Five Years of Ublituximab in Relapsing Multiple Sclerosis: Results from the Open-Label Extension of ULTIMATE I and II Studies

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OBJECTIVE

- To evaluate the long-term clinical efficacy and safety of ublituximab (UBL)

KEY FINDINGS

- Upon completion of the double-blind period (DBP), over 85% of participants from each treatment arm entered open-label extension (OLE). 70.4% and 76.2% completed 3-year UBL treatment during OLE in the continuous and switch cohorts, respectively.
- Patients who continued UBL exhibited low and decreasing annualized relapse rate (ARR) throughout the observation period [ARR: 0.053, 0.032, and 0.020 for Years 3, 4, and 5, respectively. During OLE Year 1, patients who switched from teriflunomide (TER) to UBL experienced a significant reduction (-58.4%) in ARR (0.182 vs 0.076)].
- Confirmed Disability Progression (CDP) lasting 24 weeks at Year 5 was 8.0% in UBL vs 14.3% in TER-UBL patients [HR (95% CI): 0.612 (0.414, 0.904); p=0.0126], and 92% remained progression free with continuous UBL treatment.
- Confirmed Disability Improvement (CDI) lasting 24 weeks at Year 5 was 17.0% in UBL vs 12.2% in TER-UBL patients [HR (95% CI): 1.472 (1.048, 2.067); p=0.0249], resulting in one in six patients experiencing improvement in disability after 5 years of continuous UBL treatment.
- In the cohort that received continuous UBL for at least 5 years, the IgM and IgG levels [mean (SE)] were 0.69 (0.04) g/L and 8.06 (0.13) g/L, respectively, and remained above the lower limit of normal (LLN).

BACKGROUND

- Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20 and is glycoengineered for enhanced antibody-dependent cellular cytotoxicity (ADCC).[1]
- Ublituximab exhibits enhanced ADCC and Fcγ-receptor (FcγR) binding relative to all other currently approved anti-CD20 therapies used in multiple sclerosis (MS).[2,3]
- Ublituximab is administered in lower doses and with shorter infusion times compared with other currently infused anti-CD20 therapies,[1] administered in 1-hour infusions after the first infusion.[4]
- ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) are identical, Phase 3, randomized, multicenter, double-blind, active-control studies evaluating the efficacy and safety of UBL versus TER in participants with relapsing multiple sclerosis (RMS).[5]
- In ULTIMATE I and II studies, UBL demonstrated significant reduction in disease activity vs TER over 2 years, demonstrating a statistically significant reduction in ARR for UBL compared with TER as well as significant improvements in the number of Gd+ T1 lesions and the number of new/enlarging T2 lesions.[4,5] Results from an additional 3 years of OLE period are presented below.

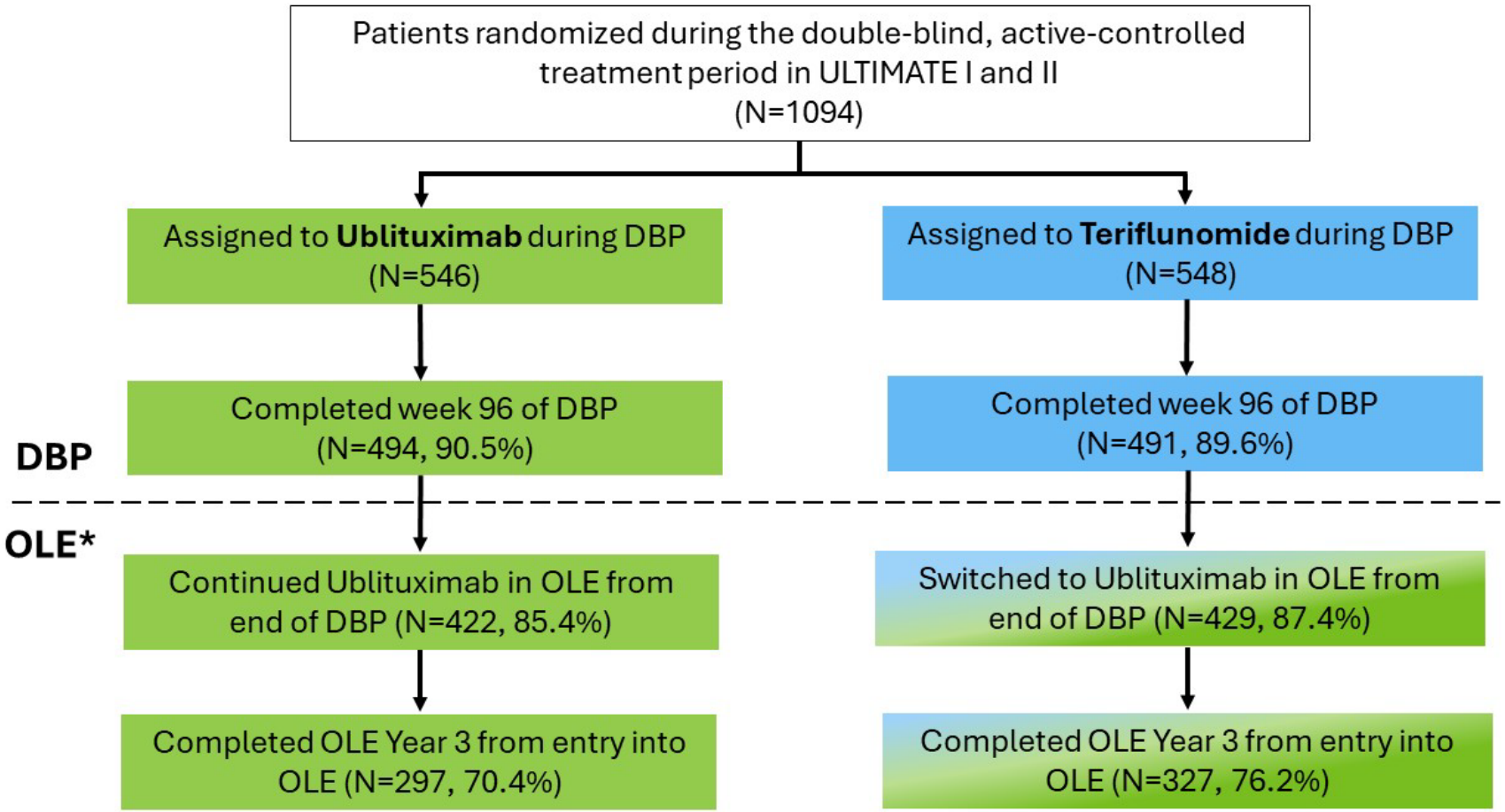
METHODS

- The active-controlled ULTIMATE I (N=549) and II (N=545) studies evaluated UBL 450 mg intravenous infusion every 24 weeks (following Day 1 infusion of 150 mg and Day 15 infusion of 450 mg) vs TER 14 mg orally once daily for 96 weeks.[5]
- After 2 years of randomized, active-controlled, DBP, RMS patients either continued UBL treatment (UBL-UBL) or switched from TER to UBL (TER-UBL).
- Adjusted ARR were analyzed using generalized estimating equations. The 24-week CDP and 24-week CDI were estimated by Kaplan-Meier method and Cox regression model.
- 24-week CDP was defined as an increase of ≥1.0 point from the baseline EDSS score if the baseline score was ≤5.5 or an increase of ≥0.5 points if the baseline score was >5.5, sustained for at least 24 weeks.
- 24-week CDI was defined as a reduction from the baseline EDSS score of ≥1.0 point, or ≥0.5 points if the baseline EDSS score was >5.5, sustained for at least 24 weeks.
- Safety analysis contains patients treated with UBL in DBP and OLE, and patients who received UBL in the OLE phase after switching from TER. COVID events were excluded.

RESULTS

- Patient Disposition
- Annualized Relapse Rate
- Confirmed Disability Progression
- Confirmed Disability Improvement
- Safety
- IgM Levels
- IgG Levels

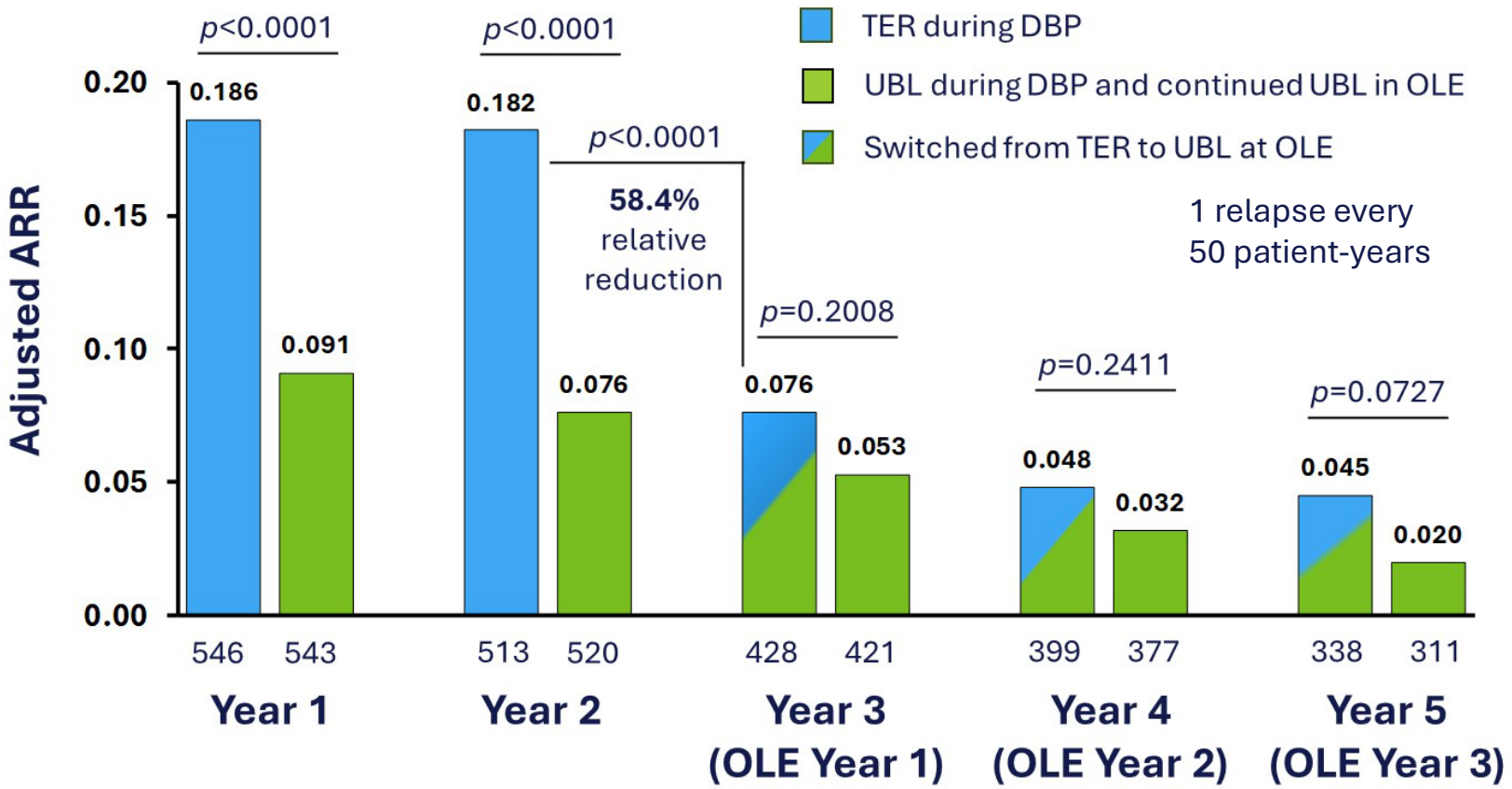
Figure 1: Patient disposition in ULTIMATE I/II and OLE phase



- In the pooled ULTIMATE I and II groups, upon completion of DBP, over 85% of participants from each treatment arm entered OLE **(Figure 1).**
- 85.4% (N=422) continued UBL treatment and entered OLE, and 87.4% (N=429) switched from TER in DBP to UBL in OLE.
- 70.4% and 76.2% completed 3-year UBL treatment during OLE in the continuous and switch cohorts, respectively.

*OLE period:15-Nov-2019 until data cutoff on 01-Jan-2024. DBP = Double-blind period; OLE = Open-label extension. Patients completing DBP had to re-enroll for OLE. The median gap between DBP and OLE was approximately 8 months.

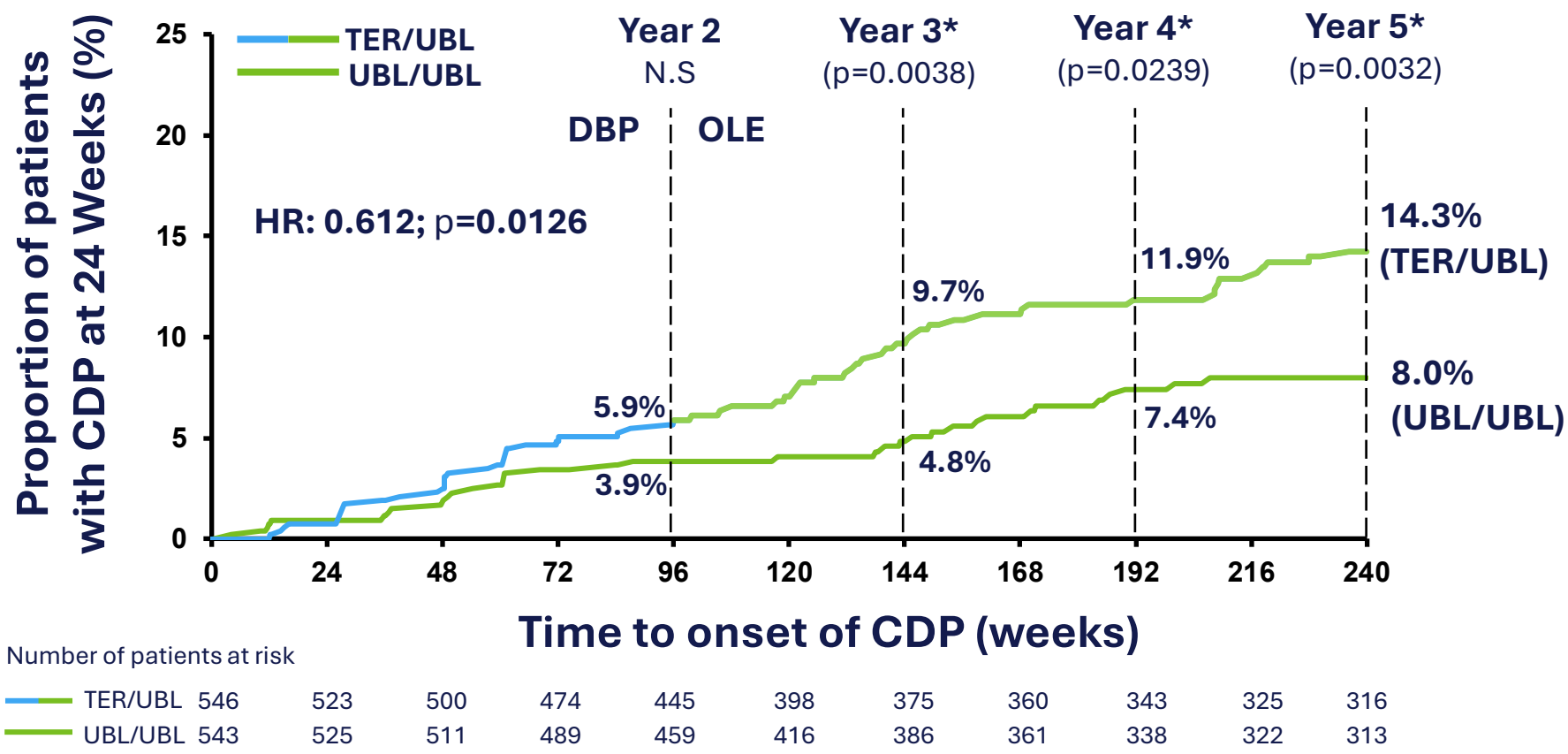
Figure 2: Annualized relapse rates (ARR) during Years 1 and 2 of DBP and Years 1-3 of OLE



- During OLE Year 1, patients who switched from TER to UBL experienced a significant reduction [-58.4%] in ARR [0.182 vs 0.076], with rate ratio (95% CI): 0.416 (0.289, 0.599), $p<0.0001$ **(Figure 2).**
- Patients who continued UBL 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 TER to UBL also showed decreasing ARR with slightly higher rates compared to continuous UBL group [ARR: 0.076, 0.048, and 0.045 for Years 3, 4, and 5, respectively]
- At Year 5 of continuous UBL treatment, patients exhibited a relapse rate corresponding to 1 relapse every 50 patient-years (PY).

Data Cutoff: 01-Jan-2024. DBP = Double-blind period; OLE = Open-label extension; TER = Teriflunomide; UBL = Ublituximab; GEE = Generalized Estimating Equation model for the relapse count per patient 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. Independent Relapse Adjudication Panel (IRAP) evaluated each case based on all available relapse data provided by treating and blinded examining neurologist. The IRAP made the final determination of whether the neurological events met the criteria for a protocol-defined relapse.

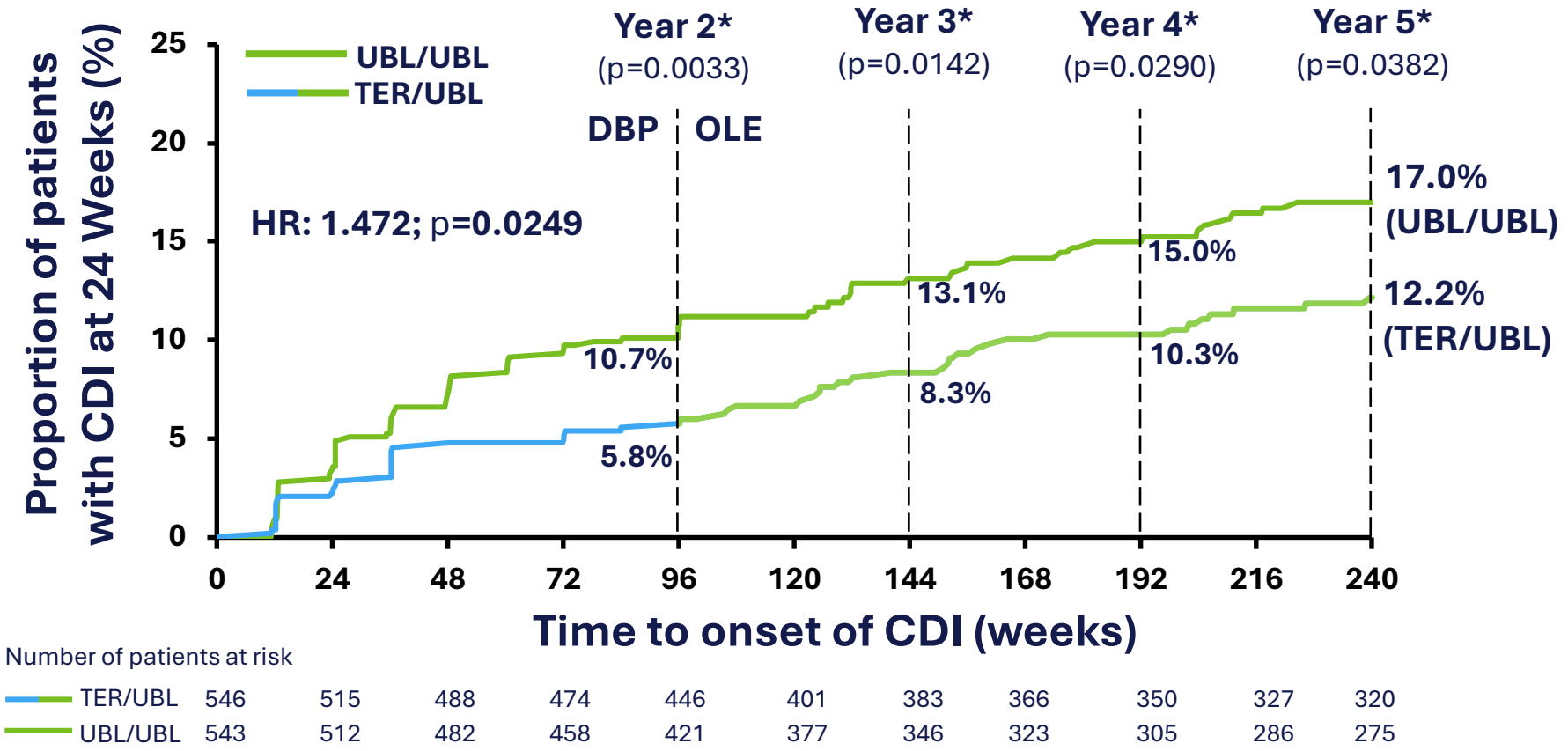
Figure 3: Time to onset of Confirmed Disability Progression (CDP) for at least 24 weeks



Data Cutoff: 01-Jan-2024. The 24-week CDP was derived for OLE based on Double Blinded Phase EDSS baseline. DBP = Double-blind period; HR = hazard ratio; OLE = Open-label extension; TER = Teriflunomide; UBL= Ublituximab; N.S = not significant
*Estimation by Kaplan-Meier method & hazard ratio is estimated using Cox regression model with treatment group as covariate. Time to onset of CDP is the time from randomization in DBP to the onset of CDP, including gap period between DBP and OLE where applicable.

- Over 5 years of treatment with UBL, 24-week CDP remained very low, and the risk of CDP was reduced by 38.8% in patients receiving continuous UBL therapy compared with those switching after 2 years of TER to UBL: hazard ratio (95% CI): 0.612 (0.414, 0.904); *p*=0.0126 **(Figure 3).**
- At the end of OLE Year 1 (Year 3 since randomization), the proportion of patients with 24-week CDP was 4.8% vs 9.7% for UBL-UBL and TER-UBL, respectively; *p*=0.0038.
- At end of Year 4 and Year 5 since randomization, 24-week CDP was observed in 7.4% vs 11.9% (*p*=0.0239), and 8.0% vs 14.3% (*p*=0.0032) of patients, respectively.

Figure 4: Time to onset of Confirmed Disability Improvement (CDI) for at least 24 weeks



Data Cutoff: 01-Jan-2024. The 24-week CDI was derived for OLE based on Double Blinded Phase EDSS baseline. DBP = Double-blind period; HR = hazard ratio; OLE = Open-label extension; TER = Teriflunomide; UBL= Ublituximab

*Estimation by Kaplan-Meier method & hazard ratio is estimated using Cox regression model with treatment group as covariate. Time to onset of CDI is the time from randomization in DBP to the onset of CDI, including gap period between DBP and OLE where applicable.

- Over 5 years of treatment with UBL, the likelihood to achieve 24-week CDI was 47.2% higher in patients receiving continuous UBL therapy compared with those switching after 2 years of TER to UBL: hazard ratio (95% CI): 1.472 (1.048, 2.067); *p*=0.0249 **(Figure 4).**
- At the end of OLE Year 1 (Year 3 since randomization), the proportion of patients with 24-week CDI was 13.1% vs 8.3% for UBL-UBL and TER-UBL, respectively; *p*=0.0142
- At the end of Year 4 and Year 5 since randomization, 24-week CDI was observed in 15.0% vs 10.3% (*p*=0.0290), and 17.0% vs 12.2% (*p*=0.0382) of patients, respectively.

RESULTS

Safety

- The rate of all AEs were calculated using exposure-adjusted incidence rate (EAIR) per 100 PY with 95% CI. Treatment-emergent adverse events (TEAE) in the overall UBL population in the pooled DBP+OLE period was 205.08 [200.46, 209.81], which was lower than the rate observed in UBL cohort from DBP (374.84 [363.79, 386.22]) **(Figure 5).**
- The EAIR per 100 PY [95% CI] for serious adverse events (SAE) in the pooled UBL cohort was 5.88 [5.14, 6.73], which was consistent with the rate observed in DBP (5.59 [4.37, 7.14]).
- Overall infection rate (any grade) was lower in the pooled UBL cohort (48.61 [46.39, 50.94]) compared to DBP (80.92 [75.88, 86.30]).
- Rates of serious infections remained consistent between pooled UBL (2.58 [2.11, 3.16]) and DBP (2.10 [1.40, 3.13]) cohorts.
- IRRs were lower in the pooled UBL cohort (26.69 [25.06, 28.43]) compared to DBP (54.12 [50.02, 58.55]).
- Incidence rate of all malignancies was 0.17 [0.07, 0.37] in the pooled UBL cohort, which was consistent with DBP (0.17 [0.04, 0.70]).

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RESULTS

Safety (cont.)

- TEAE leading to treatment discontinuation in the overall UBL population in the pooled DBP+OLE period was 1.69 [1.32, 2.18], which was consistent with DBP (1.66 [1.06, 2.60]).
- No cases of PML were identified in the overall UBL exposed population in the pooled ULTIMATE DBP and OLE studies, as of the analysis cutoff date of January 1, 2024.
- The overall safety profile remained consistent with up to 5 years of continuous UBL treatment.

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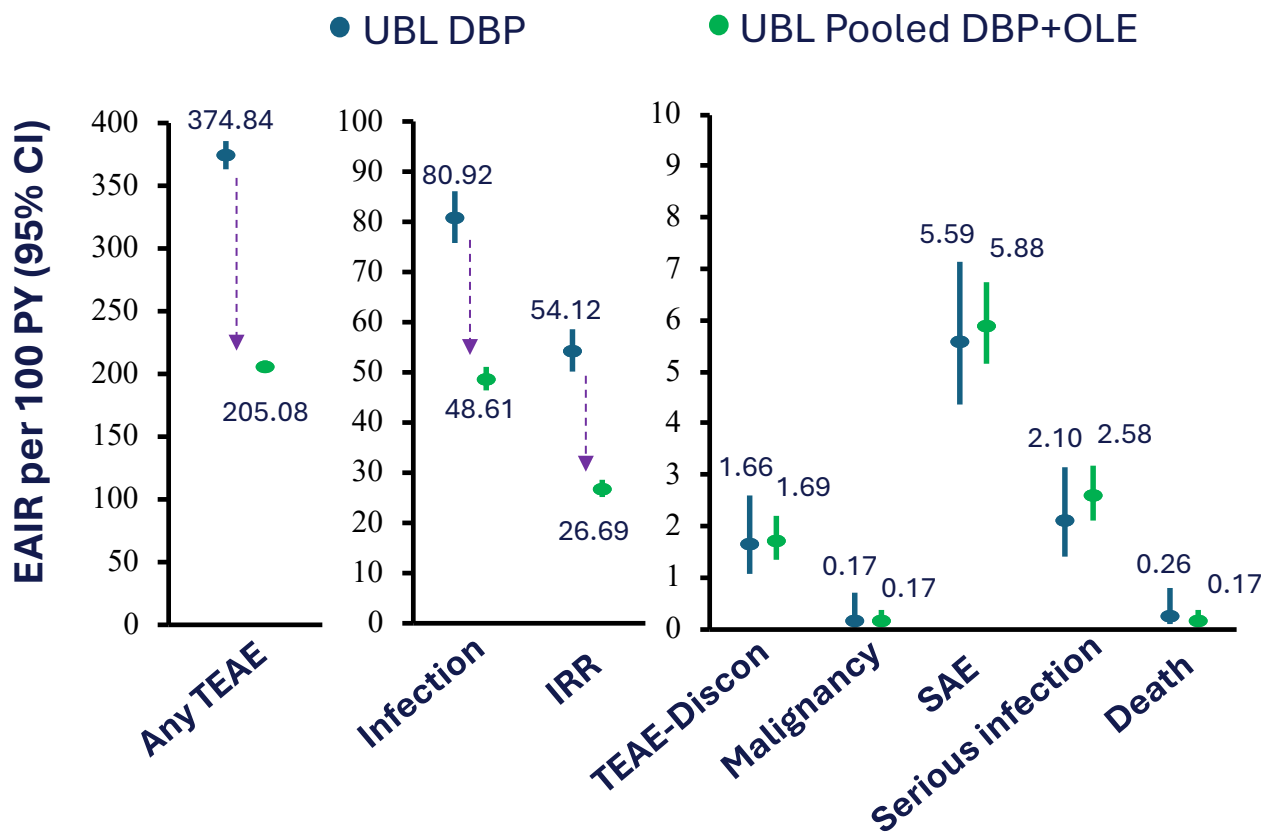
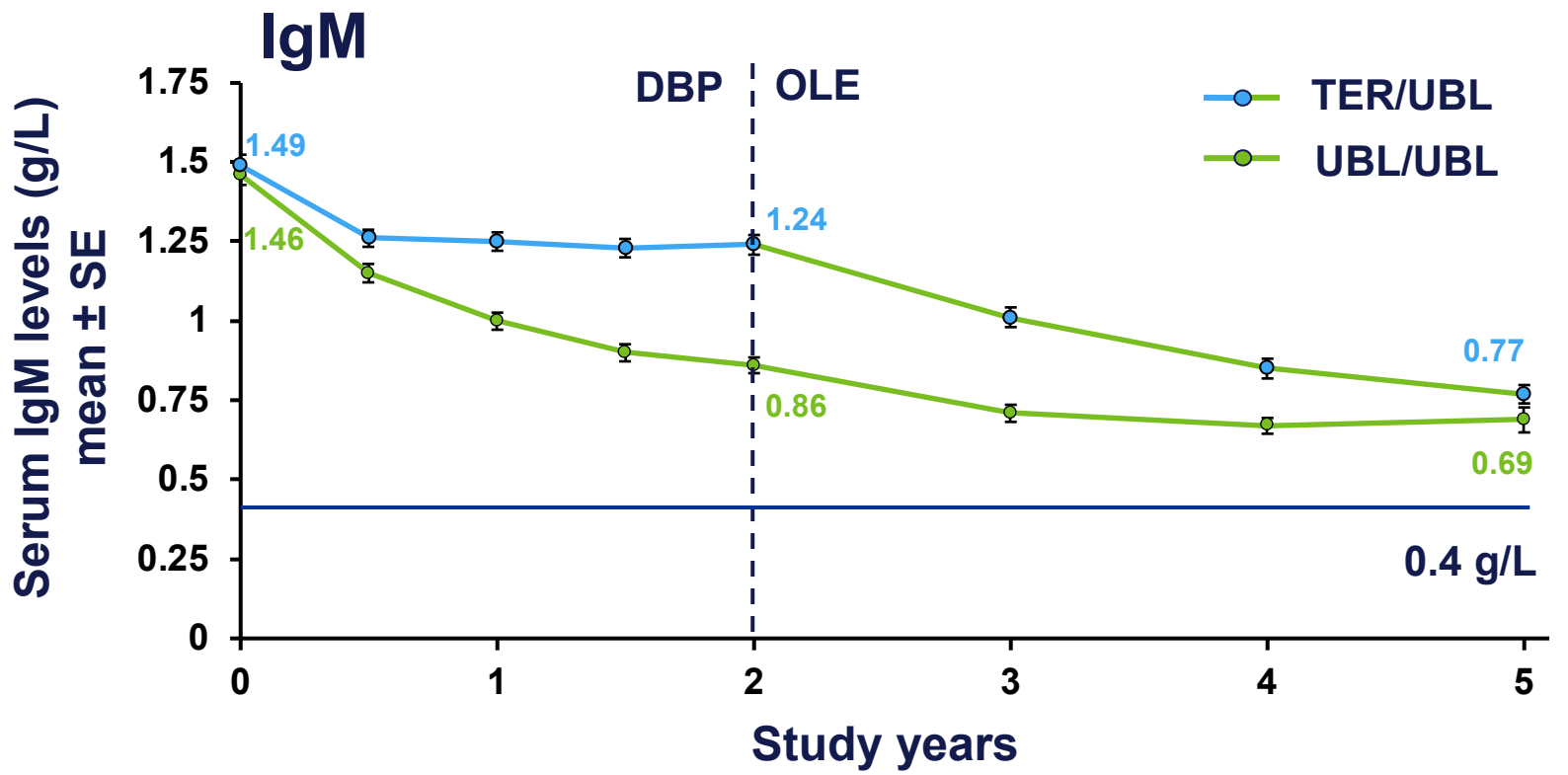
Figure 5: Safety summary for Ublituximab group from DBP and pooled DBP+OLE phases of ULTIMATE I and II



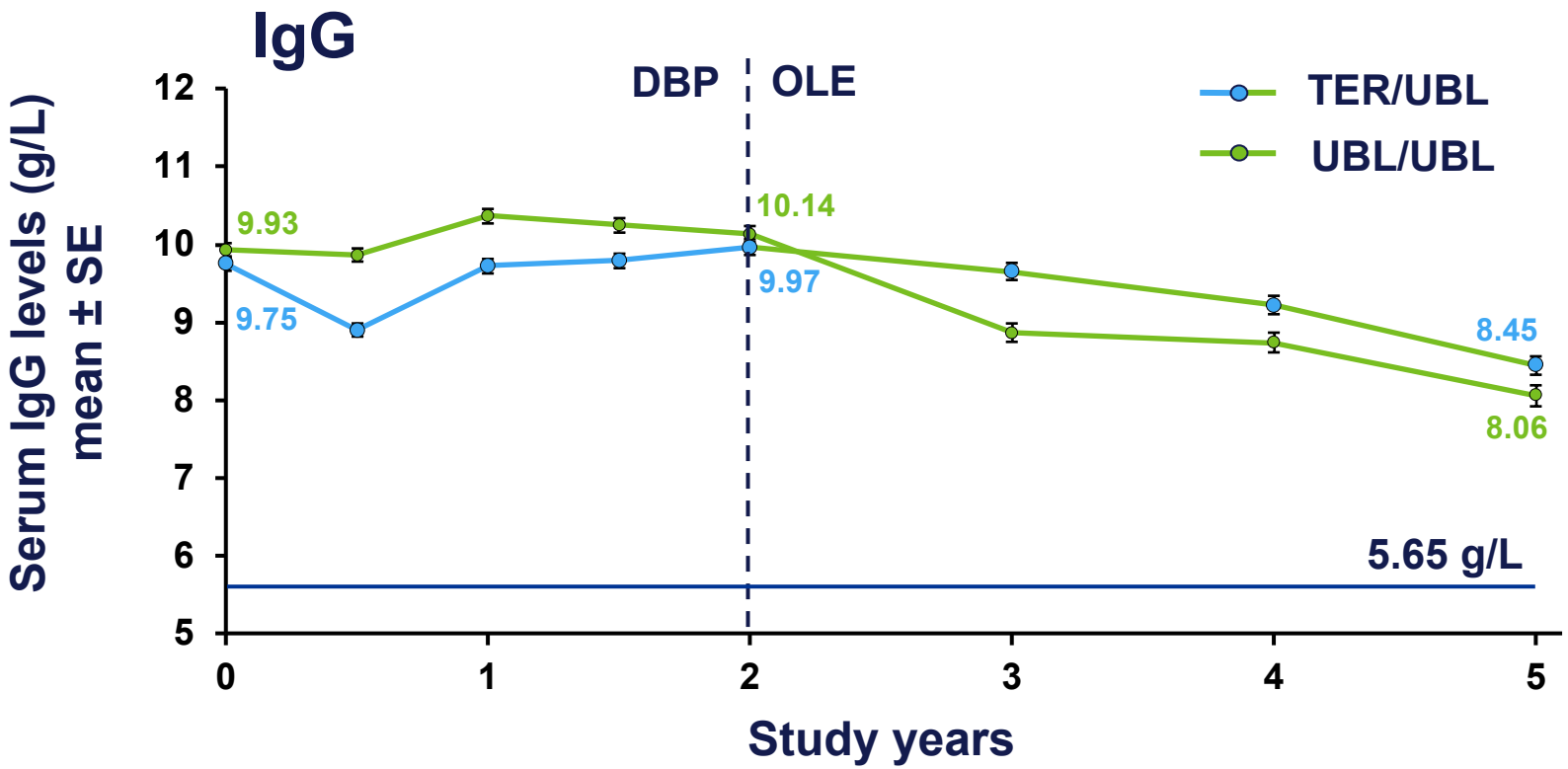
DBP = Double-blind phase; OLE = Open-label extension (OLE period:15-November-2019 until data cutoff on 01-January-2024);UBL = Ublituximab; EAIR = Exposure- adjusted incidence rate as number of events per 100 patient years; PY = Patient years; CI = confidence interval; TEAE = Treatment-emergent adverse events; IRR = Infusion-related reactions; TEAE-Discon = Treatment-emergent adverse events leading to treatment discontinuation; SAE: Serious adverse events; SI: Serious infections. COVID events were excluded from analysis. Pooled DBP+OLE: All patients who received at least 1 dose of ublituximab during Phase 3 double-blind and open-label extension period. DBP period: All patients who received at least 1 dose of ublituximab during ULTIMATE I/II Phase 3 double-blind period. Discontinuations during DBP period do not include discontinuations associated with oral placebo treatment. Infusion-related reaction is based on Investigator-flagged events. Malignancy represents cancer diagnoses and does not include all neoplasms (e.g. benign growths) within the associated System Organ Class (SOC). During DBP, deaths in ublituximab group were due to pneumonia (deemed to be possibly related to treatment), encephalitis (after measles), and salpingitis (after ectopic pregnancy). During OLE alone, deaths were due to pneumonia, viral encephalitis, and non-specific interstitial pneumonia.

Figure 6: IgM levels remained above LLN over the 5-year period for patients treated with ublituximab



- Immunoglobulin levels remained stable during OLE, and the mean IgM levels remained above the LLN.
- In the continuous cohort that received UBL for at least 5 years, the mean (SE) IgM levels were 0.69 (0.04) g/L. The IgM levels remained stable and above the LLN (0.4 g/L) **(Figure 6).**

Figure 7: IgG levels remained above LLN over the 5-year period for patients treated with ublituximab



- Immunoglobulin levels remained stable during OLE, and the mean IgG levels remained above the LLN.
- In the continuous cohort that received UBL for at least 5 years, the mean (SE) IgG levels were 8.06 (0.13) g/L. The IgG levels remained stable and above the LLN (5.65 g/L) **(Figure 7).**

Conclusions

- Early initiation of UBL and continued treatment over a period of 5 years provided MS patients with sustained clinical benefit.
- The ARR in Year 5 of continuous treatment with UBL was 0.02, equivalent to one relapse occurring in 50 PY.
- Patients treated with continuous UBL exhibited a lower rate of disability progression compared to those initially treated with TER, suggesting a potential benefit of early initiation of high-efficacy disease-modifying therapies.
- The overall safety profile of UBL remained consistent over 5 years of continuous treatment in an exposure-adjusted analysis of AEs, with no new safety signals emerging with prolonged treatment.
- Immunoglobulin levels remained stable with prolonged treatment, and the mean IgM and IgG levels remained above the LLN. There was no association between decreased immunoglobulin levels and risk of serious infections.

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DISCLOSURES

Dr. Cree is a consultant for Alexion, Atara, Autobahn, Avotres, Biogen, EMD Serono, Gossamer Bio, Horizon, Neuron23, Novartis, Sanofi, TG Therapeutics and Therini; and receives grant/research support from Genentech; and is also on the advisory board for Autobahn. Dr. Hartung has received honoraria for consulting and speaking at symposia from Bayer Pharma AG, Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, Teva, and Sanofi-Aventis, with approval by the rector of Heinrich-Heine University. Dr. Alvarez has received compensation for advisory boards, lectures, and consultancy with Actelion/Janssen, Alexion, Bayer, Biogen, Celgene/BMS, EMD Serono/Merck, Genentech/Roche, Genzyme, Novartis, Sanofi, and TG Therapeutics, and research support from Biogen, Genentech/Roche, Novartis, TG Therapeutics, Patient Centered Outcomes Research Institute, National Multiple Sclerosis Society, National Institutes of Health, and Rocky Mountain MS Center. Dr. Qian has received speaking and consulting honoraria from Biogen, BMS, Genzyme, Genentech, Viela Bio, and TG Therapeutics. Dr. Wray has received compensation for serving on a Scientific Advisory or Data Safety Monitoring board for Biogen, Bristol Myers Squibb/Celgene, EMD Serono, Novartis, Roche/Genentech, and Sanofi/Genzyme; and has received compensation for serving on a Speakers Bureau for Biogen, Bristol Myers Squibb, EMD Serono, Roche/Genentech, and Sanofi/Genzyme. The institution of Dr. Wray has received research support from Biogen, Hope, Bristol Myers Squibb/Celgene, Novartis, Roche/Genentech, Sanofi/Genzyme, and TG Therapeutics. Dr. Robertson has received grant support from Anokion, Atara Biotherapeutics, Biogen, CorEvitas, EMD Serono, Genentech, GW Pharmaceuticals, Janssen, Novartis, PCORI, PRIME CME, Sanofi, and TG Therapeutics; has received consulting fees from Alexion, Biogen, Bristol Myers Squibb, EMD Serono, Genentech, Greenwich Biosciences, Horizon, Janssen, Mallinckrodt, Novartis, Sanofi, and TG Therapeutics; has received honoraria or speaker fees from Alexion, Biogen, Bristol Myers Squibb, EMD Serono, Genentech, Horizon, Janssen, PRIME CME, Sanofi and TG Therapeutics. Dr. Huang has received consultant and/or speaker fees for Biogen, Novartis, and Teva Neuroscience. Dr. Selmaj has received honoraria for speaking, consulting, and serving on advisory boards for Merck, Novartis, Roche, Biogen, Celgene, BMS, and TG Therapeutics. Dr. Wynn has received grant support and/or speaking fees from EMD Serono, Genentech/Roche, Novartis, Sanofi, TG Therapeutics, Bristol Myers Squib, Mallinckrodt, Eli Lilly, Immunic, MAPI Therapeutics, Viatris, Innocare, Kyverna, and Abata. Dr. Fox, Koby Mok, Yanzhi Hsu, Yihuan Xu, Chris Rowland, Karthik Bodhinathan, Peter Sportelli, Jackie Parker, and Hari P. Miskin are all employees of TG Therapeutics, Inc. Dr. Steinman has received compensation for consulting with TG Therapeutics.