Long-Term Efficacy and Safety of Ublituximab in Relapsing Multiple Sclerosis: Results from 6 Years of ULTIMATE I and II Open-Label Extension

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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, Kyverna, Neuron23, Novartis, Sanofi, Siemens and TG Therapeutics and received research support from Genentech and Kyverna 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 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.

BACKGROUND

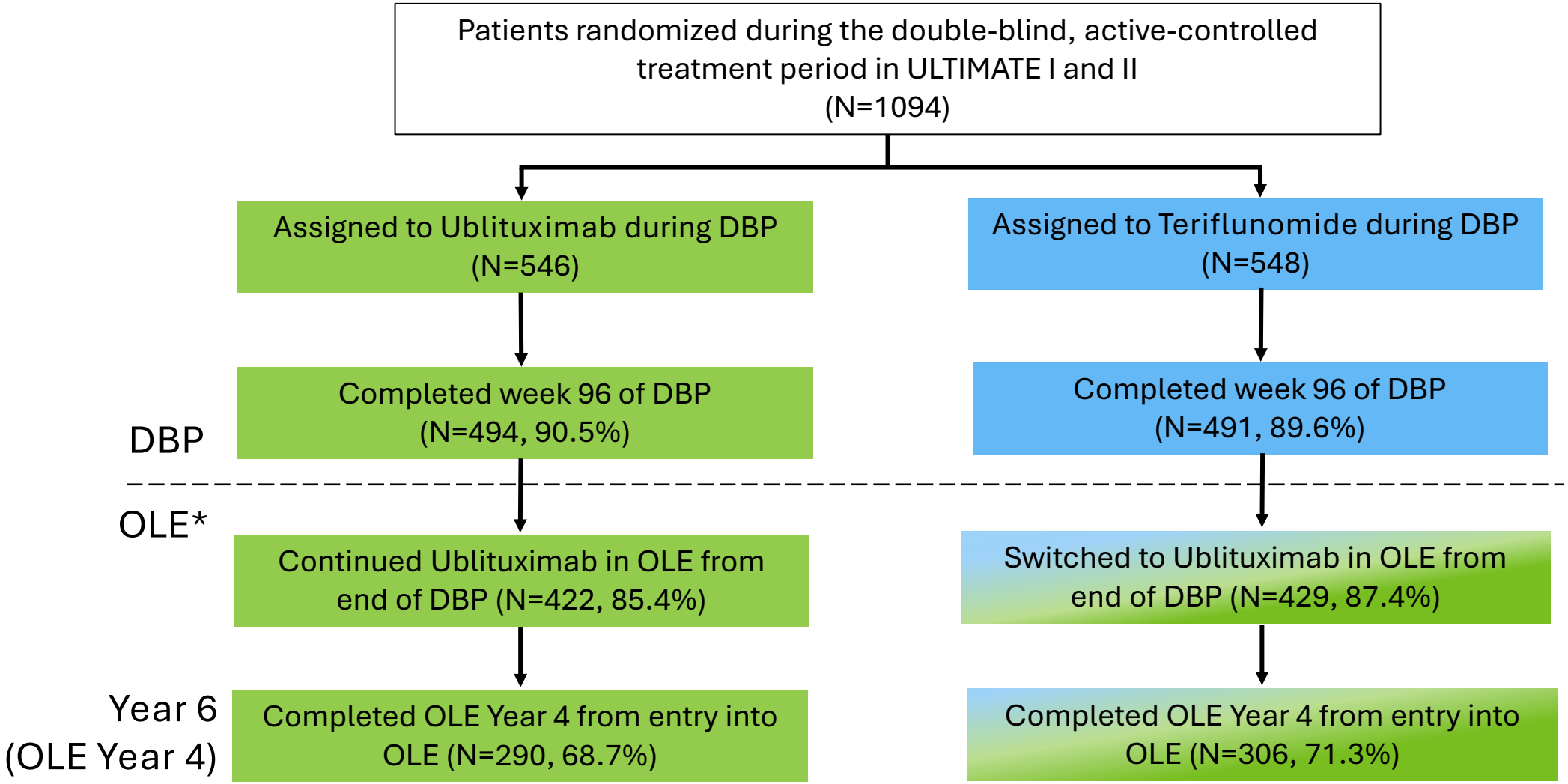
- Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20 and is glycoengineered for enhanced antibody-dependent cellular cytotoxicity (ADCC)[1] and Fcγ-receptor (FcγR) binding, enabling administration at lower doses with shorter infusion times.[1,2,3]
- Ublituximab, approved for treating relapsing multiple sclerosis (RMS) in adults, demonstrated significant clinical benefit vs teriflunomide in two 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), in ULTIMATE I and II.[4]
- These benefits continued to be observed over 5 years during the open-label extension period.[5]
- Results from 2 years of double-blind phase (DBP) and 4 years of open-label extension (OLE) has yielded 6 years of long-term data on safety and efficacy of ublituximab, which are presented here.

METHODS

- After 2 years of randomized, active-controlled treatment during 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 also continued ublituximab treatment during OLE, as presented before.[5]
- 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 analyses 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.
- All patients with evaluable data as of Jan 1, 2025, were included in the analysis, adding approximately 658 patient-years of exposure to the prior 5-year analysis.[5]

Patient disposition during 6 years of ULTIMATE I/II plus OLE

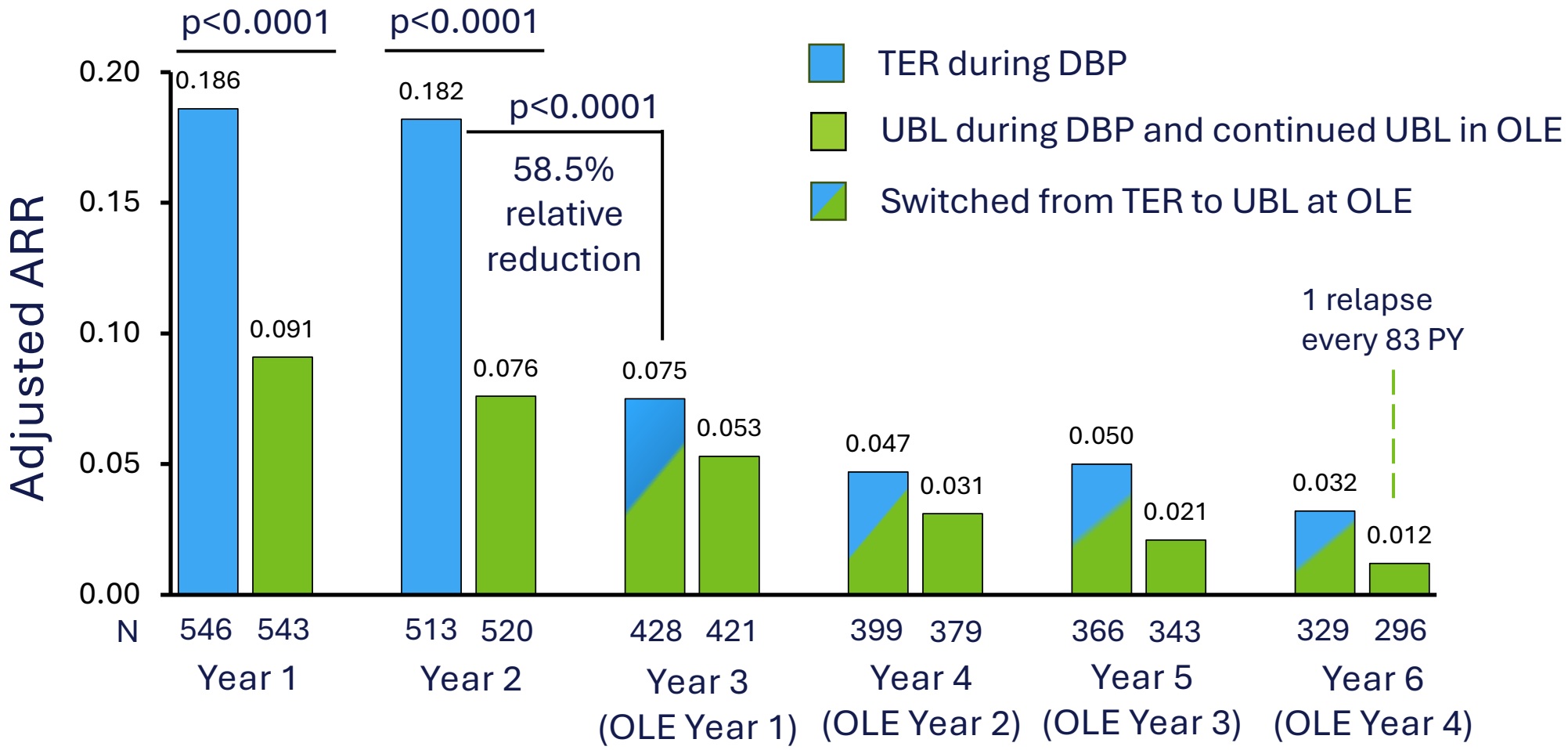
- Upon completion of DBP, over 85% of participants from each treatment arm entered OLE
- 68.7% and 71.3% completed 4-year UBL treatment after entering OLE, in the continuous and switch cohorts, respectively



*OLE period:15-Nov-2019 until data cutoff on 01-Jan-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 (10.9%), adverse event (6.3%), lost to follow-up (1.1%), and other (1.4%).

Annualized relapse rate during 6 years of ULTIMATE I/II plus OLE

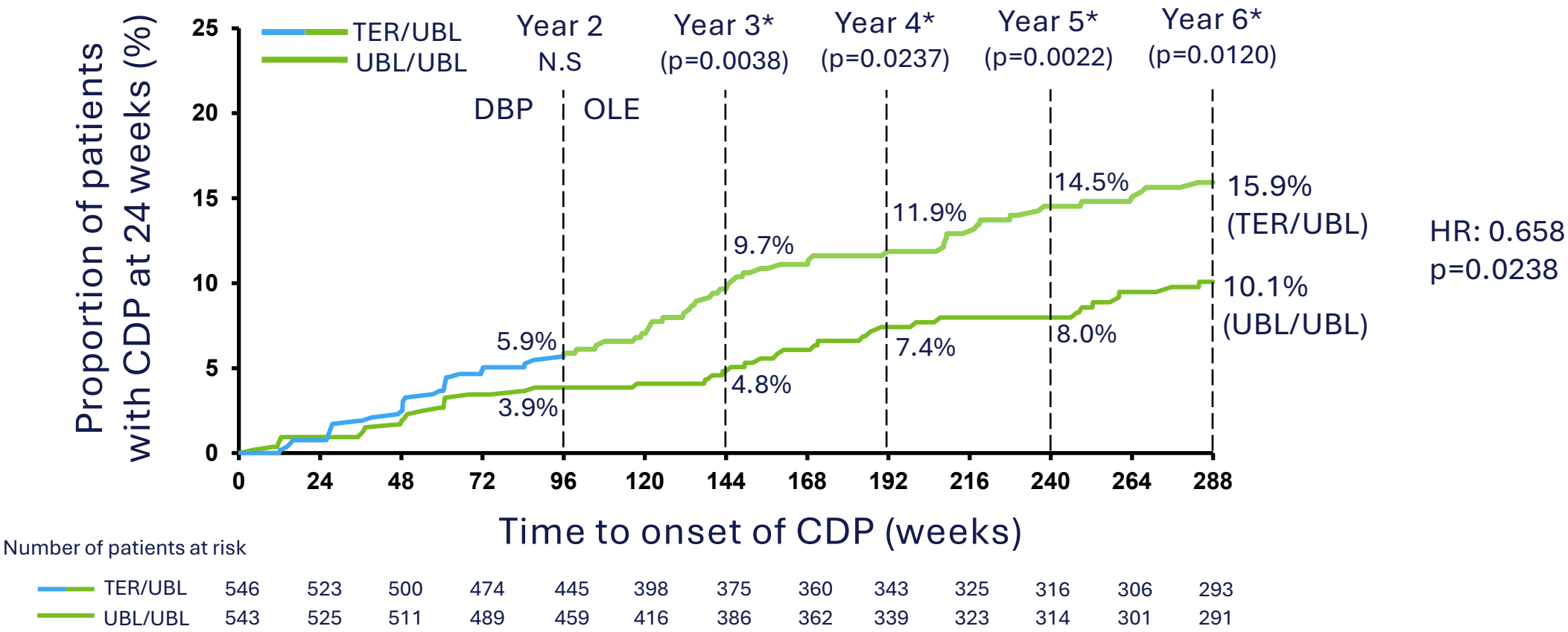
- Both the continuous and switch cohorts exhibited low and decreasing ARR during the OLE phase
- An ARR of 0.012 was observed for the continuous cohort at year 6, corresponding to 1 relapse every 83 PY
- During OLE Year 1, patients who switched from TER to UBL experienced a significant reduction in ARR (58.5%)



Data Cutoff: 1-Jan-2025. DBP = Double-blind period; OLE = Open-label extension; TER = Teriflunomide; UBL = Ublituximab; PY = Patient-years, 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.

24 week Confirmed Disability Progression (CDP) observed during 6 years of Ublituximab treatment

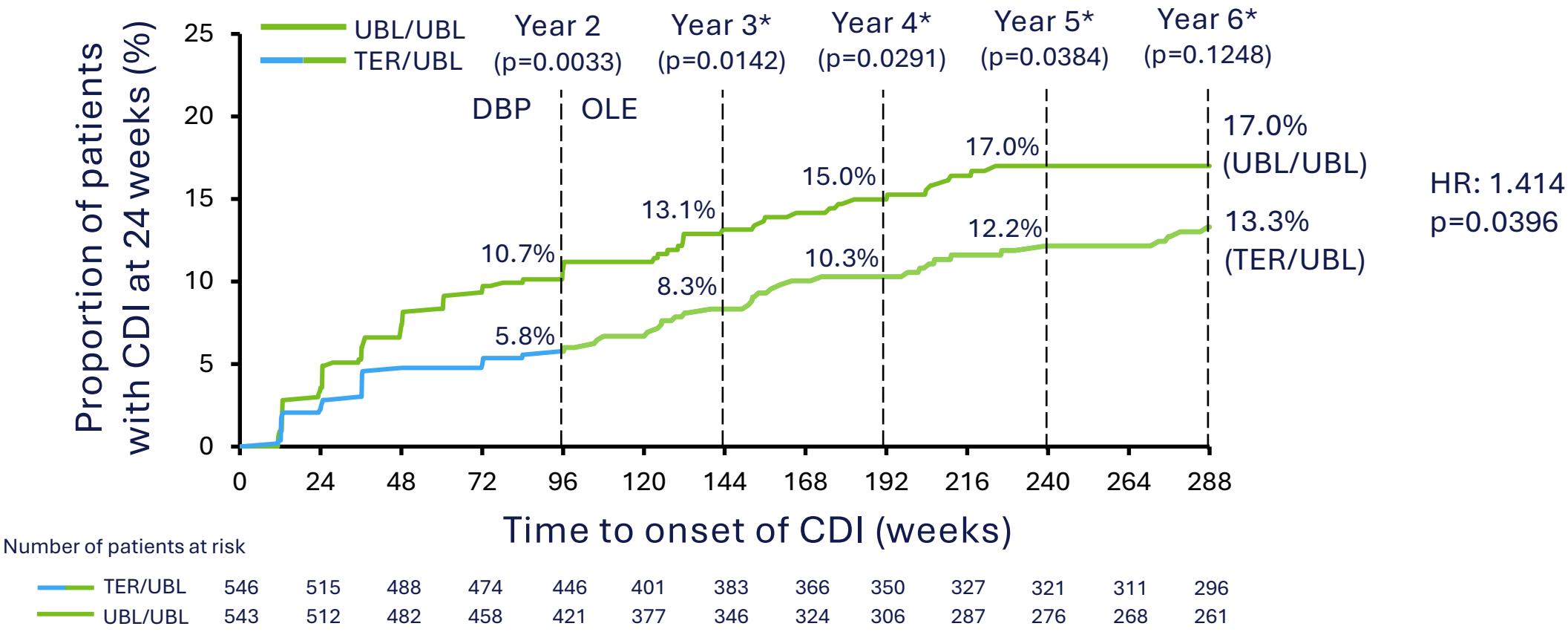
- At year 6 since randomization, 24-week CDP was observed in 10.1% and 15.9% (p=0.0238) of participants in the continuous and switch cohorts, respectively



Data Cutoff: 1-Jan-2025. The 24-week CDP was derived for OLE based on Double-blind period 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.

24 week Confirmed Disability Improvement (CDI) observed during 6 years of Ublituximab treatment

- At year 6 since randomization, 24-week CDI was observed in 17% and 13.3% (p=0.0396) of participants in the continuous and switch cohorts, respectively



Data Cutoff: 31-Dec-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; 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 CDI is the time from randomization in DBP to the onset of CDI, including gap period between DBP and OLE where applicable.

Summary of safety outcomes in ublituximab-treated patients during 6 years of ULTIMATE I/II and OLE

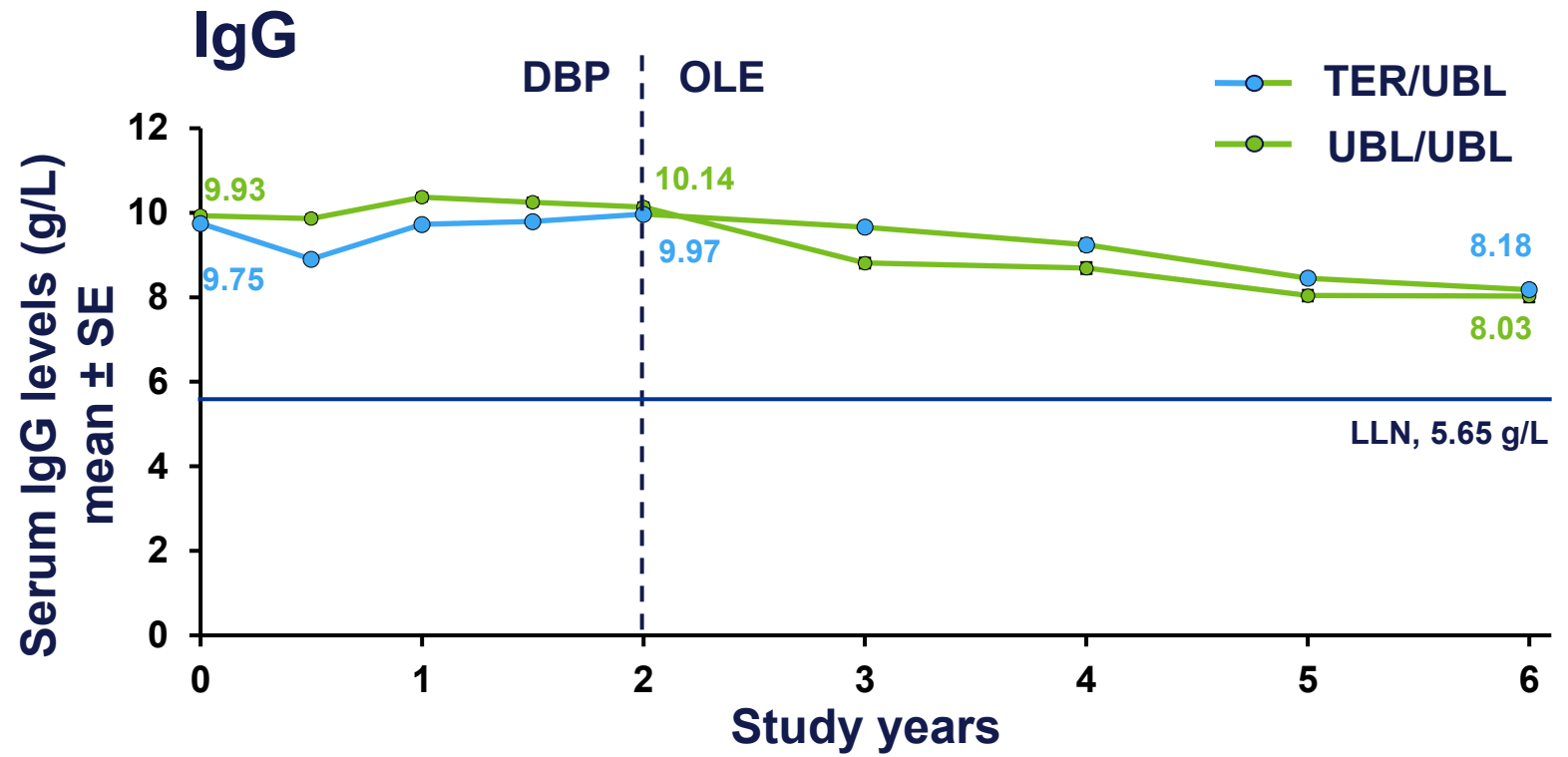
- The overall safety profile of UBL remained consistent over 6 years of continuous treatment in an exposure-adjusted analysis. Overall, the EAIRs remained stable with prolonged treatment.

	Ublituximab, ULTIMATE I/II DBP (n=545, PY=1145.57) EAIR [95% CI]	Ublituximab, Pooled DBP+OLE (n=974, PY=4261.55) EAIR [95% CI]
Any TEAE	374.84 [363.79, 386.22]	191.15 [187.04, 195.35]
TEAE leading to treatment discontinuation	1.66 [1.06, 2.60]	1.64 [1.30, 2.08]
Infection	80.92 [75.88, 86.30]	47.94 [45.91, 50.06]
Infusion-related reaction	54.12 [50.02, 58.55]	22.67 [21.28, 24.14]
Malignancy	0.17 [0.04, 0.70]	0.21 [0.11, 0.41]
Serious adverse event	5.59 [4.37, 7.14]	6.12 [5.42, 6.91]
Serious infection	2.10 [1.40, 3.13]	2.86 [2.40, 3.42]
Death	0.26 [0.08, 0.81]	0.19 [0.09, 0.38]

DBP = Double-blind phase; OLE = Open-label extension (OLE period:15-November-2019 until data cutoff on 1-Jan-2025; 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. The terms “COVID-19” and “COVID-19 pneumonia” were excluded. 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 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 phase alone, deaths were due to death of unknown cause in 1 patient, meningitis/pneumonia/sepsis in 1 patient, non-specific interstitial pneumonia in 1 patient, viral encephalitis in 1 patient, and pneumonia in 1 patient.

IgG levels in ublituximab-treated participants during 6 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 6 years [mean (SD), 8.03 (2.37) g/L and 8.18 (2.06) g/L, respectively]

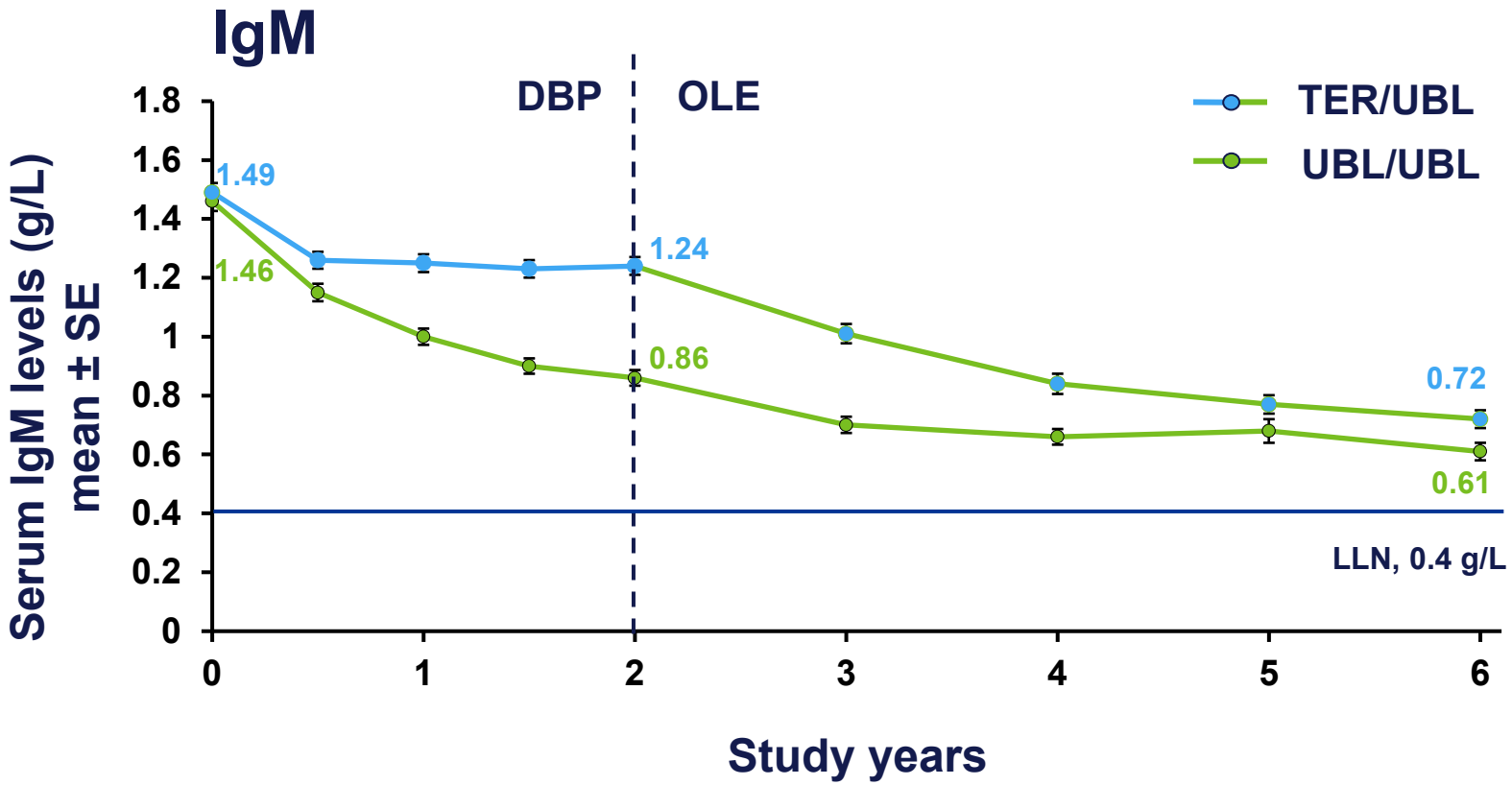


TER/UBL	546	532	517	505	493	346	251	288	286
UBL/UBL	540	530	525	511	492	342	249	277	263

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

IgM levels in ublituximab-treated participants during 6 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 6 years [mean (SD), 0.61 (0.48) g/L and 0.72 (0.52) g/L, respectively]



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

CONCLUSIONS

- Early initiation of UBL and continued treatment over a period of 6 years provided MS patients with sustained clinical benefit.
- The ARR in Year 6 of continuous treatment with UBL was 0.012, equivalent to 1 relapse every 83 PY.
- 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 6 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 6 years.

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