MS Relapse Redefined: Addressing the Radiological/ Pseudoexacerbation Paradox with High Efficacy Therapy in the ULTIMATE I and II Trials

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OBJECTIVES

- To develop a methodology to reduce the impact of pseudoexacerbations on the annualized relapse rates in ULTIMATE trials of ublituximab versus teriflunomide
- To explore the implications of MRI-supported relapses on clinical trial size and power.

KEY FINDINGS

- 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]
- Applying the stringent criteria of 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]
- Using the 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.
- 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.

CONCLUSIONS

- MRI-supported relapses increased the stringency of MS relapses and provides a truer assessment of clinical efficacy.
- 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 be determined with smaller studies conducted more quickly.

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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

- The proportion of patients with relapses were compared in the ublituximab and teriflunomide arms of the pooled ULTIMATE trials.
  - Relapses in the ULTIMATE trials were defined as clinical episodes reported by subjects and meeting the criteria below as documented by neurological assessments and confirmed by an Independent Relapse Adjudication Panel:
  - Criteria 1: An increase of ≥ 0.5 points in the EDSS score (unless EDSS = 0, then an increase of at least 1.0 points is required) from the previous clinically stable assessment.

    [OR]
  - Criteria 2: ≥ 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).
- MRI-supported relapses - A more stringent relapse definition meeting the above criteria but additionally requiring n/eT2 lesions on MRI subsequent to the relapse event.
  - Relapse counts per patient were modeled using generalized estimating equation model with logarithmic link function and treatment, region and baseline EDSS strata as covariate and log(years of treatment) as offsets. For epoch analysis of MRI-supported relapses by year 1 and 2, treatment alone was used as covariate to accommodate convergence of the model.
  - Power calculations were calculated to estimate the effect on trial design.

RESULTS

- Baseline characteristics for the modified intention to treat (ITT) populations are shown in **Table 1.**

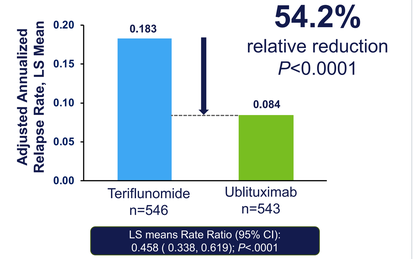
Table 1. Participant Demographics and Baseline Characteristics in the modified ITT population

Characteristic Mean ± standard deviation or n (%)	Teriflunomide N = 546	Ublituximab N = 543
Age (years)	36.6 ± 9.30	35.8 ± 8.63
Gender, Female, n (%)	355 (65%)	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
Number of baseline Gadolinium (Gd+) lesions, n (%)		
0	290 (54.0%)	284 (52.3%)
≥1	247 (46.0%)	258 (47.5)
Baseline T2 lesion count	62.2 ± 39.17	64.7 ± 39.90
Baseline T2 lesion count volume (mL)	15.27 ± 16.66	15.3 ± 14.81
Baseline brain volume (cm³)	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.

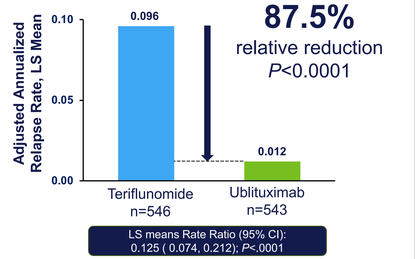
- In the ULTIMATE I and II trials, using the original protocol definition of relapses, a relative reduction in ARR of 54.2% was observed for ublituximab vs teriflunomide [LS means Rate Ratio (95% CI): 0.458 (0.338, 0.619); P<.0001; ARR of 0.183 for teriflunomide and 0.084 in ublituximab] **(Figure 1).**
- Applying the stringent criteria of 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).**

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. Redefined criteria, relapse was confirmed by additionally requiring n/eT2 lesions on MRI subsequent to the relapse event.

Figure 2. Annualized relapse rates (redefined); MRI Supported Relapses



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RESULTS

- In the ULTIMATE I and II trials, using the original protocol definition of relapses, the ARR reduction for ublituximab vs. teriflunoimide was 51.5% in Year 1 [LS means Rate Ratio (95% CI): 0.485 (0.341, 0.689); P<0.0001] and 58% in Year 2 [LS means Rate Ratio (95% CI): 0.420 (0.286, 0.616); P<0.0001] **(Figure 3).**
- Applying the criteria of MRI-supported relapses, the ARR reduction for ublituximab vs. teriflunoimide was 82.7% in Year 1 [LS means Rate Ratio (95% CI): 0.173 (0.098, 0.303); P<0.0001] and 92.8% in Year 2 [LS means Rate Ratio (95% CI): 0.072 (0.028, 0.187); P<0.0001] **(Figure 4).**

Figure 3. ARR by Year 1 and Year 2; per original protocol definition; pooled ULTIMATE I and II

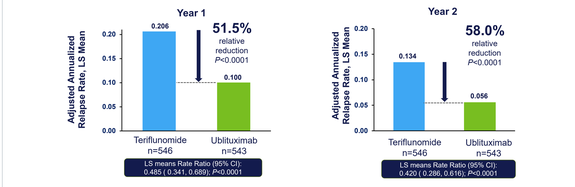

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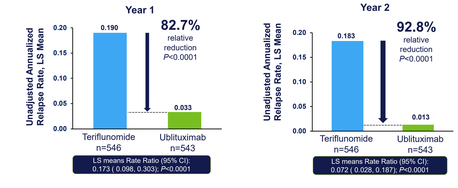
Figure 4. Redefined ARR by Year 1 and Year 2; MRI-supported relapse criteria only



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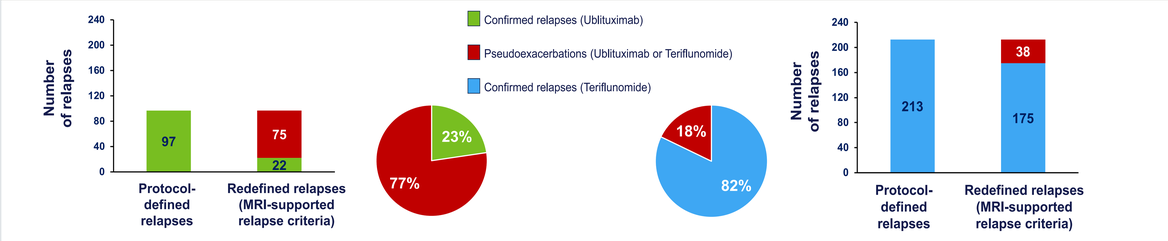
- Using the MRI-supported relapse criteria, 75 of 97 events (~77%) in ublituximab-treated participants and 38 of the 213 (~18%) events in the teriflunomide-treated participants were identified as pseudoexacerbations **(Figure 5).**

Figure 5. Number of relapses measured under original definition and under the MRI-supported relapse" criteria

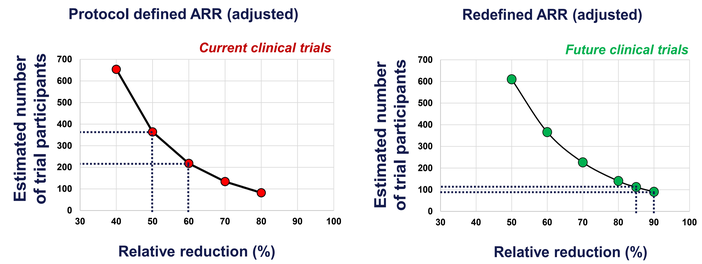


- Power analysis of sample size using redefined ARR (MRI-supported relapse) reduced the number of trial participants needed to demonstrate significant difference between treatment arms **(Table 2).**
- Applying the stringent criteria of MRI-supported relapses, the estimated sample size is reduced by approximately two-thirds to reach statistical significance between two arms. These findings have implications for future clinical trial design **(Figure 6).**

Table 2. Estimated sample size for trial participants

Protocol Defined Relapse					
Power	0.8	0.8	0.8	0.8	0.8
Alpha	0.05	0.05	0.05	0.05	0.05
Exposure time (years)	1.75	1.75	1.75	1.75	1.75
Event rate (ctrl)	0.183	0.183	0.183	0.183	0.183
Event rate (trt)	0.1098	0.0915	0.0732	0.0549	0.0366
Event ratio	0.6	0.5	0.4	0.3	0.2
Reduction	40%	50%	60%	70%	80%
Neg Binom Disp	2	2	2	2	2
N1	327	182	109	67	41
N2	327	182	109	67	41
N	654	364	218	134	82
Redefined Relapse					
Power	0.8	0.8	0.8	0.8	0.8	0.8
Alpha	0.05	0.05	0.05	0.05	0.05	0.05
Exposure time (years)	1.75	1.75	1.75	1.75	1.75	1.75
Event rate (ctrl)	0.096	0.096	0.096	0.096	0.096	0.096
Event rate (trt)	0.048	0.0384	0.0288	0.0192	0.0144	0.0096
Event ratio	0.5	0.4	0.3	0.2	0.15	0.1
Reduction	50%	60%	70%	80%	85%	90%
Neg Binom Disp	2	2	2	2	2	2
N1	305	183	113	70	56	45
N2	305	183	113	70	56	45
N	610	366	226	140	112	90

Figure 6. Estimated sample size for trial participants for original ARR and redefined ARR



- Power analysis of sample size using redefined ARR impacted the estimated number of trial participants needed for varying study durations of 24-, 48-, and 72-weeks **(Table 2 and Figure 7).**

Table 3. Estimated sample size for trial participants; assessing impact of redefined relapses on trial duration

	Redefined Relapse								
	24-week trial			48-week trial			72-week trial		
Power	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Alpha	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Exposure time (years)	0.46	0.46	0.46	0.92	0.92	0.92	1.38	1.38	1.38
Event rate (ctrl)	0.096	0.096	0.096	0.096	0.096	0.096	0.096	0.096	0.096
Event rate (trt)	0.0192	0.0144	0.0096	0.0192	0.0144	0.0096	0.0192	0.0144	0.0096
Event ratio	0.2	0.15	0.1	0.2	0.15	0.1	0.2	0.15	0.1
Reduction	80%	85%	90%	80%	85%	90%	80%	85%	90%
Neg Binom Disp	2	2	2	2	2	2	2	2	2
N1	227	182	147	117	94	75	80	64	51
N2	227	182	147	117	94	75	80	64	51
N	454	364	294	234	188	150	160	128	102

Figure 7. Estimated sample size under redefined relapses for 24-, 48-, and 72-week trial duration