

Seven-Year Safety and Efficacy Outcomes for Ublituximab Treatment in Relapsing MS



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CONCLUSIONS

- Early initiation of UBL and continued treatment over a period of 7 years provided MS patients with sustained clinical benefit.
- The ARR at Year 7 of continuous treatment with UBL was 0.018.
- Patients treated with UBL continuously exhibited a lower rate of disability progression compared to those initially treated with TER, demonstrating the benefits of early initiation of high-efficacy disease-modifying therapies.
- The overall safety profile of UBL remained consistent over 7 years of continuous treatment in an exposure-adjusted analysis of AEs.
- Mean serum IgG and IgM levels remained above LLN on continuous UBL treatment for 7 years.

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DISCLOSURES:

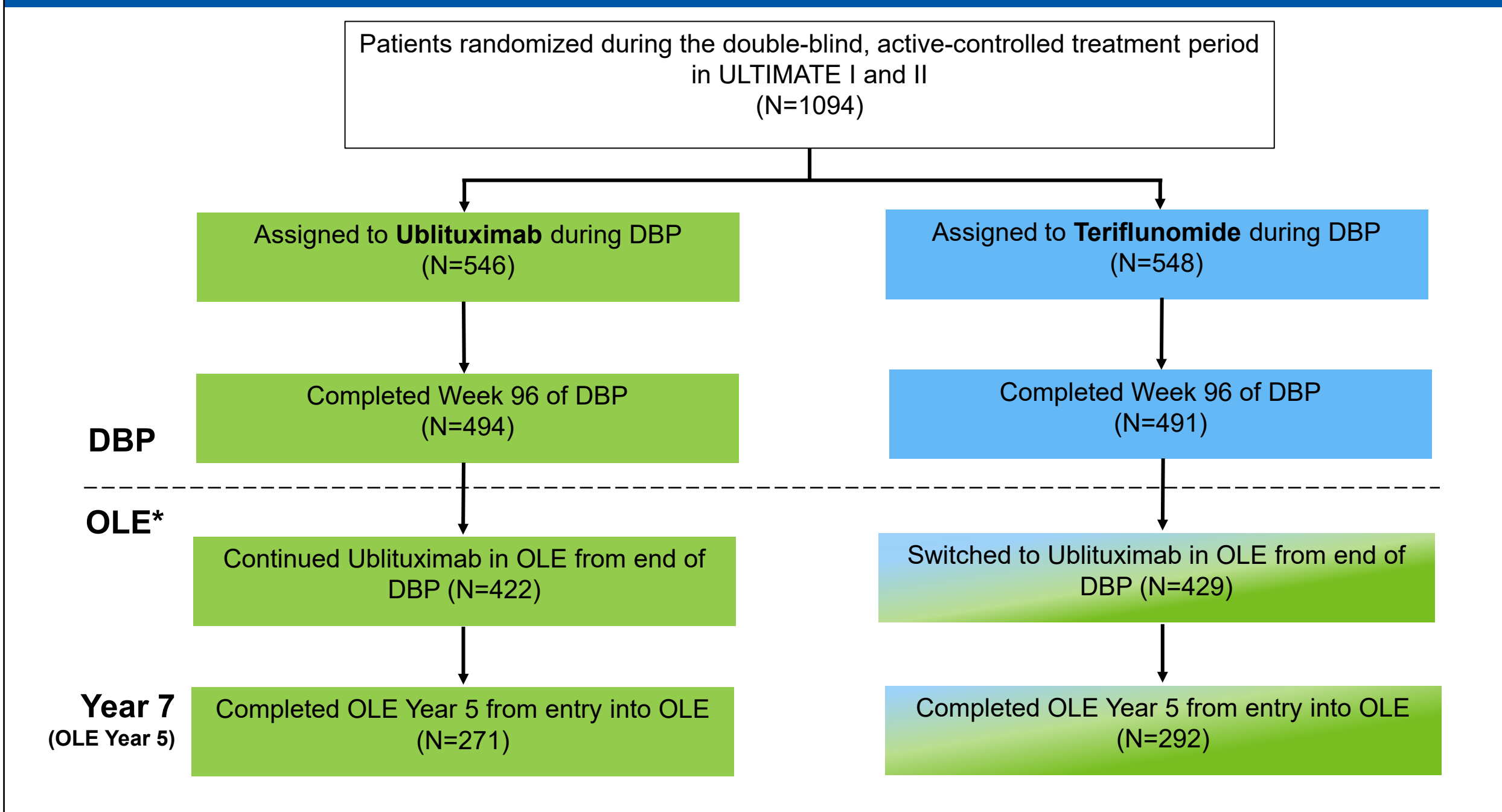
Bruce Cree has received honoraria for consulting from Alexion, Alumis, Avotres, Biogen, Boston Pharma, EMD Serono, Hexal/Sandoz, Horizon, Immunic AG, Kyvera, Neuron23, Novartis, Sanofi, Siemens and TG Therapeutics and received research support from Genentech and Kyvera and is on an advisory board for 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. 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 Squibb, Mallinckrodt, Eli Lilly, Immunic, MAPI Therapeutics, Viatrix, Innocare, Kyvera, 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.

BACKGROUND

- Ublituximab (UBL) is a novel monoclonal antibody that targets a unique epitope of CD20 and is glycoengineered for enhanced antibody-dependent cellular cytotoxicity (ADCC)¹ and Fcγ-receptor (FcγR) binding, enabling administration at lower doses with shorter infusion times.^{1,2,3}
- Ublituximab, approved for relapsing multiple sclerosis (RMS) in adults, demonstrated significant clinical benefit vs teriflunomide (TER) in two identical Phase 3, randomized, multicenter, double-blind, active-control studies evaluating the efficacy and safety of UBL versus TER over approximately 2 years in participants with relapsing multiple sclerosis (RMS), in ULTIMATE I and II.⁴
- These benefits were sustained through 6 years of continuous UBL treatment.^{5,6}
- Results from 2 years of the double-blind period (DBP) and 5 years of the open-label extension (OLE) have yielded 7 years of long-term data on the safety and efficacy of ublituximab, which are presented here.

RESULTS

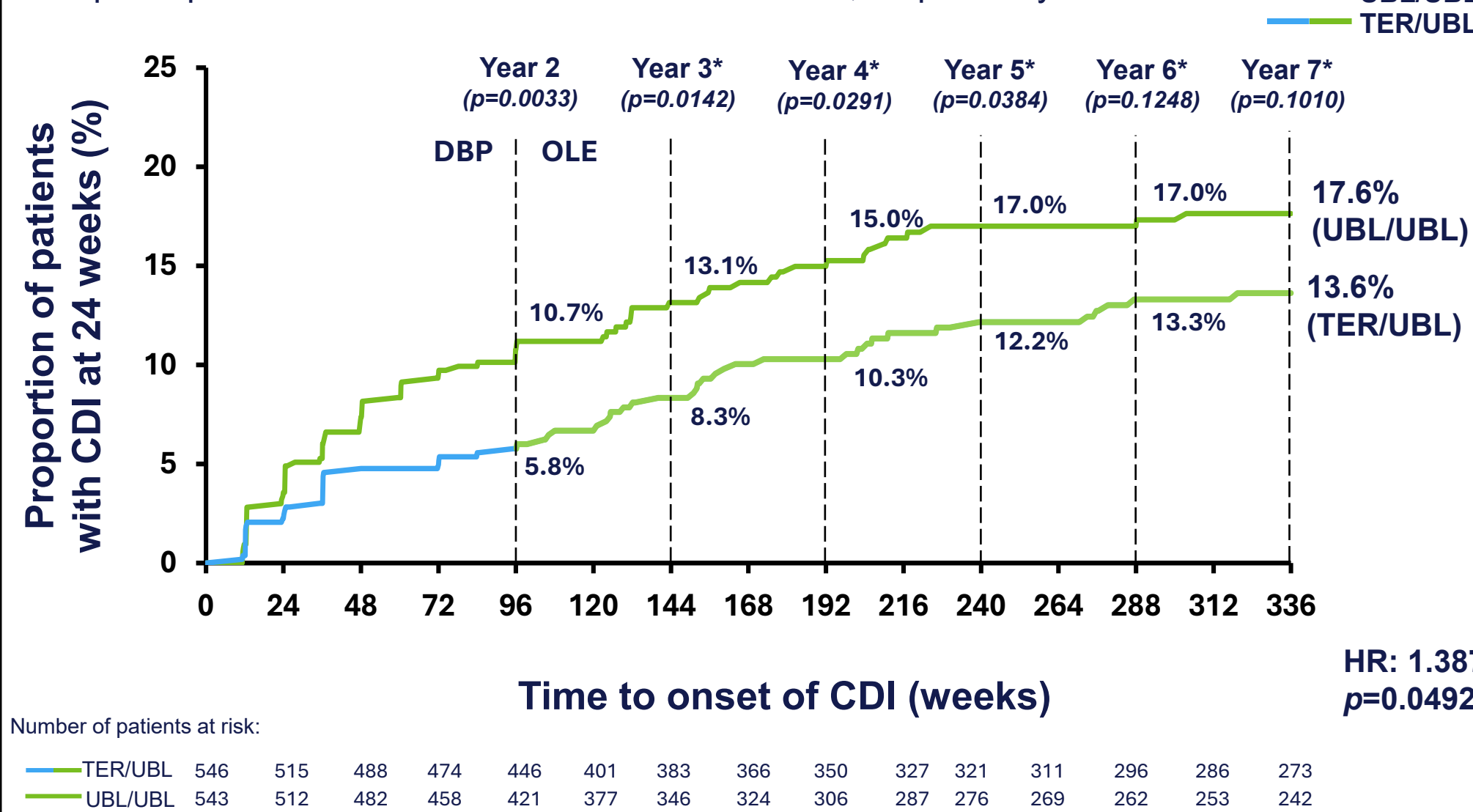
Figure 1. Patient Disposition During 7 Years of ULTIMATE I/II and OLE



*OLE period: 15-Nov-2019 until data cutoff on 31-Dec-2025. 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. Overall, reasons for discontinuation were mostly due to withdrawal by subject (12.8%), adverse event (7.2%), investigator/sponsor decision (2.0%), lost to follow-up (1.4%), and other reasons (3.4%).

Figure 4. 24-Week CDI during 7 Years of Ublituximab Treatment

- At Year 7 since randomization, 24-week CDI was observed in 17.6% and 13.6% (p=0.0492) of participants in the continuous and switch cohorts, respectively.

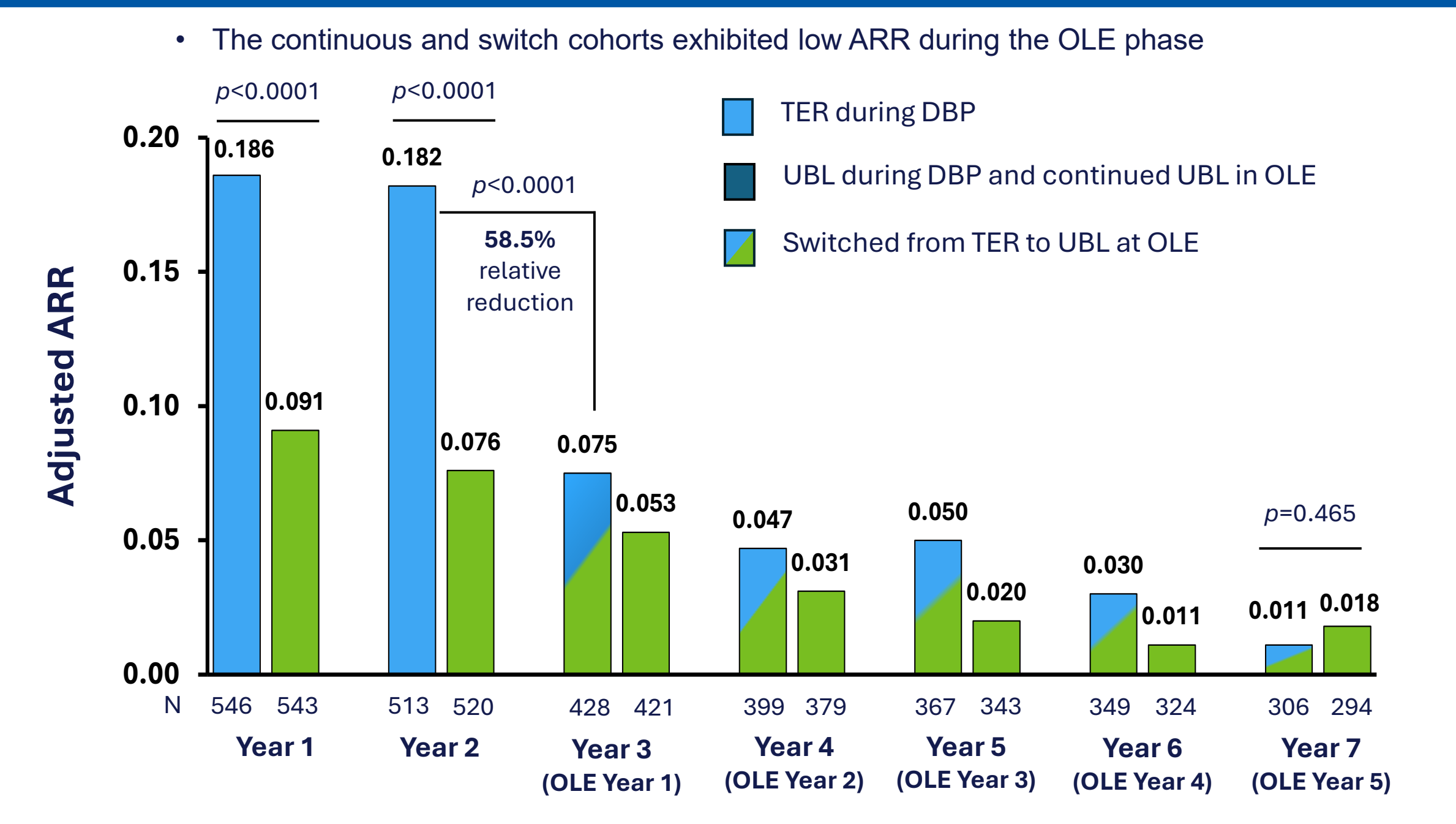


The 24-week CDI was derived for OLE based on Double Blinded Period EDSS baseline. CDI = Confirmed Disability Improvement; DBP = Double-blind period; HR = hazard ratio; N.S. = not significant. OLE = Open-label extension; TER = Teriflunomide; UBL = Ublituximab. *Estimation by Kaplan-Meier method & hazard 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.

METHODS

- After 2 years of randomized, active-controlled treatment during the DBP in ULTIMATE I (N=549) and II (N=545) studies, RMS patients either continued UBL treatment (UBL-UBL) or switched from TER to UBL (TER-UBL).
- All safety and efficacy analyses were based on the pooled ULTIMATE I and II participants, who received at least one dose of UBL in the DBP and OLE.⁵
- Adjusted annualized relapse rate (ARR) was analyzed using generalized estimating equations. The 24-week Confirmed Disability Progression (CDP) and 24-week Confirmed Disability Improvement (CDI) were estimated by the Kaplan-Meier method and a 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 analyses were performed on 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.
- All patients with evaluable data as of 31 December 2025 were included in the analysis, adding approximately 610 patient-years of exposure to the prior 6-year analysis.⁶

Figure 2. ARR During 7 Years of ULTIMATE I/II and OLE



ARR = Annualized relapse rate; DBP = Double-blind period; OLE = Open-label extension; TER = Teriflunomide; UBL = Ublituximab.

Figure 5. Summary of Safety Outcomes in Ublituximab-Treated Patients During 7 Years of ULTIMATE I/II and OLE

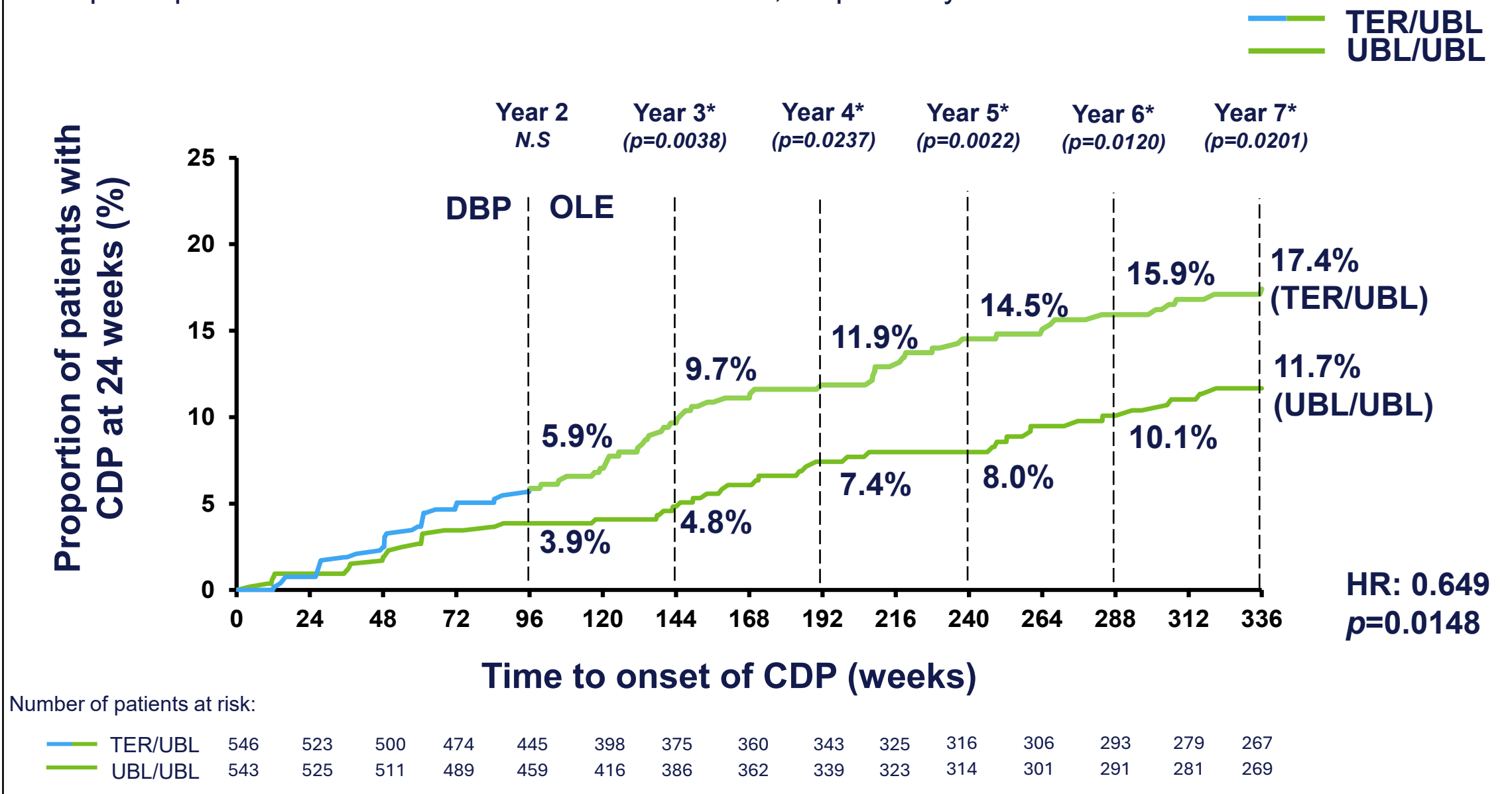
- The overall safety profile of UBL remained consistent over 7 years of continuous treatment in an exposure-adjusted analysis. Overall, the EAIRs remained stable with prolonged treatment.

	Ublituximab, ULTIMATE I/II DBP (n=545, PY=1145.57) EAIR [95% CI]	Ublituximab, Pooled DBP+OLE (n=974, PY=4872.01) EAIR [95% CI]
Any TEAE	374.84 [363.79, 386.22]	183.52 [179.75, 187.36]
TEAE leading to treatment discontinuation	1.66 [1.06, 2.60]	1.77 [1.43, 2.18]
Infection	80.92 [75.88, 86.30]	48.40 [46.48, 50.39]
Infusion-related reaction	54.12 [50.02, 58.55]	19.99 [18.77, 21.29]
Malignancy	0.17 [0.04, 0.70]	0.27 [0.15, 0.46]
Serious adverse event	5.59 [4.37, 7.14]	6.83 [6.14, 7.61]
Serious infection	2.10 [1.40, 3.13]	3.14 [2.68, 3.68]
Death	0.26 [0.08, 0.81]	0.21 [0.11, 0.38]

CI = Confidence interval; DBP = Double-blind period; EAIR = Exposure-adjusted incidence rate as number of events per 100 patient-years; OLE = Open-label extension (OLE period: 15-Nov-2019 until data cutoff on 31-Dec-2025); PY = Patient-years; TEAE = Treatment-emergent adverse event; UBL = Ublituximab. The terms "COVID-19" and "COVID-19 pneumonia" were excluded. DBP included all patients who received at least 1 dose of ublituximab during ULTIMATE I/II Phase 3 double-blind period. Pooled DBP+OLE included all patients who received at least 1 dose of ublituximab during Phase 3 DBP and OLE period. Discontinuations during the DBP do not include discontinuations associated with oral placebo treatment. Infusion-related reactions were 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 the DBP, deaths in ublituximab group were due to pneumonia (deemed to be possibly related to treatment), encephalitis (after measles), and sialpingitis (after ectopic pregnancy). During the OLE phase alone, deaths were due to unknown cause in 2 patients, meningitis/pneumonia/sepsis in 1 patient, meningitis tuberculosis in 1 patient, non-specific interstitial pneumonia in 1 patient, peripheral t-cell lymphoma (unspecified) in 1 patient, and viral encephalitis in 1 patient.

Figure 3. 24-Week CDP during 7 Years of Ublituximab Treatment

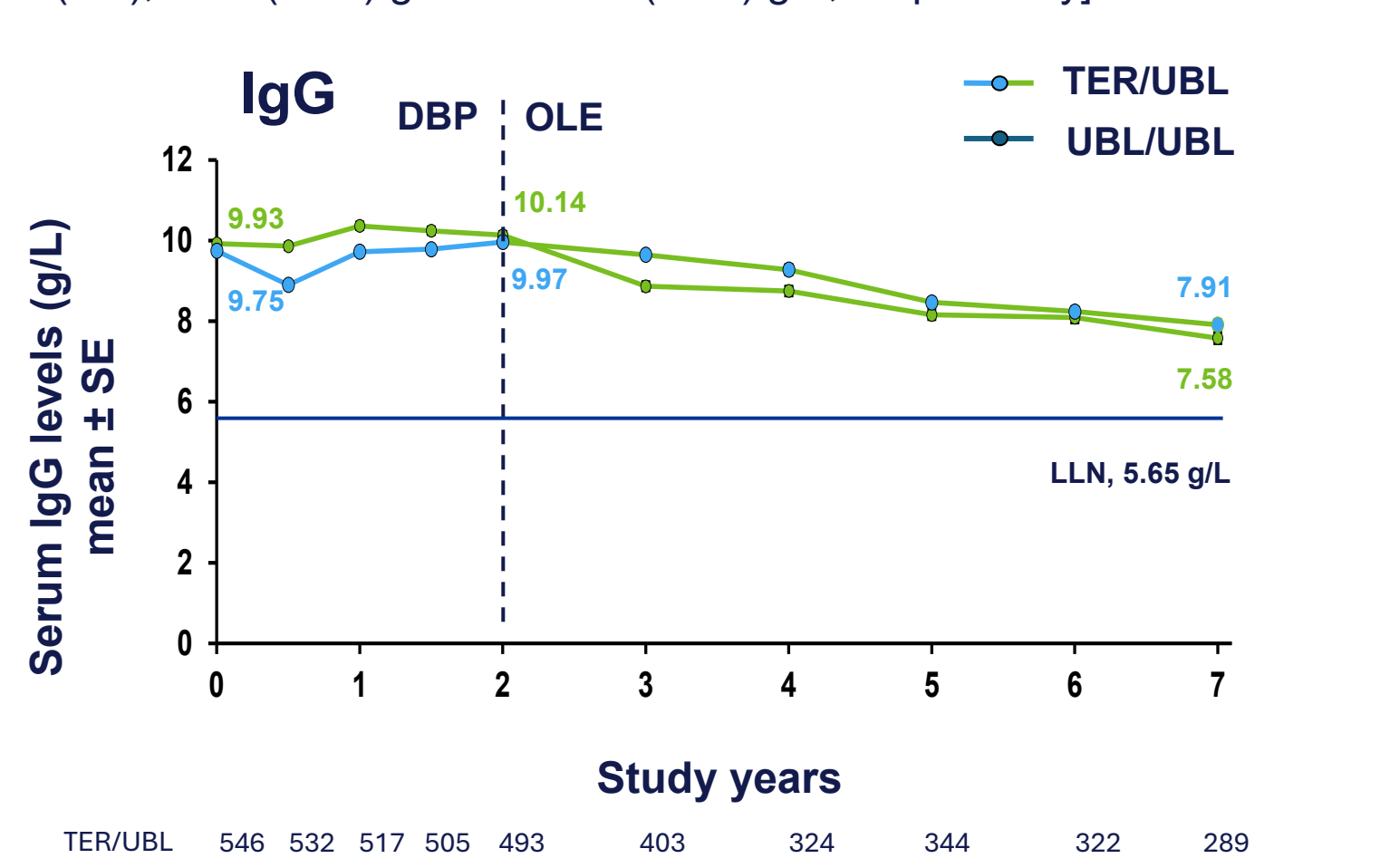
- At Year 7 since randomization, 24-week CDP was observed in 11.7% and 17.4% (p=0.0148) of participants in the continuous and switch cohorts, respectively.



The 24-week CDP was derived for OLE based on Double-blind period EDSS baseline. CDP = Confirmed Disability Progression; DBP = Double-blind period; HR = Hazard ratio; N.S.=not significant; 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 CDP is the time from randomization in DBP to the onset of CDP, including gap period between DBP and OLE where applicable.

Figure 6. IgG Levels in Ublituximab-Treated Participants During 7 Years of ULTIMATE I/II and OLE

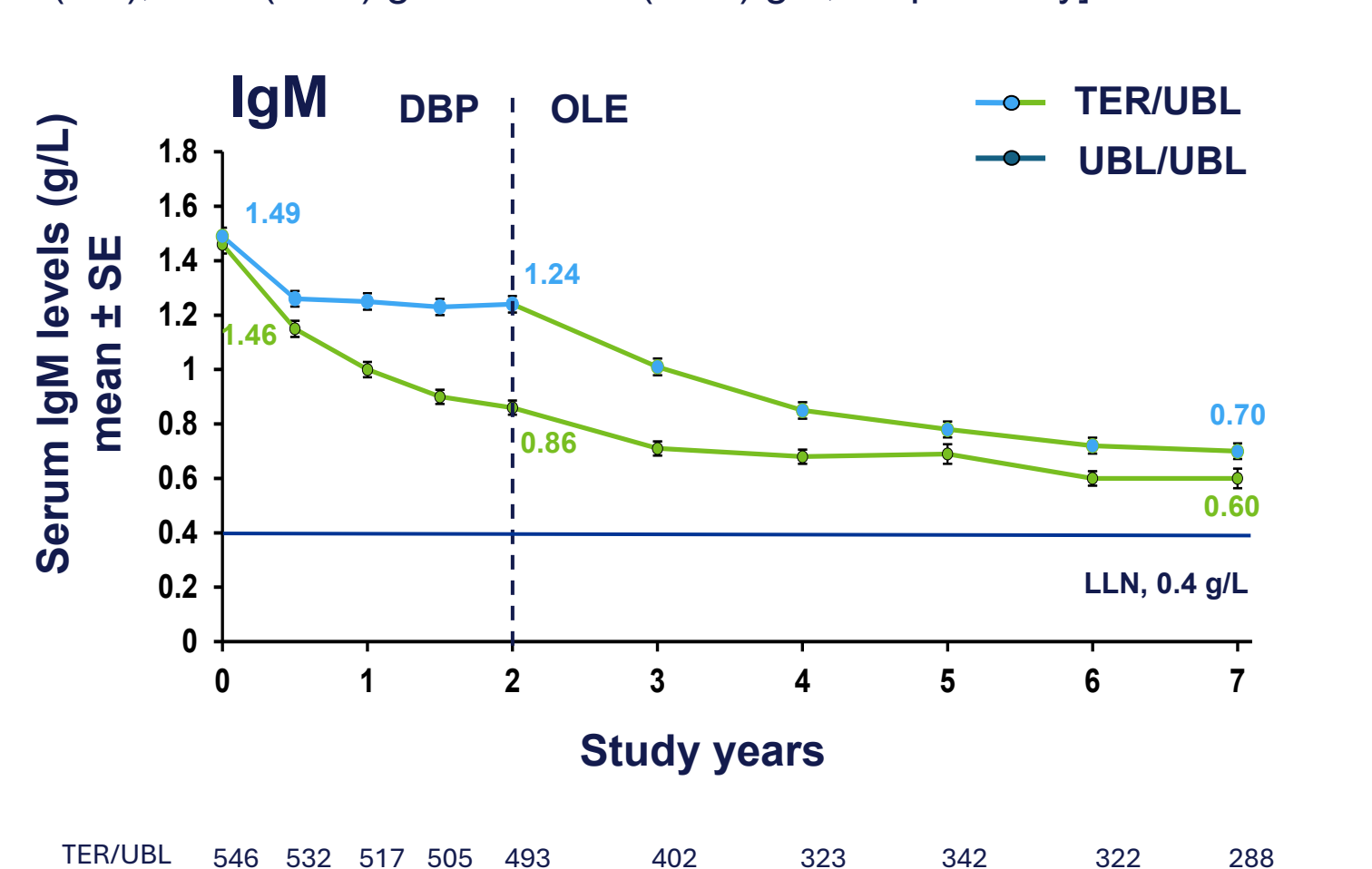
- Mean serum IgG levels remained above LLN for both the continuous UBL treatment and TER to UBL switch cohorts for 7 years [mean (SD), 7.58 (2.29) g/L and 7.91 (2.12) g/L, respectively].



DBP = Double-blind period; LLN = Lower limit of normal; OLE = Open-label extension; TER = Teriflunomide; UBL = Ublituximab

Figure 8. IgM Levels in Ublituximab-Treated Participants During 7 Years of ULTIMATE I/II and OLE

- Mean serum IgM levels remained above LLN for both the continuous UBL treatment and TER to UBL switch cohorts for 7 years [mean (SD), 0.60 (0.58) g/L and 0.70 (0.49) g/L, respectively].



DBP = Double-blind period; LLN = Lower limit of normal; OLE = Open-label extension; TER = Teriflunomide; UBL = Ublituximab