Summary Review

Date	April 30, 2021
From	Paul Lee, MD, PhD, Deputy Director, Division of Neurology (DN) 2 Nick Kozauer, MD, Director, DN2
Subject	Cross-Discipline Team Leader Summary Review
NDA#	202992 Supplement 13 (incorporates information based on at least one adequate and well-controlled clinical study) (b) (4) [redacted]
Applicant	Sanofi
Date of Submission	November 2, 2020
PDUFA Goal Date	May 2, 2021
Proprietary Name	Aubagio
Established or Proper Name	Teriflunomide
Dosage Form(s)	7 and 14 mg tablets
Current Indication(s)/Population(s)	Treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
Applicant Proposed Indication(s)/Population(s)	(b) (4) [redacted]
Applicant Proposed Dosing Regimen(s)	

	(b) (4) [redacted]
Recommendation on Regulatory Action	S-13: Approval (b) (4) [redacted]
Recommended Indication(s)/Population(s)	Not applicable
Recommended Dosing Regimen(s) (if applicable)	Not applicable

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

The applicant provides evidence from a 166-patient, adequate and well-controlled clinical trial (Study EFC 11759) that investigated whether teriflunomide reduced the likelihood of experiencing a clinical relapse relative to placebo treatment in children 10 through 17 years old with relapsing forms of multiple sclerosis (MS). The trial results do not demonstrate substantial evidence of efficacy for teriflunomide in the treatment of children with MS. The trial did not approach a statistically significant (p=0.2949) reduction in the primary efficacy outcome measure, time to first relapse, for patients treated with teriflunomide as compared to patients treated with a placebo. This lack of a clinical benefit is supported by a number of sensitivity analyses. The applicant suggested that the failure to achieve a significant finding in the analysis of the primary efficacy outcome was due to a trial design feature that allowed patients with high activity on neuroimaging to enter the open-label treatment period early; however, review of the trial findings determined that teriflunomide still failed to demonstrate efficacy at preventing relapses in pediatric patients with MS regardless of their neuroimaging findings. Teriflunomide exposure in pediatric patients resulted in many expected safety risks represented in current labeling. Teriflunomide appeared to cause pancreatitis and elevated serum creatine phosphokinase more frequently in pediatric patients. (b) (4) supplement providing the safety update to labeling that will be approved to advise of the differential safety risks identified in pediatric patients to inform potential off-label use.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pediatric multiple sclerosis represents approximately 5-10% of all cases of relapsing forms of multiple sclerosis (MS). • With rare exceptions, pediatric MS follows a relapsing course; progressive forms of MS are very rare in pediatric MS. Children with pediatric MS experience more relapses on an annual basis, and have a higher number of new or enlarging brain lesions	Pediatric MS is a serious, disabling disease for which there remains an unmet need. Relapses are significant clinical events that cause temporary disability in pediatric MS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	noted on magnetic resonance imaging (MRI) in comparison to adult patients with MS. • A meaningful clinical benefit for a child with MS would be a significant reduction in the likelihood of experiencing a relapse.	
Current Treatment Options	• Gilenya (fingolimod) is the only approved treatment for patients with MS who are 10 through 17 years old. Other therapies approved for use in adults with MS are used in children with MS but without evidence of effectiveness.	There remains a significant unmet medical need for effective therapies to treat relapsing forms of MS in children.
Benefit	• In the controlled efficacy trial included in this application (Study EFC11759), the analysis of the primary efficacy outcome measure, time to first confirmed clinical relapse, was not significantly different between teriflunomide-treated and placebo-treated patients with pediatric MS (p=0.2949). This result was supported by a number of sensitivity analyses. • (b) (4) [redacted] .	An adequate and well-controlled clinical trial in pediatric MS failed to demonstrate a significant treatment effect in reducing the likelihood of experiencing a relapse relative to placebo treatment.
Risk and Risk Management	• Many of the risks associated with the use of teriflunomide in children with MS are described in current approved labeling. • Pancreatitis and elevated serum creatine phosphokinase appear to occur more frequently in pediatric patients with MS treated with teriflunomide than were noted in studies with adults. An increase in serum creatine phosphokinase was reported in 6% of patients treated with teriflunomide (as opposed to no patients treated with placebo) and represents a new safety concern were teriflunomide to be used in children.	The risks of teriflunomide use in pediatric patients with MS appear generally similar to those experienced by adult patients, but a higher frequency of pancreatitis and serum creatine phosphokinase was identified in the blinded clinical trial.

2. Background

The applicant has submitted findings from an adequate and well-controlled 166-patient clinical trial (Study EFC11759) that compared teriflunomide treatment to placebo in pediatric patients with MS. (b) (4)

Regulatory History

Teriflunomide was approved for the treatment of adults with relapsing forms of MS on September 12, 2012, with a PREA post-marketing requirement (PMR 1924-1) to conduct a deferred study in children 10 through 17 years of age.

Due to slow recruitment, a deferral extension request was granted on December 14, 20117, and the PMR 1924-1 final report due date was updated to August 2020.

A Pediatric Written Request was issued on March 7, 2013, with an original due date of June 30, 2016. The PMR due date was revised to August 2020; however, the due date for the Written Request was not revised at that time and remained June 30, 2016.

On July 24, 2020, the applicant submitted a supplement (S-13) to NDA 202992 containing the findings from its pediatric study that was intended to fulfill both PMR 1924-1 and the Pediatric Written Request. This submission met the revised final report deadline for PMR 1924-1 of August 2020, but failed to meet the existing Written Request deadline of June 30, 2016. After discussion with the applicant, the Agency's Pediatric Exclusivity Committee agreed to reissue the Written Request with a new deadline of November 2, 2020. Additionally, the Division issued a deferral extension for PMR 1924-1 to November 2, 2020, since a resubmission would occur beyond the previously agreed upon deferred due date for PMR 1924-1. With agreement to a new deadline for PMR 1924-1 and the Written Request, on September 22, 2020, the applicant withdrew S-13.

On November 2, 2020, the applicant re-submitted the efficacy supplement (S-13) containing the findings of the pediatric trial to fulfill PMR 1924-1 and the Written Request. The submission was given a priority review because the supplemental application was submitted in response to a Pediatric Written Request. After review of the submission determined that there were new safety signals in pediatric patients (b) (4)

(b) (4) the supplement with clinical data proposing the information from the pediatric study for incorporation into teriflunomide labeling as required by Best Pharmaceuticals for Children (b) (4) Pediatric exclusivity was granted on March 31, 2021.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) provided an assessment of the chemistry, manufacturing, and controls (CMC) portion of the application. Dr. Richard Matsuoka provided a primary review, and Dr. David B. Lewis provided a secondary review. The OPQ team recommends approval. The review notes that the applicant provided no changes to the CMC sections of the application, and the applicant has provided a categorical exclusion for Environmental Assessment which was deemed acceptable by the OPQ review team. (b) (4)

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. Melissa Banks-Muckenfuss. Dr. Lois Freed provided a supervisory review. Dr. Banks-Muckenfuss recommends against approval because of the toxicities observed in rats at clinically relevant exposures and inadequacies in the neurobehavioral and T-cell-dependent antibody response (TDAR) assessments. Dr. Freed acknowledges Dr. Banks-Muckenfuss's concerns regarding the deficiencies in the submission but concludes that the toxicology findings that the applicant provided are adequate to support approval. Dr. Freed states that the applicant's findings demonstrate clear drug-related developmental effects, specifically impaired immune function in the TDAR assay, increased locomotor activity, and reduced sperm count, when teriflunomide was administered during the postnatal period in rats at doses resulting in plasma exposure substantially lower than that anticipated in pediatric patients. While additional findings are not needed to inform labeling changes, Dr. Freed states that the question of whether additional studies are needed to address several deficiencies identified in the trial, such as persistence of the reduction in the TDAR, remains open.

The principal conclusions of the nonclinical reviews are as follows:

- The applicant had submitted dose-ranging and pivotal toxicology studies conducted in juvenile animals to the original IND application (IND 67476) and this supplement to the NDA. In the mid-dose (MD) and high-dose (HD) groups, an increase in platelet counts at the high dose, and a decrease in lymphocyte count (39-59%) in all dose groups, was observed and was correlated with microscopic changes in lymphoid organs (*e.g.*, thymic and lymph node atrophy).

- In the pivotal 7-week toxicology study, microscopic findings in toxicity animals were observed in spleen (decreased lymphoid hyperplasia and hemopoiesis) and lymph nodes and Peyer's patches (reduced/absent germinal follicles) in MD and HD males and females. While the applicant's neurohistological assessment in this study did not include special stains, Dr. Freed was satisfied that the microscopic findings provided further evidence of the expected effects on lymphoid tissues and hemopoiesis observed in the dose-ranging study.

- Teriflunomide resulted in suppression of the antibody response (IgM and IgG) at the MD and HD treatments when measured after the first and second neo-antigen challenges. Both Drs. Freed and Banks-Muckenfuss noted that the TDAR was not evaluated in recovery animals, and that there was a dose-related increase in B-lymphocytes in MD and HD treated males and females which was not consistent with the TDAR results. Dr. Freed concluded the TDAR results were adequate, but without a TDAR assay in recovered animals, based on the expected higher exposure in pediatric patients, the assumption would be that the observed reduced antibody response would be long-lasting.

- The assessment of neurobehavioral effects in the pivotal toxicology study was incomplete; startle effect was not evaluated and an inadequate number of animals were evaluated in the Morris water maze test. Additionally, the same animals were used for multiple tests leading to potential confounding with repeated testing. Dr. Freed concluded that despite these issues, the increased locomotor responses in the assessment was interpretable as a significant neurobehavioral treatment-associated effect.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) Review was written by Drs. Xiaohan Cai and Ye Yuan. The team leaders for this review were Drs. Angela Men and Atul Bhattaram. The OCP team concludes that the population pharmacokinetic

(popPK) analysis [redacted] (b) (4)

[redacted] (b) (4) the applicant submitted findings from Study EFC11759 which included an initial blinded eight-week run-in phase during which four blood samples were obtained (pre-dose, Week 2, Week 3, and Week 4) for a popPK analysis. The initial dosing of pediatric patients was evaluated in patients weighing ≤ 40 kg and > 40 kg. Dose adjustments would occur with a goal of achieving a trough serum concentration similar to the trough exposure for teriflunomide in adult patients. The schematic for the run-in is as follows:

Figure 1: Schematic for Dose Adjustments in Study EFC11759

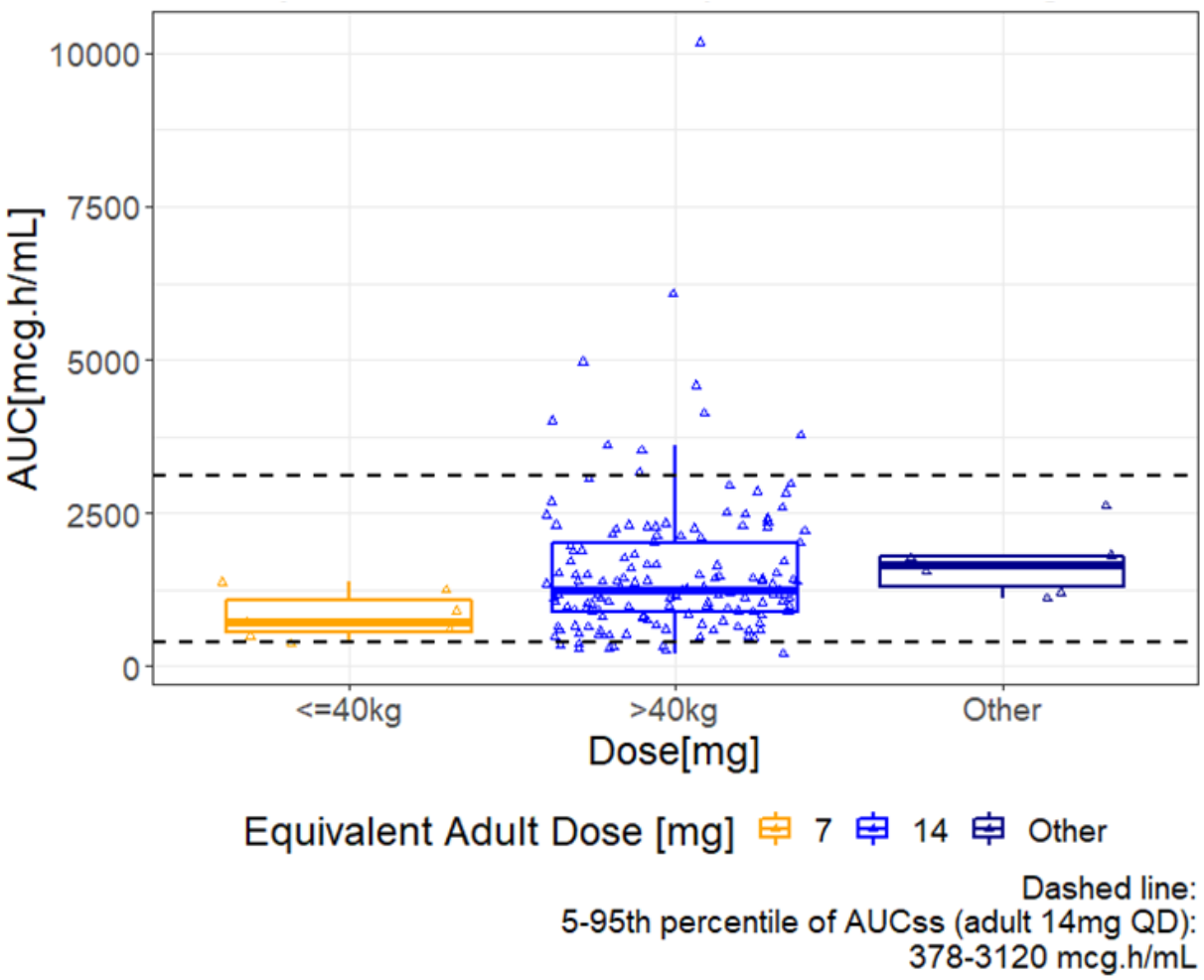
Body weight	8-week PK run-in phase (7 mg adult equivalent dose)	Post-PK run-in phase (14 mg adult equivalent dose)
≤40 kg	3.5 mg once daily	>95th percentile of 7 mg adult exposure → 3.5 mg once daily
		≤95th percentile of 7 mg adult exposure → 7 mg once daily
> 40 kg	7 mg once daily	>95th percentile of 7 mg adult exposure → 7 mg once daily
		≤95th percentile of 7 mg adult exposure → 14 mg once daily

Source: Table 1, Clinical Pharmacology Review

The evaluation of the pharmacokinetics (PK) of teriflunomide in Study EFC11759 compared PK parameters obtained in pediatric patients to the established PK parameters in adult patients.

The steady state area under the curve (AUC) for the pediatric patients was as follows:

Figure 2: Steady State AUC for Teriflunomide 7 mg and 14 mg Doses in Study EFC11759



Source: Figure 1, Clinical Pharmacology Review

(b) (4) dosing regimen, based on body weights of > 40 kg or ≤ 40 kg, provides similar steady state exposure in pediatric patients of 10 years of age and older and adult patients.

As depicted in Figure 3 in this review, data from the PK run-in period were included in the trial's efficacy analyses. There was a discussion in the OCP review that patients in the run-in period may have experienced sub-therapeutic dosing because, at the end of PK run-in phase (*i.e.*, Week 8), the mean trough concentration of teriflunomide for pediatric patients receiving a 7 mg adult equivalent dose was 20.76 µg/mL, which was 44.3% lower than that predicted for adults receiving 14 mg (37.26 µg/mL). A lower exposure may have created an increased risk of a subsequent clinical relapse for

teriflunomide-treated patients and reduced the treatment difference between the teriflunomide and placebo treatment arms. An exploratory analysis conducted by OCP of the relapses occurring after the PK run-in showed that while pediatric patients in the teriflunomide treatment group had fewer numerical relapses than the placebo group, the difference in relapse numbers between treatment groups did not reach nominal significance (p=0.066). The OCP team therefore could not rule out an impact of lower exposures in the run-in impacting the treatment effect. As discussed in the clinical review, the pre-specified sensitivity analysis of the post-run-in time to first relapse was not statistically significant (which aligns with the failure to demonstrate significance in the overall time to first relapse analysis). There were two other sensitivity analyses that failed to demonstrate a meaningful treatment effect on relapses that were unrelated to the run-in period, and an exploratory analysis of the annualized relapse rate was also not significantly different between treatment groups. Therefore, the lack of a finding of a treatment effect on relapses for teriflunomide in Study EFC11759 is not obviously attributable to sub-therapeutic exposures in the PK run-in phase of the trial.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Laura Baldassari was the clinical reviewer for this application. Dr. Sharon Yan was the biometrics reviewer. Dr. Baldassari finds that the application does not provide substantial evidence of efficacy for teriflunomide in the treatment of pediatric patients with relapsing forms of MS. Dr. Yan agrees that the results of Study EFC11759 are not statistically significant.

Study EFC11759

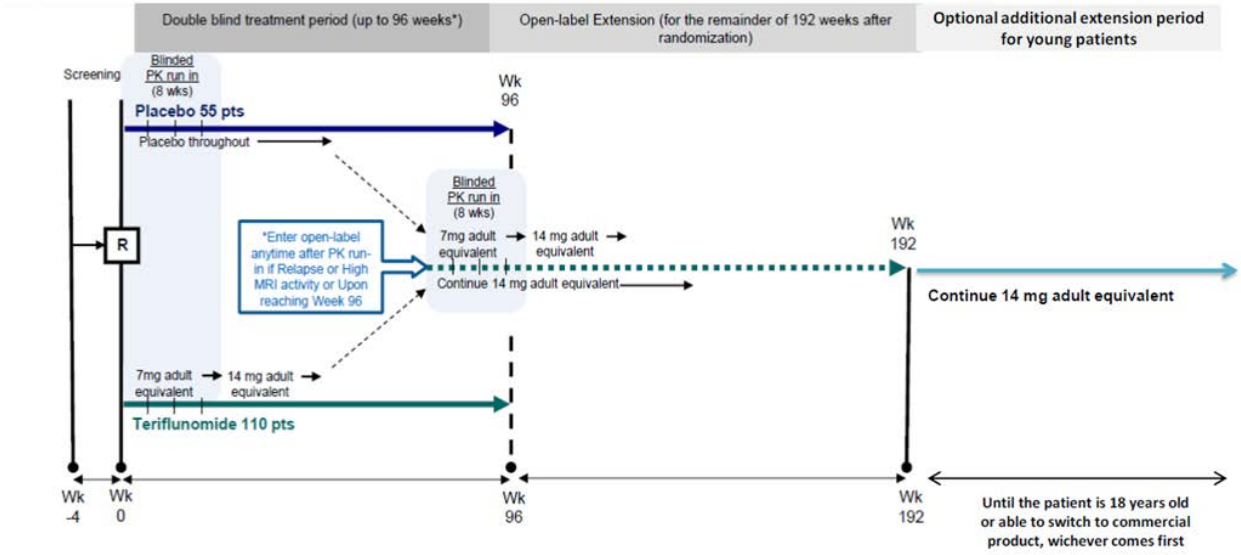
The applicant submitted data from an adequate and well-controlled efficacy Phase 3 study, Study EFC11759, a Phase 3, multicenter, 166-patient, double-blind, placebo-controlled, randomized, superiority study that evaluated the effectiveness, safety, and tolerability of teriflunomide 7 mg and 14 mg daily compared to placebo in patients 10-17 years of age with relapsing forms of MS.

Enrollment criteria stipulated enrollment of patients who met the 2010 McDonald diagnostic criteria for MS and the 2012 International Pediatric MS Study Group criteria for pediatric MS with at least 1 relapse in 12 months prior to screening or at least 2 relapses in 24 months prior to screening.

Blinding measures included the identical appearance of teriflunomide and placebo (film-coated tablets in child resistant blister packs), both of which were dosed on a daily basis. Additionally, this trial involved both a treating and examining neurologist; the examining neurologist conducted disability assessments and did not share findings with the treating neurologist. A central, independent, blinded facility provided brain imaging reviews and interpretations. The randomization code was broken only in "exceptional circumstances" when knowledge of the trial assignment was essential for treating the patient, which occurred only once during the trial.

Patients who experienced a confirmed relapse, or who had evidence of high MRI activity (see discussion to follow), would exit the double-blind trial and be offered open-label treatment with teriflunomide as depicted in the following trial schematic:

Figure 3: Study EFC11759 Trial Schematic



Source: Figure 2, Clinical Review

High MRI Activity Exit from Double-blind Trial Option

Patients with high MRI activity, as defined in the protocol and reproduced in Figure 4, were able to exit the blinded treatment phase and enter the open-label extension (OLE) period. Patients continued in the OLE for a total follow-up of 192 weeks (if OLE entry was due to confirmed relapse or high MRI activity) or 196 weeks (if OLE entry followed 96-week study completion). Patients who discontinued study treatment and/or did not wish to continue teriflunomide underwent an accelerated elimination procedure.

Figure 4: Applicant Definition of High MRI Activity in Trial EFC11759

In case of at least 5 new/enlarged T2 lesions at the MRI of Week 24, an additional MRI was performed at Week 36. The patients then had the option to continue into the open-label period early to receive teriflunomide treatment in case of high MRI activity defined as:

- At least 9 new/enlarged T2 lesions at Week 36, or,
- At least 5 new/enlarged T2 lesions on each of the 2 consecutive MRI scans of Week 36 and Week 48, or,
- At least 5 new/enlarged T2 lesions on each of the 2 consecutive MRI scans of Week 48 and Week 72.

Source: Applicant Clinical Study Report, page 34

Statistical Analysis

The primary efficacy endpoint of this study was the time to first confirmed clinical relapse after randomization. Relapses were defined as "new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the Examining Neurologist and documented by the Functional System Scores (FSS). The subject must have objective signs on the Examining Neurologist's examination confirming the event and must then be reviewed and confirmed by an independent Relapse Adjudication Panel (RAP)." Additionally, the protocol specifies that "new or recurrent symptoms that occur less than 30 days following the onset of a relapse should be considered part of the same relapse."

The proportion of patients free of confirmed clinical relapse at Weeks 24, 48, 72, and 96 were to be estimated based on Kaplan-Meier methods.

The secondary efficacy endpoints of this study were as follows:

- Proportion of clinical relapse-free patients at 24, 48, 72, and 96 weeks
- MRI endpoints based on central reading:
    - Number of new/newly enlarged T2 lesions
    - Number of gadolinium (Gd)-enhancing T1 lesions
    - Change in volume of T2 lesions
    - Change in volume of T1 hypointense lesions
    - Number of new hypointense T1 lesions
    - Proportion of patients free of new or enlarged MRI T2 lesions at 48 weeks and 96 weeks

    - Percentage change of brain volume.
- Cognitive outcomes measured by the symbol digit modalities test (SDMT) and Cognitive Battery tests

The analyses of the numbers of new/newly enlarged T2 lesions and the numbers of Gd-enhancing T1 lesions were controlled for Type I error through use of a step-down testing procedure that was applied to the two key secondary efficacy endpoints in the order specified as follows:

1. Number of new/newly enlarged T2 lesions
2. Number of Gd-enhancing T1 lesions

Each hypothesis was to be formally tested only if the preceding tested outcome was significant at a 5% level.

Results
There were 166 patients randomized 2:1 (teriflunomide:placebo) into Study EFC11759 as follows: 109 treated with teriflunomide 7 mg or 14 mg daily, and 57 treated with placebo daily. Patients were enrolled at 57 sites in 22 countries worldwide. The majority (42.8%) of the enrolled patients came from countries in Europe. Approximately 3% of the patients in this study were from the United States.

The intent-to-treat population for the primary efficacy analysis was defined as all randomized patients. The rate of completion of treatment in randomized assignment was 93.6% for the teriflunomide treatment group versus 93.0% for the placebo treatment group, respectively. The most common reason for trial discontinuation in teriflunomide treatment was an adverse event (5.5%), and for placebo treatment was perceived lack of efficacy or withdrawal of consent (both 2.5%). The completion rates for patients remaining in the double blind treatment for 96-weeks (the study's duration) were 51.4% for patients in teriflunomide treatment and 28.1% for patients in placebo treatment. The most common reason for early trial completion for teriflunomide-treated and placebo-treated patients were confirmed relapses (29.4% and 38.6%, respectively.)

Demographic and baseline disease-related characteristics of the randomized patients were relatively well-matched between the two treatment arms. As is expected for a clinical trial enrolling pediatric patients with MS, the majority of the patients were female (66.9%), between 15 and 18 years old (61.5%), and the majority were White (70.5%). Dr. Baldassari noted a difference in patients less than 12 years old in favor of

placebo (12.3% versus 8.3%) but this small discrepancy did not appear to have a significant impact on the trial's outcomes.

Primary Outcome Assessment

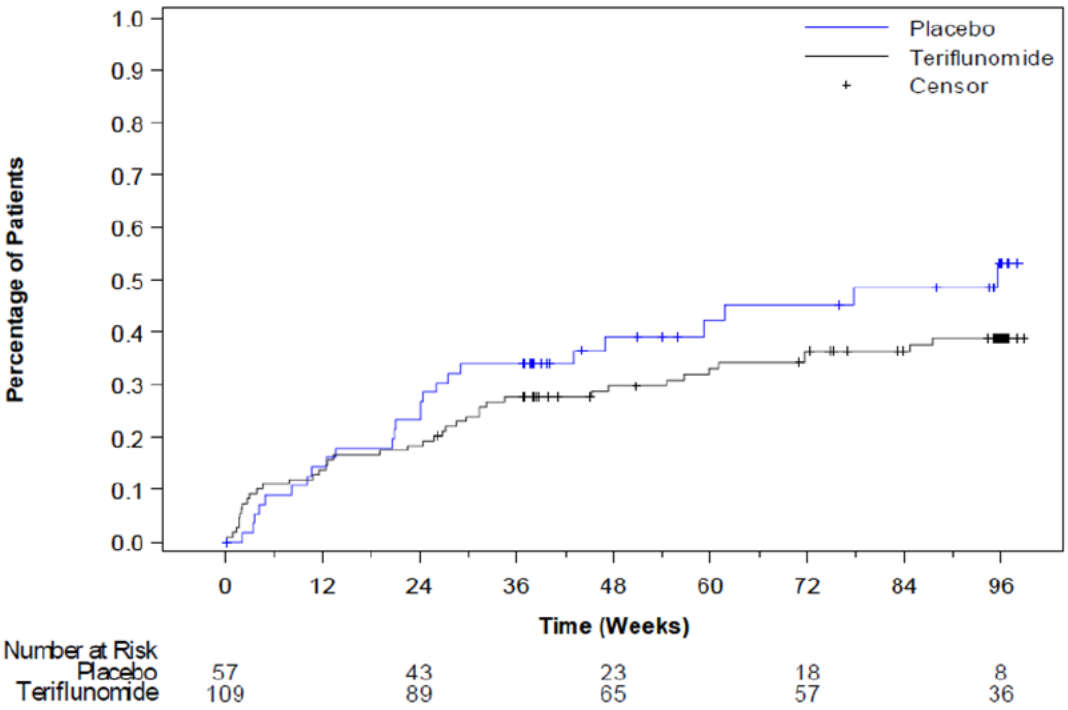
Time to First Confirmed Clinical Relapse

The biometrics reviewer, Dr. Yan, confirmed the applicant's primary efficacy outcome analysis which demonstrated that a confirmed clinical relapse (CCR) occurred in 36.7% of the patients in the teriflunomide group and in 43.9% in the placebo group during the double-blind treatment period. The median time to first confirmed relapse was 95.6 weeks for placebo; the median time for first CCR was not calculated for the teriflunomide treatment arm because less than half of patients in this treatment arm experienced this event. The log-rank test of the time to first CCR resulted in a relative reduction in p-value of 0.2949. Therefore, the study did not meet its primary endpoint.

The estimated probability of CCR at Week 96, using the Kaplan-Meier method was 0.531 in the placebo group and 0.389 in the teriflunomide group. The estimated hazard ratio of teriflunomide to placebo was 0.657, corresponding to an estimated relative risk reduction for a CCR of 34.3%, from the Cox proportional hazard model.

The Kaplan-Meier plot of time to first CCR in the double-blind period is presented in the following figure:

Figure 5: Kaplan-Meier Plot of Time to First Confirmed Clinical Relapse



Source: Figure 3, Biometrics Review

Dr. Yan also replicated the findings from the four pre-specified sensitivity analyses of the primary efficacy outcome measure.

The first sensitivity analysis was time to first CCR or high MRI activity meeting protocol criteria for switching into the OLE period, whichever came first. Thirty-nine patients on placebo (68.4%) and 54 patients on teriflunomide (49.5%) experienced either of these events. The relative risk of either of these events was 43.4% compared to placebo and was nominally significant (p=0.0409). However, Dr. Yan indicates that the high MRI activity provision was inconsistently applied and that some patients remained in the double-blind trial despite meeting criteria for high activity because of a protocol allowance that required high activity be identified or confirmed on specific visit MRI exams to trigger a switch to OLE. Therefore, some patients with high MRI activity remained in the double-blind trial and therefore had not been entirely removed from the patient population contributing to the negative study finding.

Dr. Yan also compared the number of new or enlarging T2 lesions and risk of a CCR and found that T2 lesion numbers did relate to a CCR in either treatment group during the double-blind trial, and as such, the loss of high MRI activity placebo-treated patients from the double-blind trial did not likely impact the efficacy findings as greatly as might be predicted.

In her clinical review, Dr. Baldassari noted that the patients who exited the double-blind trial due to high MRI activity did not experience relapses soon after entering the OLE. Her exploratory analysis noted that, overall, only 34.5% (n = 10) of patients who exited the double-blind trial for high MRI activity experienced an investigator-confirmed clinical relapse during the OLE: 40.0% (n = 6) of placebo-teriflunomide patients and 28.6% (n = 4) of teriflunomide-teriflunomide patients who exited double-blind treatment due to high MRI activity. Additionally, descriptive analysis of the time to first confirmed clinical relapse during the OLE indicated that the patients who experienced high MRI activity did not have an impending relapse: the overall median time to first confirmed relapse in OLE was 404.0 days after OLE switch (Range: 80 to 716 days). Thus, the removal of high MRI activity patients from the double-blind trial did not appear to deplete the primary analysis of a subgroup with higher relapse potential from the double-blind trial. (b) (4) The evidence indicated this protocol measure did not lead to removal of a critical subgroup at high risk of relapse disproportionately from the double-blind trial.

(b) (4) MRI outcomes are not be able to provide alternative primary evidence of efficacy given the clear lack of a statistically convincing finding that teriflunomide treatment reduced the likelihood of relapse. Also, high MRI activity was not prespecified as a primary or secondary trial endpoint and is a *post hoc* outcome assessment. As shown in the exploratory analyses by the biometrics and clinical reviewers, high MRI activity as defined in this trial was not predictive of relapse risk and thus is neither statistically appropriate to consider as an endpoint in this trial nor obviously clinically meaningful.

The second pre-specified sensitivity analysis was time to first clinical relapse (confirmed or unconfirmed) during the double-blind treatment period. The proportion of patients with any clinical relapse was 38.5% in the teriflunomide group versus 45.6% in the placebo group, a finding that was not nominally significant (p=0.2366).

The third pre-specified sensitivity analysis was time to first confirmed clinical relapse after the PK run-in phase. Twenty-three patients on placebo (40.4%) and 33 patients on teriflunomide (30.3%) experienced a confirmed clinical relapse after the PK run-in period, and this analysis was not nominally significant (p=0.08). The concern regarding the PK run-in exposure were discussed previously in the summary of the clinical pharmacology review.

The fourth pre-specified sensitivity analysis was time to first clinical relapse including relapses during the PK run-in phase and relapses reported after study drug discontinuation and up to 96 weeks after randomization. This analysis indicated that 50.9% of patients on placebo and 38.5% on teriflunomide experienced relapses within these time windows. This analysis did not meet nominal significance (p=0.1821).

In her review, Dr. Baldassari discusses an additional *post hoc* sensitivity analysis provided by the applicant examining time to first meeting of high MRI activity criteria for switching into the OLE period. Fifteen patients on placebo (26.3%) and 15 patients on teriflunomide (13.8%) experienced high MRI activity during the double-blind period. This *post hoc* exploratory analysis was nominally significant in favor of teriflunomide (nominal p<0.007); however, as Dr. Baldassari explains, the analysis was *post hoc* and presumes that MRI outcomes are capable of surmounting a failure to demonstrate a treatment effect on a clinically meaningful outcome, relapses, which is not justified broadly in the evaluation of efficacy trials in MS. Additionally, as Dr. Yan discusses in her review, high MRI activity was not predictive of relapse potential and was not clinically meaningful based on data obtained in this specific study. Therefore, this *post hoc* analysis is not capable of providing an interpretable, meaningful efficacy assessment.

Key Secondary Outcome Measures

Number of New or Enlarging T2 Lesions

In Study EFC11759, 45/57 (79.0%) placebo-treated patients, and 100 of the 109 (91.7%) teriflunomide-treated patients had at least one post-baseline MRI performed. Among these patients, 38/45 (84.4%) patients in the placebo group and 85/100 (85%) patients in the teriflunomide group had at least 1 new/enlarging T2 lesion. The median number of new/enlarging T2 lesions per scan was 5.0 for the placebo group and 4.1 for the teriflunomide group. After adjusting for age, region and pubertal status, the estimated new/enlarging T2 lesion numbers per scan was 10.515 for the placebo group and 4.735 for the teriflunomide group. The risk reduction in the new/enlarging T2 lesions for teriflunomide was 55% (nominal p=0.0006) as compared to placebo.

Number of T1 Gadolinium-enhancing Lesions

At baseline, treatment groups were balanced with respect the T1 Gd-enhancing lesion numbers; 24/45 (53.3%) of the patients in the placebo group and 53/100 (53.0%) of the patients in the teriflunomide group had at least one T1 Gd-enhancing lesions. The median number of T1 Gd-enhancing lesions was 1.0 for both treatment groups.

Post-baseline, the median number of T1 Gd-enhancing lesions per scan was 0.8 for the placebo group and 0.2 for the teriflunomide group. After adjusting for age, region, pubertal status and baseline T1 lesion numbers, the estimated mean for the number of T1 Gd-enhancing lesions per scan was 7.505 for the placebo group and 1.897 for the teriflunomide group, representing a risk reduction of 75% (nominal $p<0.0001$) for the teriflunomide compared to placebo.

The following table describes the key secondary MRI outcome measures in this study:

Table 1: Analysis of New/Enlarging Lesions and T1 Gadolinium-enhancing Lesions

	Teriflunomide N=109	**Placebo N=57**
New/enlarging T2 lesions		
Number of patients with MRI scans	100	45
Patients with new/enlarging T2, n (%)	85 (85.0%)	38 (84.4%)
Mean (Standard Deviation) per scan	7.2 (9.3)	17.8 (26.3)
Median per scan	4.1	5.0
Min; Max per scan	0; 42	0; 134
Adjusted number new/enlarging T2 per scan		
LS mean (95% Confidence Interval)	4.735 (2.122, 10.567)	10.515 (4.705, 23.500)
Relative risk (95% Confidence Interval)	0.45 (0.285, 0.711)	
Nominal p-value	0.0006	
T1 Gd-enhancing lesions		
Patients with post-baseline MRI scans, n	100	45
Baseline		
N	98	45
Patients with T1 Gd lesions, n (%)	53 (53.0%)	24 (53.3%)
Mean (Standard Deviation)	3.6 (6.42)	3.5 (6.88)
Median	1.0	1.0
Min; Max	0; 36	0; 35
Post-baseline		
Patients with T1 Gd lesions, n (%)	55 (55.0%)	32 (71.1%)
Mean (Standard Deviation) per scan	1.4 (3.6)	5.1 (11.7)
Median per scan	0.2	0.8
Min; Max per scan	0; 26	0; 56
LS mean (95% Confidence Interval)	1.897 (0.656, 5.489)	7.505 (2.482, 22.695)
Relative risk (95% Confidence Interval)	0.235 (0.126, 0.505)	
Nominal p-value	<0.0001	

Source: Adapted from Table 5, Biometrics Review

Dr. Yan confirmed the analysis findings of the two key secondary endpoints, the numbers of new/enlarging T2 lesions and T1 Gd-enhancing lesions. MRI outcome assessments are reported in labeling for approved therapies to treat relapsing forms of MS but are not considered to be substantial clinically meaningful outcomes that can serve as primary evidence of efficacy in efficacy trials in patients with MS. The failure to demonstrate a treatment effect on relapses, a clinically meaningful event for patients with MS, is sufficient basis to conclude that Study EFC11759 was a negative trial, and these MRI findings are not an adequate basis to support any alternative conclusions regarding teriflunomide's efficacy in treating pediatric MS.

Efficacy Conclusions

The findings from an adequate and well-controlled trial in pediatric MS, Study EFC 11759, that were included in this application failed to demonstrate a statistically significant difference between teriflunomide and placebo treatment on the prespecified primary efficacy analysis of a clinically meaningful outcome, time to first confirmed relapse (a non-significant relative reduction in time to first CCR of 34.3%, p=0.2949). Additionally, three out of four pre-specified sensitivity analyses also failed to support any evidence of a treatment effect of teriflunomide relative to placebo. The only marginally nominally significant pre-specified sensitivity analysis was driven by MRI outcomes which are not considered to be adequate evidence of effectiveness in efficacy trials in patients with MS. (b) (4) Based on these conclusions, Study EFC11759 failed to provide any statistically significant results on analyses of any prespecified assessments of clinically meaningful outcomes. The results of the applicant's *post hoc* exploratory analyses, that are of very limited interpretability for the reasons discussed in this review, as well as nominally significant results based on imaging outcomes, are incapable of overcoming the trial's lack of demonstration of clinical benefit of treatment. (b) (4)

3. Safety

Dr. Laura Baldassari reviewed this application as the primary safety reviewer.

The following table summarizes the extent of exposure to teriflunomide in the applicant's pediatric MS development program encompassing both the double-blind and OLE periods of Study EFC11759 through the most recent application update:

Table 2: Teriflunomide Pediatric Safety Population: Duration of Exposure

Dosage	Number of patients exposed to the study drug					
	≥ 1 dose	≥ 90 days	≥ 180 days	≥ 360 days	≥ 540 days	≥ 720 days
Teriflunomide 7mg	N = 20	N = 15	N = 13	N = 10	N = 9	N = 7
Teriflunomide 14mg	N = 141	N = 139	N = 138	N = 127	N = 112	N = 87
Combined Teriflunomide 7mg + 14mg	N = 161	N = 154	N = 151	N = 137	N = 121	N = 94

Source: Table 28, Clinical Safety Review

The safety database provided by the applicant is adequate because, even with the caveat that pediatric MS is a rare disease and represents a minority fraction of the total worldwide with MS, the applicant's database contains data that exceed the International Council on Harmonization recommendations for chronically-administered medications (*i.e.*, 100 patients exposed for one year).

Deaths

As of November 19, 2019, the original cut-off date of the application, there were no deaths reported in Trial EFC11759. The applicant reported no deaths in the 120-Day Safety Update to the application.

Serious Adverse Events

During the double-blind period of EFC11759, 12 (11%) patients randomized to teriflunomide treatment and 6 (10.5%) patients randomized to placebo treatment experienced 16 and 7 serious adverse events (SAEs), respectively.

Nearly half of the SAEs reported in association with teriflunomide exposure represented serious examples of adverse events already represented in teriflunomide's approved labeling, such as increased risk of infections (appendicitis, tuberculosis, upper respiratory tract infection, n=1 each), increased hepatic transaminase (n=2), and reduced lymphocytes (neutropenia, n=1).

There was a report of an SAE of an anal fistula requiring hospitalization and surgical excision with pathology noting inflammatory tissue changes potentially consistent with inflammatory bowel disease. Dr. Baldassari notes that a pending labeling supplement (to be acted on contemporaneously with this action) will add colitis as an identified risk associated with teriflunomide, and this event may represent an event within this inflammatory bowel disease spectrum.

Several SAEs likely represented sequelae related to MS (diplopia, epilepsy, n=1 apiece), were a pre-existing condition (cardiomyopathy, n=1), or clearly were accidents unrelated to treatment (traumatic nerve injury caused by knife, lumbar vertebral fracture and increased creatine phosphokinase experienced in a traumatic car accident, n=1 each).

There were two syncopal events classified as SAEs that occurred in the same patient on Day 462 of teriflunomide treatment. Dr. Baldassari concluded that the limited description of the events appeared consistent with vasovagal syncope precipitated reportedly by lack of sleep, and she noted the patient had a history of syncope before entering the trial and does not see a clear role for teriflunomide in these events.

Dr. Baldassari concluded that two of the SAEs reported in Study EFC11759 represented potential new safety concerns with teriflunomide exposure in pediatric patients. There was a case of elevated serum creatine phosphokinase (CPK) in a patient in the setting of increased exercise. As discussed below, elevated serum CPK was also reported in other pediatric patients treated with teriflunomide as a treatment-related adverse event and had not been identified in clinical trials of adult patients with MS. There was a single case of acute pancreatitis requiring hospitalization in a child treated with teriflunomide. Pancreatitis is rare in children; this patient was noted to have a pancreatic cyst that potentially increased the risk of pancreatitis. However, pancreatitis had been identified as a safety risk associated with teriflunomide in postmarketing reports, and the presence of a single serious case in the double-blind trial period in this small pediatric trial, with other evidence discussed below, is concerning that the risk of pancreatitis may be higher in teriflunomide-exposed children than in exposed adults.

Discontinuations

In the double-blind treatment period of EFC11759, 6/109 (5.5%) patients in the teriflunomide group discontinued study treatment due to adverse events and 1 patient (0.9%) discontinued due to perceived lack of efficacy. The adverse events reported in the 6 patients who discontinued teriflunomide treatment were acute pancreatitis (n=2), alanine aminotransferase increased (n=1), hyperlipasaemia (n=1),

pulmonary tuberculosis (n=1), and affective disorder (n=1). No patients in the placebo group discontinued double-blind treatment due to an AE.

Three patients discontinued teriflunomide due to pancreatic disorder-related events: 2 due to acute pancreatitis and 1 due to hyperlipasaemia. One of these events was a SAE and discussed in the SAE summary. As discussed in Dr. Baldassari's review, while pancreatitis was identified in postmarketing experience with teriflunomide in adult use, the presence of several cases impacting treatment in pediatric patients is concerning and justifies updated labeling to describe an apparent higher risk of pancreatitis in children exposed to teriflunomide.

The case of pulmonary tuberculosis represented a trial screening failure; an increased frequency of infections is a labeled risk for teriflunomide. Likewise, increased liver transaminases is a known toxicity with teriflunomide, and labeling for teriflunomide has a boxed warning for liver toxicity.

Dr. Baldassari reviewed the event reported as an "affective disorder" occurred on Day 1 of treatment (and thus hard to attribute to a treatment effect) and that the description of the event was consistent with a clinical relapse. The applicant confirmed that this event had been an adjudicated as a CCR and was included in the primary outcome analysis.

Treatment-Emergent Adverse Events
During the double-blind period of Study EFC11759, 96 (88.1%) patients randomized to teriflunomide and 47 (82.5%) patients randomized to placebo experienced at least 1 AE.

The following table summarizes the most common treatment-emergent adverse events (TEAEs) in logical groupings that occurred in patients enrolled in Study EFC11759:

Table 3: Grouped Treatment Emergent Adverse Events Occurring in ≥ 5% of Patients Taking Teriflunomide During Double Blind Treatment in Study EFC11759

Grouped Terms	Teriflunomide (n = 109)	Placebo (n = 57)
Infection, all	71 (65.1%)	27 (47.4%)
URI, cold, rhinitis, upper respiratory tract infection, flu-like illness	57 (52.3%)	18 (31.6%)
Alopecia	24 (22.0%)	7 (12.3%)
Infection, viral	20 (18.3%)	5 (8.8%)
Abdominal pain, distension, bloating, spasm, IBS, megacolon	18 (16.5%)	4 (7.0%)
Influenza	10 (9.2%)	4 (7.0%)
Dizziness, lightheadedness	9 (8.3%)	4 (7.0%)
Leukopenia (neutropenia and/or lymphopenia)	8 (7.3%)	1 (1.8%)
CPK increased	7 (6.4%)	0 (0%)
Asthenia, fatigue, malaise, weakness, narcolepsy	7 (6.4%)	3 (5.3%)
Fever, rigors	6 (5.5%)	2 (3.5%)
Weight loss, catabolic state, cachexia, failure to thrive	6 (5.5%)	2 (3.5%)

Source: Adapted from Table 36, Clinical Safety Review

The most common TEAEs reported in Study EFC11759 confirm the presence of many TEAEs known to be associated with teriflunomide, namely, infections, alopecia, reduced lymphocytes, and abdominal pain.

Dr. Baldassari highlights the presence of increased serum CPK as a TEAE not previously identified in association with teriflunomide. She recommends that this new safety signal should be reported in labeling as a TEAE of teriflunomide seen at higher frequency in children.

Adverse Events of Special Interest and Special Safety Concerns

Teriflunomide was approved approximately nine years ago for the treatment of relapsing forms of MS in adults. There are several safety issues known to occur with chronic administration of teriflunomide that were examined in this pediatric trial; Dr. Baldassari includes a full discussion of all adverse events of special interest in her review. This review will focus the most pertinent serious risks for pediatric patients.

Liver Injury

The current approved labeling for teriflunomide contains a boxed warning for hepatotoxicity. TEAEs listed under the adverse event "liver function analyses" occurred in 5 patients exposed to teriflunomide (4.6%) compared to 1 patient exposed to placebo (1.8%). No Hy's Law cases were reported in this pediatric trial, and there were no cases of liver failure. The current labeling for teriflunomide has a boxed warning that indicates a serious risk of hepatotoxicity, and screening measures in this trial reflected the labeling recommendations which appeared to ensure relatively safe use in the pediatric patients in this trial. Only one SAE related to liver toxicity occurred that resulted in treatment discontinuation. The existing labeling for teriflunomide for hepatic toxicity appears adequate to ensure safe use were teriflunomide prescribed to children.

Bone Marrow Effects/Immunosuppression Potential/Infections

Teriflunomide administration is associated with a reduction in circulating lymphocytes. The frequency of the most worrisome lymphopenia, neutropenia was 5.5% in patients treated with teriflunomide versus 0% on placebo. Dr. Baldassari noted that this incidence, and the incidences of other bone marrow effects, were similar to those observed in adult trials with teriflunomide.

Teriflunomide has immune suppressant effects. Not surprisingly, infections occurred more than 20% more frequently in teriflunomide-treated patients compared with placebo-treated patients. TEAEs from the "Infections and Infestations" system organ class were reported in 66.1% (n = 72) of patients on teriflunomide and 45.6% (n = 26) on placebo. The increased risk of infection in pediatric patients was neither more frequent nor more serious than had been observed in adult patients.

Increased Blood Pressure

Increases in mean systolic and diastolic blood pressure compared to placebo were observed in adult patients who received teriflunomide in placebo-controlled studies. In this pediatric study, hypertension was an adverse reaction in 3.1% and 4.3% of patients treated with 7 mg or 14 mg of teriflunomide compared with 1.8% of patients treated with placebo. (b) (4) existing language is adequate for the approved adult population.

Safety Conclusions

Teriflunomide has established associations with adverse reactions, some serious or fatal, but the risks of most treatment-emergent events can be reduced through minimally invasive screening and can generally be mitigated by discontinuation of therapy. The identified risks in this pediatric trial are largely consistent with what is known regarding the safety profile of teriflunomide in adult patients. On review, elevated serum CPK and pancreatitis represent two significant risks in pediatric patients that should be reported in labeling were a patient to receive teriflunomide on an off-label basis. As discussed in Section 2, there has been an (b) (4) approval of a supplement (S-13) that allows inclusion of the new safety findings (b) (4)

4. Advisory Committee Meeting

There was no advisory committee meeting.

5. Pediatrics

The Approval Letter for Aubagio issued September 12, 2012, included a postmarketing requirement (PMR 1924-1) to conduct a deferred pediatric study under PREA. A Pediatric Written Request was issued on March 7, 2013, and was revised September 2020. The applicant was notified on March 31, 2021, that pediatric exclusivity had been granted.

6. Other Relevant Regulatory Issues

Office of Scientific Investigations review

The Office of Scientific Investigations (OSI) reviewer for this application was Dr. Cara Alfaro. Due to the current pandemic, in lieu of onsite inspections, Regulatory Review Assessments (RRAs) were conducted for two clinical sites in Turkey. RRAs were conducted for sites directed by Drs. Banu Anlar and Kivilcim Gucuyener because OSI had identified that these two investigators' sites had significantly fewer reported relapses in teriflunomide-treated subjects (therefore higher efficacy) than other sites with comparable enrollment. The RRA of Dr. Anlar's records confirmed that 1 of 4 teriflunomide-treated patients at this site experienced a confirmed relapse as had been reported. The RRA of Dr. Gucuyener's records noted that one subject (# (b) (6)) who experienced a relapse within 30 days on enrollment (and therefore did not meet the study's eligibility criteria) had been enrolled. OSI recommended a sensitivity analysis eliminating this patient from the analyzed study population. Elimination of

this patient from the study analysis did not appreciably change the study's results nor did it change the conclusions of the clinical and biometrics reviewers.

7. Labeling

See the final negotiated product label. (b) (4) an approval of the supplement (S-13) with clinical data to provide the safety-related labeling additions, as required under the Best Pharmaceuticals for Children Act. A brief description of the negative results from Study EFC11759 will also be described in Section 8.2. The Division of Medical Policy Programs and The Office of Prescription Drug Promotion also reviewed the labeling and provided recommendations. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

8. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Not applicable.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Not applicable.

9. Recommended Comments to the Applicant

No comments.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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