Disability Improvements With Ublituximab in Relapsing Multiple Sclerosis (RMS): Expanded Disability Status Scale (EDSS), 9-Hole Peg Test (9-HPT), and Timed 25-Foot Walk (T25FW) Evaluations From the Phase 3 ULTIMATE I and II Studies

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OBJECTIVE

- To evaluate sustained confirmed disability improvement (CDI) and clinically meaningful improvements in 9-HPT and T25FW with ublituximab

KEY FINDINGS

- In pooled post hoc analyses of ULTIMATE I and II:
  - Among ublituximab patients who demonstrated 12-week CDI, 95.4% (62/65) sustained the improvement through the end of the study
  - In patients with a baseline EDSS score ≥2.0, more patients in the ublituximab group than teriflunomide group had EDSS improvements of 1.0 and 1.5 points at Weeks 60, 72, 84, and 96 ($P<0.05$ for all)
  - At 96 weeks, a ≥20% improvement in 9-HPT was observed in 11.4% vs 5.5% (dominant hand; $P=0.0009$) and 11.4% and 5.7% (nondominant hand; $P=0.0016$) of ublituximab- vs teriflunomide-treated patients, respectively

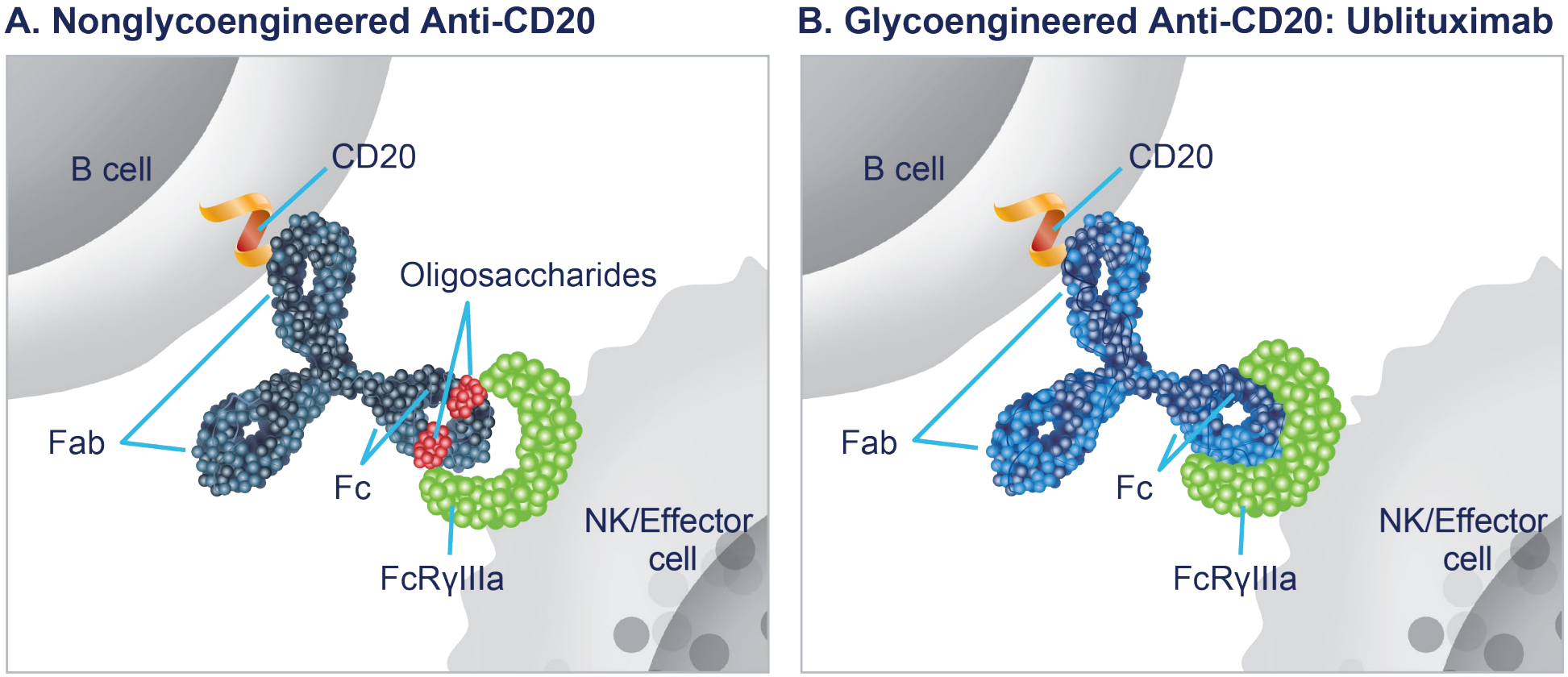
CONCLUSION

- In addition to the previously reported prespecified 12- and 24-week CDI analyses, post hoc evaluations of sustained 12-week CDI, EDSS improvements, and 9-HPT provide further evidence of clinically meaningful disability improvement with ublituximab in the ULTIMATE I and II studies

BACKGROUND

- Ublituximab is a novel monoclonal antibody that targets a unique epitope of CD20 and is glycoengineered for enhanced antibody-dependent cellular cytotoxicity **(Figure 1)**[1,2]
- Ublituximab is administered in lower doses and with shorter infusion times compared with other currently infused anti-CD20 therapies[3]
- ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) are identical, Phase 3, randomized, multicenter, double-blind, active-control studies evaluating the efficacy and safety of ublituximab vs teriflunomide in patients with RMS[3]
- ULTIMATE I and II met their primary endpoint, demonstrating a statistically significant reduction in annualized relapse rate for ublituximab compared with teriflunomide as well as significant improvements in the number of gadolinium-enhancing T1 lesions and the number of new/enlarging T2 lesions[3]
- In a prespecified pooled tertiary analysis, improvements with ublituximab vs teriflunomide were seen in both 12-week CDI (12.0% vs 6.0%, respectively; *P*=0.0003) and 24-week CDI (9.6% vs 5.1%, respectively; *P*=0.0026)[3]

Figure 1. Ublituximab Is Glycoengineered to Enhance ADCC



(A) In nonglycoengineered anti-CD20 antibodies, the core fucose of Fc-linked oligosaccharides sterically blocks interaction with FcγRIIIa, reducing affinity.[4,5] **(B)** Ublituximab is glycoengineered to have a low fucose content in the Fc region, which allows for closer interaction and enhanced affinity for all variants of FcγRIIIa.[5-7]

ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer.

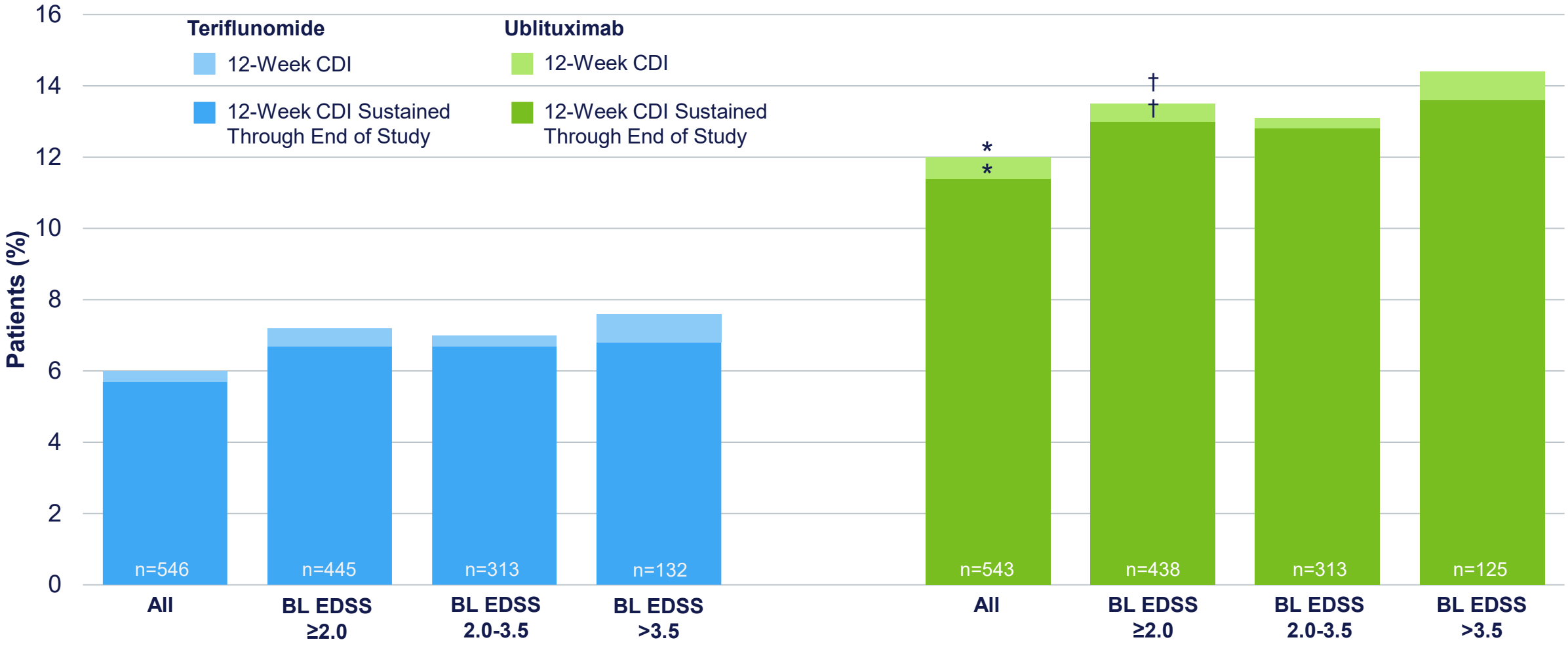
METHODS

- ULTIMATE I and II enrolled a total of 1094 adult patients from 10 countries with a diagnosis of RMS (relapsing-remitting or secondary-progressive) with disease activity[3]
- Patients received ublituximab 450 mg administered by 1-hour intravenous infusion every 24 weeks (following Day 1 infusion of 150 mg and Day 15 infusion of 450 mg) or teriflunomide 14 mg oral once daily for 96 weeks[3]
- Clinical evaluations were performed every 12 weeks, and magnetic resonance imaging assessments were performed at Weeks 12, 24, 48, and 96
- CDI was defined as a reduction from the baseline EDSS score of ≥1.0 point (or 0.5 point if the baseline EDSS score was >5.5) that was sustained and confirmed at the next scheduled visit(s) ≥12 or ≥24 weeks after the initial documentation of neurological improvement
- Sustained CDI, CDI at different EDSS thresholds, and clinically meaningful improvements in 9-HPT (≥20% or ≥5 seconds improvement from baseline)[8,9] and T25FW (≥20% improvement from baseline)[10] were evaluated in pooled post hoc analyses

RESULTS

- The proportion of patients achieving 12-week CDI and, of those, the proportion who had sustained CDI through the end of the study are shown in **Figure 2**
- Higher rates of 12-week CDI occurred with ublituximab vs teriflunomide for all patients (12.0% vs 6.0%, respectively; *P*=0.0005) and regardless of baseline EDSS score
- A higher proportion of ublituximab-treated patients had sustained CDI compared with teriflunomide-treated patients (all patients: 11.4% vs 5.7%, respectively; *P*=0.0005)
- 95.4% (62/65) of ublituximab-treated patients sustained CDI through the end of the study

Figure 2. Sustained CDI Through End of Study



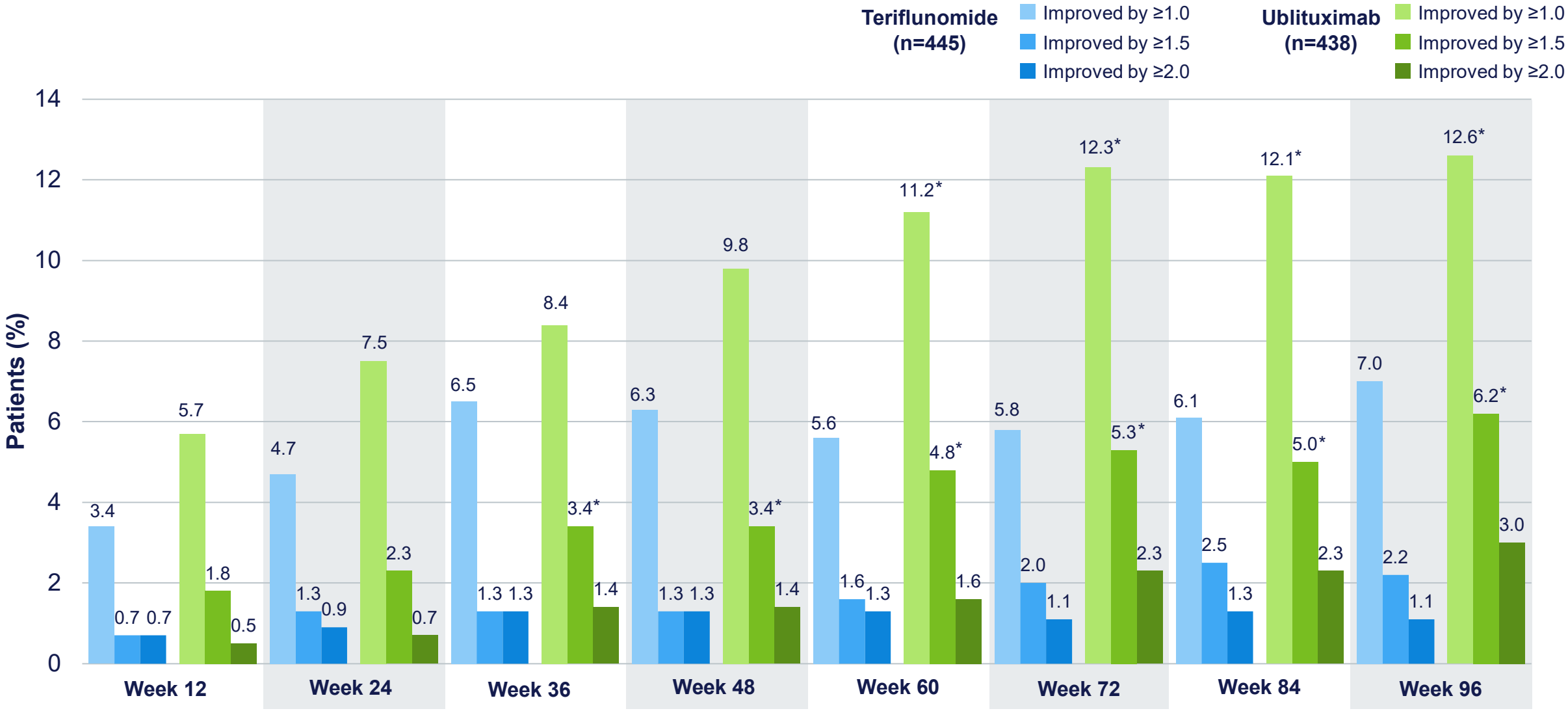
*P=0.0005 for all patients and †P<0.01 for patients with baseline EDSS ≥2.0 for 12-week CDI and for 12-week CDI sustained through end of study for all patients: ublituximab vs teriflunomide. Statistics were not performed for other comparisons. Pooled post hoc analysis. Modified intention-to-treat population. Sustained CDI requires that end of study EDSS score is not higher than baseline score.

BL, baseline; CDI, confirmed disability improvement; EDSS, Expanded Disability Status Scale.

RESULTS (continued)

- Among patients with a baseline EDSS score ≥2.0, more patients in the ublituximab group than teriflunomide group had EDSS improvements of 1.0 and 1.5 points at Weeks 60, 72, 84, and 96 ($P<0.05$ for all) **(Figure 3)**

Figure 3. EDSS Improvement (Baseline EDSS Score ≥2.0)

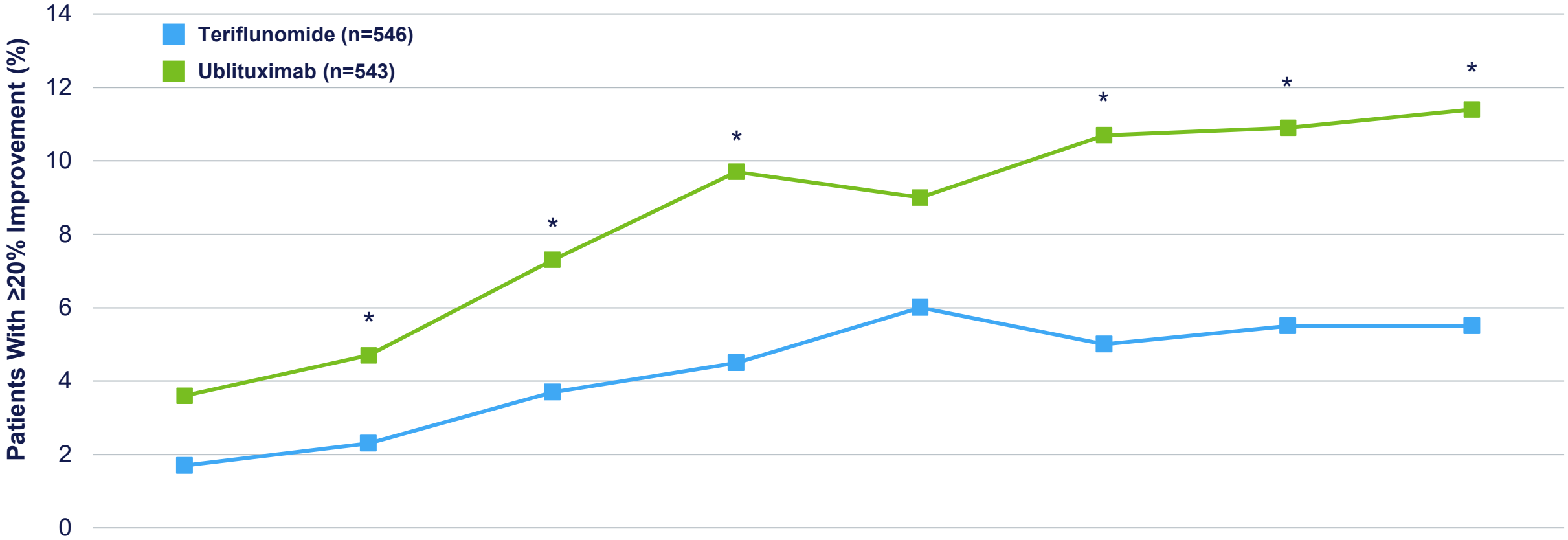


*P<0.05. Pooled post hoc analysis. Modified intention-to-treat population.
EDSS, Expanded Disability Status Scale.

RESULTS (continued)

- At 96 weeks, the proportion of patients with an EDSS score ≤2.0 was 38.9% (211/543) vs 33.3% (182/546) with ublituximab vs teriflunomide, respectively (*P*=0.058), despite similar proportions at baseline (ublituximab, 34.4%; teriflunomide, 34.8%)
- Improvements of ≥20% and ≥5 seconds in 9-HPT in the dominant hand **(Figure 4)** and nondominant hand **(Figure 5)** were observed for ublituximab vs teriflunomide

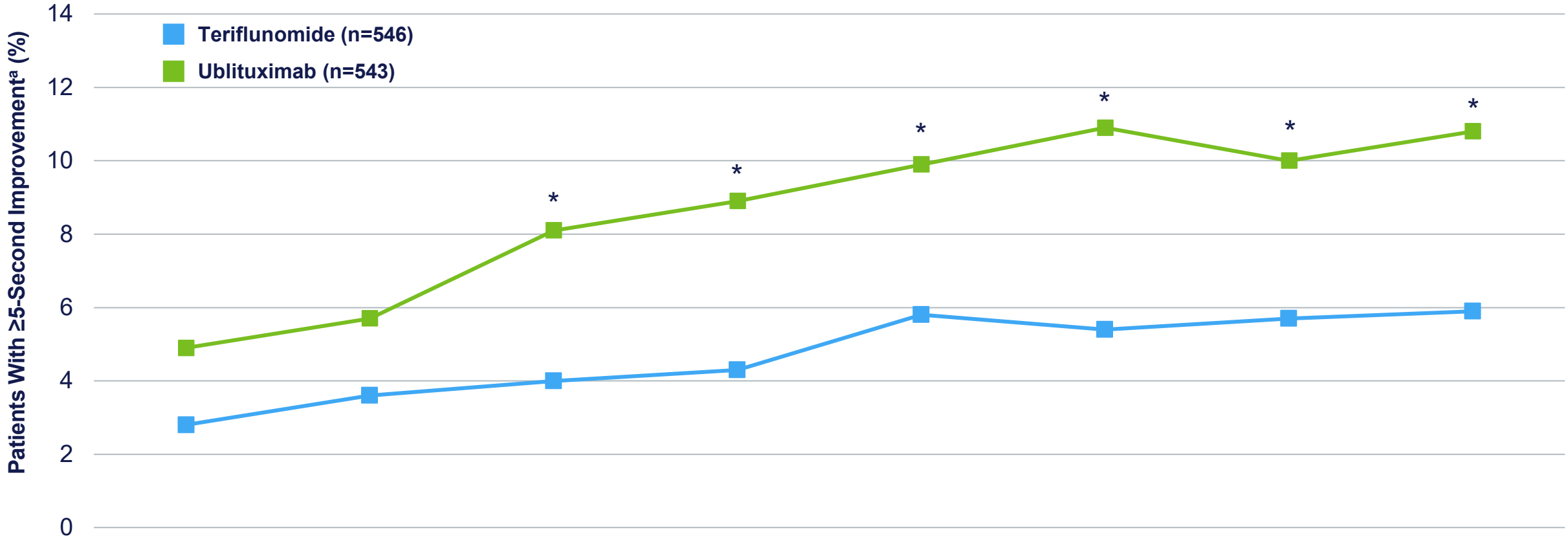
Figure 4A. ≥20% Improvement in 9-HPT Score From Baseline (Dominant Hand)



Week	12	24	36	48	60	72	84	96
Teriflunomide, n/N	9/537	12/527	19/520	23/511	30/503	25/501	27/488	27/489
Ublituximab, n/N	19/534	25/528	38/521	50/518	46/513	54/505	53/488	56/491

*P<0.05. Pooled post hoc analysis. Modified intention-to-treat population. Percentage is based on the number of patients at visit at each timepoint. Average time of 2 tests at each timepoint.
9-HPT, 9-Hole Peg Test.

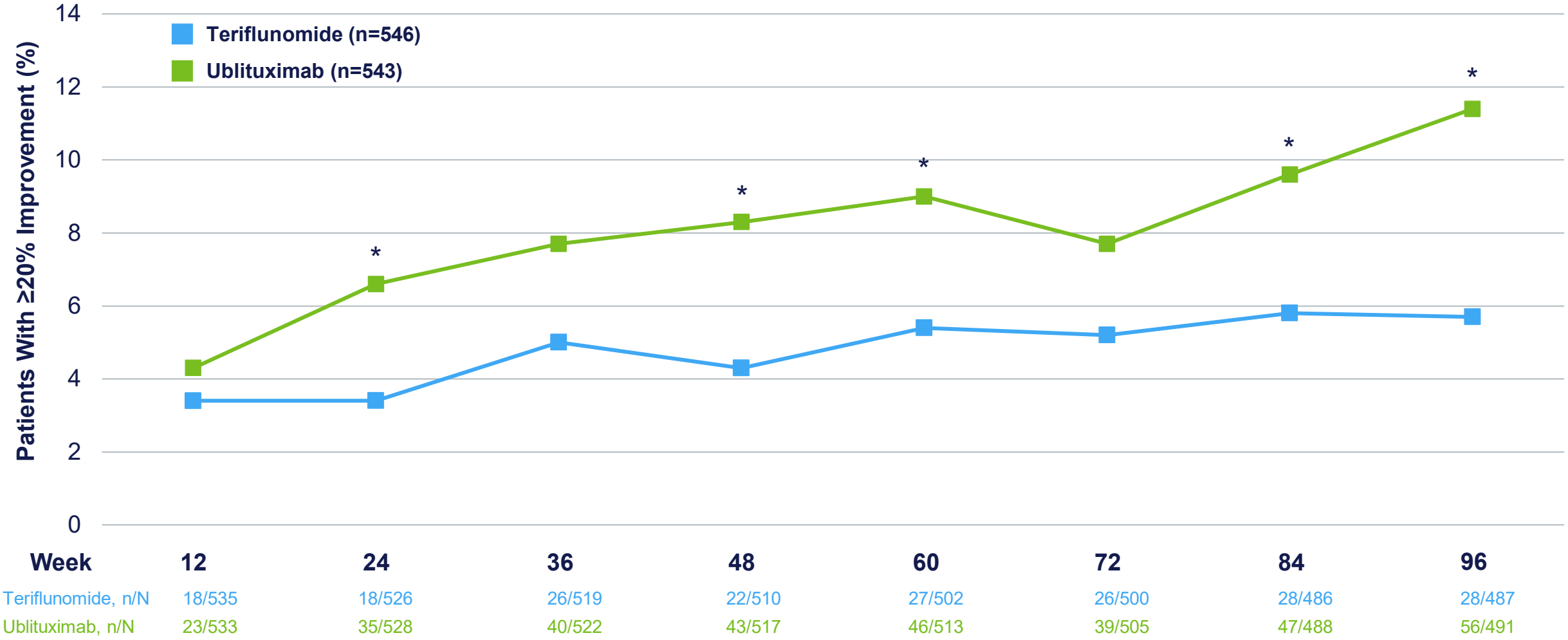
Figure 4B. ≥5-Second Improvement[a] in 9-HPT Score From Baseline (Dominant Hand)



Week	12	24	36	48	60	72	84	96
Teriflunomide, n/N	15/537	19/527	21/520	22/511	29/503	27/501	28/488	29/489
Ublituximab, n/N	26/534	30/528	42/521	46/518	51/513	55/505	49/488	53/491

[a]Raw score. *P<0.05. Pooled post hoc analysis. Modified intention-to-treat population. Percentage is based on the number of patients at visit at each timepoint. Average time of 2 tests at each timepoint.
9-HPT, 9-Hole Peg Test.

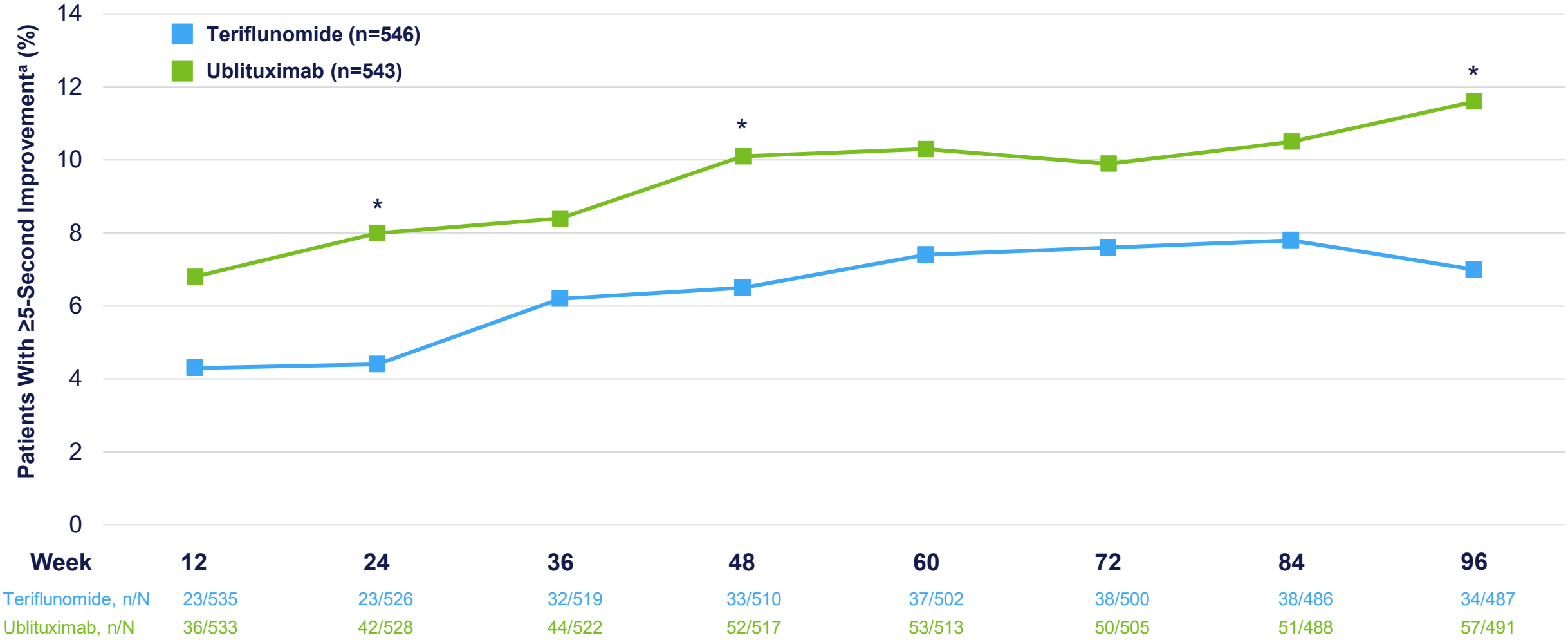
Figure 5A. ≥20% Improvement in 9-HPT Score From Baseline (Nondominant Hand)



Week	12	24	36	48	60	72	84	96
Teriflunomide, n/N	18/535	18/526	26/519	22/510	27/502	26/500	28/486	28/487
Ublituximab, n/N	23/533	35/528	40/522	43/517	46/513	39/505	47/488	56/491

*P<0.05. Pooled post hoc analysis. Modified intention-to-treat population. Percentage is based on the number of patients at visit at each timepoint. Average time of 2 tests at each timepoint.
9-HPT, 9-Hole Peg Test.

Figure 5B. ≥5-Second Improvement[a] in 9-HPT Score From Baseline (Nondominant Hand)



Week	12	24	36	48	60	72	84	96
Teriflunomide, n/N	23/535	23/526	32/519	33/510	37/502	38/500	38/486	34/487
Ublituximab, n/N	36/533	42/528	44/522	52/517	53/513	50/505	51/488	57/491

[a]Raw score. *P<0.05. Pooled post hoc analysis. Modified intention-to-treat population. Percentage is based on the number of patients at visit at each timepoint. Average time of 2 tests at each timepoint.
9-HPT, 9-Hole Peg Test.

RESULTS (continued)

- At baseline, the median T25FW score was 5.35 and 5.40 seconds for the ublituximab and teriflunomide groups, respectively
- At 96 weeks,12.8% of ublituximab-treated and 11.7% of teriflunomide-treated patients had ≥20% improvement from baseline in T25FW score (*P*=NS)

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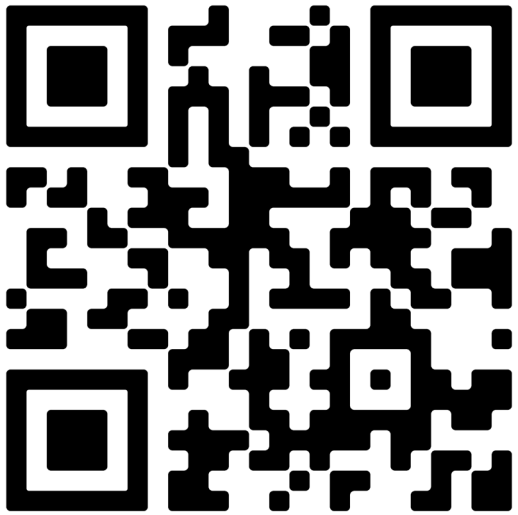

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