Office of Clinical Pharmacology Review

NDA Number	202992/S13
Link to EDR	\\CDSESUB1\evsprod\nda202992\0221
Submission Date	11/2/2020
Submission Type	Priority review
Brand Name	Aubagio®
Generic Name	Teriflunomide
Dosage Form and Strength	7 and 14 mg tablets
Route of Administration	Oral
Proposed Indication	Relapsing forms of multiple sclerosis (b) (4)
Applicant	Sanofi-Aventis U.S. LLC
Associated IND	IND 067476
OCP Review Team	Xiaohan Cai, Ph.D. / Angela Men, M.D., Ph.D. Ye Yuan, Ph.D. / Atul Bhattaram, Ph.D.
OCP Final Signatory	Mehul U. Mehta, Ph.D.

1 Table of Contents

1 EXECUTIVE SUMMARY

Aubagio® (teriflunomide) was approved on September 12, 2012 for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS). The approved doses in adult patients are 7 mg and 14 mg orally once daily (QD). (b) (4) .

In Study EFC11759/TERIKIDS, the selected dosing regimen for teriflunomide in pediatric patients 10 years of age and older with RMS was supported by matching the systemic exposure with the approved dose of 14 mg QD in adults using the population pharmacokinetics (PopPK) modeling approach. However, Aubagio failed to show statistically significant delay (p=0.2949) in time to reach first clinical relapse among pediatric multiple sclerosis patients 10 years of age and older in the 96-week double blind phase of Study EFC11759/TERIKIDS. The failure on the primary endpoint is likely due to multiple reasons including the study design of the rescue provision, a lower exposure comparing to adults receiving 14 mg QD during the 8-week PK run-in period, and differences between pediatric and adult MS (Refer to the clinical review by Dr. Laura Baldassari). Pediatric MS is known to have a higher degree of inflammatory disease activity (i.e., more clinical relapses and higher numbers of new and enlarging lesions on MRI) compared to the adult population, which could mean that some treatments shown to be effective for adult patients with MS may not be effective when evaluated against a more aggressive disease variant.

The primary focus of the review is to evaluate the teriflunomide pharmacokinetics (PK) in pediatric patients (b) (4) .

1.1 Recommendations

From a clinical pharmacology perspective, the population PK analysis (b) (4) Aubagio dosing regimen in pediatric patients 10 years of age and older provides similar exposure as observed in adult patients receiving 14 mg once daily treatment at steady state. (b) (4)

2 SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

The key clinical pharmacology findings show that the selection of teriflunomide dosing regimen in pediatric patients 10 years of age and older in study EFC11759/TERIKIDS provides a similar exposure as 14 mg once daily treatment in adults at steady state.

For pediatric patients with BW >40 kg treated with 14 mg QD, the steady-state *AUC_{0-24} of teriflunomide (1246, 390-3592 µg*h/mL) was in the range with that estimated in adult patients treated with the same dosing regimen (1040, 378-3120 µg*h/mL). For pediatric patients with BW ≤ 40 kg, the dosing regimen of 7 mg QD led to somewhat lower steady-state AUC_{0-24} (711, 406-1337 µg*h/mL), although within the range with that estimated in adult patients treated with 14 mg QD (1040, 378-3120 µg*h/mL). Note that approved doses for adults are 7 mg and 14 mg QD.

2.1.1 General dosing

(b) (4)

3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 General Pharmacology and Pharmacokinetic Characteristics

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase, required for the de novo pyrimidine synthesis. Aubagio® (teriflunomide) was approved on September 12, 2012 for the treatment of RMS in adult patients. The approved dosing regimen in adults is 7 mg and 14 mg administered orally once daily, with or without food. The general pharmacology and PK of teriflunomide has been reviewed previously as part of the original NDA (NDA 202922 clinical pharmacology review by Dr. Veneeta Tandon, archived July 2, 2012). The ADME of teriflunomide is summarized as below:

*AUC_{0-24} descriptive statistics are (Median, 5^{th}- 95^{th} percentile)

ADME	
Absorption	Median time to reach maximum plasma concentrations is between 1 to 4 hours post-dose following oral administration of teriflunomide. Food does not have a clinically relevant effect on teriflunomide pharmacokinetics.
Distribution	Teriflunomide is extensively bound to plasma protein (>99%) and is mainly distributed in plasma. The volume of distribution is 11 L after a single intravenous (IV) administration.
Metabolism	Teriflunomide is the major circulating moiety detected in plasma. The primary biotransformation pathway to minor metabolites of teriflunomide is hydrolysis, with oxidation being a minor pathway. Secondary pathways involve oxidation, N-acetylation and sulfate conjugation. Human cytochrome P450 (CYP) enzymes (CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4 and 3A5) or flavine monooxygenase (FMO) enzymes (FMOs 3 and 5) were not involved in the metabolism of teriflunomide.
Elimination	Teriflunomide is eliminated mainly through direct biliary excretion of unchanged drug as well as renal excretion of metabolites. Over 21 days, 60.1% of the administered dose is excreted via feces (37.5%) and urine (22.6%). After an accelerated elimination procedure with cholestyramine, an additional 23.1% was recovered (mostly in feces). Median terminal half-life was 17.8 and 19.4 days for the 7 mg and the 14 mg doses, respectively.

To fulfill the post marketing requirement (PMR1924-1) and the FDA Written Request (WR) Letter dated March 7, 2013, the sponsor submitted the efficacy and safety results of the Phase 3 Study EFC11759/TERIKIDS. Study EFC11759/TERIKIDS evaluated the efficacy and safety of teriflunomide administered in pediatric patients 10 years of age and older for the treatment of RMS. This study consisted of two periods:

- A double-blinded (DB) placebo-controlled treatment period up to 96 weeks: this included a blinded PK run-in phase of 8 weeks to provide individual PK parameters to allow the dose adjustment to the 14 mg adult-equivalent dose for the rest of the study from Week 8. This period assessed the efficacy and safety for up to 96 weeks.
- An open-label (OL) period of additional 96 weeks (up to a total follow-up of 192 weeks): this period also included a PK run-in phase of 8 weeks for patients previously in the placebo group during the DB period to provide individual PK parameters to allow the dose adjustment to the 14 mg adult-equivalent dose for the rest of the study.

PK of teriflunomide was evaluated in both DB and OL periods of study EFC11759 using trough plasma concentration. In addition, the DB and OL periods of Study EFC11759 included an initial blinded 8-week PK run-in phase, intended to allow the dose adjustment from Week 8 to the rest of the study to reach exposure similar to the steady state exposure in adults being treated with 14 mg once daily. In absence of prior PK data in children, patients started the PK run-in phase to target a similar exposure to adults

being treated with 7 mg once daily, i.e, 3.5 mg for patients with BW ≤40 kg or 7 mg for patients with BW >40 kg. Individual predicted PK parameters (C_{max} and AUC_{0-24}) during PK run-in, using PK samples collected up to Week 4, were compared to the adult 7 mg PK predicted parameter range: C_{max} of 8.03 to 49.1 mg/mL and AUC_{0-24} of 184 to 1160 µg.h/mL. Depending on the individual PK parameters assessed during the PK run-in, the dose after the PK run-in (Week 8) was increased, i.e, 3.5 mg increased to 7 mg for patients weighing ≤40 kg, and 7 mg to 14 mg for patients weighing >40 kg, or maintained to ensure that the patients would reach exposure similar to adults being treated with 14 mg once daily. The following chart was used to guide the dose adjustment in the DB and OL periods:

Table 1 - Chart for dose adjustment in double-blind and open-label periods of TERIKIDS

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

During PK run-in phase, at least three blood samples per subject were collected at pre-dose, at Week 2, 3, and 4 for the PopPK analysis. After PK run-in period, Pre-dose PK samples were collected at Weeks 8, 12, 24, 36 and end of treatment for both the DB and OL period. Individual exposure parameters of teriflunomide at steady state was analyzed with PopPK analysis (Appendix 4.2 Pharmacometric Review).

3.2 Clinical Pharmacology Review Questions

3.2.1 Does the [redacted] (b) (4) dosing regimen in pediatric patients (10-17y) provide similar steady-state exposure as observed in adult patients receiving 14mg once daily treatment?

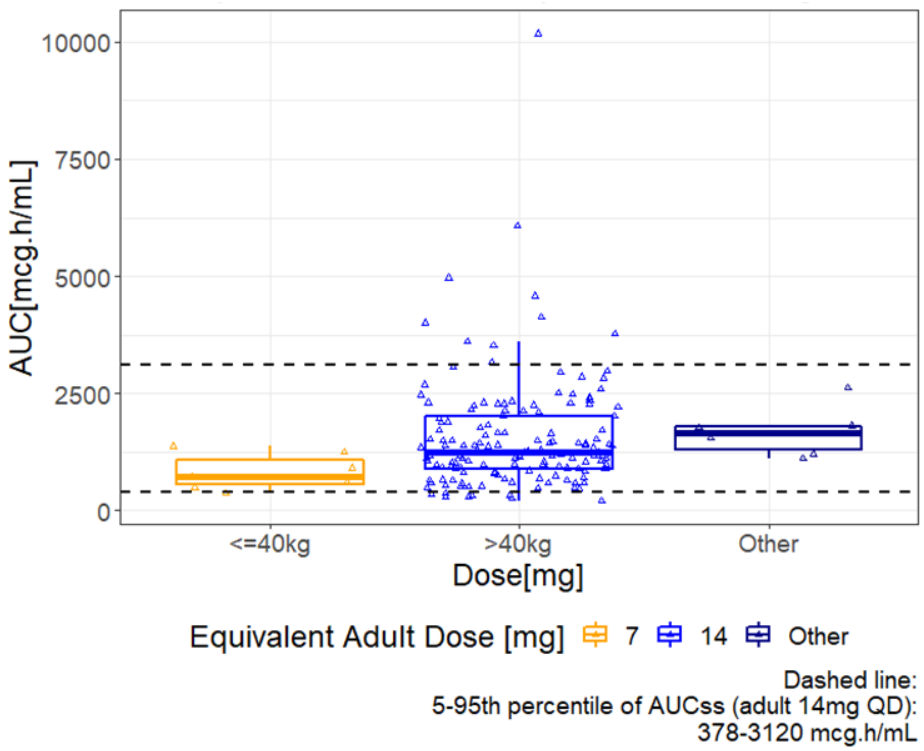
Yes. The proposed dosing regimen, based on body weight > 40 kg or ≤ 40 kg, provides similar steady-state exposure in pediatric patients of 10 years of age and older and adult patients.

[redacted] (b) (4) the sponsor developed a PopPK model based on the data obtained from Phase 3 pediatric study EFC11759/TERIKIDS. Individual exposure parameters, including AUC, C_{max}, and C_{min}, during steady state were derived using model predicted PK parameters. The estimated steady state AUC_{0-24} was compared with adult steady state AUC (378-3120 µg*h/mL, 5th-95th percentile) for the following groups of pediatric patients (Figure 1):

- <=40kg: Patients with body weight constantly ≤ 40kg received 7mg once daily (N=7)

- >40 kg: Patients with body weight constantly > 40kg received 14mg once daily treatment (N=145)
- Other: Patients with fluctuated body weight body weight above or below 40kg received teriflunomide dose accordingly (N=6).

Figure 1. Steady state AUC for the [redacted] (b) (4) regimen



For the 7 patients with body weight constantly ≤ 40kg, 6 patients (86%) had AUC_{ss} within 5^{th} to 95^{th} percentile of AUC_{ss} of adults receiving 14mg once daily. For the 145 patients with body weight above 40kg constantly during the treatment, 127 (88%) patients had AUC_{ss} within 5^{th} to 95^{th} percentile of AUC_{ss} of adults receiving 14mg once daily. For the 6 patients with body weight fluctuated as below or above 40kg during the treatment, their AUC_{ss} were within AUC_{ss} of adults receiving 14mg once daily. In conclusion, [redacted] (b) (4) regimen in pediatric patients can provide similar steady state exposure with that of adult patients receiving 14mg once daily treatment.

3.2.2 Do lower concentrations of teriflunomide in pediatric patients during the PK run-in phase contribute to the overall lack of efficacy in pediatric patients when compared to placebo?

In the DB period of study EFC11759/TERIKIDS, patients were randomized to either teriflunomide or placebo at 2:1 ratio (110 patients on teriflunomide versus 55 patients on placebo) to receive treatments for up to 96 weeks. The primary efficacy endpoint was the time to first confirmed clinical relapse

occurring from randomization (including relapses during the PK run-in phase) to the end of the randomized during the placebo-controlled study treatment period.

Aubagio failed to show statistically significant delay (p=0.2949) in time to reach first clinical relapse among pediatric RMS patients 10 years of age and older in the 96-week double blind phase of study EFC11759/TERIKIDS. Study EFC11759 included an 8-week PK run-in phase for individualized dose adjustment to target adult exposure receiving 14 mg once daily. During the PK run-in period, patients received 7 mg adult equivalent dose of teriflunomide once daily (3.5 mg for patients with BW ≤40 kg or 7 mg for patients with BW >40 kg). After the PK run-in period, patients in the teriflunomide group received 14 mg adult equivalent dose of teriflunomide once daily (7 mg for patients with BW ≤40 kg or 14 mg for patients with BW >40 kg). At the end of PK run-in phase (Week 8), the mean trough concentration of teriflunomide for pediatric patients receiving 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). To test the impact of the lower teriflunomide exposure during PK run-in phase on the efficacy primary endpoint, relapse data was analyzed with a truncated dataset by removing patients with observations of either clinical relapse or censoring during the run-in phase. The analysis of relapse data after the PK run-in showed that pediatric patients in Aubagio group had lower relapses than the placebo group without reaching statistical significance (p=0.066). However, with the truncated dataset, the median time to first confirmed clinical relapse increased from 75.3 weeks to 94.6 weeks for teriflunomide treated patients, whereas the median time for placebo group remained relatively the same (slightly increased from 39.1 weeks to 43.1 weeks). The lower levels of teriflunomide during the first 8-week PK run-in phase, in addition to other factors including the study design of the rescue provision and differences in pediatric and adult MS, may contribute to the lack of efficacy for Aubagio in pediatric RMS patients.

4 APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Teriflunomide plasma concentrations were quantified in Study EFC11759/TERIKIDS at two bioanalytical sites: (b) (4) Since the original teriflunomide submission, the bioanalytical method (Method HMRHPP) was partially validated at (b) (4) under (b) (4) study DOH1165. The bioanalytical method HMRHPP was transferred to (b) (4) with additional cross-validation tests under (b) (4) study DOH1199. The summary of two method validation studies are listed below:

Table 2: Summary of bioanalytical studies associated with Study EFC11759/TERIKIDS

Methods report (Report location)	Matrix (Anticoagulant)	Analytes	Type of method	Calibration range (µg/mL)	Precision CV%		Accuracy A%		Clinical studies
					Within run	Between run	Within run	Between run	
DOH1165[a] (5.3.1.4)	Teriflunomide (sodium heparin)	Plasma	LC-MS/MS	0.0100 to 3.00	1.3% to 4.3%	2.7% to 4.4%	-4.8% to 8.0%	-2.8% to 4.3%	EFC11759/TERIKIDS
DOH1199 (5.3.1.4)	Teriflunomide (sodium heparin)	Plasma	LC-MS/MS	0.0100 to 3.00	0.5% to 3.5%	NA	-6.2% to 3.3%	NA	EFC11759/TERIKIDS

a Including Addendum 1
NA: not applicable

In method transfer test conducted at [redacted] (b) (4) under Study DOH1199, the overall passing rate was 66.7% for a total of 30 incurred samples selected and thus met the site's acceptance criteria. However, the results from this cross-laboratory validation test showed a passing rate of 40% from 15 incurred samples from Study POP11432 and a passing rate of 93% from 15 incurred samples from Study INT11932. All incurred samples from Study POP11432 were analyzed with a dilution factor of 1 and all incurred samples from Study INT11932 were analyzed with a dilution factor of 100 at [redacted] (b) (4) in Study DOH1199. During the review, the sponsor was requested to explain the discrepant cross-laboratory validation results. The sponsor speculated that the aged patient matrix of samples from Study POP11432 (severe renal impaired patients) might have led to matrix effect that was not observed in Study INT11932, and thus higher failure rate of Study POP11432 than that of Study INT11932. Among the 9 (out of 15) results that failed acceptance criteria (±[redacted] (b) (4)%) in the POP11432 incurred study samples, 4 of 9 results had borderline failures with a %difference between 20.0 to 20.5%.

Reviewer's comments: The responses provided by the sponsor are not unreasonable. However, the different cross-laboratory validation results from Study POP11432 and Study INT11932 should have minimal impact on the bioanalytical results of Study EFC11759/TERIKIDs for the following additional reasons:

1. *98.6% samples from Study EFC11759/TERIKIDs had teriflunomide concentration above the upper limit of the calibration range at 3000 ng/mL and required dilution of 10 to 100-fold for the bioanalysis. The potential matrix effect should be minimized with sample dilution for up to 100-fold.*
2. *The incurred sample reanalysis (ISR) passing rate for Study EFC11759/TERIKIDs samples analyzed at [redacted] (b) (4) and [redacted] (b) (4) was 92.9% and 95.2%, respectively.*

4.2 Pharmacometric Review

4.2.1 Summary of Findings

An overall summary of findings of the Pharmacometric Review is provided in Section 3.3.1 and 3.3.2 of the QBR.

4.2.2 Pertinent regulatory background

AUBAGIO is a pyrimidine synthesis inhibitor indicated in adult patients for the treatment of relapsing forms of MS. The currently approved dosage for adult MS patients is 7mg or 14mg orally once daily. The

(b) (4)

4.2.3 *Results of Sponsor's Analysis*

Study EFC11759/TERIKIDS was a 2-year, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate efficacy, safety, tolerability, and PK of teriflunomide administered orally once daily in pediatric patients with RMS followed by an OL extension. During the 8-week PK run-in phase, patients were treated with either 3.5 mg (body weight ≤40 kg) or 7 mg (body weight>40 kg) teriflunomide once daily. At the end of PK run-in phase, a 14 mg once daily adult equivalent dose was given (Table 1). This dose was selected using individual PK parameters (maximum concentration [C_{max}] and area under the curve over 24-hour period [AUC_{0-24}]).

Table 1. Chart for dose adjustment in double-blind and open-label periods of TERIKIDS (2.7.2 Summary of Clinical Pharmacology studies (Pediatric) Table 1)

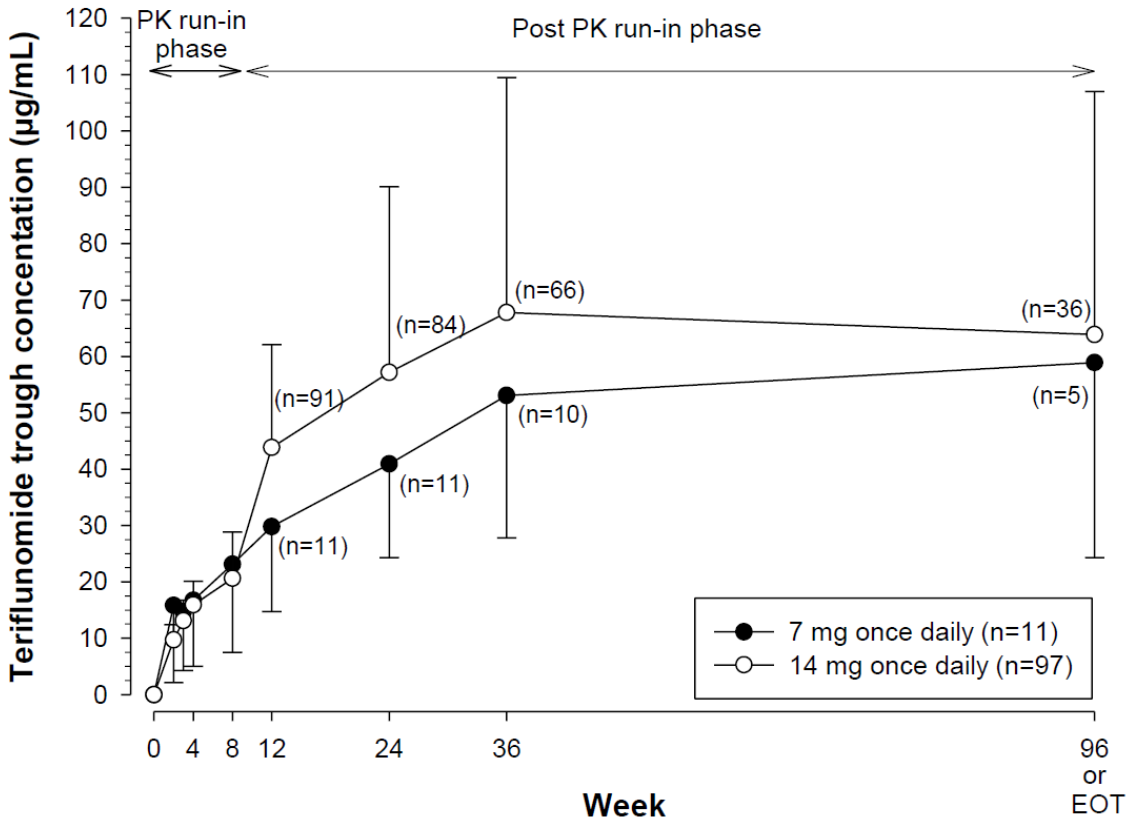
Body weight	8-week PK run-in phase (7 mg adult equivalent dose)	Post-PK run-in phase (14 mg adult equivalent dose)
≤40 kg	3.5 mg once daily	>95th percentile of 7 mg adult exposure → 3.5 mg once daily
		≤95th percentile of 7 mg adult exposure → 7 mg once daily
> 40 kg	7 mg once daily	>95th percentile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

Teriflunomide steady-state trough concentrations were in the same range after 7 mg and 14 mg once daily as expected due to dose adaptation at the end of the PK-run phase (Figure 1).

Dataset composed of 1277 teriflunomide concentrations from 154 patients were used to develop a PopPK model. This model was a 2-compartment model with allometric scaling (body weight) applied to distribution volumes and to plasma clearance. Only the effect of bilirubin on CL was identified as

significant covariate. The individual predicted PK parameters were utilized to derive the steady state AUC, C_{max}, and C_{min}.

Figure 1. Teriflunomide trough concentration in Study EFC11759/TERIKIDS over 96 weeks or end of treatment (mean ± standard deviation) - Double-blind treatment period (2.7.2 Summary of Clinical Pharmacology studies (Pediatric) Figure 1)



During PK run-in, 14 patients with body weight > 40 kg receiving a 7 mg adult equivalent dose were treated with 7 mg once daily. Their individual steady state $_{AUC0-24}$ were less than the 95th percentile of adult range of steady state exposures at 7 mg once daily (Figure 2). Four patients with body weight ≤ 40 kg receiving a 7 mg adult equivalent dose were treated with 3.5 mg once daily only, their individual exposures were below the 95th percentile of adult exposures after a 7 mg once daily dose (Figure 3).

After PK run-in, 133 patients with body weight > 40 kg received a 14 mg adult equivalent dose. Among them, 127 were treated with 14 mg once daily and 6 were treated with 7 mg once daily. For the 127 patients treated with 14 mg once daily, individual steady state exposures were within the range to those observed in adult patients with the same dosing regimen (Figure 2). For the 6 patients treated with 7 mg once daily, 4 patients had a steady state AUC_{0-24} below the 95th percentile of adult AUC_{0-24} after a 7 mg once daily dose (Figure 2). In a situation where these 4 patients would have received 14 mg once daily, their anticipated steady state AUC_{0-24} would not exceed the 95th percentile of adult steady state AUC_{0-24}

for patients receiving 14 mg once daily. Two patients had a steady state AUC_{0-24} above the 95th percentile of adult AUC_{0-24} after a 7 mg once daily dose (Figure 2). In a situation where these 2 patients would have received 14 mg once daily, their anticipated steady state AUC_{0-24} would exceed the 95th percentile, however, within the maximum observation, of adult steady state AUC_{0-24} for patients receiving 14 mg once daily. Three patients with body weight ≤ 40 kg were treated with 7 mg once daily. Their individual exposures were in the range of adult exposures after receiving 14 mg once daily treatment (Figure 3).

Figure 2. Teriflunomide steady state AUC0-24 in pediatric patients with body weight >40 kg following 7 mg or 14 mg adult equivalent once daily dosing regimens - Comparison with adult patients following 14 mg once daily dosing regimen (2.7.2 Summary of Clinical Pharmacology studies (Pediatric) Figure 3)

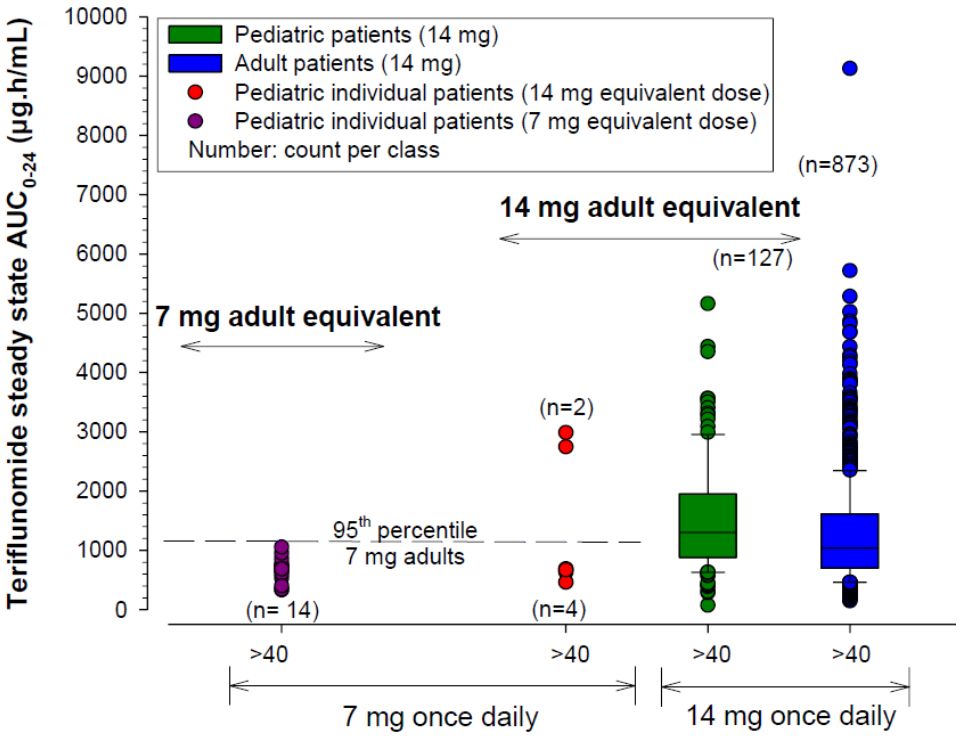
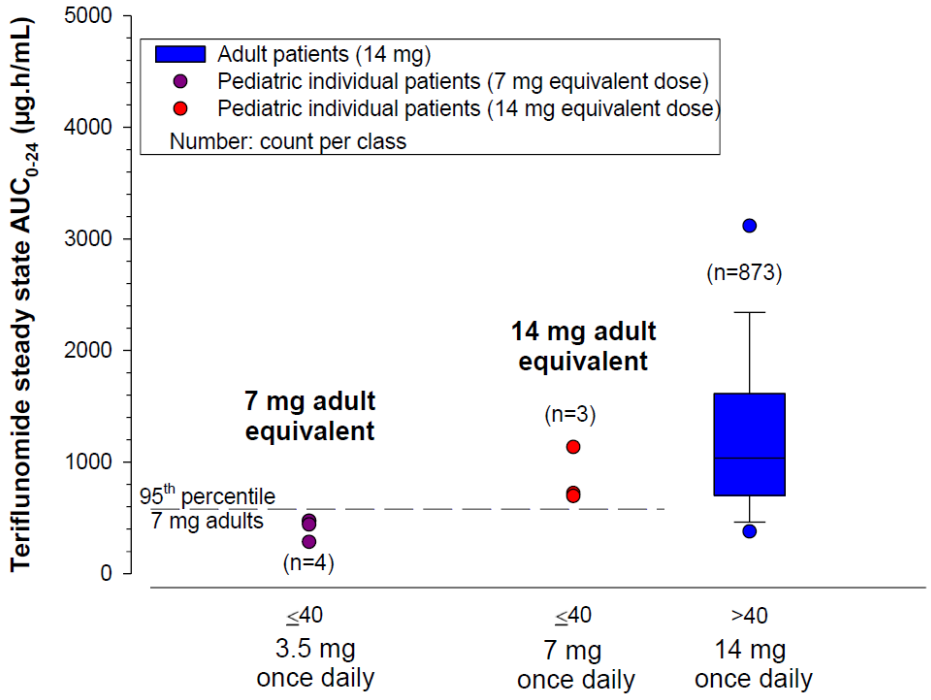


Figure 3. Teriflunomide steady state AUC0-24 in pediatric patients with body weight ⩽40 kg following 7 mg or 14 mg adult equivalent once daily dosing regimens - Comparison with adult patients following 14 mg once daily dosing regimen (2.7.2 Summary of Clinical Pharmacology studies (Pediatric) Figure 4)



Reviewer's comment: The popPK model was successfully reproduced. The 14mg once daily regimen led to a higher mean trough concentration than the 7mg once daily regimen and the range of trough concentration for these two regimens were partially overlapped. The steady-state concentration of (b) (4) regimen matched well with the targeted exposure of adult patients who receiving 14 mg once daily treatment, whereas the 7 mg once daily adult equivalent dose regimen could not reach the target. Please see more details in REVIEWER's ANALYSIS.

In total, 166 randomized patients were included in the efficacy analysis for double-blind period. The primary endpoint of the analysis was the time to reach first confirmed clinical relapse. Demographic characteristics at baseline were generally well balanced between treatment groups. The disease characteristics at baseline were generally similar among treatment groups. Teriflunomide reduced the risk of confirmed clinical relapse by 34.3% (HR: 0.66; 95% CI: 0.39 to 1.11, p=0.2949) compared to placebo in the DB period without reaching statistical significance (Table 2 and Figure 4).

Table 2. Analysis of time to first confirmed clinical relapse after randomization during the double-blind period - ITT population (2.5 Clinical Overview Addendum (Pediatric) Table 2)

	Placebo (N=57)	Teriflunomide (N=109)
Number of patients with confirmed clinical relapse during the double-blind treatment period, N (%)	25 (43.9)	40 (36.7)
Number of patients who were censored, N (%)	32 (56.1)	69 (63.3)
Time to first confirmed clinical relapse (weeks)		
Number	57	109
Mean (SD)	49.25 (33.66)	62.60 (36.12)
Median	39.14	75.29
Min ; Max	0.1 ; 98.0	0.1 ; 98.7
Kaplan-Meier estimates of probability of confirmed clinical relapse during the double-blind treatment period (95% CI) at [a]		
24 Weeks	0.232 (0.132 ; 0.349)	0.183 (0.117 ; 0.261)
48 Weeks	0.391 (0.259 ; 0.521)	0.298 (0.214 ; 0.386)
72 Weeks	0.452 (0.305 ; 0.588)	0.364 (0.272 ; 0.456)
96 Weeks	0.531 (0.360 ; 0.676)	0.389 (0.293 ; 0.483)
Hazard Ratio (95% CI) [b]		
	-	0.657 (0.388 ; 1.113)
Stratified Log-Rank test p-value [c]		
	-	0.2949

Note: Confirmed clinical relapse 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).

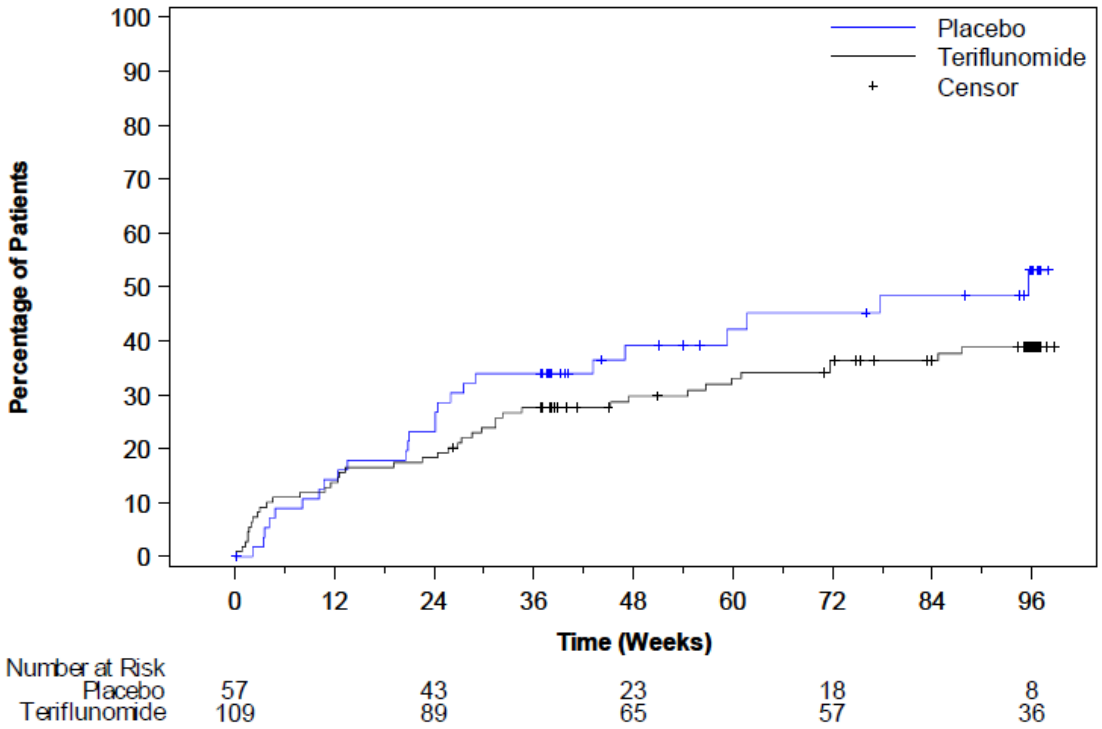
Time to event is calculated as date of confirmed clinical relapse - randomization date + 1 day.

The North Africa and North America were combined for region stratum due to small sample size.

a Derived from Kapan-Meier estimates

b Derived using Cox proportional-hazards model with treatment group, region and pubertal status, age and number of relapses in the year prior to randomization as covariates and with robust variance estimation.

Figure 4. Kaplan-Meier plot of time to first confirmed clinical relapse after randomization - ITT population - Study EFC11759 - Double-blind period (2.7.3 Summary of Clinical Efficacy (Pediatric) Figure 3)



Reviewer's comment: The hazard ratio and stratified log-rank test results were confirmed by the reviewers with very close p-values to sponsor's analysis. Although teriflunomide treatment showed a trend to reduce the risk of clinical relapse, the result did not reach statistical significance. The Kaplan-Meier estimate for the probability of clinical relapse were reproduced by the reviewers. Please see more details in REVIEWER's ANALYSIS that explored the impact of run-in PK period on the efficacy outcome of AUBAGIO that was not significantly different from placebo.

4.2.4 Reviewer's Analysis

4.2.4.1 Introduction

AUBAGIO is a pyrimidine synthesis inhibitor indicated in adult patients for the treatment of relapsing forms of MS. (b) (4)

(b) (4) the sponsor developed a population PK model based on Phase III pivotal study EFC11759/TERIKIDS. Individual exposure parameters, including AUC, C_{max}, and C_{min}, during steady state were derived using model predicted PK parameters. The estimated individual steady state exposures in 10-17 y old subjects were matched with those of adults receiving 14mg orally

once daily treatment. In this analysis, the reviewers adopted the sponsor's population PK model to estimate the individual teriflunomide exposure at steady states and confirmed sponsor's findings.

The primary efficacy endpoint of study EFC11759/TERIKIDS is the time to reach first confirmed clinical relapse. Multiple methods were used to analyze the efficacy data: 1) the cox regression model was used to estimate the hazard ratio; 2) the stratified log-rank test was applied to test the null hypothesis that teriflunomide group and placebo group had equal probability of maintaining clinical relapse free status at any time; 3) Kaplan-Meier estimates were plotted. The efficacy analysis showed the teriflunomide treatment reduced the risk for clinical relapse. However, the results did not reach statistical significance. In this analysis, the reviewers confirmed the sponsor's findings and investigated whether the lower AUC of AUBAGIO during PK run-in contributed to the lack of efficacy.

4.2.4.2 Objectives

Analysis objectives are:

4.2.4.2.1 To compare the steady state exposure of teriflunomide in pediatric patients 10 years of age and older (b) (4) dosing regimen to those of adult patients receiving 14mg once daily treatment.

4.2.4.2.2 To test the impact of low exposure during PK run-in phase on the lack of efficacy.

4.2.5 Methods

4.2.5.1 Data Sets

Data sets used are summarized in Table 3.

Table 3. Analysis Data Sets

Study Number	Name	Link to EDR
EFC11759/TERIKIDS	adpc.xpt	\\CDSESUB1\evsprod\NDA202992\0221\m5\datasets\efc11759-db\analysis\adam\datasets
EFC11759/TERIKIDS	advs.xpt	\\CDSESUB1\evsprod\NDA202992\0221\m5\datasets\efc11759-db\analysis\adam\datasets
EFC11759/TERIKIDS	ex.xpt	\\CDSESUB1\evsprod\NDA202992\0221\m5\datasets\efc11759-db\tabulations\sdtm
EFC11759/TERIKIDS	poppk.xpt	\\CDSESUB1\evsprod\NDA202992\0221\m5\datasets\poh0475\analysis\legacy\datasets

4.2.5.2 Software

Population PK model fitting was performed in NONMEM 7.3 and Pirana 2.9.4 and final model simulation was performed in R 4.0.3 using deSolve package. Efficacy analysis and plotting were performed in R 4.0.3.

4.2.5.3 Models

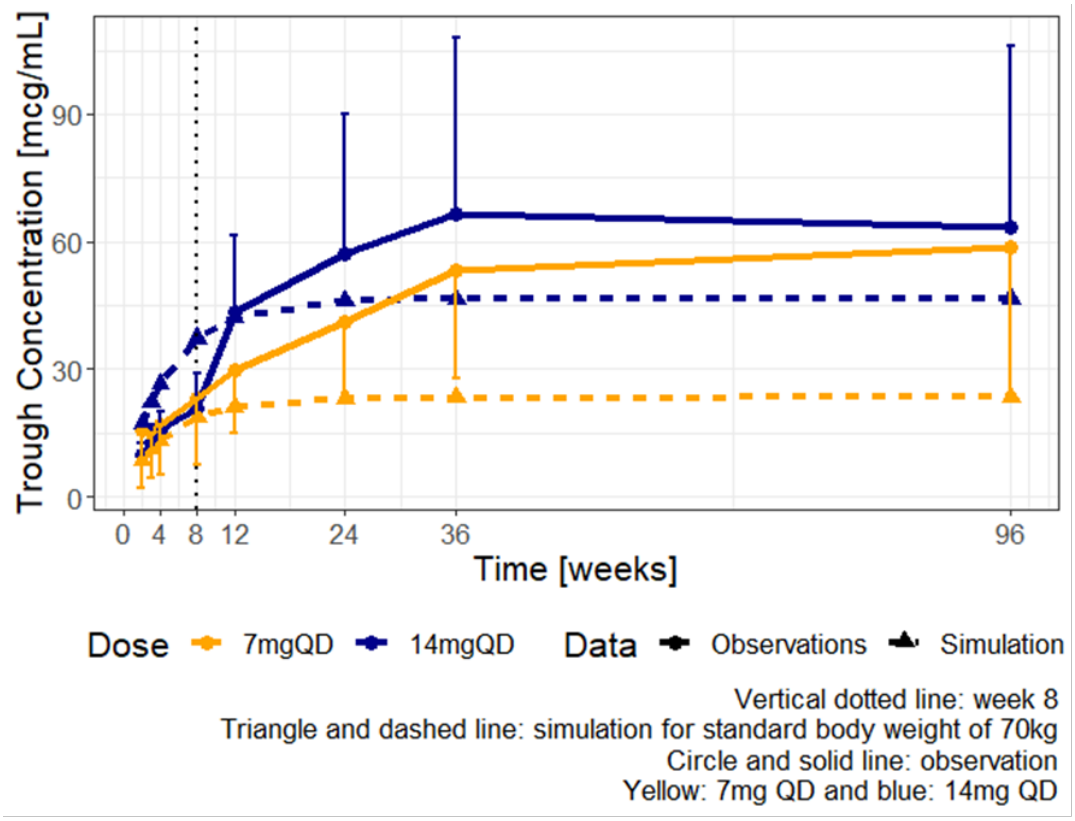
The reviewers adopted sponsor's final population PK model, which was a 2-compartment model with 1st order absorption and linear elimination from central compartment. The individual predicted PK parameters were used to perform simulation and to estimate the steady state exposure.

Log-rank test with stratification of region and pubertal status was performed to test the null hypothesis that teriflunomide group and placebo group had equal probability of maintaining clinical relapse free status at any time. Hazard ratio was estimated using Cox regression model with treatment group, region, pubertal status, age, and number of relapses in the year prior to randomization as predictors.

4.2.6 Results

The reviewers adopted sponsor's final population PK model. The observed trough concentration was plotted with simulated trough concentration for patients with standard adult body weight of 70kg in Figure 5. The circle points and solid lines showed observed trough concentration at corresponding timepoints. The triangle points and dashed lines represented simulation for adult patients with standard body weight of 70kg. Yellow and blue indicated 7mg QD and 14 mg QD, respectively. The trough concentration during 8-week PK run-in phase were lower compared to that of post PK run-in phase. The individual estimated PK parameters were used to derive the predicted steady state exposure parameters, including AUC, C_{max}, and C_{min}. The results were consistent with sponsor's result (Table 4).

Figure 5. Observed trough concentration vs. simulated trough concentration with standard adult body weight of 70kg



Descriptive statistics of baseline weight (kg) in study TERIKIDS

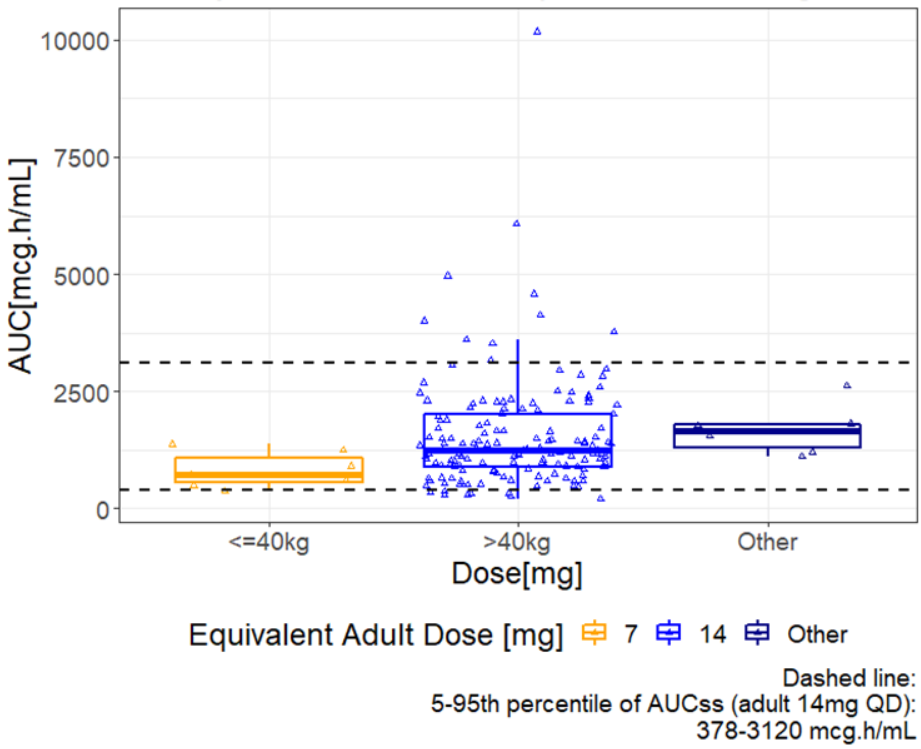
Dose	mean	min	percentile25	median	percentile75	max
14mg QD	58.6	38.5	50	57	65.5	93
7mg QD	48.5	32	36.5	40.4	54.5	105

Table 4. Descriptive statistics of exposure values computed at steady state– Comparison between sponsor's and reviewer's analysis (sponsor's analysis from Population Pharmacokinetic Analysis Report POH0475 Table 17)

	Sponsor						Reviewer			
Parmeter	Adult patients (n=873)		Pediatric patients (n=136)				Pediatric Patients (n=136)			
	14 mg		7 mg (n=9)		14 mg (n=127)		7 mg (n=9)		14 mg (n=127)	
	Mean (CV%)	Median, 9-95th Percentile	Mean (CV%)	Median, 9-95th Percentile	Mean (CV%)	Median, 9-95th Percentile	Mean (CV%)	Median, 9-95th Percentile	Mean (CV%)	Median, 9-95th Percentile
$AUC_{0\text{-}24SS}$ (mcg.h/mL)	1290 (68.9%)	1040, 378-3120	1192 (81.0%)	696, 530-2888	1539 (60.0%)	1302, 486-3376	1175.7 (76.4%)	747.7, 543-2761	1547 (59.3%)	1303, 477-3348
C_{maxSS} (mcg/mL)	54.5 (68.0%)	44.3, 16.4-131	50.2 (80.3%)	29.5, 22.4-120.1	64.9 (59.2%)	54.7, 21.0-141.2	49.5 (75.7%)	31.7, 22.9-115.6	65.2 (58.6%)	54.9, 20.6-136.0
C_{minSS} (mcg/mL)	52.9 (69.7%)	42.4, 15.2-128	49.0 (82.0%)	28.2, 21.7-119.6	63.2 (61.0%)	53.6, 19.1-140.0	48.3 (78.4%)	30.3 22.2-114.2	63.4 (60.4%)	53.3, 18.8-134.3

The reviewers resampled individual PK parameters for each patient following omega distribution estimated from final population PK model. Instead of receiving real dose regimen, all the patients were assumed to receive [redacted] (b) (4) regimen solely based on observed body weight. In the new analysis, 7 patients with body weight constantly ≤ 40kg received 7mg once daily treatment, 145 patients with body weight constantly > 40kg received 14mg once daily treatment, and 6 patients with body weight above and below 40kg received teriflunomide dose accordingly. For the 6 patients with fluctuated body weight, mean dose were used to derive the exposure parameters. The estimated steady state AUC_{0-24} were compared with adult steady state AUC (Figure 6). For the 7 patients with body weight constantly ≤ 40kg, one of them had steady state AUC slightly below 5th percentile of adult 14mg once daily steady state AUC. For the 145 patients with body weight constantly > 40kg, 10 patients and 8 patients had steady state AUC over 95th percentile and below 5th percentile of adult 14mg once daily treatment steady state AUC, respectively. Among the 10 patients with high exposure, only 1 of them had steady state AUC slightly higher than maximum AUC_{ss} of adult patients receiving 14mg once daily treatment. For the 6 patients with body weight both below and above 40kg, their steady state AUC were within the range of 5th-95th percentile of AUC_{ss} in adults receiving 14mg once daily treatment. The reviewer concludes that the [redacted] (b) (4) regimen in pediatric patients can provide similar steady state exposure with that of adult patients receiving 14mg once daily treatment.

Figure 6. Steady state AUC for [redacted] (b) (4) regimen

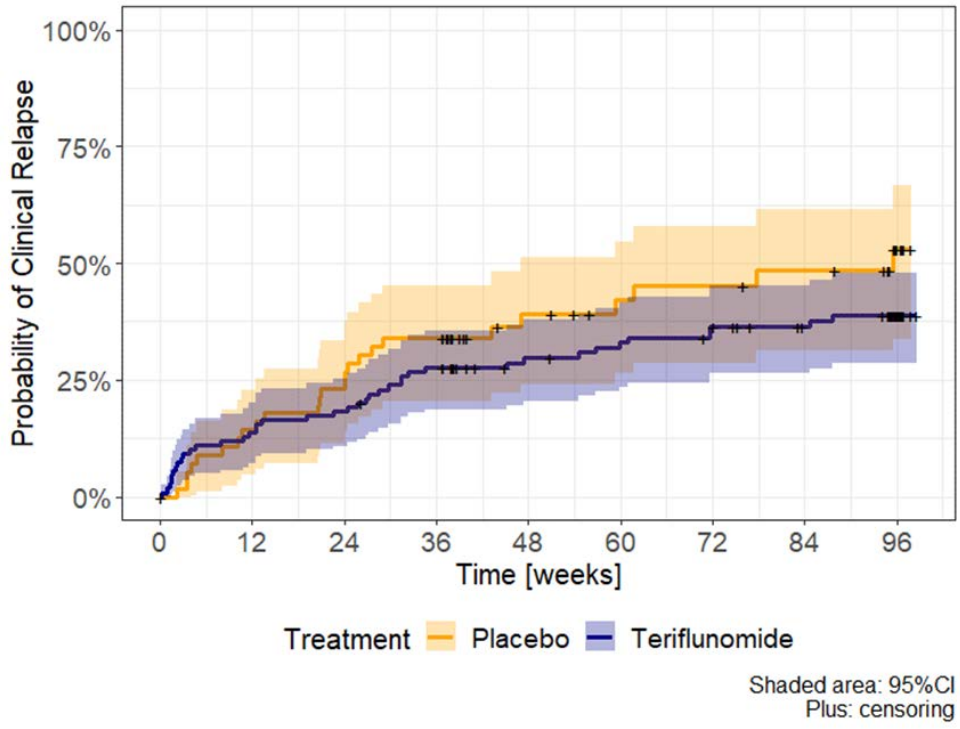


The Kaplan-Meier estimates for probability of clinical relapse was reproduced (Table 5) and plotted (Figure 7) by reviewers. Stratified log-rank test was applied to test the null hypothesis that teriflunomide treatment and placebo group had equal probability to have clinical relapse at any time point. The hazard ratio was estimated using cox regression model. The results were consistent with sponsor's result (Table 5).

Table 5. Analysis of time to first confirmed clinical relapse after randomization during the double-blind period - ITT population (sponsor's result from 2.5 Clinical

	Sponsor		Reviewer	
	Placebo (N=57)	Teriflunomide (N=109)	Placebo (N=57)	Teriflunomide (N=109)
Number of patients with confirmed clinical relapse during the double-blind treatment period, N (%)	25 (43.9)	40 (36.7)	25 (43.9)	40 (36.7)
Number of patients who were censored, N (%)	32 (56.1)	69 (63.3)	32 (56.1)	69 (63.3)
Time to first confirmed clinical relapse (weeks)				
Number	57	109	57	109
Mean (SD)	49.25 (33.66)	62.60 (36.12)	49.3 (33.7)	62.6 (36.1)
Median	39.14	75.29	39.14	75.29
Min ; Max	0.1 ; 98.0	0.1 ; 98.7	0.143; 98	0.143; 98.7
Kaplan-Meier estimates of probability of confirmed clinical relapse during the double-blind treatment period (95% CI) at				
24 Weeks	0.232 (0.132 ; 0.349)	0.183 (0.117 ; 0.261)	0.2321 (0.1132,0.3351)	0.1835 (0.1075,0.253)
48 Weeks	0.391 (0.259 ; 0.521)	0.298 (0.214 ; 0.386)	0.3912 (0.2419,0.5111)	0.2977 (0.2054,0.3793)
72 Weeks	0.452 (0.305 ; 0.588)	0.364 (0.272 ; 0.456)	0.4521 (0.2869,0.579)	0.3639 (0.2633,0.4507)
96 Weeks	0.531 (0.360 ; 0.676)	0.389 (0.293 ; 0.483)	0.5312 (0.3385,0.6677)	0.3889 (0.285,0.4776)
Hazard Ratio (95%CI)*	0.657 (0.388 ; 1.113)		0.6582 (0.4188, 1.034)	
Stratified Log-Rank test p-value	0.2949		0.289945	

Figure 7. Kaplan-Meier plot of time to first confirmed clinical relapse after randomization - ITT population



To test the impact of low exposure during PK run-in phase on the efficacy primary endpoint, 19 patients with observations of either clinical relapse or censoring during PK run-in were removed from original 166 patients. The truncated dataset was further used for stratified log-rank test and cox regression (Table 6). The hazard ratio slightly increased after excluding the PK run-in phase observations. Also, the median time to first confirmed clinical relapse increased from 75.3 weeks to 94.6 weeks for teriflunomide treated patients, whereas the median time for placebo group remain relatively the same (slightly increased from 39.1 weeks to 43.1 weeks). We conclude that the lack of efficacy could be partially due to the low teriflunomide exposure during PK run-in phase.

Table 6. Analysis of time to first confirmed clinical relapse after randomization during the double-blind period - ITT population removing PK

	Placebo (N=51)	Teriflunomide (N=96)
Number of patients with confirmed clinical relapse during the double-blind treatment period, N (%)	20 (39.2)	27 (28.1)
Number of patients who were censored, N (%)	31 (60.8)	69 (71.9)
Time to first confirmed clinical relapse (weeks)		
Number	51	96
Mean (SD)	54.7 (31.3)	70.7 (30.4)
Median	43.1	94.6
Min ; Max	8.14; 98	10.9 ; 98.7
Kaplan-Meier estimates of probability of confirmed clinical relapse during the double-blind treatment period (95% CI) at		
24 Weeks	0.1569 (0.0509,0.251)	0.0729 (0.0194,0.1235)
48 Weeks	0.3315 (0.1807,0.4545)	0.2026 (0.1166,0.2802)
72 Weeks	0.3983 (0.2271,0.5316)	0.2778 (0.1779,0.3655)
96 Weeks	0.4852 (0.2808,0.6315)	0.3061 (0.2011,0.3973)
Hazard Ratio (95%CI)	0.6769 (0.4283, 1.070)	
Stratified Log-Rank test p-value	0.066	

4.2.7 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
run1.mod	Final PPK model for NONMEM	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Teriflunomide_NDA202992S13_Ye\PPK Analyses\Final Model

Review_final.R	GOF of final PPK model, individual PK parameter calculation, simulation data preparation	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Teriflunomide_NDA202992S13_Ye\PPK Analyses\Final Model
Simulation_run-in.R	Simulation for PK run-in phase	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Teriflunomide_NDA202992S13_Ye\PPK Analyses\Final Model
Simulation_postrun-in.R	Simulation for post PK run-in phase	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Teriflunomide_NDA202992S13_Ye\PPK Analyses\Final Model
Efficacy.R	Efficacy analysis	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Teriflunomide_NDA202992S13_Ye\ER Analyses\Final Model

---

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/

XIAOHAN CAI
04/08/2021 12:15:38 PM

YE YUAN
04/08/2021 12:19:32 PM

VENKATESH A BHATTARAM
04/08/2021 01:08:55 PM

YUXIN MEN
04/08/2021 01:31:14 PM

MEHUL U MEHTA
04/08/2021 01:56:45 PM