleted in most patients within 24 hours of receiving the initial 150 mg dose of ublituximab. B-cells were significantly reduced from a mean (±SD) of 7.3% (±3.3%) at screening/baseline to 0.2% (±0.6%; *p* < 0.001) at 24 hours after the first ublituximab dose. By week 4 of active treatment, all 48 patients who received ublituximab had a B-cell response (Figure 4), with median peripheral B-cell depletion of >99% from baseline. B-cell reductions were sustained pre-dose at week 24 and also at week 48.

*T1-weighted gadolinium-enhancing lesions.* The mean (±SD) number of T1-weighted gadolinium-enhancing lesions at baseline was 3.63 (±7.80). At entry, 39% of all patients had ≥1 T1 gadolinium-enhancing lesion, including 26% of patients with ≥4 gadolinium-enhancing lesions. At study weeks 24 and 48, no patient had a new or persisting gadolinium-enhancing lesion on any brain MRI scan (100% reduction from baseline; *p* = 0.003).

*T2-weighted lesions.* Mean T2-weighted MRI lesion volume at baseline in the mITT population was 15,410 mm³. By week 24, mean T2-weighted lesion volume was decreased by 7.3% from baseline (*p* = 0.006) and was further decreased by 3.6% between week 24 and week 48 (*p* = 0.019), for a total decrease from baseline of 10.6% (*p* = 0.002; Figure 5). Seven patients (15%) had a total of eight new or enlarging T2-weighted brain lesions between baseline and week 24, and a single patient developed two new/enlarging lesions between week 24 and week 48. Overall, the mean (±SD) number of new or enlarging T2 lesions from baseline to week 24 was 0.20 (±0.43) and from week 24 to week 48 was 0.04 (±0.29).

*ARR.* At baseline, 86% of patients had experienced one or more relapses in the previous year (mean 1.45 ± 1.05 relapses). The ARR at week 48 in the ITT population was 0.07, with a mean follow-up of approximately 47 weeks (Figure 6). Overall, 93% of patients remained relapse free on-study.

*Disability/EDSS.* At baseline, the mean (±SD) EDSS score in the ITT population was 2.44 (±1.36), and the median EDSS score was 2.5. The mean EDSS score in the ITT population (last observation carried forward) at week 24 was 2.19 (±1.32) and at week 48 was 2.49 (±1.43). At the 48-week study assessment, eight patients (17%) met criteria for 24-week confirmed disability improvement, 32 patients (67%) did not meet the criteria for confirmed disability improvement or
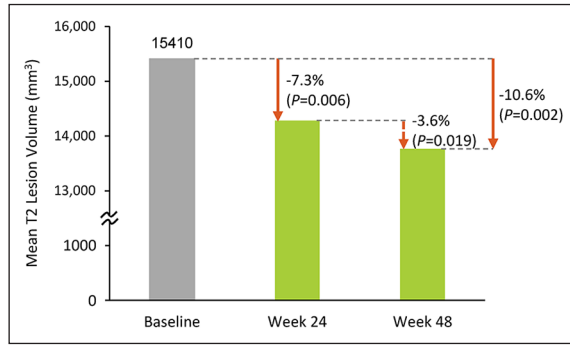
**Figure 5.** Ublituximab effects on T2-weighted lesion volume changes during the study.
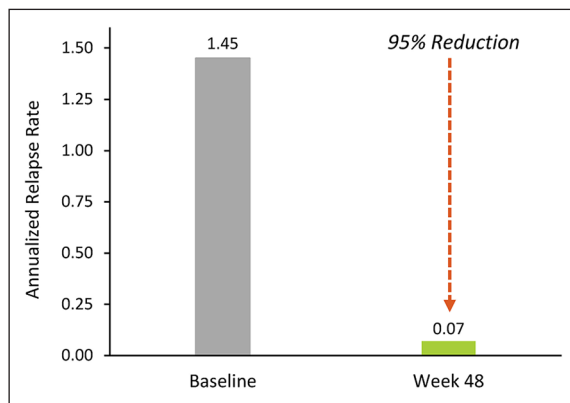


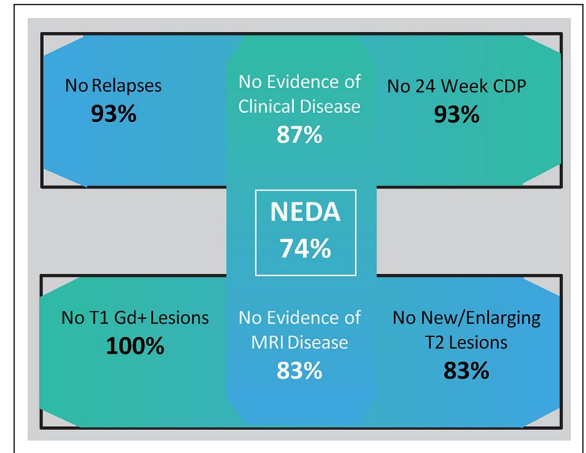**Figure 6.** Annualized relapse rate at baseline and week 48.



**Figure 7.** Proportion of patients with no evidence of disease activity (NEDA) at week 48.
NEDA was assessed for 46 patients (96% of all participants) with all available efficacy evaluations and was defined as absence of disease relapse, no MRI activity (no T1-weighted gadolinium (Gd+)-enhancing lesions and no new/enlarging T2-weighted lesions), and no 24-week confirmed disability progression (CDP).

**Table 3.** Adverse events occurring in ⩾5% of patients treated with ublituximab (any causality).

| Adverse event | All patients (N=48) | |
|---|---|---|
| | Any grade | Grade 3–4 |
| | *n* (%) | |
| Infusion-related reaction | 28 (58) | 0 |
| Arthralgia | 7 (15) | 0 |
| Hypoesthesia | 7 (15) | 0 |
| Nausea | 7 (15) | 0 |
| Upper respiratory tract infection | 7 (15) | 0 |
| Dizziness | 6 (13) | 0 |
| Influenza | 6 (13) | 0 |
| Fatigue | 5 (10) | 1 (2) |
| Headache | 5 (10) | 0 |
| Cough | 5 (10) | 0 |
| Diarrhea | 5 (10) | 0 |
| Nasopharyngitis | 5 (10) | 0 |
| Sinusitis | 5 (10) | 0 |
| Back pain | 4 (8) | 0 |
| Constipation | 4 (8) | 0 |
| Abdominal pain upper | 3 (6) | 0 |
| Contusion | 3 (6) | 0 |
| Depression | 3 (6) | 0 |
| Fungal infection | 3 (6) | 0 |
| Migraine | 3 (6) | 0 |
| Pyrexia | 3 (6) | 0 |
| Rash | 3 (6) | 0 |
| Vision blurred | 3 (6) | 0 |
| Vomiting | 3 (6) | 0 |

progression, and only 4 patients (8%) met criteria for 24-week confirmed disability progression.

*NEDA.* At week 48, 46 patients (96%) had received all assessments to be evaluated for NEDA. Of them, 34 patients (74%) achieved clinical and MRI outcomes consistent with NEDA (Figure 7).

### Safety and tolerability
Ublituximab was generally well tolerated (Table 3). No patient discontinued the study due to a drug-related AE. Only one grade 3 AE, fatigue, was considered possibly related to ublituximab. No serious infections were reported, and no deaths occurred on-study.

The most common ublituximab-related AEs were IRRs, which were reported for 24 patients (50%). All IRRs were CTCAE severity grade 1 or 2. Of the total 141 ublituximab infusions, 77% did not result in an IRR. IRRs were most frequent on the first infusion day (*n*=21; 44%). IRR frequencies on day 15 and at week 24 did not appear to increase with higher doses

**Table 4.** Infusion-related reactions (IRRs) considered at least possibly related to ublituximab, by ublituximab dosing cohort and infusion day.

| Cohort number (8 patients/ cohort) | IRRs on week 1 day 1 *n* (%) (ublituximab dosing) | IRRs on week 3 day 15 *n* (%) (ublituximab dosing) | IRRs at week 24 *n* (%) (ublituximab dosing) | Total number of patients with at least 1 IRR *n* |
|---|---|---|---|---|
| 1 | 3 (37.5) (150 mg/4 h) | 1 (12.5) (450 mg/3 h) | 1 (12.5) (450 mg/1.5 h) | 4 |
| 2 | 2 (25) (150 mg/4 h) | 1 (12.5) (450 mg/1.5 h) | 3 (37.5) (450 mg/1 h) | 3 |
| 3 | 1 (12.5) (150 mg/4 h) | 1 (12.5) (450 mg/1 h) | 1 (12.5) (600 mg/1 h) | 2 |
| 4 | 4 (50) (150 mg/3 h) | 0 (600 mg/1 h) | 0 (600 mg/1 h) | 4 |
| 5 | 6 (75) (150 mg/2 h) | 2 (25) (600 mg/1 h) | 2 (25) (600 mg/1 h) | 6 |
| 6 | 5 (62.5) (150 mg/1 h) | 0 (600 mg/1 h) | 0 (600 mg/1 h) | 5 |
| Total | 21 | 5 | 7 | 24 |

h: hour; IRR: infusion-related reaction.

or faster infusion times (Table 4): IRR frequencies with 1-hour infusions were 63% (5/8) on day 1, 9% (3/32) on day 15, and 15% (6/40) at week 24.

The most frequent AE during the placebo phase was grade 1–2 nasopharyngitis (*n*=3, 25%). No IRRs were reported for placebo infusions (Table 5).

**Table 5.** All adverse events occurring in patients during the placebo phase.

| Adverse event | Placebo patients (*N*=12) | |
|---|---|---|
| | Any grade | Grade 3–4 |
| | *n* (%) | |
| Nasopharyngitis | 3 (25) | 0 |
| Fatigue | 1 (8) | 1 (8) |
| Balance disorder | 1 (8) | 0 |
| Dizziness | 1 (8) | 0 |
| Hypoesthesia | 1 (8) | 0 |
| Influenza-like illness | 1 (8) | 0 |
| Infusion-related reaction | 1 (8) | 0 |
| Insomnia | 1 (8) | 0 |
| Muscle spasms | 1 (8) | 0 |
| Muscle twitching | 1 (8) | 0 |
| Nausea | 1 (8) | 0 |
| Neuralgia | 1 (8) | 0 |
| Pain | 1 (8) | 0 |
| Paraesthesia | 1 (8) | 0 |
| Rash | 1 (8) | 0 |
| Sinusitis | 1 (8) | 0 |
| Stress | 1 (8) | 0 |
| Vertigo | 1 (8) | 0 |
| Vessel puncture site bruise | 1 (8) | 0 |

## Discussion

The potent ADCC activity of ublituximab led to efficient peripheral CD19+ B-cell depletion in most patients within 24 hours of receiving the initial 150-mg dose of ublituximab, with >95% depletion in all treated patients and >99% median depletion by week 4. Moreover, B-cell depletion within the 95% target range was largely maintained before ublituximab dosing at week 24 and was sustained at week 48.

Ublituximab showed promising efficacy, with three fourths of all ublituximab-treated patients showing no evidence of clinical or MRI disease activity during the 48-week treatment period. New T2 lesions detected on-study occurred mainly before week 24, when the drug may have not yet had its full effect. At this writing, 38 patients (79%) continue to receive ublituximab in an extension phase of the study.

New or persisting T1-weighted gadolinium-enhancing lesions on brain MRI, indicative of blood-brain barrier disruption and histologically correlated with active inflammation,[14] were not detected in any ublituximab-treated patient at week 24 or at week 48. While other anti-CD20s have shown dramatic

decreases in T1 gadolinium-enhancing lesions, none have demonstrated a complete eradication.[3,5,15] As might be expected, reductions in inflammatory lesions were accompanied by clinical improvements. At week 48, the mean relapse rate was reduced by 95% from baseline, and 93% of patients remained relapse free on-study. Moreover, 92% of patients had no 24-week confirmed disability progression, including 17% of patients who showed confirmed improvement in EDSS scores. In this patient population, with mean disease duration of approximately 8 years at entry, overall burden of disease as indicated by T2 lesion volume was significantly reduced by more than 10% from baseline at week 48 with ublituximab.

Lovett-Racke et al.[16] evaluated longitudinal changes in lymphocyte profiles during B-cell depletion by ublituximab in patients in this study. During treatment, there were favorable shifts in the T-cell repertoire, including a significant reduction in proinflammatory CD4 + Th1 cells and increased proportions of CD4+CD25$^{hi}$Foxp3 T-cells (Tregs). Moreover, proinflammatory memory T-cells were reduced and naïve T-cell populations expanded over the course of the study. These changes may have contributed to the clinical efficacy of ublituximab.

Ublituximab was well tolerated with no patient withdrawals due to a drug-related AE. As seen with other anti-CD20 mAbs, the most common AEs with ublituximab were IRRs, which occurred most frequently at the first infusion and decreased in incidence with subsequent infusions.[3,5] All reported IRRs on-study were mild to moderate in severity (all grade 1 or 2). After the first ublituximab dose, IRR frequencies did not appear to increase with increasing dose or at the rapid infusion rate of 1 hour. That all 45 patients who completed the 48-week trial entered the extension phase of the study further attests to the favorable tolerability profile of ublituximab.

Infusion of 450-mg ublituximab administered over times as rapid as 1 hour produced high levels of B-cell depletion, eradicated all new and persisting T1-weighted gadolinium-enhancing lesions, and reduced T2-weighted lesion burden. Given the efficacy and tolerability of this dose and infusion time, ublituximab is currently being tested against an active comparator, teriflunomide, in patients with RMS in the phase 3 ULTIMATE trials (ClinicalTrials.gov NCT03277261 and NCT03277248).

### Authors' Note
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