CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA 761238
Drug Name:	Ublituximab (TG-1101)
Indication(s):	Relapsing forms of Multiple Sclerosis (RMS)
Applicant:	TG Therapeutics, Inc
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1 EXECUTIVE SUMMARY

The efficacy of ublituximab was studied in two identical Phase III, 120-week, randomized, multicenter, global, double-blinded, double-dummy, active-controlled studies in subjects with relapsing forms of multiple sclerosis (RMS). Both studies met the primary endpoint, demonstrating a statistically significant reduction in annualized relapse rate (ARR) with the treatment of ublituximab as compared to teriflunomide. There was a 59% reduction of ARR in Study TG1101-RMS301 ($p<0.0001$) and a 49% reduction in Study TG1101-RMS302 ($p=0.0022$). The efficacy on ARR was robust, supported by sensitivity analyses and subgroup analyses.

Both studies also showed statistically significant treatment effect in MRI-related endpoints. Ublituximab significantly reduced the number of T1 Gd-enhancing lesions by 97% for each study, and significantly reduced the number of new or enlarging T2 lesions by 92% and 90% respectively for Studies TG1101-RMS301 and TG1101-RMS302, compared to teriflunomide.

There was no statistically significant difference in disability progression confirmed at 12 weeks based on the pooled data of the 2 studies, although the result numerically favored the ublituximab treatment group (hazard ratio =0.843, $p=0.5099$).

Overall, the efficacy of ublituximab in subjects with RMS was demonstrated in the two pivotal studies.

2 INTRODUCTION

2.1 Overview

Ublituximab has been developed under Investigational New Drug (IND) application 127265 for the treatment of RMS. The clinical efficacy program consisted of 2 pivotal studies TG1101-RMS301 and TG1101-RMS302 (referred to as Studies 301 and 302 hereafter). These were two identical Phase III, 120-week, randomized, multicenter, global, double-blinded, double-dummy, active-controlled studies. The primary endpoint was ARR. The protocols for these studies were agreed upon with the FDA through a Special Protocol Assessment.

2.2 Data Sources

Materials reviewed for this application include the clinical study reports, raw and derived datasets, SAS codes used to generate the derived datasets and tables, protocols, statistical analysis plans, and documents of regulatory communications, which are located in the following directories: \\CDSESUB1\evsprod\BLA761238\0001.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Documentation of statistical analysis methods was included with sufficient details for this reviewer to reproduce the applicant's key efficacy results.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 301 was initiated on September 19, 2017 and completed on November 06, 2020. Study 302 was initiated on August 25, 2017 and completed on November 12, 2020. The final version of Statistical Analysis Plan (SAP) was dated September 4, 2020 for both studies. The master SAP was dated November 11, 2020 which specified the analysis of the time to confirmed disability progression using pooled data of the 2 studies.

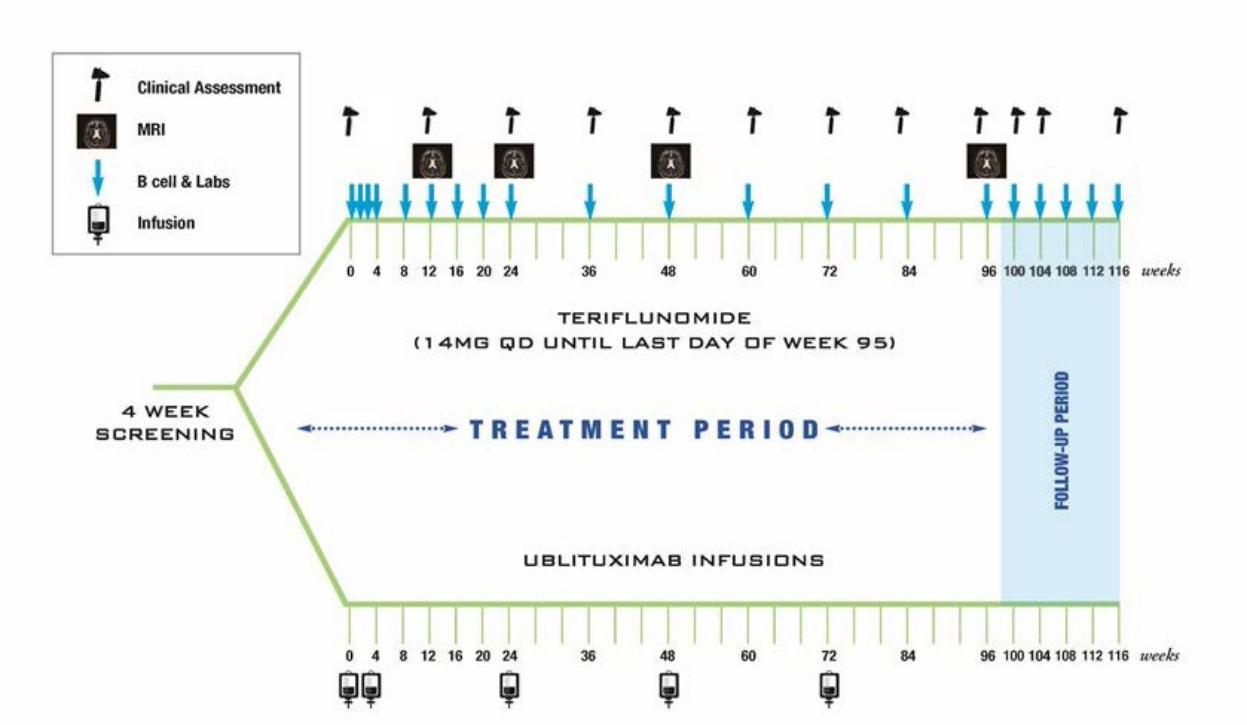
Study Design

Studies 301 and 302 were identical in design. Each study was a 120-week, randomized, multicenter, double-blind, double-dummy, active comparator-controlled study in subjects with RMS. Subjects enrolled in each pivotal study were 18 to 55 years of age (inclusive) and with at least 1 relapse in the previous year, at least 2 relapses in the previous 2 years, or had the presence of a T1 gadolinium-enhancing lesion in the previous year. Subjects were also required to have an Expanded Disability Status Scale (EDSS) score from 0 to 5.5 at Baseline.

The studies included a 4-week Screening Period, a 96-week Treatment Period, and a 20-week Follow-up Period. After screening, qualified subjects were randomized in a 1:1 ratio to receive either ublituximab/oral placebo or teriflunomide/IV placebo. Subjects received ublituximab or IV placebo infusions on Week 1 Day 1, Week 3 Day 15, and Weeks 24, 48, and 72. Oral teriflunomide (14 mg) or placebo was taken daily starting at Week 1 Day 1 until the last day of

Week 95. Neurological evaluations were performed at Baseline, every 12 weeks, and at the time of a suspected relapse. Each episode of relapse was confirmed by the Independent Relapse Adjudication Panel (IRAP). Brain MRI scans were performed at Baseline and at Weeks 12, 24, 48, and 96.

Figure 1. Schematic of Phase 3 Study Design



Efficacy Endpoint

The primary endpoint was ARR defined as the number of IRAP-confirmed relapses per year.

The key secondary efficacy endpoints were as follows:

1. Total number of gadolinium enhancing (Gd-enhancing) T1 lesions per MRI scan by Week 96;
2. Total number of new and enlarging T2 hyperintense lesions per MRI scan by Week 96;
3. Time to Confirmed Disability Progression (CDP)for at least 12 weeks occurring during the 96-week, double-blind treatment period;
4. Proportion of subjects with no evidence of disease activity (NEDA) from Week 24 to Week 96;
5. Proportion of subjects reaching impaired symbol digit modality test (SDMT) from Baseline to Week 96;
6. Percentage change in brain volume from Baseline to Week 96.

3.2.2 Statistical Methodologies

Analysis Method

The primary efficacy analysis set was Modified Intent-to-Treat (mITT) Population, consisting of all randomized subjects who received at least 1 dose of study treatment and had at least 1 baseline and post-baseline efficacy assessment. The mITT-MRI population consisted of subjects in the mITT population who had baseline and post-baseline MRI efficacy assessments and was used for the analyses of MRI-related variables.

Analyses of the primary efficacy endpoint

The primary analysis was a negative binomial regression model that included the total number of confirmed relapses with onset between randomization date and the day of last treatment as response variable, treatment group, EDSS strata (baseline EDSS score ≤3.5 versus >3.5), and clinic region (USA and Western Europe, Eastern Europe) as covariates. To account for different treatment durations among subjects, the log-transformed standardized treatment duration was included in the model as an "offset" variable. For participants who withdrew from their active treatment, all data up to the time of withdrawal from treatment was used in the primary analysis. Sensitivity analysis using data over the entire study period was also performed.

Specified sensitivity analysis for the primary endpoint included the following:

1. The primary analysis were repeated based on all reported MS relapses (rather than just confirmed ones).
2. An analysis of time to first IRAP-confirmed relapse using Cox proportional hazards model that included treatment, region, number of relapses in previous year, baseline EDSS score strata, baseline number of T1 Gd-enhancing lesions, sex, and the subject's age at baseline as covariates.
3. To assess the effects of treatment withdrawals, the primary analysis was repeated that included relapses which occurred after permanent discontinuation of study medication and natural log (time on study in years) was used as the offset variable.
4. To assess the impact of the dropouts from the trial for all participants who provided withdrawal of consent excluding deaths, multiple imputation was used to impute the expected number of relapses a participant would have had if they had continued to participate in the trial. To perform the imputation, 10 replicates were used since a relapse on treatment was relatively low frequency event. The covariates used to model and predict the imputations included treatment, region, number of relapses in previous year, baseline EDSS score strata, baseline number of T1 Gd-enhancing lesions, sex and age.

Analyses of the secondary efficacy endpoints

The MRI count variables (total number of Gd-enhancing T1-lesions per MRI scan, total number of new and enlarging T2 hyperintense lesions per MRI scan) were analyzed using negative binomial regressions with an offset based on the log-transformed number of post-baseline MRI scans and covariates of region, baseline EDSS strata, and corresponding baseline lesion count.

The 12-week CDP was defined as an increase in EDSS of at least 1 point higher than the baseline EDSS (or at least 0.5 if the baseline EDSS is >5.5) and was considered confirmed (CDP) when the increase in the EDSS was confirmed (same criteria) at a regularly scheduled visit 12 weeks

after the initial documentation of neurological worsening. For each of these events, the time from randomization to the date of the first measurement of the increased EDSS as required was the "time to event". If no event occurred, the time to CDP was regarded as censored at the last scheduled EDSS assessment. The 12-week CDP was analyzed using pooled data from the 2 studies. The median time-to-event as well as the proportion of subjects remaining event-free at times of interest was estimated using Kaplan-Meier methods. The time to onset of CDP was compared between treatment using a log-rank test stratified by region, baseline EDSS strata and study.

Interim Analyses

A blinded interim analysis for sample size re-estimation was planned to be performed when 210 of the 220 participants per arm had been randomized by an independent committee, Blinded Assessment Relapse Team (BART), reporting to TG Therapeutics. The sample size was reassessed based on the pooled annualized relapse rate (ARR). If the combined total rate <= 0.19, the sample size would be increased by 30 per treatment group in each study. The BART committee met on October 15, 2020 and recommended adding 30 subjects to the sample size (n=220 + 30).

Multiplicity Adjustment

A gatekeeping procedure was used where each test was tested at α=0.05. For the 12-week CDP endpoint, the testing was based on pooled data from the 2 studies to achieve sufficient statistical power to detect relevant treatment differences. This test was considered confirmatory only if all tests for the primary endpoint and first 2 secondary endpoints were statistically significant (α=0.05) in both studies. All subsequent tests were continued at α=0.05 level within each individual study, only if the pooled analysis of CDP was statistically significant.

3.2.3 Study 301

3.2.3.1 Patient Disposition, Demographic and Baseline Characteristics

For study 301, 549 participants were randomized (274 in the ublituximab group and 275 in the teriflunomide group). One randomized participant was not treated. The 96-week Treatment Period was completed by 240 (87.6%) participants in the ublituximab group and 252 (91.6%) participants in the teriflunomide group (Table 1).

Table 1. Study 301: Disposition

	Ublituximab (N=274) n (%)	Teriflunomide (N=275) n (%)	Total (N=549) n (%)
ITT Population	274 (100)	275 (100)	549 (100)
mITT Population	271 (98.9)	274 (99.6)	545 (99.3)
mITT-MRI Population	265 (96.7)	270 (98.2)	535 (97.4)
Completed treatment period (96 weeks)	240 (87.6)	252 (91.6)	492 (89.6)
Study drug prematurely discontinued	34 (12.4)	23 (8.4)	57 (10.4)
Reason for discontinuation			
Adverse Event	17 (6.2)	1 (0.4)	18 (3.3)
Subject withdrawal of consent	6 (2.2)	15 (5.5)	21 (3.8)
Investigator / Sponsor decision	4 (1.5)	2 (0.7)	6 (1.1)
Pregnancy	2 (0.7)	0	2 (0.4)
Lost to Follow-Up	2 (0.7)	2 (0.7)	4 (0.7)
Lack of Efficacy	2 (0.7)	2 (0.7)	4 (0.7)
Alternative Treatment	1 (0.4)	0	1 (0.2)
COVID-19	0	0	0
Other	0	1 (0.4)	1 (0.2)

Source: CSR Table 12.

The baseline demographic and disease characteristics were comparable between the two groups. Overall, majority of the study population was White (97%) and female (63%), and the mean age was 37 years at baseline. The mean time since MS diagnosis from randomization was 4.7 years, the mean number of relapses in the prior year was 1.3, and the mean EDSS score at baseline was 2.9 (Table 2).

Table 2. Study 301: Demographic and Baseline Characteristics (mITT Population)

	Ublituximab (N=271)	Teriflunomide (N=274)	Total (N=545)
Age (years)			
Mean (SD)	36.2 (8.42)	37.0 (9.63)	36.6 (9.05)
<38 years, n (%)	150 (55.4)	146 (53.3)	296 (54.3)
≥38 years, n (%)	121 (44.6)	128 (46.7)	249 (45.7)
Gender, n (%)			
Female	166 (61.3)	179 (65.3)	345 (63.3)
Male	105 (38.7)	95 (34.7)	200 (36.7)
Race, n (%)			
White	264 (97.4)	266 (97.1)	530 (97.2)
Black or African American	6 (2.2)	6 (2.2)	12 (2.2)
Native Hawaiian or Other Pacific Islander	1 (0.4)	0	1 (0.2)
Other	0	2 (0.7)	2 (0.4)
Region, n (%)			
USA and Western Europe	26 (9.6)	31 (11.3)	57 (10.5)
Eastern Europe	245 (90.4)	243 (88.7)	488 (89.5)
Time since diagnosis (years)			
Mean	4.9	4.5	4.7
SD	5.24	4.96	5.10
Number of relapses in the prior year			
Mean	1.3	1.4	1.3
SD	0.65	0.67	0.66
Baseline EDSS			
Mean	3.0	2.9	2.9
SD	1.21	1.17	1.19
<=3.5 n (%)	200 (73.8)	208 (75.9)	408 (74.9)
>3.5 n (%)	71 (26.2)	66 (24.1)	137 (25.1)
Number of Gd-enhancing lesions, n (%)			
0	153 (56.5)	156 (56.9)	309 (56.7)
>=1	117 (43.2)	116 (42.3)	233 (42.8)
Missing	1 (0.4)	2 (0.7)	3 (0.6)

Source: CSR Tables 15 & 16 and FDA reviewer.

3.2.3.2 Results and Conclusions

Analyses of the primary endpoint

The least squares (LS) mean for the ARR was 0.076 in the ublituximab group and 0.188 in the teriflunomide group. The treatment effect of ublituximab versus teriflunomide was statistically significant in favor of ublituximab at a rate ratio of 0.406 ($p<0.0001$), corresponding to a relative reduction of 59.4% (Table 3). All prespecified sensitivity analyses were consistent with the primary analysis. There were several instances of unblinding events affecting 3% of the patients. Sensitivity analysis excluding these patients from the analysis showed minimal impact on the

results for the primary efficacy endpoint (result not shown in table). The efficacy analysis set of mITT Population excluded subjects who did not have post-baseline efficacy assessment, which has minimal impact on the assessment of treatment effect because the number of patients without post-baseline efficacy assessment was small (<1%).

Table 3. Study 301: Annualized Relapse Rate

	Ublituximab (N=271)	**Teriflunomide (N=274)**
Primary analysis		
LS means annualized relapse rate (95% CI)	0.076 (0.042, 0.138)	0.188 (0.124, 0.283)
Rate ratio: ublituximab / teriflunomide	0.406 (0.268, 0.615)	
P-value	<0.0001	
Sensitivity analysis: Including all subject-reported relapses		
LS means annualized relapse rate (95% CI)	0.205 (0.133, 0.317)	0.475 (0.359, 0.629)
Rate ratio: ublituximab / teriflunomide	0.431 (0.299, 0.623)	
P-value	<0.0001	
Sensitivity analysis: IRAP-confirmed relapses including follow-up		
LS means annualized relapse rate (95% CI)	0.070 (0.040, 0.125)	0.180 (0.119, 0.273)
Rate ratio: ublituximab / teriflunomide	0.390 (0.265, 0.575)	
P-value	<0.0001	
Sensitivity analysis: Multiple imputation of withdrawn subjects		
LS means annualized relapse rate (95% CI)	0.077 (0.042, 0.138)	0.189 (0.124, 0.287)
Rate ratio: ublituximab / teriflunomide	0.405 (0.267, 0.616)	
P-value	<0.0001	
Sensitivity analysis: time to first confirmed relapse		
Proportion free of confirmed relapses at 96 weeks, (%), 95% CI	86.0 (81.2, 89.7)	74.4 (68.7, 79.2)
Hazard Ratio (ublituximab/ teriflunomide)	0.50 (0.33, 0.75)	
P-value	0.0009	

Source: CSR Table 20, Table 21, and Table 14.2.1.4, confirmed by FDA reviewer.

Analyses of the secondary endpoints

The difference of treatment effect in the total number of Gd-enhancing T1 lesions per MRI scan was statistically significant in favor of ublituximab at a ratio of 0.033 ($p<0.0001$; Table 4). The LS mean was 0.016 in the ublituximab group and 0.491 in the teriflunomide group. Sensitivity analyses were consistent with the primary analysis.

The difference of treatment effect in the total number of new and enlarging T2 hyperintense lesions per MRI scan was statistically significant in favor of ublituximab at a ratio of 0.076 ($p<0.0001$; Table 4). The LS mean was 0.213 in the ublituximab group and 2.789 in the teriflunomide group. Sensitivity analyses were consistent with the primary analysis.

Table 4. Study 301: Summary of Secondary Endpoints

	Ublituximab (N=265)	**Teriflunomide (N=270)**
Total number of Gadolinium-enhancing T1 lesions per MRI scan per subject		
n	264	269
Least squares means (95% CI)	0.016 (0.008, 0.032)	0.491 (0.355, 0.679)
Ratio: ublituximab / teriflunomide	0.033 (0.019, 0.058)	
p value	<0.0001	
Total number of new and enlarging T2 hyperintense lesions per MRI scan per subject		
n	260	267
Least squares means (95% CI)	0.213 (0.144, 0.316)	2.789 (2.136, 3.643)
Ratio: ublituximab / teriflunomide	0.076 (0.056, 0.104)	
p value	<0.0001	

Source: CSR Table 22 and Table 24, confirmed by the reviewer.

The analyses of 12-week CDP were based on pooled data from Study 301 and Study 302. The time to CDP for at least 12 weeks was not statistically significant using a stratified log-rank test (hazard ratio =0.843, p=0.5099; Table 5). The proportion of participants with CDP for at least 12 weeks was low and similar in both treatment groups (28 [5.2%] in the ublituximab group and 32 [5.9%] in the teriflunomide group). All subsequent secondary endpoints were not formally tested because the analysis of CDP was not statistically significant.

Table 5. Time to Confirmed Disability Progression for at Least 12 Weeks in Studies 301 and 302 Pooled

	Pooled	
	Ublituximab (N=543)	**Teriflunomide (N=546)**
Number of subjects with CDP for at least 12 weeks, n (%)	28 (5.2)	32 (5.9)
CDP for at least 12 weeks – stratified log-rank test		
Hazard ratio (95% CI)	0.843 (0.504, 1.407)	
p value	0.5099	

Source: CSR Table 26, confirmed by the reviewer.

3.2.4 Study 302

3.2.4.1 Patient Disposition, Demographic and Baseline Characteristics

For study 302, 545 participants were randomized (272 in the ublituximab group and 273 in the teriflunomide group). All randomized participants were treated. The 96-week Treatment Period was completed by 254 (93.4%) participants in the ublituximab group and 239 (87.5%) participants in the teriflunomide group (Table 6).

Table 6. Study 302: Disposition

	Ublituximab (N=272) n (%)	Teriflunomide (N=273) n (%)	Total (N=545) n (%)
ITT Population	272 (100)	273 (100)	545 (100)
mITT Population	272 (100)	272 (99.6)	544 (99.8)
mITT-MRI Population	272 (100)	267 (97.8)	539 (98.9)
Completed treatment period (96 weeks)	254 (93.4)	239 (87.5)	493 (90.5)
Study drug prematurely discontinued	18 (6.6)	34 (12.5)	52 (9.5)
Reason for discontinuation			
Adverse Event	3 (1.1)	1 (0.4)	4 (0.7)
Subject withdrawal of consent	6 (2.2)	23 (8.4)	29 (5.3)
Investigator / sponsor decision	2 (0.7)	2 (0.7)	4 (0.7)
Pregnancy	4 (1.5)	1 (0.4)	5 (0.9)
Lost to Follow-Up	0	2 (0.7)	2 (0.4)
Lack of Efficacy	0	2 (0.7)	2 (0.4)
Alternative Treatment	0	2 (0.7)	2 (0.4)
COVID-19	3 (1.1)	0	3 (0.6)
Other	0	1 (0.4)	1 (0.2)

Source: CSR Table 12.

The baseline demographic and disease characteristics were similar between the two groups. Overall, majority of the study population was White (99%) and female (65%), and the mean age was 35 years at baseline. The mean time since MS diagnosis from randomization was 5.0 years,

the mean number of relapses in the prior year was 1.3, and the mean EDSS score at baseline was 2.9 (Table 7).

Table 7. Study 302: Demographic and Baseline Characteristics (mITT Population)

	Ublituximab (N=272)	Teriflunomide (N=272)	Total (N=544)
Age (years)			
Mean (SD)	34.5 (8.76)	36.2 (8.96)	35.3 (8.89)
<38 years, n (%)	176 (64.7)	156 (57.4)	332 (61.0)
≥38 years, n (%)	96 (35.3)	116 (42.6)	212 (39.0)
Gender, n (%)			
Female	178 (65.4)	176 (64.7)	354 (65.1)
Male	94 (34.6)	96 (35.3)	190 (34.9)
Race, n (%)			
White	269 (98.9)	268 (98.5)	537 (98.7)
Black or African American	2 (0.7)	3 (1.1)	5 (0.9)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.2)
Other	1 (0.4)	1 (0.4)	2 (0.4)
Region, n (%)			
USA and Western Europe	27 (9.9)	22 (8.1)	49 (9.0)
Eastern Europe	245 (90.1)	250 (91.9)	495 (91.0)
Time since diagnosis (years)			
Mean	5.0	5.0	5.0
SD	5.62	5.17	5.40
Number of relapses in the prior year			
Mean	1.3	1.2	1.3
SD	0.65	0.65	0.65
Baseline EDSS			
Mean	2.8	3.0	2.9
SD	1.31	1.20	1.26
<=3.5 n (%)	218 (80.1)	206 (75.7)	424 (77.9)
>3.5 n (%)	54 (19.9)	66 (24.3)	120 (22.1)
Number of Gd-enhancing lesions, n (%)			
0	131 (48.2)	135 (49.6)	266 (48.9)
>=1	141 (51.8)	135 (49.6)	276 (50.7)
Missing	0	2 (0.7)	2 (0.4)

Source: CSR Tables 15 & 16 and FDA reviewer.

3.2.4.2 Results and Conclusions

Analyses of the primary endpoint

The LS mean for the ARR was 0.091 in the ublituximab group and 0.178 in the teriflunomide group. The treatment effect of ublituximab versus teriflunomide was statistically significant in favor of ublituximab at a rate ratio of 0.509 (p=0.0022), corresponding to a relative reduction of

49.1% (Table 8). All prespecified sensitivity analyses were consistent with the primary analysis. There were several instances of unblinding events affecting <1% of the patients. Sensitivity analysis excluding these patients from the analysis showed minimal impact on the results for the primary efficacy endpoint (result not shown in table). The efficacy analysis set of mITT Population excluded subjects who did not have post-baseline efficacy assessment, which has minimal impact on the assessment of treatment effect because the number of patients without post-baseline efficacy assessment was small (<1%).

Table 8. Study 302: Annualized Relapse Rate

	Ublituximab (N=272)	**Teriflunomide (N=272)**
Primary analysis		
LS means annualized relapse rate (95% CI)	0.091 (0.049, 0.169)	0.178 (0.109, 0.291)
Rate ratio: ublituximab / teriflunomide	0.509 (0.330, 0.784)	
P-value	0.0022	
Sensitivity analysis: Including all subject-reported relapses		
LS means annualized relapse rate (95% CI)	0.174 (0.105, 0.288)	0.277 (0.186, 0.411)
Rate ratio: ublituximab / teriflunomide	0.630 (0.428, 0.928)	
P-value	0.0193	
Sensitivity analysis: IRAP-confirmed relapses including follow-up		
LS means annualized relapse rate (95% CI)	0.094 (0.054, 0.166)	0.190 (0.122, 0.296)
Rate ratio: ublituximab / teriflunomide	0.494 (0.331, 0.740)	
P-value	0.0006	
Sensitivity analysis: Multiple imputation of withdrawn subjects		
LS means annualized relapse rate (95% CI)	0.090 (0.048, 0.171)	0.181 (0.109, 0.299)
Rate ratio: ublituximab / teriflunomide	0.500 (0.323, 0.773)	
P-value	<0.0001	
Sensitivity analysis: time to first confirmed relapse		
Proportion free of confirmed relapses at 96 weeks, (%), 95% CI	87.4(82.8, 90.8)	72.1(66.2, 77.2)
Hazard Ratio (Ublituximab/Teriflunomide)	0.43 (0.28, 0.65)	
P-value	<0.0001	

Source: CSR Table 20, Table 21, and Table 14.2.1.4, confirmed by FDA reviewer.

Analyses of the secondary endpoints

The difference of treatment effect in the total number of Gd-enhancing T1 lesions per MRI scan was statistically significant in favor of ublituximab at a ratio of 0.035 (p<0.0001; Table 9). The LS mean was 0.009 in the ublituximab group and 0.250 in the teriflunomide group. Sensitivity analyses were consistent with the primary analysis.

The difference of treatment effect in the total number of new and enlarging T2 hyperintense lesions per MRI scan was statistically significant in favor of ublituximab at a ratio of 0.100 (p<0.0001; Table 9). The LS mean was 0.282 in the ublituximab group and 2.831 in the teriflunomide group. Sensitivity analyses were consistent with the primary analysis.

Table 9. Study 301: Summary of Secondary Endpoints

	Ublituximab (N=272)	**Teriflunomide (N=267)**
Total number of Gadolinium-enhancing T1 lesions per MRI scan per subject		
n	272	267
Least squares means (95% CI)	0.009 (0.004, 0.017)	0.250 (0.162, 0.385)
Ratio: ublituximab / teriflunomide	0.035 (0.019, 0.064)	
p value	<0.0001	
Total number of new and enlarging T2 hyperintense lesions per MRI scan per subject		
n	272	267
Least squares means (95% CI)	0.282 (0.200, 0.397)	2.831 (2.128, 3.767)
Ratio: ublituximab / teriflunomide	0.100 (0.073, 0.136)	
p value	<0.0001	

Source: CSR Table 22 and Table 24, confirmed by the reviewer.

The analysis of 12-week CDP based on pooled data from the 2 studies was not statistically significant, as described in Section 3.2.3.2. Therefore, all subsequent secondary endpoints were not formally tested.

3.3 Evaluation of Safety

Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The subgroup analyses in the CSR dropped EDSS strata and region from the pre-specified list of covariates. The applicant made this post-hoc change because of convergence issues for some of the full models examining the treatment by subgroup interaction. However, the convergence

issue does not affect the analyses within each subgroup of age, gender, race and geographical regions. Therefore, the reviewer performed the subgroup analyses for each individual subgroup as specified in the SAP and the results are in Table 10 and Table 11. There appeared to have a treatment effect on ARR favoring ublituximab across the subgroups with a reasonable sample size.

For the subgroups of Other races, the comparisons between the treatment group may not be informative due to the small number of subjects (15 in Study 301 and 7 in Study 302) and relapse events (5 in Study 301 and 0 in Study 302) in this subgroup.

Similarly for the subgroups of USA/Western Europe region, the number of subjects (57 in Study 301 and 49 in Study 302) and relapse events (7 in Study 301 and 6 in Study 302) was small. The subgroup results may not be meaningful even though the 95% CIs for the rate ratio excluded 1 in favor of the teriflunomide control group. Additionally, contradictory subgroup findings were seen for the key secondary endpoints. For example, for the subgroups of USA/Western Europe region in Study 301, the treatment effect in the number of Gd-enhancing T1 lesions favored ublituximab with a rate ratio of 0.0158 and 95% CI of (0.048, 0.514) (analysis conducted by the reviewer and result not shown in table). Therefore, the results for the subgroups of USA/Western Europe region were inconclusive.

Table 10. Study 301: Annualized Relapse Rate - Subgroup Analyses

Subgroup	Ublituximab (N=271)		Teriflunomide (N=274)		Rate Ratio (95%CI)*
	n	ARR (LS mean and 95%CI)	n	ARR (LS mean and 95%CI)	
Gender					
Female	166	0.104 (0.052, 0.210)	179	0.175 (0.107, 0.287)	0.594 (0.365, 0.967)
Male	105	0.038 (0.013, 0.107)	95	0.188 (0.089, 0.395)	0.201 (0.092, 0.438)
Race					
Other races	7	0.393 (0.117, 1.318)	8	0.131 (0.046, 0.377)	2.998 (0.670, 13.415)
White	264	0.046 (0.020, 0.106)	266	0.046 (0.020, 0.106)	0.377 (0.248, 0.572)
Age					
<38	150	0.079 (0.033, 0.191)	146	0.336 (0.196, 0.577)	0.235 (0.125, 0.441)
≥38	121	0.075 (0.035, 0.161)	128	0.082 (0.040, 0.168)	0.907 (0.507, 1.624)
Region					
USA/Western Europe	26	0.281 (0.113, 0.700)	31	0.046 (0.014, 0.146)	6.137 (1.758, 21.426)
Eastern Europe	245	0.100 (0.069, 0.144)	243	0.285 (0.224, 0.362)	0.350 (0.229, 0.534)

*Analyzed using negative binomial models with treatment, region, and Baseline EDSS strata as covariates.
Source: FDA reviewer.

Table 11. Study 302: Annualized Relapse Rate - Subgroup Analyses

Subgroup	Ublituximab (N=272)		Teriflunomide (N=272)		Rate Ratio (95%CI)*
	n	ARR (LS mean and 95%CI)	n	ARR (LS mean and 95%CI)	
Gender					
Female	178	0.093 (0.043, 0.205)	176	0.179 (0.095, 0.338)	0.523 (0.316, 0.864)
Male	94	0.085 (0.033, 0.216)	96	0.172 (0.086, 0.345)	0.493 (0.223, 1.088)
Race					
Other races	3	N/A	4	N/A	N/A
White	269	0.100 (0.054, 0.185)	268	0.198 (0.121, 0.326)	0.504 (0.327, 0.777)
Age					
<38	176	0.083 (0.036, 0.191)	156	0.206 (0.102, 0.418)	0.401 (0.228, 0.706)
≥38	96	0.101 (0.045, 0.229)	116	0.135 (0.073, 0.248)	0.750 (0.395, 1.427)
Region					
USA/Western Europe	27	0.255 (0.101, 0.646)	22	0.024 (0.004, 0.137)	10.842 (1.453, 80.914)
Eastern Europe	245	0.118 (0.079, 0.174)	250	0.257 (0.201, 0.328)	0.458 (0.291, 0.720)

*Analyzed using negative binomial models with treatment, region, and Baseline EDSS strata as covariates.
Source: FDA reviewer.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

For the subgroup of USA/Western Europe region in both studies, the treatment effect in ARR favored the teriflunomide arm and the 95% CIs for the rate ratio excluded 1. However, these results may not be meaningful as the number of subjects in this subgroup was small and the MRI endpoint showed contradictory results favoring the ublituximab arm. Therefore, the results for the subgroup of USA/Western Europe region were inconclusive.

5.2 Collective Evidence

In both studies, ublituximab significantly lowered the ARR, number of T1 Gd-enhancing lesions and number of new or enlarging T2 lesions compared to teriflunomide. There was no statistically significant difference in disability progression confirmed at 12 weeks between ublituximab-treated and teriflunomide-treated patients (Table 12).

Table 12. Summary of Key Efficacy Results in Studies 301 and 302

	Study 301		Study 302	
	Ublituximab	Teriflunomide	Ublituximab	Teriflunomide
Primary Endpoint				
Annualized Relapse Rate	0.076	0.188	0.091	0.178
Relative Reduction	59% (p<0.0001)		49% (p = 0.0022)	
Secondary Endpoints				
Mean number of T1 Gd-enhancing lesions per MRI	0.016	0.491	0.009	0.250
Relative Reduction	97% (p<0.0001)		97% (p<0.0001)	
Mean number of new or enlarging T2 hyperintense lesions per MRI	0.213	2.789	0.282	2.831
Relative Reduction	92% (p<0.0001)		90% (p<0.0001)	
Proportion of Patients with 12-week Confirmed Disability Progression	5.2% Ublituximab vs. 5.9% teriflunomide			
Risk Reduction (Pooled Analysis)	16% (p = 0.5099)			

5.3 Conclusions and Recommendations

The efficacy of ublituximab in subjects with RMS was demonstrated in the two pivotal studies, showing robust treatment effect of ublituximab in the primary and first two key secondary endpoints compared to teriflunomide.

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