No association between decreases in serum immunoglobulin (Ig) levels below lower limit of normal (LLN) and serious infections (SI) with long term ublituximab (UBL) treatment in patients with Relapsing Multiple Sclerosis (RMS)

Lawrence Steinman[1], Edward Fox[9], Hans-Peter Hartung[2], Enrique Alvarez[3], Peiqing Qian[4], Sibyl Wray[5], Derrick Robertson[6], Krzysztof Selmaj[7], Daniel Wynn[8], Koby Mok[9], Yanzhi Hsu[9], Yihuan Xu[9], Chris Rowland[9], Karthik Bodhinathan[9], Peter Sportelli[9], Jackie Parker[9], Hari P. Miskin[9], **Bruce A.C. Cree**[10]

[1]Beckman Center for Molecular Medicine, Stanford University, Stanford, CA; [2]Heinrich Heine University Medical School, Düsseldorf, Germany; Brain and Mind Center, University of Sydney, Australia; Department of Neurology, Palacky University, Olomouc, Czech Republic; [3]University of Colorado, Aurora, CO; [4]Swedish Medical Center, Seattle, WA; [5]Hope Neurology, Knoxville, TN; [6]University of South Florida, Tampa, FL; [7]Department of Neurology, University of Warmia and Mazury, Olsztyn, and Center of Neurology, Lodz, Poland; [8]Consultants in Neurology, Northbrook, IL; [9]TG Therapeutics, Morrisville, NC;
[10]Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, CA

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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. Huang has also received consultant and/or speaker fees for Biogen, Novartis, and Teva Neuroscience. 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.

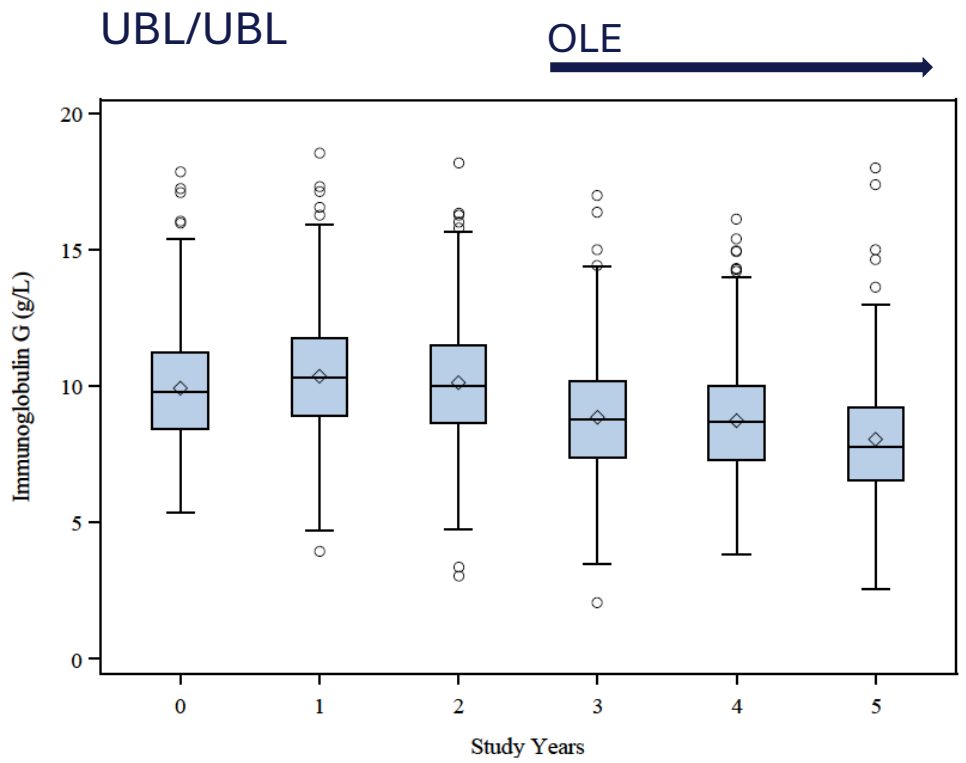
BACKGROUND

- Ublituximab (UBL) is a novel monoclonal antibody that targets a unique epitope of CD20 and is glycoengineered for enhanced antibody-dependent cellular cytotoxicity (ADCC).[1]
- UBL exhibits enhanced ADCC and Fcγ-receptor (FcγR) binding and administered in lower doses and with shorter infusion times (1-hour infusions after the first infusion).[2,3,4]
- ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) were 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). UBL demonstrated significant reduction in disease activity vs TER over 2 years in ULTIMATE I and II Phase 3 trials.[5]
- After 2 years of randomized, active-controlled, double-blind phase (DBP), RMS patients either continued UBL treatment (UBL-UBL) or switched from TER to UBL (TER-UBL) in the open-label extension (OLE) phase.
- During OLE participants demonstrated significant reduction in disease activity. ARR in Year 5 of continuous treatment with UBL was 0.02, equivalent to one relapse occurring in 50 PY, and participants exhibited lower rate of disability progression compared to those initially treated with TER. Overall safety profile of UBL remained consistent over 5 years of continuous treatment.[6]
- Immunoglobulin and infection profile with prolonged UBL treatment from DBP and OLE are presented here.

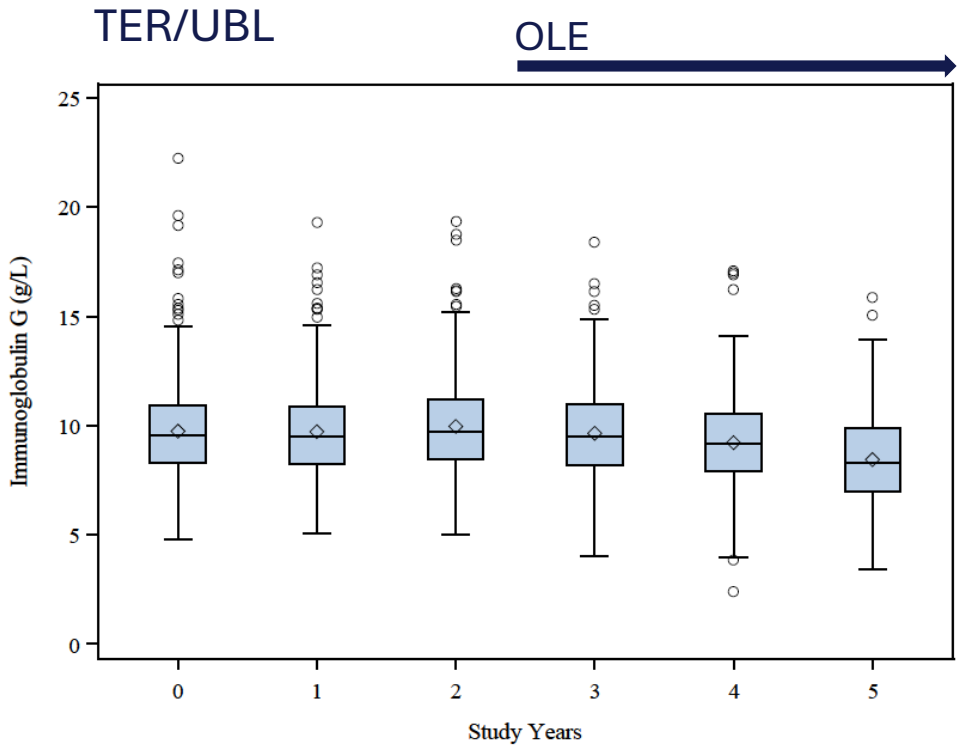
METHODS

- 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).
- Mean serum Ig levels were calculated through the 5-year period (data cut off: 1-January-2024), and patients with Ig levels above or below the lower limit of normal (LLN) threshold at any time during UBL therapy and rates of serious infections (SI) were analyzed. Per protocol, Ig's were sampled on Day 1, 15 and every 24 weeks during DBP, and every 48 weeks during OLE, and SIs associated with such Ig sampling were analyzed.
- Per protocol, patients in ULTIMATE I and II and OLE continued treatment if Ig values fell below LLN and were allowed to enter OLE with no restriction on Ig values being above or below LLN.
- LLN thresholds were set at 5.65 g/L for IgG, 0.4 g/L for IgM, 0.7 g/L for IgA and severity of LLN drops in g/L was classified as mild: <5.65 to ≥ 4.0, moderate: <4.0 to ≥ 2.0, severe: <2.0 for IgG, and mild: <0.4 to ≥0.36, moderate: <0.36 to ≥ 0.2, and severe: <0.2 for IgM.
- Rates of SIs per 100 PYs and 95% CI were estimated by Poisson regression model. Multiple SIs in one participant are counted multiple times. The terms "COVID-19" and "COVID-19 pneumonia" were excluded due to the temporal and geographic bias of the COVID-19 pandemic.

IgG levels remained above LLN over 5 years for patients treated with ublituximab



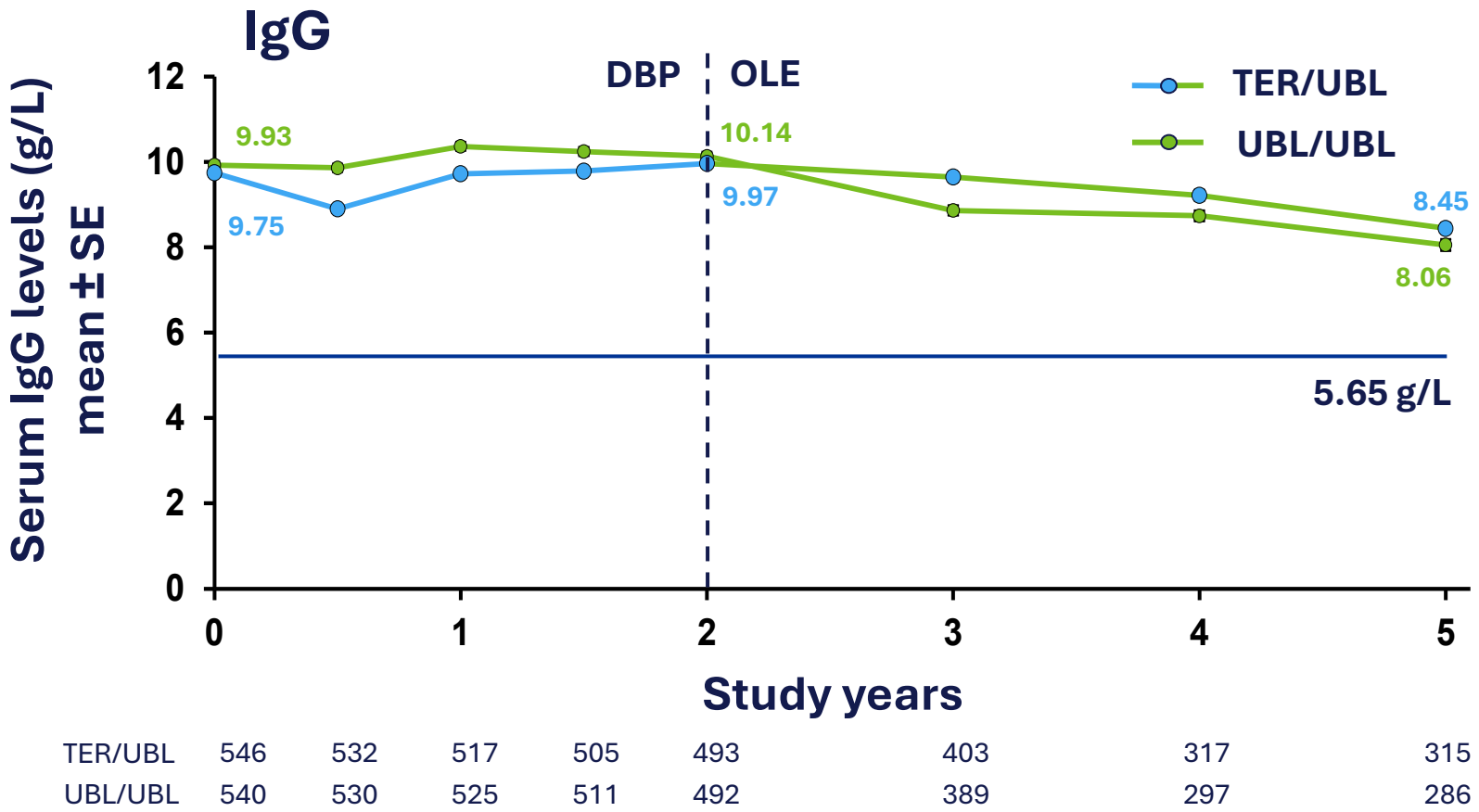
UBL/UBL, N	540	525	492	389	297	286



TER/UBL, N	546	517	493	403	317	315

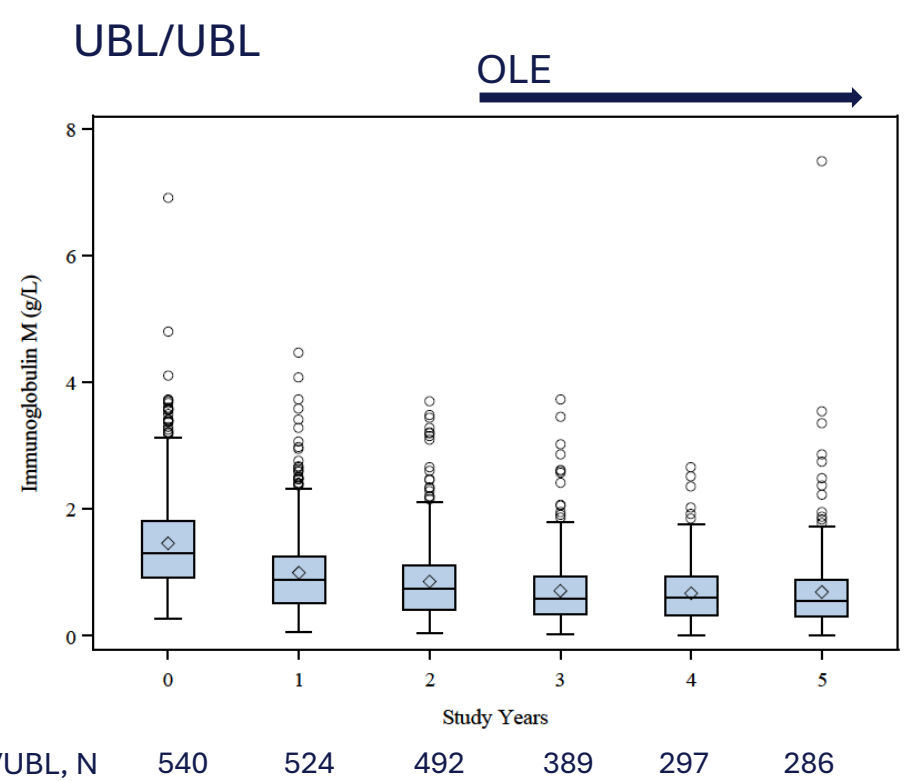
- At Year 5, the median IgG levels were 7.77 (interquartile range [IQR], 6.55-9.21; range, 3-18) for the continuous cohort and 8.30 (IQR, 7.00-9.90; range 3-16) for the switch cohort.

IgG levels remained above LLN over 5 years for patients treated with ublituximab

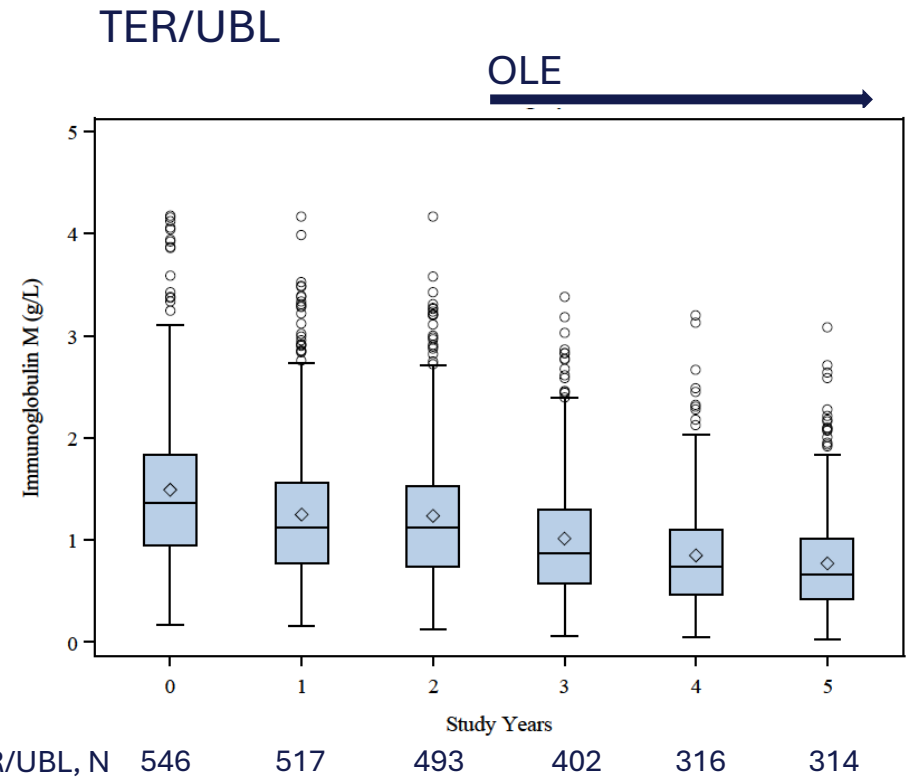


- In the continuous cohort that received UBL for at least 5 years, the mean (SE) IgG levels were 8.06 (0.13) g/L. The IgG levels remained stable and above the LLN (5.65 g/L).

IgM levels remained above LLN over 5 years for patients treated with ublituximab



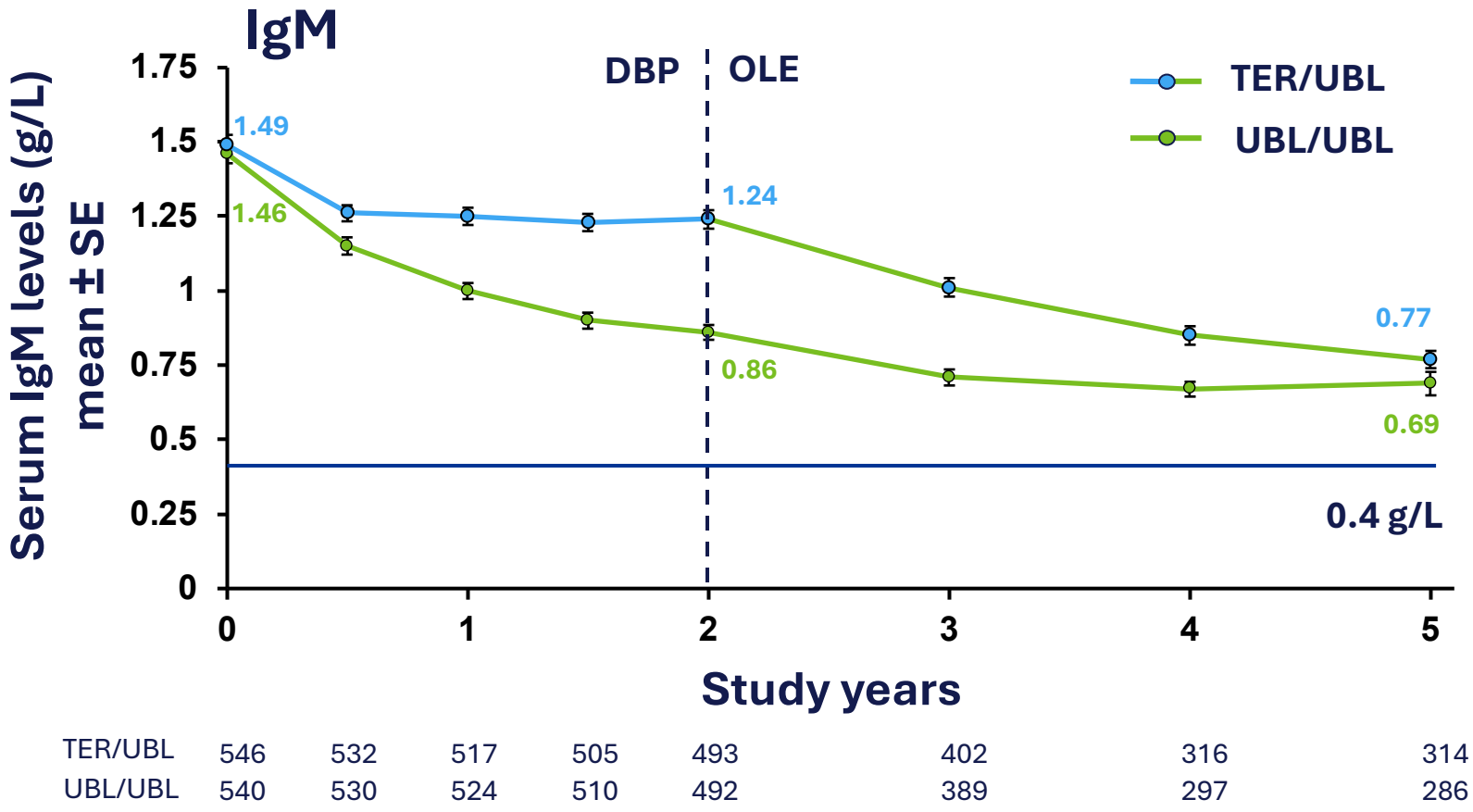
UBL/UBL, N	540	524	492	389	297	286



TER/UBL, N	546	517	493	402	316	314

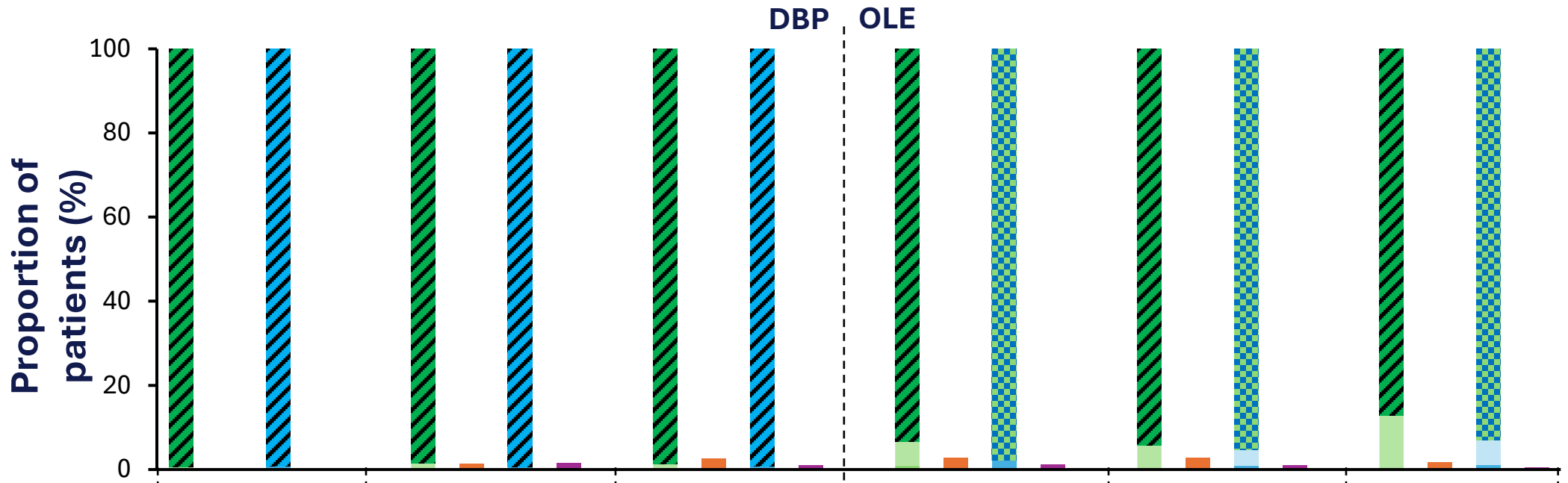
- At Year 5, the median IgM levels were 0.55 (interquartile range [IQR], 0.31-0.89; range, 0-8) for the continuous cohort and 0.66 (IQR, 0.42-1.01; range, 0-3) for the switch cohort.

IgM levels remained above LLN over 5 years for patients treated with ublituximab



- 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).

Proportion of patients ≥LLN and <LLN by severity for IgG evaluation



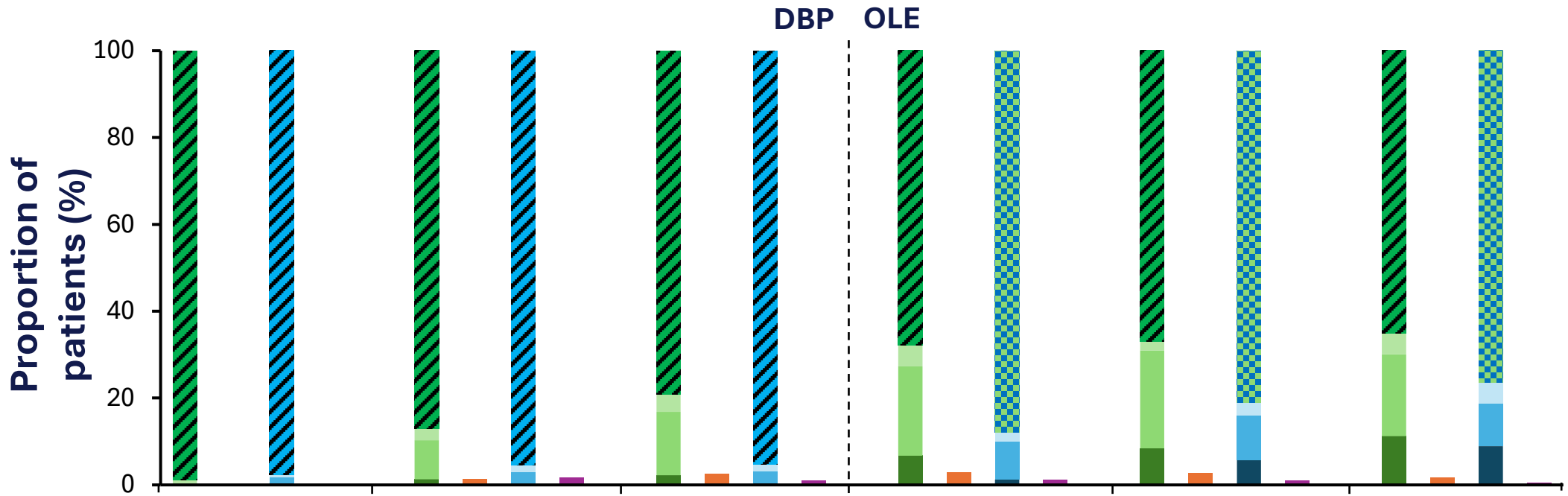
SI (%)			1.3	1.6	2.5	1	2.8	1.1	2.7	1	1.7	0.4				
Normal (≥LLN, %)	99.4	99.3	98.5	99.4	98.6	99.2	93.3	97.8	94.3	95.3	87.1	93.0				
Mild (%)	0.6	0	1.3	0	1	0	5.7	0	5.4	3.8	12.6	6				
Moderate (%)	0	0.7	0.2	0.6	0.4	0.8	1	2.2	0.3	0.9	0.3	1				
Time (weeks)	0		48		96		144*		192		240					

≥LLN UBL and UBL-UBL
≥LLN TER
≥LLN TER-UBL
<LLN UBL-UBL
Mild
Moderate
<LLN TER-UBL
Mild
Moderate
SI (total) UBL
SI (total) TER

SI= serious infections; LLN=lower limit of normal, LLN definitions: IgG 5.65 g/L, IgM 0.4 g/L, IgA 0.7 g/L. LLN drops in g/L was classified as mild: <5.65 to ≥ 4.0, moderate: <4.0 to ≥ 2.0, severe: <2.0 for IgG. SI (%) represent total incidences regardless of LLN status and are calculated for the 48-week period preceding the depicted timepoint, i.e., SI (%) at W48 represents SI onset in the treatment window between W1D1 and W48.
* The data for W144 corresponds to treatment window between OLE W1D1 and OLE W48.

- None of the patients showed severe drops in IgG levels below LLN on continuous UBL treatment for 5 years.
- Decreases in IgG levels below LLN were only mild to moderate in nature during 5 years of UBL treatment.
- The frequency of serious infections remained constant over time and was not affected by increases in the proportion of participants <LLN.

Proportion of patients ≥LLN and <LLN by severity for IgM evaluation



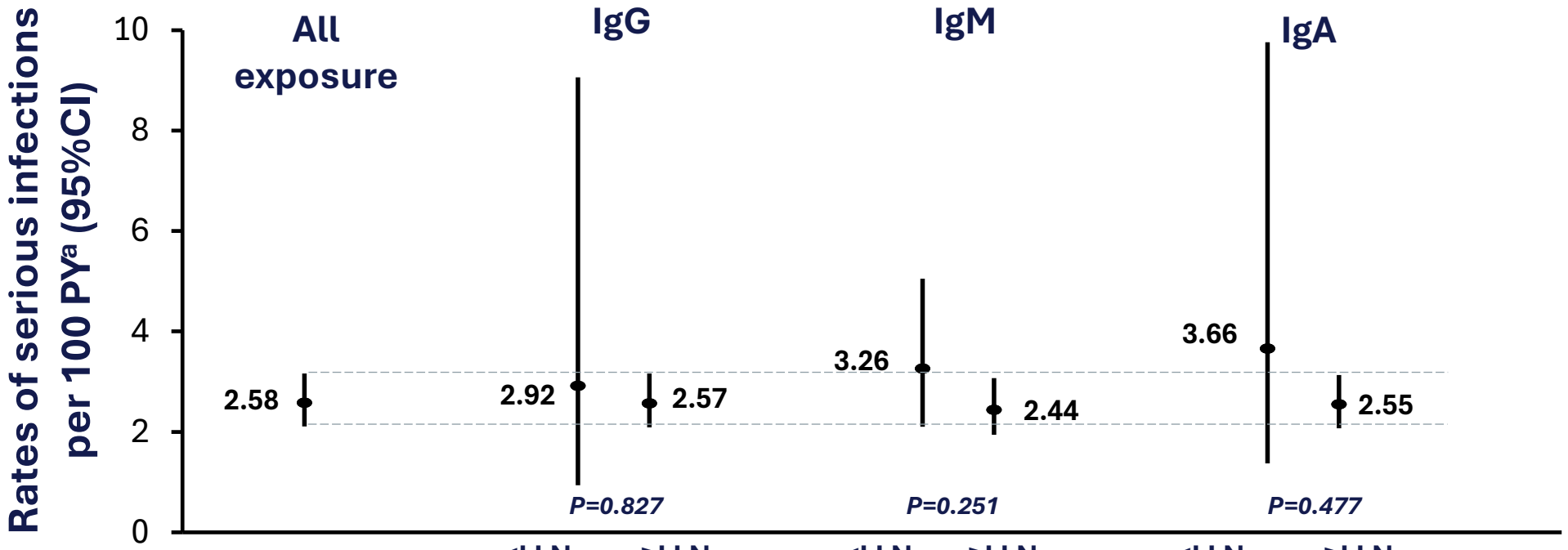
SI (%)			1.3	1.6	2.5	1	2.8	1.1	2.7	1	1.7	0.4
Normal (≥LLN, %)	98.9	97.6	87.0	95.4	79.1	95.1	67.9	87.8	67.0	81.0	65.0	76.4
Mild (%)	0.7	0.7	2.7	1.7	4.1	1.6	4.9	2.2	2	2.8	4.9	4.8
Moderate (%)	0.4	1.3	9	2.7	14.6	2.8	20.6	8.7	22.6	10.4	18.9	9.9
Severe (%)	0	0.4	1.3	0.2	2.2	0.4	6.7	1.2	8.4	5.7	11.2	8.9
Time (weeks)	0		48		96		144*		192		240	

SI= serious infections; LLN=lower limit of normal, LLN definitions: IgG 5.65 g/L, IgM 0.4 g/L, IgA 0.7 g/L. LLN drops in g/L was classified as mild: <0.4 to ≥0.36, moderate: <0.36 to ≥ 0.2, and severe: <0.2 for IgM. SI (%) shown here are calculated for the 48-week period preceding the depicted timepoint, i.e., SI (%) at W48 represents SI onset in the treatment window between W1D1 and W48.

*The data for W144 corresponds to treatment window between OLE W1D1 and OLE W48.

- The proportion of patients with decreases in IgM levels below LLN were mostly mild to moderate in nature.
- The frequency of serious infections remained constant over time and was not affected by increases in the proportion of participants <LLN.

Rates of SI per 100 PY in ublituximab-treated patients for Ig values <LLN and ≥LLN



		<LLN	≥LLN	<LLN	≥LLN	<LLN	≥LLN
Patient-years (PY)[b]	3603.90	102.63	3501.27	613.36	2990.54	109.23	3494.66
No. of SIs	93	3	90	20	73	4	89

SI= serious infection; PY=patient years; LLN = lower limit of normal, defined as: IgG 5.65 g/L, IgM 0.4 g/L, IgA 0.7 g/L. Analysis includes patients who received any dose of Ublituximab during the DBP and OLE periods. Gap period (if any) between DBP and OLE was excluded. [a] Rates of SIs per 100 PYs, 95% CI and p-values were estimated by Poisson regression model. Multiple SIs in one participant are counted multiple times. The terms "COVID-19" and "COVID-19 pneumonia" were excluded. [b] PY as sum of exposures (in years) during each lab episode (< LLN or ≥ LLN) from the date of randomization (ublituximab arm in DBP) to the end of DBP and from OLE ICF date (for participants entered in OLE) to the last participant date in OLE or cutoff date 1 Jan 2024 (if ongoing).

- There was no apparent association between decreased immunoglobulin levels and risk of serious infections in ublituximab-treated patients.
- Exposure-adjusted incidence rates of SIs were comparable in patients with Ig values <LLN and ≥LLN.

CONCLUSIONS

- The mean serum Ig levels remained above the LLN through 5 years of DBP and OLE.
- There was no apparent association between decreases in immunoglobulin levels and risk of serious infections in ublituximab-treated patients.
- None of the patients showed severe drops in IgG levels below LLN on continuous UBL treatment for 5 years. Decreases in IgG levels below LLN were only mild to moderate in nature during 5 years of UBL treatment.
- The proportion of patients with decreases in IgM levels below LLN were mostly mild to moderate in nature during 5 years of UBL treatment.
- The frequency of serious infections remained constant over time and was not affected by increases in the proportion of participants <LLN.
- No cases of PML were observed.
- UBL confers a benefit risk balance suitable for long-term clinical management of RMS.

REFERENCES

1. Babiker HM, et al. Expert Opin. Invest. Drugs. 2018;27(4):407-412.
2. Alvarez E, et al. Presented at: CMSC; 1-4 June 2022; National Harbor, MD, USA. Oral presentation DMT03.
3. Foley J et al. Presented at 75th AAN Annual Meeting, April 22-27, 2023, Boston, MA. P7-011.
4. BRIUMVI® (ublituximab-xiiy) Prescribing Information. TG Therapeutics, Inc. 2022.
5. Steinman L, et al. N Engl J Med. 2022;387(8):704-714.
6. Cree BAC, et. al. Presented at ECTRIMS, September 18-20, 2024, Copenhagen, DK. P324

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