CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	202992
Priority or Standard	Priority
Submit Date(s)	11/02/2020
Received Date(s)	11/02/2020
PDUFA Goal Date	05/02/2021
Division/Office	Division of Neurology 2, Office of Neuroscience
Reviewer Name(s)	Laura E. Baldassari, MD, MHS
Review Completion Date	04/08/2021
Established/Proper Name	Teriflunomide
(Proposed) Trade Name	Aubagio
Applicant	Sanofi
Dosage Form(s)	7mg, 14mg tablets
Applicant Proposed Dosing Regimen(s)	7mg or 14mg orally daily
Applicant Proposed Indication(s)/Population(s)	Relapsing forms of multiple sclerosis in adults (b) (4) (b) (4)
Recommendation on Regulatory Action	(b) (4) (b) (4) (Labeling change with clinical data) - Approval
Recommended Indication(s)/Population(s) (if applicable)	Not Applicable

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

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NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

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1. Executive Summary

1.1. Product Introduction

Teriflunomide (Aubagio) is a once-daily oral immunomodulatory drug that selectively and reversibly inhibits dihydroorotate dehydrogenase. Teriflunomide is an active metabolite of leflunomide, which is approved to treat rheumatoid arthritis in adults. Treatment with teriflunomide causes a reversible reduction in serum lymphocytes; the exact mechanism by which teriflunomide exerts therapeutic effects in multiple sclerosis (MS) is unknown. Based on findings from two adequate and well-controlled trials, NDA 202922 for teriflunomide was approved on 09/12/2012 for the treatment of adults with relapsing forms of MS. Teriflunomide is approved in both 7 mg and 14 mg doses in the United States

In this sNDA, the sponsor provided data from Trial EFC11759, a Phase 3 study in pediatric patients ages 10 to 17 with relapsing forms of MS, in response to a PREA Postmarketing Requirement and Written Request originally issued on March 7, 2013. The interim results of an open label extension study for Trial EFC11759 were also included in the submission.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Trial EFC11759 was an adequate and well-controlled clinical trial capable of providing substantial evidence of efficacy. However, Trial EFC11759 did not achieve a statistically significant finding in its primary endpoint, the time to first confirmed clinical relapse. This failure on the primary endpoint is likely multifactorial, due to early exit from the double blind trial as a result of high MRI activity, the occurrence of relapses during the PK run-in period, and a high level of inflammatory disease activity in the pediatric MS population. Additionally, analyses of secondary endpoints indicate a marginal effect of teriflunomide on most clinical and some MRI endpoints. The sponsor proposes that early exit from the double-blind period due to high MRI activity could have contributed to the failure to achieve a significant finding on the primary endpoint of this trial, but in considering all evidence presented by the sponsor, namely the results of Trial EFC11759, teriflunomide does not appear to provide a clinically significant treatment effect to patients with pediatric MS.

1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

An adequate and well-controlled trial of teriflunomide in pediatric patients aged 10 to 18 years with relapsing MS did not meet its primary endpoint, and therefore failed to provide substantial evidence that treatment with teriflunomide reduces the risk of confirmed clinical relapse compared to placebo. In addition to the lack of a significant effect on the primary endpoint of time to first confirmed clinical relapse, the treatment effects of teriflunomide on other clinical and MRI endpoints were not consistent with the expected outcomes for an effective therapy for MS. The sponsor hypothesized that the provision for patients to exit double-blind treatment and enter the open label extension period due to high MRI activity resulted in failure on the primary endpoint. However, a comparison of the patients who experienced high MRI activity and those who experienced confirmed clinical relapse revealed that these populations were distinct from one another, indicating that high MRI activity was not an appropriate substitute for clinical relapse, and that MRI findings could not serve as an adequate and interpretable outcome in the absence of primary evidence of a clinically meaningful treatment effect on relapses. In addition to the lack of compelling evidence supportive of a meaningful treatment effect, the safety data in this single trial were concerning. Though pancreatitis was identified as a potential adverse reaction associated with teriflunomide in adults in the postmarketing setting, pancreatitis appears to be more common in the exposed pediatric population. Another adverse reaction associated with teriflunomide of particular concern in the pediatric population is elevated creatine phosphokinase. Therefore, in a benefit-risk assessment, the findings from a single adequate and well-controlled trial failed to show persuasive evidence of efficacy, and suggest a less favorable safety profile of teriflunomide in pediatric patients with relapsing MS, [redacted] (b) (4)

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating, and neurodegenerative disease affecting the central nervous system. • Relapsing forms of MS are defined by the occurrence of clinical relapses, which are events characterized by new onset neurological symptoms associated with disability, from which there is variable	Treatment of relapsing forms of multiple sclerosis is intended to reduce the frequency of clinical relapses. Clinical relapses can be permanently disabling and reduce quality of life.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	recovery. Relapsing forms of MS include clinically isolated syndrome, relapsing remitting MS, and active secondary progressive MS. Pediatric onset MS is almost always relapsing, and progressive forms of MS are rare in the pediatric population. • The prevention of relapses is paramount to the treatment of patients with relapsing forms of MS, in order to prevent new neurological symptoms that can lead to temporary or permanent disability.	
Current Treatment Options	• There are 20 products approved for treatment of relapsing forms of MS, but only Gilenya (fingolimod) is approved for use in the pediatric population with MS (≥10 years of age). • Currently approved MS therapeutics have demonstrated efficacy in reducing the risk of clinical relapse, which is presumed to be related to immunomodulatory or immunosuppressive mechanisms of action that impact the neuroinflammatory aspect of the disease.	Treatment of relapsing forms of multiple sclerosis generally involves immunomodulation or immunosuppression intended to reduce the frequency of clinical relapse. Many therapies approved for the treatment of relapsing forms of MS in adults are labeled to prevent accumulation of disability. Currently, only one treatment for MS (fingolimod) is indicated for use in patients ≥ 10 years of age. In a single adequate and well-controlled trial (Trial D2311), fingolimod was shown to have a statistically significant and clinically meaningful reduction in patients with MS who were between 10 and 18 years old.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Teriflunomide has been shown to reduce relapse frequency and delay accumulation of disability in adults with relapsing multiple sclerosis. • A single pivotal trial and several supportive trials served as the basis of its approval for relapsing forms of MS in 2012. • In a pediatric study (Trial EFC11759), teriflunomide did not demonstrate a statistically significant difference in time to first confirmed clinical relapse compared to placebo, which was the primary endpoint. However, some MRI-based sensitivity analyses and key secondary endpoints indicated marginal benefit of teriflunomide compared to placebo.	Though teriflunomide has demonstrated substantial evidence of effectiveness in adults with relapsing MS, a single adequate and well-controlled trial in pediatric patients did not demonstrate a significant effect on preventing clinical relapses.
Risk and Risk Management	• Warnings and Precautions in the current approved labeling for teriflunomide include hepatotoxicity and drug-induced liver injury (boxed warning), embryofetal toxicity (boxed warning), bone marrow effects/immunosuppression potential/infections, hypersensitivity reactions, serious skin reactions, Drug Reaction with Eosinophilia and Systemic Symptoms, peripheral neuropathy, increased blood pressure, respiratory effects, and concomitant use with immunosuppressive or immunomodulating therapies. • Other common adverse reactions reported in clinical studies of teriflunomide include headache (16 to 18%), increased ALT (13 to 15%), diarrhea (13 to 14%), alopecia (10 to 13%), nausea (8 to 11%), paresthesia, arthralgia, neutropenia (4 to 6%), and hypertension (3 to 4%). • Other safety concerns listed in current teriflunomide labeling include cardiovascular effects, acute renal failure, hypophosphatemia, psoriasis or worsening of psoriasis, thrombocytopenia, interstitial lung	Many of the currently labeled most common risks associated with teriflunomide exposure identified in adult patients with MS were also reported in a clinical trial which enrolled pediatric patients with MS. The labeling for teriflunomide will be updated to note that pancreatitis and increased CPK were identified in the pediatric population at apparently higher frequency than adult patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	disease, and pancreatitis. • Safety review of pediatric data in this sNDA indicated that children experienced many of the same AEs as adults on teriflunomide, but also that pancreatitis associated with teriflunomide may be more likely to affect children. Other pediatric population-specific safety concerns include elevated creatine phosphokinase.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

■	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	■	Clinical outcome assessment (COA) data, such as		
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		■	Clinician reported outcome (ClinRO)	Section 6.1.2
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating, and neurodegenerative disorder affecting the central nervous system. The cause of MS is

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unknown, but is hypothesized to be related to a complex interaction of genetic and environmental risk factors.[1, 2] MS is the most common cause of non-traumatic neurologic disability in young adults, and it is estimated that approximately 1 million people in the United States have MS.[3] Disease manifestations can be diverse, and include weakness, incoordination, visual impairment, sensory loss, gait dysfunction, fatigue, cognitive impairment, and bowel/bladder dysfunction.

Relapsing forms of MS are defined by the occurrence of clinical relapses, which are events characterized by new onset neurological symptoms associated with disability, from which there is variable recovery. Relapsing forms of MS include clinically isolated syndrome, relapsing remitting MS (RRMS), and active secondary progressive MS. The prevention of relapses is paramount to the treatment of patients with relapsing forms of MS; relapses degrade the quality of life in patients with MS, and prevention of relapses prevents new neurological symptoms that can lead to disability.

Relapsing-remitting MS is the most common MS phenotype, as it accounts for approximately 85% of MS cases at symptom onset.[4] Patients with RRMS present with clinical relapses, from which there is a spectrum of recovery. The median age of RRMS onset is approximately 28 to 30 years.[5-7] In general, the frequency of relapse decreases over time,[8, 9] with an estimate of relapse decrease by 17% for every 5 years of disease duration.[8] The decrease in relapse risk is thought to be more pronounced in patients with older age of onset.

Over time, the majority of patients with RRMS transition from predominantly inflammatory to more neurodegenerative driving forces of the disease, with development of secondary progressive MS (SPMS).[10] The transition to SPMS is an age-dependent process,[11-13] and it is estimated that approximately 30 to 40% of patients with SPMS have relapses superimposed upon this typical gradual decline.[6, 14] The time from RRMS diagnosis to SPMS conversion is age of onset-dependent, and ranges from 18.9 to 20 years for all patients per several natural history studies.[8, 12, 15, 16] Generally, the younger a patient is at the time of RRMS onset, the longer the disease duration prior to SPMS conversion. However, several studies have demonstrated that patients who receive MS treatments have substantially decreased risk of and delayed conversion to SPMS compared to patients in the pre-treatment era.[17-23] Additionally, use of some therapies approved to treat MS has been shown to delay reaching disability milestones.[17, 20-22]

Patients with MS who have their first clinical event prior to the age of 18 years are considered to have pediatric MS. Onset of pediatric MS usually occurs in childhood and early adolescence, and comprises approximately 10% of adults with MS.[24] The median age of onset of pediatric MS is estimated to be approximately 14 to 16 years.[25, 26]

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Patients with pediatric MS generally present with similar syndromes as adults with MS, but ataxia, encephalopathy, seizures, and brainstem syndromes are more common in children below the age of 10.[24] The majority of patients with pediatric MS have a relapsing-remitting course, similar to the natural history of most patients with adult onset MS. Patients with pediatric MS tend to have more complete recovery from relapses despite relatively high relapse frequency early in the disease course compared to adults. Pediatric MS patients have longer time to disability milestones but younger median age at these milestones compared to those with adult onset MS.[25, 26]

2.2. Analysis of Current Treatment Options

There are over twenty unique therapies approved for treatment of relapsing forms of MS, including clinically isolated syndrome, relapsing remitting MS, and active secondary progressive MS (Table 1). All currently approved MS therapeutics have demonstrated efficacy in reducing the risk of clinical relapse.

The overall treatment strategy for adult MS, immunomodulation to reduce relapse frequency, is thought to be applicable to the pediatric population as well. However, only fingolimod (Gilenya) is approved for use in pediatric patients ≥ 10 years of age. Labeling for cladribine specifically states that its use in pediatric patients is not recommended due to the risk of malignancy.

Table 1 (Reviewer). FDA-Approved Treatments for Relapsing Forms of Multiple Sclerosis

Product Name	Relevant Indication (Current)	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety Issues
Interferon beta-1b (Betaseron)	Relapsing forms of MS[1]	1993	SC every other day	ARR[2] 0.9 vs. placebo 1.31	Injection site reactions, hepatotoxicity, depression
Interferon beta-1a (Avonex)	Relapsing forms of MS	1996	IM weekly	ARR 0.67 vs. placebo 0.82	Injection site reactions, hepatotoxicity, depression
Glatiramer acetate (Copaxone)	Relapsing forms of MS	1996	SC daily or three times a week	Relapse rate 0.6/2 years vs. placebo 2.4 in Study 1	Injection site reactions, lipoatrophy
Mitoxantrone (Novantrone)	SPMS, progressive relapsing, or worsening RRMS	2000	IV q 3 months, duration limited by cardiotoxicity	Reduction in # relapses (0.4 and 0.73 vs. 1.2 placebo) in study 1; reduction in Gd+ T1 lesions, ARR, EDSS change in Study 2	Leukemia, cardiotoxicity

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Product Name	Relevant Indication (Current)	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety Issues
Interferon beta-1a (Rebif)	Relapsing forms of MS	2002	SC three times a week	29 to 32% reduction in # relapses over 2 years vs. placebo	Injection site reactions, hepatotoxicity, depression
Natalizumab (Tysabri)	Relapsing forms of MS	2004	IV every 4 weeks	67% reduction in ARR vs. placebo	PML, hepatotoxicity
Interferon beta-1b (Extavia)	Relapsing forms of MS	2009	SC every other day	ARR 0.9 vs. placebo 1.31	Injection site reactions, hepatotoxicity, depression
Fingolimod (Gilenya)	Relapsing forms of MS, ages ≥10 years	2010	PO daily	ARR 0.18 vs 0.4 placebo; 0.16 vs. 0.33 Avonex	Macular edema, infection, bradycardia, respiratory effects, liver injury, infection
Teriflunomide (Aubagio)	Relapsing forms of MS	2012	PO daily	22 to 36% reduction in ARR vs. placebo	Hepatotoxicity, peripheral neuropathy, teratogenicity
Dimethyl fumarate (Tecfidera)	Relapsing forms of MS	2013	PO twice daily	44 to 53% reduction in ARR vs. placebo	Lymphopenia, GI effects, flushing
Peginterferon beta-1a (Plegridy)	Relapsing forms of MS	2014	SC every 2 weeks	36% ARR reduction vs. placebo	Injection site reactions, hepatotoxicity, depression
Alemtuzumab (Lemtrada)	Relapsing remitting and active SPMS, patients who have failed ≥2 other MS treatments	2015	IV, 3 to 5 days 1 year apart	49 to 55% ARR reduction vs interferon beta-1a	Serious and fatal autoimmune conditions, infusion reactions, stroke, malignancy
Ocrelizumab (Ocrevus)	Relapsing forms of MS; PPMS	2017	IV every 6 months	46 to 47% ARR reduction vs. interferon beta-1a	Infusion-related reactions, infection, possible breast cancer
Monomethyl fumarate (Bafiertam)	Relapsing forms of MS	2018	PO twice daily	See Tecfidera (505(b)(2))	Lymphopenia, GI effects, flushing
Siponimod (Mayzent)	Relapsing forms of MS	2019	PO daily	55% ARR reduction vs. placebo	Macular edema, infection, bradycardia, respiratory effects, liver injury, infection
Cladribine (Mavenclad)	Relapsing forms of MS (excluding CIS), in patients who have failed another MS treatment	2019	2 PO courses 1 year apart	58% ARR reduction vs. placebo	Malignancies, teratogenicity, lymphopenia, infections, hematologic toxicity, liver injury
Diroximel fumarate (Vumerity)	Relapsing forms of MS	2019	PO twice daily	See Tecfidera (505(b)(2))	Lymphopenia, GI effects, flushing

Product Name	Relevant Indication (Current)	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety Issues
Ozanimod (Zeposia)	Relapsing forms of MS	2020	PO daily	38 to 48% relative ARR reduction vs. interferon beta-1a	Macular edema, infection, bradycardia, respiratory effects, liver injury, infection
Ofatumumab (Kesimpta)	Relapsing forms of MS	2020	SC every 4 weeks	51 to 59% relative ARR reduction vs. teriflunomide	Infections, injection-related reactions, reduction in immunoglobulins, fetal risk
Ponesimod (Ponvory)	Relapsing forms of MS	2021	PO daily	30.5% relative ARR reduction vs. teriflunomide	Macular edema, infection, bradycardia, respiratory effects, liver injury, infection

[1]Relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease; [2] ARR: Annualized relapse rate

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Teriflunomide was originally approved on September 12, 2012, for the treatment of relapsing forms of MS. The sponsor currently markets teriflunomide in the US for relapsing forms of MS in adults.

3.2. Summary of Presubmission/Submission Regulatory Activity

Please refer to the Clinical Review for NDA 202992 by Dr. Jody Green regarding the complete regulatory history of teriflunomide prior to its original approval on September 12, 2012.

Initial pre-IND meeting request: September 16, 2003

Original IND submission: March 30, 2004

Proposed Pediatric Study Request submission: January 11, 2011

Pre-NDA meeting: March 28, 2011

NDA 202992 submission: August 12, 2011

NDA 202992 approval: September 12, 2012

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The approval letter required the sponsor to perform a trial in patients aged 10 to 17 but waived the requirement for a trial in children ages 9 and younger (PMR 1924-1) because studies in patients less than 10 years old are impracticable. A Deferral Extension request was granted on 12/14/2017 due to slow recruitment, 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. However, this date was not extended with the Deferral Extension request for the PMR.

Pediatric sNDA original submission: July 24, 2020

The original submission for this sNDA met the deadline for the PREA PMR, but not the Written Request. Due to a procedural misunderstanding, the sponsor had not amended the Written Request due date; therefore a submission of July 24, 2020 was beyond the due date of record, June 30, 2016. After discussion with the sponsor, 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 PREA PMR deferral extension to November 2020 since a resubmission would occur beyond the previous agreed deferred PREA PMR date.

Pediatric sNDA withdrawal: September 22, 2020

Following a teleconference with the Agency on September 10, 2020, the sponsor withdrew the sNDA on September 22, 2020. The revised Written Request and PREA PMR deferral extension were sent to the sponsor on October 22, 2020.

Pediatric sNDA resubmission: November 2, 2020

3.3. Foreign Regulatory Actions and Marketing History

Per the most recent Periodic Benefit-Risk Evaluation Report submitted to the Agency on December 11, 2020, teriflunomide is currently marketed for the treatment of MS in over 50 countries worldwide. Teriflunomide was approved for the treatment of MS in the European Union on August 26, 2013. The 14mg daily dose is approved in all countries, but the 7mg daily dose is only approved in the US, Taiwan, and China.

Teriflunomide has not been approved for use in pediatric populations anywhere in the world.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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4.1. Office of Scientific Investigations (OSI)

Remote regulatory record review was conducted for 2 study sites in Turkey. Please refer to the Office of Scientific Investigations (OSI) review for further details. Briefly, the inspection found that one patient at one of the sites may have been inappropriately enrolled in the trial due to experiencing a relapse within 30 days of randomization. However, no other major issues were identified.

4.2. Product Quality

Please refer to the Chemistry, Manufacturing, and Control (CMC) review.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Please refer to the Nonclinical Review.

4.5. Clinical Pharmacology

Please refer to the Clinical Pharmacology review.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

One Phase 3 trial with an open label extension in pediatric patients with relapsing MS was referenced in this sNDA (Trial EFC11759). The characteristics of this trial are summarized in Table 2.

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Table 2 (Reviewer). Listing of Clinical Trials of Teriflunomide in Pediatric MS Patients

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
EFC11759	Phase 3, multicenter, randomized, double-blind, placebo-controlled study	Teriflunomide 3.5mg (≤40kg) or 7mg (>40kg) [14mg equivalent based on results of PK run-in] or placebo PO daily	Primary endpoint: Time to first confirmed clinical relapse	96 week double blind treatment period, followed by open label extension (up to 192 weeks)	166 randomized (109 teriflunomide, 57 placebo)	Pediatric patients 10 to 17 years of age with relapsing forms of MS.	57 active centers in 22 countries worldwide, 54 centers randomized at least 1 patient

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5.2. Review Strategy

The results of Trial EFC11759, specifically the double blind treatment period, were the primary source of efficacy and safety data for this sNDA. Interim results from the open label extension period were submitted with this sNDA and were considered for the efficacy and safety analyses as well. Safety information from the 120 Day Safety Update, which provided further data from the open label extension period was also reviewed.

The safety population for Trial EFC11759 was defined as "all randomized patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment patients actually received."

In the protocol for Trial EFC11759, the sponsor defined an adverse event (AE) as "any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment."

Serious adverse events (SAEs) were defined as "any untoward medical occurrence that at any dose:

- Results in death or,
- Is life-threatening or,

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization or,
- Results in persistent or significant disability/incapacity or,
- Is a congenital anomaly/birth defect or,
- Is a medically important event."

The sponsor defined the treatment-emergent adverse events (TEAEs) period as "from first dose of IMP up to 4 weeks (28 days) after last dose of IMP or up to inclusion in open label treatment phase, whichever occurs first. The TEAE period can be divided into 2 distinct periods:

- Treatment Period from first dose of IMP to last dose of IMP,
- Accelerated elimination period from 1 day after treatment period up to 4 weeks (28 days) after last dose of IMP or up to inclusion in open label treatment phase, whichever occurs first."

The ADAE dataset included verbatim terms by the investigators (AETERM) and preferred terms (AEDECOD) to which these verbatim terms were coded under the Medical Dictionary for

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Regulatory Activities (MedDRA) version 22.0. Events were coded by their primary System Organ Class (AESOC in ADAE).

Trial EFC11759 included assessments of AEs, SAEs, MRIs, vital signs, electrocardiograms (ECGs), pubertal status, and laboratory abnormalities, which were reviewed.

6. Review of Relevant Individual Trials (b) (4)

6.1. Trial EFC11759

6.1.1. Study Design

Overview and Objective

Trial EFC11759, also known as "TERIKIDS," is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study of teriflunomide in pediatric patients 10 to 17 years of age with relapsing forms of MS.

The primary objective of this study was to "assess the effect of teriflunomide in comparison to placebo on disease activity as measured by time to first clinical relapse after randomization in children and adolescents 10 to 17 years of age with relapsing forms of multiple sclerosis."

Secondary objectives were:

- "To assess the effect of teriflunomide in comparison to placebo on disease activity/progression measured by brain MRI and on cognitive function.
- To evaluate the safety and tolerability of teriflunomide in comparison to placebo.
- To evaluate the PK of teriflunomide."

Trial Design

Trial EFC11759 consisted of an up to 4-week screening period, a 96-week double-blind treatment (DBT) period, and an optional open label extension (OLE) period for up to 192 weeks following randomization. Another additional, optional, extension period was offered to patients who were not at least 18 years old at the time of study completion (at Week 192), in order to provide treatment until they turned 18 years old or achieved an age when they could switch to commercial teriflunomide. After discontinuing treatment, patients entered a 4-week follow-up period.

Patients were randomized 2:1 to either teriflunomide or placebo. The DBT also included a blinded, 8-week PK run-in phase (4 weeks of PK sample collection and 4 weeks of analysis).

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During this run-in phase, patients received either placebo, teriflunomide 3.5mg (if ≤40kg), or teriflunomide 7mg (if >40kg). Based on these data, individual dose adjustments (as defined in the protocol) were made to ensure that patients would have exposure equivalent to the 14mg adult dose for the remainder of the study. If a patient experienced a relapse during the PK run-in period, re-consent/assent was required.

If a patient experienced a confirmed relapse after the PK run-in phase, he or she was given the option to enter the OLE. If the relapse was not confirmed, he or she could either continue or discontinue DBT.

High MRI Activity Exit from DBT Option

Patients with "High MRI Activity," as defined in the protocol and reproduced in Figure 1, were able to exit DBT and enter the 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 DBT completion). Patient who discontinued study treatment and/or did not wish to continue teriflunomide underwent an accelerated elimination procedure.

Figure 1 (Sponsor). 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**: Sponsor Clinical Study Report, page 34*

> ***Reviewer Comment:** The allowance for an exit from DBT due to "high MRI activity" was intended to improve recruitment for a placebo-controlled trial by providing a "rescue option" that ensured patients in the placebo treatment arm would be allowed a quicker transition to OLE treatment based on neuroinflammatory activity. However, this option reduced double-blind treatment exposure, affecting the number and types of patients in the DBT period, and ultimately reduced the study's power.*
>
> *While this exit option may have been seemingly appropriate as a patient-centric design feature, its statistical impact was not trivial. The protocol could have considered ensuring a minimum placebo exposure for all patients, regardless of MRI activity, or additional consideration for adequate numbers of patients and relapse events in the DBT*

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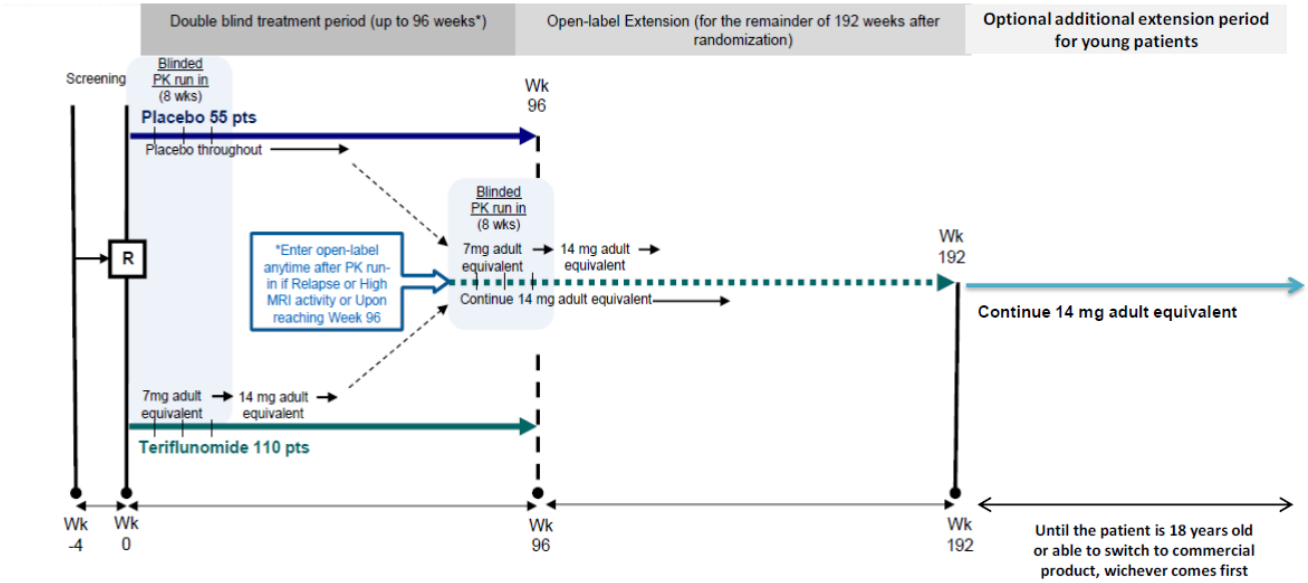
period.

Though this rescue option did not render the results of this trial uninterpretable, it does have the potential to compromise outcome interpretability related to relapses. Therefore, this feature should not be utilized in future trials in pediatric MS. Please refer to the full discussion of the impact of this option's impact on Trial EFC117459 below.

Study Schematic

The Trial EFC11759 Study Schematic is shown in Figure 2.

Figure 2 (Sponsor). Trial EFC11759 Study Schematic



R: Randomization

This review includes data from both the DBT and OLE periods for efficacy, but the primary efficacy determination will be based upon the DBT period data.

Eligibility Criteria

Key inclusion criteria for EFC11759 included:

- Relapsing MS per 2010 McDonald Criteria[27] and 2012 International Pediatric MS Study Group (IPMSSG) criteria for pediatric MS,[28] with:
  - At least 1 relapse in 12 months prior to screening, or
  - At least 2 relapses in 24 months prior to screening
- ≥10 and <18 years of age at randomization

  - In Russian Federation, ≥13 and ≤17 years of age from 12/18/2014 to 07/26/2016 per protocol amendment
- Signed informed consent/assent obtained from patient and patient's legal representative (parents or guardians) according to local regulations.

Key exclusion criteria for EFC11759 included:

- Expanded Disability Status Scale (EDSS) >5.5 at screening or randomization
- Relapse within 30 days of randomization
- Body weight <20 kg
- Patients must not have used adrenocorticotrophic hormone or systemic corticosteroids for 2 weeks prior to MRI assessment
- Treated with:
  - Glatiramer acetate, interferons or dimethyl fumarate within 1 month prior to randomization.
  - Fingolimod or intravenous immunoglobulins within 3 months prior to randomization.
  - Natalizumab, other immunosuppressant or immunomodulatory agents such as cyclophosphamide, azathioprine, cyclosporine, methotrexate, mycophenolate, within 6 months prior to randomization.
  - Cladribine or mitoxantrone within 2 years prior to randomization.
- Treated with alemtuzumab at any time.
- Liver function impairment or persisting elevations (AST/ALT/direct bilirubin >2x ULN)
- Female patients of child-bearing potential or male patient not using highly effective (double barrier) contraceptive and /or female patients of childbearing potential who are unwilling to or unable to be tested for pregnancy.
- Patients with significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia:
  - Hemoglobin<10g/dL,
  - Absolute white blood cell count <3000 cells/mm3 (µL) and/or,
  - Platelet count <150 000 cells/mm3 (µL) and/or,
  - Absolute neutrophil ≤1500 cells/mm3 (µL)
- Persisting elevations (confirmed by retest) of serum amylase or lipase greater than 3-fold the upper limit of normal.
- Active pancreatitis or known history of chronic pancreatic disease.
- Moderate to severe impairment of renal function, as shown by serum creatinine >133 µmol/L (or >1.5 mg/dL).
- History of HIV infection
- Positive tuberculin test leading to suspicion of tuberculosis (e.g., unless known to have been treated for tuberculosis in the past, or interpreted in light of vaccination; if in doubt, chest X-ray is recommended).

Please refer to complete eligibility criteria reproduced in Appendix 13.2.

Blinding during the DBT period was protected by the identical appearance of teriflunomide and placebo (film-coated tablets in child resistant blister packs), both with daily dosing. Additionally, this trial involved both a treating and examining neurologist; the examining neurologist conducted EDSS assessments. Brain MRIs were reviewed and interpreted at a central, independent, blinded facility. The randomization code was broken only in "exceptional circumstances" when knowledge of the IMP was essential for treating the patient.

Study Endpoints

The primary efficacy endpoint was 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."

Secondary endpoints included the following:

- Proportion of clinical relapse-free patients at 24, 48, 72, and 96 weeks
- MRI endpoints:
    - Number of new/newly enlarged T2 lesions (**key**)
    - Number of gadolinium-enhancing T1 lesions (**key**)
    - 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
- Expanded Disability Status Scale (EDSS) Score
- Cognitive outcome measured by the Symbol Digit Modalities Test (SDMT) and cognitive battery tests
- Teriflunomide PK

The proportion of disease-free patients was an exploratory endpoint.

Two independent physicians were also employed as central raters, one for adjudication of pubertal status at MS disease onset, and the other as a central scorer for the brief visual memory test-revised (BVMT-R).

Other efficacy assessments included brain MRI, EDSS, SDMT, and cognitive battery testing.

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Brain MRIs were reviewed by blinded central neuroradiologists, as mentioned previously.

The schedule of assessments for Trial EFC11759 is presented in Figure 3.

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Figure 3 (Sponsor). Trial EFC11759 Schedule of Assessments for Double Blind Treatment Period

	Baseline		Treatment period																	Post drug elimination follow up		Unscheduled
Week (W)[a]	W-4	Rand[b]	W4	W8	W12	W16	W20	W24	W30	W36	W42	W48	W54	W60	W66	W72	W78	W84	W90	W96/ EOT	EOT +2W	EOT +4W	Relapse visit [v]
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20[c]	21[d]	22[d]	
Entry procedures																							
Informed consents[e] and assent	X																						X[e]
Review inc/excl criteria	X	X																					
Demographics	X																						
Medical/surgical history	X																						
Tuberculosis test[s]	X																						
Prior medications	X	X																					
Randomization		X																					
Efficacy																							
EDSS	X	X						X				X				X				X			X[p]
SDMT		X						X				X				X				X			
Cognitive Battery Test[u]		X																		X			
Brain MRI [q]	X[f]							X				X				X				X			

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	Baseline		Treatment period																	Post drug elimination follow up		Unscheduled
Week (W)[a]	W-4	Rand[b]	W4	W8	W12	W16	W20	W24	W30	W36	W42	W48	W54	W60	W66	W72	W78	W84	W90	W96/ EOT	EOT +2W	EOT +4W	Relapse visit [v]
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20[c]	21[d]	22[d]	
Safety																							
Adverse event reporting[g]		<----------																		---------->			
Vital signs[h]	X	X	X	X	X			X		X		X		X		X		X		X	X	X	X
Physical examination[t]	X	X			X			X		X		X		X		X		X		X	X		
ECG 12-leads		X																		X	X[r]	X[r]	
Tanner[i]		X						X				X				X				X			
Clinical routine laboratories[k,j]	X	X	X		X			X		X		X		X		X		X		X			
Clinical safety laboratories[j,l,o]				X		X	X		X		X		X		X		X		X		X	X	
Immunoglobulins / TSH		X						X				X				X				X			
Treatments																							
Concomitant medications		<----------																		---------->			
Dispense study drugs/IVRS call		X		X	X			X		X		X		X		X		X		X[v]			
Accountability / compliance				X	X			X		X		X		X		X		X		X			
Teriflunomide PK sampling[m]			XXX	X	X			X		X										X	X[n]	X[n]	

BVMT-R = brief visuospatial memory test-revised, ECG = electrocardiogram, EOT = end of treatment (EOT= First visit after last study drug intake), EDSS = expanded disability status scale, FS = functional score, IVRS = interactive voice response system, MRI = magnetic resonance imaging, PK = pharmacokinetic, SDMT = symbol digit modalities test, TSH = thyroid stimulating hormone

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Statistical Analysis Plan

The intention-to-treat (ITT) population was used for the primary efficacy analysis. The primary efficacy endpoint, time to first confirmed clinical relapse, was analyzed via stratified log rank test with covariates of region and baseline pubertal status. A hazard ratio and associated 95% confidence interval were calculated using a Cox proportional hazards model with robust variance estimation and covariates of region, baseline pubertal status, age at study entry, and number of relapses in the year prior to randomization. Relapses occurring at any time within the DBT period, including during the PK run-in phase, were included in the primary efficacy analysis.

The sponsor also prespecified the following sensitivity analyses for the primary endpoint:

- Time to first confirmed clinical relapse or high MRI activity after randomization
- Time to first clinical relapse (confirmed or unconfirmed) after randomization
- Time to first confirmed clinical relapse occurring after the PK run-in phase but before treatment discontinuation; patients who had a relapse during the PK run-in were included, but were right censored at the time of treatment discontinuation.
- Time to first confirmed relapse including relapses during PK run-in phase and relapses reported after study drug discontinuation and up to 96 weeks after randomization.

The sponsor also planned subgroup analyses for the primary endpoint by demographic and other characteristics, as described in the Statistical Analysis Plan.

Secondary endpoints were analyzed using Kaplan-Meier methods (proportion of relapse-free patients and proportion of patients free of new/enlarged T2 lesions at weeks 48 and 96), negative binomial regression with robust variance estimation (new/enlarged T2 lesions, T1 gadolinium-enhancing lesions, and T1 hypointense lesions), and mixed-effects models with repeated measures (change from baseline of T2 lesion volume, T1 hypointense lesion volume, and percentage change in brain volume).

Descriptive statistics were reported by treatment group at each visit for EDSS and cognitive battery results.

To control for multiplicity, the sponsor utilized a step down testing procedure only for the 2 key secondary efficacy endpoints at p=0.05. No adjustments were made for other secondary efficacy endpoints.

Please refer to the Statistical Review for full details regarding the Statistical Analysis Plan.

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Protocol Amendments

Four global and 2 local amendments were made to the protocol. Both local amendments were specific to Russia. Key changes with global amendments are summarized in Table 3.

Both Russian local amendments pertained to recruitment age. One amendment on 12/18/2014 restricted recruitment age to 13 to 17 years (rather than 10 to 17 years). The second local amendment on 07/26/2016 again revised the recruitment age to harmonize with the global protocol (10 to 17 years).

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Table 3 (Reviewer). Summary of Trial EFC11759 Global Protocol Amendments

Amendment Number	Date	Description
1	12/18/2013	1. Addition of MRI at weeks 24, 48, 96 2. Addition of MRI at week 36 in case of at least 5 new/enlarged T2 lesions 3. Addition of MRI endpoints (change in T2 lesion volume, change in T1 hypointense lesion volume, number of new T1 hypointense lesions, and brain atrophy) 4. Addition of immunoglobulin (IgG, IgM, IgA) measurements at baseline and every 24 weeks 5. Change from Poisson regression model to negative binomial model for analysis of number of new/enlarged T2 lesions and T1 gadolinium-enhancing lesions per MRI scan; ordinal logistic regression including treatment group, region, pubertal status, and age used to analyze endpoints to reduce impact of outliers.
2	06/11/2014	1. Extension of open-label period up to 192 weeks post-randomization 2. Addition of MRI at week 72 3. Addition of criterion for switch into open-label period following week 72 MRI 4. Modification of required minimum washout period for previous MS treatment 5. Exclusion of patients with prior alemtuzumab treatment 6. Addition of note regarding potential lactose in teriflunomide tablets 7. Addition of note regarding contraception and local additional requirements (per UK/MHRA) 8. Addition of endpoints: a. Proportion of patients free of new or enlarged MRI T2 lesions at Weeks 28 and 96 b. Proportion of disease-free patients (exploratory endpoint) 9. Addition of measurement of TSH every 24 weeks and at end of trial
3	08/02/2018	1. Addition of optional additional extension period, including description of assignment, safety monitoring, informed consent, and provision for separate data reporting 2. Change of inclusion criteria for MS based on McDonald Criteria 2010 and IPMSG version 2012 based on relapse preceding screening, not randomization 3. Age eligibility changed from ≤ 17 to < 18 years 4. Modification of total expected number of patients to include 20% pre-pubertal patients or 10% of patients under age 13 at time of inclusion into study, and at least 25% male patients
4	09/11/2019	1. Addition of biomarker research

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6.1.2. Study Results

Compliance with Good Clinical Practices

Section 4 of the Clinical Study Report (CSR) indicates that the study was "conducted in accordance with consensus ethical principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for Good Clinical Practice (GCP). The Investigators obtained independent ethics committee or institutional review board approval for the study protocol and all amendments. Additionally, Section 8 of the CSR states that the sponsor "conducted Investigator meetings and training sessions for clinical research associates as well as individual site initiation meetings to develop a common understanding of the clinical study protocol, case report form, and study procedures, in compliance with GCP."

Financial Disclosures

Please refer to Appendix 13.3. The sponsor provided Form 3455 in module 1.3.4, indicating that 6 out of 391 (1.5%) Clinical Investigators had disclosable financial interests, all under the category of "any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria." Five of these 6 Investigators were from the (b) (6), which accounts for a small proportion of the patients in this study ((b) (6)%, n = (b) (6). The sixth Investigator was from (b) (6), from which (b) (6) patients were enrolled ((b) (6)%). The sponsor also submitted Form 3454 indicating that all other Clinical Investigators had no disclosable financial interests. Given the protocols for randomization and blinding incorporated by the sponsor, and the small number of patients potentially enrolled by Investigators with disclosable financial interests, the potential impact of disclosed financial interest on overall efficacy or safety outcomes was minimal.

Data Quality and Integrity

The sponsor conducted regular site monitoring via either external vendors or sponsor personnel. An audit certificates was provided in the submission, and indicated that inspections were performed for 7 study sites (on-site), the central MRI reading service provider (b) (4)), the clinical laboratory service provider (b) (4) the data review/surveillance and DMC activities, and Sanofi Global Clinical Trial Management.

The CSR indicated that treatment assignment blinding was broken at the local level only (by the Investigator) for 2 patients who experienced acute pancreatitis while receiving teriflunomide. No other unblinding occurred during the double-blind treatment period.

> ***Reviewer comment:*** *The protocol indicated that "in case of an SAE, the code must be broken only in exceptional circumstances when knowledge of the IMP is essential for*

> *treating the patient." One of these cases (Subject ID (b) (6)) was an SAE, so unblinding to determine whether study treatment could be the cause of pancreatitis is appropriate. The second case (Subject (b) (6)) was not categorized as an SAE, but did lead to treatment discontinuation (Section 8.4.3). However, the code was broken 6 days after the patient's last DBT exposure.*

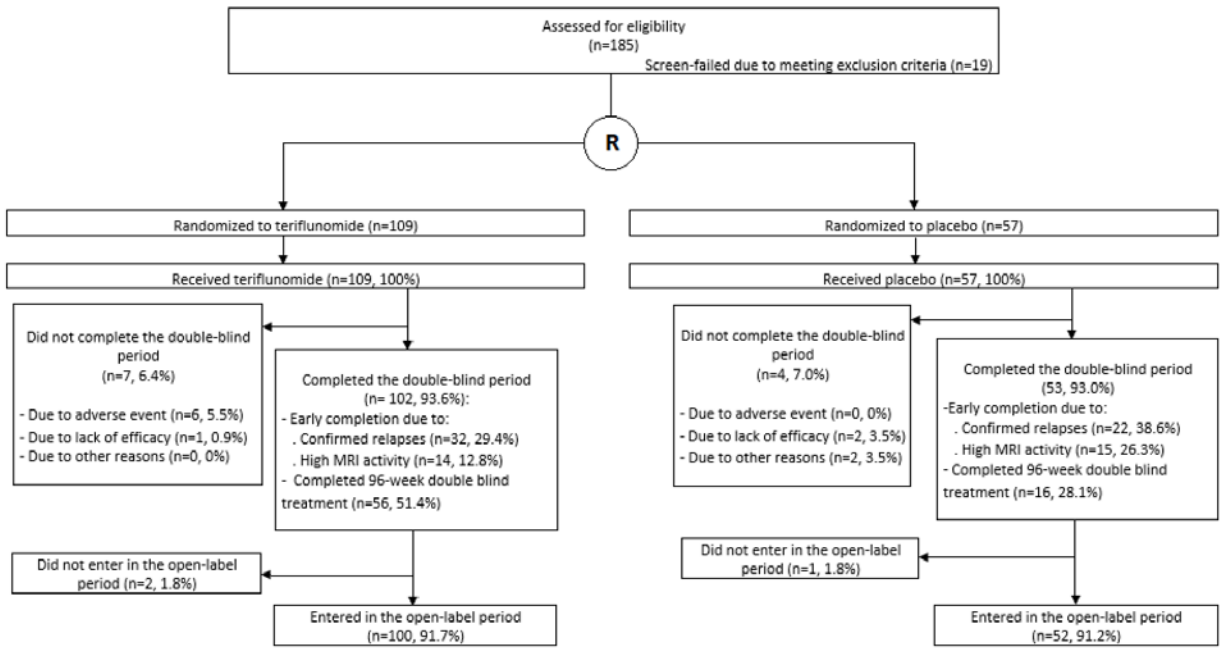
Additionally, the sponsor indicated that due to a database configuration error, sponsor personnel in certain countries (China, Greece, Russia, and Turkey) received SAE Acknowledgment of Receipt that contained unblinded treatment information. Seven patients were impacted by this disclosure. However, the sponsor personnel were not able to revise Case Report Forms and this event occurred during the open label period. Therefore, there does not appear to be an effect of this deviation on the main efficacy results from the double blind treatment period.

Patient Disposition

One hundred eighty-five patients were screened at 57 active centers worldwide, and 166 were randomized across 54 centers. The first patient was screened on July 16, 2014, and the last patient completed the study on October 25, 2019. Of these 166 patients, 109 were assigned to receive teriflunomide and 57 to placebo in the DBT period.

Patient disposition is depicted in Figure 4. Of the patients randomized to teriflunomide (n = 109), 7 did not complete the DBT period (6 due to adverse events, 1 due to lack of efficacy), 46 (42.2%) completed the DBT period early (32 [29.4%] due to confirmed relapse, 14 [12.8%] due to high MRI activity), and 56 (51.4%) completed the 96-week DBT period. Of the patients randomized to placebo (n = 57), 4 did not complete the DBT period (0 due to adverse events, 2 due to lack of efficacy, and 2 other [informed consent withdrawal]), 37 (64.9%) completed the DBT period early (22 [38.6%] due to confirmed relapse, 15 [26.3%] due to high MRI activity), and 16 (28.1%) completed the 96-week DBT period. One hundred patients (91.7%) randomized to teriflunomide and 52 (91.2%) to placebo entered the open-label extension period.

Figure 4 (Sponsor). Patient Disposition Flow Diagram



Source: Sponsor Trial EFC11759 Clinical Study Report, Figure 2 (p. 51)

Adverse events leading to permanent discontinuation of study treatment occurred in 6 patients receiving teriflunomide during the double blind treatment period. These AEs included pulmonary tuberculosis (n = 1), hyperlipasaemia (n = 1), affective disorder (n = 1), pancreatitis acute (n = 2), and alanine aminotransferase increased (n = 1). Please refer to Section 8.4.3 for complete discussion of these adverse events.

The Intention to Treat (ITT) and safety populations were identical, with 109 patients on teriflunomide and 57 on placebo.

Additionally, 152 patients entered the OLE period, 100 of whom received teriflunomide and 52 of whom received placebo in the DBT period.

The 120-Day Safety Update indicated that in the interval from November 28, 2019, through December 1, 2020, 32 additional patients completed the OLE (12 placebo/teriflunomide, 20 teriflunomide/teriflunomide). Cumulatively, 62/152 (40.8%) of patients completed the OLE period.

Protocol Violations/Deviations

Six critical or major efficacy-related protocol deviations occurred during the DBT period, 4 in the

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placebo group (7.0%) and 2 in the teriflunomide group (1.8%). In the placebo group, 3 patients had an IMP interruption >2 consecutive weeks, 1 patient experienced overdose cumulatively over 3 days (this patient also had IMP interruption), and 1 did not meet selection criteria related to MS diagnosis and prior relapse activity. In the teriflunomide group, 1 patient had a relapse within 30 days of randomization, and 1 patient did not meet selection criteria related to MS diagnosis and prior relapse activity.

Thirty-one other critical or major protocol deviations occurred during the DBT Period, 5 in the placebo group (8.8%) and 16 in the teriflunomide group (14.7%). Of these 16 deviations among patients on teriflunomide, 6 were related to protocol adherence, 5 informed consent, 2 laboratory/diagnostic samples, 1 clinical safety, 1 inclusion/exclusion criteria, 1 randomization issue, and 1 patient with significantly impaired bone marrow function or cytopenias. Of the 5 deviations among patients on placebo, 1 was related to clinical safety, 1 informed consent, 2 investigational product, 1 laboratory/diagnostic samples, and 1 protocol adherence. The informed consent-related deviations occurred when "patients and/or parents/guardians agreed and signed the informed consent either with a slight delay or on an incorrect version of informed consent/assent forms."

Regarding randomization irregularities, one patient experienced stratification error in the teriflunomide group.

In terms of drug-dispensing irregularities, 2 patients experienced erroneous kit dispensation (1 placebo, 1 teriflunomide) and it was noted that a kit was not available for 1 patient on teriflunomide.

During the OLE period, 7 critical or major efficacy-related protocol deviations occurred, 4 in the teriflunomide-teriflunomide group (4.0%) and 3 in the placebo-teriflunomide group (5.8%). All of these deviations involved IMP interruption greater than 2 consecutive weeks. Twenty other critical or major protocol deviations occurred during the OLE Period, 9 in the placebo-teriflunomide group (17.3%) and 11 in the teriflunomide-teriflunomide group (11.0%). The most frequently reported critical or major protocol deviation was related to protocol adherence (5.9%, n = 9).

Table of Demographic Characteristics

Demographic characteristics of patients included in the primary efficacy analysis for Trial EFC11759 are presented in Table 4. The patient population appears to be generally consistent with that reported for pediatric relapsing MS in other studies, based upon the age, sex, and race characteristics.

A small percentage of patients included in Trial EFC11759 were from the United States, but the majority of patients were from Europe (42.8%), the Middle East (27.1%), and Asia (22.3%).

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Table 4 (Reviewer). Demographic characteristics of patients in the primary efficacy analysis (Intention to Treat Population)

	Placebo (N = 57) % (n)	**Teriflunomide** (N = 109) % (n)	**Total** (N = 166) % (n)
Sex			
Male	31.6 (18)	33.9 (37)	33.1 (55)
Female	68.4 (39)	66.1 (72)	66.9 (111)
Age at randomization			
Mean (SD[1], years)	14.7 (2.1)	14.6 (2.0)	14.6 (2.0)
Median (IQR[2], years)	15 (2.5)	15 (3.0)	15 (3.0)
Min, max (years)	10, 17	10, 17	10, 17
Age Group			
<12 years	12.3 (7)	8.3 (9)	9.6 (16)
≥12 to <15 years	19.3 (11)	33.9 (37)	28.9 (48)
≥15 to <18 years	68.4 (39)	57.8 (63)	61.45(102)
Race			
White	73.7 (42)	68.8 (75)	70.5 (117)
Asian	21.1 (12)	22.9 (25)	22.3 (37)
Black or African American	1.8 (1)	3.7 (4)	3.0 (5)
Other	3.5 (2)	4.6 (5)	4.2 (7)
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	0 (0)
Ethnicity			
Hispanic or Latino	0 (0)	1.8 (2)	1.2 (2)
Not Hispanic or Latino	91.2 (52)	92.7 (101)	92.2 (153)
Unknown/Not reported	8.8 (5)	5.5 (6)	6.6 (11)
Region			
United States	3.5 (2)	2.8 (3)	3.0 (5)
Rest of the World	96.5 (55)	97.3 (106)	96.7 (161)
Region			
Europe	42.1 (24)	43.1 (47)	42.8 (71)
Middle East	28.1 (16)	26.6 (29)	27.1 (45)
Asia	21.1 (12)	22.9 (25)	22.3 (37)
North America	3.5 (2)	3.7 (4)	3.6 (6)
North Africa	5.3 (3)	3.7 (4)	4.2 (7)

[1]SD: Standard deviation; [2]: Interquartile range

Reviewer comment: *Overall, demographic characteristics appeared to be balanced between the placebo and teriflunomide groups, but there was a higher percentage of patients <12 years of age in the placebo group (12.3%) compared to teriflunomide (8.3%).*

Demographic characteristics of patients who entered the open-label period are presented in Table 5. Overall, the characteristics of patients in the open-label period appear similar to those in the double-blind period.

Table 5 (Reviewer). Demographic characteristics of patients in open label period

	Placebo-Teriflunomide (N = 52) % (n)	**Teriflunomide-Teriflunomide** (N = 100) % (n)	**All Teriflunomide Open-Label** (N = 152) % (n)
Sex			
Male	30.8 (16)	34.0 (34)	32.9 (50)
Female	69.2 (36)	66.0 (66)	67.1 (102)
Age			
Mean (SD[1], years)	14.6 (2.1)	14.6 (2.0)	14.6 (2.1)
Median (IQR[2], years)	15.0 (3.0)	15.0 (3.0)	15.0 (3.0)
Min, max (years)	10, 17	10, 17	10, 17
Age Group			
<12 years	13.5 (7)	9.0 (9)	10.5 (16)
≥12 to <15 years	19.2 (10)	35.0 (35)	29.6 (45)
≥15 to <18 years	67.3 (35)	56.0 (56)	59.9 (91)
Race			
White	71.2 (37)	68.0 (68)	69.1 (105)
Asian	23.1 (12)	24.0 (24)	23.7 (36)
Black or African American	1.9 (1)	3.0 (3)	2.6 (4)
Other	3.9 (2)	5.0 (5)	4.6 (7)
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	0 (0)
Ethnicity			
Hispanic or Latino	0 (0)	2.0 (2)	1.3 (2)
Not Hispanic or Latino	90.4 (47)	92.0 (0)	91.5 (139)
Unknown/Not reported	9.6 (5)	6.0 (6)	7.2 (11)
Region			
United States	3.9 (2)	3 (3.0)	3.3 (5)
Rest of the World	96.2 (50)	97.0 (97)	96.7 (147)
Region			
Europe	42.3 (22)	43.0 (43)	42.8 (65)
Middle East	26.9 (14)	25.0 (25)	25.7 (39)
Asia	23.1 (12)	24.0 (24)	23.7 (36)
North America	5.8 (3)	4.0 (4)	4.6 (7)
North Africa	1.9 (1)	4.0 (4)	3.3 (5)

[1]SD: Standard deviation; [2]: Interquartile range

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Other key baseline characteristics for patients in Trial EFC11759 are presented in Table 6.

Overall, 6.0% of patients (n = 10) were pre-pubertal, which is below the enrollment target specified in the Written Request (20%).

> ***Reviewer comment:*** *Though the proportion of pre-pubertal patients was below that specified in the Written Request, the age distribution of pediatric MS onset is skewed toward post-pubertal ages, and the program's goal of 20% pre-pubertal enrollment would be very difficult to achieve. Since the age distribution of this trial population generally reflects that of the pediatric MS population, the lower proportion of pre-pubertal patients than stated in the Written Request did not impact the Division's ability to interpret efficacy and safety data.*

Table 6 (Reviewer). Baseline characteristics of patients in primary efficacy analysis (Intention to Treat Population)

	Placebo (N = 57) % (n)	**Teriflunomide** (N = 109) % (n)	**Total** (N = 166) % (n)
Pubertal Status[1]			
Pubertal (Tanner Stage >I)	91.2 (52)	95.4 (104)	94.0 (156)
Pre-pubertal (Tanner Stage I)	8.8 (5)	4.6 (5)	6.0 (10)
Weight (DBWGTBL)			
Mean (SD[2], years)	58.6 (14.9)	57.8 (12.2)	58.0 (13.1)
Median (IQR[3], years)	57 (20.3)	57 (15.2)	57 (15.8)
Min, max (years)	29.5, 109.2	31, 101	29.5, 109.2
> 40kg, % (n)	89.5 (51)	95.4 (104)	93.4 (155)
≤ 40 kg, % (n)	10.5 (6)	4.6 (5)	6.6 (11)
Height (DBHGTBL)			
Mean (SD[2], cm)	162.8 (11.3)	161.0 (10.8)	161.6 (10.9)
Median (IQR[3], cm)	163 (11.8)	162 (11.2)	162.5 (11.3)
Min, max (cm)	131, 184	123, 181	123, 184
Body Mass Index (DBBMIBL)			
Mean (SD[2], kg/m^2)	21.9 (4.2)	22.3 (4.2)	22.1 (4.2)
Median (IQR[3], kg/m^2)	20.9 (4.9)	21.2 (5.2)	21.2 (5.1)
Min, max (kg/m^2)	15.5, 35.9	13.9, 39.7	13.9, 39.7
Smoking status			
Never	98.3 (56)	94.5 (103)	95.8 (159)
Former	1.8 (1)	0.9 (1)	1.2 (2)
Current	0 (0)	3.7 (4)	2.4 (4)
Unknown	0 (0)	0.9 (1)	0.6 (1)

[1]Defined by STRATUM2 in ADSL dataset; [2]SD: Standard deviation; [3]: Interquartile range

Relevant baseline disease characteristics are presented in Table 7, baseline MRI characteristics in Table 8, and information regarding prior MS treatment is presented in Table 9.

Overall, treatment groups were balanced on key patient disease characteristics, but patients in the placebo group were more likely to have prior MS treatment (24.6%) compared to those in

the teriflunomide group (17.4%). Additionally, those in the teriflunomide group were more likely to have received systemic corticosteroids prior to trial entry (67.0% vs 56.1%).

Table 7 (Reviewer). MS disease characteristics of patients in primary efficacy analysis (Intention to Treat Population)

	Placebo (N = 57) % (n)	**Teriflunomide** (N = 109) % (n)	**Total** (N = 166) % (n)
Time from MS diagnosis to randomization			
Mean (SD[1], years)	1.4 (1.7)	1.4 (1.8)	1.4 (1.8)
Median (IQR[2], years)	0.7 (1.6)	0.7 (1.7)	0.7 (1.6)
Min, max (years)	0.1, 8.9	0.1, 10.8	0.1, 10.8
Time from first MS symptoms to randomization			
Mean (SD[1], years)	2.3 (2.2)	2.4 (2.1)	2.3 (2.1)
Median (IQR[2], years)	1.7 (2.3)	1.5 (2.6)	1.6 (2.5)
Min, max (years)	0.2, 11.1	0.2, 10.8	0.2, 11.1
Number of relapses within prior year			
Mean (SD[1])	1.4 (0.7)	1.6 (0.7)	1.5 (0.7)
Median (IQR[2])	1.0 (1.0)	1.0 (1.0)	1.0 (1.0)
Min, max	0, 3	1, 4	0, 4
0 (% (n))	5.3 (3)	0 (0)	3 (1.8)
1 (% (n))	57.9 (33)	54.1 (59)	55.4 (92)
2 (% (n))	29.8 (17)	38.6 (42)	35.5 (59)
≥ 3 (% (n))	7.0 (4)	7.3 (8)	7.2 (12)
Number of relapses within prior 2 years			
Mean (SD[1])	2.0 (1.0)	2.1 (1.0)	2.1 (1.0)
Median (IQR[2])	2.0 (1.5)	2.0 (2.0)	2.0 (2.0)
Min, max	1, 6	1, 5	1, 6
0 (% (n))	0 (0)	0 (0)	0 (0)
1 (% (n))	35.1 (20)	33.9 (37)	34.3 (57)
2 (% (n))	40.4 (23)	33.9 (37)	36.1 (60)
3 (% (n))	19.3 (11)	21.1 (23)	20.5 (34)
≥ 4 (% (n))	5.3 (3)	11.0 (12)	9.0 (15)
Number of overall relapses			
Mean (SD[1])	2.8 (2.0)	2.8 (1.7)	2.8 (1.8)
Median (IQR[2])	2.0 (2.0)	2.0 (1.8)	2.0 (1.0)
Min, max	1, 9	1, 10	1, 10
0 (% (n))	0 (0)	0 (0)	0 (0)
1 (% (n))	26.3 (15)	18.5 (20)	21.2 (35)
2 (% (n))	33.3 (19)	33.3 (36)	33.3 (55)
3 (% (n))	21.1 (12)	23.2 (25)	22.4 (37)
≥ 4 (% (n))	19.3 (11)	25.0 (27)	23.0 (38)
Time since last relapse			
Mean (SD[1], months)	5.8 (4.0)	5.0 (3.1)	5.3 (3.4)
Median (IQR[2], months)	5.0 (4.7)	4.3 (3.5)	4.3 (3.9)
Min, max (months)	1.6, 21.0	1.0, 13.3	1.0, 21.0
History of Acute Disseminated Encephalomyelitis (% (n))	7.0 (4)	6.4 (7)	6.6 (11)
Baseline EDSS			
Mean (SD[1])	1.4 (0.9)	1.2 (0.9)	1.3 (0.9)

	Placebo (N = 57) % (n)	**Teriflunomide** (N = 109) % (n)	**Total** (N = 166) % (n)
Median (IQR[2])	1.5 (1.0)	1.5 (0.5)	1.5 (0.5)
Min, max	0, 4	0, 3.5	0, 4

[1]SD: Standard deviation; [2]: Interquartile range

Table 8 (Reviewer). Baseline MRI Characteristics in primary efficacy analysis (Intention to Treat) Population

	Placebo (N = 57) % (n)	**Teriflunomide** (N = 109) % (n)	**Total** (N = 166) % (n)
Gadolinium-enhancing lesions			
Mean (SD[1], n)	3.9 (7.7)	3.9 (7.4)	3.9 (7.5)
Median (IQR[2], n)	1.0 (5.0)	1.0 (4.5)	1.0 (5.0)
Min, max (n)	0, 38	0, 39	0, 39
Present (% (n))	54.4 (31)	53.2 (58)	53.6 (89)
Absent (% (n))	45.6 (26)	46.8 (51)	46.4 (77)
Normalized brain volume[3]			
Mean (SD[1], n)	1556691.9 (82124.5)	1542591.1 (81499.1)	1547462.3 (81742.1)
Median (IQR[2], n)	1568515.4 (96279.7)	1530122.4 (81499.1)	1547462.3 (81742.1)
Min, max (n)	1284155.3, 1729884.0	1338870.6, 1745655.6	1284155.3, 1745655.6
T2 Lesion count			
Mean (SD[1], n)	60.3 (40.8)	50.8 (38.2)	54.0 (39.2)
Median (IQR[2], n)	53.0 (65.5)	46.0 (46.0)	46.0 (51.5)
Min, max (n)	4, 191	2, 213	2, 213
T2 Lesion volume (mL)			
Mean (SD[1], n)	13.4 (14.4)	13.1 (17.5)	13.2 (16.5)
Median (IQR[2], n)	7.8 (15.5)	6.6 (13.0)	7.3 (13.6)
Min, max (n)	0.5, 80.9	0.03, 96.6	0.03, 96.6
Hypointense T1 lesion volume (mL)			
Mean (SD[1], n)	2.5 (5.8)	2.7 (5.3)	2.6 (5.5)
Median (IQR[2], n)	1.2 (2.3)	0.6 (2.0)	0.8 (2.1)
Min, max (n)	0, 42.7	0, 33.9	0, 42.7

[1]SD: Standard deviation; [2]: Interquartile range; [3]N = 165 (108 teriflunomide, 57 placebo)

Table 9 (Reviewer). Prior MS Treatments at Baseline in primary efficacy analysis (Intention to Treat) Population

	Placebo (N = 57) % (n)	**Teriflunomide** (N = 109) % (n)	**Total** (N = 166) % (n)
Prior MS therapies			
Any previous MS treatment	24.6 (14)	17.4 (19)	19.9 (33)
Interferon beta-1a	17.5 (10)	10.1 (11)	12.7 (21)
Interferon beta-1b	1.8 (1)	5.5 (6)	4.2 (7)
Glatiramer acetate	8.8 (5)	2.8 (3)	4.8 (8)
Fingolimod	1.8 (1)	0 (0)	0.6 (1)
No prior MS treatment	75.4 (43)	82.6 (90)	80.1 (133)
Other prior immunotherapy			
Corticosteroids for systemic use	56.1 (32)	67.0 (73)	63.3 (105)
Immunoglobulins[1]	47.4 (27)	42.2 (46)	44.0 (73)
Azathioprine	3.5 (2)	1.8 (2)	2.4 (4)
Cyclosporine	1.8 (1)	1.8 (2)	1.8 (3)
Methotrexate	1.8 (1)	0 (0)	0.6 (1)
Mycophenolate mofetil	1.8 (1)	0.9 (1)	1.2 (2)
Tacrolimus	0 (0)	0.9 (1)	0.6 (1)

[1]Immunoglobulins defined as CMDECOD "Immunoglobulin G Human," "Immunoglobulin Human Normal," and "Immunoglobulins NOS" in ADCM dataset.

The treatment groups were also similar in terms of medical history, with prior diagnoses reported by 94.7% (n = 54) patients on placebo and 92.7% (n = 101) patients on teriflunomide. The most common prior diagnoses included physical examination procedures and organ system status (77.2% placebo, 81.7% teriflunomide), herpes viral infections (7.0% placebo, 11.0% teriflunomide), upper respiratory tract infections (14.0% placebo, 7.3% teriflunomide), headaches (8.8% placebo, 7.3% teriflunomide), and dermatitis and eczema (7.0% placebo, 8.3% teriflunomide).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Treatment compliance was monitored via counting dispensed and unused tablets at weeks 8, 12, and then every 12 weeks at each mandatory on site visit until end of treatment. Overall, compliance was similar between the two treatment groups.

Median treatment compliance at the end of the PK run-in period was over 99% in both arms (99.64% teriflunomide, 99.68% placebo), but 2 patients had compliance of <80% (75.4% in a teriflunomide patient, 75.4% in a placebo patient). Four patients in the teriflunomide group (3.7%) and 3 patients in the placebo group (5.3%) had above-planned dosing. Under-planned dosing occurred in 58 (53.2%) patients on teriflunomide and 32 (56.1%) patients on placebo.

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Most under-planned dosing occurred in ≤20% of doses, but 1 patient in each group had >20% under-planned doses.

Treatment compliance was also evaluated by body weight, and the sponsor's analysis is presented in Table 10. The mean percent compliance was similar across body weight groups, but comparison is limited by the relatively small number of patients ≤40kg.

Table 10 (Reviewer). Treatment compliance by body weight at baseline

	Placebo (N = 57)			**Teriflunomide** (N = 109)		
	≤ 40kg (N = 6)	> 40kg (N = 51)	All (N = 57)	≤ 40kg (N = 5)	> 40kg (N = 104)	All (N = 109)
Percent compliance						
Mean (SD[1])	94.3 (9.7)	98.4 (3.1)	98.0 (4.3)	98.9 (1.0)	98.4 (3.7)	98.4 (3.6)
Median	98.77	99.70	99.68	98.89	99.78	99.64
Min, max	75.4, 100	82.6, 100	75.4, 100	97.5, 100	68.2, 100	68.2, 100
Overall compliance						
≥ 80% (n (%))	5 (83.3)	51 (100.0)	56 (98.2)	5 (100.0)	103 (99.0)	108 (99.1)
< 80% (n (%))	1 (16.7)	0 (0)	1 (1.8)	0 (0)	1 (1.0)	1 (0.9)
Under-planned dose %						
Mean (SD[1])	5.8 (9.7)	1.5 (3.1)	2.0 (4.3)	1.0 (1.0)	1.6 (3.7)	1.6 (3.6)
Median	1.23	0.30	0.32	0.93	0.21	0.30
Min, max	0, 24.6	0, 17.4	0, 24.6	0, 2.5	0, 31.8	0, 31.8
≤ 20% (n (%))	3 (50.0)	28 (54.9)	31 (54.4)	4 (80.0)	53 (51.0)	57 (52.3)
> 20% (n (%))	1 (16.7)	0 (0)	1 (1.8)	0 (0)	1 (1.0)	1 (0.9)

[1]SD: Standard deviation
Source: Sponsor Trial EFC11759 Clinical Study Report, Tables 14 and 15

Concomitant Medications

Important concomitant medications, including corticosteroid treatment for MS relapses, in the randomized population are listed in Table 11. Systemic corticosteroid use for MS relapse was more common in patients on placebo (49.1%) compared to teriflunomide (37.6%). Overall systemic anti-infective medication use was similar across both treatment groups, but concomitant use of antibacterials, antivirals, and antimycotics were more common in the teriflunomide group.

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Table 11 (Reviewer). Important concomitant medications

	Placebo (N = 57) n (%)	**Teriflunomide** (N = 109) n (%)	**Total** (N = 166) n (%)
Any concomitant medication	56 (98.2)	109 (100)	165 (99.4)
Potential immunomodulatory treatments			
Immune sera and immunoglobulins	2 (3.5)	2 (1.8)	4 (2.4)
Immunostimulants	26 (45.6)	58 (53.2)	84 (50.6)
Antineoplastic agents	2 (3.5)	3 (2.8)	5 (3.0)
Immunosuppressants	0 (0)	1 (0.9)	1 (0.6)
Corticosteroids for systemic use	27 (47.4)	35 (32.1)	62 (37.3)
Systemic corticosteroid treatment for MS relapse	28 (49.1)	41 (37.6)	69 (41.6)
Systemic Antiinfectives	55 (96.5)	104 (95.4)	159 (95.8)
Antibacterials for systemic use	18 (31.6)	48 (44.0)	66 (39.8)
Antivirals for systemic use	6 (10.5)	15 (13.8)	21 (12.7)
Antimycotics for systemic use	2 (3.5)	6 (5.5)	8 (4.8)
Antimycobacterials	0 (0)	1 (0.9)	1 (0.6)
Other			
Bile and liver therapy	1 (1.8)	11 (10.1)	12 (7.2)
Thyroid therapy	0 (0)	1 (0.9)	1 (0.6)
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	14 (24.6)	23 (21.1)	37 (22.3)
Anti-emetics and anti-nauseants	4 (7.0)	12 (11.0)	16 (9.6)
Antihypertensives	0 (0)	2 (1.8)	2 (1.2)

Source: Demographic tables submitted under Module 16.2.4

Rescue Medication Use

During double-blind treatment, 41 patients on teriflunomide (37.6%) and 28 patients on placebo (49.1%) received systemic corticosteroids for MS relapse.

> ***Reviewer comment****: These findings related to rescue medication use indicate that all patients who experienced a confirmed clinical relapse (n = 25 placebo, n = 40 teriflunomide) received systemic corticosteroids. Additionally, these data are reflective of the higher incidence of confirmed clinical relapses in the placebo group.*

Efficacy Results – Primary Endpoint

The primary endpoint for Trial EFC11759 was time to first confirmed clinical relapse, which was not met. Twenty-five patients on placebo (43.9%) and forty on teriflunomide (36.7%) experienced a confirmed clinical relapse while in the DBT period. Thirty-two patients on placebo (56.1%) and 69 patients on teriflunomide (63.3%) were censored for this analysis.

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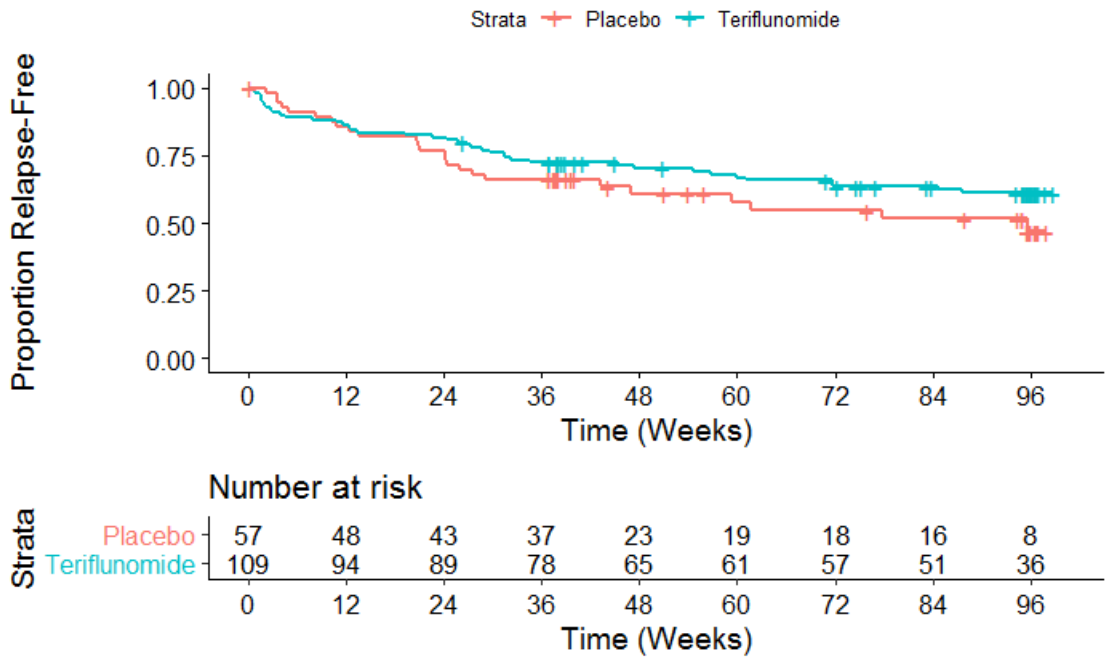
A Kaplan-Meier curve for this time to event analysis is presented in Figure 5.

> ***Reviewer comment****: It is important to note relatively small sample sizes remaining in each group at the end of the DBT period (n = 8 [14.0%] for placebo and n = 36 [33.0%] for teriflunomide at 96 weeks) due to discontinuations/withdrawals from the study, confirmed relapses, and early transition to OLE due to high MRI activity.*

The median time to first confirmed relapse was 95.6 weeks for placebo, and was not calculated for teriflunomide because less than half of patients in this treatment arm experienced this event. Additionally, the log-rank test p-value for this analysis was 0.205. The sponsor also conducted a stratified log-rank test by region (REGION1) and pubertal status (STRATUM2, pre- vs. post-pubertal), and the p-value was 0.2949, which was reproduced by this reviewer.

Figure 5 (Reviewer). Kaplan Meier Survival Curve for Primary Endpoint (Time to First Confirmed Clinical Relapse)



The sponsor calculated Kaplan-Meier estimates for the probability of confirmed clinical relapse during DBT, which are reproduced in Table 12. The probability of confirmed clinical relapse was numerically higher at each timepoint for patients in the placebo group.

Reference ID: 4776272

Table 12 (Sponsor). Kaplan-Meier Estimates of the Probability of Confirmed Clinical Relapse

	Placebo (N=57)	Teriflunomide (N=109)
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)

Source: Partially reproduced from Sponsor's Clinical Study Report, Table 16

A Cox proportional hazards model, adjusted for region (REGION1), pubertal status (STRATUM2, pre- vs. post-pubertal), age (AGE), and number of relapses in the year prior to randomization (MSRN1Y), and incorporating robust variance estimates, was also utilized for the primary analysis by this reviewer. This model resulted in a hazard ratio (HR) for treatment of 0.67 (95% CI 0.39 to 1.13) using the survival package (version 3.2-7) in RStudio (version 1.1.456, R version 3.6.1). This estimate was similar to that of the sponsor's result, which was HR 0.66 (95% CI 0.39 to 1.11). Again, this result was not statistically significant.

> ***Reviewer Comment:*** *Per the sponsor's ADTTE dataset, 1 patient in the teriflunomide group (Subject ID (b) (6)) experienced a confirmed relapse on Day 1 of the DBT period. However, the ADRL dataset did not indicate that this relapse was confirmed by the RAP. This patient was documented to have discontinued study treatment due to an adverse event, coded as "affective disorder" on Day 1 of DBT. The narrative submitted for this AE indicates that she experienced an MS relapse involving the brainstem that required hospitalization. It was therefore unclear whether this patient should technically be counted as a confirmed relapse in the primary analysis.*
>
> *An Information Request was sent to the sponsor on March 12, 2021, with response received on March 18, 2021. The sponsor clarified that this patient did have a confirmed, adjudicated relapse on DBT Day 1, and this was included as such in the primary efficacy analysis.*

Summary of Primary Endpoint Results

Trial EFCC11759 did not meet its primary endpoint, time to first confirmed clinical relapse.

> ***Reviewer Comment:*** *The sponsor's pre-specified primary efficacy endpoint analysis of time to first confirmed clinical relapse was not significant (p=0.2949). Time to first relapse is an accepted endpoint for clinical efficacy trials in MS, including pediatric-onset MS given its almost uniformly relapsing course. A non-significant finding on this endpoint is consistent with a failure to demonstrate a clinically meaningful treatment effect for*

teriflunomide relative to placebo for patients with MS in this trial. See further discussion in Section 7.1.

Efficacy Results – Secondary and other relevant endpoints

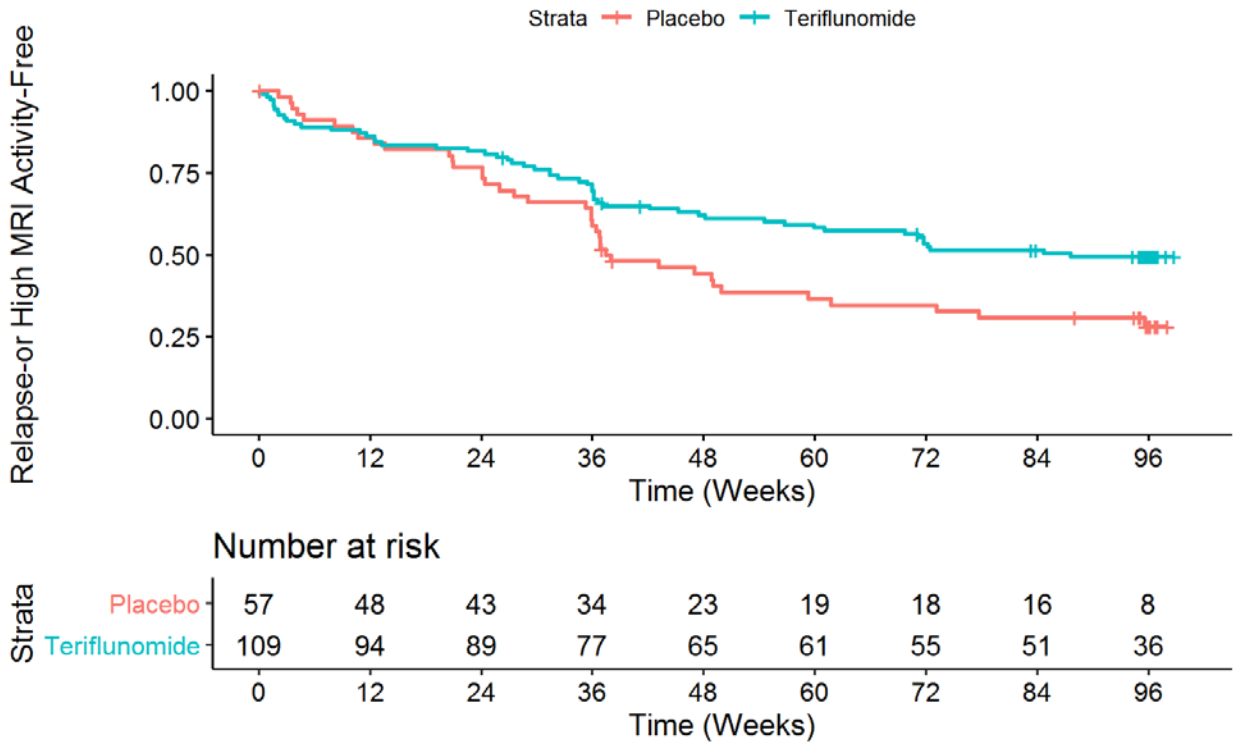
Sensitivity Analyses for Primary Endpoint (DBT)

The sponsor also conducted several pre-specified sensitivity analyses for the primary endpoint, which were reproduced by this reviewer.

The first pre-specified sensitivity analysis was time to first confirmed clinical relapse or high MRI activity criteria. Thirty-nine patients on placebo (68.4%) and 54 patients on teriflunomide (49.5%) experienced either of these events. A Kaplan-Meier curve for this time to event analysis is presented in Figure 6. The unadjusted log-rank test p-value for this analysis was 0.02, and the stratified log-rank test p-value (again by region and pubertal status) was 0.04, which did meet statistical significance. Additionally, the adjusted Cox proportional hazards model, using the same covariates and robust variance estimation as the primary endpoint, yielded a HR 0.56 (95% CI 0.36 to 0.86), which is also statistically significant.

Reference ID: 4776272

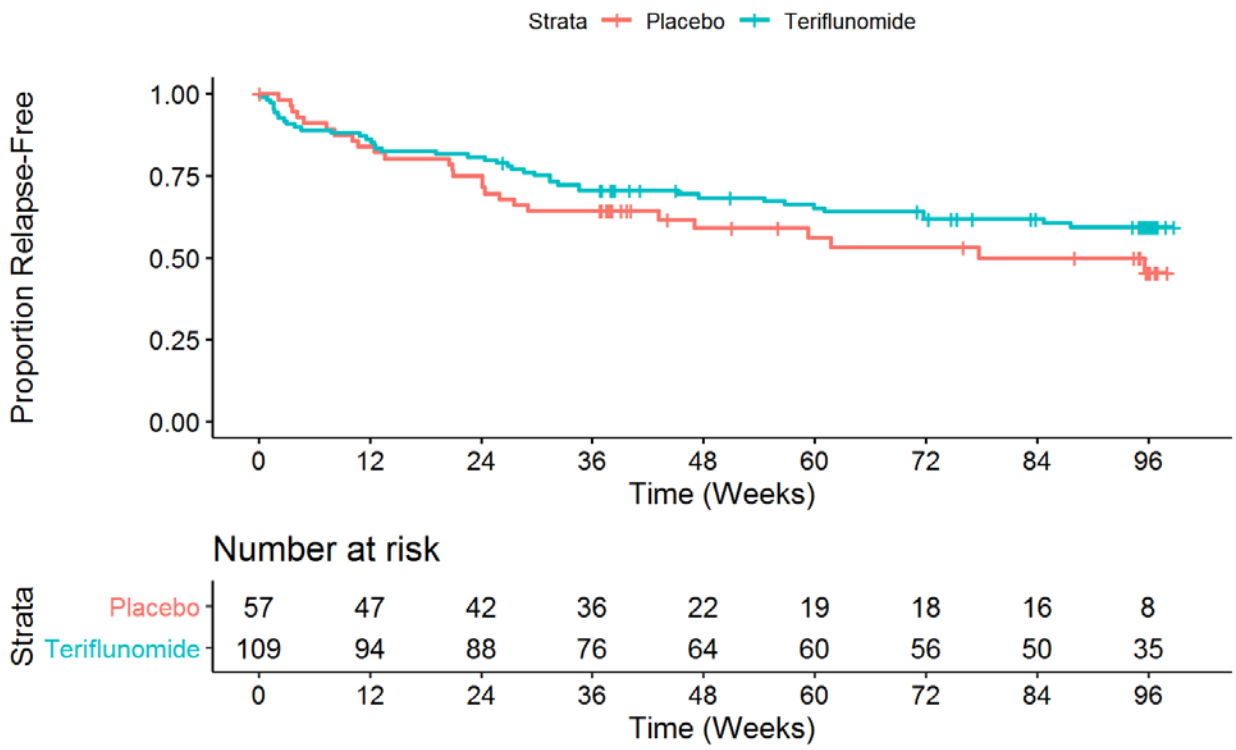
Figure 6 (Reviewer). Kaplan Meier Survival Curve for Time to Either First Confirmed Clinical Relapse or High MRI Activity



The second pre-specified sensitivity analysis was time to first clinical relapse (confirmed or unconfirmed) during the DBT period. Twenty-six patients on placebo (45.6%) and 42 patients on teriflunomide (38.5%) experienced clinical relapse. A Kaplan-Meier curve for this time to event analysis is presented in Figure 7. The unadjusted log-rank test p-value for this analysis was 0.2, and the stratified log-rank test p-value (again by region and pubertal status) was also 0.2, which did not meet statistical significance. Additionally, the adjusted Cox proportional hazards model using the same covariates and robust variance estimation as the primary endpoint, yielded a HR 0.68 (95% CI 0.41 to 1.14), which is also not statistically significant.

Reference ID: 4776272

Figure 7 (Reviewer). Kaplan-Meier Survival Curve for Time to First Relapse

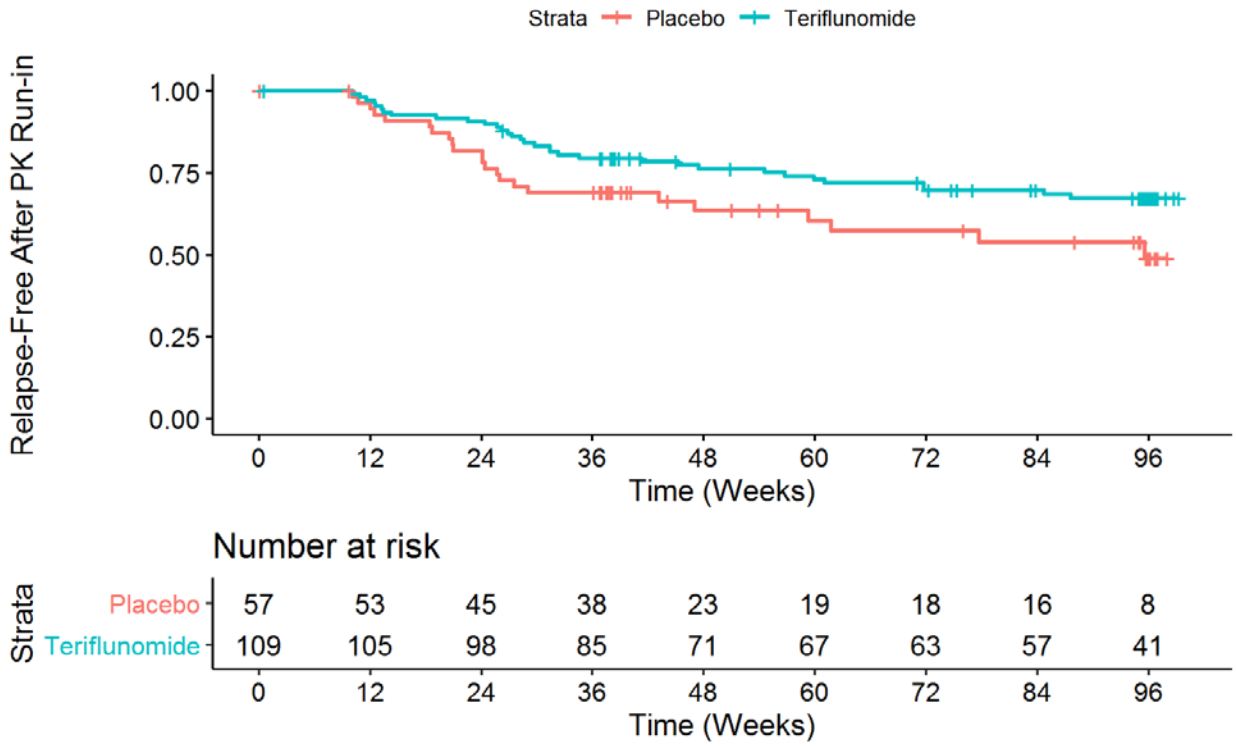


The third pre-specified sensitivity analysis was time to first confirmed clinical relapse after the PK run-in phase. This analysis is of interest for the efficacy determination because, theoretically, patients may not achieve optimal dosing of teriflunomide until after the PK run-in phase. Based on the ADTTE dataset, 18 patients experienced confirmed clinical relapse during the PK run-in phase (within 8 weeks of DBT initiation), 5 in the placebo group (8.8%) and 13 (11.9%) on teriflunomide. Patients who experienced confirmed clinical relapse during the PK run-in period were permitted to continue in the DBT period following re-consent/assent.

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. A Kaplan-Meier curve for this time to event analysis is presented in Figure 8. The unadjusted log-rank test p-value for this analysis was 0.05, and the stratified log-rank test p-value (again by region and pubertal status) was 0.08, which did not meet statistical significance. Additionally, the adjusted Cox proportional hazards model using the same covariates and robust variance estimation as the primary endpoint yielded a HR 0.52 (95% CI 0.29 to 0.93), which is statistically significant.

Reference ID: 4776272

Figure 8 (Reviewer). Kaplan Meier Survival Curve for Time to First Confirmed Clinical Relapse After the PK Run-in Period



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. The sponsor's analysis as reported in the Clinical Study Report, Section 10.1.2.4, indicated that 50.9% of patients on placebo and 38.5% on teriflunomide experienced this event, and that their analysis did not meet statistical significance (HR 0.642, 95% CI 0.391 to 1.055, p=0.1821).

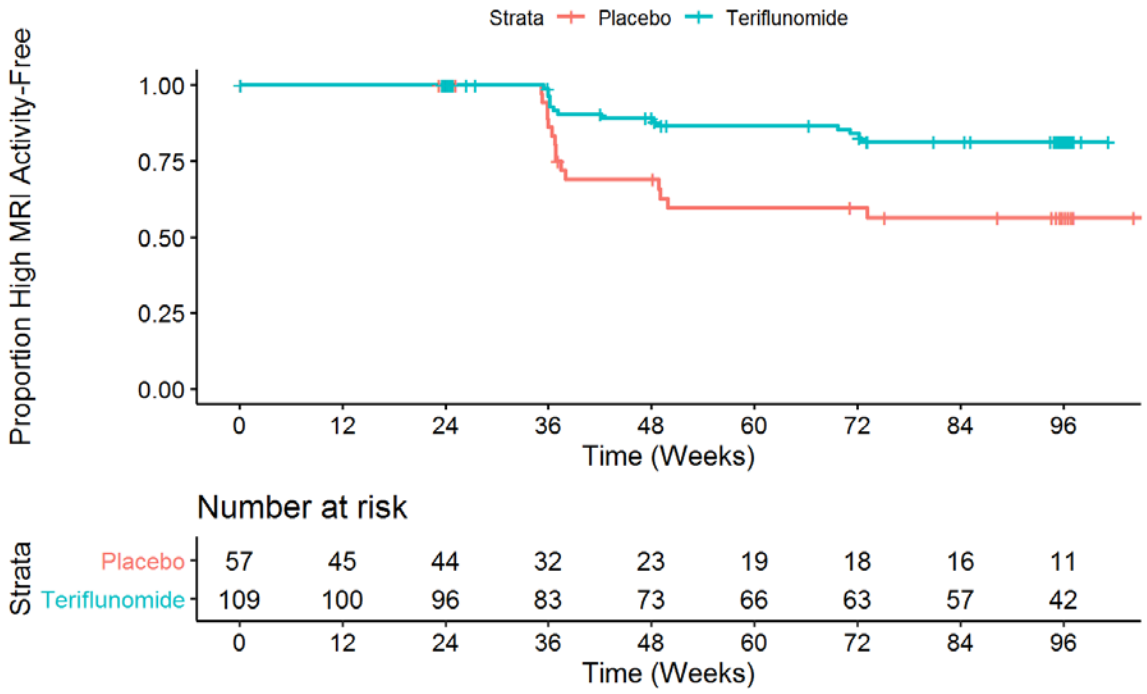
A post-hoc sensitivity analysis was also conducted by the sponsor for time to first meeting of high MRI activity criteria for switching into the OLE period. Fifteen patients on placebo (26.3%) and 15 patients on teriflunomide (13.8%) experienced high MRI activity during the DBT period.

High MRI activity led to early DBT completion for 14 patients on teriflunomide and 15 on placebo. The discrepancy between high MRI activity occurrence and DBT period completion reasons is due to 1 patient who experienced high MRI activity while presumably awaiting relapse confirmation. This patient (Subject ID (b) (6) in the teriflunomide group experienced a clinical relapse at day 317, which was confirmed, and the patient exited DBT due to confirmed clinical relapse on day 346. However, this patient underwent a Week 48 MRI 22 days after clinical relapse onset but prior to confirmation and was determined to have High MRI

activity. Since the clinical relapse occurred first, this patient is considered to have exited DBT due to the relapse, but also experienced high MRI activity.

A Kaplan-Meier curve for time to first high MRI activity is presented in Figure 9. The unadjusted log-rank test p-value for this analysis was 0.003, and the stratified log-rank test p-value (again by region and pubertal status) was 0.007, indicating statistical significance. Additionally, the adjusted Cox proportional hazards model using the same covariates and robust variance estimation as the primary endpoint yielded a HR 0.34 (95% CI 0.16 to 0.73), which is also statistically significant.

Figure 9 (Reviewer). Kaplan Meier Survival Curve for Time to First High MRI Activity



A summary of the primary endpoint and prespecified sensitivity analyses is presented in Table 13.

Reference ID: 4776272

Table 13 (Reviewer). Summary of Primary Efficacy Endpoint and Sensitivity Analyses

	Median Time to Event (weeks)				
	Teriflunomide (n = 109)	**Placebo (n = 57)**	**Unadjusted log-rank test p-value**	**Stratified[1] log-rank test p-value**	**Adjusted[2] HR (95% CI) from Cox PH**
Time to first confirmed clinical relapse	NA[3] Mean 71.6[4]	95.6 (95% CI 47, NA) Mean 64.5	0.205	0.2949	0.67 (0.39, 1.13)
Time to first confirmed clinical relapse OR high MRI activity	87.6 (95% CI 59.9, NA[3]) Mean 65.3	37.4 (95% CI 35.9, 61.7) Mean 51.9	0.02	0.04	0.56 (0.36, 0.86)
Time to first clinical relapse for double blind period	NA Mean 70.2	95.6 (95% CI 43.1, NA) Mean 62.9	0.2	0.2	0.68 (0.41, 1.14)
Time to first confirmed clinical relapse after PK run-in	NA Mean 79.0	95.6 (95% CI 59.3, NA) Mean 68.5	0.05	0.08	0.52 (0.29, 0.93)
Time to high MRI activity	NA Mean 99.0	NA (95% CI 49, NA) Mean 80.6	0.003	0.007	0.34 (0.16, 0.73)

[1]Stratified by region (REGION1) and pubertal status (STRATUM2) per sponsor's analysis
[2]Adjusted for region (REGION1), pubertal status (STRATUM2), age (AGE), and number of relapses in prior year (MSRN1Y) per sponsor's analysis
[3]NA indicates that value cannot be calculated because <50% of patients in treatment arm experienced event of interest at end of follow-up
[4]Mean time to event values represent restricted mean survival, calculated using survival package (version 3.2-7) in RStudio (version 1.1.456)

Reviewer comment: *Overall, in these sensitivity analyses, any statistically significant results appear to be driven by MRI outcomes rather than by clinical relapses. Effects on relapses (time to first confirmed clinical relapse, time to first confirmed clinical relapse after PK run-in, and time to first clinical relapse for double blind period) are either not statistically significant (in the case of time to first confirmed relapse and time to first relapse in the double blind period), or are marginal and driven by MRI findings (p=0.04 for time to first confirmed clinical relapse or high MRI activity).*

It is also important to note the mean time to event estimates for each analysis; for clinical events, the difference between placebo and teriflunomide is relatively small (e.g. 71.6 weeks for teriflunomide versus 64.5 weeks for placebo on time to first confirmed clinical relapse). A numerical difference of 7.1 weeks, less than two months, between

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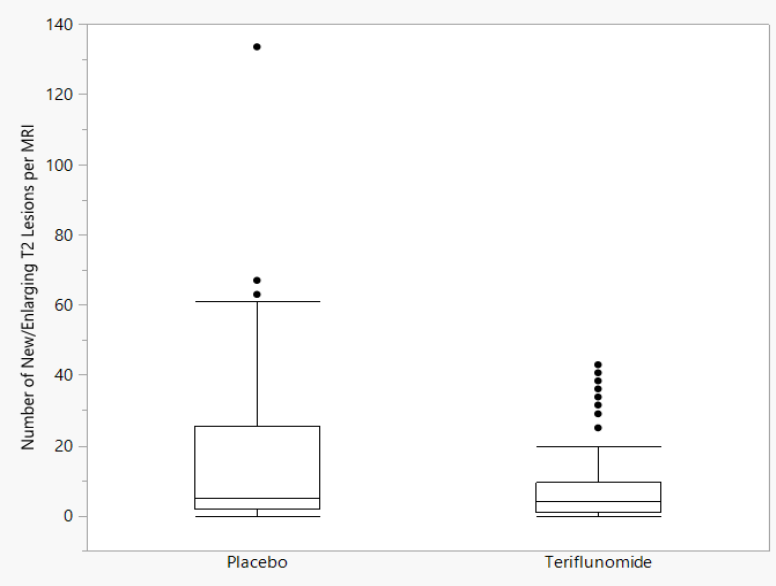
treatment and placebo is not a clinically meaningful delay in experiencing a relapse for any patient population with a relapsing form of MS. These results do not present persuasive evidence of a strong therapeutic effect of teriflunomide in this pediatric MS population.

Secondary Endpoints (DBT)

One key secondary endpoint was the number of new or enlarged T2 lesions, for which 145 patients (100 teriflunomide, 45 placebo) had data. The sponsor analyzed this endpoint using negative binomial regression, adjusted for region, pubertal status, and age. The adjusted number of new/newly enlarged T2 lesions per MRI was 10.52 (95% CI 4.71 to 23.50) for placebo and 4.74 (2.12 to 10.57) for teriflunomide (relative risk 0.45, 95% CI 0.29 to 0.71, p = 0.0006), a statistically significant difference.

This reviewer conducted additional exploratory analyses on key MRI data. The mean number of new or enlarged lesions post-baseline per MRI during DBT was 17.76 (26.3) for placebo and 7.20 (9.3) for teriflunomide (p = 0.01). The median (IQR) number was 5.0 (23.8) for placebo and 4.1 (8.1) for teriflunomide (p = 0.09) (Figure 10). The cumulative number of new or enlarged lesions post-baseline during DBT was 34.26 (49.9) for placebo and 18.0 (18.4) for teriflunomide (p = 0.04). The median (IQR) number was 17.0 (29.0) for placebo and 13.0 (21.0) for teriflunomide (p = 0.16). These data are presented in Table 14.

Figure 10 (Reviewer). Boxplot for Number of New/Enlarging T2 Lesions per MRI during Double-Blind Treatment



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The other key secondary endpoint was the number of gadolinium-enhancing T1 lesions, for which 145 patients (100 teriflunomide, 45 placebo) had data. The sponsor analyzed this endpoint using negative binomial regression, adjusted for region, pubertal status, and age. The adjusted number of gadolinium-enhancing T1 lesions per MRI was 7.51 (95% CI 2.48 to 22.70) for placebo and 1.90 (95% CI 0.66 to 5.49) for teriflunomide (relative risk 0.25, 95% CI 0.13 to 0.51, $p < 0.0001$), a statistically significant difference.

The mean number of gadolinium-enhancing T1 lesions post-baseline per MRI during DBT was 5.06 (11.7) for placebo and 1.40 (3.6) for teriflunomide ($p = 0.05$). The median (IQR) number was 0.8 (4.3) for placebo and 0.2 (1.0) for teriflunomide ($p = 0.01$) (Figure 11). The cumulative number of gadolinium-enhancing T1 lesions post-baseline during DBT was 8.58 (19.2) for placebo and 3.16 (7.2) for teriflunomide ($p = 0.07$). The median (IQR) number was 2.0 (7.5) for placebo and 1.0 (3.0) for teriflunomide ($p = 0.01$). These data are presented in Table 14.

Figure 11 (Reviewer). Boxplot for Number of Gadolinium-Enhancing Lesions per MRI during Double-Blind Treatment

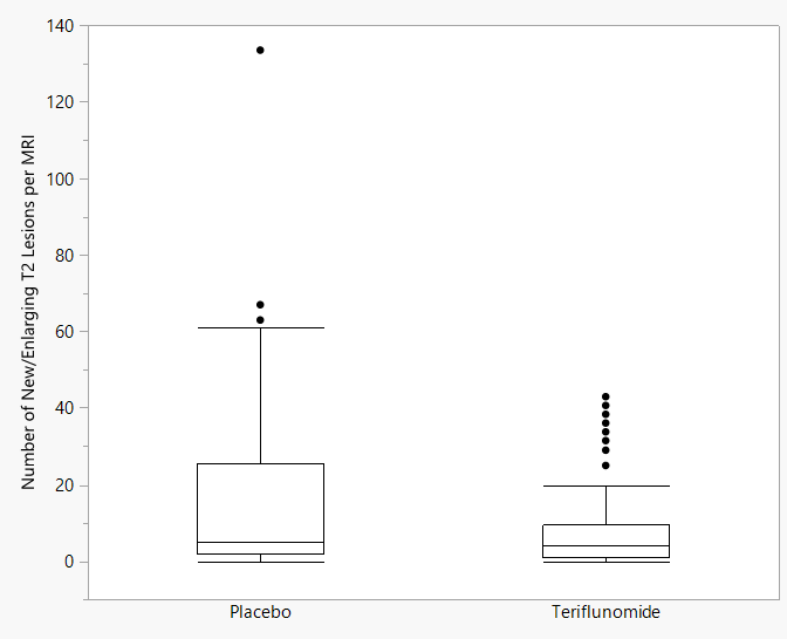

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Table 14 (Reviewer). Summary of MRI-related Secondary Endpoint Data

			Teriflunomide (n = 100)	Placebo (n = 45)	p-value
New/Enlarging T2 lesions	Number per MRI	Mean (SD)	7.23 (9.3)	17.8 (26.3)	0.01[1]
		Median (IQR)	4.1 (8.4)	5.0 (23.8)	0.09[2]
	Cumulative number	Mean (SD)	18.0 (18.4)	34.3 (49.9)	0.04
		Median (IQR)	13.0 (21.0)	17.0 (29.0)	0.16
Gadolinium-enhancing T1 lesions	Number per MRI	Mean (SD)	1.41 (3.6)	5.06 (11.7)	0.05
		Median (IQR)	0.2 (1.0)	0.8 (4.3)	0.01
	Cumulative number	Mean (SD)	3.16 (7.2)	8.58 (19.2)	0.07
		Median (IQR)	2.0 (7.5)	1.0 (3.0)	0.01

[1]p-value calculated using two-sided Student's t-test (for means) assuming unequal variances; [2]p-value calculated using Wilcoxon Rank Sum test

> ***Reviewer comment****: Differences in unadjusted post-baseline new or newly enlarged T2 lesions and gadolinium-enhancing T1 lesions were not consistently statistically significant. Therefore, these MRI data alone were not considered adequately persuasive as substantial evidence of effectiveness in the setting of the negative primary clinical endpoint.*

The sponsor also conducted analyses of other MRI-related efficacy endpoints. T2 lesion volume change from baseline was 0.073 mL for teriflunomide and 0.201 mL for placebo at week 96 (least square mean difference from placebo was -0.128 (standard error 0.049) mL (p = 0.01). T2 lesion volume per MRI was significantly lower in the teriflunomide group compared to placebo (13.8 (SD 23.0) mL vs. 15.7 (SD 18.1) mL, p = 0.0223). In terms of T1 hypointense lesion volume per MRI and change from baseline, no differences were observed between teriflunomide and placebo. However, the sponsor indicated that teriflunomide was associated with a 49% reduction in new hypointense T1 lesions per MRI compared to placebo, a finding which was statistically significant (p = 0.0236).

The sponsor also calculated the proportion of patients free of new or enlarged T2 lesions over the DBT period. At week 48, 17.4% of patients on teriflunomide (n = 19) and 10.5% of patients on placebo (n = 6) were free of new or enlarged T2 lesions. At week 96, 10.1% of patients on teriflunomide (n = 11) and 3.5% of patients on placebo (n = 2) were free of new or enlarged T2 lesions.

> ***Reviewer Comment:*** *MRI outcomes are considered appropriate endpoints for use in exploratory, dose-ranging, or proof-of-concept studies. MRI outcome data can also be*

reported in labeling of therapies approved to treat MS due to its potential to inform both prescribers and patients with MS. However, MRI outcomes are neither established nor accepted as surrogates for clinical outcomes in MS and therefore are not acceptable as primary efficacy outcomes in the Phase 3 trial setting.

Therefore, significant findings on MRI outcomes are not considered to be supportive of substantial evidence of effectiveness in the absence of a clinically meaningful effect on an acceptable endpoint (e.g., time to first relapse or annualized relapse rate).

The proportion of confirmed clinical relapse-free patients at weeks 24, 48, 72, and 96 was estimated using Kaplan-Meier methods (Table 15). The proportion of relapse-free patients was lower in the placebo group at each timepoint. The sponsor also estimated the proportion of patients who were clinical relapse free at each timepoint using Kaplan-Meier methods as a secondary endpoint, and these results were similar to the data presented in Table 15.

Table 15 (Reviewer). Kaplan-Meier Estimates of Proportion of Confirmed Clinical Relapse-Free Patients at Designated Time Points

	Teriflunomide (n = 109)	**Placebo (n = 57)**
Number (%) of patients with confirmed clinical relapse	40 (36.7)	25 (43.9)
Kaplan-Meier Estimate of % (95% CI) patients who were confirmed relapse-free at:		
24 weeks	81.7 (74.7, 89.3)	76.8 (66.5, 88.7)
48 weeks	70.2 (62.1, 79.5)	60.9 (48.9, 75.8)
72 weeks	63.6 (54.9, 73.7)	54.8 (42.1, 71.3)
96 weeks	61.1 (52.2, 71.5)	46.9 (33.2, 66.1)

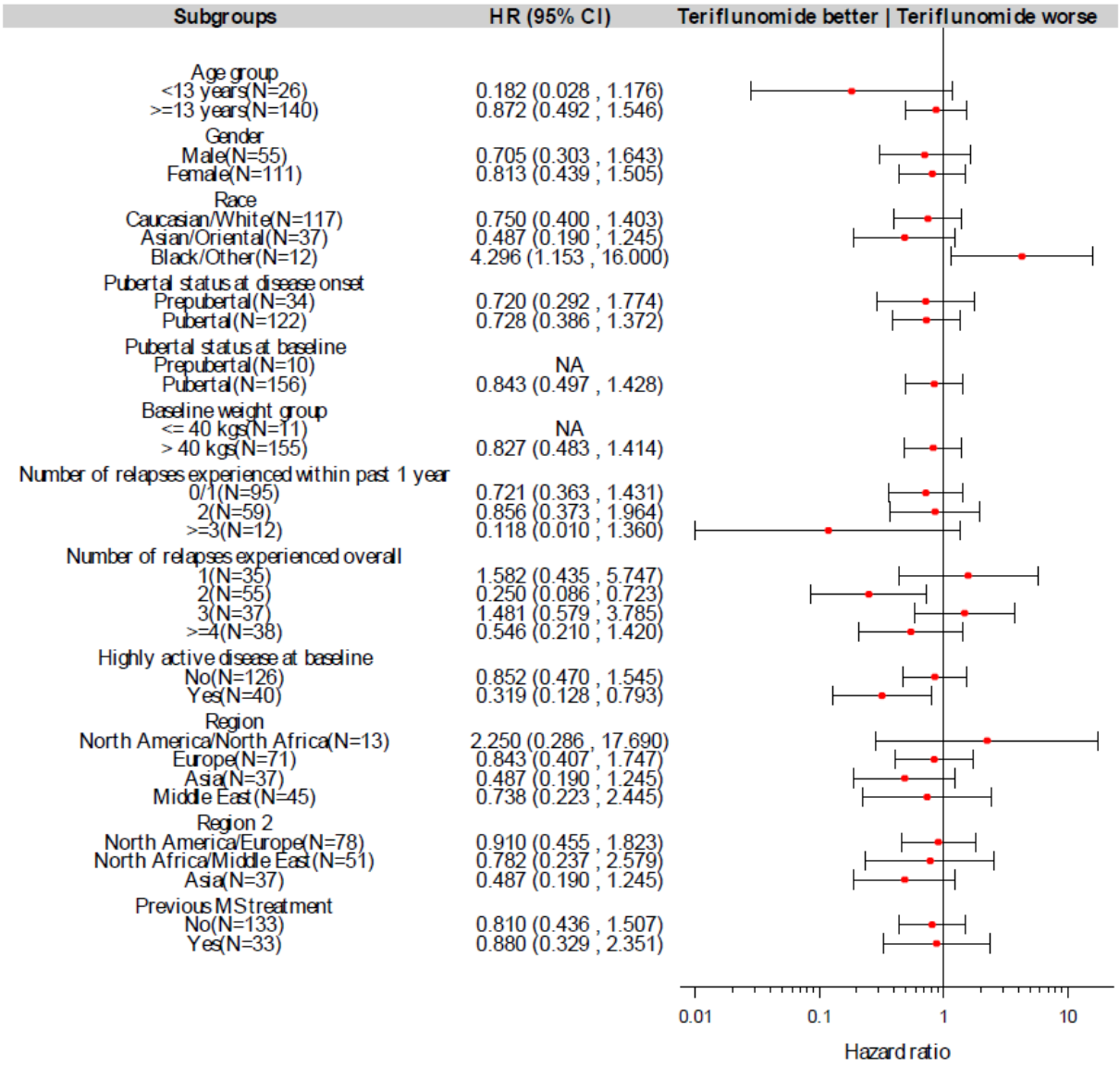
Reviewer Comment: *The proportion of patients with confirmed clinical relapse was similar between the treatment groups. The proportions of patients who were relapse-free at the specified time points were numerically lower in the teriflunomide group.*

Subgroup Analyses

The sponsor conducted several subgroup analyses for the primary efficacy endpoint, time to first confirmed clinical relapse (Figure 12). Notable findings include the analysis by race, which indicates that analysis in patients who identified as Black or Other (n = 12) favored placebo over teriflunomide (HR 4.30, 95% CI 1.15, 16.00). Additionally, teriflunomide appeared to have more of an effect in patients considered to have highly active disease at baseline (n = 40) compared to those who did not (n = 126). Highly active disease was defined as having 2 or more relapses in the past year, and ≥1 gadolinium enhancing lesions on brain MRI. The hazard ratio comparing teriflunomide to placebo was 0.32 (95% CI 0.13 to 0.79) for patients with highly active disease

at baseline, compared to a hazard ratio of 0.85 (95% CI 0.47 to 1.55) for those who did not. Otherwise, no statistically significant differences were observed across the subgroup analyses.

Figure 12 (Sponsor). Subgroup Analyses for Time to First Confirmed Clinical Relapse (Primary Efficacy Endpoint)



Reviewer comment: *The observed differences in these subgroup analyses suggest that teriflunomide has a greater impact on disease activity in those with higher disease activity at baseline, particularly via the composite "highly active disease at baseline" definition. The trend in the analyses associated with the number of relapses in the past year also supports this observation, particularly in patients who have experienced at*

least 3 relapses in the past year (HR 0.12, 95% CI 0.01 to 1.36), even though this was not a statistically significant result.

The result in the Black/African-American or Other race subgroup that favors placebo is of interest, because Black/African-American patients with MS tend to have more aggressive disease courses compared to other populations and may have differential responses to MS immunomodulatory treatments.[29, 30] However, over half of this subgroup (n = 7) was classified as "Other" race, so it is difficult to interpret this finding as specific to Black/African American patients.

Overall, the trends in these different subgroups suggest that teriflunomide was at least able to provide partial treatment effect to patients with high disease activity. However, the relatively short observed median reduction in time to first relapse is not consistent with a clinically meaningful change for pediatric patients with MS.

Dose/Dose Response

Dose-response testing was not conducted in Trial EFC11759, as dosing was weight-based and was adjusted to the PK equivalent of the 14mg daily adult dose of teriflunomide.

Durability of Response

Not applicable.

Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

MRI Data

The sponsor hypothesizes in the CSR that the statistical significance observed on sensitivity analyses indicates that the primary endpoint was not statistically significant due to the utilization of high MRI activity criteria with early DBT exit in this study. However, an exploratory analysis involving comparison of the radiological characteristics of patients who exited DBT due to confirmed clinical relapse or high MRI activity conducted by Dr. Sharon Yan (the biometrics reviewer for this application) indicates that these patient populations may be different in terms of disease activity (Figure 13). Specifically, these patient populations were very different in terms of the number of T2 lesions per MRI. Patients on placebo who exited DBT due to confirmed relapse had a median of 2.7 new T2 lesions per MRI, compared to a median of 23.0 in those who exited DBT due to high MRI activity. Patients on teriflunomide who exited DBT due to confirmed relapse had a median of 7.0 new T2 lesions per MRI, compared to a median of

13.7 in those who exited DBT due to high MRI activity. This marked difference in the number of T2 lesions per MRI between these two distinct groups suggests that the patients who exited DBT due to high MRI activity should likely not be considered identical to those who had confirmed clinical relapses. Additionally, it is unknown whether these patients would have had a confirmed clinical relapse if they remained in DBT in either treatment condition.

Figure 13 (Reviewer). Comparison of Patients with High MRI Activity vs. Confirmed Relapse, by Treatment Group

	Placebo N=57	Teriflunomide N=109
N (%) of patients with MRI scans	45	100
Patients with T2 lesions, n (%)	38 (84.4)	85 (85.0)
Number of T2 lesions per scan		
Mean	17.8	7.2
Median	5.0	4.1
Min; Max	0; 134	0; 42
Patients with High MRI activity, n	15	15
Number of T2 lesions per scan		
Mean	37.7	19.2
Median	23.0	13.7
Min; Max	6; 134	5; 40.0
Patients with confirmed relapse, n	14 / 25	31 / 40
Number of T2 lesions per scan		
Mean	12.8	9.2
Median	2.7	7.0
Min; Max	0; 61	0; 42

Source: sNDA 202992 Statistical Presentation, Midcycle Meeting by Dr. Sharon Yan

Further comparison of patients who exited DBT due to confirmed clinical relapse and high MRI activity was also conducted by this reviewer (Table 16). Overall, these groups appear to be similar in terms of age. Patients on teriflunomide who exited DBT due to confirmed clinical relapse were more likely to be female than those who exited due to high MRI activity. Asian patients were more likely to exit DBT due to confirmed clinical relapse than high MRI activity. As mentioned above, the most dramatic difference between the groups was in terms of number of new/enlarging T2 lesions per MRI. Additionally, patients on teriflunomide who exited due to confirmed clinical relapse had a much lower lesion burden in terms of both gadolinium-enhancing lesions and new/enlarging T2 lesions.

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Table 16 (Reviewer). Comparison of Patients who Exited Double Blind Treatment due to High MRI Activity vs. Confirmed Clinical Relapse, by Treatment Group

	DBT Exit due to High MRI Activity (n = 29)		DBT Exit due to Confirmed Clinical Relapse (n = 54)	
	Placebo (n = 15)	Teriflunomide (n = 14)	Placebo (n = 22)	Teriflunomide (n = 32)
Age				
Mean (SD)	14.9 (1.9)	14.7 (2.5)	14.4 (2.4)	14.8 (1.5)
Median (IQR)	15.0 (2.0)	15.0 (5.0)	15.0 (3.5)	15.0 (2.0)
Min, Max	10, 17	10, 17	10, 17	11, 17
Sex				
Female (% (n))	66.7 (10)	64.3 (9)	63.6 (14)	78.1 (25)
Male (% (n))	33.3 (5)	35.7 (5)	36.4 (8)	21.2 (7)
Pubertal status				
Pubertal	93.3 (14)	92.9 (13)	81.8 (18)	100.0 (32)
Pre-pubertal	6.7 (1)	7.1 (1)	18.2 (4)	0 (0)
Race				
White	80.0 (12)	78.6 (11)	72.3 (16)	59.4 (19)
Asian	13.3 (2)	14.3 (2)	27.3 (6)	25.0 (8)
Other	6.7 (1)	7.1 (1)	0 (0)	12.5 (4)
Black or African American	0 (0)	0 (0)	0 (0)	3.1 (1)
Gadolinium-enhancing lesions per MRI				
N	15	14	11	24
Mean (SD)	8.1 (14.3)	6.3 (7.6)	7.5 (15.5)	1.3 (1.8)
Median (IQR)	4.0 (6.5)	4.0 (8.3)	1.0 (8.0)	0.4 (2.3)
Min, Max	0, 55.5	0, 26	0, 51	0, 6
New/Enlarging T2 Lesions per MRI				
N	15	14	11	24
Mean (SD)	37.7 (34.0)	19.9 (12.6)	14.8 (19.4)	10.3 (9.9)
Median (IQR)	23.0 (41.5)	15.5 (4.3)	2.7 (28.0)	7.3 (9.4)
Min, Max	6.3, 133.5	5.3, 40	0, 61	0, 42

In order to address the sponsor's assertion that patients who exited DBT due to High MRI Activity would experience clinical relapse if they remained in DBT, relapses during OLE were tabulated for these patients (Table 17). All patients who exited DBT due to High MRI Activity (n = 29) continued in the OLE period. However, the majority of these patients did not go on to experience a clinical relapse during OLE. Specifically, only 34.5% (n = 10) experienced an investigator-confirmed clinical relapse during OLE: 40.0% (n = 6) of placebo-teriflunomide patients and 28.6% (n = 4) of teriflunomide-teriflunomide patients who exited DBT due to high MRI activity. Additionally, descriptive analysis of the time to first confirmed clinical relapse during 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). The time to first confirmed relapse was slightly lower

in patients on placebo-teriflunomide (median 404.0 days) versus those on teriflunomide-teriflunomide (median 365.5 days).

Time to first clinical relapse during OLE for patients who exited DBT due to High MRI activity was also analyzed using Kaplan-Meier methods to account for censoring (Table 17). The median time to first confirmed OLE relapse for patients previously on placebo was 716 days, and was not able to be calculated for those previous on teriflunomide due to >50% of patients remaining relapse-free. The log-rank test p-value comparing patients who received teriflunomide and placebo during DBT was 0.2773, indicating a non-statistically significant difference between the groups.

Table 17 (Reviewer). Open-Label Extension Relapses in Patients who Exited DBT due to High MRI Activity

	Patients who Exited DBT due to High MRI Activity		
	Placebo (n = 15)	**Teriflunomide (n = 14)**	**All (n = 29)**
% (n) of patients with confirmed relapse during OLE	40.0 (6)	28.6 (4)	34.5 (10)
Time to first confirmed relapse in OLE (among those with relapse), in Days			
Mean (SD)	375.5 (246.2)	335.3 (165.0)	359.4 (207.8)
Median (IQR)	404.0 (482.3)	365.5 (312.3)	404.0 (388.3)
Min, Max	80, 716	118, 492	80, 716
Time to first confirmed relapse in OLE (Kaplan-Meier method), in Days			
Median	716.0	NA[1]	
Log-rank test p-value	-	-	0.2773

[1]NA: Median not calculated due to <50% of patients in group experiencing relapse

> ***Reviewer comment:*** *Overall, these analyses further support the statement above that high MRI activity is not an appropriate surrogate for clinical relapse. Additionally, patients who exited DBT due to high MRI activity did not have a relapse within 80 days of switching to open-label treatment.*

Change in EDSS

Change from baseline EDSS was calculated for each patient during the DBT period, regardless of DBT duration (Table 18). Baseline records were selected using the sponsor's ABLFL=Y in the ADQS dataset. The last EDSS value for each patient in the DBT period was selected using visits flagged as ANL01FL=Y by the sponsor. Change in EDSS was calculated as (*last EDSS value – baseline EDSS value*), and was compared between treatment arms for the DBT period. Patients treated with teriflunomide during DBT had a statistically significantly lower change in EDSS compared to those on placebo (mean change 0.22 versus 0.67, p = 0.02). Additionally, fewer

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patients on teriflunomide had worsening EDSS compared to those on placebo (31.2% vs. 45.6%, respectively). The proportion of patients with a stable EDSS was similar between the two groups (45.6% placebo vs. 51.4% teriflunomide). Patients on teriflunomide were also more likely to experience improving EDSS compared to those on placebo (17.5% vs. 8.8%).

Table 18 (Reviewer). Change in EDSS During Double Blind Treatment

	Placebo (N = 57) % (n)	**Teriflunomide** (N = 109) % (n)	**p-value**
Change in EDSS over DBT period			
Mean (SD[1], n)	0.67 (1.1)	0.22 (0.9)	0.02[2]
Median (IQR[3], n)	0 (1.0)	0 (0.5)	0.01[4]
Min, max (n)	-1, 4.5	-2, 3.5	
% (n) with worsening EDSS	45.6 (26)	31.2 (24)	NA
% (n) with improving EDSS	8.8 (5)	17.4 (19)	NA
% (n) with stable EDSS	45.6 (26)	51.4 (56)	NA

[1]SD: Standard deviation; [2]Calculated via t-test assuming unequal variances; [3]IQR: interquartile range; [4]Calculated via Wilcoxon rank-sum test

The sponsor calculated change in EDSS at Weeks 24, 48, 72, and 96 during DBT. The mean (SD) change in EDSS from baseline at Week 96 was -0.2 (0.7) for placebo (n = 19) and 0.1 (0.7) for teriflunomide. Though no formal statistical comparisons were conducted by the sponsor, there did not appear to be any substantial cross-sectional differences between teriflunomide and placebo regarding EDSS change from baseline except at week 24.

Other Relapse-Related Endpoints and Annualized Relapse Rate

The time to first confirmed clinical relapse was tabulated for patients who experienced a confirmed clinical relapse in the DBT period (n = 25 placebo, n = 40 teriflunomide). These results indicate that most confirmed clinical relapses occurred within the first 8 weeks (32.5%) for teriflunomide and over the first 36 weeks for placebo (76.0%) (Table 19). This analysis does not take into account other patients who left DBT for other reasons (i.e., were censored).

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Table 19 (Reviewer). Time to First Confirmed Clinical Relapse Among Those with Relapse in the DBT Period

	Placebo (N = 25) % (n)	**Teriflunomide** (N = 40) % (n)
0 to 8 weeks	20.0 (5)	32.5 (13)
8 to 16 weeks	20.0 (5)	12.5 (5)
16 to 24 weeks	12.0 (3)	5.0 (2)
24 to 36 weeks	24.0 (6)	25.0 (10)
36 to 48 weeks	8.0 (2)	5.0 (2)
48 to 60 weeks	4.0 (1)	7.5 (3)
60 to 72 weeks	4.0 (1)	7.5 (3)
72 to 84 weeks	4.0 (1)	0 (0)
84 to 96 weeks	4.0 (1)	5.0 (2)

Source: ADTTE dataset (AVALW for PARAMCD = TTFCCR)

Though the sponsor did not calculate an annualized relapse rate (ARR) for the DBT period, this reviewer calculated both individual and group ARRs for patients in the DBT period on an exploratory basis. Relevant calculations and a summary of unadjusted ARR and other confirmed clinical relapse-related data are presented in Table 20. Among patients who experienced a confirmed clinical relapse, the median time to relapse was 23.5 weeks for patients on teriflunomide and 21.0 weeks for those on placebo. The mean times to confirmed clinical relapse were also similar between the groups.

> ***Reviewer comment:*** *ARRs were calculated in an exploratory analysis and should be interpreted with caution in the context of a time to event-driven trial.*

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Table 20 (Reviewer). Relapses and Annualized Relapse Rate during the Double Blind Treatment Period

	Teriflunomide (n = 109)	Placebo (n = 57)	Ratio (if applicable)
Number (%) of patients who experienced confirmed relapse	40 (36.7)	25 (43.9)	
Number of relapses experienced per patient during DBT (n (%))			
0	70 (64.2)	32 (56.1)	
1	33 (30.3)	21 (36.8)	
2[1]	6 (5.5)	4 (7.0)	
Time to first confirmed clinical relapse in DBT (among those with relapse, weeks)			
N	40	25	
Mean (SD)	26.7 (25.2)	27.0 (24.5)	
Median (IQR)	23.5 (39.4)	21.0 (26.9)	
Min, Max	0.14, 87.6	2.1, 95.6	
DBT Duration (years)[2]			
Mean (SD)	1.34 (0.6)	0.99 (0.6)	
Median (IQR)	1.81 (1.1)	0.75 (1.3)	
Min, Max	0.01, 1.90	0.003, 1.88	
Individual ARR			
Mean (SD)	0.74 (1.5)	1.19 (1.8)	0.622
Median (IQR)	0 (0.85)	0 (2.0)	
Min, Max	0, 8.80	0, 8.02	
Group ARR			
Sum DBT Duration (years)	145.74	56.57	
Sum DBT Relapses	45	29	
Group ARR	0.309	0.513	0.602 (95% CI 0.370, 0.996)[3]

[1]Patients who experienced a confirmed clinical relapse during the PK run-in period had the option to continue in the DBT period; [2]From ADES, PARAMCD = DURD01; [3]Calculated using package rateratio.test (version 1.0-2) in RStudio (version 1.1.456)

Individual unadjusted ARRs for confirmed relapses in the ITT population were determined by calculating the number of relapses per patient during DBT, as presented in the ADRL dataset. The number of rows for confirmed relapses were tabulated by subject ID (USUBJID). DBT duration was provided by the sponsor in the ADES (PARAMCD = DURD01). Individual ARR was calculated for each patient by the number of confirmed relapses in DBT/duration of DBT in years. The mean ARR for patients on teriflunomide was 0.74 (SD 1.5), compared to 1.19 (SD 1.8) in the placebo group. The mean ARR ratio was 0.622.

Group ARRs for confirmed relapses in the ITT population were determined by calculating the number of confirmed relapses across each treatment group and the time spent in DBT in each group (sum of DBT duration for each patient, calculated above). Group ARR was calculated by

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the number of confirmed relapses in DBT/person-years in DBT for each treatment group. The group ARR for teriflunomide was 0.309, and for placebo was 0.513. Using the rateratio.test package (version 1.0-2) in RStudio (version 1.1.456), the ARR ratio was 0.602 (95% CI 0.370 to 0.996), which indicates borderline statistical significance.

OLE Period Efficacy

The efficacy data cut-off for the OLE period was November 27, 2019.

Forty-five investigator-confirmed relapses occurred in 34 patients (22.4%) during the OLE period. Thirteen patients previously treated with placebo (25.0%) experienced at least 1 relapse, and 21 patients who received teriflunomide during both DBT and OLE periods (21.0%) experienced at least 1 relapse. The number of relapses per patient are presented in Table 21. In general, the frequency of relapse was similar between the groups over a median OLE exposure of 1.33 (IQR 1.3) years.

The sponsor calculated the time to first clinical relapse across the combined DBT and OLE periods using Kaplan-Meier methods and a Cox proportional hazards model. In this analysis, it is important to note that relapses in the DBT were confirmed by the RAP, but in the OLE, relapses were investigator-determined. During the combined DBT and OLE period, clinical relapse occurred in 44.0% of patients on teriflunomide/teriflunomide and 61.5% of patients on placebo/teriflunomide. The estimated median time to confirmed relapse was 86 weeks for placebo/teriflunomide and 102 weeks for teriflunomide/teriflunomide. The sponsor's calculated hazard ratio was 0.611 (95% CI 0.381 to 0.980), indicating a borderline statistically significant reduction in the risk of confirmed clinical relapse in patients who received teriflunomide/teriflunomide. However, the stratified log-rank test was not statistically significant (p = 0.0980).

> ***Reviewer comment****: Analysis of the time to first clinical relapse across combined DBT and OLE periods is limited by the differences in relapse determination (i.e., adjudication versus investigator-determined) across these different time periods.*

Unadjusted group and individual ARRs for investigator-confirmed clinical relapses were also calculated (as described above) for the OLE period (Table 21). The ARR during OLE (0.220) was lower than that of the DBT period for either group (0.309 teriflunomide, 0.513 placebo).

> ***Reviewer comment****: ARR comparison between the DBT and OLE periods, as well as ARR calculation in general, is limited by the time to event design of the trial. Patients with high levels of disease activity during DBT generally exited early, and did not accrue substantial amounts of person-time in the DBT period. Additionally, it is important to consider selection bias when interpreting these data, as patients in the OLE period are*

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less likely to have high levels of disease activity due to regression to the mean. Moreover, patients with high levels of disease activity may be less likely to participate in OLE periods in general. The lack of a comparator arm in the OLE makes outcome interpretation speculative, particularly in the setting of lack of treatment effect on relapses in the DBT period. These serious limitations lead to limited utility and interpretability of this analysis.

Among patients who experienced an investigator-confirmed clinical relapse in the OLE period (n = 34), the median time to relapse was 31.2 weeks (Table 21). In patients who received placebo in the DBT period, the median time to first confirmed relapse was 30.6 weeks, compared to a median of 31.9 weeks in those who received teriflunomide in the DBT period.

Table 21 (Reviewer). Relapses and ARR during the Open Label Extension Period

	Placebo-Teriflunomide (n = 52)	Teriflunomide-Teriflunomide (n = 100)	Overall (n = 152)
Number (%) of patients who experienced investigator-confirmed relapse	13 (25.0)	21 (21.0)	34 (22.4)
Number (%) of Investigator-confirmed relapses per patient			
0	39 (75.0)	79 (79.0)	118 (77.6)
1	10 (19.2)	14 (14.0)	24 (15.8)
2	3 (5.8)	6 (6.0)	9 (5.9)
3	0 (0)	1 (1.0)	1 (0.7)
Time to first investigator-confirmed clinical relapse in OLE (among those with relapse, weeks)			
N	13	21	34
Mean (SD)	39.5 (29.5)	34.9 (22.4)	36.7 (25.0)
Median (IQR)	30.6 (46.8)	31.9 (54.4)	31.2 (44.4)
Min, Max	10.9, 102.3	1.0, 74.7	1.0, 102.3
Duration of exposure in OLE (years)			
Mean (SD)	1.55 (1.0)	1.23 (0.8)	1.34 (0.9)
Median (IQR)	1.43 (1.5)	1.15 (1.4)	1.33 (1.3)
Min, Max	0.003, 3.53	0.003, 3.44	0.003, 3.53
Individual Unadjusted ARR			
Mean (SD)	0.22 (0.5)	0.29 (0.8)	0.27 (0.7)
Median (IQR)	0 (0.2)	0 (0)	0 (0)
Min, Max	0, 2.13	0, 5.29	0, 5.29
Group Unadjusted ARR			
Total OLE Duration (years)	80.85	123.24	204.09
Total # OLE Relapses	16	29	45
Group ARR	0.198	0.235	0.220

Change in EDSS was also calculated across the DBT and OLE periods. One-hundred thirty-three

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out of 152 patients treated in the OLE period had an EDSS reported during the OLE period. Therefore, the analysis below is based upon these 133 patients (49 Placebo-Teriflunomide, 84 Teriflunomide-Teriflunomide). There did not appear to be a statistically significant difference in EDSS change between placebo-teriflunomide and teriflunomide-teriflunomide groups. The mean EDSS change for placebo-teriflunomide was 0.37 and for teriflunomide-teriflunomide was 0.23 (p = 0.50).

Table 22 (Reviewer). Change in EDSS During Combined Double Blind Treatment and Open Label Extension Periods

	Placebo-Teriflunomide (n = 49)	Teriflunomide-Teriflunomide (n = 84)	p-value
Change in EDSS over Combined DBT+OLE period			
Mean (SD[1], n)	0.37 (1.2)	0.23 (1.0)	0.50[2]
Median (IQR[3], n)	0 (1.0)	0 (0.5)	0.43[4]
Min, max (n)	-1.5, 4.5	-2.0, 4.0	
% (n) with worsening EDSS	42.9 (21)	28.6 (24)	NA
% (n) with improving EDSS	22.4 (11)	19.1 (16)	NA
% (n) with stable EDSS	34.7 (17)	52.4 (44)	NA

[1]SD: Standard deviation; [2]Calculated via t-test assuming unequal variances; [3]IQR: interquartile range; [4]Calculated via Wilcoxon rank-sum test

> ***Reviewer Comment:*** *Though pediatric MS is typically associated with higher ARR and more lesions compared to adult MS, accrual of disability is generally less pronounced in this population. Therefore, a substantial change in EDSS over the course of this relatively short trial, for either treatment arm, was not expected.*

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

One pivotal efficacy trial (Trial EFC11759) was considered in this application to support the approval of teriflunomide for the treatment of pediatric RMS. The prior approval of teriflunomide in adult patients with RMS was based on data from several controlled trials in adults with RMS.

> ***Reviewer comment:*** *This submission comprises findings from a single trial of pediatric patients with MS. Pediatric-onset MS is a rare disease with an estimated incidence of 0.51/100,000 person-years,[31] so patient recruitment for multiple trials would be unreasonable. Therefore, this single trial was conducted in response to a Written*

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> *Request and was submitted to fulfill a PREA PMR, both requesting a single trial. Teriflunomide has demonstrated substantial evidence of effectiveness in the treatment of adults with RMS, so this single trial submission does not require consideration of a single trial for a determination of substantial evidence of effectiveness in MS. This supplement proposes expansion of the existing indication to include patients with RMS between the ages of 10 and 17.*

The efficacy of teriflunomide in pediatric patients in Trial EFC11759 was compared to that of adult patients treated with teriflunomide in pivotal trials (Table 23) and also pediatric patients treated with fingolimod in a pivotal trial (D2311) (Table 24). Comparison of Trial EFC11759 to Trials EFC6049 and EFC10531 (teriflunomide trials in adults with MS) demonstrated similar ARRs, magnitude of ARR reduction versus placebo, and hazard ratios for time to first relapse. However, differences in MRI data indicate that pediatric patients generally experience higher numbers of gadolinium-enhancing lesions compared to adults, which suggests a higher degree of inflammatory disease activity in pediatric MS.

> ***Reviewer comment:*** *The finding that ARR-related data was similar across adult and pediatric trials of teriflunomide was somewhat surprising, as patients with pediatric onset MS are known to have higher ARR and relapse activity compared to adults.*

Though comparison of trial efficacy data is limited by differences in trial design and patient populations, it appears that the patient populations of Trials EFC11759 and D2311 were generally similar in terms of sex, pubertal status, time since MS onset, EDSS at baseline, relapses in the prior 12 months, and burden of gadolinium-enhancing T1 lesions on MRI at baseline (Table 25). However, patients in Trial EFC11759 were slightly younger than those in Trial D2311, and Trial D2311 had more Caucasian and Hispanic/Latino patients than Trial EFC11759. Additionally, patients in Trial EFC11759 were less likely to have received previous MS treatment than those in Trial D2311. It is important to consider these differences when interpreting a comparison of trial results.

Several key differences between the results of Trials EFC11759 and D2311 should be noted and may inform the determination of efficacy for teriflunomide in pediatric MS. First, the unadjusted ARR for the teriflunomide group in Trial EFC11759 is more than double than that of the fingolimod-treated group in D2311 (0.31 vs. 0.14). Second, the ARR reduction between fingolimod and interferon beta-1a was more pronounced than that between teriflunomide and placebo (81.9% vs. 39.2%, respectively). Third, the median time to first relapse was higher for fingolimod (86.9 weeks) compared to teriflunomide (75.3 weeks). Fourth, the estimated proportion of relapse free patients was higher in those on fingolimod (86.0%) versus teriflunomide (59.4% at 96 weeks). Finally, the adjusted mean number of gadolinium-enhancing lesions per MRI was higher in patients on teriflunomide (1.90) compared to patients on fingolimod (0.44) and interferon beta-1a (1.28) in D2311. These data suggest that teriflunomide

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may not provide adequate control of disease activity in pediatric MS compared to fingolimod, the only approved treatment for pediatric MS. However, without a superiority trial directly comparing teriflunomide to fingolimod, it is difficult to make a definitive statement about relative efficacy of these two treatments.

Table 23 (Reviewer). Comparison of Teriflunomide Efficacy in Pediatric and Adult Pivotal Trials

Trial	Treatment Arm	N	Adjusted ARR	Unadjusted ARR	Time to first relapse	% relapse free	New/enlarging T2 Lesions	New T1 enhancing lesions
EFC11759 (TeriKids)	Teriflunomide	109	NA	0.31 (group ARR) Rate ratio 0.60 (0.37, 1.00) **39.2% reduction**	Median 75.29 weeks (range 0.1 to 98.7 wks.) HR 0.657, 95% CI 0.388 to 1.113, p = 0.2949	59.4% (at week 96)	Adjusted mean #/scan 4.735 (2.122, 10.567) 55.0% reduction	Adjusted mean #/scan 1.897 (0.656, 5.489) 74.7% reduction
	Placebo	57	NA	0.51	Median 39.14 weeks (range 0.1 to 98.7 wks.)	45.5%	10.515 (4.705, 23.500)	7.505 (2.482, 22.695)
EFC6049 (TEMSO)	Teriflunomide 7mg	365	0.370 (0.318, 0.432) **Relative risk reduction 31%**	0.368	Not reported in days, but HR 0.756 (0.611, 0.937)	53.7% (at week 108)	Only calculated T2LV	Mean # lesions/scan 0.570 (0.43, 0.75)
	Teriflunomide 14mg	358	0.369 (0.308, 0.441) **Relative risk reduction 31%**	0.369	HR 0.719 (0.577, 0.895)	56.5%	Only calculated T2LV	0.261 (0.17, 0.41)
	Placebo	363	0.539 (0.466, 0.623)	0.534	NA	45.6%	Only calculated T2LV	1.331 (1.06, 1.67)
EFC10531 (TOWER)	Teriflunomide 7mg	407	0.389 **Relative risk reduction 22%**	0.383	Not reported in days, but HR 0.698 (0.562, 0.868)	58.2% (at week 108)	MRI endpoints not included	NA
	Teriflunomide 14mg	370	0.319 **Relative risk reduction 36%**	0.309	HR 0.631 (0.502, 0.794)	57.1%	NA	NA
	Placebo	388	0.501	0.487	NA	46.8%	NA	NA

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Table 24 (Reviewer). Comparison of Teriflunomide and Fingolimod Efficacy in Pediatric Trials

Trial	Treatment Arm	N	Adjusted ARR	Unadjusted ARR	Time to first relapse	% relapse free	New/ enlarging T2 Lesions	New T1 enhancing lesions
EFC11759 (TeriKids)	Teriflunomide	109	NA	0.31 (group ARR) Rate ratio 0.60 (0.37, 1.00) **39.2% reduction**	Median 75.29 weeks (range 0.1 to 98.7 wks.) HR 0.657, 95% CI 0.388 to 1.113, p = 0.2949	59.4% (at week 96)	Adjusted mean #/scan 4.735 (2.122, 10.567) **55.0% reduction**	Adjusted mean #/scan 1.897 (0.656, 5.489) **74.7% reduction**
	Placebo	57	NA	0.51	Median 39.14 weeks (range 0.1 to 98.7 wks.)	45.5%	10.515 (4.705, 23.500)	7.505 (2.482, 22.695)
D2311 (PARADIGMS)	Fingolimod	107	0.122 (0.078, 0.192) **81.9% reduction**	0.139	Median 86.9 weeks (range 1.3 to 109.9 wks.)	86.0%	Annualized rate of new lesions 4.39 (3.62-5.37) **52.6% reduction**	Adjusted mean # lesions/scan up to 24 months 0.44 (0.31, 0.61) **66.0% reduction**
	Interferon beta-1a	107	0.675 (0.515, 0.885)	0.734	Median 62.9 weeks (range 0.3 to 106.7 wks.)	45.8%	9.27 (7.66, 11.21)	1.28 (0.93,1.76)

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Table 25 (Reviewer). Comparison of Patient Populations in Teriflunomide and Fingolimod Pediatric Trials

	EFC11759 (TeriKids)			**D2311 (PARADIGMS)[1]**		
	Teriflunomide (n = 109)	**Placebo (n = 57)**	**All**	**Fingolimod (n = 107)**	**Interferon beta (n = 108)**	**All (n = 215)**
% (n) Female	66.1 (72)	68.4 (39)	66.9 (111)	65.4 (70)	59.3 (64)	62.3 (134)
Age (mean (SD))	14.6 (2.0)	14.7 (2.1)	14.6 (2.0)	15.2 (2.0)	15.4 (1.6)	15.3 (1.8)
% (n) pubertal	95.4 (104)	91.2 (52)	94.0 (156)	91.6 (98)	99.1 (107)	95.3 (205)
Race (% (n))						
Caucasian	68.8 (75)	73.7 (42)	70.5 (117)	93.5 (100)	89.8 (97)	91.6 (197)
Black/African American	3.7 (4)	1.8 (1)	3.0 (5)	0.9 (1)	3.7 (4)	2.3 (5)
Asian	22.9 (25)	21.1 (12)	22.3 (37)	0.9 (1)	0 (0)	0.5 (1)
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)	2.8 (3)	1.9 (2)	2.3 (5)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	4.6 (5)	3.5 (2)	4.2 (7)	1.9 (2)	4.6 (5)	3.3 (7)
Ethnicity (% (n))						
Hispanic or Latino	1.8 (2)	0 (0)	1.2 (2)	8.4 (9)	10.2 (11)	9.3 (20)
Not Hispanic or Latino	92.7 (101)	91.2 (52)	92.2 (153)	91.6 (98)	89.8 (97)	90.7 (195)
Unknown/NR	5.5 (6)	8.8 (5)	6.6 (11)	NA	AN	NA
Disease characteristics						
Years since MS onset (median [min, max])	1.5 [0.2, 10.8]	1.7 [0.2, 11.1]	1.6 [0.2, 11.1]	1.2 [0,9]	1.8 [0,11]	NA
EDSS at baseline (median [min, max])	1.5 [0, 4]	1.5 [0, 3.5]	1.5 [0, 4]	1.5 [0, 5.5]	1.5 [0, 4.0]	NA
Relapses in prior 12 months (median [min, max])	1.0 [1, 4]	1.0 [0, 3]	1.0 [0, 4]	1.0 [0, 4]	1.0 [0, 7]	NA
Gd+ T1 lesions at baseline (median [min, max])	1.0 [0, 39]	1.0 [0, 38]	1.0 [0, 39]	1.0 [0, 52]	0 [0, 37]	NA
% (n) without Gd+ T1 lesions at baseline	46.8 (51)	45.6 (26)	46.4 (77)	44.3 (47)	55.1 (59)	NA
% (n) with any prior MS treatment	17.4 (19)	24.6 (14)	19.9 (33)	35.5 (38)	38.0 (41)	NA

[1] Trial D2311 data from sNDA 22527 Clinical Review by Dr. Paul Lee

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7.1.1. Primary Endpoints

The primary efficacy endpoint in the double-blind treatment phase was time to first confirmed clinical relapse, which did not meet statistical significance (stratified log-rank test p-value=0.29). An adjusted Cox Proportional Hazards model yielded a hazard ratio of 0.67 (95% CI 0.39 to 1.13), also indicating that the treatment effect of teriflunomide was not significant.

Please refer to Section 6.1.2 for assessment of the primary endpoint from Trial EFC11759.

7.1.2. Secondary and Other Endpoints

Please refer to Section 6.1.2 for assessment of secondary and other endpoints from Trial EFC11759.

7.1.3. Subpopulations

Please refer to Section 6.1.2 for analysis of subpopulations.

7.1.4. Dose and Dose-Response

Dose-response testing was not conducted in Trial EFC11759, as dosing was weight-based and was adjusted to the PK equivalent of the 14mg daily adult dose of teriflunomide.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Not applicable.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Not applicable.

7.2.2. Other Relevant Benefits

Please refer to Section 6.1.2 for other relevant benefits.

7.3. Integrated Assessment of Effectiveness

Trial EFC11759 did not meet its primary endpoint, which was time to first confirmed clinical relapse. This failure on the primary endpoint is likely multifactorial. The sponsor contends that this failure was due to the rescue provision stating that patients who met predetermined criteria for high MRI activity could exit double-blind treatment and enter the open label

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extension period. This scenario likely led to patients who may have had relapses exiting the DBT period prior to relapse, resulting in a lower duration of the DBT period for some patients and small sample sizes in both treatment arms towards the end of follow-up. However, comparing patients who exited DBT due to relapse versus high MRI activity demonstrated that these populations differed substantially in terms of MRI activity. Additionally, patients who exited DBT due to high MRI activity did not experience clinical relapse until a median time of 404.0 days into open-label treatment. Therefore, utilizing high MRI activity within a sensitivity analysis as an alternative to a primary clinical endpoint measuring relapse for efficacy determination is inappropriate based on the observation in this trial that patients with high MRI activity did not experience a relapse for approximately one year after exiting the DBT.

Second, the 8-week PK run-in period may have also contributed to the primary endpoint failure. Patients had the option to remain in the DBT period if they experienced a confirmed clinical relapse during the PK run-in period. Relapse during the PK run-in period led to the non-trivial attrition of 13 (11.9%) patients in the teriflunomide group and 5 (8.8%) patients in the placebo group. Six patients in the teriflunomide group and 4 in the placebo group remained in the DBT period following a relapse during the PK run-in, then had a second confirmed clinical relapse later in DBT that led to exit. However, a pre-specified sensitivity analysis of time to first confirmed clinical relapse after the PK run-in did not demonstrate a statistically significant difference between teriflunomide and placebo. Therefore, while the relapses that occurred during the PK run-in period may have reduced the power of this small trial, the sensitivity analysis confirmed that relapses during the PK run-in period did not render the trial incapable of generating an interpretable outcome for relapses in the subsequent DBT period.

Though the sponsor's analysis of key MRI-based secondary endpoints reached statistical significance, differences in unadjusted post-baseline new or newly enlarged T2 lesions and gadolinium-enhancing T1 lesions were not consistently statistically significant. Significant findings on MRI outcomes are not considered to be supportive of substantial evidence of effectiveness in the absence of a clinically meaningful effect on an acceptable endpoint (e.g., time to first relapse or annualized relapse rate). Therefore, these MRI data alone were not considered adequately persuasive as substantial evidence of effectiveness in the setting of the negative primary clinical endpoint.

Finally, examination of several clinically meaningful endpoints, including annualized relapse rate, failed to demonstrate a compelling treatment effect of teriflunomide in the pediatric population enrolled in this trial. 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. Though substantial evidence of effectiveness of teriflunomide has been demonstrated in the adult population, the results of this trial suggest that teriflunomide is

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inadequate to treat the pediatric-onset form of MS.

8. Review of Safety

8.1. Safety Review Approach

Safety data from Trial EFC11759, a Phase 3, single, adequate, controlled study of teriflunomide in pediatric patients with RMS, was reviewed for this efficacy supplement. The safety data from trials of teriflunomide conducted in adults with RMS are intended to support the pediatric RMS safety data and inform this review. The safety database for the DBT period of Trial EFC11759 was comprised of 109 patients who received at least 1 dose of teriflunomide (and 57 who received placebo). The OLE period consisted of 152 patients, 52 of whom received placebo and 100 teriflunomide during DBT. The sponsor submitted adverse events in the ADAE dataset.

Teriflunomide is an immunomodulatory drug that selectively and reversibly inhibits dihydroorotate dehydrogenase. Previously submitted data from adult clinical trials and postmarketing experience have identified several safety concerns associated with teriflunomide use in adults. These safety risks include hepatotoxicity, embryofetal toxicity, bone marrow effects/immunosuppression/infections, hypersensitivity, serious skin reactions (including Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]), peripheral neuropathy, increased blood pressure, respiratory effects, and alopecia. Selection of adverse events of interest discussed in additional detail for this review are based upon the known safety profile of teriflunomide and data from Trial EFC11759. Additionally, the impact of teriflunomide on growth and sexual development in the pediatric population was investigated.

For this safety review, adverse events were compared between treatment arms for the double-blind and OLE periods, and also analyzed by sex, age (<12 versus ≥ 12 years) and pubertal status (Tanner Stage 1 versus >1).

Dr. Rui Li, Senior Clinical Analyst, performed several of the reported safety analyses in conjunction with this reviewer, including tabulation of TEAEs during DBT and OLE periods (Sections 8.4.2, 8.4.3, and 8.4.5), descriptive analyses of laboratory data (Section 8.4.6) and vital signs (Section 8.4.7), and subgroup analyses for safety (Section 8.6).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The safety population was defined as “all randomized patients exposed to double-blind study medication, regardless of the amount of treatment administered.” The safety population is therefore identical to the Efficacy and Intention to Treat populations (n = 57 placebo, n = 109

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teriflunomide). The data cutoff date for this analysis (including the completed DBT and ongoing OLE period) is November 27, 2019.

The sponsor identified a total of 109 pediatric patients exposed to teriflunomide at any dose during DBT, and 71 pediatric patients exposed to any dose for ≥ 360 days during DBT. Table 26 summarizes the exposure to teriflunomide in this pediatric development program. The mean duration of teriflunomide double-blind exposure in this study was 488.0 days (median 660 days). Table 27 provides data regarding teriflunomide exposure in the DBT period, and Table 28 provides data regarding teriflunomide exposure in the combined DBT plus OLE period.

Table 26 (Reviewer). Safety Population, Size, and Denominators of all Teriflunomide Trials

Safety Database for Teriflunomide N = 161 patients <18 years old			
Clinical Trial Groups	**Teriflunomide [any dose]**	**Active Control**	**Placebo**
Phase 3 placebo-controlled study for RMS in pediatric MS (Trial EFC11759)	109 DBT	-	57
Phase 3 Open Label Extension study for RMS in pediatric MS (Trial EFC11759)	152 OLE (100 treated with teriflunomide in both OLE and DBT)	-	-
Trial EFC6049 (TEMSO)	723	-	363
Trial EFC10531 (TOWER)	777	-	388
Trial EFC6260 (TOPIC)	417	-	197
Trial 2001	179	-	61
Trial EFC10891 (TENERE)	111	104	-

Table 27 (Reviewer). Duration of Exposure in Double-Blind Period

Dosage at end of PK run-in[1]	Number of patients exposed to the study drug:				
	≥1 dose	≥8 weeks	≥6 months	≥12 months	≥18 months
Teriflunomide 7mg	N= 12	N= 11	N= 11	N= 7	N= 5
Teriflunomide 14mg	N= 97	N= 97	N= 88	N= 64	N= 54

[1] Exposure data from ADES dataset, PARAMCD = DURD01; 1 patient in teriflunomide arm (USUBJID 011759-250-0001-00004) discontinued DBT at 4 days into the PK run-in period (dose = 7mg)

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Table 28 (Reviewer). Duration of Exposure in Combined Double-Blind and Open Label Periods

Dosage[1]	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

[1] Exposure data from ADES dataset; patients were categorized by teriflunomide dosage at end of DBT PK run-in period (if assigned to teriflunomide during DBT) or at end of OLE (if teriflunomide only received during OLE).

Reviewer comment:

120 Day Safety Update

The 120 Day Safety Update provided additional exposure data for patients ongoing in the OLE period. During the interval from November 28, 2019 through December 1, 2020, 32 additional patients completed the OLE (12 placebo/teriflunomide, 20 teriflunomide/teriflunomide). The sponsor reported that the cumulative duration of treatment exposure was 32.45 patient-years for teriflunomide 7mg, and 242.71 patient-years for teriflunomide 242.71 patient-years. This safety update provides an additional 11.23 patient-years for teriflunomide 7mg and 60.22 patient-years for teriflunomide 14mg, since November 27, 2019.

The sponsor reported the median duration of study treatment was 672.5 days for teriflunomide 7mg and 673 days for teriflunomide 14mg. The 120 Day Safety Update provides an additional 81.5 days for teriflunomide 7mg and 170 days for teriflunomide 14mg.

8.2.2. Relevant characteristics of the safety population

The safety population for Trial EFC11759 was identical to the Intention to Treat population utilized for the efficacy analysis. Please refer to Section 6.1.2 for patient characteristics of the safety population.

8.2.3. Adequacy of the safety database

In addition to the existing safety database for teriflunomide, an approved drug, this trial adds a total of 161 pediatric patients exposed to teriflunomide. The demographic characteristics of the enrolled patients are similar to the intended treatment population, although there are few patients who are below age 12, weigh <40 kg, and are pre-pubertal. The results of this trial may therefore not be as generalizable to the youngest, least mature patients.

The submitted patient exposure data demonstrate that exposure in Trial EFC11759 met the ICH

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guidelines for chronically administered medications, as 137 patients were exposed to teriflunomide for at least a year over the combined DBT plus OLE period.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The sponsor's safety data appeared reliable and consistent. The sponsor responded appropriately to several Information Requests regarding safety analysis and datasets.

8.3.2. Categorization of Adverse Events

Please refer to Section 5.2 for protocol definitions of adverse events, serious adverse events, and treatment-emergent adverse events.

AE verbatim terms were coded to preferred terms using MedDRA v22.0. AEs were graded in severity as mild, moderate, or severe according to the *National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.1*.

8.3.3. Routine Clinical Tests

General Lab Tests

During the DBT period of Trial EFC11759, the following routine clinical laboratory parameters were assessed at screening, randomization, Weeks 4, 12, then every 12 weeks, then at end of treatment:

- Hematology and differential panel (hemoglobin, hematocrit, red blood cell count, red blood cell morphology, mean corpuscular volume, white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelets)
- Coagulation panel (prothrombin time, activated partial thromboplastin time)
- Complete chemistry panel (glucose, creatinine, blood urea nitrogen [BUN], sodium, potassium, chloride, bicarbonate, magnesium, uric acid, aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT], lactate dehydrogenase [LDH], total bilirubin, direct/indirect bilirubin, alkaline phosphatase [ALP], calcium, inorganic phosphorus, total protein, albumin, globulin, albumin/globulin ratio, triglycerides, cholesterol, and creatine phosphokinase [CPK])
- Pancreatic enzymes (serum amylase and lipase)
- Urinalysis (pH, ketones, protein, glucose, blood, urobilinogen, bilirubin, microscopic sediment, specific gravity)
- Serum pregnancy test (for pubescent females)

Additional safety laboratory testing was conducted at Weeks 8, 16, 20, 30, then every 12 weeks through end of treatment:

- Hematology and differential panel

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- Liver function tests
- Pancreatic enzymes

Thyroid stimulating hormone (TSH) was evaluated at baseline, every 24 weeks, and at end of treatment. Serum immunoglobulins (IgG, IgM, and IgA) were assessed at randomization and every 24 weeks.

The sponsor defined threshold values for laboratory parameters of special interest for monitoring purposes:

- Neutrophils <1000/mm^3
- Platelets <100,000/mm^3
- AST or ALT >2-3x ULN
- Acute renal failure (serum creatinine >150 µmol/L [1.7 mg/dL] or creatinine clearance < 50ml/min)
- Rhabdomyolysis (CPK >3x ULN)
- Amylase or lipase >2x ULN

Per the Study Protocol, all abnormal laboratory values were immediately rechecked for confirmation prior to determining whether study drug should be discontinued.

Submission Specific Tests

Peripheral neuropathy is a known risk with teriflunomide. Adverse event screening for Trial EFC11759 included assessment of signs and symptoms of peripheral neuropathy by the treating neurologist. Patients who reported the presence of symptoms concerning for peripheral neuropathy underwent confirmation with electromyography/nerve conduction studies (EMG/NCS). A Peripheral Neuropathy reporting form was also completed.

Trial EFC11759 was the first controlled trial of teriflunomide in children and adolescents. Evaluations of physical and sexual development, specifically Tanner stage assessments, were performed every 24 weeks and at end of treatment (either at the study site or by pediatricians independent of the study clinic).

Vital Signs

Trial EFC11759 included assessments of systolic and diastolic blood pressure (both supine and standing), heart rate (both supine and standing), temperature, and weight at each clinic visit. Height was recorded at Visit 2 and at end of treatment.

Electrocardiograms (ECGs)

In Trial EFC11759, ECGs were performed at baseline and at end of treatment (or premature treatment discontinuation).

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Laboratory parameter, vital sign, or ECG abnormalities were recorded as AEs if they were determined to be clinically significant or were pre-defined as an adverse event of pre-specified monitoring (AEPM).

8.4. Safety Results

8.4.1. Deaths

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

8.4.2. Serious Adverse Events

8.4.2.1. Double-Blind Period

During DBT, 12 patients on Teriflunomide (11.0%) and 6 patients on placebo (10.5%) experienced 16 and 7 serious adverse events (SAEs), respectively (Table 29).

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Table 29 (Reviewer). Serious Adverse Events in Trial EFC11759 Double-Blind Period, by Primary System Organ Class

Preferred Term	Teriflunomide (n = 109)	Placebo (n = 57)
Number of patients with any SAE	**11.0 (12)[1]**	**10.5 (6)**
Nervous System Disorders (SOC)		
Syncope	1.8 (2)	1.8 (1)
Epilepsy	0.9 (1)	1.8 (1)
Investigations (SOC)		
Blood creatine phosphokinase increased	1.8 (2)	0 (0)
Alanine aminotransferase increased	0.9 (1)	0 (0)
Transaminases increased	0.9 (1)	0 (0)
Gastrointestinal Disorders (SOC)		
Anal fissure	0 (0)	1.8 (1)
Anal fistula	0.9 (1)	0 (0)
Pancreatitis acute	0.9 (1)	0 (0)
Infections and Infestations (SOC)		
Appendicitis	0 (0)	1.8 (1)
Pulmonary tuberculosis	0.9 (1)	0 (0)
Upper respiratory tract infection	0.9 (1)	0 (0)
Injury, Poisoning and Procedural Complications (SOC)		
Joint dislocation	0 (0)	1.8 (1)
Lumbar vertebral fracture	0.9 (1)	0 (0)
Peripheral nerve injury	0.9 (1)	0 (0)
Blood and Lymphatic System Disorders (SOC)		
Neutropenia	0.9 (1)	0 (0)
Cardiac Disorders (SOC)		
Cardiomyopathy	0.9 (1)	0 (0)
Congenital, Familial and Genetic Disorders (SOC)		
Familial Mediterranean Fever	0 (0)	1.8 (1)
Eye disorders (SOC)		
Diplopia	0.9 (1)	0 (0)
Respiratory, Thoracic, and Mediastinal Disorders (SOC)		
Asthma	0 (0)	1.8 (1)

[1]Reported as %(n); Primary SOC defined by AESOC in ADAE

In the sponsor's dataset ADAE, each AE was classified according to the primary System Organ Class (SOC), which is the basis of the AE categorization in this review to avoid redundancies. The sponsor also reported other associated SOCs in AEBODSYS, for which a given AE could have multiple instances. For example, the primary SOC for the Preferred Term (PT) Nasopharyngitis is Infections and Infestations (under AESOC), but each instance of this PT was also documented

with both AEBODSYS Infections and Infestations and Respiratory, Thoracic, and Mediastinal Disorders.

Narratives for SAEs in each treatment arm are discussed below.

Teriflunomide (n = 12)

1. *Subject ID* (b) (6): A 15 year-old Caucasian girl from Bulgaria with a medical history of obesity, Hashimoto's disease, and rhinopharyngitis developed the SAE **anal fistula** while receiving double-blind treatment with teriflunomide. She developed 2 perianal fistulae (non-serious, mild intensity) on Day 232 while on DBT. She was switched to open-label teriflunomide on Day 254 due to confirmed clinical relapse on Day 220. On Day 379, the anal fistulae became serious and required hospitalization for surgical treatment. She also had a sacral cyst that was surgically excised. Histology demonstrated "inflammatory infiltration." Study drug was discontinued on Day 466 due to withdrawal of consent by the patient's family.

   Reviewer comment: *The differential diagnosis for anal fistulae includes Crohn's disease, which has been reported in association with teriflunomide use in the postmarketing setting. A Changes Being Effected supplement for addition of colitis to Section 6.2 of teriflunomide labeling is currently under review. This event is potentially related to teriflunomide exposure.*

2. *Subject ID* (b) (6): A 17 year-old Chinese girl with a medical history of binocular ametropia developed the SAE **syncope** in the setting of anorexia and weight loss on Day 23, as well as the nonserious AEs amylase increased, monocytopenia, neutropenia, and leukopenia at various times while receiving double-blind treatment with teriflunomide. She completed double-blind treatment, and transitioned to open-label treatment on Day 673. She also experienced an SAE of syncope in the OLE period on Day 722, which was attributed to not eating.
   - On Day 137, she experienced the nonserious AE amylase increased (amylase 96 IU/L, 1.26x ULN)
   - On Day 164, she experienced the nonserious AEs leukopenia (White blood cell [WBC] count 3.85 $x10^9$/L, LLN 4.35 $x10^9$/L), monocytopenia (0.23 $x10^9$/L, LLN 0.40 $x10^9$/L), and neutropenia (Absolute neutrophil count [ANC] 1.62 $x10^9$/L, LLN 1.65 $x10^9$/L, baseline 3.35 $x10^9$/L)
   - No changes were made to her study treatment following these events. On Day 212, she was considered as recovered from these events, as WBC count was 4.59 $x10^9$/L, neutrophil count was 2.77 $x10^9$/L, and amylase was 75 IU/L (0.99x ULN).

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- On Day 295, she again experienced leukopenia and neutropenia. Neutropenia recovered on Day 338, but she experienced leukopenia on Day 338 (WBC 3.52 $x10^9$/L), which recovered on Day 380.
- Study drug was permanently discontinued due to amylase and lipase increase during the OLE period, with the last dose administered on Day 1057.

Reviewer comment: *The SAE of syncope is not likely to be related to teriflunomide, but the non-serious AEs of increased amylase, leukopenia, monocytopenia, and neutropenia are likely related to teriflunomide.*

3. *Subject ID* (b) (6) A 15 year-old Chinese boy with a medical history of myocarditis developed the SAE **pulmonary tuberculosis** while receiving double-blind treatment with teriflunomide. He had a history of "close contact with pulmonary tuberculosis." On Day 277, an in-school physical examination raised suspicion for tuberculosis that led to a confirmed diagnosis of tuberculosis and hospitalization on Day 280. Chest CT was consistent with pulmonary tuberculosis. He was treated with ethambutol, pyrazinamide, rifampicin, and mecobalamin. Study drug was permanently discontinued on Day 287 due to tuberculosis.

   Reviewer Comment: *Tuberculosis testing in this patient at screening was negative (on* (b) (6)*, per CRF). Both skin and serum testing were permitted per protocol, but the CRF does not indicate which test was conducted in this patient. Though this patient tested negative for latent TB at screening, it is possible that this was a false negative result, or he was exposed while enrolled in the trial. Tuberculosis infection has been observed in prior studies of teriflunomide, and screening for latent tuberculosis is recommended in current labeling.*

4. *Subject ID* (b) (6) An 11 year-old Chinese girl with a medical history of viral encephalitis, "demyelination disease," and epilepsy developed the SAEs **epilepsy and upper respiratory tract infection** while receiving double-blind treatment with teriflunomide. She exited DBT on Day 308 and entered the OLE period due to confirmed relapse.
   - On Day 100, she experienced epilepsy (generalized tonic-clonic seizures are described in the narrative) leading to hospitalization. She also was diagnosed with an upper respiratory tract infection during this episode.
   - She developed another SAE of upper respiratory tract infection on Day 182, which led to hospitalization.
   - On Day 289, she was diagnosed with the SAE secondary epilepsy, which led to hospitalization in the setting of a fever.

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- She also experienced infection-related SAEs (upper respiratory tract infection, central nervous system infection, and lung infection) during open-label treatment (see Section 8.4.2.2).

Reviewer comment: *Baseline concomitant medications for this patient included levetiracetam, indicating the presence of a seizure disorder that could be related to her diagnosis of MS or prior viral encephalitis. It is not uncommon for patients with underlying seizure disorders who develop an infection to have breakthrough seizure activity.*

5. *Subject ID* (b) (6) A 16 year-old boy from France with a medical history of asthma and hair loss developed the SAEs **lumbar vertebral fracture, blood CPK increased, and transaminases increased** while receiving double-blind treatment with teriflunomide. He completed 96 weeks of double-blind treatment and entered the OLE period on Day 673, in which he continued until Day 1001. He exited the OLE period due to availability of commercial teriflunomide. These SAEs occurred in the setting of a road traffic accident on Day 423, which required hospitalization. During this hospitalization, he experienced the SAEs blood CPK increased (512 IU/L) and transaminases increased (maximum AST 240 IU/L [4.8x ULN] and ALT 602 IU/L [12.04x ULN]). These values improved over the following days, and were normal on Day 436.

   Reviewer comment: *The elevated CPK and transaminases events are likely related to acute trauma and do not appear to be related to teriflunomide treatment.*

6. *Subject ID* (b) (6) A 16 year-old girl from France with a medical history of painful menarche and headache developed the SAEs **alanine aminotransferase increased and blood CPK increased** while receiving double-blind treatment with teriflunomide. She completed the DBT early and entered the OLE period on Day 518 due to confirmed clinical relapse. She exited the OLE period on Day 812 due to lack of efficacy. On Day 169, she experienced nonserious AEs of increased ALT (95 IU/L, >2x ULN) and increased CPK (1033 IU/L, ULN 169 IU/L). AST was mildly elevated at 69 IU/L (1.73x ULN). Bilirubin, GGT, and ALP were normal. These events became serious on Day 171 and led to hospitalization. The patient reported that she practiced bodybuilding prior to the AEs. Her AST, ALT, and CPK downtrended and recovered by Day 209. While in the open-label period, on Day 603, she experienced non-serious AEs of CPK increased to 353 IU/L. At that time, ALT, GGT, and ALP were normal. This event of CPK increased became serious on Day 628, with CPK of 2358 IU/L, and mildly elevated AST (58 IU/L) and ALT (43 IU/L). The increased CPK was thought to be related to “intensive sport activity practices.” Her CPK elevation improved on Days 631 (372 IU/L) and 632 (138 IU/L), with avoidance of intensive exercise. Teriflunomide dosing was interrupted from Day 628 to Day 637, but then was permanently discontinued on Day 812 due to lack of efficacy.

Reviewer comment: *Though strenuous exercise can result in CPK elevations, a role of teriflunomide cannot be excluded (See Section 8.5.11).*

7. *Subject ID* (b) (6) A 14 year-old boy from France with no reported medical history developed the SAE **diplopia** while receiving double-blind treatment with teriflunomide. Diplopia occurred on Day 6, and became serious on Day 8, in the setting of a suspected MS relapse. Associated neurological examination findings included left nystagmus, and mild left hand weakness. No ocular motor dysfunction was observed. Per the narrative "there was no evidence suggestive of flare-up of multiple sclerosis; therefore, it was decided not to undertake corticosteroid therapy." He continued on teriflunomide DBT, completed the DBT period due to confirmed relapse on Day 346, and switched to OLE on Day 347.

   Reviewer comment: *The etiology of this patient's diplopia is not clear from the provided narrative. A relapse or pseudorelapse of MS are both possibilities, but a definitive diagnosis was not provided.*

8. *Subject ID* (b) (6) A 14 year-old Caucasian boy from Israel with no reported medical history developed the SAE **peripheral nerve injury** (left hand nerve injury, digits II to III, "caused accidentally by kitchen knife") while receiving double-blind treatment with teriflunomide (Day 531).

   Reviewer comment*: This SAE is a physical injury that is unrelated to study treatment.*

9. *Subject ID* (b) (6) This patient was a 14 year-old Caucasian girl from Russia with a pertinent medical history of "heart congenital malformations, diagonal trabeculae of left ventricular cavity, moderate hypertrophy of back left ventricles, incomplete doubling of the right kidney, hyperandrogenemia, and growth inhibition unknown etiology." She developed the SAE **cardiomyopathy** (cardiomyopathy secondary to congenital cardiac abnormalities) on Day 23 of double-blind treatment with teriflunomide.

   Reviewer comment*: The time to onset and existence of a congenital heart malformation suggest that this event is not likely to be related to teriflunomide. However, both the chronicity and nature of her cardiomyopathy and related symptoms are not clear, so a contribution of teriflunomide to her presentation cannot be ruled out.*

10. *Subject ID* (b) (6) A 15 year-old Caucasian boy from Tunisia with a history of cyclic neutropenia developed the SAE **neutropenia**, as well as pancytopenia and white blood cell count decreased, at various time points while receiving double-blind and open-label treatment with teriflunomide. He experienced neutropenia (neutrophil count <1 $x10^9$/L) and decreased WBC count (nadir 2.65 $x10^9$/L, LLN 4.35 $x10^9$/L) on Days 137, 141, 211,

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and 252 during DBT. Study drug treatment was temporarily interrupted due to neutropenia on Day 141, and was reinitiated on Day 151. No infections were reported in the setting of these laboratory abnormalities.

He switched to open-label teriflunomide on Day 270 due to meeting high MRI activity criteria. On Day 283, his ANC was 0.65 $x10^9$/L (baseline 1.32 $x10^9$/L), and WBC count was 2.10 $x10^9$/L (baseline 3.53 $x10^9$/L). On Day 301, the neutropenia became serious due to being considered medically significant. Teriflunomide was temporarily interrupted due to neutropenia, with the last dose administered on Day 302. On Day 310, ANC was 0.59 $x10^9$/L and WBC was 1.88 $x10^9$/L. On Day 329, ANC was 0.81 $x10^9$/L and WBC 2.31 $x10^9$/L. On Day 333, he was considered recovered from neutropenia. Teriflunomide was resumed on Day 346, and on Day 364, ANC was 0.89 $x10^9$/L, followed by ANC of 1.64 $x10^9$/L on Day 385. ANC again decreased on Day 484 to 0.83 $x10^9$/L. He experienced an additional SAE (intentional overdose), during the OLE period, as described in Section 8.4.2.2. Teriflunomide was again interrupted on Day 663, and a date of re-initiation was not reported. His ANC was 1.21 $x10^9$/L on Day 812.

The sponsor provided an updated narrative with the 120 Day Safety Update, indicating that he experienced ANC<1.0 $x10^9$/L on Days 1030, 1113, and 1155.

Reviewer comment: *The nature of this patient's preexisting cyclic neutropenia is unclear, but may have contributed to the event of neutropenia during trial participation. True cyclic neutropenia is a rare genetic disorder characterized by recurrent neutropenia (typically every 3 weeks, lasting 3 to 5 days) associated with fever, malaise, mucosal ulcerations, and abdominal discomfort.[32] However, the events of leukopenia and neutropenia could be related to teriflunomide, as the lack of periodicity and associated symptoms (e.g. fever, mucosal ulcerations) in this patient is not consistent with classic cyclic neutropenia.*

11. *Subject ID* (b) (6) A 15 year-old Caucasian boy from Turkey with a history of nystagmus developed the SAE **acute pancreatitis**, as well as increased amylase/lipase (>2x ULN) and decreased neutrophil count (<1 $x10^9$/L), at various time points while receiving double-blind treatment with teriflunomide (Days 461 through 676). Double-blind treatment was discontinued on Day 491 due to these AEs. He presented with epigastric pain on Day 461, and initial amylase and lipase values were 106 IU/L and 158 IU/L, respectively. Amylase and lipase values reported for this patient were 946 IU/L and 1887 IU/L on Day 499, and were followed by hospitalization on Day 500. Further evaluation using MRCP suggested autoimmune pancreatitis associated with IgG4, but serum IgG4 was normal and it was determined that this patient had a congenital anomaly in the cystic duct that could predispose to pancreatitis. Peak amylase and lipase values were 1483 IU/L (Day 503) and 2777 IU/L (Day 502), respectively.

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Additionally, he experienced ALT and AST >2x ULN on Day 517 (ALT 113 IU/L, AST 67 IU/L). His last known serum lipase was 60 IU/L, and amylase was 84 IU/L at Day 737.

Reviewer comment: *This patient's presentation is concerning for pancreatitis related to teriflunomide.*

12. *Subject ID* (b) (6) A 14 year-old Caucasian girl from Great Britain with a history of "psychosocial moodiness," migraine, syncope, possible seizures, and intermittent uveitis developed the SAE **syncope** (vasovagal) on Day 462 while receiving double-blind treatment with teriflunomide. This event was attributed to her "being overtired after an early flight." On Day 518, she again experienced syncope while with her friend in the Emergency Department. She described a nonserious event of "seizure explanation very vague and patient could not remember...reports that at friend's house and became dizzy and had seizure." She also reported seeing blue dots/spots in her eyes. She completed DBT but was not treated in the OLE.

Reviewer comment: *This patient likely experienced vasovagal syncope unrelated to study drug. The report of seizure does not indicate clear epileptic features, as she experienced dizziness prior to the event likely indicative of recurrent vasovagal syncope.*

<u>Placebo (n = 6)</u>

1. *Subject ID* (b) (6) A 16 year-old Chinese boy with no reported medical history developed the SAE **epilepsy** and non-serious AE alanine aminotransferase increased while being treated with placebo. Concomitant medications included traditional Chinese medication. He switched to open-label teriflunomide on Day 182 due to confirmed clinical relapse.
    - On Day 91, he experienced non-serious ALT elevation to 71 IU/L (1.65x ULN) and GGT elevation to 137 IU/L (2.69x ULN), with normal AST and bilirubin. He was started on oral glycyrrhizin, without interruption in study treatment. On Day 163, ALT normalized to 37 IU /L. GGT remained elevated at 127 IU/L. However, his last known laboratory values on Day 312 were ALT 117 IU/L (2.72x ULN), AST 46 IU/L (1.15x ULN), and GGT 150 IU/L (2.94x ULN).
    - On Day 176, he experienced a non-serious AE of persistent epilepsy, which became serious and required hospitalization on Day 252. He was treated with carbamazepine, phenobarbital, levetiracetam, and piracetam. He reportedly stabilized.

Reviewer comment: *The etiology of this patient's persistent liver function testing abnormalities are unclear, but may be related to concomitant use of traditional Chinese medication. Regarding epilepsy, the narrative could suggest a history of seizures with the*

inclusion of carbamazepine in this patient's list of prior medications. Seizures can occur in patients with MS, potentially in the setting of relapse.

2. *Subject ID* (b) (6) A 15 year-old Caucasian boy from Estonia with a medical history of allergic dermatitis, tonsillectomy, primary headache, hypermetropia, nevus, anemia, acne, and metatarsal fracture developed the SAE of **joint dislocation (left clavicle dislocation)** in the setting of a fall from a horse while receiving placebo. This injury required surgical repair and hospitalization.

3. *Subject ID* (b) (6) A 17 year-old Caucasian girl from France with a medical history of chronic constipation, anal fissure, asiderotic anemia, and "heavy legs" developed the SAE **anal fissure** (aggravation of anal fissure) on Day 14 of receiving placebo. She underwent exeresis of the fissure, and recovered on Day 14. She discontinued study drug due to lack of efficacy on Day 259.

4. *Subject ID* (b) (6) A 10 year-old Caucasian boy from Israel with a history of childhood asthma developed the SAE **asthma** while receiving double-blind treatment with placebo. On day 302, he experienced a nonserious AE of asthma exacerbation, which became serious on Day 308 due to hospitalization. He was discharged on Day 310, and was considered recovered on Day 349.

5. *Subject ID* (b) (6) A 15 year-old Caucasian girl from Turkey with no reported medical history developed the SAEs **appendicitis (Day 115) and Familial Mediterranean Fever (Day 222)** while receiving placebo. Manifestations of Familial Mediterranean Fever included leukocytosis (WBC 17.68 $x10^9$/L), inguinal pain, inability to walk, and right hip joint effusion on MRI. She received colchicine and azathioprine 75mg. Study drug was discontinued due to an adverse event of ALT increase on Day 558.

   Reviewer comment*: The timing and chronicity of azathioprine treatment is unclear, but this drug is considered immunosuppressive and therefore may have impacted study results.*

6. *Subject ID* (b) (6) A 15 year-old African-American girl in the US with a medical history of asthma, depression, anxiety, migraines, vitamin D deficiency, and iron deficiency developed the SAE **syncope** while receiving placebo. She switched to open-label treatment with teriflunomide after completing DBT on Day 484. Teriflunomide was discontinued on Day 554 due to elevated ALT (153 IU/L, 4.5x ULN).
   - On Day 150, a nonserious event of "left sided neuropathy without nerve conduction study" was reported. She was considered as recovered from the neuropathy on Day 345. She again experienced this event on Day 346. On Day

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360, she had a nonserious event of "nerve pain around joints." Examination by the investigator found no evidence of peripheral neuropathy.

- On Day 412, she had a serious event of syncope in the setting of gastroenteritis and acute orthostatic hypotension. She presented to the ER with recurrent syncopal episodes, vomiting, and right upper quadrant abdominal pain. She received IV fluids, improved, and was discharged.
- On Day 432, she experienced MS relapse.
- On Day 434, she was hospitalized with recurrent syncopal episodes and vomiting in the setting of right eye optic neuritis. She was considered as recovered from these events by Day 466.

Reviewer comment*: The syncopal episodes are likely related to dehydration in the setting of recurrent vomiting. Based on the narrative and information provided, there is no objective evidence of peripheral neuropathy and an EMG/NCS was not performed. See Section 8.5.7.*

8.4.2.2. Open Label Extension Period

During the OLE period, 23 patients (15.1%) experienced 32 SAEs while on open-label teriflunomide. SAEs were more common in patients who had received placebo in the DBT period (n = 13, 25.0%) compared to those who continued teriflunomide (n = 10, 10.0%). SAEs occurring in the OLE period are presented by primary SOC in Table 30.

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Table 30 (Reviewer). Serious Adverse Events in Trial EFC11759 Open-Label Period, by Primary System Organ Class

Preferred Term	Teriflunomide-Teriflunomide (n = 100)	Placebo-Teriflunomide (n = 52)	Overall (n = 152)
Number of patients with any SAE	**10.0 (10)**	**25.0 (13)**	**15.1 (23)**
Infections and Infestations (SOC)			
Acute sinusitis	0 (0)	1.9 (1)	0.7 (1)
Bronchitis	0 (0)	1.9 (1)	0.7 (1)
Central nervous system infection	1.0 (1)	0 (0)	0.7 (1)
Lung infection	1.0 (1)	0 (0)	0.7 (1)
Tonsillitis	0 (0)	1.9 (1)	0.7 (1)
Upper respiratory tract infection	1.0 (1)	0 (0)	0.7 (1)
Nervous System Disorders (SOC)			
Hypoaesthesia	1.0 (1)	1.9 (1)	1.3 (2)
Band sensation	1.0 (1)	0 (0)	0.7 (1)
Headache	0 (0)	1.9 (1)	0.7 (1)
Syncope	1.0 (1)	0 (0)	0.7 (1)
Uhthoff's phenomenon	1.0 (1)	0 (0)	0.7 (1)
Investigations (SOC)			
Blood creatine phosphokinase increased	2.0 (2)	1.9 (1)	2.0 (3)
Alanine aminotransferase increased	0 (0)	3.8 (2)	1.3 (2)
Gastrointestinal Disorders (SOC)			
Constipation	1.0 (1)	0 (0)	0.7 (1)
Food poisoning	0 (0)	1.9 (1)	0.7 (1)
Pancreatitis	1.0 (1)	0 (0)	0.7 (1)
Pancreatitis acute	1.0 (1)	0 (0)	0.7 (1)
General Disorders and Administration Site Conditions (SOC)			
Asthenia	0 (0)	1.9 (1)	0.7 (1)
Gait disturbance	1.0 (1)	0 (0)	0.7 (1)
Pyrexia	0 (0)	1.9 (1)	0.7 (1)
Injury, Poisoning, and Procedural Complications (SOC)			
Overdose	1.0 (1)	0 (0)	0.7 (1)
Skin laceration	1.0 (1)	0 (0)	0.7 (1)
Respiratory, Thoracic, and Mediastinal Disorders (SOC)			
Asthma	0 (0)	3.8 (2)	1.3 (2)
Blood and Lymphatic System Disorders (SOC)			
Neutropenia	1.0 (1)	0 (0)	0.7 (1)
Hepatobiliary Disorders (SOC)			
Hepatic function abnormal	0 (0)	1.9 (1)	0.7 (1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps) (SOC)			
Pancreatic neoplasm	1.0 (1)	0 (0)	0.7 (1)
Psychiatric Disorders (SOC)			
Affective disorder	0 (0)	1.9 (1)	0.7 (1)

[1]Reported as %(n); Primary SOC defined by AESOC in ADAE

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Narratives for SAEs of interest during the OLE period are discussed below.

Infections

Central nervous system (CNS) infection, Upper respiratory tract infection, and Lung infection (Subject ID (b) (6) Please refer to the discussion of this patient in Section 8.4.2.1. This patient is an 11 year-old Chinese girl with a medical history of viral encephalitis, "demyelination disease," and epilepsy developed the SAEs epilepsy and upper respiratory tract infection while receiving double-blind treatment with teriflunomide. She exited DBT on Day 308 and entered the OLE period due to confirmed relapse. During the OLE period, on Day 547, she was diagnosed with non-serious AEs of CNS infection and upper respiratory tract infection in the setting of fever to 39°C and headache. The CRF for this patient mentions the diagnosis of viral encephalitis, with symptoms of headache and fever. She was hospitalized and treatment included ceftriaxone, piperacillin/tazobactam, valproate, and dexamethasone. It does not appear that a lumbar puncture was obtained at this time. She was discharged on Day 569.

An Information Request was sent on March 12, 2021, with a response received on March 18, 2021, requesting additional details regarding the diagnosis of CNS infection. The sponsor indicated that during the hospitalization for these events, the patient underwent EEG (showing "extensive mild abnormalities") and brain MRI (showing "bilateral cerebral hemisphere diffuse white matter lesions and brain atrophy"). The Investigator stated that the "diagnosis of CNS infection was based on the patient's high blood test results [CRP 13.9 mg/L, Bacterial toxin test ≤5 pg/ml], limb convulsions, and abnormal EEG." The Investigator "confirmed that no precise pathogen had been identified for what was considered a viral encephalitis which recovered...and updated the verbatim to 'CNS infection from viral etiology (pathogen unknown).'" The site also confirmed that no lumbar puncture was performed at that time.

> ***Reviewer comment:*** *Based upon the information provided, there does not appear to be objective or clear evidence of a CNS infection. The patient had headache and fever in the setting of an upper respiratory tract infection. A diagnosis of CNS infection or viral encephalitis should be documented in association with cerebrospinal fluid analysis and is generally not a purely clinical diagnosis. The patient has a reported history of viral encephalitis, but there does not appear to be an active new viral CNS infection based on the information provided and documented improvement.*

On Day 678, she was diagnosed with a non-serious AE of lung infection of severe intensity, which became serious and led to hospitalization on Day 681. Associated symptoms included "poor mental state, moderate appetite and sleep, fecal incontinence, and fever." She also had episodes concerning for generalized seizures. Evaluation included a chest CT which demonstrated a "funicular shadow" in the left upper lobe and diffuse ground glass "dense shadow" in both lungs, "which confirmed the diagnosis of lung infection." A pathogen was not

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identified for this infection. Treatment included levetiracetam, valproate, donepezil, topiramate, phenobarbital, diazepam, and oxiracetam. No antimicrobial therapy was mentioned in the narrative. She recovered and was discharged on Day 691, and was "advised for long-time bed confinement."

> ***Reviewer comment:*** *The patient's chest CT could be consistent with an infectious etiology given the left upper lobe consolidation, but no pathogenic organism was identified, and the patient did not appear to receive treatment for this infection.*

Tonsillitis and Bronchitis (Subject ID (b) (6) An 11 year-old boy from China with no medical history was treated with placebo in DBT and switched to open-label teriflunomide on Day 222 due to confirmed relapse. On Day 329, he was diagnosed with acute tonsillitis and hospitalized with fever to 39°C. He was treated with cefoperazone, amoxicillin/clavulanic acid, and dexamethasone. He continued on teriflunomide and recovered by Day 337. On Day 344, he was diagnosed with acute bronchitis which led to hospitalization due to cough and dyspnea. He again received antibiotics, budesonide, and antiviral medication; he recovered by Day 399. On Day 518, he experienced **neutrophils < 1 x10^9/L (ANC 0.9 x10^9/L).** On Day 561, he was diagnosed with suppurative tonsillitis associated with fever. He received amoxicillin/clavulanic acid and penicillin, and was hospitalized on Day 565. He experienced other **nonserious adverse events of monocyte count decreased, neutrophil count decreased, white blood cell count decreased** after this episode of tonsillitis. Treatment with teriflunomide was ongoing at the time of the narrative (Day 1057), and per the narrative, he had not recovered from these non-serious AEs at the time of the last report.

Acute sinusitis (Subject ID (b) (6) A 16 year-old boy from Russia with a complicated medical history including multiple upper respiratory tract infections (pharyngitis, influenza, bronchitis, laryngitis), deformity of the gallbladder, partial right bundle branch block, sinus tachycardia, "additional trabecula of the left ventricular cavity, trophic changes of ventricular myocardium, moderate sinus arrhythmia, hypotension of the right kidney's pelvis, and mitral valve prolapse." Concomitant medications at baseline included atenolol and pentoxifylline. He was treated with placebo during DBT and switched to open-label teriflunomide on Day 69 due to confirmed relapse. He developed a nonserious AE of acute sinusitis on Day 367, which became serious due to hospitalization on Day 369. Treatment included cefotaxime, and he recovered and was discharged on Day 377. He continued on teriflunomide and completed open-label treatment on Day 1355.

> ***Reviewer comment:*** *Infections are not unexpected in the setting of immunosuppressive and immunomodulatory therapies, such as teriflunomide.*

Fever (Subject ID (b) (6) A 17 year-old boy from Russia with no medical history received placebo in DBT, then switched to open-label teriflunomide on Day 310 due to meeting High MRI

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Activity criteria. On Day 988, he had a fever of 39.8°C and was hospitalized for suspected tick-borne encephalitis. He was diagnosed with the SAE of "unclear fever of unknown cause." He recovered on Day 989 and was discharged at his request. No clear source of infection was identified. Teriflunomide was temporarily interrupted due to pyrexia, then permanently discontinued on Day 991 due to withdrawal of consent by the patient.

Pancreatic Disorders

Pancreatic Neoplasm and Pancreatitis Acute (Subject ID (b) (6) A 13 year-old girl from China with a history of ichthyosis and bacterial meningitis was treated with teriflunomide in DBT, and switched to open-label teriflunomide on Day 230 due to confirmed clinical relapse. On Day 317, she experienced epigastric pain and nausea, which led to diagnosis of "occupancy of uncinate process of pancreas" (coded as pancreatic neoplasm). On Day 320, she experienced nausea and abdominal pain, and was diagnosed with a non-serious AE of acute pancreatitis. At that time, serum lipase was 191 IU/L and amylase was 92 IU/L. Teriflunomide was discontinued due to this episode of acute pancreatitis on Day 320.

She underwent continued pancreatic monitoring following teriflunomide discontinuation. On Day 327, abdominal MRI demonstrated a nodule in the uncinate process with "nature of pseudopapilloma and inflammatory lesions." The Safety Evaluation Report regarding pancreatitis submitted by the sponsor indicated that the patient had a "benign tumor of pancreatic uncinate process...[identified as a] pseudopapilloma." On Day 329, her acute pancreatitis became serious; serum amylase and lipase peaked at 377 IU/L and 969 IU/L. She was hospitalized on Day 339, and an abdominal CT scan demonstrated acute pancreatitis with peripheral infiltration, fatty infiltration in the liver, and a small pericardial effusion. CT angiography demonstrated "roughness of celiac trunk, proximal splenic artery, and proximal common hepatic artery with uneven thickness of lumen." Treatment included anisodamine, esomeprazole, alanyl glutamine, and traditional Chinese medications. Her symptoms improved following treatment, but her family refused the recommended surgery and she was discharged. On Day 356, her symptoms recurred, and CT scan again demonstrated acute pancreatitis with peripheral inflammation. She received treatment with octreotide and was discharged. Her amylase and lipase were normal on Days 375 and 504.

> ***Reviewer comment****: The etiology and nature of the pancreatic imaging abnormality is not clear based on the provided narrative, but a structural abnormality or obstruction could have predisposed the patient to developing pancreatitis. It is also unclear whether this abnormality was present prior initiation of study treatment. Based on the description in the narrative, the pancreatic imaging abnormality could represent a solid pseudopapillary tumor, which is a rare, generally benign neoplasm that can occur in young women.[33] However, these tumors typically do not have pancreatitis as a presenting feature. An autoimmune pancreatitis is also on the differential diagnosis for this patient, but the*

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narrative did not provide sufficient information to make this determination (e.g., IgG4 testing or histopathology).

Pancreatitis (Subject ID (b) (6) Please refer to the discussion of this patient during DBT in Section 8.4.2.1. Briefly, this patient is a 17 year-old girl from China who was treated with teriflunomide in the DBT period, during which she experienced AEs of syncope (SAE), neutropenia, leukopenia, and monocytopenia. Study drug was permanently discontinued due to amylase and lipase increase during the OLE period, with the last dose administered on Day 1057. She experienced an SAE of pancreatitis on Day 1066 leading to hospitalization, and had amylase and lipase >2x ULN between Days 1053 and 1087. Peak values were amylase 400 IU/L and lipase 1814 IU/L. Treatment included rabeprazole, compound digestive enzymes, lansoprazole, and octreotide. She was discharged on Day 1073, but was re-hospitalized on Day 1092 and was discharged on Day 1100. She was considered recovered by Day 1117, as amylase and lipase were within normal limits. Amylase and lipase were also normal on Day 1226 (per 120-Day Safety Update).

Elevated CPK

Blood CPK increased SAEs occurred in 3 patients during the OLE period, 1 of whom also experienced CPK increase during DBT with teriflunomide:

- *Subject ID* (b) (6) Please refer to the discussion of this patient in the DBT period in Section 8.4.2.1.
- *Subject ID* (b) (6) This patient is a 14 year-old boy from France who was treated with teriflunomide in the DBT period, completed the DBT period due to confirmed relapse on Day 346, and switched to OLE on Day 347. He experienced the SAE diplopia during DBT (See Section 8.4.2.1). Teriflunomide was permanently discontinued due to lack of efficacy on Day 542, but on Day 543, the patient developed the SAE of CPK increase of unknown etiology. He reported fatigue, but no pain and examination did not indicate any pain on muscle palpation. CPK was 2536 IU/L. He reported running regularly and working out one day a week. Subsequent CPK assessments on Days 578 and 572 indicated improvement to 687 IU/L and 535 IU/L, respectively. He was considered recovered on Day 591 (CPK 179 IU/L).
- *Subject ID* (b) (6) This patient is a 16 year-old Caucasian girl from Turkey with no medical history who received placebo during DBT, then switched to open-label teriflunomide on Day 264 due to meeting high MRI activity criteria. On Day 691, she was diagnosed with the SAE CPK increase to 766 IU/L (4.5x ULN) in the setting of unremarkable AST, ALT, ALP, total bilirubin, and GGT. Her CPK increased to 1396 on Day 698. She then experienced a nonserious AE of ALT increase due to ALT 92 IU/L on Day 705. AST was 1.6x ULN (53 IU/L). She was evaluated by a hepatologist, and was continued on teriflunomide. Her AST and ALT peaked on Day 712, with values of AST 52

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IU/L and 106 IU/L. CPK improved to 129 IU/L and she was considered recovered on Day 749. Her last teriflunomide dose was on Day 767. She was considered recovered from the elevated ALT on Day 805 with ALT 34 IU/L and AST 17 IU/L. Her last known CPK value was 178 IU/L on Day 1111.

***Reviewer comment**: These 3 cases of CPK elevation are concerning, as increased CPK has not been reported with teriflunomide previously. The first case (Subject ID (b) (6) was mild and could be related to intensive exercise given spontaneous recovery with rest. However, dechallenge was positive but rechallenge was negative. The second case (Subject ID (b) (6) could indicate positive dechallenge. The third case (Subject ID (b) (6) could be related to teriflunomide, but an etiology is unclear. Please refer to Section 8.5.11 for further discussion of the potential relationship of teriflunomide and elevated CPK.*

Hepatic Disorders

Alanine aminotransferase increased (Subject ID (b) (6) A 17 year-old Caucasian girl from Israel who received placebo during DBT and switched to teriflunomide open-label on Day 184 due to confirmed relapse. On Day 353, she experienced ALT increase >2x ULN to 68 IU/L, which became serious on Day 374 with AST 174 IU/L (5.1x ULN) and ALT 278 IU/L (8.2x ULN). Teriflunomide was permanently discontinued on Day 379 due to this SAE, at which time AST was 131 IU/L and ALT was 289 IU/L. An abdominal ultrasound was normal on Day 433. Her AST/ALT downtrended and she was considered recovered on Day 531 (AST 17 IU/L, ALT 12 IU/L). She was diagnosed with drug-induced liver injury due to teriflunomide.

Alanine aminotransferase increased (Subject ID (b) (6) A 16 year-old boy from Russia with a history of mononucleosis, chicken pox, and hypothyroidism who received placebo during DBT and switched to teriflunomide open-label on Day 323 due to confirmed relapse. On Day 351, he experienced nonserious AEs of ALT increase (186 IU/L, 4.3x ULN) and AST increase (72 IU/L, 1.8x ULN). GGT, ALP, and total bilirubin were normal. Teriflunomide was permanently discontinued due to this AE on Day 352. On Day 358, the AE of ALT increased became serious, with ALT of 391 IU/L (9.1x ULN), AST 166 IU/L (4.2x ULN), and GGT 62 IU/L (1.2x ULN). He denied any symptoms, and hepatic evaluation was negative for an etiology of his AST/ALT elevation. AST/ALT improved and were normal on Day 400 following cholestyramine accelerated elimination procedure. These AST/ALT elevations were considered related to teriflunomide.

Hepatic function abnormal (Subject ID (b) (6) A 16 year-old boy from China with no medical history was treated with placebo during DBT and switched to open-label teriflunomide on Day 182 due to confirmed clinical relapse. He experienced liver function testing abnormalities during DBT with placebo, as described in Section 8.4.2.1. Following initiation of teriflunomide in the OLE period, he continued to have persistent ALT elevations >2x ULN, with an SAE of abnormal hepatic function reported on Day 262 (ALT 430 IU/L, AST 175 IU/L, GGT 276

IU/L). He was considered recovered on Day 483, with last known ALT 58 IU/L and AST 40 IU/L. An etiology for his AST/ALT elevations was not identified.

> ***Reviewer comment****: This patient's persistent AST elevation is not likely to be related to teriflunomide, as it began during DBT with placebo. The etiology is unclear, but it may have been exacerbated by teriflunomide use.*

Neutropenia

One patient (*Subject ID* (b) (6) a 15 year-old boy from Tunisia with a history of cyclic neutropenia, experienced an SAE of neutropenia during both DBT and OLE periods. Please refer to the discussion of this patient in the DBT period in Section 8.4.2.1.

Other

One patient (*Subject ID* (b) (6) a 15 year-old boy from Tunisia with a history of cyclic neutropenia, experienced an SAE of overdose (suicide attempt; in addition to neutropenia discussed above) during the OLE period. On Day 662, he consumed 17 additional tablets of teriflunomide, and experienced "sensory disorders and tingling" for 1 to 2 hours. He was hospitalized on Day 663 and received oral activated charcoal and oral cholestyramine. Teriflunomide was temporarily interrupted on Day 663. At a follow-up appointment on Day 668, the patient was euthymic and reported that he regretted his suicide attempt, which was a reaction to school failure.

One patient (*Subject ID* (b) (6) a 12 year-old girl from China, experienced the SAE "adolescent mood disorder" (coded as emotional disorder of childhood) associated with self-harming behaviors (per narrative, she "[cut her finger with a blade]") and required hospitalization on Day 921 in the setting of open-label teriflunomide. She was treated with sertraline and oxazepam, and was discharged on Day 1031.

<u>120 Day Safety Update</u>

During the interval from (b) (6) through (b) (6), 6 patients (3.9%) experienced a treatment emergent SAE (4 in teriflunomide/teriflunomide group, 2 in placebo/teriflunomide group) (Table 31).

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Table 31 (Reviewer). Serious Adverse Events in Trial EFC11759 Open-Label Period by System Organ Class, 120-Day Safety Update Interval

Preferred Term	Teriflunomide-Teriflunomide (n = 100)	Placebo-Teriflunomide (n = 52)	Overall (n = 152)
Number of patients with any SAE (interval)	**4.0 (4)**	**3.8 (2)**	**3.9 (6)**
Infections and Infestations			
Coronavirus infection	1.0 (1)	0 (0)	0.7 (1)
Upper respiratory tract infection	1.0 (1)	0 (0)	0.7 (1)
Psychiatric disorders			
Adjustment disorder	0 (0)	1.9 (1)	0.7 (1)
Depression suicidal	1.0 (1)	0 (0)	0.7 (1)
Nervous system disorders			
Multiple sclerosis	1.0 (1)	0 (0)	0.7 (1)
Uhthoff's phenomenon	1.0 (1)	0 (0)	0.7 (1)
Skin and subcutaneous tissue disorders			
Drug eruption	1.0 (1)	0 (0)	0.7 (1)
Pregnancy, puerperium and perinatal conditions			
Pregnancy	0 (0)	1.9 (1)	0.7 (1)
Ear and labyrinth disorders			
Sudden hearing loss	0 (0)	1.9 (1)	0.7 (1)

Reviewer comment: *The event of sudden hearing loss was provided in the SAE narratives, but was not tabulated in the sponsor's 120 Day Safety Update Report. The narrative indicates that this event occurred the setting of an infection.*

The case of **drug eruption** was reported in Subject ID (b) (6) (discussed in Sections 8.4.2.2 and 8.4.6), an 11 year-old Chinese girl with a medical history of viral encephalitis, "demyelination disease," and epilepsy. She experienced the SAEs epilepsy, upper respiratory tract infection, and secondary epilepsy during DBT. During the OLE, she experienced the SAEs encephalitis viral (previously coded as CNS infection), upper respiratory tract infection, and pneumonia (lung infection).

In the reporting interval, she also experienced the SAE "aggravating multiple sclerosis in children" (coded as MS, on Day 1228) of mild intensity leading to hospitalization. Per the narrative description, she was also likely experiencing seizures at that time. She experienced an SAE of upper respiratory tract infection on Day 1309 that led to hospitalization. She was treated with dexamethasone IV, penciclovir IV, ceftriaxone IV, cefdinir PO, methylprednisolone PO, and "relevant hormones." She recovered and was discharged on Day 1328. On Day 1355, she experienced a non-serious TEAE of drug eruption (thought to be related to non-investigational medical product, which was not specified), which became serious on Day 1365 after she experienced a non-serious event of drug-induced liver injury (DILI) on Day 1362 (ALT 5.18x ULN). She was hospitalized, and received an "unspecified corrective treatment for drug

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eruption." No concurrent laboratory information, specifically her eosinophil count, was submitted for this event. She recovered on Day 1369 from DILI, which was not thought to be related to teriflunomide. She recovered on Day 1385 from drug eruption.

She was again hospitalized on Day 1413 due to the SAE epilepsy in the setting of recent fever. On Day 1423, she was hospitalized due to the SAE pneumonia (non-serious AE of pneumonia reported on Day 1418). She also had ongoing seizure activity during this time. She was treated with valproate, midazolam, and piperacillin/tazobactam.

One patient (Subject ID (b) (6)) experienced the SAE coronavirus infection on Day 1107, with symptoms of headache, congestion, fever, loss of taste or smell, fatigue, and myalgia. He tested positive on Day 1111, and did not require hospitalization. He received symptomatic/supportive treatment, and he was considered recovered on Day 1117. Teriflunomide was permanently discontinued on Day 1187 due to new MRI lesions.

> ***Reviewer comment:*** *Overall, these results are consistent with observations during the DBT and original OLE data. Please see Section 8.5.6 for discussion of the patient with drug eruption.*

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Discontinuations Due to Adverse Events

Double Blind Period

In the DBT period, 6 patients in the teriflunomide group discontinued study treatment due to adverse events. Two were due to acute pancreatitis, 1 alanine aminotransferase increased, 1 hyperlipasaemia, 1 pulmonary tuberculosis, and 1 affective disorder. No patients in the placebo group discontinued double-blind treatment due to an AE.

Three patients discontinued double-blind teriflunomide due to **pancreatic disorder-related events:** 2 due to acute pancreatitis and 1 due to hyperlipasaemia**.**

One case of acute pancreatitis (*Subject ID* (b) (6) was classified as an SAE and is discussed in Section 8.4.2.1.

The second case of acute pancreatitis (*Subject ID* (b) (6) occurred in a 15 year-old Caucasian boy from France who discontinued DBT with teriflunomide on Day 587 due to development of acute pancreatitis on Day 551. Initial lipase was 187 IU/L, and amylase was 94 IU/L. He was initially asymptomatic, but developed left hypochondrium pain, nausea, and vomiting in the following 9 to 11 days. Lipase peaked at 246 IU/L (6.31x ULN) on Day 560. He continued on teriflunomide, and had persistently elevated lipase >2x ULN on Days 568, 574,

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576, 579, 581, and 583. He experienced epigastric pain and nausea between Days 584 and 614. Abdominal MRI on Day 587 was consistent with acute pancreatitis; lipase was 78 IU/L at that time. He experienced abdominal pain on Day 592 that recovered with paracetamol. Teriflunomide was permanently discontinued on Day 587. Amylase and lipase were normal on Day 610. He underwent further testing with MR cholangiopancreatography, which demonstrated "sausage-like pancreas with diffuse hyperintense signal that could indicate...autoimmune pancreatitis with non-tumorous appearance." He then underwent genetic testing which indicated the presence of a gene that could result in increased susceptibility to pancreatitis. He had 2 additional episodes of abdominal pain that were thought to be unrelated to pancreatitis on Days 672 and 698. Repeat MR cholangiography demonstrated "clear decrease in T2 hyperintense signal and diffusion of the tail of the pancreas." At the time of the last report, he was recovering from acute pancreatitis.

The patient who discontinued double-blind treatment with teriflunomide due to hyperlipasaemia was a 16 year-old girl from Russia (*Subject ID* (b) (6) who was documented to have lipase of 2163 IU/L (34.33x ULN) and amylase 498 IU/L (6.55x ULN) on Day 422. She initially continued on teriflunomide, and repeat testing on Day 464 demonstrated improved lipase to 246 IU/L and amylase to 100 IU/L. On Day 553, she experienced a non-serious AE of "reactive asymptomatic hyperlipasaemia (drug-induced)" (coded as hyperlipasaemia) with lipase 329 IU/L and amylase 79 IU/L. She did not experience associated clinical symptoms, and no abnormalities were seen on ultrasound. Teriflunomide was discontinued on Day 583 and she received oral cholestyramine. On Day 588, lipase was 197 IU/L and amylase was 66 IU/L, and both values normalized by Day 603.

One patient, a 12 year-old Caucasian girl from Turkey with alpha-1 antitrypsin deficiency (*Subject ID* (b) (6) discontinued double-blind teriflunomide on Day 184 due to the AE **ALT increased**. She initially experienced ALT>2x ULN on Day 57 (ALT 83 IU/L, AST 49 IU/L), which persisted Days 85, 87, and 94. She was considered recovered on Day 102 (ALT 57 IU/L). She again experienced ALT>2x ULN from Days 138 to 180, peaking at ALT 144.2 IU/L (4.37x ULN) on Day 151. On Day 180, ALT was 121 IU/L (3.46x ULN), and AST was 64 IU/L (1.83x ULN). Teriflunomide was permanently discontinued on Day 184. On Day 192, ALT remained elevated at 116 IU/L (AST 60 IU/L), and increased to 186 IU/L on Day 197. She was considered recovered from ALT increased on Day 242, with ALT of 35 IU/L and AST of 29 IU/L. The investigator attributed her ALT increase to her history of alpha-1 antitrypsin deficiency and potentially her concomitant medication amlodipine, which was also discontinued.

> ***Reviewer comment:*** *Though alpha-1 antitrypsin deficiency can lead to liver disease and hepatic enzyme elevations, it is not possible to rule out a contribution of teriflunomide to this patient's adverse event, especially given the known safety profile of teriflunomide.*

The case of **pulmonary tuberculosis** was classified as an SAE and is discussed in Section 8.4.2.1.

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The patient who discontinued study treatment due to the AE of **affective disorder** (Subject ID (b) (6) was a 15 year-old Black girl from France who began double-blind treatment with teriflunomide and experienced MS relapse with the nonserious adverse event of mood disorder on Day 1. She was hospitalized for MS relapse, which was characterized by "moderate walking difficulties, lower limb difficulties, right hand and arm function, right facial motor, ...other bulbar symptoms, ...[and] severe speech difficulty and fatigue." She was treated with IV corticosteroids. Brain MRI on Day 11 "revealed significant impairment of the brainstem responsible for the disorder of consciousness." She was considered recovered from affective disorder on Day 12. The sponsor confirmed that this was an adjudicated confirmed clinical relapse via Information Request response received on March 18, 2021.

> ***Reviewer comment:*** *This patient experienced an MS relapse on Day 1 of double-blind treatment. The coding of this event as "affective disorder" is not consistent with the documented brain MRI and neurological examination findings consistent with a new brainstem lesion. Since this event occurred on Day 1 of treatment, it is unlikely to be related to teriflunomide. Please refer to Section 6.1.2.*

Open Label Period

In the OLE period, 8 patients experienced 9 AEs that led to treatment discontinuation, six of whom had received placebo in the DBT period. The reported PTs for these events were: alanine aminotransferase increased (n = 5), amylase increased (n = 1), lipase increased (n = 1), neuropathy peripheral (n = 1), and pancreatitis acute (n = 1).

Five patients experienced the TEAE **ALT increased** during the OLE period:

- *Subject ID* (b) (6) This subject experienced an SAE of hepatic function abnormal, and is discussed in Section 8.4.2.2.
- *Subject ID* (b) (6) This subject experienced an SAE of ALT increased, and is discussed in Section 8.4.2.2.
- *Subject ID* (b) (6) This subject experienced an SAE of ALT increased, and is discussed in Section 8.4.2.2.
- *Subject ID* (b) (6) This patient was a 15 year-old girl from Turkey who received placebo during DBT and switched to open-label teriflunomide on Day 555 due to confirmed relapse. During DBT, she experienced the SAEs appendicitis and familial Mediterranean fever. Initiation of oral azathioprine was also mentioned in the DBT narrative. On Day 555 (open-label period), she had ALT >2x ULN (143 IU/L), with normal AST, bilirubin, and GGT. On Day 557, ALT was 110 IU/L. She received her last dose of teriflunomide on Day 558. ALT improved to 60 IU/L on Day 561 and 31 IU/L on Day 565.
- *Subject ID* (b) (6) This patient was a 15 year-old Black/African-American girl from the United States who received placebo during DBT and switched to open-label

teriflunomide on Day 484 after completing 96 weeks of DBT. On Day 550, she experienced ALT elevated (153 IU/L, 4.5x ULN), with AST 73 IU/L (1.83x ULN). On Day 552, ALT improved to 131 IU/L. The provided narrative indicates that the patient was asymptomatic and denied any acetaminophen or alcohol use. Teriflunomide was discontinued on Day 554. She was considered recovered from the ALT increase on Day 571, with ALT 32 IU/L.

Two patients experienced **pancreatic disorder-related events**:

- *Subject ID* (b) (6) This patient experienced the SAEs amylase increased and lipase increased during OLE, and is discussed in Section 8.4.2.2.
- *Subject ID* (b) (6) This patient experienced the SAE pancreatitis acute during OLE, and is discussed in Section 8.4.2.2.

One patient experienced the AE **neuropathy peripheral** during the OLE period. *Subject ID* (b) (6) was a 10 year-old boy from Turkey who was treated with placebo during DBT and switched to open-label teriflunomide on Day 92 due to confirmed clinical relapse. During DBT, he experienced the AE epilepsy between Days 78 and 108, and on Day 114, EEG demonstrated generalized epileptiform discharges. He started valproic acid 200mg, and subsequent EEG on Day 344 was normal. Peripheral neuropathy is documented as starting on Day 513, and teriflunomide was permanently discontinued on Day 520. The patient experienced inability to walk due to plantar foot/leg pain, and neurological examination demonstrated loss of temperature sensation in the bilateral hands and legs. An EMG/NCS was performed on Day 519, which was interpreted as "polyneuropathic involvement characterized by mild loss of axons, predominantly in the lower extremities and sensory fibers." Teriflunomide was discontinued, and the patient was considered recovered on Day 522.

Per the ADEM dataset, on Day 422 of open-label treatment, this patient was noted to have abnormal cutaneous sensation in a "glove and sock distribution," specifically loss of sensation and "sensory lancinating." Neurological examination demonstrated hyperactive patellar and normal ankle reflexes. An EMG/NCS was performed, and individual parameter values were provided without reference ranges in the dataset.

> ***Reviewer comment:*** *The EMG/NCS results provided were compared to proposed age normative values by Ryan et al.,[34] and suggest a sensorimotor axonal neuropathy with a mild degree of demyelination (decreased sensory and motor amplitudes with mildly decreased conduction velocity). This pattern of neuropathy has been documented in association with leflunomide, of which teriflunomide is the active metabolite.[35]*

Additionally, one patient discontinued open-label treatment due to **pregnancy**. *Subject ID* (b) (6) was a 17 year-old girl from Turkey who received teriflunomide during DBT, then switched to open-label teriflunomide on Day 183 due to confirmed relapse. She experienced

lipase >2x ULN on Day 165 (lipase 188 IU/L, amylase 142 IU/L), which normalized by Day 183 without intervention. Her pregnancy test was positive on Day 223, at which time she was 4 weeks pregnant. Teriflunomide was permanently discontinued on Day 217 due to pregnancy, and the patient refused accelerated elimination. She delivered an infant via cesarean section on Day 460, and no structural defects or functional abnormalities of the newborn were reported to date.

120 Day Safety Update

During the interval from (b) (6) through (b) (6), 9 additional patients (5 placebo/teriflunomide, 4 teriflunomide/teriflunomide) discontinued treatment during this interval; 4 due to adverse event, 2 lack of efficacy, 3 "other" and 7 patient decision. The sponsor reported that 1 patient experienced a TEAE (nonserious pancreatitis acute, of mild intensity) in the interval that led to permanent discontinuation, but indicated that another patient experienced alopecia areata of severe intensity that was not counted in this tabulation due to a "data cleaning issue unresolved before the data lock point."

> ***Reviewer comment:*** *Based upon the reasons for discontinuation provided, it is likely that some patients had multiple reasons for treatment discontinuation, but it the reasons per patient were not provided. Additionally, some numbers in the sponsor's report are discrepant due to a "data cleaning issue."*

The patient who discontinued treatment due to **alopecia areata** (*Subject ID* (b) (6) was a 17 year-old girl from Tunisia with a history of diabetes mellitus and hair loss in the teriflunomide/teriflunomide group. She experienced the nonserious but severe AE alopecia areata on Day 637. She was treated with Capil Plus and topical minoxidil.

The patient who discontinued treatment due to **acute pancreatitis** (Subject ID (b) (6) was a 12 year-old girl from Ukraine who switched from double-blind teriflunomide to open-label on Day 260 due to meeting High MRI Activity Criteria. On Day 981, she experienced pancreatitis associated with lipase 2.67x ULN and amylase 1.82x ULN. On Day 987, amylase and lipase increased to 7.78x ULN and 7.13x ULN, respectively. A pancreatic ultrasound on Day 988 was consistent with pancreatitis. She began treatment with butylscopolamine and esomeprazole. She was also found to have superficial gastritis on Day 989. She discontinued teriflunomide due to pancreatitis on Day 987. Her amylase and lipase improved on Days 994, 1000, 1008, and 1022.

> ***Reviewer comment:*** *The positive dechallenge in this case of pancreatitis suggests a likely association with teriflunomide.*

In this reporting interval, another patient (*Subject ID* (b) (6) discontinued teriflunomide

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due to **pregnancy**. A positive pregnancy test was reported on Day 948, and treatment was discontinued on Day 949. The patient underwent termination of the pregnancy on Day 973.

AEs leading to Treatment Interruption

Double blind treatment interruption occurred in 6 patients in the teriflunomide group, and the PTs reported for these events were: neutropenia (n = 2), basophil count increased (n = 1), epilepsy (n = 1), influenza (n = 1), leukopenia (n = 1), monocytopenia (n = 1), and neutrophil count decreased (n = 1).

Open label treatment interruption occurred in 5 patients, and the reported PTs for these events were: alopecia (n = 1), blood creatine phosphokinase increased (n = 1), lipase increased (n = 1), neutropenia (n = 1), overdose (n =1), and pyrexia (n = 1). Events leading to treatment interruption were more frequent in patients who had received placebo in the DBT period (5.8%) compared to those who had received teriflunomide (2.0%).

8.4.4. Significant Adverse Events

Marked Hematological and Other Laboratory Abnormalities (Non-serious)

Hematological Abnormalities

Marked hematological abnormalities are discussed in Section 8.4.2 (Serious Adverse Events). Clinically significant hematological abnormalities are summarized in Table 57 (Section 8.4.6).

Increased Creatine Phosphokinase

During DBT, 3 patients on teriflunomide experienced CPK >10x ULN (compared to 0 on placebo):

1. *Subject ID* (b) (6) experienced **CPK >20x ULN, AST >5x ULN with AST at 2x ULN** at DBT Week 36. This patient was a 16 year-old Caucasian boy from Lebanon who completed the 96-week DBT period (on teriflunomide) and switched to open-label treatment on Day 674. On Day 253 experienced several severe laboratory abnormality-related TEAEs in the setting of "extreme physical activity," including AST 7.3x ULN, ALT 2.3x ULN**, CPK 104x ULN (42,504 IU/L)**, and LDH 5.7x ULN. These values improved on Day 259 (AST 1.0x ULN, ALT 1.4x ULN, CPK 19.1x ULN, and LDH 1.1x ULN), and the patient continued on teriflunomide. His laboratory values normalized on Day 297, and he was considered recovered on Day 340.

2. *Subject ID* (b) (6) experienced CPK >20x ULN at DBT Week 12. This patient was a 17

year-old Caucasian girl from Lebanon who completed the 96-week DBT period (on teriflunomide) and switched to open-label treatment. At DBT Week 12, CPK was 4772 IU/L (ref. range 18-169) in the setting of a TEAE myalgia. AST at that time was 70 IU/L (1.75x ULN). Repeat testing 3 days later showed a CPK of 716 IU/L (4.2x ULN), and subsequent testing was within normal limits until 5 months later (323 IU/L, 1.9x ULN at DB Visit 10). She experienced intermittent elevations in CPK throughout treatment (323 IU/L at DB Visit 10, 1604 IU/L at DB Visit 14, and 214 IU/L at OL Visit 18. She was continued on teriflunomide throughout these events.

3. *Subject ID* (b) (6) experienced CPK >10x ULN at DBT Week 24. This patient was a 13 year-old Black boy from the Netherlands who completed the 96-week DBT period (on teriflunomide) and switched to open-label treatment. At DB Week 24, CPK was 4763 IU/L (ref. range 18-363, 13.1x ULN). Repeat testing at Visit 10 (2 months later) was within normal limits. He also experienced CPK elevation to 2350 IU/L (6.5x ULN) at OLE Visit 4, which improved 2 days later to 882 IU/L. He experienced a third CPK elevation at OLE visit 9 to 2654 IU/L. His last CPK value on treatment was 92 IU/L. His CPK elevations were considered related to "intensive sport training." He was continued on teriflunomide throughout these events.

   Reviewer comment: *It is possible that these patients experienced these laboratory abnormalities due to extreme physical activity (Subjects* (b) (6) *and* (b) (6) *but a contribution of teriflunomide cannot be excluded. The greater severity of the CPK elevation (rather than AST) suggests that these laboratory abnormalities were likely due to a primary muscular process, rather than a primary hepatic disorder.*

Adverse Events that Led to Intervention

Adverse events that led to interruption or withdrawal of study treatment are discussed in 8.4.3. No patients had a dose reduction due to an adverse event.

During the DBT period, 239 AEs leading to concomitant medication use occurred in 81 (74.3%) patients receiving teriflunomide, and 99 AEs in 37 (64.5%) patients receiving placebo.

During the OLE period, 170 AEs leading to concomitant medication use occurred in 58 (58.0%) patients in the teriflunomide-teriflunomide group, 98 AEs in 33 (63.5%) patients in the placebo-teriflunomide group, and 268 AEs in 91 (59.9%) patients overall.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Double Blind Period

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During the DBT period, 96 patients on teriflunomide (88.1%) and 47 patients on placebo (82.5%) experienced at least 1 AE.

The number of patients in each treatment arm experiencing at least 1 AE from each SOC (using AEBODSYS) is presented in Table 32. AEs were most commonly reported under the SOCs Infections and Infestations, Respiratory, thoracic, and mediastinal disorders, Skin and subcutaneous tissue disorders, and Nervous system disorders.

Table 32 (Reviewer). Trial EFC11759 TEAE System Organ Classes (AEBODSYS) During Double-Blind Period

MedDRA SOC (AEBODSYS)	Teriflunomide (n = 109)	Placebo (n = 57)
Infections and Infestations	66.1 (72)	45.6 (26)
Respiratory, thoracic, and mediastinal disorders	65.1 (71)	43.9 (25)
Skin and subcutaneous tissue disorders	48.6 (53)	26.3 (15)
Nervous system disorders	36.7 (40)	38.6 (22)
Gastrointestinal disorders	38.5 (42)	33.3 (19)
Investigations	24.8 (27)	14.0 (8)
Injury, poisoning, and procedural complications	18.3 (20)	19.3 (11)
Musculoskeletal and connective tissue disorders	20.2 (22)	14.0 (8)
General disorders and administration site conditions	19.3 (21)	14.0 (8)
Eye disorders	15.6 (17)	15.8 (9)
Vascular disorders	17.4 (19)	8.8 (5)
Psychiatric disorders	13.8 (15)	14.0 (8)
Cardiac disorders	15.6 (17)	8.8 (5)
Immune system disorders	11.9 (13)	10.5 (6)
Metabolism and nutrition disorders	9.2 (10)	8.8 (5)
Ear and labyrinth disorders	8.3 (9)	7.0 (4)
Reproductive system and breast disorders	5.5 (6)	12.3 (7)
Renal and urinary disorders	8.3 (9)	5.3 (3)
Blood and lymphatic system disorders	6.4 (7)	5.3 (3)
Endocrine disorders	2.8 (3)	3.5 (2)
Hepatobiliary disorders	0 (0)	5.3 (3)
Congenital, familial and genetic disorders	0 (0)	3.5 (2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0)	1.8 (1)
Pregnancy, puerperium and perinatal conditions	0.9 (1)	0 (0)

Source: N Categories (SUBJID) of Trial EFC11759 ADAE where SAF01FL and TRTEMFL ='Y' by AEBODSYS and ACTARM.

Treatment emergent AEs occurring in ≥2% of patients on teriflunomide are presented in

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Table 33. The most commonly reported AEs in Trial EFC11759 were infections (particularly nasopharyngitis and upper respiratory tract infection), headache, alopecia, paresthesia, and abdominal pain.

Table 33 (Reviewer). Treatment Emergent Adverse Events Occurring in ≥2% of Patients on Teriflunomide During Double Blind Treatment, by Primary SOC

Primary System Organ Class (AESOC)	Preferred Term	Teriflunomide (n = 109)	Placebo (n = 57)
Infections and Infestations	Nasopharyngitis	25.7 (28)	8.8 (5)
	Upper respiratory tract infection	21.1 (23)	10.5 (6)
	Influenza	9.2 (10)	7.0 (4)
	Pharyngitis	6.4 (7)	1.8 (1)
	Bronchitis	4.6 (5)	1.8 (1)
	Rhinitis	3.7 (4)	3.5 (2)
	Sinusitis	3.7 (4)	3.5 (2)
	Tonsillitis	3.7 (4)	3.5 (2)
	Respiratory tract infection viral	3.7 (4)	0 (0)
	Gastroenteritis	2.8 (3)	5.3 (3)
Skin and subcutaneous tissue disorders	Alopecia	21.1 (23)	12.3 (7)
	Acne	4.6 (5)	7.0 (4)
	Rash	3.7 (4)	3.5 (2)
Nervous system disorders	Headache	16.5 (18)	22.8 (13)
	Paraesthesia	11.0 (12)	1.8 (1)
	Dizziness	8.3 (9)	7.0 (4)
	Hypoaesthesia	5.5 (6)	5.3 (3)
	Presyncope	2.8 (3)	0 (0)
Gastrointestinal disorders	Abdominal pain	11.0 (12)	1.8 (1)
	Nausea	8.3 (9)	7.0 (4)
	Diarrhoea	7.3 (8)	7.0 (4)
	Abdominal pain upper	5.5 (6)	3.5 (2)
	Vomiting	4.6 (5)	8.8 (5)
Respiratory, thoracic, and mediastinal disorders	Oropharyngeal pain	6.4 (7)	3.5 (2)
	Cough	5.5 (6)	5.3 (3)
	Nasal congestion	2.8 (3)	1.8 (1)
	Dyspnoea	2.8 (3)	0 (0)
	Rhinitis allergic	2.8 (3)	0 (0)
Injury, poisoning, and procedural complications	Fall	5.5 (6)	7.0 (4)
	Accidental overdose	3.7 (4)	5.3 (3)
	Contusion	3.7 (4)	0 (0)
Investigations	Weight decreased	5.5 (6)	3.5 (2)
	Blood CPK increased	5.5 (6)	0 (0)
	White blood cell count decreased	3.7 (4)	1.8 (1)
	ALT increased	2.8 (3)	1.8 (1)
	Protein urine present	2.8 (3)	1.8 (1)

Primary System Organ Class (AESOC)	Preferred Term	Teriflunomide (n = 109)	Placebo (n = 57)
	Neutrophil count decreased	2.8 (3)	0 (0)
	Weight increased	2.8 (3)	0 (0)
General disorders and administration site conditions	Pyrexia	5.5 (6)	3.5 (2)
	Fatigue	3.7 (4)	5.3 (3)
	Non-cardiac chest pain	3.7 (4)	0 (0)
	Influenza like illness	2.8 (3)	1.8 (1)
Eye disorders	Eye pain	3.7 (4)	7.0 (4)
Psychiatric disorders	Anxiety	3.7 (4)	5.3 (3)
Musculoskeletal and connective tissue disorders	Back pain	4.6 (5)	3.5 (2)
	Pain in extremity	3.7 (4)	3.5 (2)
	Musculoskeletal pain	2.8 (3)	0 (0)
Blood and lymphatic system disorders	Anaemia	2.8 (3)	1.8 (1)
	Neutropenia	2.8 (3)	0 (0)
Ear and labyrinth disorders	Ear pain	2.8 (3)	3.5 (2)
	Tinnitus	2.8 (3)	1.8 (1)
Cardiac disorders	Palpitations	2.8 (3)	0 (0)

Source: Trial EFC11759 ADAE where SAF01FL and TRTEMFL ='Y' by ACTARM.

> ***Reviewer comment:*** *The occurrence of infections, alopecia, paresthesia, abdominal pain, blood CPK increased, white blood cell count decreased, ALT increased, neutrophil count decreased, and neutropenia was higher in patients on teriflunomide.*

TEAEs with a ≥5% difference in incidence between teriflunomide and placebo are presented in Table 34.

Table 34 (Reviewer). Treatment Emergent Adverse Events with Incidence Difference Between Teriflunomide and Placebo ≥5%, by Primary SOC

Primary System Organ Class	Preferred Term	Teriflunomide (n = 109)	Placebo (n = 57)
Infections and infestations	Nasopharyngitis	25.7 (28)	8.8 (5)
	Upper respiratory tract infection	21.1 (23)	10.5 (6)
Nervous system disorders	Paraesthesia	11.0 (12)	1.8 (1)
Gastrointestinal disorders	Abdominal pain	11.0 (12)	1.8 (1)
Skin and subcutaneous tissue disorders	Alopecia	21.1 (23)	12.3 (7)
Nervous system disorders	Headache	16.5 (18)	22.8 (13)
Investigations	Blood creatine phosphokinase increased	5.5 (6)	0 (0)
Psychiatric disorders	Insomnia	0 (0)	5.4 (3)

Source: Trial EFC11759 ADAE where SAF01FL and TRTEMFL ='Y' by ACTARM.

Adverse event severity during the DBT period is tabulated by treatment group in Table 35.

Table 35 (Reviewer). Adverse Event Severity During Double-Blind Treatment, Trial EFC11759

Severity	Teriflunomide (n = 109)	Placebo (n = 57)
Mild	43.1 (47)	54.4 (31)
Moderate	37.6 (41)	21.1 (12)
Severe	7.3 (8)	7.0 (4)
Total	**88.1 (96)**	**82.5 (47)**

Source: Trial EFC11759 ADAE where SAF01FL and TRTEMFL ='Y' by ACTARM.

A review of all TEAEs using MedDRA search terms grouped using logical clinical associations of disorders was also conducted. The results of this analysis for terms reported by at least 5% of patients on teriflunomide and at a greater frequency than placebo are presented in Table 36. Again, infections were the most common TEAE (particularly upper respiratory tract infections), followed by alopecia.

Table 36 (Reviewer). Safety Grouping Analysis of TEAEs, Double-blind Period

Grouping Term[1]	Teriflunomide (n = 109)	Placebo (n = 57)
Infection, all	65.1 (71)	47.4 (27)
URI, cold, rhinitis, upper respiratory tract infection, flu-like illness	52.3 (57)	31.6 (18)
Alopecia	22.0 (24)	12.3 (7)
Infection, viral	18.3 (20)	8.8 (5)
Abdominal pain, distension, bloating, spasm, IBS, megacolon	16.5 (18)	7.0 (4)
Influenza	9.2 (10)	7.0 (4)
Paraesthesia, hypoaesthesia	11.0 (12)	3.5 (2)
Dizziness, lightheadedness	8.3 (9)	7.0 (4)
Asthenia, fatigue, malaise, weakness, narcolepsy	6.4 (7)	5.3 (3)
Leukopenia (neutropenia and/or lymphopenia)	7.3 (8)	1.8 (1)
Fever, rigors	5.5 (6)	3.5 (2)
Weight loss, catabolic state, cachexia, failure to thrive	5.5 (6)	3.5 (2)
CPK increased	6.4 (7)	0 (0)
Chest pain (non-cardiac or unknown)	5.5 (6)	0 (0)

[1]Terms reported by at least 5% of patients on teriflunomide, and at a greater frequency than placebo

One case of PT gastrointestinal hemorrhage, described as "hemorrhage of lower digestive tract-mild" occurred in 1 patient on teriflunomide (Subject ID (b) (6) a 10 year-old boy in China. This AE occurred on Day 361 of DBT (Week 51), and lasted 26 days. Study treatment dose was not changed, and no corrective treatment was needed. It was determined that this event was not related to study treatment. At baseline, this patient had a platelet count of 150 to 155 $x10^9$/L. His platelet counts ranged from 111 to 128 $x10^9$/L over DBT weeks 12 through 24. At the time of this AE, his platelet count was normal (151 $x10^9$/L at Week 42 and 177 $x10^9$/L at Week

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54). The nature of this AE is unclear based on CRF review, but the CRF also mentions "topical polyps" without a specified location.

Of note, nail disorder TEAEs were reported in Trial EFC11759. Nail disorders are currently under review as a Changes Being Effected Supplement for addition to the Postmarketing Adverse Reactions section in teriflunomide labeling. During DBT, the PTs onychomadesis and paronychia occurred in 1 patient each in the teriflunomide group (0.9%) versus 0% in placebo. During OLE, onychoclasis occurred in 1 patient in the teriflunomide-teriflunomide group (0.7%).

> ***Reviewer comment****: Though nail disorder events were infrequent in Trial EFC11759, the events only occurred in the teriflunomide group, which supports an association and therefore inclusion in labeling.*

Other TEAEs classified as Adverse Events of Special Interest (AESI) by the sponsor not discussed elsewhere in this review include the following:

- **Gastrointestinal disorders:** The frequency of nausea, vomiting, and diarrhea was similar between the treatment groups.
- **Cardiac arrhythmias:** No case of cardiac arrythmias were reported in either group during DBT.
- **Embolic and thrombotic events:** One patient in the teriflunomide group (Subject ID (b) (6) experienced the PT hemiparesis ("weakened left side") that was thought to be related to MS rather than a vascular event (See Section 8.4.2, as patient also experienced the SAE syncope). No cases occurred in the placebo group.
- **Hemorrhages:** The frequency of treatment-emergent hemorrhages was similar between the treatment groups (5.3% on placebo, 7.3% on teriflunomide). The case of gastrointestinal hemorrhage in a patient on teriflunomide is discussed above. Epistaxis occurred in 1.8% of patients in each group. Menorrhagia occurred in 1.8% of patients on placebo. PTs in the SOC Injury, Poisoning, and procedural complications were more common in the teriflunomide group (5.5% versus 1.8%), but these were in the setting of physical injury: 4 patients on teriflunomide experienced contusion, 1 periorbital hemorrhage, and 1 subcutaneous hematoma. One patient on placebo experienced subcutaneous hematoma.
- **Convulsions:** Two patients in the teriflunomide group (1.8%) and 2 in the placebo group (3.5%) experienced treatment-emergent convulsions, with the most commonly reported PT epilepsy (3.5% placebo versus 0.9% teriflunomide). One patient in the teriflunomide group who experienced epilepsy as an SAE (*Subject ID* (b) (6) is discussed in Section 8.4.2.
- **Psychiatric disorders:** The frequency of treatment-emergent psychiatric disorders was similar between the treatment groups (14.0% on placebo, 13.8% teriflunomide). The most commonly reported psychiatric disorder PT was anxiety (5.3% on placebo, 3.7% on teriflunomide). One psychiatric disorder event led to treatment discontinuation in a

patient on teriflunomide (Subject ID (b) (6) discussed in Section 8.4.3). The sponsor reported in the 120 Day Safety Update that 3 psychiatric disorder SAEs occurred during OLE: one intentional overdose and suicide attempt in a teriflunomide-teriflunomide patient, one depression suicidal in a teriflunomide-teriflunomide patient, and one adjustment disorder in a placebo-teriflunomide patient.

Reviewer comment: *Overall, the AESIs mentioned above did not appear to occur at a higher frequency in the teriflunomide group.*

Open-Label Extension

During the OLE period, 68 patients who received teriflunomide (68.0%) during DBT and 43 patients who received placebo (82.7%) during DBT experienced at least 1 TEAE. Overall, 111 patients (73.0%) experienced an AE during the OLE.

The number of patients in each treatment arm experiencing at least 1 TEAE from each SOC (using AEBODSYS) during OLE is presented in Table 37.

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Table 37 (Reviewer). Trial EFC11759 TEAE System Organ Classes (AEBODSYS) During Open-Label Period

MedDRA SOC (AEBODSYS)	TFN-TFN (n = 100)	PBO-TFN (n = 52)	Overall (n = 152)
Infections and Infestations	47.0 (47)	46.2 (24)	46.7 (71)
Respiratory, thoracic and mediastinal disorders	46.0 (46)	46.2 (24)	46.1 (70)
Gastrointestinal disorders	29.0 (29)	34.6 (18)	30.9 (47)
Nervous system disorders	24.0 (24)	36.5 (19)	28.3 (43)
Skin and subcutaneous tissue disorders	24.0 (24)	26.9 (14)	25.0 (38)
Investigations	15.0 (15)	23.1 (12)	17.8 (27)
Musculoskeletal and connective tissue disorders	12.0 (12)	21.2 (11)	15.1 (23)
General disorders and administration site conditions	14.0 (14)	15.4 (8)	14.5 (22)
Injury, poisoning and procedural complications	13.0 (13)	17.3 (9)	14.5 (22)
Vascular disorders	7.0 (7)	21.2 (11)	11.8 (18)
Psychiatric disorders	6.0 (6)	19.2 (10)	10.5 (16)
Cardiac disorders	6.0 (6)	17.3 (9)	10.5 (16)
Eye disorders	9.0 (9)	9.6 (5)	9.9 (15)
Renal and urinary disorders	8.0 (8)	11.5 (6)	9.2 (14)
Immune system disorders	5.0 (5)	13.5 (7)	9.2 (14)
Ear and labyrinth disorders	7.0 (7)	3.8 (2)	5.9 (9)
Metabolism and nutrition disorders	7.0 (7)	3.8 (2)	5.9 (9)
Reproductive system and breast disorders	6.0 (6)	5.8 (3)	5.9 (9)
Blood and lymphatic system disorders	5.0 (5)	3.8 (2)	4.6 (7)
Endocrine disorders	1.0 (1)	1.9 (1)	1.3 (2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2.0 (2)	0 (0)	1.3 (2)
Pregnancy, puerperium and perinatal conditions	2.0 (2)	0 (0)	1.3 (2)
Hepatobiliary disorders	0 (0)	1.9 (1)	0.7 (1)

TFN: Teriflunomide; PBO: Placebo
Source: N Categories (SUBJID) of Trial EFC11759 ADAE where SAF02FL and TRTEMFL ='Y' by AEBODSYS and TRTA.

Treatment emergent AEs occurring in ≥5% of patients in either treatment arm during OLE are presented in Table 38.

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Table 38 (Reviewer). Treatment Emergent Adverse Events Occurring in ≥5% of Patients in Either Group During Open-Label Treatment, by Primary SOC

System Organ Class	Preferred Term	TFN-TFN (n = 100)	PBO-TFN (n = 52)	Overall (n = 152)
Infections and Infestations	All	88.0 (88)	82.7 (43)	86.2 (131)
	Nasopharyngitis	16.0 (16)	15.4 (8)	15.8 (24)
	Upper respiratory tract infection	17.0 (17)	11.5 (6)	15.1 (23)
	Influenza	4.0 (4)	7.7 (4)	5.3 (8)
	Rhinitis	5.0 (5)	3.8 (2)	4.6 (7)
	Urinary tract infection	5.0 (5)	1.9 (1)	3.9 (6)
	Gastroenteritis	5.0 (5)	0 (0)	3.3 (5)
	Respiratory tract infection	5.0 (5)	0 (0)	3.3 (5)
	Bronchitis	0 (0)	5.8 (3)	2.0 (3)
Skin and subcutaneous tissue disorders	Alopecia	9.0 (9)	17.3 (9)	11.8 (18)
Nervous system disorders	Headache	12.0 (12)	9.6 (5)	11.2 (17)
	Dizziness	2.0 (2)	11.5 (6)	5.3 (8)
	Hypoaesthesia	1.0 (1)	7.7 (4)	3.3 (5)
	Syncope	1.0 (1)	5.8 (3)	2.6 (4)
Investigations	Alanine aminotransferase increased	3.0 (3)	15.4 (8)	7.2 (11)
Gastrointestinal disorders	Diarrhoea	5.0 (5)	9.6 (5)	6.6 (10)
	Oropharyngeal pain	6.0 (6)	3.8 (2)	5.3 (8)
	Abdominal pain	5.0 (5)	3.8 (2)	4.6 (7)
	Nausea	4.0 (4)	5.8 (3)	4.6 (7)
Injury, poisoning, and procedural complications	Accidental overdose	6.0 (6)	3.8 (2)	5.3 (8)
General disorders and administration site conditions	Fatigue	3.0 (3)	7.7 (4)	4.6 (7)
Psychiatric disorders	Depression	0 (0)	7.7 (4)	2.6 (4)
Respiratory, thoracic, and mediastinal disorders	Asthma	0 (0)	5.8 (3)	2.0 (3)

TFN: Teriflunomide; PBO: Placebo
Source: Trial EFC11759 ADAE where SAF02FL and TRTEMFL ='Y' by ACTARM.

Adverse event severity during the OLE period is tabulated by treatment group in Table 39.

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Table 39 (Reviewer). Adverse Event Severity During Open-Label Treatment, Trial EFC11759

Severity	Teriflunomide-Teriflunomide (n = 100)	Placebo-Teriflunomide (n = 52)	Overall (n = 152)
Mild	41.0 (41)	32.7 (17)	38.2 (58)
Moderate	20.0 (20)	40.4 (21)	27.0 (41)
Severe	7.0 (7)	9.6 (5)	7.9 (12)
Total	**68.0 (68)**	**82.7 (43)**	**73.0 (111)**

Source: Trial EFC11759 ADAE where SAF02FL and TRTEMFL ='Y' by ACTARM.

A review of all TEAEs using MedDRA search terms grouped using logical clinical associations of disorders was also conducted. The results of this analysis for TEAEs reported by at least 5% of patients are presented in Table 40. Overall, the results are similar to that of the DBT period, with infections being the most common TEAEs. Alopecia and hepatic injury were more common in the placebo-teriflunomide group during the OLE period, suggesting that these events may be more likely to occur early in the course of treatment.

Table 40 (Reviewer). Safety Grouping Analysis of TEAEs, Open-Label Period

Grouping Term	Teriflunomide-Teriflunomide (n = 100)	Placebo-Teriflunomide (n = 52)	Overall (n = 152)
Infection, all	49.0 (49)	44.2 (23)	47.4 (72)
URI, cold, rhinitis, upper respiratory tract infection, flu-like illness	43.0 (43)	28.8 (15)	38.2 (58)
Alopecia	9.0 (9)	17.3 (9)	11.8 (18)
Diarrhea, colitis, enteritis, proctitis, gastroenteritis, C. diff	10.0 (10)	13.5 (7)	11.2 (17)
Headache	12.0 (12)	9.6 (5)	11.2 (17)
Infection, viral	7.0 (7)	17.3 (9)	10.5 (16)
Abdominal pain, distension, bloating, spasm, IBS, megacolon	9.0 (9)	9.6 (5)	9.2 (14)
GOT, GPT, GGTP, LFTs (Hepatic injury)	4.0 (4)	15.4 (8)	7.9 (12)
Fall, dizziness, balance disorder, gait disturbance, difficulty walking	3.0 (3)	17.3 (9)	7.9 (12)
Asthenia, fatigue, malaise, weakness, narcolepsy	4.0 (4)	13.5 (7)	7.2 (11)
Dyspepsia, nausea, vomiting, indigestion, epigastric pain, gastritis	6.0 (6)	9.6 (5)	7.2 (11)
Nausea, vomiting	5.0 (5)	7.7 (4)	5.9 (9)
Eye other	6.0 (6)	5.8 (3)	5.9 (9)
Dizziness, lightheadedness	2.0 (2)	11.5 (6)	5.3 (8)
Influenza	4.0 (4)	7.7 (4)	5.3 (8)
Somnolence, fatigue, sedation	3.0 (3)	9.6 (5)	5.3 (8)

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120 Day Safety Update

During the interval from November 28, 2019 through December 1, 2020, 55 patients (36.2%) experienced a TEAE. The frequency of infections was similar between the groups (23.1% placebo-teriflunomide versus 19.0% teriflunomide-teriflunomide). Hepatic disorder TEAEs occurred in 2.6% (n= 4) of patients during the reporting interval, including 1 case of DILI and 1 case of hepatic steatosis. Two additional cases of pancreatic disorders were reported (1 pancreatitis acute, reported as SAE, and amylase increased) among patients in the teriflunomide-teriflunomide group. One additional TEAE of neutropenia occurred in a teriflunomide-teriflunomide patient, and 2 patients (1 in each group) experienced neutrophil count decreased. WBC count decreased also occurred in 1 patient in the teriflunomide-teriflunomide group.

> ***Reviewer comment:*** *Overall, the TEAEs that occurred in the 120 Day Safety Update reporting interval were similar to that in the original submission. No new safety concerns were identified.*

8.4.6. Laboratory Findings

Laboratory data from ADAE were analyzed and reviewed for the DBT and OLE periods. This analysis will focus on laboratory parameters of interest that were identified based on prior knowledge of the safety profile of teriflunomide in adults, as well as the adverse event data presented for Trial EFC11759. Laboratory values were evaluated at each scheduled timepoint (designated by sponsor's ANL01FL=Y in ADLB dataset), and descriptive analyses (including analyses of change from baseline) are presented for Baseline, Week 4, Week 24, Week 48, and Week 96 of the DBT period. OLE data were also reviewed for overall consistency with DBT period findings. Laboratory data collected via local laboratories or outside of scheduled study visits are discussed in the context of adverse events.

Hematology

Leukocyte Count

Teriflunomide is known to decrease leukocytes, including lymphocytes and neutrophils. In placebo-controlled trials of adults with relapsing MS, patients on teriflunomide had a 15% mean decrease in WBCs the first 6 weeks of treatment and WBCs remained low during treatment.

Overall leukocyte count (# cells $x10^9$/L) were evaluated at each visit during DBT, with representative timepoints shown in Table 41. Shift analyses indicated that 7.3% of patients on teriflunomide (n = 8) and 1.8% of patients on placebo (n = 1) experienced decreased leukocyte count from baseline values of >$3x10^9$/L to 1.5-3 x 10^9/L.

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Shift analysis for the combined DBT plus OLE periods indicated that patients in the teriflunomide-teriflunomide group were more likely to experience leukocyte count <3.0 x 10^9/L than those on placebo-teriflunomide (15.0% versus 7.7%, respectively). This observation suggests that the incidence of leukopenia with teriflunomide could increase with prolonged use.

Please refer to Section 8.5.3 for discussion of TEAEs related to leukocyte count (e.g., leukopenia).

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Table 41 (Reviewer). Trial EFC11759 Leukocyte Count (x10^9/L) Over Time, Double-Blind Period

Time	Parameter	Teriflunomide (n = 109)	Placebo (n = 57)
Baseline	Mean (SD)	6.8 (2.4)	6.3 (1.4)
	Median	6.1	6.2
	Min, Max	3.2, 14.9	3.7, 9.6
Week 4	N	108	56
	Mean (SD)	6.3 (2.4)	7.1 (4.2)
	Median	5.9	6.2
	Min, Max	2.8, 15.1	3.6, 32.5
	Mean (SD) change from baseline	-0.5 (2.5)	0.9 (3.8)
	Median change from baseline	-0.6	-0.1
	Min, Max change from baseline	-10.3, 7.7	-3.8, 24.4
	% (n) of patients with WBC 1.5 to 3.0 x10^9/L	1.9 (2)	0 (0)
	% (n) of patients with WBC ≤ 1.5 x10^9/L	0 (0)	0 (0)
Week 24	N	100	44
	Mean (SD)	5.7 (1.8)	6.3 (1.6)
	Median	5.4	5.8
	Min, Max	3.0, 11.9	3.1, 10.3
	Mean (SD) change from baseline	-1.1 (2.1)	0.03 (1.9)
	Median change from baseline	-0.9	0.3
	Min, Max change from baseline	-10.2, 4.6	-4.0, 5.3
	% (n) of patients with WBC 1.5 to 3.0 x10^9/L	0 (0)	0 (0)
	% (n) of patients with WBC ≤ 1.5 x10^9/L	0 (0)	0 (0)
Week 48	N	73	24
	Mean (SD)	5.7 (1.5)	6.7 (2.4)
	Median	5.5	6.2
	Min, Max	3.2, 10.2	3.6, 12.4
	Mean (SD) change from baseline	-1.2 (2.2)	0.6 (2.2)
	Median change from baseline	-0.8	0.04
	Min, Max change from baseline	-11.5, 1.4	-1.7, 6.5
	% (n) of patients with WBC 1.5 to 3.0 x10^9/L	0 (0)	0 (0)
	% (n) of patients with WBC ≤ 1.5 x10^9/L	0 (0)	0 (0)
Week 96	N	50	14
	Mean (SD)	5.7 (1.6)	6.5 (1.8)
	Median	5.4	5.9
	Min, Max	3.1, 9.2	4.6, 10.9
	Mean (SD) change from baseline	-0.8 (1.8)	0.05 (1.0)
	Median change from baseline	-0.7	-0.3
	Min, Max change from baseline	-8.2, 4.1	-1.3, 1.9
	% (n) of patients with WBC 1.5 to 3.0 x10^9/L	0 (0)	0 (0)
	% (n) of patients with WBC ≤ 1.5 x10^9/L	0 (0)	0 (0)

Source: ADLB where SAF01FL=Y, APERIOD = 1, ANL01FL=Y, by ACTARM.

Neutrophils

In placebo-controlled trials of adults with relapsing MS, absolute neutrophil count <1.5 x 10^9/L occurred in 12% of those on teriflunomide 7mg and 16% on teriflunomide 14mg, compared to 7% on placebo.

Absolute neutrophil count (# cells x10^9/L) were evaluated at each visit during DBT, with representative timepoints shown in Table 42. Patients on teriflunomide during DBT experienced lower ANC compared to those on placebo (Figure 14).

Shift analyses indicated that 12.8% of patients on teriflunomide (n = 14) and 10.7% of patients on placebo (n = 6) who had baseline ANC >1.5 x10^9/L experienced ANC of 1.0 to 1.5 x10^9/L during DBT. Additionally, 4.6% of patients on teriflunomide (n = 5) experienced ANC 0.5 to 1.0 x10^9/L during DBT from a baseline ANC >1.5 x10^9/L, compared to 0 patients on placebo.

Shift analysis for the combined DBT plus OLE periods indicated that the proportion of patients experiencing ANC <1.0 x10^9/L was similar between the teriflunomide-teriflunomide and placebo-teriflunomide groups (28.0% versus 32.7%, respectively). Additionally, the proportion of patients experiencing ANC <0.5 x 10^9/L was similar between the groups.

Please refer to Section 8.5.3 for discussion of TEAEs related to neutrophil count (e.g., neutropenia).

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Table 42 (Reviewer). Trial EFC11759 Neutrophil Count (x10^9/L) Over Time, Double-Blind Period

Time	Parameter	Teriflunomide (n = 109)	Placebo (n = 57)
Baseline	Mean (SD)	4.1 (2.1)	3.6 (1.3)
	Median	3.5	3.4
	Min, Max	1.3, 12.5	1.4, 6.2
Week 4	N	108	56
	Mean (SD)	3.7 (1.9)	4.2 (3.0)
	Median	3.5	3.4
	Min, Max	1.0, 12.5	1.2, 19.5
	Mean (SD) change from baseline	-0.4 (2.3)	0.6 (2.7)
	Median change from baseline	-0.3	-0.01
	Min, Max change from baseline	-9.6, 7.4	-2.9, 13.8
	% (n) of patients with ANC ≤ 1.0 x 10^9/L	0 (0)	0 (0)
	% (n) of patients with ANC ≤ 0.5 x 10^9/L	0 (0)	0 (0)
Week 24	N	100	44
	Mean (SD)	3.3 (1.5)	3.7 (1.3)
	Median	3.0	3.4
	Min, Max	1.0, 8.4	1.5, 7.0
	Mean (SD) change from baseline	-0.9 (2.1)	0.03 (1.5)
	Median change from baseline	-0.6	0.2
	Min, Max change from baseline	-9.7, 5.3	-3.2, 3.6
	% (n) of patients with ANC ≤ 1.0 x 10^9/L	1.0 (1)	0 (0)
	% (n) of patients with ANC ≤ 0.5 x 10^9/L	0 (0)	0 (0)
Week 48	N	73	24
	Mean (SD)	3.2 (1.2)	3.9 (2.1)
	Median	3.0	3.3
	Min, Max	1.2, 7.0	1.7, 8.8
	Mean (SD) change from baseline	-1.0 (2.0)	0.5 (2.1)
	Median change from baseline	-0.6	0.1
	Min, Max change from baseline	-10.6, 1.1	-1.9, 6.3
	% (n) of patients with ANC ≤ 1.0 x 10^9/L	0 (0)	0 (0)
	% (n) of patients with ANC ≤ 0.5 x 10^9/L	0 (0)	0 (0)
Week 96	N	50	14
	Mean (SD)	3.3 (1.3)	3.9 (1.8)
	Median	2.9	3.5
	Min, Max	1.0, 6.0	1.9, 8.5
	Mean (SD) change from baseline	-0.6 (1.8)	0.2 (1.2)
	Median change from baseline	-0.4	0.2
	Min, Max change from baseline	-7.7, 3.4	-1.3, 3.3
	% (n) of patients with ANC ≤ 1.0 x 10^9/L	0 (0)	0 (0)
	% (n) of patients with ANC ≤ 0.5 x 10^9/L	0 (0)	0 (0)

Source: ADLB where SAF01FL=Y, APERIOD = 1, ANL01FL=Y, by ACTARM.

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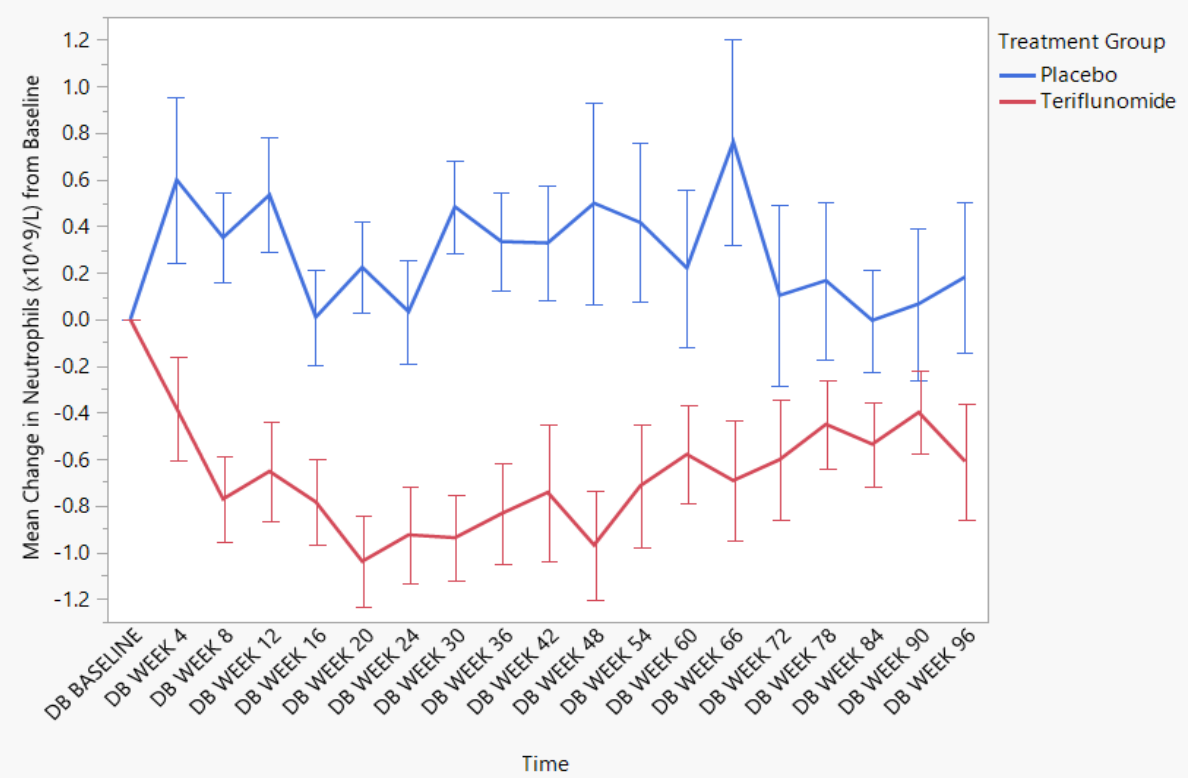
Figure 14 (Reviewer). Mean Change in Neutrophils (x10^9/L) from Baseline Over Double-Blind Period, Trial EFC11759



Source: ADLB where APERIOD=1, ANL01FL=1, PARAMCD = NEUT, by ACTARM

Lymphocytes

In placebo-controlled trials of adults with relapsing MS, absolute lymphocyte count <0.8 x 10^9/L occurred in 10% of those on teriflunomide 7mg and 12% on teriflunomide 14mg, compared to 6% on placebo.

Absolute lymphocyte count (# cells x10^9/L) were evaluated at each visit during DBT, with representative timepoints shown in Table 42. Patients on teriflunomide during DBT experienced decreased ALC compared to those on placebo (

Figure **15**).

Shift analyses indicated that 12.8% of patients on teriflunomide (n = 14) and 5.4% of patients on placebo (n = 3) with baseline ALC >1.0 x10^9/L experienced ALC 0.5 to 1.0 x10^9/L during DBT.

Shift analysis for the combined DBT plus OLE periods indicated that patients in the teriflunomide-teriflunomide group were more likely to experience ALC <1.0 x 10^9/L than those

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on placebo-teriflunomide (31.0% versus 23.1%, respectively). This observation suggests that the incidence of lymphopenia with teriflunomide could increase with prolonged use.

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Table 43 (Reviewer). Trial EFC11759 Lymphocyte Count (x10^9/L) Over Time, Double-Blind Period

Time	Parameter	Teriflunomide (n = 109)	Placebo (n = 57)
Baseline	Mean (SD)	2.1 (0.6)	2.1 (0.6
	Median	2.0	2.0
	Min, Max	1.0, 4.0	1.0, 3.5
Week 4	N	108	56
	Mean (SD)	1.9 (0.6)	2.3 (1.0)
	Median	1.8	2.1
	Min, Max	0.9, 4.7	1.1, 7.8
	Mean (SD) change from baseline	-0.1 (0.5)	0.2 (0.9)
	Median change from baseline	-0.1	0.2
	Min, Max change from baseline	-2.1, 2.3	-1.5, 5.9
	% (n) of patients with ALC ≤ 1.0 x 10^9/L	2.8 (3)	0 (0)
	% (n) of patients with ALC ≤ 0.5 x 10^9/L	0 (0)	0 (0)
Week 24	N	100	44
	Mean (SD)	1.9 (0.5)	2.1 (0.5)
	Median	1.9	2.0
	Min, Max	0.7, 3.3	1.2, 3.5
	Mean (SD) change from baseline	-0.2 (0.5)	0.01 (0.5)
	Median change from baseline	-0.2	0.03
	Min, Max change from baseline	-1.6, 1.0	-1.4, 1.4
	% (n) of patients with ALC ≤ 1.0 x 10^9/L	1.0 (1)	0 (0)
	% (n) of patients with ALC ≤ 0.5 x 10^9/L	0 (0)	0 (0)
Week 48	N	73	24
	Mean (SD)	1.9 (0.5)	2.2 (0.7)
	Median	1.8	2.2
	Min, Max	1.0, 3.2	1.2, 3.5
	Mean (SD) change from baseline	-0.2 (0.5)	0.1 (0.5)
	Median change from baseline	-0.2	0.15
	Min, Max change from baseline	-1.4, 0.8	-1.1, 1.0
	% (n) of patients with ALC ≤ 1.0 x 10^9/L	2.7 (2)	0 (0)
	% (n) of patients with ALC ≤ 0.5 x 10^9/L	0 (0)	0 (0)
Week 96	N	50	14
	Mean (SD)	1.9 (0.5)	2.0 (0.6)
	Median	1.8	1.9
	Min, Max	0.7, 3.4	1.3, 3.2
	Mean (SD) change from baseline	-0.2 (0.5)	-0.1 (0.7)
	Median change from baseline	-0.3	0.1
	Min, Max change from baseline	-1.3, 0.9	-1.4, 0.8
	% (n) of patients with ALC ≤ 1.0 x 10^9/L	2.0 (1)	0 (0)
	% (n) of patients with ALC ≤ 0.5 x 10^9/L	0 (0)	0 (0)

Source: ADLB where SAF01FL=Y, APERIOD = 1, ANL01FL=Y, by ACTARM.

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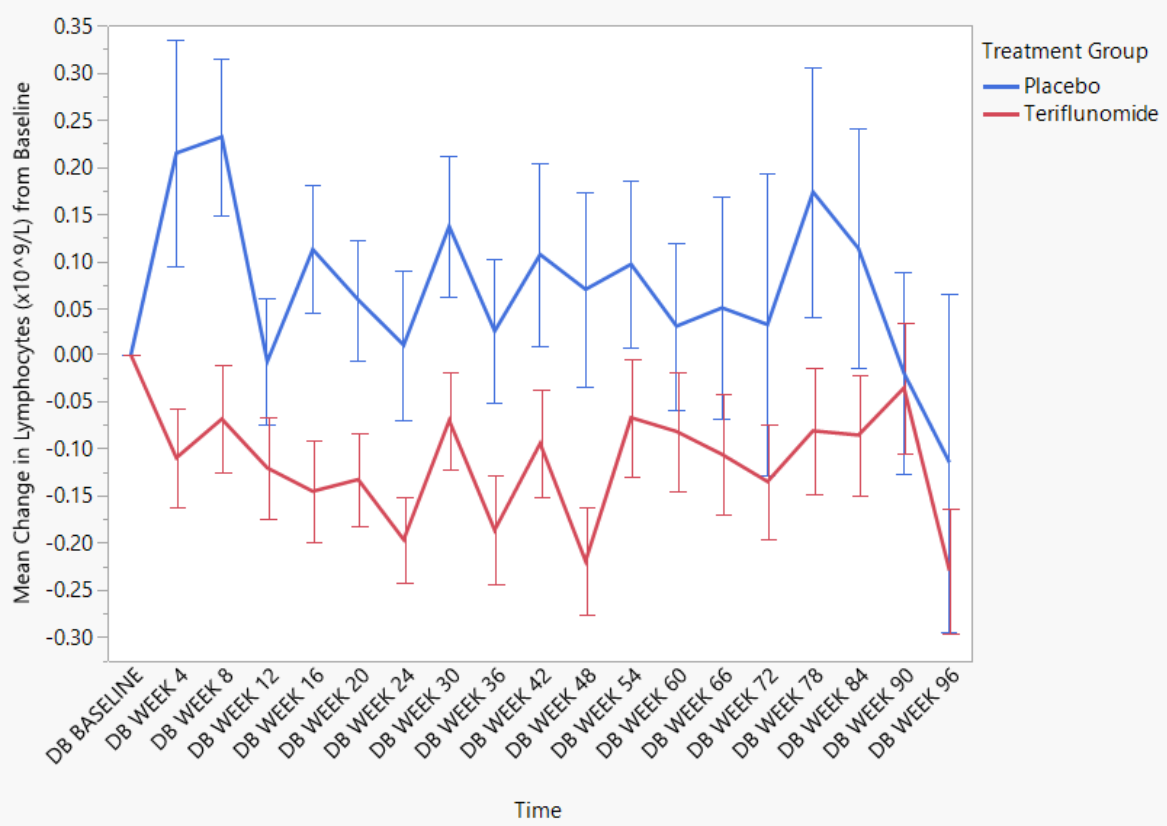
Figure 15 (Sponsor). Trial EFC11759 Mean Change in Lymphocyte Count (x10^9/L) from Baseline, Double-Blind Period



Source: ADLB where APERIOD=1, ANL01FL=1, PARAMCD = LYM, by ACTARM

Platelets

Thrombocytopenia, including rare cases of platelet counts <50 x10^9/L, has been reported with teriflunomide in the postmarketing setting.

In Trial EFC11759, patients on teriflunomide during DBT experienced decreased platelet count compared to those on placebo (Table 44, Figure 16). However, no TEAEs related to platelet count (e.g., thrombocytopenia, platelet count decreased) were reported. No patients with platelet count <50 x10^9/L were reported.

Shift analyses indicated that a similar proportion of patients with baseline platelets >150 x10^9/L on teriflunomide and placebo experienced a platelet count between 100 and 150 x10^9/L during DBT (7.3% versus 7.1%, respectively). However, patients on teriflunomide were more likely to experience a platelet count between 50 and 100 x10^9/L compared to those on placebo (1.8% versus 0%, respectively).

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As discussed in Section 8.4.5, 1 case of PT gastrointestinal hemorrhage, described as "hemorrhage of lower digestive tract-mild" occurred in 1 patient on teriflunomide (Subject ID (b) (6)). At baseline, this patient had a platelet count of 150 to 155 $x10^9$/L. His platelet counts ranged from 111 to 128 $x10^9$/L over DBT weeks 12 through 24. At the time of this AE, his platelet count was normal (151 $x10^9$/L at Week 42 and 177 $x10^9$/L at Week 54). The nature of this AE is unclear based on CRF review, but the CRF also mentions "topical polyps" without a specified location.

Shift analysis for the combined DBT plus OLE periods indicated that patients in the teriflunomide-teriflunomide group were more likely to experience platelet count <100 x 10^9/L than those on placebo-teriflunomide (3.0% versus 0%, respectively). This observation suggests that the incidence of the reduction in platelet counts observed with teriflunomide could increase with prolonged use. However, the proportions of patients with platelet counts 100 to 150 $x10^9$/L were similar between the groups.

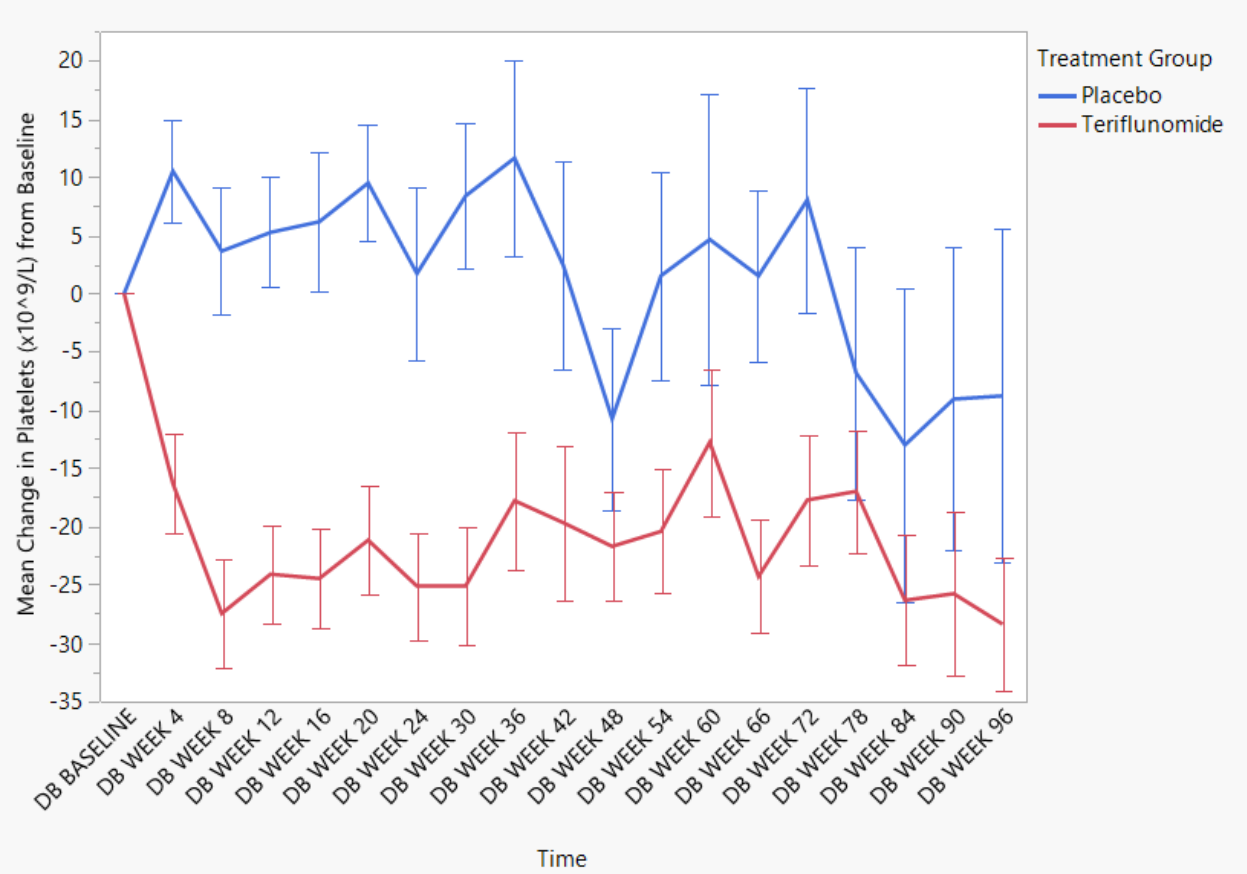
Reference ID: 4776272

Table 44 (Reviewer). Trial EFC11759 Platelet Count (x10^9/L) Over Time, Double-Blind Period

Time	Parameter	Teriflunomide (n = 109)	Placebo (n = 57)
Baseline	Mean (SD)	270.5 (58.8)	262.7 (60.0)
	Median	266.0	254.0
	Min, Max	150.0, 414.0	161.0, 420.0
Week 4	N	107	56
	Mean (SD)	255.3 (62.9)	274.4 (65.1)
	Median	249.0	270.5
	Min, Max	99.0, 436.0	150.0, 399.9
	Mean (SD) change from baseline	-16.3 (44.0)	10.5 (33.1)
	Median change from baseline	-18.0	12.5
	Min, Max change from baseline	-133.0, 124.0	-54.0, 67.0
	% (n) of patients with Platelets 100 to 150 x10^9/L	0.9 (1)	1.8 (1)
	% (n) of patients with Platelets 50 to 100 x10^9/L	0.9 (1)	0 (0)
Week 24	N	100	43
	Mean (SD)	245.7 (62.1)	265.1 (64.4)
	Median	242.5	263.0
	Min, Max	117.0, 394.0	147.0, 446.0
	Mean (SD) change from baseline	-25.1 (46.0)	1.7 (48.5)
	Median change from baseline	-32.0	1.0
	Min, Max change from baseline	-139, 93.0	-88.0, 200.0
	% (n) of patients with Platelets 100 to 150 x10^9/L	5.0 (5)	2.3 (1)
	% (n) of patients with Platelets 50 to 100 x10^9/L	0 (0)	0 (0)
Week 48	N	72	24
	Mean (SD)	251.3 (59.1)	248.6 (64.6)
	Median	248.0	230.5
	Min, Max	136.0, 377.0	127.0, 434.0
	Mean (SD) change from baseline	-21.7 (39.7)	-10.8 (38.4)
	Median change from baseline	-26.5	-7.0
	Min, Max change from baseline	-93.0, 89.0	-92.0, 53.0
	% (n) of patients with Platelets 100 to 150 x10^9/L	4.2 (3)	4.2 (1)
	% (n) of patients with Platelets 50 to 100 x10^9/L	0 (0)	0 (0)
Week 96	N	50	14
	Mean (SD)	241.7 (53.5)	262.9 (61.1)
	Median	239.5	260.5
	Min, Max	147.0, 368.0	125.0, 360.0
	Mean (SD) change from baseline	-28.4 (40.1)	-8.8 (53.5)
	Median change from baseline	-28.5	-23.5
	Min, Max change from baseline	-122.0, 75.0	-80.0, 86.0
	% (n) of patients with Platelets 100 to 150 x10^9/L	2.0 (1)	7.1 (1)
	% (n) of patients with Platelets 50 to 100 x10^9/L	0 (0)	0 (0)

Source: ADLB where SAF01FL=Y, APERIOD = 1, ANL01FL=Y, by ACTARM.

Figure 16 (Reviewer). Trial EFC11759 Mean Change in Platelet Count (x10^9/L) from Baseline, Double-Blind Period



Source: ADLB where APERIOD=1, ANL01FL=1, PARAMCD = PLAT, by ACTARM

Hemoglobin

Overall, the mean change from baseline in hemoglobin was similar between the teriflunomide and placebo groups during DBT (Table 45). Two patients on teriflunomide (1.8%) and 1 patient on placebo (1.8%) experienced hemoglobin <100 g/L during DBT. Both teriflunomide patients experienced this value at Week 4. However, per the sponsor's analysis, 8.3% of patients on teriflunomide (n = 9) and 1.8% of patients on placebo (n = 1) experienced a decrease from baseline of ≥20 g/L.

Reference ID: 4776272

Table 45 (Reviewer). Trial EFC11759 Hemoglobin (g/L) Over Time, Double-Blind Period

Time	Parameter	Teriflunomide (n = 109)	Placebo (n = 57)
Baseline	Mean (SD)	136.8 (12.5)	134.1 (12.7)
	Median	137.0	132.0
	Min, Max	104.0, 173.0	109.0, 165.0
Week 4	N	108	56
	Mean (SD)	138.0 (13.5)	134.1 (13.0)
	Median	139.0	133.5
	Min, Max	94.0, 179.0	103.0, 165.0
	Mean (SD) change from baseline	1.3 (7.6)	0.6 (5.3)
	Median change from baseline	2.0	0.5
	Min, Max change from baseline	-24.0, 29.0	-10.0, 11.0
Week 24	N	100	44
	Mean (SD)	135.4 (12.7)	132.5 (12.5)
	Median	134.0	131.0
	Min, Max	108.0, 180.0	113.0, 159.0
	Mean (SD) change from baseline	-1.4 (7.8)	-1.8 (6.2)
	Median change from baseline	-1.0	-1.0
	Min, Max change from baseline	-22.0, 20.0	-15.0, 12.0
Week 48	N	73	24
	Mean (SD)	135.4 (11.9)	131.6 (14.3)
	Median	133.0	130.5
	Min, Max	115.0, 176.0	111.0, 156.0
	Mean (SD) change from baseline	-1.5 (8.2)	-1.1 (7.4)
	Median change from baseline	0.0	-1.5
	Min, Max change from baseline	-21.0, 21.0	-13.0, 24.0
Week 96	N	50	14
	Mean (SD)	136.8 (14.4)	135.1 (13.0)
	Median	134.5	134.5
	Min, Max	108.0, 169.0	115.0, 156.0
	Mean (SD) change from baseline	-0.8 (10.5)	-1.9 (5.7)
	Median change from baseline	-1.0	-2.0
	Min, Max change from baseline	-23.0, 32.0	-12.0, 9.0

Hepatobiliary

Hepatotoxicity and drug-induced liver injury are significant safety concerns for teriflunomide, as it carries a boxed warning for hepatotoxicity. Liver-related laboratory parameters (AST, ALT, ALP, and total bilirubin) were descriptively analyzed by visit, including the change from baseline, for each treatment group. Additionally, patients with specified thresholds of abnormalities for each parameter (e.g., >2x ULN) at individual visits and across the DBT period were tabulated by treatment group.

Please refer to Section 8.5.2 for further discussion of hepatic disorders and hepatotoxicity.

Reference ID: 4776272

ALT (IU/L)

Overall, patients on teriflunomide experienced a mean increase in ALT during DBT compared to the placebo group (Table 46, Figure 17). At Week 24, the mean (SD) change in ALT from baseline was 6.6 (16.8) for the teriflunomide group and -0.1 (4.1) for the placebo group. Additionally, a higher proportion of patients in the teriflunomide group (4.6%, n= 5) with baseline values <2x ULN experienced ALT 2 to 5x ULN compared to those on placebo (0%, n = 0).

During DBT, 1 patient was documented as having ALT >10x ULN (*Subject ID* (b) (6)), with ALT at 12.0x ULN at Week 60. This event occurred in the setting of a road traffic accident and is discussed in Section 8.4.2.1. This value was reported by a local laboratory and is therefore not captured in the main DBT analysis.

OLE period data indicated that patients starting on teriflunomide at the start of the open-label period had a higher mean (SD) change in ALT at week 4 than those who continued on teriflunomide (9.5 (28.0) versus 3.0 (10.3) IU/L). This trend continued at most OLE timepoints, but stabilized over time. After OLE Week 108, the mean ALT change from baseline became higher in the teriflunomide-teriflunomide group.

> ***Reviewer comment:*** *After OLE Week 108, the mean ALT change from baseline became higher in the teriflunomide-teriflunomide group, potentially indicating a higher risk of hepatotoxicity with prolonged use. However, the number of patients remaining on teriflunomide is extremely low, so it is difficult to make a reliable assessment of this phenomenon.*

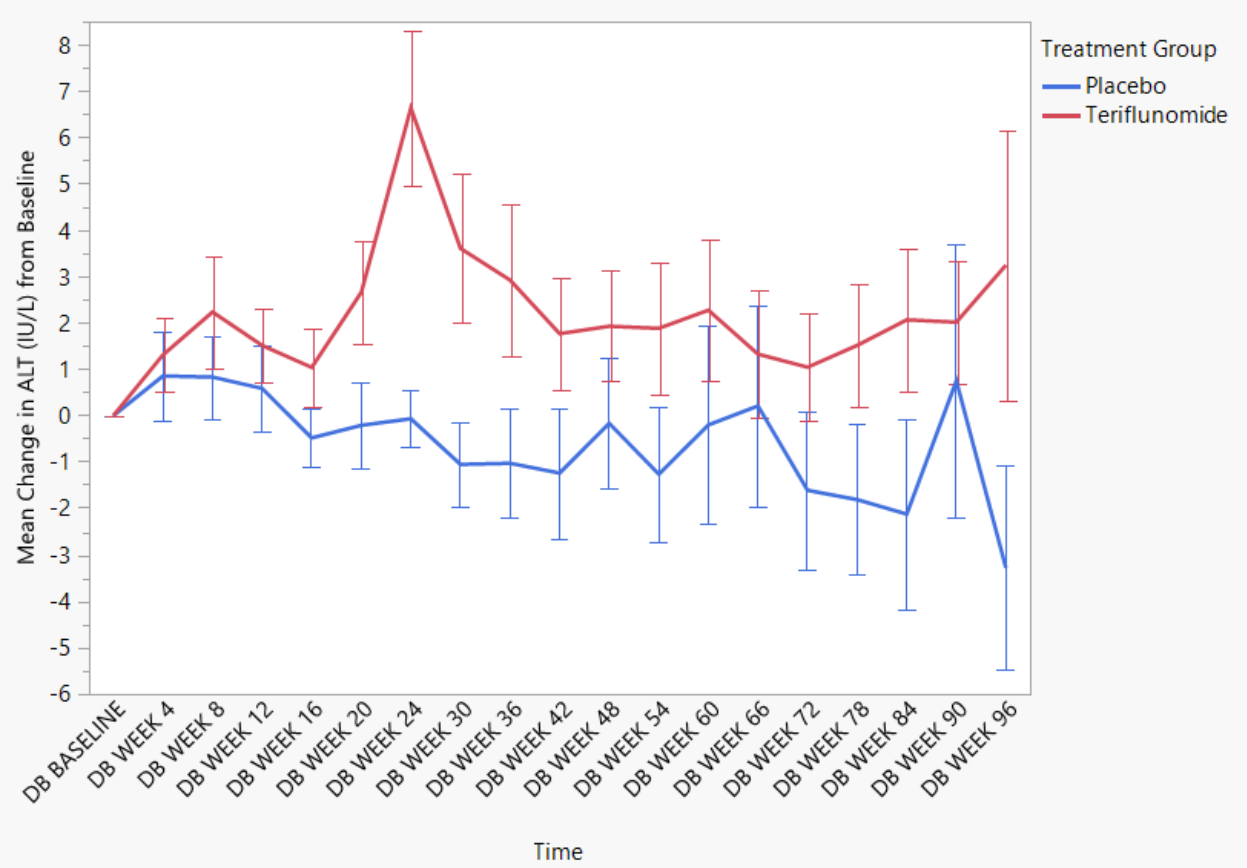
Shift analyses for the combined DBT plus OLE periods indicated that patients in the placebo-teriflunomide group were more likely to experience ALT>2x ULN compared to the teriflunomide-teriflunomide group (19.2% versus 8.0%, respectively).

Table 46 (Reviewer). Trial EFC11759 ALT (IU/L) Over Time, Double-Blind Period

Time	Parameter	Teriflunomide (n = 109)	Placebo (n = 57)
Baseline	Mean (SD)	14.4 (8.2)	13.6 (7.3)
	Median	12.0	12.0
	Min, Max	7.0, 54.0	5.0, 46.0
Week 4	N	109	56
	Mean (SD)	15.7 (8.7)	14.6 (10.2)
	Median	13.0	11.0
	Min, Max	6.0, 57.0	4.0, 51.0
	Mean (SD) change from baseline	1.3 (8.2)	0.9 (7.2)
	Median change from baseline	1.0	0.0
	Min, Max change from baseline	-40.0, 37.0	-7.0, 44.0
	% (n) of patients with ALT >2x ULN	0 (0)	0 (0)
	% (n) of patients with ALT >5x ULN	0 (0)	0 (0)
Week 24	N	100	45
	Mean (SD)	21.4 (18.0)	14.2 (8.5)
	Median	15.0	12.0
	Min, Max	6.0, 95.0	5.0, 50.0
	Mean (SD) change from baseline	6.6 (16.8)	-0.1 (4.1)
	Median change from baseline	3.5	0
	Min, Max change from baseline	-38.0, 79.0	-9.0, 12.0
	% (n) of patients with ALT >2x ULN	3.0 (3)	0 (0)
	% (n) of patients with ALT >5x ULN	0 (0)	0 (0)
Week 48	N	72	24
	Mean (SD)	16.8 (8.9)	15.0 (7.5)
	Median	14.0	14.0
	Min, Max	7.0, 64.0	6.0, 34.0
	Mean (SD) change from baseline	1.9 (10.1)	-0.17 (6.9)
	Median change from baseline	2.0	-2.5
	Min, Max change from baseline	-34.0, 42.0	-9.0, 16.0
	% (n) of patients with ALT >2x ULN	0 (0)	0 (0)
	% (n) of patients with ALT >5x ULN	0 (0)	0 (0)
Week 96	N	52	14
	Mean (SD)	18.1 (20.8)	13.9 (8.4)
	Median	13.0	11.5
	Min, Max	7.0, 155.0	5.0, 29.0
	Mean (SD) change from baseline	3.3 (21.1)	-3.3 (8.2)
	Median change from baseline	21.1	-4.5
	Min, Max change from baseline	-28.0, 141.0	-14.0, 15.0
	% (n) of patients with ALT >2x ULN	1.9 (1)	0 (0)
	% (n) of patients with ALT >5x ULN	0 (0)	0 (0)

Source: ADLB where SAF01FL=Y, APERIOD = 1, ANL01FL=Y, by ACTARM.

Figure 17 (Reviewer). Trial EFC11759 Mean Change in ALT (IU/L) from Baseline, Double-Blind Period



Source: ADLB where APERIOD=1, ANL01FL=1, PARAMCD = ALT, by ACTARM

AST (IU/L)

The mean AST change from baseline was higher in the teriflunomide group than the placebo group for Weeks 24, 48, and 96 (Table 47). Additionally, a higher proportion of patients in the teriflunomide group experienced increased AST compared to those on placebo.

During DBT, 1 patient was documented as having AST >5x ULN (Subject ID [redacted] (b) (6)), with AST at 7.3x ULN at Double Blind Treatment Week 36. This patient is discussed in Section 8.4.4.

Shift analyses indicated that 0 patients on placebo had AST >2x ULN during DBT, but 0.9% of patients on teriflunomide (n = 1) experienced AST 2 to 5x ULN and 0.9% (n = 1) experienced AST 5-10x ULN during DBT.

Reference ID: 4776272

Similar to ALT, OLE period data indicated that patients starting on teriflunomide at the start of the open-label period had a slightly higher mean (SD) change in AST at week 4 than those who continued on teriflunomide (1.8 (9.0) versus 0.4 (6.4) IU/L). This trend continued at most OLE timepoints, but stabilized over time. However, similar to ALT, after OLE Week 108, the mean AST change from baseline became higher in the teriflunomide-teriflunomide group, potentially indicating a higher risk of hepatotoxicity with prolonged use.

Shift analyses for the combined DBT plus OLE periods indicated that patients in the teriflunomide-teriflunomide group were more likely to experience AST>2x ULN compared to the placebo-teriflunomide group (7.0% versus 1.9%, respectively).

Table 47 (Reviewer). Trial EFC11759 AST (IU/L) Over Time, Double-Blind Period

Time	Parameter	Teriflunomide (n = 109)	Placebo (n = 57)
Baseline	Mean (SD)	17.7 (5.4)	17.4 (4.4)
	Median	17.0	17.0
	Min, Max	10.0, 39.0	9.0, 30.0
Week 4	N	108	56
	Mean (SD)	17.6 (5.1)	17.7 (5.5)
	Median	16.5	17.0
	Min, Max	10.0, 37.0	9.0, 35.0
	Mean (SD) change from baseline	-0.1 (5.5)	0.3 (3.9)
	Median change from baseline	0.0	0.0
	Min, Max change from baseline	-25.0, 16.0	-7.0, 12.0
	% (n) of patients with AST >2x ULN	0 (0)	0 (0)
	% (n) of patients with AST >5x ULN	0 (0)	0 (0)
Week 24	N	100	44
	Mean (SD)	20.4 (10.2)	16.8 (4.4)
	Median	18.0	16.0
	Min, Max	12.0, 82.0	8.0, 27.0
	Mean (SD) change from baseline	2.5 (9.6)	-0.7 (3.3)
	Median change from baseline	1.5	0.0
	Min, Max change from baseline	-21.0, 61.0	-8.0, 6.0
	% (n) of patients with AST >2x ULN	1.0 (1)	0 (0)
	% (n) of patients with AST >5x ULN	0 (0)	0 (0)
Week 48	N	72	24
	Mean (SD)	18.6 (5.4)	17.2 (3.9)
	Median	17.0	17.5
	Min, Max	11.0, 42.0	10.0, 28.0
	Mean (SD) change from baseline	0.9 (6.1)	-0.8 (5.2)
	Median change from baseline	1.0	-2.0
	Min, Max change from baseline	-16.0, 18.0	-7.0, 14.0
	% (n) of patients with AST >2x ULN	0 (0)	0 (0)
	% (n) of patients with AST >5x ULN	0 (0)	0 (0)
Week 96	N	52	14
	Mean (SD)	18.3 (7.5)	16.5 (3.2)
	Median	17.0	16.5
	Min, Max	11.0, 58.0	12.0, 22.0
	Mean (SD) change from baseline	0.6 (8.4)	-2.9 (4.3)
	Median change from baseline	0.0	-3.5
	Min, Max change from baseline	-18.0, 42.0	-8.0, 5.0
	% (n) of patients with AST >2x ULN	0 (0)	0 (0)
	% (n) of patients with AST >5x ULN	0 (0)	0 (0)

Source: ADLB where SAF01FL=Y, APERIOD = 1, ANL01FL=Y, by ACTARM.

Total Bilirubin (IU/L)

No consistent trends regarding total bilirubin over DBT were observed in patients on teriflunomide compared to those on placebo (Table 48). No patients experienced total bilirubin >2x ULN during the DBT or OLE periods.

Table 48 (Reviewer). Trial EFC11759 Total Bilirubin (IU/L) Over Time, Double-Blind Period

Time	Parameter	Teriflunomide (n = 109)	Placebo (n = 57)
Baseline	Mean (SD)	8.2 (5.5)	8.9 (5.0)
	Median	6.8	8.6
	Min, Max	1.7, 44.5	1.7, 22.2
	% (n) of patients with T. bilirubin >2x ULN	0.9 (1)	0 (0)
Week 4	N	109	56
	Mean (SD)	8.4 (4.9)	8.0 (4.3)
	Median	6.8	6.8
	Min, Max	1.7, 37.6	-1.7, 22.2
	Mean (SD) change from baseline	0.2 (3.8)	-0.9 (3.7)
	Median change from baseline	0.0	0.0
	Min, Max change from baseline	-15.4, 10.3	-12.0, 5.1
	% (n) of patients with T. bilirubin >2x ULN	0 (0)	0 (0)
Week 24	N	100	45
	Mean (SD)	8.7 (5.2)	8.1 (4.9)
	Median	6.8	6.8
	Min, Max	1.7, 35.9	1.7, 23.9
	Mean (SD) change from baseline	0.5 (4.1)	-1.2 (4.2)
	Median change from baseline	0.0	-1.7
	Min, Max change from baseline	-12.0, 20.5	-12.0, 8.6
	% (n) of patients with T. bilirubin >2x ULN	0 (0)	0 (0)
Week 48	N	72	24
	Mean (SD)	8.2 (3.9)	9.6 (5.9)
	Median	6.8	8.6
	Min, Max	1.7, 25.7	1.7, 23.9
	Mean (SD) change from baseline	0.2 (4.5)	-0.6 (5.1)
	Median change from baseline	1.7	0.9
	Min, Max change from baseline	-18.8, 10.3	-12.0, 6.8
	% (n) of patients with T. bilirubin >2x ULN	0 (0)	0 (0)
Week 96	N	51	14
	Mean (SD)	8.4 (4.5)	11.0 (6.7)
	Median	6.8	7.7
	Min, Max	1.7, 25.7	3.4, 20.5
	Mean (SD) change from baseline	0.6 (5.2)	1.1 (5.8)
	Median change from baseline	1.7	1.7
	Min, Max change from baseline	-22.2, 13.7	-6.8, 15.4
	% (n) of patients with T. bilirubin >2x ULN	0 (0)	0 (0)

Source: ADLB where SAF01FL=Y, APERIOD = 1, ANL01FL=Y, by ACTARM.

Reference ID: 4776272

Alkaline phosphatase

Patients on teriflunomide generally had higher mean total bilirubin compared to patients on placebo during DBT, but these differences did not appear to be clinically significant (Table 49). No patients experienced ALP >2x ULN during the DBT or OLE periods.

Table 49 (Reviewer). Trial EFC11759 Alkaline Phosphatase (IU/L) Over Time, Double-Blind Period

Time	Parameter	Teriflunomide (n = 109)	Placebo (n = 57)
Baseline	Mean (SD)	142.6 (96.5)	125.9 (69.4)
	Median	107.0	103.0
	Min, Max	45.0, 552.0	48.0, 371.0
Week 4	N	109	56
	Mean (SD)	142.6 (99.9)	128.3 (72.1)
	Median	101.0	98.5
	Min, Max	42.0, 622.0	41.0, 363.0
	Mean (SD) change from baseline	0.0 (23.7)	1.8 (16.1)
	Median change from baseline	1.0	1.0
	Min, Max change from baseline	-78.0, 102.0	-49.0, 44.0
	% (n) of patients with ALP >2x ULN	0 (0)	0 (0)
	% (n) of patients with ALP >3x ULN	0 (0)	0 (0)
Week 24	N	100	45
	Mean (SD)	123.3 (82.3)	115.4 (63.6)
	Median	98.0	95.0
	Min, Max	40.0, 509.0	46.0, 360.0
	Mean (SD) change from baseline	-19.6 (33.2)	-5.64 (20.7)
	Median change from baseline	-9.5	-2.0
	Min, Max change from baseline	-180.0, 51.0	-93.0, 43.0
	% (n) of patients with ALP >2x ULN	0 (0)	0 (0)
	% (n) of patients with ALP >3x ULN	0 (0)	0 (0)
Week 48	N	72	24
	Mean (SD)	117.1 (87.5)	113.8 (64.6)
	Median	85.5	86.5
	Min, Max	41.0, 512.0	55.0, 330.0
	Mean (SD) change from baseline	-24.3 (40.2)	-12.6 (21.0)
	Median change from baseline	-15.0	-4.5
	Min, Max change from baseline	-181, 102.0	-61.0, 13.0
	% (n) of patients with ALP >2x ULN	0 (0)	0 (0)
	% (n) of patients with ALP >3x ULN	0 (0)	0 (0)
Week 96	N	51	14
	Mean (SD)	106.2 (74.0)	94.2 (31.5)
	Median	82.0	83.0
	Min, Max	41.0, 427.0	52.0, 163.0
	Mean (SD) change from baseline	-44.4 (64.6)	-45.9 (62.1)
	Median change from baseline	-26.0	-29.0
	Min, Max change from baseline	-331.0, 85.0	-208.0, 10.0
	% (n) of patients with ALP >2x ULN	0 (0)	0 (0)
	% (n) of patients with ALP >3x ULN	0 (0)	0 (0)

Source: ADLB where SAF01FL=Y, APERIOD = 1, ANL01FL=Y, by ACTARM.

Reference ID: 4776272

Pancreatic enzymes

Pancreatitis has been reported in the postmarketing setting for teriflunomide in adults, but several cases of pancreatitis and elevated pancreatic enzymes that occurred in pediatric patients on teriflunomide in Trial EFC11759. Amylase and lipase were descriptively analyzed by visit, including the change from baseline, for each treatment group. Additionally, patients with specified thresholds of abnormalities for each parameter (e.g., >2x ULN) at individual visits and across the DBT period were tabulated by treatment group.

Please refer to Section 8.5.1 for further discussion of pancreatic disorder events that occurred during this study.

Amylase

Though patients on teriflunomide were more likely to experience pancreatic disorder-related AEs, elevations in mean amylase compared to baseline were not observed in the teriflunomide group (Table 50). Moreover, most time points during DBT indicated a higher mean value and change from baseline in serum amylase in the placebo group, but these differences were not clinically significant. Shift analyses indicated that 3.6% of patients on placebo (n = 2) and 2.8% of patients on teriflunomide (n = 3) experienced amylase ≥2x ULN during DBT.

Shift analysis for the combined DBT plus OLE periods indicated that the proportion of patients in the teriflunomide-teriflunomide and placebo-teriflunomide groups experiencing amylase ≥2x ULN was similar between the groups.

Table 50 (Reviewer). Trial EFC11759 Amylase (IU/L) Over Time, Double-Blind Period

Time	Parameter	Teriflunomide (n = 109)	Placebo (n = 57)
Baseline	Mean (SD)	61.5 (23.2)	64.8 (25.3)
	Median	57.0	59.0
	Min, Max	22.0, 160.0	26.0, 148.0
	% (n) of patients with Amylase >2x ULN	0.9 (1)	0 (0)
Week 4	N	109	56
	Mean (SD)	61.5 (21.9)	64.5 (26.8)
	Median	58.0	57.5
	Min, Max	20.0, 149.0	24.0, 146.0
	Mean (SD) change from baseline	0.03 (10.6)	0.2 (13.2)
	Median change from baseline	1.0	0.0
	Min, Max change from baseline	-46.0, 29.0	-40.0, 53.0
	% (n) of patients with Amylase >2x ULN	0 (0)	0 (0)
Week 24	N	100	45
	Mean (SD)	60.5 (23.1)	68.1 (23.8)
	Median	58.0	60.0
	Min, Max	23.0, 144.0	27.0, 122.0
	Mean (SD) change from baseline	-0.9 (13.3)	2.4 (11.4)
	Median change from baseline	-1.0	0.0
	Min, Max change from baseline	-42.0, 75.0	-26.0, 27.0
	% (n) of patients with Amylase >2x ULN	0 (0)	0 (0)
Week 48	N	72	24
	Mean (SD)	60.3 (21.9)	84.4 (92.2)
	Median	58.0	61.5
	Min, Max	20.0, 120.0	27.0, 496.0
	Mean (SD) change from baseline	-3.3 (10.3)	21.3 (90.6)
	Median change from baseline	-2.5	3.5
	Min, Max change from baseline	-40.0, 21.0	-10.0, 445.0
	% (n) of patients with Amylase >2x ULN	0 (0)	4.2 (1)
Week 96	N	52	14
	Mean (SD)	58.7 (20.3)	68.3 (26.4)
	Median	59.5	60.0
	Min, Max	21.0, 107.0	37.0, 143.0
	Mean (SD) change from baseline	0.2 (9.1)	-2.8 (9.6)
	Median change from baseline	0.0	-0.5
	Min, Max change from baseline	-22.0, 22.0	-24.0, 11.0
	% (n) of patients with Amylase >2x ULN	0 (0)	0 (0)

Source: ADLB where SAF01FL=Y, APERIOD = 1, ANL01FL=Y, by ACTARM.

Lipase

Serum lipase data was similar to that of serum amylase. Again, though patients on teriflunomide were more likely to experience pancreatic disorder-related AEs, elevations in mean lipase compared to baseline were not observed in the teriflunomide group (Table

Reference ID: 4776272

51Table 50). Moreover, most time points during DBT indicated a higher mean value and change from baseline in serum lipase in the placebo group, but these differences were not clinically significant. Shift analyses indicated that among patients with baseline lipase <2x ULN, 3.7% of patients on teriflunomide (n = 4) and 1.8% of patients on placebo (n = 1) experienced lipase ≥2x ULN during DBT.

Shift analysis for the combined DBT plus OLE periods indicated that the proportion of patients in the teriflunomide-teriflunomide and placebo-teriflunomide groups experiencing lipase ≥2x ULN was similar between the groups.

Table 51 (Reviewer). Trial EFC11759 Lipase (IU/L) Over Time, Double-Blind Period

Time	Parameter	Teriflunomide (n = 109)	Placebo (n = 57)
Baseline	Mean (SD)	27.4 (10.7)	28.3 (10.6)
	Median	25.0	26.0
	Min, Max	14.0, 65.0	13.0, 69.0
Week 4	N	109	56
	Mean (SD)	28.1 (10.2)	28.0 (10.1)
	Median	26.0	25.0
	Min, Max	14.0, 58.0	13.0, 61.0
	Mean (SD) change from baseline	0.7 (5.6)	-0.2 (6.0)
	Median change from baseline	1.0	0.0
	Min, Max change from baseline	-14.0, 21.0	-13.0, 21.0
	% (n) of patients with Lipase >2x ULN	0 (0)	0 (0)
Week 24	N	99	45
	Mean (SD)	28.0 (14.8)	29.8 (15.0)
	Median	24.0	25.0
	Min, Max	12.0, 96.0	13.0, 94.0
	Mean (SD) change from baseline	0.6 (11.8)	1.9 (10.9)
	Median change from baseline	-1.0	0.0
	Min, Max change from baseline	-24.0, 75.0	-12.0, 64.0
	% (n) of patients with Lipase >2x ULN	0 (0)	0 (0)
Week 48	N	73	24
	Mean (SD)	26.3 (12.3)	27.5 (13.0)
	Median	22.0	22.0
	Min, Max	13.0, 69.0	13.0, 69.0
	Mean (SD) change from baseline	-2.1 (7.0)	0.3 (5.3)
	Median change from baseline	-2.0	0.0
	Min, Max change from baseline	-23.0, 31.0	-11.0, 14.0
	% (n) of patients with Lipase >2x ULN	0 (0)	0 (0)
Week 96	N	52	14
	Mean (SD)	24.3 (9.8)	28.2 (10.6)
	Median	22.0	25.5
	Min, Max	12.0, 55.0	19.0, 53.0
	Mean (SD) change from baseline	-2.0 (8.5)	0.9 (6.9)
	Median change from baseline	-2.0	2.5
	Min, Max change from baseline	-20.0, 38.0	-12.0, 13.0
	% (n) of patients with Lipase >2x ULN	0 (0)	0 (0)

Source: ADLB where SAF01FL=Y, APERIOD = 1, ANL01FL=Y, by ACTARM.

Renal function

No patients in Trial EFC11759 experienced serum creatinine >115 µmol/L (1.3 mg/dL) or blood urea nitrogen (BUN) > 8.5 mmol/L (23.8 mg/dL) during DBT. Additionally, no consistent differences in change from baseline for BUN or creatinine were observed in either the placebo or teriflunomide groups.

Reference ID: 4776272

Shift analyses indicated 1.8% of patients on teriflunomide (n = 2) experienced BUN ≥7 mmol/L, compared to 7.0% on placebo (n = 4) during DBT. For the combined DBT plus OLE periods, shift analysis demonstrated that the proportion of patients with BUN ≥7 mmol/L was higher in the placebo-teriflunomide group compared to the teriflunomide-teriflunomide group (19.2% versus 10.0%, respectively).

Electrolytes

Peak and nadir values of serum electrolytes were descriptively analyzed, and clinically significant values were tabulated by treatment arm across the DBT and OLE periods.

Phosphorus

In adult clinical trials, 18% of teriflunomide-treated patients had hypophosphatemia with serum phosphorus levels of at least 0.6 mmol/L, compared to 7% of placebo-treated patients. Additionally, 4% of teriflunomide-treated patients had hypophosphatemia with serum phosphorus between 0.3 and 0.6 mmol/L, compared with 0.8% of placebo-treated patients.

No patients experienced serum phosphorus <0.6 mmol/L during DBT. Three patients on teriflunomide (2.8%) and no patients on placebo (0%) experienced serum phosphorus ≤LLN during DBT. No consistent differences in change from baseline for serum phosphorus were observed in either the placebo or teriflunomide groups.

However, one patient in the teriflunomide-teriflunomide group who had a baseline serum phosphorus >0.6 mmol/L at baseline experienced a serum phosphorus level between 0.3 and 0.6 mmol/L during the OLE period.

Sodium

No patients experienced clinically significant abnormalities in sodium (i.e., <128 or >150 mmol/L) during the DBT or OLE periods (Table 52). Additionally, no clinically significant differences in sodium levels between teriflunomide and placebo were observed during DBT. No TEAEs related to serum sodium were reported during DBT or OLE.

Reference ID: 4776272

Table 52 (Reviewer). Trial EFC11759 Sodium (mmol/L) Summary, Double-Blind Period

	Teriflunomide (n = 109)	Placebo (n = 57)
Baseline		
Mean (SD) (mmol/L)	139.6 (2.0)	139.3 (1.6)
Median (mmol/L)	140.0	139.0
Min, max (mmol/L)	132.0, 144.0	136.0, 143.0
# patients <128 mmol/L	0 (0)	0 (0)
# patients > 150 mmol/L	0 (0)	0 (0)
Lowest post-baseline value		
Mean (SD) (mmol/L)	138.4 (1.7)	137.8 (1.5)
Median (mmol/L)	138.0	138.0
Min, max (mmol/L)	133.0, 143.0	135.0, 141.0
# patients <128 mmol/L	0 (0)	0 (0)
# patients > 150 mmol/L	0 (0)	0 (0)
Peak post-baseline value		
Mean (SD) (mmol/L)	142.4 (2.0)	141.0 (1.7)
Median (mmol/L)	142.0	141.0
Min, max (mmol/L)	134.0, 150.0	138.0, 145.0
# patients <128 mmol/L	0 (0)	0 (0)
# patients > 150 mmol/L	0 (0)	0 (0)

Reference Range: 135 to 148 mmol/L

Potassium

The mean peak and nadir post-baseline values for serum potassium (mmol/L) did not differ between the teriflunomide and placebo groups during DBT (Table 53). However, patients on teriflunomide were more likely to have potassium <3.5 mmol/L or >6.0 mmol/L compared to placebo. Hyperkalemia was listed as a potential safety concern in the Written Request for which this study was submitted; though no TEAEs of hyperkalemia occurred, 1 patient on teriflunomide in DBT experienced serum potassium >6.0 mmol/L. In the combined DBT+OLE periods, 2 additional patients on teriflunomide-teriflunomide and 4 additional patients on placebo-teriflunomide experienced serum potassium <3.5 mmol/L.

During DBT, One TEAE of blood potassium decreased was reported in patient on placebo during DBT. One patient experienced the TEAE hypokalemia during OLE (teriflunomide-teriflunomide group).

Reference ID: 4776272

Table 53 (Reviewer). Trial EFC11759 Potassium (mmol/L) Summary, Double-Blind Period

	Teriflunomide (n = 109)	Placebo (n = 57)
Baseline		
Mean (SD) (mmol/L)	4.2 (0.4)	4.2 (0.4)
Median (mmol/L)	4.1	4.2
Min, max (mmol/L)	3.4, 5.5	3.3, 5.1
# patients < 3.5 mmol/L	0.9 (1)	1.8 (1)
# patients > 6.0 mmol/L	0 (0)	0 (0)
Lowest post-baseline value		
Mean (SD) (mmol/L)	3.9 (0.3)	3.9 (0.3)
Median (mmol/L)	3.9	4.0
Min, max (mmol/L)	3.2, 4.7	3.3, 4.6
# patients < 3.5 mmol/L	5.5 (6)	3.6 (2)
# patients > 6.0 mmol/L	0 (0)	0 (0)
Peak post-baseline value		
Mean (SD) (mmol/L)	4.5 (0.4)	4.5 (0.4)
Median (mmol/L)	4.5	4.5
Min, max (mmol/L)	3.5, 7.3	3.6, 5.9
# patients < 3.5 mmol/L	0 (0)	0 (0)
# patients > 6.0 mmol/L	0.9 (1)	0 (0)

Reference Range: 3.5 to 5.3 mmol/L

Chloride

No patients experienced clinically significant abnormalities in chloride during the DBT or OLE periods (Table 54). Additionally, no clinically significant differences in chloride levels between teriflunomide and placebo were observed during DBT. No TEAEs related to serum chloride were reported during DBT or OLE.

Reference ID: 4776272

Table 54 (Reviewer). Trial EFC11759 Chloride (mmol/L) Summary, Double-Blind Period

	Teriflunomide (n = 109)	Placebo (n = 57)
Baseline		
Mean (SD) (mmol/L)	102.4 (2.5)	102.0 (1.8)
Median (mmol/L)	102.0	102.0
Min, max (mmol/L)	91.0, 110.0	99.0, 105.0
Lowest post-baseline value		
Mean (SD) (mmol/L)	101.2 (1.6)	100.4 (2.0)
Median (mmol/L)	101.0	100.5
Min, max (mmol/L)	98.0, 106.0	95.0, 104.0
Peak post-baseline value		
Mean (SD) (mmol/L)	105.1 (2.0)	103.7 (1.8)
Median (mmol/L)	105.0	103.5
Min, max (mmol/L)	99.0, 111.0	100.0, 107.0

Reference Range: 98 to 109 mmol/L

Calcium

No patients experienced post-baseline clinically significant abnormalities in calcium (i.e., <2.0 or >2.7 mmol/L) during the DBT or OLE periods (Table 55). Additionally, no clinically significant differences in calcium levels between teriflunomide and placebo were observed during DBT. No TEAEs related to serum calcium were reported during DBT or OLE.

Reference ID: 4776272

Table 55 (Reviewer). Trial EFC11759 Calcium (mmol/L) Summary, Double-Blind Period

	Teriflunomide (n = 109)	Placebo (n = 57)
Baseline		
Mean (SD) (mmol/L)	2.5 (0.1)	2.5 (0.1)
Median (mmol/L)	2.5	2.5
Min, max (mmol/L)	2.3, 2.8	2.3, 2.6
# patients < 2.0 mmol/L	0 (0)	0 (0)
# patients > 2.7 mmol/L	1.8 (2)	0 (0)
Lowest post-baseline value		
Mean (SD) (mmol/L)	2.4 (0.1)	2.4 (0.1)
Median (mmol/L)	2.4	2.4
Min, max (mmol/L)	2.2, 2.6	2.2, 2.7
# patients < 2.0 mmol/L	0 (0)	0 (0)
# patients > 2.7 mmol/L	0 (0)	0 (0)
Peak post-baseline value		
Mean (SD) (mmol/L)	2.5 (0.1)	2.5 (0.1)
Median (mmol/L)	2.5	2.5
Min, max (mmol/L)	2.3, 2.7	2.4, 2.7
# patients < 2.0 mmol/L	0 (0)	0 (0)
# patients > 2.7 mmol/L	0 (0)	0 (0)

Reference Range: 2.1 to 2.7 mmol/L

Creatine phosphokinase

Elevated creatine phosphokinase (CPK) is not an established safety concern with teriflunomide or leflunomide per current USPIs. However, several cases of elevated CPK occurred in patients receiving teriflunomide during the DBT and OLE periods of Trial EFC11759; no cases of rhabdomyolysis or myositis were reported.

Overall, 14 patients on teriflunomide (12.8%) and 3 patients on placebo (5.2%) experienced a peak CPK >2x ULN during DBT. Notably, 2 patients on teriflunomide experienced CPK ≥10x ULN (See Section 8.4.4).

Please refer to Section 8.5.11 for further discussion of elevated serum CPK and CPK-related TEAEs in this trial.

Uric acid

Teriflunomide is known to increase renal uric acid clearance, and this mechanism is hypothesized to lead to uric acid nephropathy and transient acute renal failure. In Trial EFC11759, uric acid levels decreased up to Week 24, then remained stable during DBT in patients on teriflunomide compared to placebo (Figure 18). Additionally, the proportion of

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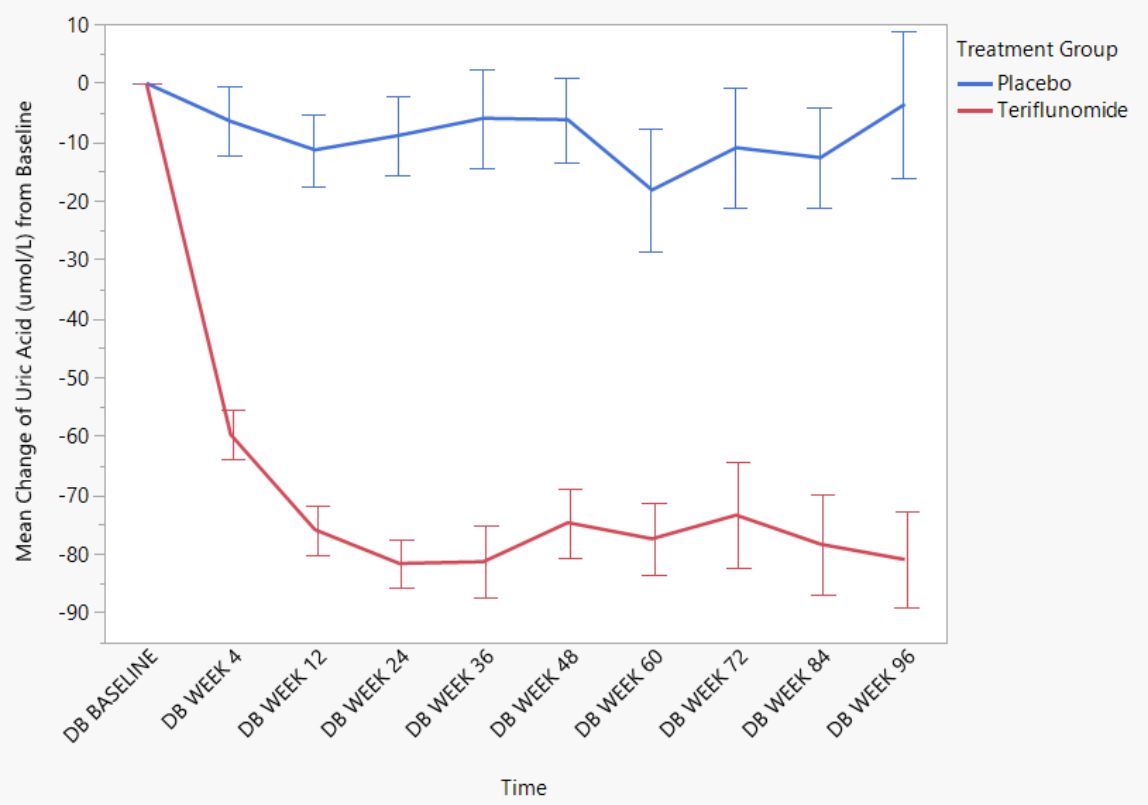
patients with uric acid <120 µmol/L post-baseline during DBT was higher in the teriflunomide group (11.9%) compared to placebo (3.6%). Patients on teriflunomide had a lower last uric acid value on treatment compared to those on placebo (mean (SD) 215.9 (84.1) versus 280.7 (76.7) µmol/L, respectively).

Figure 18 (Reviewer). Mean Change from Baseline of Uric Acid (µmol/L) During Double-Blind Treatment, by Treatment Group, Trial EFC11759



Overall, this decrease in uric acid remained stable in patients who continued on teriflunomide during the OLE period, and patients who started teriflunomide during the OLE period experienced this decrease in uric acid that stabilized around Week 24 of treatment. However, the small sample size at later time points limits interpretation of this trend.

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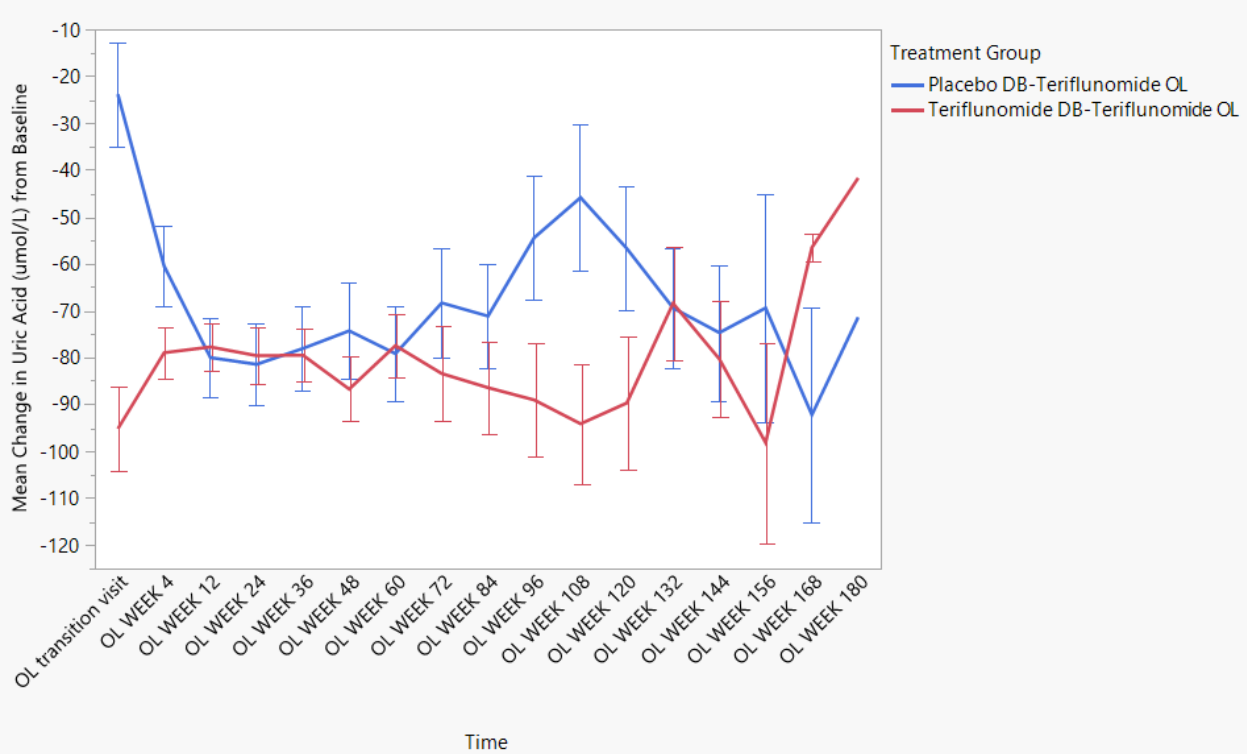
Figure 19 (Reviewer). Mean Change from Baseline of Uric Acid (µmol/L) During Open-Label Treatment, by Treatment Group, Trial EFC11759



***Reviewer comment**: Though no patients in Trial EFC11759 experienced renal failure, this decrease in uric acid levels is indicative of a potential risk of uric acid nephropathy. It is unknown if the risk of uric acid nephropathy increases with prolonged use of teriflunomide.*

Immunoglobulins

During DBT, patients on teriflunomide experienced reductions in mean IgG, IgM, and IgA compared to placebo. Representative mean (SD) values from baseline and Week 24 are presented in Table 56. TEAEs of blood immunoglobulin G decreased and blood immunoglobulin M decreased occurred in 1 teriflunomide patient each during OLE.

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Table 56 (Reviewer). Trial EFC11759 Double-Blind Treatment Immunoglobulin Changes

	Teriflunomide (n = 109)		Placebo (n = 57)	
	N	**Mean (SD)**	**N**	**Mean (SD)**
IgG (g/L)				
Baseline	106	10.1 (2.1)	56	10.5 (1.9)
Week 24	99	9.4 (1.8)	45	10.9 (2.1)
Last on treatment value	105	9.6 (1.9)	49	10.8 (2.1)
IgM (g/L)				
Baseline	106	1.3 (0.5)	56	1.3 (0.5)
Week 24	99	1.0 (0.4)	45	1.3 (0.5)
Last on treatment value	105	1.1 (0.4)	49	1.3 (0.6)
IgA (mg/L)				
Baseline	106	1640.5 (816.9)	56	1628.4 (646.1)
Week 24	99	1514.3 (647.5)	45	1771.3 (715.9)
Last on treatment value	105	1523.6 (657.9)	49	1828.2 (818.7)

Source: ADLB where SAF01FL=Y, APERIOD = 1; ABLFL=Y for baseline values; AWEEK = DB Week 24 & ANLFL01 = Y for Week 24 values; LVOTDBFL=Y for Last on treatment value

Serum IgG <6.0 g/L occurred in 7 patients (6.4%) who received teriflunomide and 0 patients (0%) who received placebo, post-baseline during DBT. Serum IgM< 0.4 g/L occurred in 5 patients (4.6%) who received teriflunomide and 0 patients (0%) who received placebo, post-baseline during DBT. Serum IgA <600 mg/L occurred in 4 patients (3.7%) who received teriflunomide and 0 patient (0%) who received placebo, post-baseline during DBT.

A TEAE of blood immunoglobulin M decreased occurred in 1 teriflunomide patient (*Subject ID* (b) (6)) during DBT (0.9%). During OLE, 1 patient in the teriflunomide-teriflunomide group experienced TEAEs of blood immunoglobulin M decreased and blood immunoglobulin G decreased (*Subject ID* (b) (6)).

Four patients who experienced infections that were considered SAEs were evaluated for immunoglobulin levels closest to the time of infection:

- *Subject ID* (b) (6) experienced pulmonary TB at Day 277 during DBT. Serum IgG was 7.47 g/L (<LLN) at baseline, and at Week 24 (Day 168), IgG was 7.52 g/L. Serum IgM decreased from 1.06 g/L at baseline to 0.77 g/L at Week 24.
- *Subject ID* (b) (6) experienced a serious upper respiratory tract infection at Day 182, in the setting of decreased IgG to 7.11 g/L (<LLN) from a normal baseline value. This patient also experienced a reported CNS infection and another upper respiratory tract infection at Day 547, in the setting of decreased IgG of 6.7 g/L (<LLN) at Week 36 of the OLE. IgA and IgM were normal. At Day 373, this patient experienced a lung infection in the setting of normal IgG, IgM, and IgA.
- *Subject ID* (b) (6) experienced SAEs of tonsillitis and bronchitis on Days 329 and 344 during the OLE, and Week 24 OLE values were <LLN for both IgG and IgM (7.37 g/L and

0.33 g/L, respectively).

- *Subject ID* (b) (6) experienced an SAE of acute sinusitis on Day 369 during the OLE, and Week 96 OLE values for IgG, IgM, and IgA were within normal limits.

Reviewer comment: *Though these serious infections were uncommon during Trial EFC11759, teriflunomide was associated with a decrease in serum IgG, IgM, and IgA compared to placebo. Some patients with serum IgG<LLN also experienced infection-related events, but none appear to be opportunistic infections.*

Urinalysis

No clinically significant differences in urine pH or specific gravity were observed in the sponsor's analysis between teriflunomide and placebo groups during DBT. This reviewer evaluated other urinalysis parameters as well; similar proportions of patients in the teriflunomide and placebo groups experienced the presence of calcium oxalate crystals, urine erythrocytes >ULN, urine glucose ≥+1, urine ketones ≥+1, urine leukocytes >ULN, urine occult blood, and urobilinogen ≥+1.

Patients on teriflunomide were more likely to have post-baseline, on-treatment abnormalities in urine protein. Overall, 54.1% (n = 59) patients on teriflunomide had ≥+1 urine protein post-baseline, compared to 33.3% (n = 19) patients on teriflunomide. However, the frequency of urine protein ≥+2 was low and was similar between the groups: 6.4% (n = 7) for teriflunomide and 5.3% (n = 3) for placebo. Additionally, during DBT, 4.6% of patients on teriflunomide (n = 5) experienced the TEAEs protein urine present, proteinuria, or protein urine, compared to 1.8% (n = 1) on placebo. One patient in the teriflunomide-teriflunomide group experienced the TEAE proteinuria during OLE, and 2 patients experienced the TEAE protein urine present in the 120 Day Safety Update reporting interval.

Reviewer comment*: Proteinuria was not identified as a safety concern in adult trials of teriflunomide. The similar frequency of higher levels of proteinuria between the treatment groups is somewhat reassuring, but TEAEs related to proteinuria were higher in the teriflunomide group.*

Uric acid nephropathy due to increased renal clearance of uric acid is a safety concern with teriflunomide. Uric acid crystals were present in urine in 4.6% (n = 5) of patients on teriflunomide at baseline, compared to 0% (n = 0) on placebo. Post-baseline, 16.5% (n = 18) patients on teriflunomide had urine uric acid crystals, compared to 7.0% (n = 4) on placebo.

Reviewer comment*: The presence of uric acid crystals, in conjunction with the decreases in serum uric acid as discussed below, could indicate a risk of uric acid nephropathy in the pediatric population, as observed in adults.*

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No cases of hematuria were reported as TEAEs in Trial EFC11759.

Summary of Shift Analyses

Shift analyses for laboratory data of interest, specifically the number of patients who met designated laboratory abnormality thresholds during the DBT period, are summarized in Table 57.

Overall, patients on teriflunomide were more likely to experience elevated AST, ALT, lipase, and CPK compared to those on placebo. Patients on teriflunomide were more likely to experience decreased leukocyte counts, neutrophil counts (particularly 0.5 to 1.0 $x10^9$/L), lymphocyte counts, platelets, and serum phosphate compared to those on placebo.

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Table 57 (Reviewer). Trial EFC11759 Double-Blind Treatment Laboratory Abnormality Summary, % (n) Patients Experiencing Post-Baseline Peak/Nadir Lab Value Indicated During Double-Blind Treatment

Parameter	Value	Teriflunomide (n = 109)	Placebo (n = 57)
AST	2-5x ULN	0.9 (1)	0 (0)
	5-10x ULN	0.9 (1)	0 (0)
	>10x ULN	0 (0)	0 (0)
ALT	2-5x ULN	4.6 (5)	0 (0)
	5-10x ULN	0 (0)	0 (0)
	>10x ULN	0 (0)	0 (0)
Total Bilirubin	1.5-2x ULN	0.9 (1)	1.8 (1)
	>2x ULN	0 (0)	0 (0)
Leukocyte Count ($x10^9$/L)	2.0 to 3.5 $x10^9$/L	23.9 (26)	7.1 (4)
	<2.0 $x10^9$/L	0 (0)	0 (0)
Absolute Neutrophil Count ($x10^9$/L)	≤0.5 $x10^9$/L	0 (0)	0 (0)
	0.5 to 1.0 $x10^9$/L	5.5 (6)	0 (0)
	1.0 to 1.5 $x10^9$/L	13.8 (15)	14.3 (8)
Absolute Lymphocyte Count ($x10^9$/L)	≤0.5 $x10^9$/L	0 (0)	0 (0)
	0.5 to 1.0 $x10^9$/L	12.8 (14)	5.4 (3)
Platelets ($x10^9$/L)	≤ 50 $x10^9$/L	0 (0)	0 (0)
	50 to 100 $x10^9$/L	1.8 (2)	0 (0)
	100 to 150 $x10^9$/L	9.2 (10)	7.1 (4)
Amylase	2-5x ULN	1.8 (2)	1.8 (1)
	5-10x ULN	0.9 (1)	1.8 (1)
	>10x ULN	0 (0)	0 (0)
Lipase	2-5x ULN	2.8 (3)	1.8 (1)
	5-10x ULN	0 (0)	0 (0)
	>10x ULN	0.9 (1)	0 (0)
Creatine phosphokinase	2-3x ULN	4.6 (5)	1.8 (1)
	3-5x ULN	2.8 (3)	1.8 (1)
	5-10x ULN	2.8 (3)	1.8 (1)
	10-20x ULN	0.9 (1)	0 (0)
	>20x ULN	1.8 (2)	0 (0)
Phosphate	≤ 0.6 mmol/L	0 (0)	0 (0)
	Any value <LLN	2.8 (3)	0 (0)

Source: ADLB where SAF01FL=Y, DBWTHIFL = Y or DBWTLOFL = Y (depending on value of interest); ULN-based categories for AST, ALT, ALP, Total Bilirubin, Hemoglobin, and CK per sponsor's ANRIND variable.

120 Day Safety Update

The sponsor's analysis for data obtained during the interval from November 28, 2019 through December 1, 2020 did not suggest an increase in the frequency of laboratory abnormalities compared to data previously reviewed for the DBT and OLE periods. No Hy's Law cases

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occurred during the reporting interval.

8.4.7. Vital Signs

Blood Pressure

Increased blood pressure is a known safety concern with teriflunomide. Systolic and diastolic blood pressure (SBP and DBP) were descriptively analyzed by visit, including change from baseline, during the DBT and OLE periods. Patients with a change of 20 mmHg in SBP or DBP were tabulated at each visit as well. Data from representative time points (baseline, Week 4, Week 24, Week 48, and Week 96) are presented in Table 58 for supine SBP and Table 59 for supine DBP. Plots of mean change in supine SBP and DBP are presented in Figure 20 and Figure 21, respectively. Please note that interpretation of change at later time points is limited by the small sample size, particularly in the placebo group.

Patients on teriflunomide generally had higher mean and median changes in supine SBP at each visit compared to those placebo (range of 0.82 [Week 12] to 7.84 [Week 96] mmHg for teriflunomide, -3.06 [Week 84, n = 16] to 0.50 [Week 60] mmHg for placebo). Additionally, the proportion of patients with a >20 mmHg change (increase) in SBP at each visit was generally higher in patients on teriflunomide compared to placebo. For example, at Week 24, 6.4% of patients on teriflunomide had an SBP increase from baseline of >20mmHg, compared to 1.8% on placebo. During the OLE period, the patients generally had a positive mean change in supine SBP from baseline, but this trend was similar in the teriflunomide-teriflunomide and teriflunomide-placebo groups. Patients who had been on teriflunomide did not appear to have a higher increase in SBP compared to those who had been on placebo during DBT, but the proportion of patients with a mean SBP change >20 mmHg was higher in the teriflunomide-teriflunomide group (maximum 7.0% at OL Week 48) compared to the placebo-teriflunomide group (maximum 5.8% at OL Week 96) at most timepoints during OLE.

For supine DBP, patients on teriflunomide tended to have a higher mean change from baseline compared to those on placebo (range of 1.43 [Week 12] to 7.95 [Week 84] mmHg for teriflunomide, 0.04 [Week 4] to 2.75 [Week 96, note n = 16] mmHg for placebo). Additionally, the proportion of patients with a >20 mmHg change (increase) in supine DBP was higher in patients on teriflunomide compared to placebo at most time points during DBT. For example, at Week 36, 3.7% of patients on teriflunomide had a DBP increase from baseline of >20mmHg, compared to 1.8% on placebo. During the OLE period, the patients generally had a positive mean change in supine DBP from baseline, but this trend was similar in the teriflunomide-teriflunomide and teriflunomide-placebo groups. Patients who had been on teriflunomide did not appear to have a higher increase in DBP compared to those who had been on placebo during DBT.

Changes in standing SBP and DBP from baseline were similar overall between the treatment

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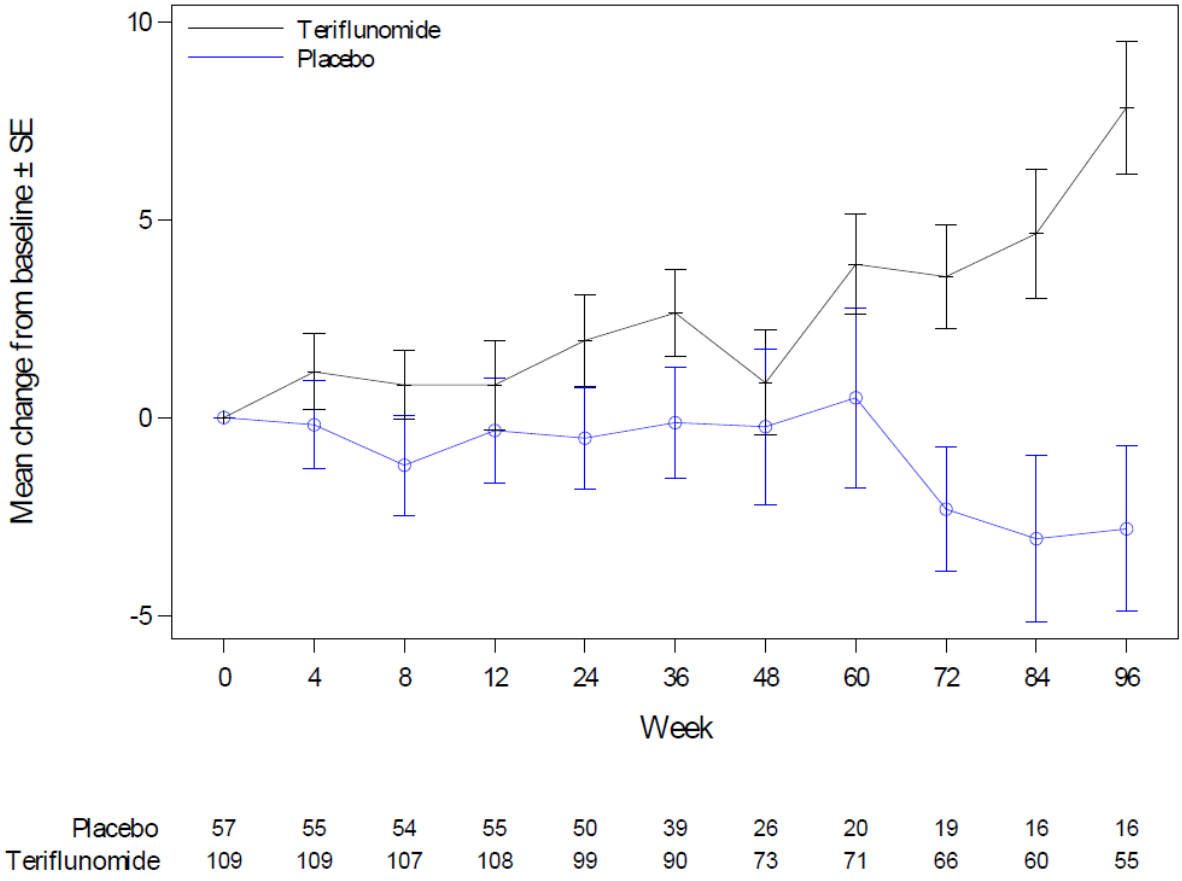
groups, but patients on teriflunomide tended to have slightly higher mean change from baseline compared to placebo. During the OLE period, patients generally had a positive mean change in standing SBP and DBP from baseline, but the magnitude of this trend was similar in the teriflunomide-teriflunomide and teriflunomide-placebo groups.

Table 58 (Reviewer). Supine Systolic Blood Pressure (mmHg) Over Double-Blind Period, Trial EFC11759

Time	Parameter	Teriflunomide (n = 109)	Placebo (n = 57)
Baseline	Mean (SD)	111.1 (11.2)	111.8 (10.0)
	Median	110.0	111.0
	Min, Max	90.0, 130.0	89.0, 132.0
Week 4	N	109	55
	Mean (SD)	112.3 (9.8)	111.7 (11.5)
	Median	112.0	110.0
	Min, Max	90.0, 139.0	90.0, 145.0
	Mean (SD) change from baseline	1.2 (10.0)	-0.2 (8.2)
	Median change from baseline	1.0	0.0
	Min, Max change from baseline	-35.0, 27.0	-20.0, 21.0
	% (n) of patients with ΔSBP >20 mmHg	1.8 (2)	1.8 (1)
	% (n) of patients with ΔSBP <-20 mmHg	1.8 (2)	0 (0)
Week 24	N	99	50
	Mean (SD)	112.9 (9.7)	111.4 (9.8)
	Median	113.0	110.0
	Min, Max	86.0, 133.0	91.0, 139.0
	Mean (SD) change from baseline	2.0 (11.6)	-0.5 (9.1)
	Median change from baseline	2.0	0.0
	Min, Max change from baseline	-28.0, 27.0	-20.0, 32.0
	% (n) of patients with ΔSBP >20 mmHg	6.4 (7)	1.8 (1)
	% (n) of patients with ΔSBP <-20 mmHg	0.9 (1)	0 (0)
Week 48	N	73	26
	Mean (SD)	110.3 (10.1)	112.9 (11.4)
	Median	110.0	111.0
	Min, Max	85.0, 134.0	96.0, 134.0
	Mean (SD) change from baseline	0.9 (11.4)	-0.2 (10.0)
	Median change from baseline	0.0	-1.00
	Min, Max change from baseline	-22.0, 23.0	-16.0, 20.0
	% (n) of patients with ΔSBP >20 mmHg	3.7 (4)	0 (0)
	% (n) of patients with ΔSBP <-20 mmHg	1.8 (2)	0 (0)
Week 96	N	55	16
	Mean (SD)	116.3 (11.0)	110.4 (8.5)
	Median	115.0	110.5
	Min, Max	91.0, 141.0	96.0, 125.0
	Mean (SD) change from baseline	7.8 (12.4)	-2.8 (8.4)
	Median change from baseline	6.0	-2.0
	Min, Max change from baseline	-16.0, 39.0	-20.0, 11.0
	% (n) of patients with ΔSBP >20 mmHg	7.3 (8)	0 (0)
	% (n) of patients with ΔSBP <-20 mmHg	0 (0)	0 (0)

Figure 20 (Sponsor). Mean Change from Baseline in Supine SBP (mmHg) over Double-Blind Treatment Period, Trial EFC11759



Placebo	57	55	54	55	50	39	26	20	19	16	16
Teriflunomide	109	109	107	108	99	90	73	71	66	60	55

Source: Figure 19, Sponsor's Clinical Study Report

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Table 59 (Reviewer). Supine Diastolic Blood Pressure (mmHg) Over Double-Blind Period, Trial EFC11759

Time	Parameter	Teriflunomide (n = 109)	Placebo (n = 57)
Baseline	Mean (SD)	65.5 (8.6)	66.5 (9.0)
	Median	64.0	66.0
	Min, Max	50.0, 90.0	41.0, 93.0
Week 4	N	109	55
	Mean (SD)	67.5 (8.1)	66.6 (9.5)
	Median	67.0	66.0
	Min, Max	50.0, 90.0	43.0, 85.0
	Mean (SD) change from baseline	2.0 (9.1)	0.04 (8.9)
	Median change from baseline	1.0	0
	Min, Max change from baseline	-21.0, 37.0	-20.0, 19.0
	% (n) of patients with ΔDBP >20 mmHg	1.8 (2)	0 (0)
	% (n) of patients with ΔDBP <-20 mmHg	0.9 (1)	0 (0)
Week 24	N	99	50
	Mean (SD)	68.2 (8.5)	67.2 (8.6)
	Median	69.0	67.0
	Min, Max	49.0, 88.0	46.0, 87.0
	Mean (SD) change from baseline	3.3 (9.0)	0.8 (9.6)
	Median change from baseline	3.0	3.0
	Min, Max change from baseline	-20.0, 26.0	-20.0, 25.0
	% (n) of patients with ΔDBP >20 mmHg	2.8 (3)	1.8 (1)
	% (n) of patients with ΔDBP <-20 mmHg	0 (0)	0 (0)
Week 48	N	73	26
	Mean (SD)	67.7 (8.6)	69.3 (12.5)
	Median	67.0	67.0
	Min, Max	50.0, 90.0	50.0, 103.3
	Mean (SD) change from baseline	3.4 (8.1)	1.8 (8.8)
	Median change from baseline	4.0	1.5
	Min, Max change from baseline	-18.0, 22.0	-12.0, 24.0
	% (n) of patients with ΔDBP >20 mmHg	0.9 (1)	3.5 (2)
	% (n) of patients with ΔDBP <-20 mmHg	0 (0)	0 (0)
Week 96	N	55	16
	Mean (SD)	69.8 (8.7)	68.8 (9.3)
	Median	70.0	69.0
	Min, Max	53.0, 96.0	54.0, 86.0
	Mean (SD) change from baseline	5.9 (8.3)	2.8 (10.9)
	Median change from baseline	7.0	3.0
	Min, Max change from baseline	-15.0, 26.0	-14.0, 20.0
	% (n) of patients with ΔDBP >20 mmHg	2.8 (3)	0 (0)
	% (n) of patients with ΔDBP <-20 mmHg	0 (0)	0 (0)

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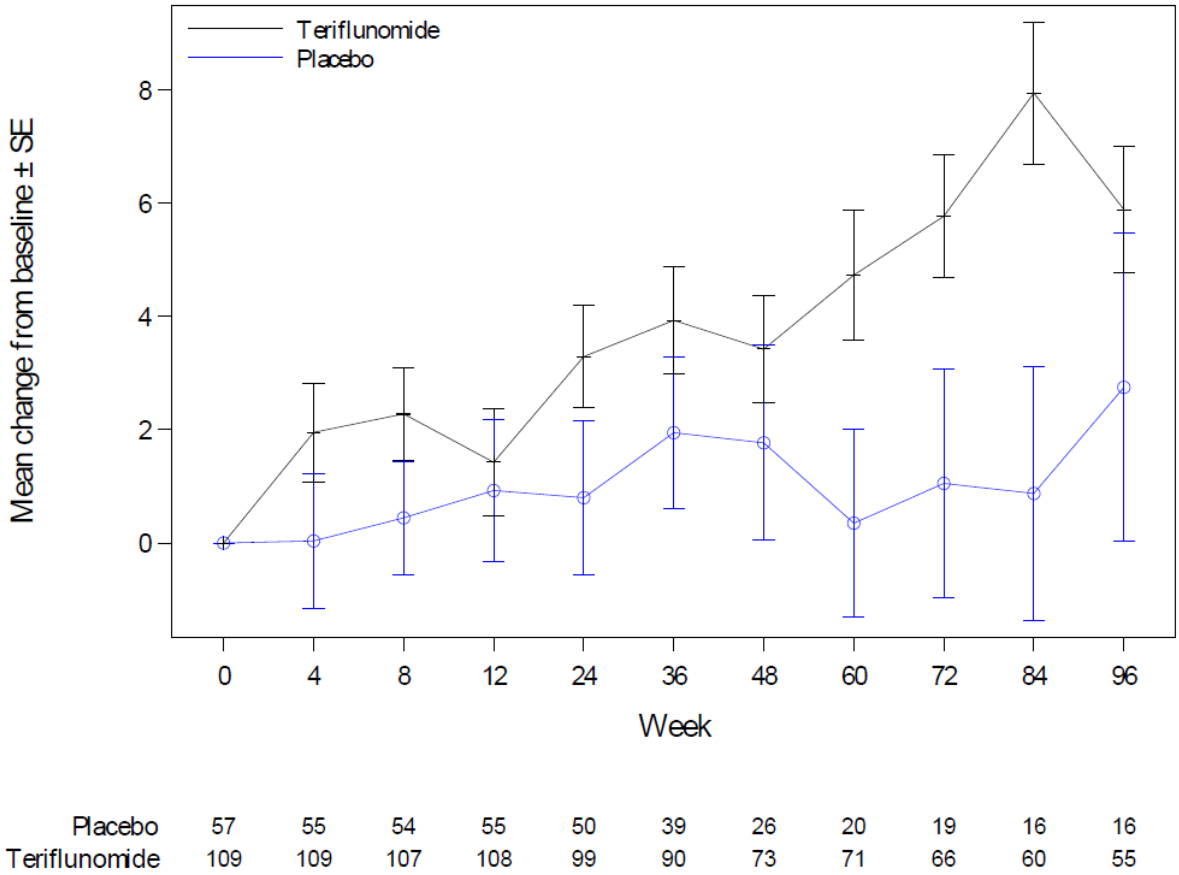
Figure 21 (Sponsor). Mean Change from Baseline in Supine Diastolic Blood Pressure (mmHg) over Double-Blind Treatment Period, Trial EFC11759



Placebo	57	55	54	55	50	39	26	20	19	16	16
Teriflunomide	109	109	107	108	99	90	73	71	66	60	55

Source: Figure 19, Sponsor's Clinical Study Report

In terms of blood pressure-related TEAEs, the PT hypertension was reported in 1 patient on placebo during DBT. Additionally, orthostatic hypotension was reported in 2 patients (3.5%) on placebo.

During OLE, 3 patients in the teriflunomide-teriflunomide group experienced increased blood pressure. The PT hypertension occurred in 2 patients in the teriflunomide-teriflunomide group. The PT blood pressure increased occurred in 1 patient in the teriflunomide-teriflunomide group as well. No cases of orthostatic hypotension occurred during OLE.

> ***Reviewer comment:*** *These findings could indicate that the risk of hypertension associated with teriflunomide increases with chronic, long-term use. Hypertension is included as a warning and precaution in current approved labeling.*

Reference ID: 4776272

Heart Rate

Teriflunomide is not known to affect heart rate. Supine heart rate (HR) was descriptively analyzed by visit, including change from baseline, during the DBT and OLE periods. Patients with a change of 10 bpm HR were tabulated at each visit as well. Data from representative time points (baseline, Week 4, Week 24, Week 48, and Week 96) are presented in Table 60. At most time points, a higher proportion of patients on teriflunomide experienced heart rate decrease >10 bpm at each timepoint compared to those on placebo. However, no clear, clinically significant trends were apparent. Again, please note that interpretation of change at later time points is limited by the small sample size, particularly in the placebo group.

During the OLE, the proportion of patients experiencing a decrease of >10 bpm in supine HR was similar between the placebo-teriflunomide and teriflunomide-teriflunomide groups. At most OLE visits, approximately 15 to 20% of patients in each group experienced a supine HR decrease of >10 bpm. Though the mean changes from baseline generally were larger decreases in the teriflunomide-teriflunomide group, the change values are unlikely to be clinically significant.

In terms of heart rate-associated AEs during DBT, the PT postural orthostatic tachycardia syndrome occurred in 1 patient in the teriflunomide group (0.9%). Palpitations occurred in 3 patients in the teriflunomide group (2.8%) as well. No events of bradycardia or tachycardia were reported.

During OLE, the PT heart rate increased occurred in 1 patient in the teriflunomide-teriflunomide group (1.0%). Palpitations occurred in 1 patient in the teriflunomide-teriflunomide group (1.0%) as well. No events of bradycardia or tachycardia were reported.

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Table 60 (Reviewer). Supine Heart Rate (mmHg) Over Double-Blind Period, Trial EFC11759

Time	Parameter	Teriflunomide (n = 109)	Placebo (n = 57)
Baseline	Mean (SD)	77.8 (12.3)	75.5 (12.1)
	Median	77.0	76.0
	Min, Max	50.0, 110.0	57.0, 108.0
Week 4	N	109	55
	Mean (SD)	76.1 (13.4)	76.8 (11.7)
	Median	75.0	73.0
	Min, Max	51.0, 120.0	57.0, 110.0
	Mean (SD) change from baseline	-1.8 (14.4)	1.2 (11.2)
	Median change from baseline	-1.0	2.0
	Min, Max change from baseline	-37.0, 47.0	-39.0, 32.0
	% (n) of patients with ΔHR >10 mmHg	13.8 (15)	10.5 (6)
	% (n) of patients with ΔHR <-10 mmHg	22.0 (24)	7.0 (4)
Week 24	N	99	50
	Mean (SD)	78.4 (12.6)	75.3 (11.5)
	Median	78.0	73.5
	Min, Max	52.0, 120.0	58.0, 106.0
	Mean (SD) change from baseline	0.1 (13.9)	0.5 (13.0)
	Median change from baseline	0	-1.0
	Min, Max change from baseline	-32.0, 61.0	-40.0, 38.0
	% (n) of patients with ΔHR >10 mmHg	14.7 (16)	17.5 (10)
	% (n) of patients with ΔHR <-10 mmHg	16.5 (18)	12.3 (7)
Week 48	N	73	26
	Mean (SD)	77.8 (11.4)	75.2 (11.8)
	Median	79.0	74.5
	Min, Max	54.0, 115.0	51.0, 93.0
	Mean (SD) change from baseline	1.2 (12.4)	0.8 (12.2)
	Median change from baseline	2.0	1.5
	Min, Max change from baseline	-40.0, 32.0	-28.0, 26.0
	% (n) of patients with ΔHR >10 mmHg	11.0 (12)	7.0 (4)
	% (n) of patients with ΔHR <-10 mmHg	11.9 (13)	7.0 (4)
Week 96	N	55	16
	Mean (SD)	78.6 (14.9)	75.4 (11.9)
	Median	76.0	75.5
	Min, Max	55.0, 125.0	57.0, 101.0
	Mean (SD) change from baseline	0.7 (13.4)	-0.6 (18.0)
	Median change from baseline	0.0	-4.0
	Min, Max change from baseline	-35.0, 27.0	-31.0, 36.0
	% (n) of patients with ΔHR >10 mmHg	12.8 (14)	7.0 (4)
	% (n) of patients with ΔHR <-10 mmHg	10.1 (11)	7.0 (4)

Temperature

In terms of body temperature, events classified under the FDA Standard Medical Query Pyrexia

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(broad) occurred in 6 patients (5.5%) on teriflunomide and 3 patients (5.3%) on placebo, a similar proportion of patients.

During the OLE, events classified under the FDA Standard Medical Query Pyrexia (broad) occurred in 5 patients (3.3%), and was more frequent in patients who had received teriflunomide during DBT (4.0%) versus placebo (1.9%).

120 Day Safety Update

The sponsor's analysis for data obtained during the interval from November 28, 2019 through December 1, 2020 did not suggest an increase in the frequency of vital sign abnormalities compared to data previously reviewed for the DBT and OLE periods.

8.4.8. Electrocardiograms (ECGs)

No ECG-related AEs were reported in ADAE. The dataset ADEG did not provide ECG interpretations, only values for PR interval, QRS interval, QT interval (uncorrected, Fridericia Correction, and Bazett Correction), RR interval, and ventricular rate. No patients had PR interval >200 msec or QTc (Fridericia formula) ≥450 msec.

8.4.9. QT

No AEs related to QT prolongation were reported in ADAE. Additionally, no patients in Trial EFC11759 had an ECG with QTc (Fridericia formula) ≥450 msec. Teriflunomide is not known to prolong the QT interval.

8.4.10. Immunogenicity

Immunogenicity is not expected with teriflunomide and was therefore not assessed in Trial EFC11759.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Pancreatitis and Pancreatic Enzyme Elevations

Pancreatitis has been reported in the postmarketing setting for teriflunomide in adults, and was added to teriflunomide labeling in 2015. Four cases of pancreatitis occurred in pediatric patients on teriflunomide in Trial EFC11759, and others experienced pancreatic enzyme elevations. Please refer to Sections 8.4.2, 8.4.3, 8.4.4, 8.4.5, and 8.4.6 for further review of pancreatic disorder-related SAEs and TEAEs, as well as amylase and lipase values across the DBT period.

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The sponsor therefore submitted a Safety Evaluation Report for pancreatitis with this efficacy supplement. A nonclinical safety signal was detected in Beagle dog for the occurrence of pancreatitis. To calculate a background rate of acute pancreatitis, the sponsor estimated the incidence using the Real-World Evidence Database (Optum Humedica) in patients 10 to <18 years of age with MS as 4.23 per 1,000 person years (compared to 0 per 1,000 person-years in patients without MS). The risk of pancreatitis also appears to be higher in adult patients with MS compared to those without MS (9.00 per 1,000 person-years versus 5.13 per 1,000 person-years).

The sponsor estimated that 4000 adults have been exposed to teriflunomide in clinical trials. In the 2300 adults enrolled in pooled placebo-controlled clinical studies of teriflunomide, the incidence of pancreatic disorder TEAEs were similar across groups (2.8%, 2.6%, and 2.8% in placebo, teriflunomide 7mg, and teriflunomide 14mg groups, respectively). Two cases of pancreatitis were reported in the placebo group. In the teriflunomide 7mg group, 1 SAE of acute pancreatitis and 3 SAEs of lipase increase were reported. In the teriflunomide 14mg group, 2 SAEs of lipase increase were reported in the teriflunomide group. Serious acute pancreatitis TEAEs occurred in 0.4% of patients on teriflunomide 7mg and 0.2% of patients on teriflunomide 14mg.

In extension studies, the incidence of acute pancreatitis ranged from 1.9% to 14.8% for teriflunomide 7mg and 1.7% to 15.2% for teriflunomide 14mg. Serious acute pancreatitis TEAEs occurred in 0.3 to 2.5% of patients on teriflunomide 7mg and 0.5 to 0.9% of patients on teriflunomide 14mg.

The sponsor also evaluated the incidence of pancreatitis in the postmarketing setting, during which an estimated 368,458 patient-years of exposure to teriflunomide have occurred. The sponsor received 276 case reports under the SMQ Acute Pancreatitis, and the mean age of these patients was 46.4 years (range 18 to 78 years, not reported in 51 reports). The most common PTs reported were pancreatitis (n = 148), lipase increased (n = 97), amylase increased (n = 32), and pancreatitis acute (n = 27). Of these 276 cases reporting 322 total events, 75% (n = 206) were serious. Teriflunomide was discontinued in 131 cases, 22 of which underwent an accelerated elimination procedure. Two cases were fatal (both had confounding factors) and 106 required hospitalization. Time to onset was unknown for 68% of events, but the median time to onset was 1.4 years (range 0 days to 10.4 years). Dechallenge was positive in 14 cases.

Additionally, the sponsor reported 176 cases of pancreatitis in the postmarketing setting, 2 of which were considered likely related to teriflunomide. One case of necrotizing pancreatitis requiring ICU admission was reported in a 46 year-old man on teriflunomide and interferon beta-1a. Two pancreatitis cases in Spain were also reported in the literature (times to onset 5 months and 15 months) and were considered likely related to teriflunomide. Five cases of pancreatitis considered possibly related to teriflunomide were reported. The sponsor also

reported 100 cases of PTs related to increased pancreatic enzymes. Of these cases, 66 reported lab values. Only 1 case had imaging findings of pancreatitis with lipase >2x ULN, but this case was also confounded by a history of alcohol consumption.

Overall, the sponsor's analysis of postmarketing data indicated a higher rate of pancreatitis associated with teriflunomide (74.9/100,000) compared to the background rate (13 to 45/100,000). In the pediatric population, the frequency of pancreatitis was also higher in patients on teriflunomide (2.4%) compared to the background rate (0.01%).

In the DBT period of Trial EFC11759, pancreatic disorders were reported in 3.7% of patients on teriflunomide (n = 4) compared to 1.8% on placebo (n = 1) (Table 61). One of the cases of the PT pancreatitis acute was an SAE (Section 8.4.2.1). Of the 4 patients on teriflunomide who experienced pancreatic disorder TEAEs, 3 led to treatment discontinuation and use of an accelerated elimination procedure (Section 8.4.3). The patient on teriflunomide who experienced isolated hyperlipasaemia had a lipase of 2163 IU/L (34.33x ULN) and an amylase 498 IU/L (6.55x ULN). All patients had positive dechallenge.

In terms of laboratory abnormalities, as discussed in Section 8.4.6, patients on teriflunomide were more likely to experience peak lipase >2x ULN compared to placebo during DBT (Table 57).

During the OLE period, the incidence of pancreatic disorders was higher in the teriflunomide/teriflunomide group (3.0%) compared to the placebo/teriflunomide group (1.9%) (Table 61). Two of the patients in the teriflunomide/teriflunomide group experienced SAEs of pancreatitis leading to treatment discontinuation. One patient had an increase in lipase to 7.5x ULN. In the 120 Day Safety Update, the sponsor reported that another patient in the teriflunomide/teriflunomide group experienced pancreatitis that led to permanent discontinuation (not reflected in Table 61).

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Table 61 (Reviewer). Summary of Pancreatic Disorder TEAEs, Trial EFC11759

	Double-Blind Treatment		Open-Label Extension		
Preferred Term	**Teriflunomide (n = 109)**	**Placebo (n = 57)**	**Teriflunomide-Teriflunomide (n = 100)**	**Placebo-Teriflunomide (n = 52)**	**All OLE patients (n = 152)**
Any pancreatic disorder	**3.7 (4)**	**1.8 (1)**	**3.0 (3)**	**1.9 (1)**	**2.6 (4)**
Pancreatic disorder SAE	0.9 (1)	0 (0)	2.0 (2)	0 (0)	1.3 (2)
Amylase >2x ULN[1]	3.7 (4)	3.5 (2)	3.0 (3)	0 (0)	2.0 (3)
Lipase >2x ULN[1]	4.6 (5)	1.8 (1)	3.0 (3)	1.9 (1)	2.6 (4)
Pancreatitis acute	1.8 (2)	0 (0)	1.0 (1)	0 (0)	0.7 (1)
Pancreatitis	NA	NA	1.0 (1)	0 (0)	0.7 (1)
Lipase increased	0.9 (1)	1.8 (1)	2.0 (2)	1.9 (1)	2.0 (3)
Amylase increased	0.9 (1)	0 (0)	2.0 (2)	0 (0)	1.3 (2)
Hyperlipasaemia	0.9 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Pancreatic neoplasm	NA	NA	1.0 (1)	0 (0)	0.7 (1)

[1]Tabulations include all available laboratory values (with ONTRTFL=Y) and therefore differ from data presented in Section 8.4.6

In the Safety Evaluation Report, the sponsor also compared the incidence of pancreatitis in Trial EFC11759 to a background rate of pancreatitis of 1/10,000 in children.[36] Overall, the incidence of pancreatitis in pediatric patients on teriflunomide in Trial EFC11759 appears to be higher than the background rate.

> ***Reviewer comment****: There appears to be a differential risk of pancreatitis between adult and pediatric patients on teriflunomide. Additionally, the higher incidence of pancreatic disorder TEAEs in the teriflunomide/teriflunomide group during the OLE suggests that the risk of pancreatic disorders in children increases over time. This risk is new and should be added to approved labeling to inform prescribers and patients of this identified risk.*

8.5.2. Hepatotoxicity

Hepatotoxicity is a known risk associated with teriflunomide, and is included in current approved labeling as a boxed warning. Some reported cases of hepatotoxicity with teriflunomide have been clinically significant and potentially life-threatening. Patients on teriflunomide should undergo regular monitoring of liver function during treatment.

During DBT, TEAEs under the Hepatobiliary disorders SOC were reported in 0% (n = 0) of patients on teriflunomide and 5.3% (n = 3) on placebo. The liver-related TEAEs that occurred during Trial EFC11759 were primarily under the Investigations SOC. TEAEs under the AE High Level Term Liver function analyses occurred in 5 patients on teriflunomide (4.6%) compared to 1 patient on placebo (1.8%). No Hy's Law cases were reported or suspected.

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In addition to the 2 SAEs, 1 AE leading to treatment discontinuation, and significant AEs reported in Sections 8.4.2, 8.4.3, and 8.4.4, two patients experienced hepatic adverse events of interest:

1. *Subject ID* (b) (6) This patient was a 16 year-old Caucasian girl from Russia who received placebo during DBT, and switched to open-label teriflunomide on Day 204 due to confirmed clinical relapse. On Day 140, the patient experienced a non-serious event of hyperbilirubinemia (total bilirubin 39 µmol/L, 1.86x ULN) with a normal baseline value of 21 µmol/L (1.0x ULN). AST, ALT, and GGT were normal. She was diagnosed with Gilbert's syndrome, and recovered on Day 169.

2. *Subject ID* (b) (6) This patient was a 17 year-old Caucasian boy from Turkey who received teriflunomide during DBT and switched to OLE on Day 672 after completing 96-week DBT. On Day 57, he experienced a non-serious TEAE of ALT increase (ALT 2.4x ULN, with AST 1.4x ULN, normal GGT, and normal total bilirubin). On Day 59, ALT was 2.2x ULN and AST 1.2x ULN. He was considered recovered on Day 64, with normal AST/ALT values. He experienced ALT>2x ULN again on Day 169, which normalized on Day 211. Study drug was not interrupted during this time.

   Reviewer comment*: It is possible that these laboratory abnormalities were related to teriflunomide given their recurrence and the known safety profile of teriflunomide, but the spontaneous resolution without drug interruption suggests an alternative etiology.*

In terms of laboratory abnormalities, as discussed in Section 8.4.6, patients on teriflunomide were more likely to experience peak ALT or AST >2x ULN compared to placebo (Table 57; Table 62). Laboratory data indicated an increase of mean ALT in the teriflunomide group compared to placebo over DBT (Figure 17). Additionally, shift analyses for the combined DBT plus OLE periods indicated that patients in the placebo-teriflunomide group were more likely to experience ALT>2x ULN compared to the teriflunomide-teriflunomide group (19.2% versus 8.0%, respectively).

A summary of the frequency of hepatic disorder TEAEs and pertinent laboratory abnormalities across DBT and OLE periods is presented in Table 62.

Table 62 (Reviewer). Summary of Hepatic Disorder TEAEs, Trial EFC11759

	Double-Blind Treatment		Open-Label Extension		
Preferred Term	**Teriflunomide (n = 109)**	**Placebo (n = 57)**	**Teriflunomide-Teriflunomide (n = 100)**	**Placebo-Teriflunomide (n = 52)**	**All OLE patients (n = 152)**
Any Hepatic disorder TEAE[1]	4.6 (5)	3.5 (2)	4.0 (4)	15.4 (8)	7.9 (12)
Hepatic disorder SAE	1.8 (2)	0 (0)	0 (0)	5.8 (3)	2.0 (3)
HLT Liver function analysis	4.6 (5)	1.8 (1)	4.0 (4)	15.4 (8)	7.9 (12)
AST>2x ULN[2]	4.6 (5)	0 (0)	6.0 (6)	7.7 (4)	6.6 (10)
ALT>2x ULN[2]	6.4 (7)	0 (0)	4.0 (4)	19.2 (10)	9.2 (14)
Alanine aminotransferase increased	2.8 (3)	1.8 (1)	3.0 (3)	15.4 (8)	7.2 (11)
Aspartate aminotransferase increased	0.9 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Transaminases increased	0.9 (1)	0 (0)	1.0 (1)	1.9 (1)	1.3 (2)
Hyperbilirubinemia	0 (0)	1.8 (1)	0 (0)	0 (0)	0 (0)
Hepatic function abnormal	0 (0)	0 (0)	0 (0)	1.9 (1)	0.7 (1)

[1] Per Hepatic disorders SMQ; [2]Tabulations include all available laboratory values (with ONTRTFL=Y) and therefore differ from data presented in Section 8.4.6

In the 120 Day Safety Update, the sponsor indicated that 1 patient in the teriflunomide-teriflunomide group had ALT 5-10x ULN after treatment discontinuation during an accelerated elimination protocol. One patient (1.0%) in the teriflunomide-teriflunomide group and 2 patients in the placebo-teriflunomide group (3.8%) experienced ALT>2x ULN in the reporting interval.

> ***Reviewer comment:*** *Data from Trial EFC11759 suggest that hepatic disorders, specifically liver function testing abnormalities, are more common in patients on teriflunomide and may be more likely to occur earlier in treatment. The risk of hepatic disorders with teriflunomide does not appear to be higher in the pediatric population compared to adult clinical trial data. The boxed warning in current approved labeling adequately conveys the known, serious hepatotoxicity risk associated with teriflunomide treatment.*

8.5.3. Bone Marrow Effects/Immunosuppression

Bone marrow effects, including decreases in leukocytes, neutrophils, and lymphocytes, have been reported in clinical trials of teriflunomide in adults, and are included in the Warnings and Precautions section of current labeling.

In order to aid in the assessment of a potential differential risk of neutropenia in pediatric and

adult patients on teriflunomide, the Division requested that the sponsor submit a Safety Evaluation Report for neutropenia. This Information Request was sent on February 3, 2021, and the sponsor submitted the requested Safety Evaluation Report for neutropenia on March 12, 2021.

The sponsor estimated that 4000 adults have been exposed to teriflunomide in clinical trials. In the 2300 adults enrolled in pooled placebo-controlled clinical studies of teriflunomide, the incidence of neutropenia-related TEAEs was higher in patients on teriflunomide (3.1%, 6.4%, and 7.7% in placebo, teriflunomide 7mg, and teriflunomide 14mg groups, respectively). The frequency of neutropenia-related SAEs appeared similar across the groups (0.4%, 0.2%, and 0.8% in placebo, teriflunomide 7mg, and 14mg, respectively), but was numerically higher in the teriflunomide 14mg group. In extension studies, the incidence of neutropenia-related TEAEs ranged from 4.7% to 9.9% for teriflunomide 7mg and 0.8% to 21.2% for teriflunomide 14mg. The frequency of neutropenia-related SAEs was 1.0% for teriflunomide 7mg and 0.3 to 0.5% for teriflunomide 14mg. The sponsor concluded that the frequency of neutropenia-related TEAEs was similar in pediatric and adult populations.

> ***Reviewer comment:*** *The frequency of neutropenia or neutrophils decreased TEAEs in Trial EFC11759 was 5.5% in patients on teriflunomide versus 0% on placebo. This incidence is similar to that observed in adult trials of teriflunomide.*

Several cases of cytopenias occurred during Trial EFC11759. Please refer to Section 8.4.6 for review of laboratory data relevant to bone marrow effects. Patients on teriflunomide were more likely to experience decreased leukocyte counts, neutrophil counts, and lymphocyte counts compared to those on placebo. Additionally, patients on teriflunomide were more likely to experience TEAEs related to bone marrow effects during DBT compared to those on placebo, particularly neutropenia, leukopenia, WBC count decreased, and neutrophil count decreased.

As discussed in Section 8.4.6, patients on teriflunomide were more likely to experience nadir ANC 0.5 to 1.0 $x10^9$/L compared to placebo (5.5% versus 0%) (Table 57). Patients on teriflunomide were more likely to experience nadir leukocyte count 2.0 to 3.5 $x10^9$/L compared to placebo (23.9% versus 7.1%). Patients on teriflunomide were also more likely to experience nadir ALC 0.5 to 1.0 x 10^9/L compared to placebo (12.8% versus 5.4%). Consistent reductions in hemoglobin were not observed in either treatment group during DBT.

The incidence of leukopenia, lymphopenia, and neutropenia TEAEs did not appear to increase with continued teriflunomide use during the OLE. Overall, patients in the placebo-teriflunomide group had similar incidence of these TEAEs as patients on teriflunomide during DBT. However, shift analysis of laboratory values (Section 8.4.6) suggested that the incidence of lower leukocyte and lymphocyte counts increased with prolonged use in the OLE period.

Reference ID: 4776272

Immunoglobulin levels were also evaluated during Trial EFC11759. Please refer to Section 8.4.6 for laboratory data for IgG, IgM, and IgA. Overall, patients on teriflunomide experienced reductions in mean IgG, IgM, and IgA compared to placebo, and some patients who experienced infections classified as SAEs had low IgG. During OLE, 1 patient in the teriflunomide-teriflunomide group had the TEAEs blood immunoglobulin G decreased and blood immunoglobulin M decreased.

A summary of the frequency of bone marrow-related TEAEs and pertinent laboratory abnormalities across DBT and OLE periods is presented in Table 63.

Table 63 (Reviewer). Bone Marrow Effect-Related TEAEs, Trial EFC11759

	Double-Blind Treatment		**Open-Label Extension**		
Preferred Term	**Teriflunomide (n = 109)**	**Placebo (n = 57)**	**Teriflunomide-Teriflunomide (n = 100)**	**Placebo-Teriflunomide (n = 52)**	**All OLE patients (n = 152)**
% (n) patients with TEAEs under Hematopoietic Cytopenias SMQ	7.3 (8)	1.8 (1)	5.0 (5)	3.8 (2)	4.6 (7)
% (n) patients with bone marrow disorder SAE	0.9 (1)	0 (0)	1.0 (1)	0 (0)	0.7 (1)
% (n) patients with HLT Neutropenias	2.8 (3)	0 (0)	1.0 (1)	0 (0)	0.7 (1)
% (n) patients with HLT Leukopenias NEC	1.8 (2)	0 (0)	1.0 (1)	1.9 (1)	1.3 (2)
% (n) patients with HLT WBC Analyses	6.4 (7)	1.8 (1)	3.0 (3)	3.8 (2)	3.3 (5)
Anaemia	2.8 (3)	1.8 (1)	2.0 (2)	0 (0)	1.3 (2)
Neutropenia	2.8 (3)	0 (0)	1.0 (1)	0 (0)	0.7 (1)
Leukopenia	1.8 (2)	0 (0)	1.0 (1)	1.9 (1)	1.3 (2)
Monocytopenia	1.8 (2)	0 (0)	0 (0)	0 (0)	0 (0)
White blood cell count decreased	3.7 (4)	1.8 (1)	3.0 (3)	3.8 (2)	3.3 (5)
Neutrophil count decreased	2.8 (3)	0 (0)	2.0 (2)	1.9 (1)	2.0 (3)
Monocyte count decreased	0.9 (1)	0 (0)	1.0 (1)	1.9 (1)	1.3 (2)
Blood immunoglobulin G decreased	0 (0)	0 (0)	1.0 (1)	0 (0)	0 (0)
Blood immunoglobulin M decreased	0.9 (1)	0 (0)	1.0 (1)	0 (0)	0 (0)

Reviewer comment: *Data from Trial EFC11759 suggest a similar risk of bone marrow effects, particularly neutropenia, between adult and pediatric patients on teriflunomide. Prolonged use of teriflunomide did not appear to increase the incidence of cytopenia-related TEAEs in Trial EFC11759.*

8.5.4. Infections

Due to its known mechanism of immunosuppression and resultant bone marrow effects (Section 8.5.3), the risk of infection is expected to be higher in patients on teriflunomide.

During DBT, TEAEs under the Infections and infestations SOC were reported in 66.1% (n = 72) of patients on teriflunomide and 45.6% (n = 26) on placebo. Infection-related SAEs during DBT are discussed in Section 8.4.2.1, and include pulmonary tuberculosis in a patient on teriflunomide.

Infection-related PTs that occurred in >1 patient in either treatment group during DBT are reported in Table 64. The most common infections were nasopharyngitis, upper respiratory tract infections, influenza, and pharyngitis.

> ***Reviewer comment:*** *Overall, these data suggest that the risk of infection is higher for patients on teriflunomide, which is not unexpected given its known and intended immunosuppressive effects and is represented in current approved labeling.*

Table 64 (Reviewer). Infections Occurring in >1 Patient in Either Treatment Group During Double-Blind Period

Preferred Term	Teriflunomide (n = 109)	Placebo (n = 57)
Infections and Infestations (SOC)	**66.1 (72)**	**45.6 (26)**
Nasopharyngitis	25.7 (28)	8.8 (5)
Upper respiratory tract infection	21.1 (23)	10.5 (6)
Influenza	9.2 (10)	7.0 (4)
Pharyngitis	6.4 (7)	1.8 (1)
Bronchitis	4.6 (5)	1.8 (1)
Gastroenteritis	2.8 (3)	5.3 (3)
Rhinitis	3.7 (4)	3.5 (2)
Sinusitis	3.7 (4)	3.5 (2)
Tonsillitis	3.7 (4)	3.5 (2)
Respiratory tract infection viral	3.7 (4)	0 (0)
Oral herpes	1.8 (2)	1.8 (1)
Tinea versicolour	0.9 (1)	3.5 (2)
Urinary tract infection	1.8 (2)	1.8 (1)
Viral upper respiratory tract infection	1.8 (2)	1.8 (1)

Other infections of note during DBT included a case of PT blastocystis infection in a patient on teriflunomide (classified as mild) and a case of PT pneumonia bacterial in a patient on teriflunomide (classified as moderate).

During OLE, TEAEs under the Infections and infestations SOC were reported in 46.7% of patients overall. The incidence was similar between the teriflunomide DB-teriflunomide OL and placebo

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DB-teriflunomide OL groups. Infection-related SAEs during OLE are discussed in Section 8.4.2.2, and include acute sinusitis (n = 1), bronchitis (n = 1), CNS infection (n = 1), food poisoning (n = 1), lung infection (n = 1), tonsillitis (n = 1), and upper respiratory tract infection (n = 1).

Herpes infections were reported during both DBT and OLE:

- DBT
  - 3 cases of PT oral herpes (2 in teriflunomide, 1 in placebo), all classified as mild
  - 1 case of herpes simplex in a patient on teriflunomide, classified as mild
- OLE
  - 1 case of PT oral herpes, classified as mild
  - 1 case of PT herpes virus infection, classified as mild
  - 1 case of PT herpes zoster, classified as mild
  - 1 case of PT varicella, classified as mild

A case of mycoplasma infection also occurred in a teriflunomide-teriflunomide patient during OLE, but was considered mild (neither serious nor severe).

8.5.5. Malignancy

The theoretical risk of malignancy, particularly lymphoproliferative disorders, is associated with any immunosuppressant or immunomodulatory therapy, and is discussed in teriflunomide labeling.

During DBT, one patient in the placebo group (a 17 year-old girl from Russia) experienced a TEAE under the SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps) with the PT ovarian cyst.

During OLE, TEAEs under the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC were reported in 1.3% of patients overall (n = 2). Both patients had received teriflunomide during DBT, and are discussed below:

1. *Subject ID* (b) (6) *PT pancreatic neoplasm*: Please refer to Section 8.4.2.2 for discussion of this case. The nature of this neoplasm in this patient on teriflunomide (described as "occupancy of uncinate process of pancreas") is unclear based upon the provided narrative due to the lack of histopathology.
2. *Subject ID* (b) (6) *PT dermal cyst*: This patient experienced a dermal cyst, described as "pylar cyst in sacral area," during open-label treatment with teriflunomide. She experienced the SAE anal fistula during DBT and is discussed in Section 8.4.2.1. Pilar cysts are generally benign findings, but can rarely become cancerous.

Reviewer comment: *Overall, it does not appear that any cases of malignancy occurred during Trial EFC11759. Malignancy is rare in children and the short duration of this trial is not expected to identify a malignancy risk. It is important to consider the unknown lifetime*

risk of malignancy related to long-term immunosuppressant exposure in childhood.

8.5.6. Hypersensitivity and Serious Skin Reactions

Cases of anaphylaxis, severe allergic reactions, and serious skin reactions (including Drug Reaction with Eosinophils and Systemic Symptoms [DRESS]) have occurred with teriflunomide.

No cases of anaphylaxis, severe allergic reactions, or serious skin reactions (including DRESS, Stevens Johnson Syndrome, or Toxic Epidermal Necrolysis) were reported during the DBT or OLE periods of Trial EFC11759.

The PT rash was reported in 3.7% of patients on teriflunomide (n = 4) and 3.5% of patients on placebo (n = 2) during DBT. One case of PT dermatitis allergic was reported in each treatment group (0.9% teriflunomide, 1.8% placebo) during DBT. One case of the PT rash macular was reported in a patient on teriflunomide during DBT (0.9%). However, no SAEs were reported that would indicate a serious allergic or skin reaction.

During the OLE, the PT rash reported in 2 patients (1.3%), 1 in each group (1.0% teriflunomide/teriflunomide, 1.9% placebo/teriflunomide). One case of PT dermatitis allergic was reported in each treatment group as well (1.0% teriflunomide/teriflunomide, 1.9% placebo/teriflunomide). Again, no SAEs were reported that would indicate a serious allergic or skin reaction.

The 120 day update reported a treatment-emergent SAE of drug eruption in a patient in the teriflunomide/teriflunomide group. This patient (subject ID (b) (6) was an 11 year-old Chinese girl with a medical history of viral encephalitis, "demyelination disease," and epilepsy. She experienced several TEAEs and SAEs during the DBT and OLE periods, as discussed in Section 8.4.2. She experienced the SAE drug eruption on Day 1365, after developing this PT as a non-serious TEAE on Day 1355. The rash was described as "rash all over the body, without patchy itching." She also experienced concomitant DILI, with ALT 5.2x ULN, on Day 1362. She was hospitalized on Day 1365, at which time she received "an unspecified corrective treatment for drug eruption." The narrative reported that the rash "had become lighter in color." She recovered from both events by Day 1385.

> ***Reviewer comment:*** *The etiology of this patient's drug eruption is not clear based upon the provided information. However, the concurrent DILI could be concerning for DRESS, but other relevant data regarding DRESS criteria (e.g., eosinophil count) were not provided. She had previously received several medications during a hospitalization that began on Day 1309, including dexamethasone, penciclovir, ceftriaxone, cefdinir, methylprednisolone, and "relevant hormones." However, the time to onset (up to 2 months) would be unusual for a drug eruption from a medication given during that hospitalization, and the long time to onset in relation to teriflunomide would also be*

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unusual for teriflunomide-related DRESS. Additionally, it appears that she is chronically treated with valproic acid for epilepsy, which also can cause rash and DILI. This patient appears to have significant intercurrent illness, given her recurrent hospitalizations and infections; several confounding factors exist for this case.

Overall, no definitive cases of hypersensitivity and serious skin reactions were reported in Trial EFC11759.

8.5.7. Peripheral Neuropathy

Peripheral neuropathy is a known adverse reaction for teriflunomide. In placebo-controlled studies of teriflunomide in adults with relapsing MS, peripheral neuropathy (including polyneuropathy and mononeuropathy) confirmed via nerve conduction studies occurred in in 1.4% and 1.9% of patients treated with 7 mg or 14 mg of teriflunomide, compared with 0.4% for placebo.

Trial EFC11759 designated peripheral neuropathy as an Adverse Event for Pre-specified Monitoring. Per the protocol, all neurological symptoms suggestive of a peripheral neuropathy would be followed up with nerve conduction studies. Patients were screened for signs and symptoms of peripheral neuropathy at each visit involving a physical examination. Study treatment was to be discontinued if a drug-related peripheral neuropathy was confirmed.

During DBT, one patient in the teriflunomide group (*Subject ID* (b) (6) experienced the PT neuralgia (AETERM "arm neuralgic pain"), and one patient in the placebo group (Subject ID (b) (6) experienced the PTs neuropathy peripheral and neuralgia (AETERM "left sided neuropathy without nerve conduction study," "nerve pain around joints...PI found paresthesia with no evidence of peripheral neuropathy."). Nerve conduction studies were not performed for either patient. One case of peripheral nerve injury were due to a physical injury rather than peripheral neuropathy (Section 8.4.2.1).

Reviewer comment: *Based on this information, it does not appear that true peripheral neuropathy occurred during the DBT period.*

In the OLE period, two patients from each group (2.0% teriflunomide-teriflunomide and 3.8% placebo-teriflunomide) experienced potential peripheral neuropathy. In the placebo-teriflunomide group, the reported PTs were neuralgia (n = 1) and neuropathy peripheral (n = 1). In the teriflunomide-teriflunomide group, the reported PTs were neuralgia (n = 1) and sensory loss (n = 1):

- In the 1 patient (*Subject ID* (b) (6) who experienced the PT **peripheral neuropathy** during the OLE period, an associated nerve conduction study demonstrated findings consistent with an axonal polyneuropathy (Section 8.4.3). This patient discontinued treatment due to this event.

- The TEAE **neuralgia** (*Subject ID* (b) (6) in the teriflunomide/teriflunomide group occurred in a 14 year-old Caucasian girl from Israel who also experienced this event during the DBT period. She was treated with carbamazepine and baclofen. This event was not considered related to teriflunomide.
- The TEAE **sensory loss** (*Subject ID* (b) (6) in the teriflunomide/teriflunomide group occurred in a 17 year-old Caucasian girl from Turkey who developed "sensory loss and tingling due to exercises" on Day 259 of the OLE period. Per the provided narrative, electromyography was normal, and she received oral thiamine/pyridoxine/cyanocobalamin. She recovered approximately 100 days later. This event was not considered related to teriflunomide.
- The TEAE **neuralgia** (*Subject ID* (b) (6) in the placebo/teriflunomide group occurred in a 13 year-old Caucasian boy from France who developed "neuropathic pain" of mild intensity on Study Day 724 during OLE. This event was not considered related to teriflunomide.

No additional cases of peripheral neuropathy were reported with the 120 Day Safety Update.

Reviewer comment: *Overall, there appears to be 1 case of drug-related peripheral neuropathy that occurred during the OLE of Trial EFC11759. No TEAEs of carpal tunnel syndrome or other mononeuropathies were reported.*

8.5.8. 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. Additionally, 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% for placebo.

In terms of blood pressure-related TEAEs, the PT hypertension was reported in 1 patient on placebo during DBT. Additionally, orthostatic hypotension was reported in 2 patients (3.5%) on placebo. No patients on teriflunomide experienced blood pressure-related TEAEs during DBT.

During OLE, 3 patients in the teriflunomide-teriflunomide group experienced increased blood pressure. The PT hypertension occurred in 2 patients in the teriflunomide-teriflunomide group. The PT blood pressure increased occurred in 1 patient in the teriflunomide-teriflunomide group as well. No cases of orthostatic hypotension occurred during OLE. Per the sponsor's CSR, 2 patients received corrective treatment for hypertension during OLE (1 calcium channel blocker and 1 calcium channel blocker plus angiotensin-2 receptor inhibitor).

Reviewer comment: *Based upon the low incidence of blood pressure-related TEAEs in Trial EFC11759, there does not appear to be a higher risk of increased blood pressure with teriflunomide in the pediatric population compared to the adult population.*

However, as discussed in Section 8.4.7, patients on teriflunomide generally had higher mean and median changes in supine SBP at each visit compared to those on placebo. Additionally, the proportion of patients with a >20 mmHg change (increase) in SBP at each visit was generally higher in patients on teriflunomide compared to placebo.

8.5.9. Respiratory Effects

Interstitial lung disease, including acute interstitial pneumonitis, has been reported in the postmarketing setting with teriflunomide. No cases of interstitial lung disease or acute interstitial pneumonitis were reported in Trial EFC11759, including 120 Day Safety Update.

During DBT, 5.5% of patients on teriflunomide (n = 6) and 5.3% of patients on placebo (n = 3) experienced the PT cough. The PT productive cough occurred in 0% of patients on teriflunomide and 1.8% patients on placebo (n = 1). During OLE, 2.0% of patients (n = 3) experienced the PT cough (2 of whom had received placebo during DBT).

During DBT, 2.8% of patients on teriflunomide (n = 3) and 0% of patients on placebo experienced the PT dyspnoea. During OLE, 0.7% of patients (n = 1) experienced the PT dyspnoea (patient received placebo during DBT).

Reviewer comment: *Overall, there was no evidence to suggest the occurrence of interstitial lung disease during Trial EFC11759.*

8.5.10. Acute Renal Failure

No adverse events of acute renal failure, acute kidney injury, nephrolithiasis, hyperkalemia, increased creatinine, or increased blood urea nitrogen were reported during Trial EFC11759.

During DBT, TEAEs under the SOC Renal and urinary disorders were reported in 8.3% (n = 9) of patients on teriflunomide and 5.3% (n = 3) on placebo.

The sponsor's 120 Day Safety Update reported one case of serum creatinine >2x baseline in a patient in the placebo/teriflunomide group on Day 1200. The patient's creatinine was within normal limits at 78 µmol/L (ref. Range 23-83), but the baseline value was 37 µmol/L.

Reviewer comment: *Overall, there was no evidence to suggest the occurrence of acute renal failure during Trial EFC11759.*

8.5.11. Increased Creatine Phosphokinase

Elevated creatine phosphokinase (CPK) is not a known safety concern with teriflunomide or leflunomide per current USPIs. However, several cases of elevated CPK occurred in patients

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receiving teriflunomide during the DBT and OLE periods of Trial EFC11759.

In response to an Information Request sent on February 3, 2021, the sponsor submitted a Safety Evaluation Report for CPK increase on March 12, 2021.

The sponsor estimated that 4000 adults have been exposed to teriflunomide in clinical trials. In the 2300 adults enrolled in pooled placebo-controlled clinical studies of teriflunomide, the incidence of increased CPK TEAEs were similar across groups (0.7%, 2.0%, and 1.6% in placebo, teriflunomide 7mg, and teriflunomide 14mg groups, respectively). One TEAE in the teriflunomide 7mg group (<0.1%) was serious. One case of rhabdomyolysis (with CPK 99x ULN) was reported in the pooled placebo-controlled population in a 31 year-old woman 10 days after intense physical exercise followed by muscle soreness that occurred 10.3 weeks after starting teriflunomide 7mg daily (Study HMR1726/2001, Patient 0011/0003). Teriflunomide was temporarily discontinued, the rhabdomyolysis resolved, and CPK remained normal with rechallenge.

> ***Reviewer comment:*** *This case of rhabdomyolysis appears to be related to strenuous exercise rather than teriflunomide, particularly given the negative rechallenge. However, a contribution of teriflunomide to this likely exercise-induced rhabdomyolysis cannot be excluded.*

Additionally, in the pooled placebo-controlled trial population, the frequency of CPK >2.5x ULN was higher in patients on teriflunomide. Specifically, CPK >2.5x ULN occurred in 3.3% of patients on placebo, 4.9% on teriflunomide 7mg, and 7.3% on teriflunomide 14mg. However, the frequency of CPK >10x ULN was not higher in patients on teriflunomide compared to placebo (0.4% and 0.6% versus 1.3%).

In extension studies, the frequency of increased CPK ranged from 0.3 to 3.7% for teriflunomide 7mg and 1.3 to 12.1% for teriflunomide 14mg. Serious increased CPK TEAEs occurred in 0% of patients on teriflunomide 7mg and 0.5 to 0.9% of patients on teriflunomide 14mg.

The sponsor also evaluated the incidence of increased CPK in the postmarketing setting, during which an estimated 460,216 patient-years of exposure to teriflunomide have occurred. Fifty-four case reports of 56 pertinent events were reviewed for this analysis: 54 events of PT blood CPK increased and 2 of PT blood CPK abnormal. The mean age of these patients was 41.6 years (range 23 to 60 years, not reported in 14 cases). Of these 54 reports, 20 were serious, 1 was fatal (rhabdomyolysis in the setting of status epilepticus, septic shock, disseminated intravascular coagulation, acute hepatic failure, and abnormal renal function), and 1 was life-threatening (in the setting of suicide attempt via teriflunomide, amitriptyline, and alcohol overdose). Teriflunomide was discontinued in 16 cases. The time to onset was unknown for

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88% of cases, but in the 12% that reported this parameter, time to onset ranged from 10 days to 3 years (mean 6.5 months).

The sponsor also reported 5 postmarketing cases of rhabdomyolysis, including the fatal case mentioned above. The sponsor classified 4 of these cases as unlikely related, and 1 as unassessable.

> ***Reviewer comment:*** *Upon review of these 5 cases presented in the sponsor's Safety Evaluation Report, one is confounded by temporal relationship with "physical effort," one by associated trauma, and one by status epilepticus (mentioned above). However, 2 cases could potentially be related to teriflunomide:*
>
> 1. *Case ID* (b) (6) *32 year-old man from the US who was hospitalized following "collapse, ...serious MS relapse" and was treated with steroids. A few days later, he experienced rhabdomyolysis, kidney failure, elevated CPK, dehydration, and influenza-like illness. Though steroids can result in acute myopathy and potentially rhabdomyolysis, it is important to consider the potential role of teriflunomide in this case.*
> 2. *Case ID* (b) (6) *50 year-old woman from the US who developed rhabdomyolysis, weakness, diffuse body aches, skin rash, fever, "possible dermatomyositis," UTI, and CPK elevation. Though another inflammatory process could be a factor, as hypothesized by the sponsor, a role of teriflunomide in her presentation cannot be excluded given the information provided.*

Additionally, the sponsor reported cases with CPK values > 500 IU/L and assessed potential relationship with teriflunomide. Three cases were possibly related, 11 were unlikely related, and 7 cases were unassessable. All 3 possibly related cases had a positive dechallenge, and a positive rechallenge was reported for 1 case.

No cases of increased CPK or rhabdomyolysis with teriflunomide were reported in the medical literature.

Overall, the sponsor's Safety Evaluation Report concluded that the available data were "sufficient to support a potential causal association between teriflunomide and CPK increase," but not teriflunomide and rhabdomyolysis. However, the sponsor did not indicate a differential risk of CPK increase between adult and pediatric populations.

> ***Reviewer comment****: In the clinical trial populations (pooled adult placebo-controlled studies and Trial EFC11759), there did appear to be a differential risk between adult and pediatric populations. In the adult trials, the frequency of CPK increase was 1.6 to 2.0% in patients on teriflunomide. In the pediatric trial, the frequency of CPK increase was*

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6.4% in patients during DBT. This reviewer therefore disagrees with the sponsor's assessment of this risk difference.

In Trial EFC11759, 10 cases of elevated CPK occurred in patients receiving teriflunomide during the DBT and OLE periods (Table 65). No cases of rhabdomyolysis or myositis were reported.

Table 65 (Reviewer). Increased Creatine Phosphokinase-Related TEAEs, Trial EFC11759

	Double-Blind Treatment		Open-Label Extension		
Preferred Term	**Teriflunomide (n = 109)**	**Placebo (n = 57)**	**Teriflunomide-Teriflunomide (n = 100)**	**Placebo-Teriflunomide (n = 52)**	**All OLE patients (n = 152)**
Any CPK-related TEAE	**6.4 (7)**	**0 (0)**	**2.0 (2)**	**1.9 (1)**	**2.0 (3)**
CPK-related SAE	**1.8 (2)**	**0 (0)**	**2.0 (2)**	**1.9 (1)**	**2.0 (3)**
HLT Skeletal and cardiac muscle analyses	6.4 (7)	0 (0)	2.0 (2)	1.9 (1)	2.0 (3)
Blood CPK increased	5.5 (6)	0 (0)	2.0 (2)	1.9 (1)	2.0 (3)
Blood CPK abnormal	0.9 (1)	0 (0)	0 (0)	0 (0)	0 (0)

Fourteen patients on teriflunomide (12.8%) and 3 patients on placebo (5.2%) experienced CPK > 2x ULN during DBT. The severity of CPK elevations during DBT are delineated in Table 57. Notably, 3 patients on teriflunomide experienced CPK >10x ULN, with 2 of these patients experiencing CPK >20x ULN. These patients are discussed in Section 8.4.4.

Reviewer comment: *There does appear to be an increased risk of CPK increase with teriflunomide compared to placebo, and this risk is numerically higher in the pediatric population based on Trial EFC11759.*

8.5.12. Alopecia

Alopecia is a known safety concern with teriflunomide, and has been reported in up to 13% of adult patients with relapsing MS in placebo-controlled studies.

In Trial EFC11759, the PT alopecia was reported in 21.1% (n = 23) of patients on teriflunomide and 12.3% (n = 7) on placebo during the DBT period. One patient on teriflunomide (0.9%) experienced alopecia areata.

During the OLE period, alopecia occurred in 11.8% (n = 18) patients, and was more frequent in patients who were treated with placebo during DBT (17.3%) rather than teriflunomide (9.0%). In the 120 Day Safety Update reporting interval, 2 additional patients (1 in each group) experienced alopecia. Additionally, one patient in the teriflunomide/teriflunomide group discontinued OLE treatment due to severe alopecia areata.

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Reviewer comment: *This adverse reaction of alopecia is a known safety concern with teriflunomide, and appears to have higher incidence in the pediatric population compared to adults. Though alopecia is not necessarily serious or life-threatening, it can have detrimental effects on a patient's body image and self-esteem.*

8.6. Safety Analyses by Demographic Subgroups

Sex

Overall, the incidence of SAEs and TEAEs appeared to be similar between male and female patients in Trial EFC11759. The incidence of hepatic events (particularly ALT increased, AST increased, transaminases increased), alopecia, and pancreatic events appeared similar between male and female patients.

Leukopenia-related AEs appeared to be more common in male patients during DBT, as 10.8% of male patients on teriflunomide (n = 4) experienced WBC decreased, versus 0% of female patients. Additionally, 10.8% of male patients (n = 4) experienced either neutropenia or neutrophil count decreased, compared to 2.8% of female patients (n = 2).

Additionally, CPK elevations (PTs blood CPK increased or blood CPK abnormal) appeared to be more common in male patients (10.8%, n = 4) compared to female patients (4.2%, n = 3) during DBT.

Table 66 (Reviewer). Safety Data by Sex, Trial EFC11759

	Female		**Male**	
Double Blind Treatment				
	Teriflunomide (n = 72)	**Placebo (n = 39)**	**Teriflunomide (n = 37)**	**Placebo (n = 18)**
% (n) patients with ≥1 SAE	9.7 (7)	10.3 (4)	13.5 (5)	11.1 (2)
% (n) patients with any TEAE	86.1 (62)	87.2 (34)	91.9 (34)	72.2 (13)
Open Label Extension				
	Teriflunomide (n = 102)	**-**	**Teriflunomide (n = 50)**	**-**
% (n) patients with ≥1 SAE	14.7 (15)	-	16.0 (8)	-
% (n) patients with any TEAE	72.5 (74)	-	74.0 (37)	-

Age

TEAEs were reviewed by age subgroups, specifically <12 versus ≥ 12 years to approximate body weight and pubertal status categories (Table 67). The small number of patients <12 years of age (n = 16) limits the ability to compare safety data between these groups. There do not appear to be any major differences in the overall incidence of TEAEs and SAEs between the groups.

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However, the incidence of TEAEs in the SOCs Infections and Infestations and Respiratory, thoracic and mediastinal disorders was higher in the younger age group during both DBT and OLE. Additionally, the incidence of leukopenia was higher in patients <12 years of age during both DBT and OLE.

Table 67 (Reviewer). Safety Data by Age, Trial EFC11759

	Age < 12 years		**Age ≥ 12 years**	
Double Blind Treatment				
	Teriflunomide (n = 9)	**Placebo (n = 7)**	**Teriflunomide (n = 100)**	**Placebo (n = 50)**
% (n) patients with ≥1 SAE	11.1 (1)	14.3 (1)	11.0 (11)	10.0 (5)
% (n) patients with any TEAE	100.0 (9)	85.7 (6)	87.0 (87)	82.0 (41)
Infections and Infestations SOC	100.0 (9)	57.1 (4)	63.0 (63)	44.0 (22)
Respiratory, thoracic and mediastinal disorders SOC	100.0 (9)	57.1 (4)	62.0 (62)	42.0 (21)
Leukopenia[1]	22.2 (2)	14.3 (1)	6.0 (6)	0 (0)
Alopecia[1]	11.1 (1)	14.3 (1)	23.0 (23)	12.0 (6)
Hepatic injury[1]	0 (0)	0 (0)	5.0 (5)	4.0 (2)
CPK increased[1]	0 (0)	0 (0)	7.0 (7)	0 (0)
Pancreatitis[1]	0 (0)	0 (0)	4.0 (4)	2.0 (1)
Open Label Extension				
	Teriflunomide (n = 16)	**-**	**Teriflunomide (n = 136)**	**-**
% (n) patients with ≥1 SAE	18.8 (3)	-	14.7 (20)	-
% (n) patients with any TEAE	81.3 (13)	-	72.1 (98)	-
Infections and Infestations SOC	75.0 (12)	-	43.4 (59)	-
Respiratory, thoracic and mediastinal disorders SOC	75.0 (12)	-	42.6 (58)	-
Leukopenia[1]	18.8 (3)	-	2.9 (4)	-
Alopecia[1]	12.5 (2)	-	11.8 (16)	-
Hepatic injury[1]	6.3 (1)	-	8.1 (11)	-
CPK increased[1]	0 (0)	-	2.2 (3)	-
Pancreatitis[1]	0 (0)	-	2.9 (4)	-

[1]Includes all related Preferred Terms

Pubertal Status

TEAEs were reviewed by pubertal status, specifically Tanner Stage 1 versus >1 (Table 68). Again, the small number of pre-pubertal patients (n = 9) limits the ability to compare safety data between these groups. The incidence of TEAEs in the SOCs Infections and Infestations and Respiratory, thoracic and mediastinal disorders was higher in the pre-pubertal group during both DBT and OLE. Additionally, the incidence of leukopenia was higher in pre-pubertal patients compared to pubertal patients during both DBT and OLE.

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Table 68 (Reviewer). Safety Data by Pubertal Status, Trial EFC11759

	Tanner Stage 1		**Tanner Stage >1**	
Double Blind Treatment				
	Teriflunomide (n = 4)	**Placebo (n = 5)**	**Teriflunomide (n = 105)**	**Placebo (n = 52)**
% (n) patients with ≥1 SAE	0 (0)	20.0 (1)	11.4 (12)	9.6 (5)
% (n) patients with any TEAE	100.0 (4)	100.0 (5)	87.6 (92)	80.8 (42)
Infections and Infestations SOC	100.0 (4)	40.0 (2)	64.8 (69)	46.2 (24)
Respiratory, thoracic and mediastinal disorders SOC	100.0 (4)	60.0 (3)	63.8 (67)	42.3 (22)
Leukopenia[1]	25.0 (1)	20.0 (1)	0 (0)	0 (0)
Alopecia[1]	0 (0)	0 (0)	22.9 (24)	13.5 (7)
Hepatic injury[1]	0 (0)	0 (0)	4.8 (5)	3.8 (2)
CPK increased[1]	0 (0)	0 (0)	6.7 (7)	0 (0)
Pancreatitis[1]	0 (0)	0 (0)	3.8 (4)	1.9 (1)
Open Label Extension				
	Teriflunomide (n = 9)	**-**	**Teriflunomide (n = 143)**	**-**
% (n) patients with ≥1 SAE	22.2 (2)	-	14.7 (21)	-
% (n) patients with any TEAE	88.9 (8)	-	72.0 (103)	-
Infections and Infestations SOC	66.7 (6)	-	45.5 (65)	-
Respiratory, thoracic and mediastinal disorders SOC	77.8 (7)	-	44.1 (63)	-
Leukopenia[1]	22.2 (2)	-	3.5 (5)	-
Alopecia[1]	0 (0)	-	12.6 (18)	-
Hepatic injury[1]	0 (0)	-	7.7 (11)	-
CPK increased[1]	0 (0)	-	2.1 (3)	-
Pancreatitis[1]	0 (0)	-	2.8 (4)	-

[1]Includes all related Preferred Terms based on logical clinical associations

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

The theoretical risk of malignancy is associated with any immunosuppressant or immunomodulatory therapy. A case of pancreatic neoplasm was reported in the OLE period of Trial EFC11759, and is discussed in Section 8.4.2.2. However, the nature of this neoplasm is unclear based upon the provided narrative due to the lack of histopathology. See Section 8.5.5. No definitive cases of treatment-emergent malignancy occurred in Trial EFC11759.

8.8.2. Human Reproduction and Pregnancy

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Teriflunomide has a boxed warning for embryofetal toxicity, as teratogenicity and embryolethality occurred in animals administered teriflunomide. Prescribers should exclude pregnancy prior to initiating teriflunomide, advise effective contraception use in females of reproductive potential being treated with teriflunomide, and discontinue teriflunomide and use an accelerated drug elimination procedure if a patient becomes pregnant.

Three patients became pregnant during Trial EFC11759:

Subject ID (b) (6) was a 16 year-old girl from Russia who received teriflunomide during DBT. She became pregnant during DBT and underwent elective abortion.

Subject ID (b) (6) was a 17 year-old girl from Turkey who received teriflunomide during DBT, then switched to open-label teriflunomide on Day 183 due to confirmed relapse. Her pregnancy test was positive on Day 223, at which time she was 4 weeks pregnant. Teriflunomide was permanently discontinued on Day 217 due to pregnancy, and the patient refused accelerated elimination. She delivered an infant via cesarean section on Day 460, and no structural defects or functional abnormalities of the newborn were reported to date.

Subject ID (b) (6) was a 15 year-old girl from China who received placebo during DBT, then switched to open-label teriflunomide on Day 254 due to meeting High MRI Activity criteria. A positive pregnancy test was reported on Day 948, and treatment was discontinued on Day 949. The patient underwent termination of the pregnancy on Day 973.

8.8.3. Pediatrics and Assessment of Effects on Growth

Physical and sexual development was assessed throughout the DBT period of Trial EFC11759.

In terms of pubertal milestones, the time to Tanner Stage V was assessed for breast stages (girls only), genitalia (boys only), and pubic hair (both boys and girls) via Kaplan-Meier analysis with associated log-rank tests. No statistically significant differences (at p=0.05) in time to these Tanner Stage V milestones were observed between the double-blind teriflunomide and placebo groups during DBT or combined DBT plus OLE periods.

One case of the TEAE menstruation delayed occurred in a patient on teriflunomide (0.9%). Otherwise, no TEAEs related to sexual development occurred during Trial EFC11759.

In terms of physical growth, height and weight were analyzed at baseline and at the last value while on DBT. Height was assessed at baseline and DB Visit 20 only. Changes in height and weight were also descriptively analyzed for each treatment group.

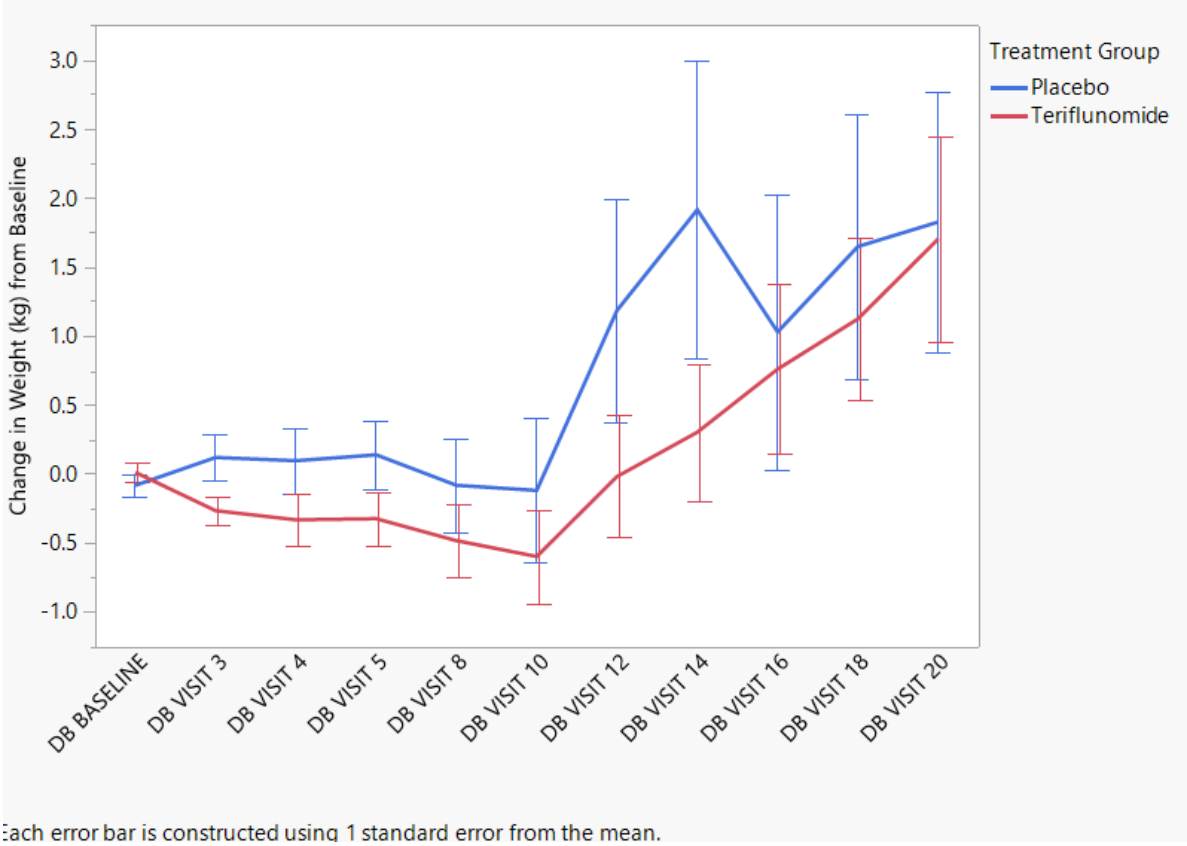
Change in height from baseline to DB Week 96 was similar between the two groups (mean (SD) 4.2 (5.9) cm for teriflunomide and 3.3 (3.0) cm for placebo; n = 65 and 19, respectively).

However, change in weight differed between the groups across DBT; patients on teriflunomide experienced, on average, weight loss from baseline of approximately 0.5 kg through DB Visit 10 (Week 36) (Figure 22). Weight appeared to increase after Week 36, and groups appeared to be similar in terms of change from baseline at Week 96 (DB Visit 20). This trend was not as pronounced during the OLE period.

Additionally, 6 patients on teriflunomide (5.5%) and 2 patients on placebo (3.5%) experienced the TEAE weight decreased during the DBT period. The TEAE weight increased occurred in 3 patients on teriflunomide (2.8%) and 0 patients on teriflunomide (0%) during the DBT period.

During the OLE period, 3 patients (2.0%) experienced the TEAE weight decreased (1 teriflunomide-teriflunomide, 2 placebo-teriflunomide). The TEAE weight increased occurred in 2 patients (both teriflunomide-teriflunomide) during OLE.

Figure 22 (Reviewer). Mean Change in Weight (kg) from Baseline during Double-Blind Treatment, Trial EFC117589



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Reviewer comment*: Overall, there were no significant differences at baseline or during the study in sexual development endpoints between teriflunomide and placebo. However, the etiology and clinical significance of the initial reduction in weight in patients on teriflunomide during the DBT period is unclear. Gastrointestinal side effects (e.g., nausea, vomiting, diarrhea) leading to poor oral intake could lead to weight loss, but the frequency of these events were similar between the treatment groups. Decreased appetite was infrequent during DBT as well (2.8% teriflunomide, 0% placebo).*

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose, Drug Abuse Potential, and Withdrawal

The assessment of abuse potential of teriflunomide was reviewed by the Controlled Substance Staff. There does not appear to be a potential for abuse with teriflunomide. There has been no evidence to date in the postmarketing experience of teriflunomide abuse.

During the DBT period of Trial EFC11759, overdose (an AESI for this trial, defined as the intake of 2 tablets in less than 24 hours) was reported in 4.6% (n = 5) of patients on teriflunomide and 5.3% (n = 3) of patients on placebo. These events were reported with either accidental overdose (n = 6) or overdose (n = 2) as the PTs. One event of accidental overdose and one event of overdose in the teriflunomide group were classified as moderate in severity. Otherwise, these events were classified as mild. The sponsor's CSR stated that there were no clinical symptoms associated with these overdose events.

During the OLE period of Trial EFC11759, accidental overdose (PTs either accidental overdose or overdose) occurred in 6.0% (n = 6) of patients in the teriflunomide-teriflunomide group and 3.8% (n = 2) patients in the placebo-teriflunomide group. In the 120-Day Safety Update reporting interval, 2 additional patients in the teriflunomide-teriflunomide group experienced accidental overdose of mild intensity.

However, one patient in the teriflunomide-teriflunomide group (Subject ID (b) (6) discussed in Section 8.4.2) had a suicide attempt involving intentional overdose with teriflunomide (18 tablets). He was hospitalized for 12 hours, experienced "sensory disorders and tingling sensations" for <2 hours and recovered after temporary teriflunomide discontinuation.

Reviewer comment: *Overall, there does not appear to be an abuse potential with teriflunomide.*

Rebound

Rebound of disease activity is a concern following discontinuation of MS treatments,

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particularly natalizumab and fingolimod. A few cases of rebound following discontinuation of teriflunomide, particularly in the setting of an accelerated elimination protocol, have been reported in the literature.[37, 38] However, a rebound phenomenon with teriflunomide is not well-characterized and has not been observed in clinical trials.

In Trial EFC11759, no confirmed relapses occurred after discontinuation of teriflunomide during DBT. Specifically, among confirmed relapses, none occurred after the recorded treatment end date in DBT (variable TR01EDT) for patients on teriflunomide.

> ***Reviewer comment:*** *Though no confirmed relapses occurred after discontinuation of teriflunomide during DBT, it is important to note that teriflunomide was discontinued most frequently due to relapse. Therefore, it is difficult to assess the frequency of rebound in this trial.*

Four potential relapses were reported during the open label post-treatment (n = 2) and open label accelerated elimination periods (n = 2), only one of which was investigator-confirmed in the open label post-treatment period. No patients on teriflunomide experienced an investigator-confirmed relapse during the open label post-treatment and open label accelerated elimination periods.

The sponsor's 120 Day Safety Update did not report any cases suggestive of rebound after cessation of teriflunomide.

> ***Reviewer comment:*** *Data from Trial EFC11759 do not suggest the presence of a rebound phenomenon with teriflunomide.*

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Since the approval of teriflunomide in adults on September 12, 2012, the following postmarketing adverse reactions have been added to the USPI:

- Drug-induced liver injury (DILI)
- Hypersensitivity reactions, some of which were severe, such as anaphylaxis and angioedema
- Severe skin reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome
- Drug reaction with eosinophilia and systemic symptoms (DRSS)
- Psoriasis or worsening of psoriasis (including pustular psoriasis)
- Thrombocytopenia
- Interstitial lung disease

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- Pancreatitis

8.9.2. Expectations on Safety in the Postmarket Setting

The expectation for teriflunomide in the postmarketing setting with respect to pediatric patients is that the previously identified and confirmed safety issues and risks will continue to be noted. Additionally, the results of this safety review raise concern for a specific signal of pancreatitis, CPK elevations, and alopecia in pediatric patients treated with teriflunomide. (b) (4)

8.9.3. Additional Safety Issues From Other Disciplines

Not applicable.

8.10. Integrated Assessment of Safety

Data from Trial EFC11759 indicate that safety concerns related to teriflunomide in adults also affect children, but also raise concerns regarding differential risks of pancreatitis, increased CPK, and alopecia in the pediatric population.

Comparison of the AEs reported with teriflunomide in the pediatric study under review to those of pooled placebo-controlled studies of teriflunomide in adults suggest a lower incidence of increased ALT, diarrhea, arthralgia, nausea, neutropenia, and hypertension in the pediatric population (Table 69). However, increases in blood pressure compared to baseline were observed in this pediatric study (Section 8.4.7), and hypertension occurred in 2 teriflunomide-teriflunomide patients during the OLE period, indicating a potential increased risk with chronic use.

However, these data indicate a higher incidence of alopecia in the pediatric population. Alopecia in the pediatric patient population, particularly adolescents, may have adverse psychological consequences for patients already at risk of psychiatric comorbidity.

Table 69 (Reviewer). Comparison of Common Adverse Reactions Between Pediatric and Adult Placebo-Controlled Patient Populations

	Trial EFC11759 (Double-Blind Period, Pediatric Patients)[1]		Pooled Placebo-Controlled Studies in Adults with RMS[2]		
Adverse reaction	**Teriflunomide (n = 109)**	**Placebo (n = 57)**	**Teriflunomide 7mg (n = 1045)**	**Teriflunomide 14mg (n = 1002)**	**Placebo (n = 997)**
Headache	16.5%	22.8%	18%	16%	15%
Increase in ALT	2.8%	1.8%	13%	15%	9%
Diarrhea	7.3%	7.0%	13%	14%	8%
Alopecia	21.1%	12.3%	10%	13%	5%
Nausea	8.3%	7.0%	8%	11%	7%
Paresthesia	11.0%	1.8%	8%	9%	7%
Arthralgia	1.8%	5.3%	8%	6%	5%
Neutropenia (or neutrophil count decreased)	5.5%	0%	4%	6%	2%
Hypertension	0%	1.8%	3%	4%	2%

[1]Source: Trial EFC11759 ADAE where SAF01FL and TRTEMFL ='Y' by ACTARM; [2]Source: Teriflunomide labeling

Though pancreatitis was identified as a safety issue for teriflunomide in the postmarketing setting in adults, the results of Trial EFC11759 indicate that the pediatric population may be more susceptible to pancreatitis associated with teriflunomide compared to adults. This differential risk of pancreatitis, which can be a life-threatening illness, is a major concern when considering use of teriflunomide in the pediatric population. Please refer to Section 8.5.1.

Increased CPK is not an established risk with teriflunomide, but occurred in 6.4% of patients on teriflunomide versus 0% on placebo during DBT. Some of these TEAEs were serious. Though confounding factors of physical activity and trauma were present in some cases, the differential risk between teriflunomide and placebo raises concern for an association with teriflunomide.

In conclusion, the risks of pancreatitis, increased CPK, and alopecia associated with teriflunomide appear to be more frequent in the pediatric population, which is concerning due to the reasons discussed above and in the respective sections of this review. Increased CPK has not been previously identified as a risk with teriflunomide. Otherwise, the safety profile of teriflunomide in the pediatric population appeared similar to that of adults.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

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10. Labeling Recommendations

10.1. Prescription Drug Labeling

Please refer to the final negotiated labeling. The safety and (lack of) efficacy results of Trial EFC11759 should be discussed in labeling, as there is potential for off-label use in pediatric MS, there are new safety findings in pediatric patients, and the trial results were submitted to fulfill a Written Request. (b) (4) .

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Teriflunomide does not have a REMS program, and no new safety issues were identified in this review that would necessitate a REMS program.

12. Postmarketing Requirements and Commitments

This efficacy supplement was submitted to fulfill the Pediatric Research Equity Act (PREA) Postmarketing Requirement 1924-1. (b) (4) .

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13. Appendices

13.1. References

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13.2. Trial EFC11759 Inclusion/Exclusion Criteria

Inclusion Criteria

1. Patients with relapsing multiple sclerosis are eligible. Patients should meet the criteria of MS based on McDonald criteria 2010 and International Pediatric Multiple Sclerosis Study Group (IPMSSG) criteria for pediatric MS, version of 2012 (8) and have:

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- At least one relapse (or attack) in the 12 months preceding screening or,
- At least two relapses (or attack) in the 24 months preceding screening.

2. <18 years of age and ≥10 years of age at randomization
    a. Specific for the Russian Federation from 18 December 2014 to 26 July 2016, ≤17 years of age and ≥13 years of age at randomization (see Appendix F).
3. Signed informed consent/assent obtained from patient and patient's legal representative (parents or guardians) according to local regulations.

Exclusion Criteria

Exclusion criteria related to study methodology

1. Expanded Disability Status Scale score >5.5 at screening or randomization visits.
2. A relapse within 30 days prior to randomization.
3. Body weight <20 kg.
4. Mental condition rendering the patient or parent/guardian unable to understand the nature, scope, and possible consequences of the study.
5. Patient or parent/guardian unlikely to comply with the protocol as determined by Investigator, e.g., uncooperative attitude, inability to return for follow-up visits.
6. Clinically relevant cardiovascular, hepatic, neurological, endocrine, or other major systemic disease making implementation or interpretation of the study results difficult or that would put the patient at risk by participating in the study.
7. Persistent significant or severe infection.
8. History of drug or alcohol abuse.
9. Patient or parent/legal guardian is the Investigator or any Sub investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof, directly involved in the conduct of the study. Any technical/administrative reason that makes it impossible to randomize the patient in the study.
10. Contraindication for MRI, i.e., presence of pacemaker, metallic implants in high-risk areas (i.e., artificial heart valves, aneurysm/vessel clips), presence of metallic material (i.e., shrapnel) in high-risk areas, known history of allergy to any contrast medium

Exclusion criteria related to treatments, which may interfere with the study

11. Patients must not have used adrenocorticotrophic hormone or systemic corticosteroids for 2 weeks prior to MRI assessment
12. Treated with:
    - Glatiramer acetate, interferons or dimethyl fumarate within 1 month prior to randomization.
    - Fingolimod or intravenous immunoglobulins within 3 months prior to randomization.

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- Natalizumab, other immunosuppressant or immunomodulatory agents such as cyclophosphamide, azathioprine, cyclosporine, methotrexate, mycophenolate, within 6 months prior to randomization.
- Cladribine or mitoxantrone within 2 years prior to randomization.

13. Treated with alemtuzumab at any time.
14. Treated with any investigational drug within 6 months prior to randomization.

Exclusion criteria related to study treatment at screening

15. Liver function impairment or persisting elevations (confirmed by retest) of alanine aminotransferase (ALT), aspartate aminotransferase (AST), or direct bilirubin greater than 2 x the upper limit of normal range (ULN) based on screening lab values.
16. Active hepatitis or hepatobiliary disease or known history of severe hepatitis.
17. Pregnant or breast-feeding female patients.
18. Female patients of child-bearing potential or male patient not using highly effective (double barrier) contraceptive and /or female patients of childbearing potential who are unwilling to or unable to be tested for pregnancy.
19. Patients wishing to parent children (be a partner in the conception of a child) during the course of the trial.
20. Patients with significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia:
    - Hemoglobin<10g/dL,
    - Absolute white blood cell count <3000 cells/mm3 (µL) and/or,
    - Platelet count <150 000 cells/mm3 (µL) and/or,
    - Absolute neutrophil ≤1500 cells/mm3 (µL)
21. Persisting elevations (confirmed by retest) of serum amylase or lipase greater than 3-fold the upper limit of normal.
22. Active pancreatitis or known history of chronic pancreatic disease.
23. Patients with a congenital or acquired severe immunodeficiency, a history of cancer (except for basal or squamous cell skin lesions which have been surgically excised, with no evidence of metastasis), lymphoproliferative disease, or any patient who has received lymphoid irradiation.
24. History of HIV infection.
25. Positive tuberculin test leading to suspicion of tuberculosis (e.g., unless known to have been treated for tuberculosis in the past, or interpreted in light of vaccination; if in doubt, chest X-ray is recommended).
26. Hypoproteinemia (e.g., in case of severe liver disease or nephrotic syndrome) with serum albumin <3.0 g/dL.
27. Moderate to severe impairment of renal function, as shown by serum creatinine >133 µmol/L (or >1.5 mg/dL).

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28. Concomitant use of cholestyramine or prior use within 4 weeks preceding randomization.
29. Known hypersensitivity to teriflunomide, leflunomide or any excipients in the formulation of IMP (note: teriflunomide tablets contain lactose therefore investigators should consider whether history of lactose intolerance, in particular Lapp lactase deficiency could affect treatment tolerability).

Acceptable methods of contraception are defined for this protocol as:

- For male:
  - True abstinence: when this is in line with the preferred and usual lifestyle of the subject (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post ovulation methods] and withdrawal are not acceptable methods of contraception),
  - Male sterilization (with the appropriate post vasectomy documentation of the absence of sperm in the ejaculate),
  - Use of condoms throughout the study, in addition to spermicides is recommended.
- For women of child bearing potential:
  - True abstinence: when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post ovulation methods] and withdrawal are not acceptable methods of contraception),
  - Highly effective oral contraceptives, such as biphasic and triphasic oral contraceptives are considered adequate. Progestogen only pills or “mini pills” which have demonstrated high efficacy will be acceptable,
  - Injectable hormones (i.e., Depo-Provera), hormonal implants, transdermal patches or intrauterine device (IUD) or intrauterine systems (IUS) or intravaginal ring (NuvaRing) which have demonstrated efficacy comparable to high efficacy oral contraceptives are adequate.

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13.3. Financial Disclosure

Covered Clinical Study (Name and/or Number): EFC11759

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 391		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 6 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Reference ID: 4776272

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/s/

LAURA E BALDASSARI
04/08/2021 05:09:50 PM

PAUL R LEE
04/30/2021 10:12:00 AM