

Five Years of Ublituximab in Multiple Sclerosis ULTIMATE I and II Open-Label Extension Study

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 Supplemental content

IMPORTANCE In the 2-year Study to Assess the Efficacy and Safety of Ublituximab in Participants With Relapsing Forms of Multiple Sclerosis (ULTIMATE) I and II randomized clinical studies, disease activity was significantly reduced with ublituximab vs teriflunomide in participants with relapsing multiple sclerosis (RMS).

OBJECTIVE To evaluate long-term ublituximab clinical efficacy and safety.

DESIGN, SETTING, AND PARTICIPANTS The 2-year, multicenter, randomized, active-controlled, double-blind period (DBP) of the ULTIMATE I and II phase 3 studies occurred September 2017 to November 2020. Enrollment in the ongoing ULTIMATE open-label extension (OLE) study began November 2019; data cutoff for this analysis was January 1, 2024.

INTERVENTION ULTIMATE OLE participants continued ublituximab (UBL-UBL) or switched from teriflunomide to ublituximab (TER-UBL).

MAIN OUTCOMES AND MEASURES Efficacy (annualized relapse rate [ARR], 24-week confirmed disability progression [CDP24], and 24-week confirmed disability improvement [CDI24]) and safety were key outcomes.

RESULTS Of 985 adults with RMS who completed ULTIMATE I and II, 851 enrolled in the ULTIMATE OLE and were included in the analysis. On DBP completion, more than 85% of participants (UBL-UBL, 422 of 494; TER-UBL, 429 of 491) entered the OLE, of whom more than 70% (UBL-UBL, 297 of 422; TER-UBL, 327 of 429) continued taking ublituximab at year 5 (OLE year 3) at data cutoff, making up the analysis population (mean [SD] age, 38.5 [9.7] years; 532 female [62.5%]). TER-UBL participants experienced a 58.4% ARR reduction at 1 year after the switch (0.182 vs 0.076; rate ratio, 0.42; 95% CI, 0.29-0.60; $P < .001$), and ARR continued to decrease to 0.048 (year 4) and 0.045 (year 5). UBL-UBL participants had further ARR reductions after the DBP (0.053, 0.032, and 0.020 for years 3, 4, and 5, respectively). At year 5, CDP24 was 8.0% in UBL-UBL participants vs 14.3% in TER-UBL participants ($P = .01$), and CDI24 was 17.0% in UBL-UBL participants vs 12.2% in TER-UBL participants ($P = .02$). Adverse events were consistent with the established safety profile from pivotal trials, with exposure-adjusted incidence rates per 100 participant-years of serious infections (excluding COVID events) of 2.10 (UBL-UBL) and 2.58 (TER-UBL). On average, immunoglobulin levels remained above the lower limit of normal, and no significant differences in serious infection rates were observed regardless of immunoglobulin level.

CONCLUSIONS AND RELEVANCE Results reveal that sustained clinical benefits were observed with 5 years of ublituximab treatment: ARR in year 5 showed 1 relapse per 50 participant-years of ublituximab treatment and 92% of UBL-UBL participants remained free from CDP24. Results confirm long-term ublituximab benefits and early initiation of high-efficacy treatment.

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Anti-CD20 monoclonal antibodies (mAbs) ushered in a paradigm shift in the management of multiple sclerosis (MS).¹ These agents act by depleting B cells through various mechanisms, including antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity.²⁻⁴ ADCC is mediated by interactions between the fragment crystallizable (Fc) domain of the anti-CD20 mAb and the corresponding Fc gamma receptor (FcγR) on effector cells (primarily natural killer [NK] cells).⁵ Complement-dependent cytotoxicity is mediated by interactions between the Fc domain and complement component C1q, activating the complement cascade and leading to cytotoxic effects. Anti-CD20 mAb-mediated B-cell depletion is thought to reduce antigen presentation by B cells to T cells and subsequent activation of pathogenic T cells, reduce production of inflammatory cytokines by B and T cells, and promote a shift away from an activated inflammatory immune environment toward an environment of immune downregulation with less activated and less mature B and T cells.⁶⁻⁸

The available mAbs have distinct molecular and biological characteristics that contribute to their mechanisms of action and may result in differences in efficacy, safety, tolerability, and administration requirements.⁹ Ublituximab is a novel recombinant chimeric immunoglobulin (Ig) G1 mAb that targets a unique CD20 epitope.¹⁰⁻¹³ Ublituximab is glycoengineered to have low fucose content in its Fc region, resulting in greater affinity for the FcγR and enhanced ADCC.¹³ Relative to other anti-CD20 therapies currently used to treat MS, ublituximab exhibits higher binding affinity for the FcγR and has 25- to 30-fold greater ADCC.^{14,15} Ublituximab is administered in lower doses and with shorter infusion times compared with other currently infused anti-CD20 therapies.³

The Study to Assess the Efficacy and Safety of Ublituximab in Participants With Relapsing Forms of Multiple Sclerosis (ULTIMATE I)¹⁶ and ULTIMATE II¹⁷ studies were identical phase 3 studies that assessed the efficacy and safety of ublituximab vs teriflunomide in participants with relapsing MS (RMS).¹⁸ In these studies, ublituximab demonstrated reduced disease activity compared with teriflunomide over 2 years, with significantly lower annualized relapse rates (ARRs) and fewer gadolinium-enhancing (Gd+) T1 and new or enlarging T2 lesions. An ongoing open-label extension (OLE) study (ULTIMATE OLE) is evaluating the long-term safety and efficacy of ublituximab therapy in people with RMS. Here, we present results from an additional 3 years of OLE data, summarizing clinical outcomes with 5 years of ublituximab treatment.

Methods

Standard Protocol Approvals, Registrations, and Participant Consent

The protocol was approved by the institutional review board or independent ethics committee at each study center. ULTIMATE OLE was conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice, all applicable regulatory requirements, and the principles of the

Key Points

Question What is the long-term clinical efficacy and safety of ublituximab in people with relapsing multiple sclerosis (RMS)?

Findings In this trial including 985 adults, participants treated with continuous ublituximab for up to 5 years in the open-label extension study after completion of the randomized Study to Assess the Efficacy and Safety of Ublituximab in Participants With Relapsing Forms of Multiple Sclerosis (ULTIMATE) had significantly lower annualized relapse rate and confirmed disability progression than those initially treated with teriflunomide. The overall safety profile of ublituximab remained consistent with no new safety signals emerging with prolonged treatment.

Meaning Results suggest that early initiation of ublituximab and continued treatment over a period of 5 years provided sustained clinical benefits in participants with RMS.

Declaration of Helsinki. All participants provided written informed consent. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Trial Design and Participants

As previously reported,¹⁸ ULTIMATE I and ULTIMATE II were identical, phase 3, multicenter, double-blind, active-control, randomized clinical studies evaluating the efficacy and safety of ublituximab vs teriflunomide in participants with RMS.¹⁸ The details of the inclusion criteria, methods, and results were previously described.¹⁸ At the conclusion of the 96-week treatment period, participants who completed ULTIMATE I or ULTIMATE II had the option to enroll in an ongoing OLE study (ULTIMATE OLE). The study protocol is available in [Supplement 1](#).

In the ULTIMATE OLE study, participants either continued ublituximab treatment (UBL-UBL) or switched from teriflunomide to ublituximab (TER-UBL). All participants, regardless of prior treatment arm, received an initial 4-hour ublituximab 150-mg infusion on day 1 followed by a 1-hour ublituximab 450-mg infusion at week 3 (day 15); subsequent ublituximab 450-mg infusions were administered for 1 hour every 24 weeks. An antipyretic was administered before each infusion (eAppendix in [Supplement 2](#)).

The 96-week, double-blind studies were conducted at 104 sites across 10 countries between September 2017 and November 2020. Participants entered ULTIMATE OLE between November 2019 and September 2021. The clinical cutoff date for this analysis was January 1, 2024.

Participants self-reported race and ethnicity, which included the options of American Indian or Alaska Native, Black or African American, Asian, Native Hawaiian and Other Pacific Islander, White, not applicable due to country's legislation, or other (specify). Race and ethnicity data were included as demographic information per CONSORT 2025 guidelines.

Efficacy Assessments

The following end points are reported for the ULTIMATE OLE study.

The ARR was defined as the number of independent relapse adjudication panel-confirmed relapses of MS per participant-year (PY) (eAppendix in Supplement 2).

Twenty-four-week-confirmed disability progression (CDP24) was defined as an increase of 1.0 or more points from the baseline Expanded Disability Status Scale (EDSS) score if the baseline score was less than or equal to 5.5 or an increase of greater than or equal to 0.5 points if the baseline score was greater than 5.5, sustained for 24 or more weeks. Twenty-four-week-confirmed disability improvement (CDI24) was defined as a reduction in EDSS score of 1.0 or more points if baseline EDSS score was less than or equal to 5.5 or greater than or equal to 0.5 points if the baseline EDSS score was greater than 5.5, sustained for 24 or more weeks. The Multiple Sclerosis Functional Composite (MSFC) is a 3-part assessment that includes quantitative tests of leg function/ambulation, arm and hand function, and cognitive function, with scores for each component converted to standard scores (*z* scores) that are then averaged to derive a single score. Decreases in MSFC scores indicate deterioration in neurological function. MSFC scores were collected yearly.

Radiographic images were not collected for most OLE participants because the study period coincided with the COVID-19 pandemic, and most trial sites and hospitals deprioritized study-related magnetic resonance imaging during this time.

Safety Assessments

Adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and graded in severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 grading system. The terms *COVID-19* and *COVID-19 pneumonia* were excluded from the analysis due to the temporal and geographic bias of the COVID-19 pandemic and to maintain consistency with previously reported 5-year OLE analysis for anti-CD20 mAb treatment.¹⁹ The lack of definitive COVID diagnosis and prophylaxis for a major portion of the ublituximab OLE period and potential misattribution of the terms *COVID* and *COVID-19 pneumonia* during that period led to their exclusion from this analysis. However, AEs with a possible COVID association (respiratory tract infections [RTIs], RTI viral, upper RTI, nasopharyngitis, pneumonia, bronchitis, and sinusitis) and all other AEs were included. Additional safety end points included the number and severity of infusion-associated events (defined as infusion-related AEs reported during or within 24 hours of infusion), the number and severity of infectious AEs, and mean changes in immunoglobulins.

Statistical Analyses

Efficacy end points were analyzed in the modified intention-to-treat (mITT) population, which consisted of all participants who received 1 or more doses of study medication during the double-blind period (DBP) or OLE and had baseline and 1 or more postbaseline efficacy assessments. ARR were analyzed using generalized estimating equations (negative binomial regression), with logarithmic link function, treatment, region, and baseline EDSS strata; year and interaction of treatment and year as covariates; and log (years of treatment)

as offset. The CDP24 and CDI24 were estimated by Kaplan-Meier method, and corresponding hazard ratios (HRs) were estimated using Cox regression models, with treatment group as covariate and based on DBP EDSS score at baseline. The percentage of participants with improvement (≥ 1 -point decrease) and worsening (≥ 1 -point increase) in EDSS scores at week 144 was calculated based on the number of participants with both baseline and OLE week 144 EDSS data, with *P* values derived from an ordinal logistic regression model.

Safety analyses included all data (pooled) among ublituximab-treated participants collected during the DBP of the ULTIMATE I and II trials and the OLE. All participants who received 1 or more ublituximab doses were included in the safety analyses (safety population) for the double-blind studies and the OLE. For all AE-related end points, the exposure-adjusted incidence rate (EAIR) per 100 PYs was calculated, along with the corresponding 95% CI. Rates of serious infections (SIs) were evaluated as described in the eAppendix in Supplement 2.

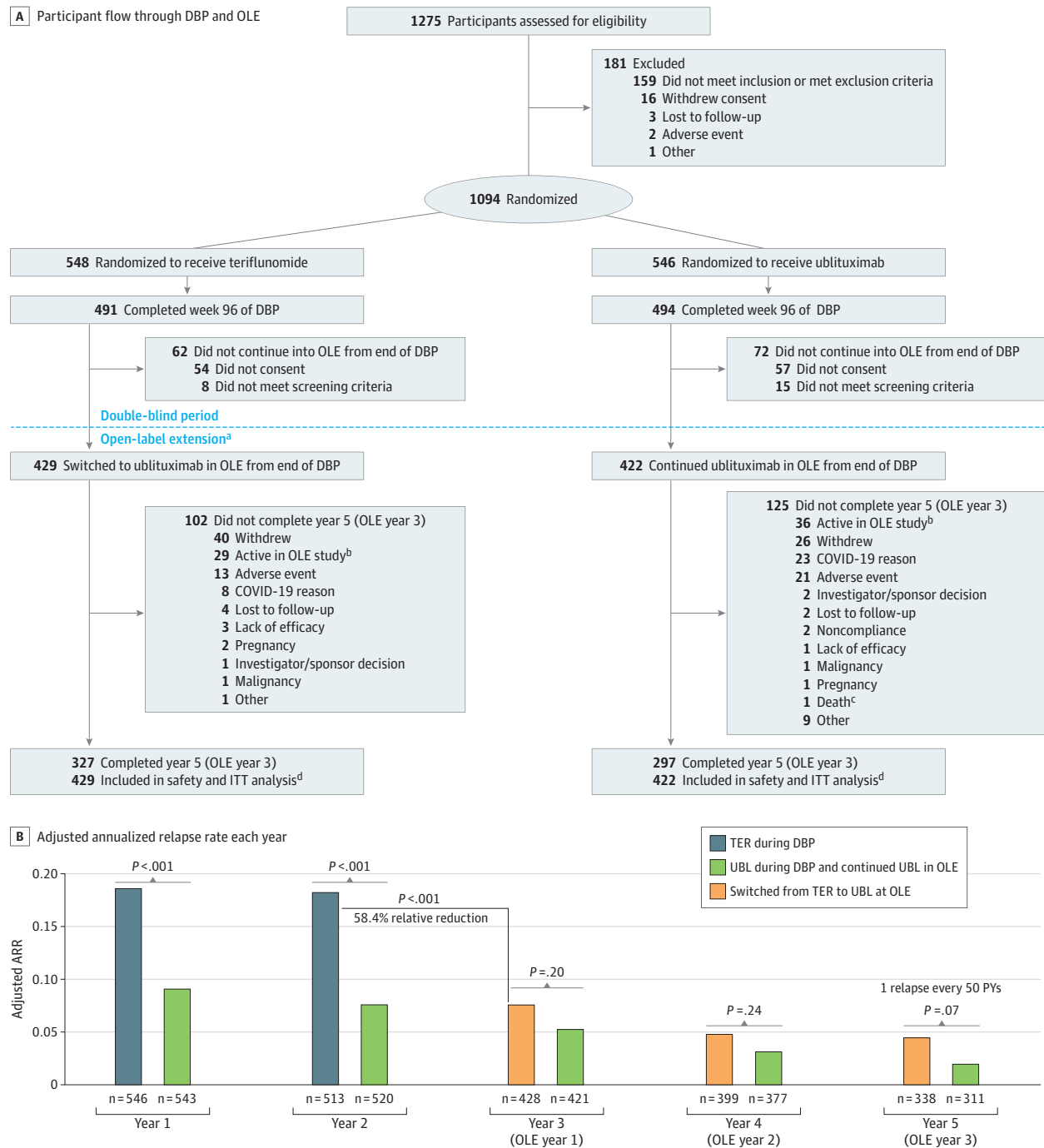
OLE analyses were post hoc (not prespecified) and performed with the use of SAS software, version 9.4 (SAS Institute); all *P* values were 2-sided, and statistical significance was evaluated at $\alpha = .05$.

Results

Participant Disposition, Demographics, and Disease Characteristics

A total of 985 adults with RMS who completed the ULTIMATE I and II studies were included in the analysis; 851 participants were enrolled in the ULTIMATE OLE study. After completing the ULTIMATE I and II DBP studies, 85.4% of ublituximab-treated participants (422 of 494) entered the OLE and continued ublituximab, and 87.4% of teriflunomide-treated participants (429 of 491) entered the OLE and switched to ublituximab, comprising the safety/mITT population (Figure 1A). Of these, more than 70% of participants (297 of 422 [70.4%; UBL-UBL] and 327 of 429 [76.2%; TER-UBL]) remained in the study after completing 3 years of OLE ublituximab treatment at year 5, making up the analysis population (mean [SD] age, 38.5 [9.7] years; 532 female [62.5%]; 319 male [37.5%]). The mean (SD) gap between DBP and OLE was 7.5 (3.17) months. A total of 36 participants (8.5%) and 29 participants (6.8%) in the UBL-UBL and TER-UBL groups, respectively, remained in the OLE between 0 and 3 years, and 89 (21.1%) and 73 (17.0%), respectively, discontinued the OLE. Participant demographics and disease characteristics at the start of the ULTIMATE OLE study were well balanced between treatment arms, with the exception of a greater proportion of participants with no Gd+ T1 lesions among those who previously received ublituximab (98.6%) vs teriflunomide (72.0%), consistent with the significant difference in treatment effects observed in the DBP (Table 1).¹⁸ Furthermore, the proportion of participants with EDSS less than or equal to 3.5 (ie, no or minimal disability to moderate disability) was greater at OLE baseline in UBL-UBL (80.1%) vs TER-UBL (73.4%), consistent with the effects on EDSS seen in the DBP.²⁰

Figure 1. Flow Chart and Bar Graph Showing Participant Disposition and Annualized Relapse Rate (ARR), Respectively



A, Participant disposition. B, ARR during years 1 and 2 of the double-blind period (DBP) and years 1 to 3 of the open-label extension (OLE). Data cutoff: January 1, 2024. PY indicates participant-year; TER, teriflunomide; UBL, ublituximab.

^aOLE period: November 18, 2019, until data cutoff on January 1, 2024. Participants completing the DBP had to re-enroll for the OLE.

^bParticipants were active in the OLE but had not yet completed year 5 (OLE year 3) as of data cutoff date.

^cOf the 3 deaths that occurred during the OLE, 1 each in the UBL-UBL and TER-UBL cohorts were not captured as a reason for discontinuation from the study.

^dAll participants in the safety population (received ≥ 1 dose of study drug) also had ≥ 1 postbaseline efficacy assessment and were included in the intention-to-treat (ITT) population.

Clinical Efficacy Assessments

During the DBP of ULTIMATE I and II, the pooled cohorts showed a significant reduction in ARR in participants treated

with ublituximab vs teriflunomide (-51.3% in year 1, -58.0% in year 2; $P < .001$ for both comparisons), indicating a reduction in MS disease activity. During year 3 (OLE year 1), partici-

Table 1. Baseline Demographics and Disease Characteristics for the Pooled ULTIMATE I and II Populations at the Start of the DBP and OLE (mITT Population)

Characteristic	DBP baseline		OLE baseline	
	TER (n = 546)	UBL (n = 543)	TER-UBL (n = 429)	UBL-UBL (n = 422)
Age, mean (SD), y	36.6 (9.3)	35.3 (8.6)	39.2 (9.4)	37.9 (8.7)
Age, No. (%), y				
<38	302 (55.3)	326 (60.0)	195 (45.5)	213 (50.5)
≥38	244 (44.7)	217 (40.0)	234 (54.5)	209 (49.5)
Sex, No. (%)				
Female	355 (65.0)	344 (63.4)	273 (63.6)	259 (61.4)
Male	191 (35.0)	199 (36.6)	156 (36.4)	163 (38.6)
Region, No. (%)				
US and Western Europe	53 (9.7)	53 (9.8)	29 (6.8)	26 (6.2)
Eastern Europe	493 (90.3)	490 (90.2)	400 (93.2)	396 (93.8)
Race, No. (%) ^a				
Black	9 (1.6)	8 (1.5)	5 (1.2)	5 (1.2)
White	534 (97.8)	533 (98.2)	422 (98.4)	416 (98.6)
Other	3 (0.5)	2 (0.4)	2 (0.5)	1 (0.2)
EDSS score, mean (SD)	2.9 (1.2)	2.9 (1.3)	3.0 (1.4)	2.7 (1.3)
EDSS score, No. (%)				
≤3.5	414 (75.8)	418 (77.0)	315 (73.4)	338 (80.1)
>3.5	132 (24.2)	125 (23.0)	111 (25.9)	82 (19.4)
Missing	0	0	3 (0.7)	2 (0.5)
Gd+ T1 lesions, No. (%)				
0	291 (53.3)	284 (52.3)	309 (72.0)	416 (98.6)
≥1	251 (46.0)	258 (47.5)	119 (27.7)	1 (0.2)
Missing	4 (0.7)	1 (0.2)	1 (0.2)	5 (1.2)
Volume of T2 lesions, mean (SD), mL	15.3 (16.7)	15.3 (14.8)	16.5 (16.9)	14.5 (13.8)

Abbreviations: DBP, double-blind period; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; mITT, modified intention-to-treat; OLE, open-label extension; TER, teriflunomide; TER-UBL, participants who switched from TER to UBL; UBL, ublituximab; UBL-UBL, participants who continued UBL; ULTIMATE, Study to Assess the Efficacy and Safety of Ublituximab in Participants With Relapsing Forms of Multiple Sclerosis.

^a Race data were collected from participants, with the provided options of the following: American Indian or Alaska Native, Black or African American, Asian, Native Hawaiian and Other Pacific Islander, White, not applicable due to country's legislation, or other (specify).¹⁸

participants who switched from teriflunomide to ublituximab experienced a significant reduction (−58.4%) in ARR (0.182 vs 0.076), with a rate ratio of 0.42 (95% CI, 0.29-0.60; $P < .001$) (Figure 1B). Participants who continued ublituximab exhibited low and decreasing ARR throughout the observation period (ARR: 0.053, 0.032, and 0.020 for years 3, 4, and 5, respectively). Those who switched from teriflunomide to ublituximab also showed decreasing ARR (0.076, 0.048, and 0.045 for years 3, 4, and 5, respectively), with slightly higher rates compared with the continuous ublituximab group. During year 5 alone, 97.7% of participants receiving continuous ublituximab and 95.0% of those switching to ublituximab after 2 years on teriflunomide were relapse free. Cumulatively over years 0 to 5, significantly more participants in the UBL-UBL vs TER-UBL groups were relapse free: 83.6% vs 68.9% ($P < .001$), which increased to 91.7% and 86.7% ($P = .02$), respectively, during years 2 to 5.

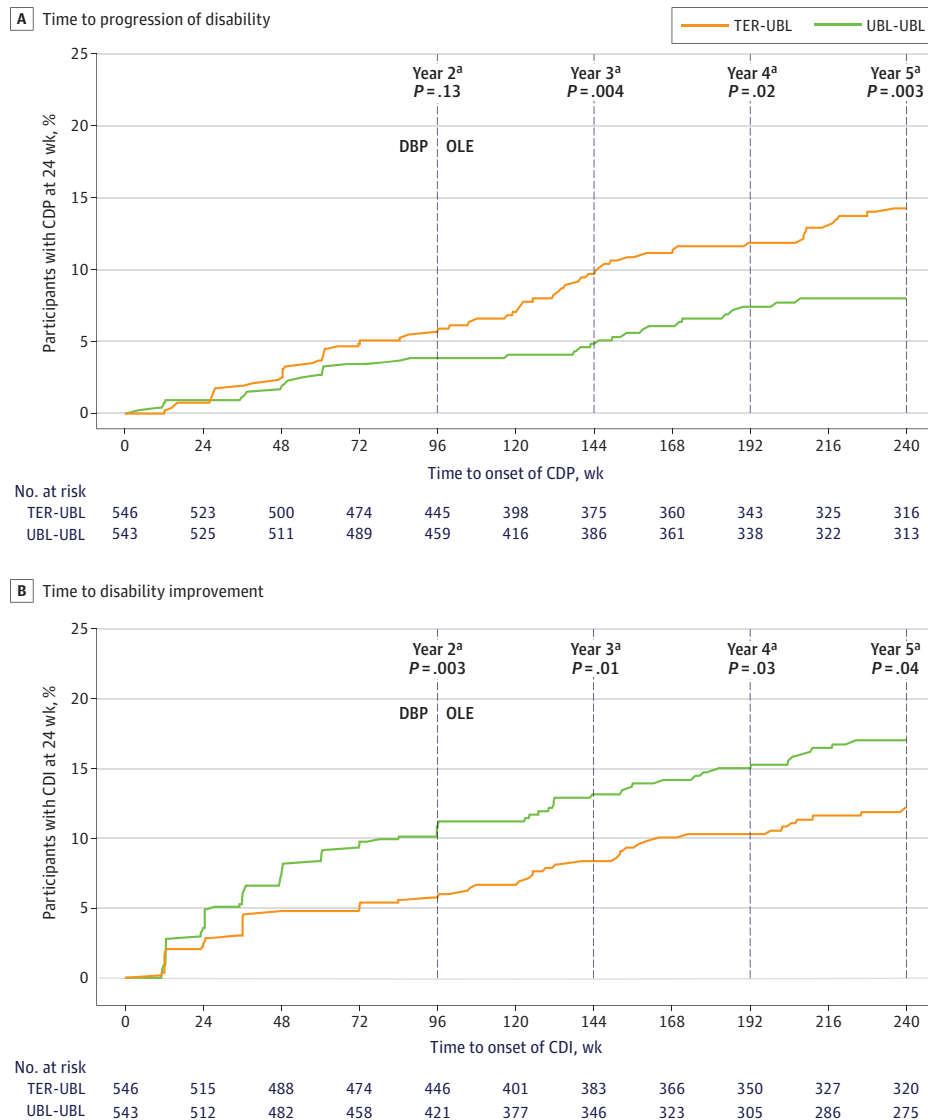
RMS is characterized by relapses and accrual of disability. Over 5 years of ublituximab treatment, CDP24 (a measure of disability accrual) remained low (8.0% in UBL-UBL participants vs 14.3% in TER-UBL participants [$P = .01$]), and participants receiving continuous ublituximab had a statistically significant 38.8% lower risk of CDP compared with those switching to ublituximab after 2 years of teriflunomide (HR, 0.61; 95% CI, 0.41-0.90; $P = .01$) (Figure 2A). At the end of year

5 since randomization, cumulatively, 92.0% of UBL-UBL participants were free of CDP24.

Treatment of RMS may, in some cases, reverse some MS-related disability. The likelihood of achieving CDI24 (a measure of disability improvement) was 47.2% relatively higher and statistically significant in participants receiving continuous ublituximab therapy over 5 years compared with those switching to ublituximab after 2 years of teriflunomide (absolute CDI24 values: 17% [UBL-UBL] vs 12.2% [TER-UBL]; HR, 1.47; 95% CI, 1.05-2.07; $P = .02$) (Figure 2B). At the end of year 5, the cumulative proportions of UBL-UBL and TER-UBL participants with CDI24 were 17.0% and 12.2%, respectively.

EDSS and MSFC scores are measures of MS-related disability. Significantly more participants receiving continuous ublituximab had EDSS score improvements from DBP baseline to year 5 compared with those who switched to ublituximab after 2 years of teriflunomide in the DBP (15.3% [UBL-UBL] vs 10.1% [TER-UBL]; $P = .02$) (eFigure 1 in Supplement 2), indicating that physical functioning improved with earlier ublituximab treatment. The shift in EDSS score from OLE baseline to OLE year 3 was similar in the continuous treatment and switch groups. Similarly, MSFC scores stayed relatively stable during the OLE (eTable 1 in Supplement 2). EDSS and MSFC data during the OLE period suggest stability

Figure 2. Kaplan-Meier Curves of Time to Onset of Confirmed Disability Progression (CDP) and Confirmed Disability Improvement (CDI) for 24 or More Weeks



Time to onset of CDP (A) and CDI (B).

^aEstimation by Kaplan-Meier method, with hazard ratio estimated using Cox regression model with treatment group as covariate. Time to onset of CDP or CDI is the time from randomization in the double-blind period (DBP) to the

onset of CDP or CDI, including gap period between the DBP and open-label extension (OLE) where applicable. TER indicates teriflunomide; TER-UBL, participants who switched from TER to UBL; UBL, ublituximab; UBL-UBL, participants who continued UBL.

in physical functioning with disease-modifying therapy (DMT; teriflunomide and/or ublituximab) for 3 to 5 years.

Safety

Incidence of safety outcomes was consistent between the DBP and pooled DBP/OLE cohorts, with EAIRs per 100 participant-years of serious infections (excluding COVID events) of 2.10 (UBL-UBL) and 2.58 (TER-UBL). EAIR per 100 PYs of treatment-emergent AEs (TEAEs) in the overall ublituximab cohort in the pooled DBP plus OLE period (DBP/OLE: 205.08; 95% CI, 200.46-209.81) was lower than the rate observed in the ublituximab cohort from the DBP (374.84; 95% CI, 363.79-

386.22) (Table 2), indicating an overall decrease in TEAE rates with longer exposure. The most common AEs in the pooled DBP/OLE cohort included infusion-related reactions (IRRs) and infections (eTable 1 in Supplement 2).

Ublituximab infusions were well tolerated over 5 years. The IRR rate was lower in the ublituximab pooled DBP/OLE cohort (26.69; 95% CI, 25.06-28.43) compared with the DBP (54.12; 95% CI, 50.02-58.55), indicating a reduction over time, and the most common IRRs in the pooled DBP/OLE cohort included chills, pyrexia, and headache. The total number of infusions completed without interruption was improved in the pooled DBP/OLE cohort (98.6%) vs DBP (96.6%).

Table 2. Summary of Adverse Events Per 100 Participant-Years During Ublituximab Treatment in the DBP of ULTIMATE I and II and in the Pooled DBP/OLE^{a,b}

AE type	EAIR (95% CI)	
	Ublituximab DBP (n = 545)	Ublituximab pooled DBP/OLE (n = 974)
Any TEAE	374.84 (363.79-386.22)	205.08 (200.46-209.81)
TEAE leading to treatment discontinuation	1.66 (1.06-2.60)	1.69 (1.32-2.18)
Infection	80.92 (75.88-86.30)	48.61 (46.39-50.94)
Infusion-related reaction	54.12 (50.02-58.55)	26.69 (25.06-28.43)
Malignancy	0.17 (0.04-0.70)	0.17 (0.07-0.37)
Serious adverse event	5.59 (4.37-7.14)	5.88 (5.14-6.73)
Serious infection	2.10 (1.40-3.13)	2.58 (2.11-3.16)
Death	0.26 (0.08-0.81)	0.17 (0.07-0.37)

Abbreviations: AE, adverse event; DBP, double-blind period; EAIR, exposure-adjusted incidence rate; OLE, open-label extension; TEAE, treatment-emergent adverse event; ULTIMATE, Study to Assess the Efficacy and Safety of Ublituximab in Participants With Relapsing Forms of Multiple Sclerosis.

^a The eAppendix in Supplement 2 contains additional information on how AEs were assessed.

^b The data cutoff was January 1, 2024. Multiple occurrences of the same AE in one participant are counted multiple times. Extension AEs that started during the gap period were excluded. COVID-19 events were excluded from the analysis. Participant-years: ublituximab DBP, 1145.569; ublituximab pooled DBP/OLE, 3603.899.

Rates of serious AEs and TEAEs leading to treatment discontinuation did not increase with time. The overall infection rate (any grade) was lower in the pooled DBP/OLE ublituximab cohort (EAIR, 48.61; 95% CI, 46.39-50.94) compared with the DBP (EAIR, 80.92; 95% CI, 75.88-86.30) (Table 2). COVID-related infection mostly occurred in the OLE phase due to the timing of the conclusion of the DBP in relation to the COVID-19 pandemic; therefore, COVID-related events were higher in the pooled DBP/OLE cohort compared with the DBP (eAppendix in Supplement 2). Ublituximab-associated infection rates and EAIRs for the most common infections are provided in eTables 2 and 3 in Supplement 2. Apart from nasopharyngitis, respiratory tract infections, and pneumonia, the EAIR 95% CIs overlapped for the UBL-UBL and TER-UBL cohorts, suggesting comparable rates of occurrence. Of note, a major limitation of this analysis is that the UBL-UBL cohort represents 5 years of observation, whereas the TER-UBL cohort represents 3 years of observation. SI rates by year were 1.3%, 2.5%, 2.8%, 2.7%, and 1.7% for the UBL-UBL cohort and 1.6%, 1.0%, 1.1%, 1.0%, and 0.4% for the TER-UBL cohort for years 1 to 5, respectively. No cases of progressive multifocal leukoencephalopathy were identified in the overall safety population in the pooled ULTIMATE DBP and OLE studies as of the analysis cutoff date of January 1, 2024.

The incidence rate of all malignancies was 0.17 (95% CI, 0.07-0.37) in the pooled DBP/OLE cohort, which was consistent with the DBP (0.17; 95% CI, 0.04-0.70). The death rate remained consistent between the DBP (0.26; 95% CI, 0.08-0.81) and the pooled DBP/OLE cohort (0.17; 95% CI, 0.07-0.37). Deaths that occurred in the ublituximab group during the OLE were due to pneumonia (deemed not related to treat-

ment), viral encephalitis (deemed probably related to treatment), and nonspecific interstitial pneumonia (deemed doubtfully related to treatment). Additional details are provided in the eAppendix in Supplement 2.

On average, IgM and IgG levels remained relatively stable (defined as being within 1.5 times upper and lower IQR limits) and above the lower limit of normal (LLN; IgM: 40 mg/dL; IgG: 565 mg/dL; to convert IgM and IgG to grams per liter, multiply by 0.01) over time (eFigure 2 in Supplement 2). At 5 years, mean (SE) IgM (Figure 3A) and IgG (Figure 3B) levels in the continuous cohort were 69 (4) mg/dL and 806 (13) mg/dL, respectively. The percentage change from baseline to year 5 in the continuous cohort was -52.7% for IgM and -18.8% for IgG. eFigure 3 in Supplement 2 shows the proportion of participants with IgG and IgM levels at or above the LLN and below the LLN by severity. At year 5, IgG reductions were limited, mild (12.6%) to moderate (0.3%), and none were severe; IgM reductions were mild (4.9%), moderate (18.9%), or severe (11.2%). Twelve participants (<1%) experienced IgG values below 400 mg/dL at any time on ublituximab. Four of these 12 participants (33%) had values less than 400 mg/dL at multiple time points (persistent), whereas 8 of 12 (67%) participants only had 1 IgG reading below 400 mg/dL. The transience vs persistence of these low IgG values was difficult to ascertain because immunoglobulins were collected every 48 weeks and the low IgG values were typically reported at the most recent time point prior to data cutoff. Additional follow-up will be necessary to determine if these IgG values less than 400 mg/dL resolved or persisted.

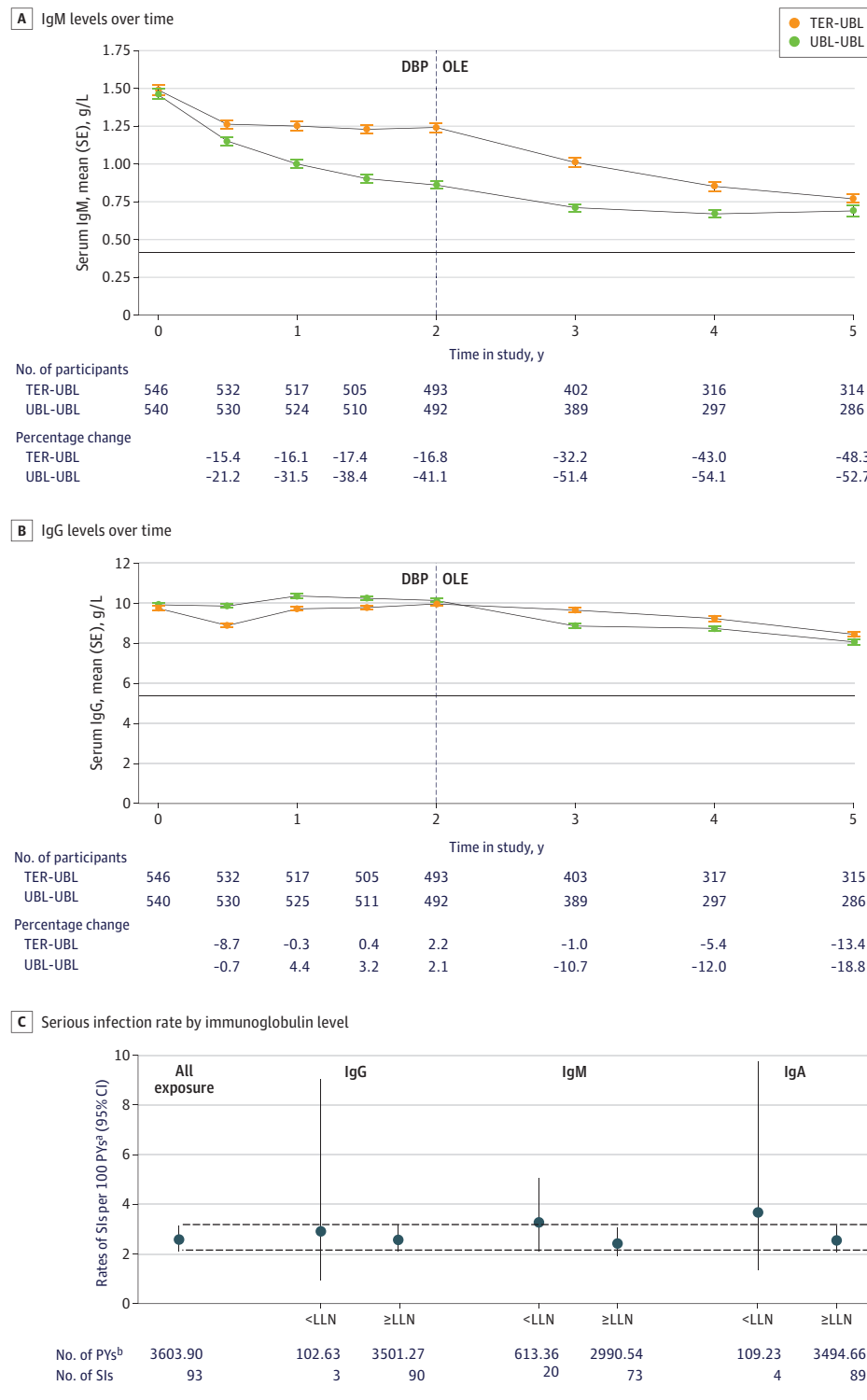
Rates of SIs did not vary based on whether immunoglobulin levels were below vs above normal levels. SI rates per 100 PYs in ublituximab-treated participants with immunoglobulin levels less than LLN or greater than or equal to LLN were 3.26 (95% CI, 2.10-5.05) and 2.44 (95% CI, 1.94-3.07) for IgM, 2.92 (95% CI, 0.94-9.06) and 2.57 (95% CI, 2.09-3.16) for IgG, and 3.66 (95% CI, 1.37-9.76) and 2.55 (95% CI, 2.07-3.13) for IgA, respectively (Figure 3C), indicating no significant difference in SI incidence regardless of immunoglobulin levels above or below LLN.

Discussion

These ULTIMATE OLE study results provide insights regarding the long-term safety and efficacy of ublituximab therapy in people with RMS. Sustained clinical benefits were observed with ublituximab treatment continued over a period of 5 years. In the OLE of the phase 3 studies, ARR continued to decline with ongoing treatment, and the ARR in year 5 of continuous ublituximab treatment was 0.020, equivalent to 1 relapse occurring in 50 PYs. These results demonstrate that ublituximab treatment was associated with significantly reduced MS disease activity, starting within 2 years of treatment with continued reductions with up to 5 years.

Although a numerically lower number of ublituximab-treated participants experienced CDP24 compared with teriflunomide-treated participants at the end of the DBP, this difference did not reach statistical significance. However, with

Figure 3. Line Graph Showing Mean Immunoglobulin M (IgM) and IgG Levels and Plot of Serious Infection (SI) Rate per 100 Participant-Years (PYs) by Immunoglobulin Levels



SI conversion factor: To convert IgG, IgM, and IgA to grams per liter, multiply by 0.01.

Lower limit of normal (LLN) is defined as IgG, 565 mg/dL; IgM, 40 mg/dL; and IgA, 70 mg/dL. Analysis includes participants who received any dose of UBL during the double-blind period (DBP) and open-label extension (OLE) periods. Gap period (if any) between DBP and OLE was excluded. TER, teriflunomide; TER-UBL, participants who switched from TER to UBL; UBL, ublituximab; UBL-UBL, participants who continued UBL.

^aRates of SIs per 100 PYs and 95% CI were estimated by Poisson regression model. Multiple SIs in 1 participant are counted multiple times. The terms COVID-19 and COVID-19 pneumonia were excluded.

^bPYs as sum of exposures (in years) during each lab episode (<LLN or ≥LLN) from the date of randomization (UBL arm in DBP) to the end of DBP and from OLE informed consent form (ICF) date (for participants entered in OLE) to the last participant date in OLE or cutoff date January 1, 2024 (if ongoing).

longer term follow-up during OLE, lower disability progression and higher probability of disability improvement were observed at year 5 for participants who received continuous ublituximab compared with those with an initial 2-year teriflunomide treatment. These data suggest that early initiation of

high-efficacy DMT was superior to initiating therapy with a moderately efficacious treatment followed by escalation to high potency therapy (the treat-to-target or tiered therapy approach) for disability prevention, complementing the growing body of evidence that MS should be treated with high-

efficacy DMTs early in the disease course rather than attempting to generate benefit following treatment failure.²¹⁻²⁴

Standards for interpreting clinically meaningful changes in the MSFC *z* score are not well established.²⁵ A decrease in MSFC *z* score by 0.14 over 2 years is proposed to represent clinically significant worsening²⁶ based on *z* score changes experienced by placebo-treated patients.²⁷ The changes observed in the OLE baseline TER-UBL group and in the OLE year 3 TER-UBL group exceeded this threshold, indicating that despite treatment with teriflunomide (a DMT proved to reduce disability worsening), ULTIMATE study participants initially treated with teriflunomide experienced clinically significant declines in the MSFC, whereas the continuous ublituximab-treated group experienced improvement in the OLE baseline period and stability thereafter. Further investigation of the MSFC subcomponents with clinically meaningful thresholds for change could yield further insight into the impact of ublituximab on RMS disability progression.

When the ULTIMATE I and II studies ended, 85.4% of ublituximab-treated participants elected to continue in the OLE, similar to the percentages of those continuing ofatumumab or ocrelizumab in the Long-Term Safety, Tolerability, and Effectiveness Study of Ofatumumab in Patients With Relapsing MS (ALITHIOS) and A Study of Ocrelizumab in Comparison With Interferon Beta-1a (Rebif) in Participants With Relapsing Multiple Sclerosis (OPERA) OLE trials, respectively.^{19,28} Also, in the pooled ULTIMATE I and II studies, there were a total of 344 women (63.4%) and 355 women (65%) in the ublituximab and teriflunomide arms, respectively; of these, 315 in each arm (91.6% for the ublituximab arm and 88.7% for the teriflunomide arm) were of childbearing age (18-49 years), which was expected given the specified age range of 18 to 55 years as an enrollment criterion. The high proportion of women of childbearing age in the ULTIMATE I and II studies is consistent with the higher prevalence of MS among women vs men (ratio approximately 2:1)^{29,30} and with the observation that MS is most commonly diagnosed among women of childbearing age.²⁹ However, it is possible that because teriflunomide was the active comparator, some women may have chosen to not participate in these trials because of teriflunomide's teratogenic effects in addition to contraception requirements, thereby possibly limiting the study's generalizability. In addition to slower disability progression, significant improvements in CDI24 with continuous ublituximab were also observed for participants switching from teriflunomide at years 4 and 5 in the ULTIMATE OLE study.

Ublituximab was well tolerated over 5 years of continuous treatment, with fewer than 2 participants per 100 PYs discontinuing treatment because of a TEAE. The OLE discontinuation rate was comparable with and numerically lower than that observed during the DBP. The rate of IRRs, which represented the most common type of TEAEs in the ULTIMATE I and II studies,¹⁸ was lower in the ublituximab pooled DBP OLE cohort compared with the DBP (26.69 vs 54.12 per 100 PYs), indicating a reduction over time. These findings are consistent with the incidence of IRRs observed during the DBP, which were most likely to occur at the first infusion, with a significantly lower risk of IRRs at the sec-

ond and subsequent infusions.¹⁸ The EAIRs of common infections were similar in the UBL-UBL and TER-UBL cohorts, with the exception of nasopharyngitis, respiratory tract infections, and pneumonia, for which EAIRs were higher in the UBL-UBL cohort. Despite adjustment for exposure duration, the longer observation period in the UBL-UBL cohort (5 years vs 3 years in the TER-UBL cohort) limits interpretation of this analysis.

The risk of SIs with highly efficacious DMTs is a well-recognized concern,^{23,31-33} particularly among people on B-cell-depleting therapies like anti-CD20 mAbs. Of note, EAIRs for SIs were consistent (overlapping 95% CIs) between the DBP (2.10; 95% CI, 1.40-3.13 per 100 PYs) and OLE + DBP (2.58; 95% CI, 2.11-3.16) with ublituximab, compared with those observed with ocrelizumab (DBP: 0.83; 95% CI, 0.43-1.45; OLE + DBP: 1.32; 95% CI, 1.08-1.60)³⁴ and ofatumumab (DBP: 1.55; 95% CI, 1.04-2.31; OLE + DBP: 1.63; 95% CI, 1.35-1.97)³⁵ in RMS. Although reductions in mean IgM and IgG levels were observed during continuous treatment with ublituximab, IgM and IgG levels in the ULTIMATE OLE study remained relatively stable with prolonged treatment and remained within 1.5 times upper and lower IQR limits, and mean levels remained above LLN. Most importantly, SI rates did not differ among ublituximab-treated participants with immunoglobulin (IgM, IgG, or IgA) levels below or above the LLN, consistent with IgG/IgM patterns observed with ofatumumab treatment.^{28,35} During the 5-year treatment period, the majority of ublituximab-treated participants maintained normal IgG levels. IgG reductions below 400 mg/dL occurred infrequently ($\leq 1\%$ annually) and showed no association with increased infection risk. These reductions did not prompt intravenous immunoglobulin supplementation or require ublituximab treatment modification. From a clinical monitoring perspective, the data suggest that routine immunoglobulin testing may not be necessary during the first 5 years of ublituximab treatment. Among participants who developed hypogammaglobulinemia, nearly all had normal baseline IgG values, and there were no baseline characteristics that predicted risk (data not shown).

In comparison, with up to 7 years of ocrelizumab treatment, mean IgM and IgG levels remained above LLN but decreased over time, and IgG levels less than LLN were associated with increased SI rate.³⁴ Overall, no association was observed between decreased immunoglobulin levels and SI risk with ublituximab, and progressive multifocal leukoencephalopathy cases were not reported during the analysis period. The 5-year observation period adds a degree of limitation to this trend. Prolonged observation will yield definitive clarity on the meaningfulness of this decline. Currently, the OLE is approved for continuation for up to 10 years. The sponsor continues to monitor and plans to report on actual declines and if there is any change in the incidence of infections in those participants who fell below the LLN. Hence, prolonged observation of immunoglobulin levels combined with continued monitoring of participants who fell below the LLN will yield more definitive clinical understanding of the decline in immunoglobulin levels.

Limitations

Key limitations include the absence of a control arm continuously treated with teriflunomide and a lack of blinding during the OLE. Additionally, at the time of analysis, only 57.0% of participants randomized in ULTIMATE I and II had completed 3 years of follow-up in the OLE, for a total of 5 years of study treatment. Neuroimaging data were not available, precluding determination of “no evidence of disease activity” status. The lack of longitudinal data on brain atrophy is a limitation of the dataset and impacts interpretation of a potential protective effect of earlier treatment. ARR was based on adjudicated relapses, which excluded investigator-only determined relapses. Additionally, gradual reduction in relapse frequency over time was described in people with RMS³⁶ and must be considered given the absence of a control arm. Disability

progression was captured at yearly intervals, and lack of disability progression or improvement events at more frequent time points is a limitation of the study.

Conclusions

Studies demonstrating the long-term efficacy and safety of DMTs are important given the lifelong and progressive nature of MS and the corresponding potential for long-term anti-CD20 mAb treatment. Balancing the safety and efficacy of MS DMTs is valuable for long-term management of people with MS, and the results of the current interim analysis highlight the improved efficacy and safety of ublituximab over 5 years of treatment in participants with RMS.

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Author Contributions: Dr Cree had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: Cree, Fox, Hartung, Alvarez, Qian, Wray, Robertson, Selmaj, Wynn, Mok, Rowland, Bodhinathan, Miskin, Steinman.

Drafting of the manuscript: Fox, Qian, Mok, Rowland, Bodhinathan, Miskin, Steinman.

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