MS Relapse Redefined: Distinguishing True Relapses from Pseudoexacerbations in the ULTIMATE I and II Trials Comparing Ublituximab vs Teriflunomide

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OBJECTIVE

- To develop a methodology to reduce the impact of pseudoexacerbations on annualized relapse rates in the ULTIMATE trials.

KEY FINDINGS

- Original ARR reduction in pooled ULTIMATE trial (ublituximab vs teriflunomide) was **54.2%.**
- Applying the stringent criteria of T2 MRI-supported relapses, the ublituximab ARR reduction increased to **87.5%** vs. teriflunomide [LS means Rate Ratio (95% CI): 0.125 (0.074, 0.212); P<.0001; ARR of 0.096 for teriflunomide and 0.012 in ublituximab]
- With application of “EDSS 0.5-point”, “FSS 2-point”, “EDSS-Max”, “FSS-Max”, “Infection-free”, “Gd+ and T2/5-wk MRI” criteria, the ARR reduction was **60.1%** (rate ratio [RR] 0.399[0.274, 0.580], p<0.0001; ARR: 0.138 for teriflunomide and 0.055 for ublituximab).
- In Year 2 (weeks 48-96), the ARR reduction was **66.4%** (RR 0.336[0.204, 0.551], p<0.0001; ARR: 0.142 for teriflunomide and 0.048 for ublituximab), aligning closer to MRI results.
- Application of all the criteria (“EDSS 1-point”, “FSS 2-point”, “EDSS-Max”, “FSS-Max”, “Infection-free”, “T2 MRI-supported relapse” criteria”) eliminated 86 of 97 events (**88.7%**) in ublituximab-treated participants and 138 of the 213 (**64.8%**) events in the teriflunomide-treated participants were identified as pseudoexacerbations.

BACKGROUND

- The primary endpoint in relapsing multiple sclerosis (MS) trials involves reducing the annualized relapse rate (ARR).
- In trials of high efficacy therapies such as ULTIMATE I and II, a paradox emerges whereby new/ enlarging (n/e)T2 lesions were reduced by > 90% while relapse reduction was 54.2%.[1]
- This paradox may be due to confounding from pseudoexacerbations: symptom recrudescence events meeting relapse criteria without focal inflammation.[2,3]
- Pseudoexacerbations are expected to contribute equal number of events to both arms in clinical trials creating noise in the primary outcome that will disproportionately affect the higher efficacy treatments due to the lower number of true relapses.

METHODS

A modified set of criteria was also applied to evaluate the consequence of each of the criteria below to parse out relapses from pseudoexacerbations.

- **"EDSS 1-point" criteria**: An increase of >= 1.0 points in the EDSS score from the previous clinically stable assessment.

  [AND]

- **"FSS 2-point" criteria**: ≥ 2 points increase on one of the appropriate FS or 1 point on two or more of the appropriate FS. The change must affect the selected FS (i.e., pyramidal, ambulation, cerebellar, brainstem, sensory or visual). The change in FS scores should correspond to the patient's symptoms (e.g., patient reported change in visual acuity should correspond to a change in the vision FS score).

  [AND]

- **"EDSS-Max" criteria**: If EDSS change meets change criteria, it must be higher than previous maximum EDSS

  [AND]

- **"FSS-Max" criteria:** If FSS change meets criteria, it too must be higher than previous max in that FSS

  [AND]

- **"Infection-free" criteria**: If meet the above 3 refined criteria, a new confirmed relapse cannot have occurred within 2-month# epochs before/after any infection AE or SAE.

  [AND]

- **"T2 MRI-supported relapse" criteria***: Any new or enlarging T2 lesions after relapse event (for available MRI)

RESULTS

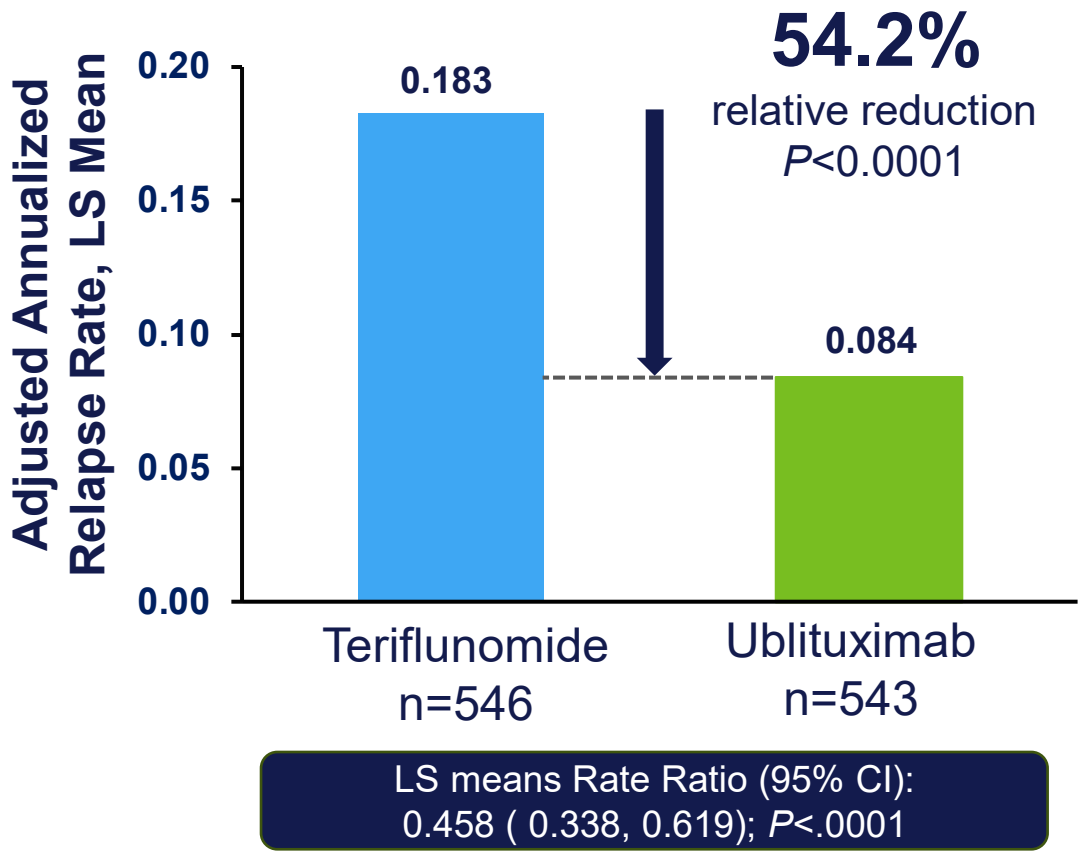
- Baseline characteristics for the modified intent to treat populations are shown in **Table 1**
- In the ULTIMATE I and II trials, using the original protocol definition of relapses, a relative reduction in ARR of **54.2%** was observed for ublituximab vs teriflunomide [LS means Rate Ratio (95% CI): 0.458 (0.338, 0.619); P<.0001; ARR of 0.183 for teriflunomide and 0.084 in ublituximab] **(Figure 1)**
- Applying the stringent criteria of T2 MRI-supported relapses, the ublituximab ARR reduction increased to **87.5%** vs. teriflunomide [LS means Rate Ratio (95% CI): 0.125 (0.074, 0.212); P<.0001; ARR of 0.096 for teriflunomide and 0.012 in ublituximab] **(Figure 2)**
- Using the T2 MRI-supported relapse criteria, 75 of 97 events (77.3%) in ublituximab-treated participants and 38 of the 213 (17.8%) events in the teriflunomide-treated participants were identified as pseudoexacerbations **(Figure 3)**

Table 1. Participant Demographics and Baseline Characteristics in the mITT population

Characteristic Mean ± SD or %	Teriflunomide (n=546)	Ublituximab (n=543)
Age (years)	36.6±9.30	35.3±8.63
Gender, Female, n (%)	355 (65.0%)	344 (63.4%)
Race, n (%)		
White	534 (97.8%)	533 (98.2%)
Black or African-American	9 (1.6%)	8 (1.5%)
Other	3 (0.5%)	2 (0.4%)
Time since MS diagnosis (years)	4.7±5.1	4.9±5.4
Number of relapses in the previous 12 months	1.3±0.7	1.3±0.6
Number of relapses in the previous 24 months	1.9±1.0	1.8±0.9
Time since most recent relapse (months)	6.2±4.8	7.1±8.5
EDSS score at Baseline	2.9±1.2	2.9±1.3
Number of baseline Gadolinium (Gd+) lesions, n (%)*		
0	290 (54.0%)	284 (52.3%)
≥1	247 (46.0%)	258 (47.5%)
BaselineT2 lesion count	62.2±39.17	64.7±39.90
BaselineT2 lesion volume (mL)	15.27±16.66	15.3±14.81
Baseline brain volume (cm^3)	1668.77±105.02	1667.32±106.61

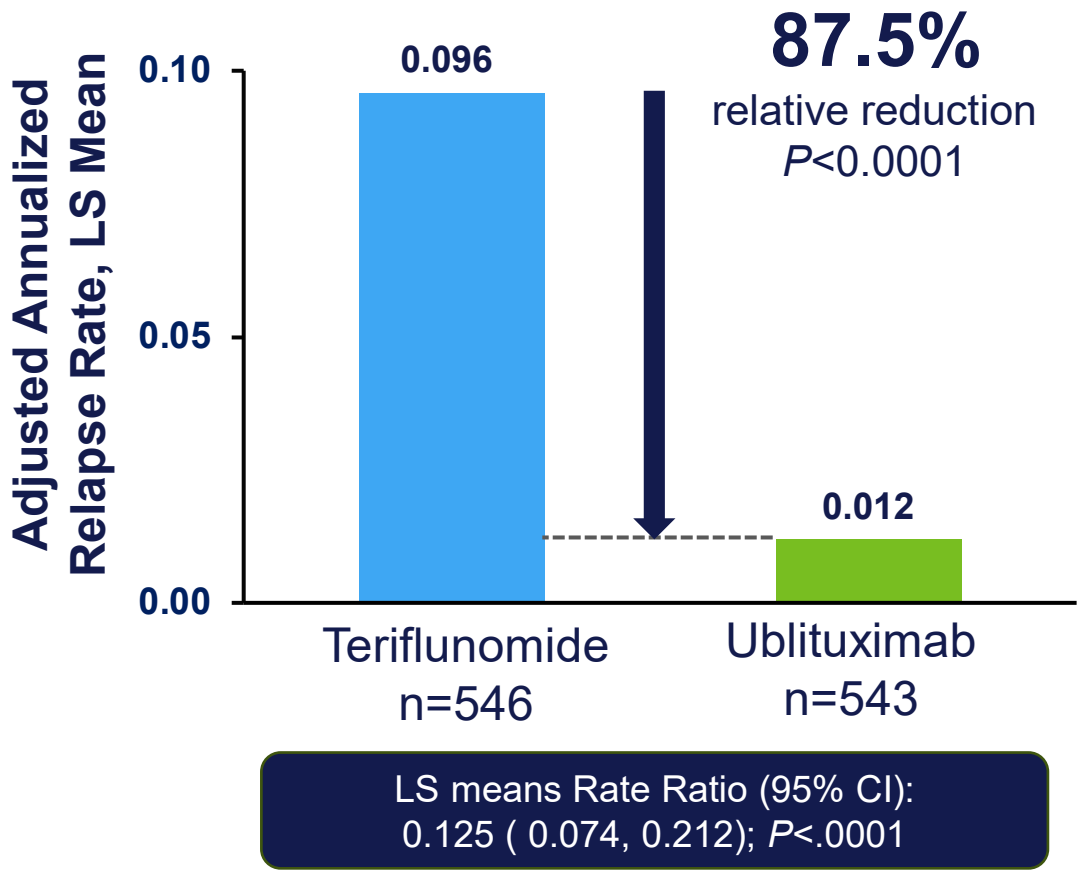
* The number of baseline (Gd+) lesions were missing for 1 (0.2%) Ublituximab and 4 (0.7%) Teriflunomide patients. Modified intention-to-treat population.
EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

Figure 1. Annualized relapse rates per original protocol definition; pooled ULTIMATE I and II



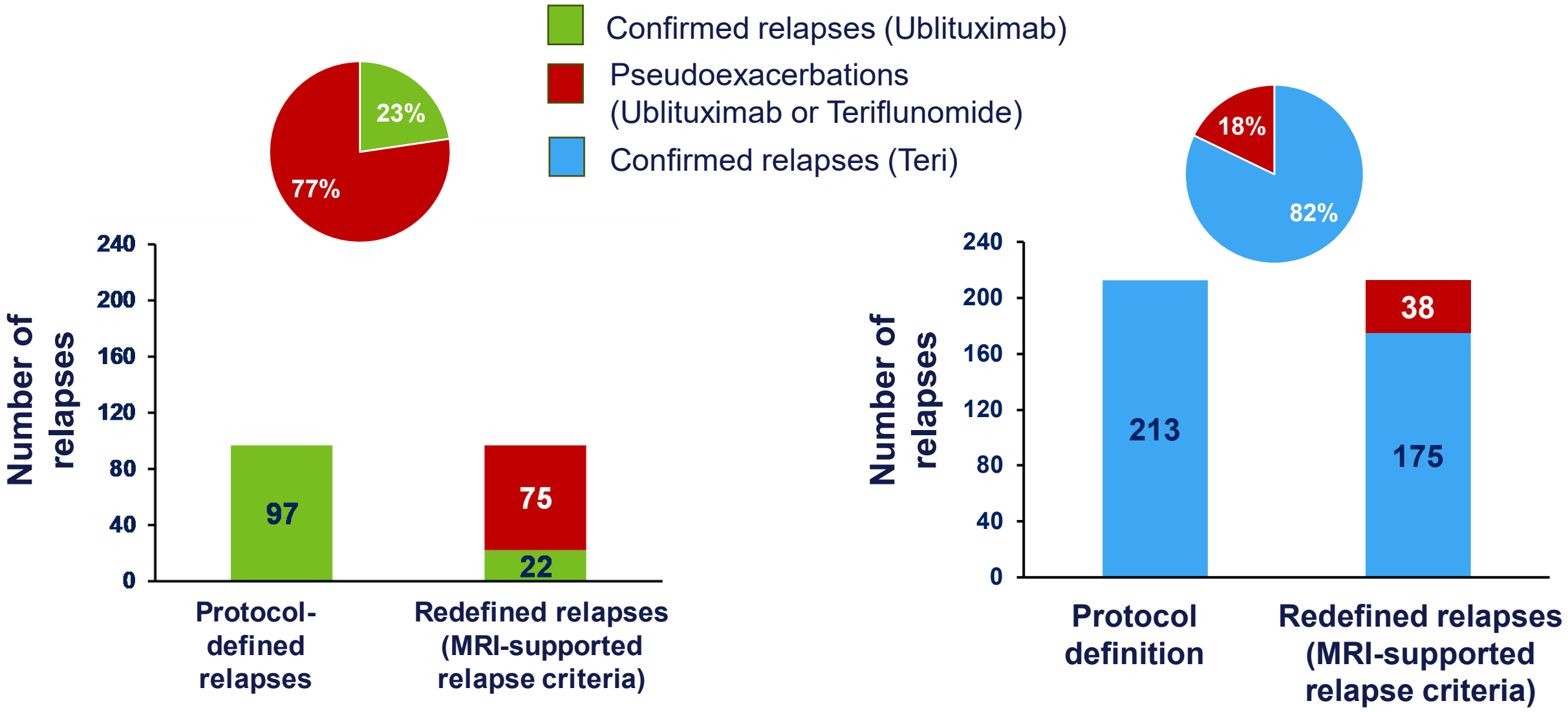
GEE - Generalized Estimating Equation model for the relapse count per patient with logarithmic link function and treatment, region and baseline EDSS strata as covariate and log (years of treatment) as offset. Applied to the IRAP confirmed relapse during treatment.

Figure 2. Annualized relapse rates (redefined); T2 MRI-supported relapses



GEE - Generalized Estimating Equation model for the relapse count per patient with logarithmic link function and treatment, region and baseline EDSS strata as covariate and log(years of treatment) as offset. Applied to the IRAP confirmed relapse during treatment. Redefined criteria: relapse was confirmed by additionally requiring n/eT2 lesions on MRI subsequent to the relapse event.

Figure 3. Relapses measured under original and redefined criteria; “T2 MRI-supported relapse” criteria



ARR of 0.096 for teriflunomide and 0.012 in ublituximab. LS means Rate Ratio (95% CI): 0.125 (0.074, 0.212); *P*<.0001

RESULTS

- Application of all the criteria (“EDSS 1-point”, “FSS 2-point”, “EDSS-Max”, “FSS-Max”, “Infection-free”, “T2 MRI-supported relapse”) eliminated 86 of 97 events (88.7%) in ublituximab-treated participants and 138 of the 213 (64.8%) events in the teriflunomide-treated participants were identified as pseudoexacerbations **(Figure 4, 5).**

- With application of “EDSS 0.5-point”, “FSS 2-point”, “EDSS-Max”, “FSS-Max”, “Infection-free”, “Gd+ and T2/5-wk MRI” criteria, the ARR reduction was **60.1%** (rate ratio [RR] 0.399[0.274, 0.580], p<0.0001; ARR: 0.138 for teriflunomide and 0.055 for ublituximab) **(Figure 6)**

  - Applying the above, the ublituximab ARR reduction during Year 1 was **52.7%** (RR 0.473 [0.298, 0.750], p<0.0015; ARR: teriflunomide 0.130, and ublituximab 0.061)**.** ARR reduction in Year 2 increased to **66.4%** (RR 0.336 [0.204, 0.551], p<0.0001; ARR: teriflunomide 0.142, and ublituximab 0.048) **(Figure 7)**

Figure 4. Relapses reported with original and redefined criteria in Ublituximab-treated patients

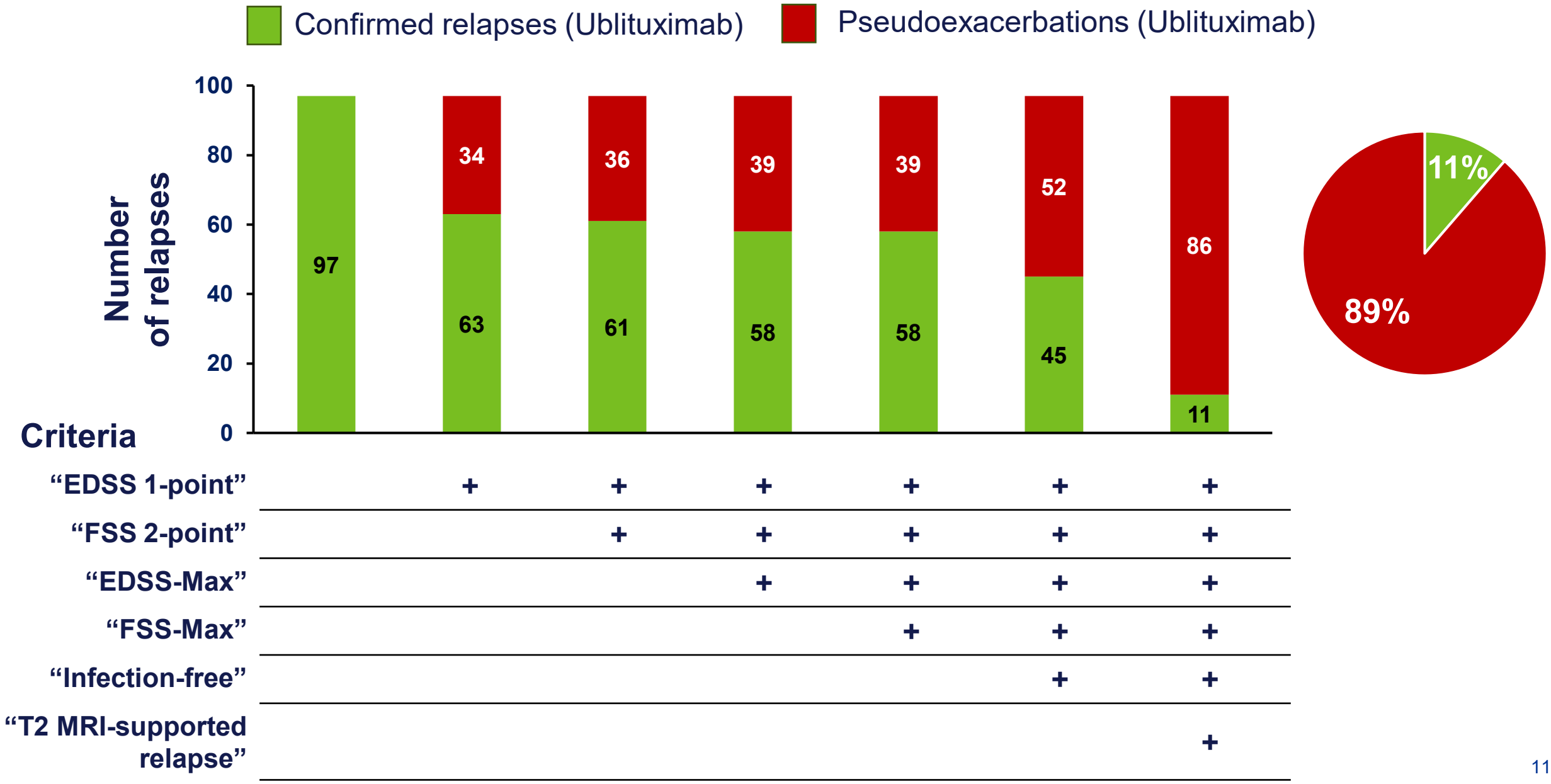
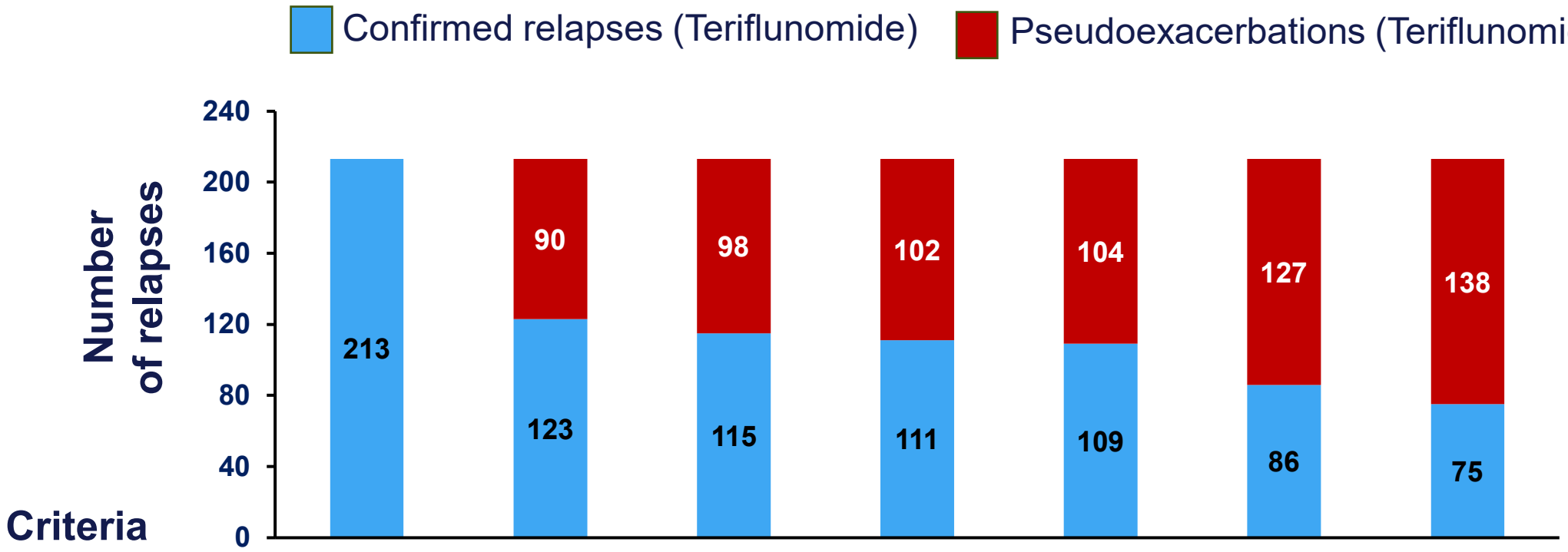
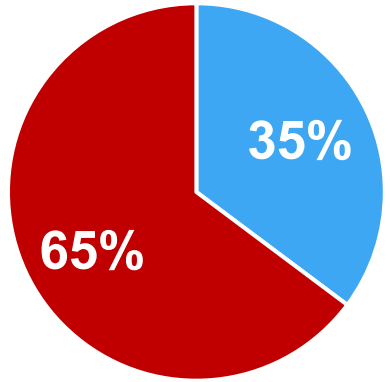


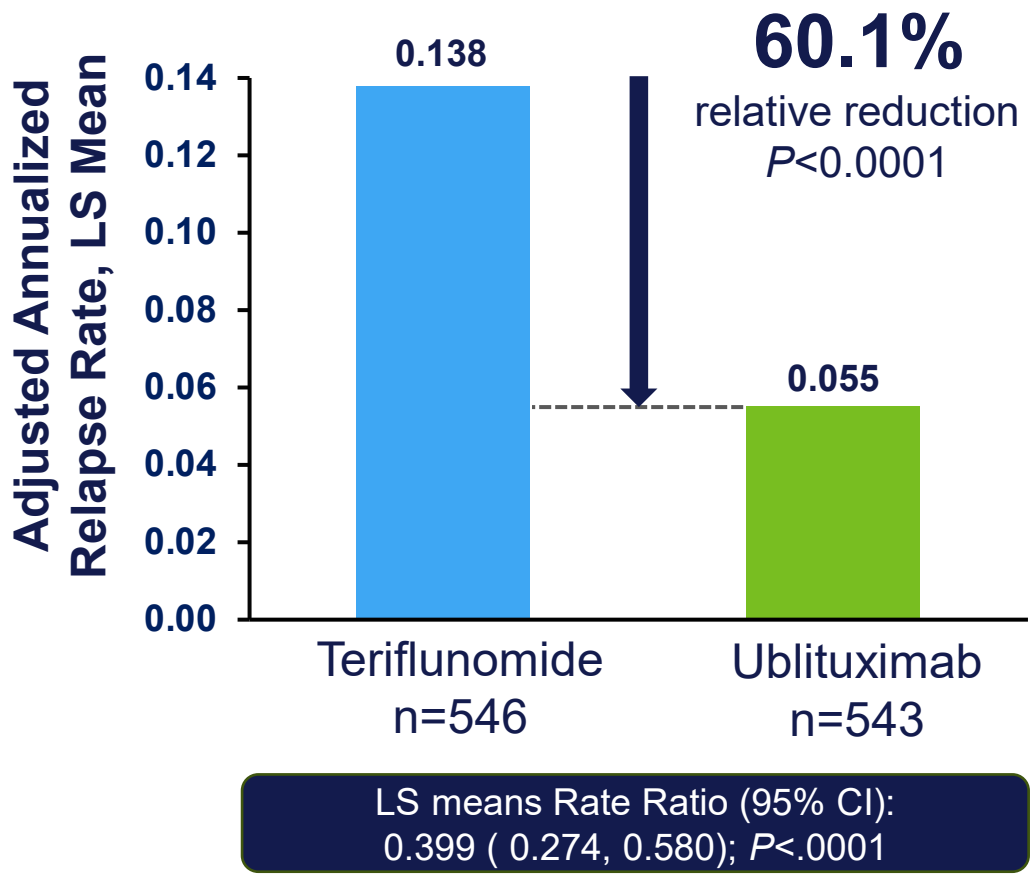
Figure 5. Relapses reported with original and redefined criteria in Teriflunomide-treated patients





Criteria						
"EDSS 1-point"	+	+	+	+	+	+
"FSS 2-point"		+	+	+	+	+
"EDSS-Max"			+	+	+	+
"FSS-Max"				+	+	+
"Infection-free"					+	+
"T2 MRI-supported relapse"						+

Figure 6. Annualized relapse rates (redefined*)

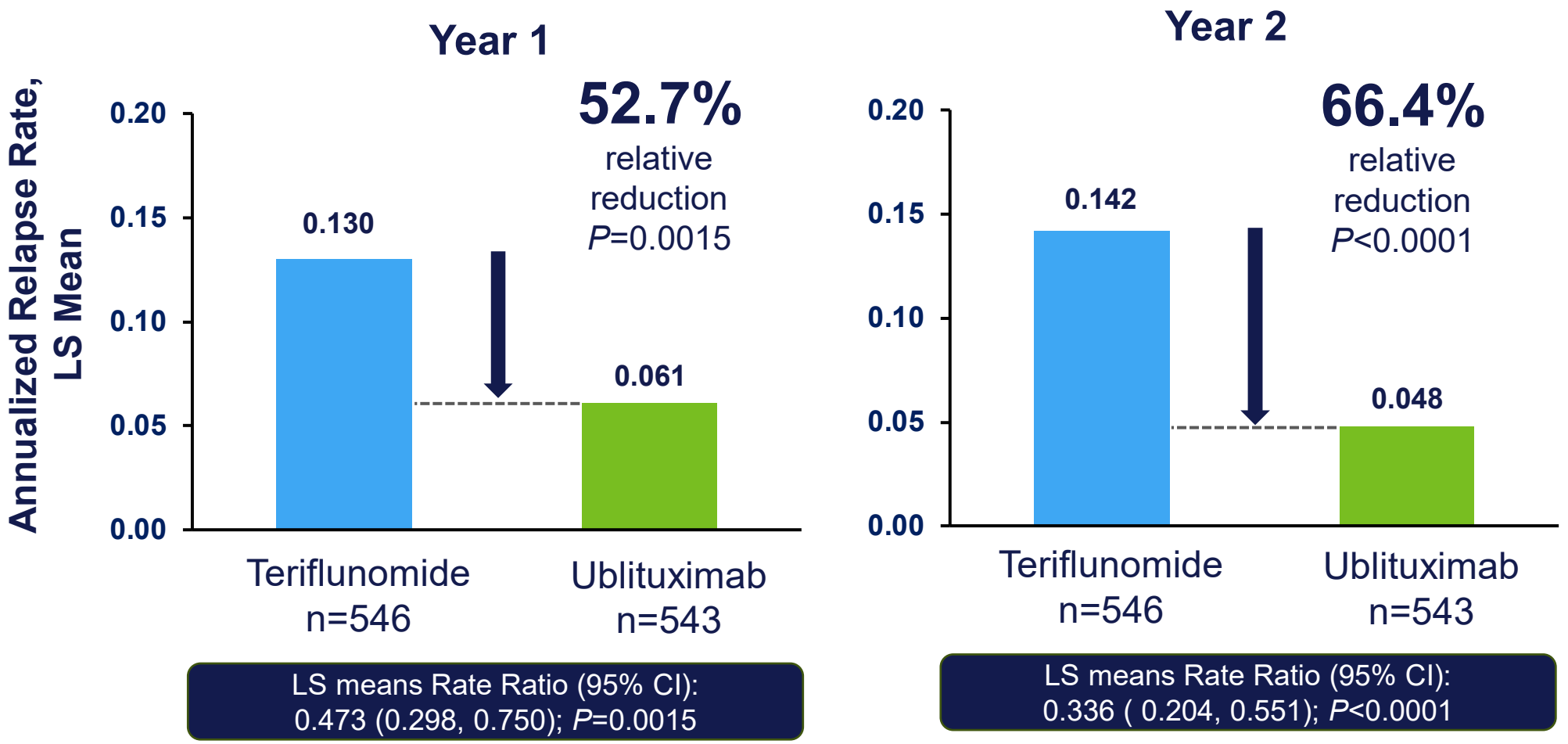


EDSS >= 0.5 (>=1 if baseline=0)
FSS increase >= 2
EDSS > previous max
FSS > previous max
No infection AE within 2 months of the relapse
Any Gd+ or n/e T2 lesion within 5 weeks of symptomatic event

*Redefined relapse as: 1. EDSS increase >= 0.5 (>=1 if baseline=0); 2. FSS increase >= 2; 3. EDSS > previous max; 4. FSS > previous max, 5. No infection AE within 2 months of the relapse; 6. Pseudo relapse if negative for Gd+ or n/e T2 lesions within 5 weeks of symptomatic event when MRI assessment was available.

GEE - Generalized Estimating Equation model for the relapse count per patient with logarithmic link function treatment as covariates and log(years of treatment) as offset. Redefined relapse: Only applied to the IRAP confirmed relapse during treatment; MRI data collected within 35 days after the relapse date has been incorporated into the analysis. MRI data beyond this timeframe was not included for this plot.

Figure 7. Annualized rates of redefined* relapses, across Year 1 and Year 2



EDSS >= 0.5 (>=1 if baseline=0)
FSS increase >= 2
EDSS > previous max
FSS > previous max
No infection AE within 2 months of the relapse
Any Gd+ or n/e T2 lesion within 5 weeks of symptomatic event

*Redefined relapse as: 1. EDSS increase >= 0.5 (>=1 if baseline=0); 2. FSS increase >= 2; 3. EDSS > previous max; 4. FSS > previous max, 5. No infection AE within 2 months of the relapse; 6. Pseudo relapse if negative for Gd+ or n/e T2 lesions within 5 weeks of symptomatic event when MRI assessment was available.
GEE - Generalized Estimating Equation model for the relapse count per patient with logarithmic link function, treatment as covariates and log(years of treatment) as offset. Redefined relapse: Only applied to the IRAP confirmed relapse during treatment; MRI data collected within 35 days after the relapse date has been incorporated into the analysis. MRI data beyond this timeframe was not included for this plot.

CONCLUSIONS

- MRI-supported relapses increased the stringency of MS relapses and provides a truer assessment of clinical efficacy.
- Efforts to optimize the relapse definition on a clinical basis alone did not identify pseudoexacerbations to the degree possible with an MRI marker.
- Limitations include measuring spinal cord relapses which would be expected to occur proportionately in both arms.
- The improved signal to noise ratio of relapse outcomes has implications for relapsing MS trial design, by allowing for smaller sample sizes where efficacy could potentially be determined with smaller studies conducted more quickly.
- Power analysis of sample size using redefined ARR (MRI-supported relapse) reduced the number of trial participants or the trial length by approximately two-thirds to reach statistical significance between two arms. These findings have implications for future clinical trial design.[4]

REFERENCES

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3. Dünschede J, Ruschil C, Bender B, Mengel A, Lindig T, Ziemann U, Kowarik, M.C. *J Clin Med*. 2023 Jan 17;12(3):739
4. Alvarez E, Bodhinathan K, Xu Y, Miskin H, Lee L, Krieger S. Presented at ACTRIMS Forum 2024; February 29 - March 2; West Palm Beach, Florida. P110

METHODS (CONTD.)

Relapse redefinition- Each episode of relapse must be confirmed by the IRAP, based on the neurological assessments performed independently by the Treating and/or Examining Neurologist by documenting:

- **"EDSS 0.5-point" criteria**: increase of ≥0.5 points in EDSS score (unless EDSS=0, then increase of ≥1 point)

  [AND]

- **"FSS 2-point" criteria**: ≥ 2 points increase on one of the appropriate FS or 1 point on two or more of the appropriate FS. The change must affect the selected FS (i.e., pyramidal, ambulation, cerebellar, brainstem, sensory or visual). The change in FS scores should correspond to the patient's symptoms (e.g., patient reported change in visual acuity should correspond to a change in the vision FS score).

  [AND]

- **"EDSS-Max" criteria**: If EDSS change meets change criteria, it must be higher than previous maximum EDSS

  [AND]

- **"FSS-Max" criteria:** If FSS change meets criteria, it too must be higher than previous max in that FSS

  [AND]

- **"Infection-free" criteria**: If meet the above 3 refined criteria, a new confirmed relapse cannot have occurred within 2-month# epochs before/after any infection AE or SAE.

  [AND]

- **"Gd+ and T2/5-wk MRI" criteria***: Relapse excluded if negative for Gd+ or n/e T2 lesions within 5 weeks of symptomatic event

METHODS (CONTD.)

- Generalized Estimating Equation (GEE) model was used for estimation of relapse rate ratios. GEE model used the relapse count per patient with logarithmic link function, and treatment as covariates and log(years of treatment) as offset.

ACKNOWLEDGMENTS

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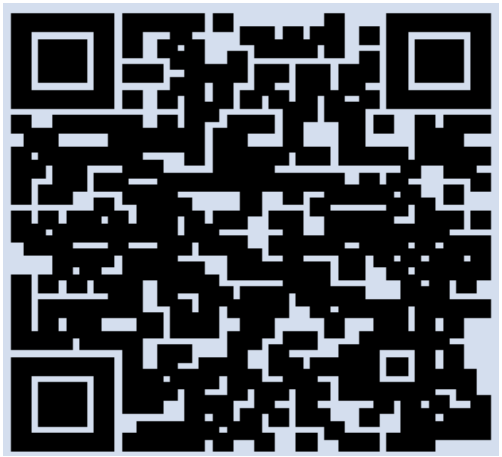

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