EU-RISK MANAGEMENT PLAN FOR AUBAGIO® (TERIFLUNOMIDE)

Data Lock Point (DLP)	**12-SEP-2023**
RMP Version number	**Version 9.1**
Date of final sign-off	**28-MAR-2024**

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	The EU-RMP v9.0 was submitted to [redacted] replace pregnancy registries (OBS12751 and OBS13499) by an enhanced pharmacovigilance process to collect further information (procedure number EMA/CHMP/PRAC/25411/2023; [redacted] and to address the [redacted] comment [redacted] on measurement of AUBAGIO plasma levels. The RMP updated to v9.1 address the comments [redacted] following the evaluation of RMP v9.0 (procedure number: EMEA/H/C/002514/IB/0046).
Summary of significant changes in this RMP	Update of the DLP (12-Sep-2023). All relevant parts/modules and Annexes (Part I, Part II Module SI, Module SIV, Module SV, Module SVII, Annex 4) have been updated to add relevant information using this DLP. Part I – ATC code has been updated (RMP v9.1). Part II Module SVII.3.1 risk characterization table of important potential risk Teratogenicity has been updated [redacted] (RMP v9.1). **Pharmacovigilance plan:** [redacted] two pregnancy registries (OBS13499 and OBS12751) have been replaced with an enhanced pharmacovigilance process. This information has been reflected throughout the document. Part III has been updated to add brief information on pharmacovigilance process for follow-up of pregnancy cases under routine pharmacovigilance activities, and delete the wordings related to pharmacovigilance process from additional pharmacovigilance activities (RMP v9.1). **Risk minimization measures:** Key elements have been updated to replace the information of pregnancy registries with enhanced pharmacovigilance process. Also, relevant information added on measurement of AUBAGIO plasma concentration. Healthcare Professional guide and patient card key safety messages have been updated accordingly. Key elements of HCP guide have been updated [redacted] (RMP v9.1). **Annexes:** Annex 2 and Annex 3 updated in RMP v9.0. Annex 4 and Annex 6 updated in RMP v9.0 and RMP v9.1.

ATC: Anatomical Therapeutic Chemical; [redacted] DLP: Data Lock Point; [redacted] EU: European Union; HCP: Healthcare Professional; [redacted] RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	8.1
Approved with procedure	EMEA/H/C/002514/II/0042

Date of approval (opinion date)	14-Apr-2023

RMP: Risk Management Plan.

Table 4 - QPPV name and signature

QPPV name	[redacted][a], [redacted]
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.

QPPV: Qualified Person Responsible for Pharmacovigilance.

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ABBREVIATIONS

4-TFMA:	4-Trifluoro-Methylaniline
AE:	Adverse Event
AESI:	Adverse Event of Special Interest
AIDS:	Acquired Immune Deficiency Syndrome
ALT:	Alanine Transaminase
AMESA:	Africa, Middle East and South Asia
AST:	Aspartate Transaminase
ATC:	Anatomical Therapeutic Chemical
AUC:	Area Under the Curve
BERD:	Birth Events Record Database
BMI:	Body Mass Index
CD:	Cluster Differentiation
CI:	Confidence Interval
CIS:	Clinically Isolated Syndrome
Cl_{cr}:	Creatinine Clearance
CMV:	Cytomegalovirus
CNS:	Central Nervous System
CTCAE:	Common Terminology Criteria for Adverse Event
DEVP:	Drug Exposure via Parent
DHO-DH:	Dihydroorotate Dehydrogenase
DLP:	Data Lock Point
DMT:	Disease Modifying Therapy
DNA:	Deoxyribonucleic Acid
e-CTD:	Electronic Common Technical Document
EDSS:	Expanded Disability Status Cycle
EEA:	European Economic Area
EPAR:	European Public Assessment Report
EU:	European Union
F:	Female
GA:	Glatiramer Acetate
GGT:	Gamma-Glutamyl Transferase
GPV:	Global Pharmacovigilance
HCP:	Healthcare Professional
HIV:	Human Immunodeficiency Virus
HLGT:	High Level Group Term
HLT:	High Level Term
HR:	Hazard Ratio
HYP:	High-Yield Process
IBD:	International Birth Date
IC_{50}:	Half-Inhibitory Maximal Concentration
ICAP:	International Charitable Access Program
IFN:	Interferon
IFN-β:	Interferon-Beta
IFNβ-1a:	Interferon Beta-1a

IFNβ-1b:	Interferon Beta-1b
IgG:	Immunoglobulin G
IgM:	Immunoglobulin M
IMP:	Investigational Medicinal Product
INN:	International Nonproprietary Name
IRR:	Incidence Rate Ratio
ITP:	Immune Thrombocytopenia
IV:	Intravenous
KLH:	Keyhole Limpet Haemocyanin
LLN:	Lower Limit of Normal
LSC:	List of Safety Concern
M:	Male
MAH:	Marketing Authorization Holder
MAOI:	Monoamine Oxidase Inhibitor
MARCO:	Margin Consolidated
MedDRA:	Medical Dictionary for Regulatory Activities
MI:	Myocardial Infarction
MS:	Multiple Sclerosis
N:	Number
NARCOMS:	North American Research Committee on Multiple Sclerosis
NEC:	Not Elsewhere Classified
NOAEL:	No-Observed-Adverse-Effect-Level
NOEL:	No-Observed-Event Level
NSAID:	Non-Steroidal Anti-Inflammatory Drug
OC:	Oral Contraceptive
OR:	Odds Ratio
PAES:	Post-Authorization Efficacy Study
PASS:	Post-Authorization Safety Study
PBRER:	Periodic Benefit-Risk Evaluation Report
PK:	Pharmacokinetic
PML:	Progressive Multifocal Leukoencephalopathy
PND:	Post-natal Day
PRAC:	Pharmacovigilance Risk Assessment Committee
PSUR:	Periodic Safety Update Report
PT:	Preferred Term
QPPV:	Qualified Person Responsible for Pharmacovigilance
RBC:	Red Blood Cell
RMP:	Risk Management Plan
RMS:	Relapsing Multiple Sclerosis
ROW:	Rest of the World
RR:	Relative Risk
SBP:	Systolic Blood Pressure
SCS:	Summary of Clinical Safety
SD:	Standard Deviation
SmPC:	Summary of Product Characteristics
SOC:	System Organ Class
SSRI:	Selective Serotonin Reuptake Inhibitor
TBILI:	Total Bilirubin

TCA:	Tricyclic Antidepressant
TEAE:	Treatment Emergent Adverse Event
UAE:	United Arab Emirates
UK:	United Kingdom
ULN:	Upper Limit of Normal
US:	United States
WBC:	White Blood Cell
WHO:	World Health Organization
WOCBP:	Women of Child-Bearing Potential

RISK MANAGEMENT PLAN - PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance(s) (INN or common name)	Teriflunomide
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants (L04AK02)
Marketing Authorization Holder	Sanofi Winthrop Industrie
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	AUBAGIO
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Teriflunomide also referred to as HMR1726 during development, is a novel immunomodulatory agent with anti-inflammatory properties.
	Summary of mode action: It selectively and reversibly inhibits the mitochondrial enzyme DHO-DH, required for the de novo pyrimidine synthesis. As a consequence, teriflunomide reduces the activation and proliferation of stimulated lymphocytes which need de novo synthesis of pyrimidine to expand. Slowly dividing or resting cells which rely on the salvage pathway for pyrimidine synthesis are unaffected by teriflunomide. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood but may include reduced number of activated lymphocytes in CNS. It is likely that teriflunomide diminishes in periphery the numbers of activated lymphocytes available to migrate into the CNS.
	Important information about its composition: Not applicable
Hyperlink to the product information	Refer to e-CTD sequence 0120, Module 1.3.1 English approved Product Information.
Indication(s) in the EEA	Current: Teriflunomide is indicated for the treatment of adult and pediatric patients aged 10 years and older with relapsing-remitting multiple sclerosis.
	Proposed: Not applicable
Dosage in the EEA	Current: In adults, the recommended dose of teriflunomide is 14 mg orally once daily. In pediatric patients (10 years of age and above), the recommended dose is dependent on body weight: • Pediatric patients with body weight >40 kg: 14 mg tablet once daily. • Pediatric patients with body weight ≤40 kg: 7 mg once daily. Pediatric patients who reach a stable body weight above 40 kg should be switched to 14 mg once daily.

	Proposed: Not applicable
Pharmaceutical form(s) and strength(s)	Current: Teriflunomide 7 mg film-coated tablet is available as a very light greenish-bluish grey to pale greenish-blue, hexagonal film-coated 7.5 mm tablet with imprint on one side ("7") and engraved with the corporate logo on the other side. Teriflunomide 14 mg film-coated tablet is available as a pale blue to pastel blue, pentagonal film-coated 7.5 mm tablet with imprint on one side ("14") and engraved with a corporate logo on the other side.
	Proposed: Not applicable
Is/will the product (be) subject to additional monitoring in the EU?	No

ATC: Anatomical Therapeutic Chemical; CNS: Central Nervous System; DHO-DH: Dihydroorotate Dehydrogenase; e-CTD: Electronic Common Technical Document; EEA: European Economic Area; EU: European Union; INN: International Nonproprietary Name; MS: Multiple Sclerosis; RMP: Risk Management Plan.

RISK MANAGEMENT PLAN - PART II MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Teriflunomide is indicated for the treatment of adult and pediatric patients aged 10 years and older with relapsing-remitting MS.

The epidemiology of MS and the relapsing-remitting form of MS is presented in the Table 6. Of note, data presented in this section are for total MS diagnoses, of which approximately 85% of people are diagnosed with relapsing-remitting MS.

Table 6 - Epidemiology of multiple sclerosis

Indication	Multiple sclerosis
Incidence	There is a wide range in the incidence of MS reported globally. [1,2,3] The average incidence has been estimated at 4.3 per 100 000 person-years. [4,5] Incidence rates in North America range from 5.1 to 46.3 per 100 000 person-years, [5,6,7] European studies report a range from 5 to 19.5 per 100 000 person-years, [1,5,8,9,10,11,12,13,14,15,16,17,18] one study has reported incidence in Australia to be 6.7 per 100 000 person-years [19] and Asia has incidence rate ranging from 0.68 to 6.5 per 100 000 person-years. [20,21,22,23,24,25,26]
Prevalence	The estimated number of people living with MS has increased over time from 2.3 million in 2013 (33 per 100 000) to 2.8 million (36 per 100 000) in 2020. [1] The prevalence varies greatly by geography, it is the highest in North America and Europe (>100 per 100 000 with some countries reporting >300 per 100 000) and lowest in Africa and Western Pacific (≤5 per 100 000). [1,3,6,20,27,28] It is important to note that even within regions the prevalence may vary by country. For example, in Europe, the highest prevalence is in San Marino (337 per 100 000) and the lowest in Albania (30 per 100 000). [1] Multiple sclerosis Prevalence in Asia varied from <1 per 100 000 in Japan to 115 per 100 000 in Iran. [20,21,22,23,24,25,29,30,31] In South America, prevalence varied from 1.5 to 23 per 100 000 with the highest prevalence in Argentina. [32,33,34]
Demographics of the population in the authorized indication	Geography, race, gender and age are all important demographic factors. Risk factors for the disease Potential risk factors as summarized in a review article by Ascherio et al (2016). [35] • Latitude and geography: those further from the equator being at higher risk-although this gradient has attenuated in the northern hemisphere. Both incidence and prevalence of disease vary widely by geographic area and appear to be increasing over time. [2,35] • Gender: women have a higher risk than men. The ratio varies from 1.5:1 to 2.5 to 1 and may differ geographically and by time. • Age: incidence is low in childhood and reaches a peak between 25 and 35 years and then declines. • Race: Whites, especially of Northern European descent, seem to have the highest risk. Although incidence may be increasing in US blacks. • Vitamin D deficiency: inadequate vitamin D increases risk (especially in early life). • Genetic: >100 genes are implicated in MS. • Obesity in early life increases risk. • Epstein-Barr virus that resulted in mononucleosis increases risk. • Smoking: smokers have a higher risk than nonsmokers and MS risk increases as smoking duration and intensity increase.
Main existing treatment options	The clinical armamentarium for treating MS has further increased over the past years. Treatment options in relapsing remitting MS are IFNβ-1a, IFNβ-1b, GA, teriflunomide,

Indication	Multiple sclerosis
	dimethyl fumarate, diroximel fumarate, fingolimod, cladribine, natalizumab, alemtuzumab, ocrezumab, mitoxantrone, ofatumumab, ozanimod, ublituximab and ponesimod. There is no global consensus on treatment strategy and/or algorithm. In an individualized approach, treatment decisions are based on the efficacy and safety profile of each drug, on their mechanism of action, and on patient preference and convenience. Only a few treatments are available as an oral dosage form: fingolimod, fumarates, teriflunomide and cladribine. Teriflunomide is among the few drugs indicated for the paediatric MS population (aged 10 years and older).
Natural history of the indicated condition in the untreated population including mortality and morbidity	Multiple sclerosis has a variable course. Studies in the US and Europe have found that relative to the general population MS is associated with increased premature mortality (RR 1.7-3.5 fold). [36] The variable course of disease can lead to progression to physical and cognitive disabilities, decreased quality of life, and comorbidities (see comorbidity section). Life expectancy may be reduced in MS populations by 3 to 11 years. [12,37,38,39,40] Multiple sclerosis is one of the most common neurological disorders and causes of disability in young adults.
Important co-morbidities	The epidemiology of the MS specific co-morbidities, as well as other most frequent conditions observed in MS patients are: • Depression, [36,37,38,39,40,41] treated with antidepressant drugs (SSRI, TCA, MAOI), anxiolytics • Urinary tract infection [36,42,43] treated with antibiotics • Diabetes [36,44,45,46] treated with antidiabetic drugs (insulins, biguanides, sulfonylureas) • Hypertension [44,45] treated with antihypertensive drugs (diuretics, beta blockers, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors) • Hypercholesterolemia/hyperlipidemia [44,45] treated with lipid lowering drugs (fibrates, statins) • Arthritis [47] treated with analgesics, Anti-inflammatory drugs (eg, NSAIDs) • Fatigue [48] treated with modafinil, amantadine • Cognitive impairment [49] Of note, there are substantial gaps regarding co-morbidities in the literature especially in regions outside of North America and Europe. Even within North America and Europe findings are inconsistent. [41]

GA: Glatiramer Acetate; IFNβ-1a: Interferon Beta-1a; IFNβ-1b: Interferon Beta-1b; MAOI: Monoamine Oxidase Inhibitor; MS: Multiple Sclerosis; NSAID: Non-Steroidal Anti-Inflammatory Drug; RMS: Relapsing Multiple Sclerosis; RR: Relative Risk; SSRI: Selective Serotonin Reuptake Inhibitor; TCA: Tricyclic Antidepressant; US: United States.

The epidemiology of MS and the relapsing-remitting form of MS in children that are 10 years old and above is presented in the Table 7.

Table 7 - Epidemiology of multiple sclerosis in 10 years or older children

Indication	Multiple sclerosis in 10 years or older children
Incidence	Studies reporting the incidence of MS in 10 years or older children are scarce. A meta-analysis of data from twelve countries reported overall incidence between 0.05 to 2.85 and estimated pooled global incidence of 0.87 (95% CI: 0.35-1.40) per 100 000 individuals annually. [50] The reported incidence rates in Europe range from 0.6 to 6.41 per 100 000 population per year [51,52,53] a UAE based study reported incidence of 2.3 per 100 000 population per year among 10 to 14-year-old

Indication	Multiple sclerosis in 10 years or older children
	and 7.2 per 100 000 population per year among 15 to 19 years old, [54] another ASIA based study conducted in Israel reported incidence of 2.6 per 100 000 population per year [55] in 12 to 18-year-olds. Achiron et al reported the incidence of 0.08 per 100 000 population per year among 15 to 18-year-old Tunisians. [56]
Prevalence	Similar to incidence, studies estimating the prevalence of MS among 10 years and above are scarce. A meta-analysis study of data from ten countries reported estimated pooled global prevalence of 8.11 (95% CI: 2.28-13.93) per 100 000 people. [50] The reported prevalence in Italy among 12 to 18 year-olds is 26.92 per 100 000 population, [51] the prevalence of MS in 15 to 19 years of age in UAE has been reported to be 30.7 per 100 000 population. [54] Prevalence in US is lower compared to the two studies above, 2.3 per 100 000 population among 10 to 14 years of age and 14.6 per 100 000 population in 15 to 19 years of age. [57]
Demographics of the population in the authorized indication	Race, gender, age, and diet are all important demographic factors. Risk factors for the disease • Family history: Positive family history of MS increases the risk. [52] • Gender: Occurrence of MS is similar in females and males (Females to males-1.2:1) up to the age of 12 years. Females predominance is observed from 12 years of age (Female to male: 2.8:1). [52] • Age: incidence increases with age, most notably after 12 years of age. [52] • Race: Whites, seem to have the highest risk. [58] • Iron: Iron levels below recommended levels are associated with increased risk. • Vitamin D deficiency: inadequate vitamin D increases risk. [59,60] • Obesity increases the risk of MS in children. [59,60] • Epstein-Barr virus infections increase the risk of pediatric MS. [61]
Main existing treatment options	Fingolimod and teriflunomide are the only drugs approved to treat MS in children 10 years and above. [62,63] However, other MS drugs are also used but their usage in the pediatric population is based on observational studies. [64] These drugs include IFNβ-1a, GA, natalizumab, dimethyl fumarate and mitoxantrone. [64]
Natural history of the indicated condition in the untreated population including mortality and morbidity	About half of the pediatric MS population shows neurological episodes with two years of onset. [65] The median time from MS onset to secondary progression is about 28 years. [65] Pediatric MS patients take approximately 10 years longer to reach secondary progression and irreversible disability and reach these landmarks at age approximately 10 years younger than adult-onset MS. [65,66] Multiple sclerosis in the pediatric population has a wide range of effects on patients including, cognitive impairment, sensory deficits, visual and motor deficits, fatigue, reduced physical activity. All of these effects lead to increase in disability among patients. [60,61,67]
Important co-morbidities	Studies relating to co-morbidities in pediatric MS population are extremely scarce, few of the reported comorbidities include: • Depression reported in up to 50% of pediatric MS population. [68] • Anxiety disorders reported in about 64% of patients. [68] • Fatigue in about three forth of pediatric MS patients is reported. [68]

CI: Confidence Interval; GA: Glatiramer Acetate; IFNβ-1a: Interferon Beta-1a; MS: Multiple Sclerosis; UAE: United Arab Emirates; US: United States.

RISK MANAGEMENT PLAN - PART II MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

The preclinical development of teriflunomide was conducted as following:

Teriflunomide was evaluated in non-clinical safety studies, consistent with the claimed indication, the intended route of administration, and the duration of treatment proposed in humans.

In general, the repeat-dose animal toxicity of teriflunomide was a reflection of exaggerated pharmacologic activity (ie, inhibition of deoxyribonucleic acid [DNA] synthesis in rapidly dividing cells). [69] Primary adverse events (AEs) were seen in bone marrow (decreased erythropoiesis and/or granulopoiesis), lymphoid organs (atrophy), oral cavity/gastrointestinal tract (epithelial degenerative changes, erosions, ulcers, bleeding), and reproductive organs (tubular degeneration of the testes in rats and mice, and atrophy of the ovary in mice). Anemia, leukopenia, lymphopenia, decreased platelet counts (thrombocytopenia), effects on the immune system (decreased lymphocytes, white blood cell [WBC], cluster differentiation [CD] CD3/CD4, CD3/CD8, B cells, immunoglobulin M [IgM] and immunoglobulin G [IgG]), and secondary infections were related to the effects on the bone marrow and/or lymphoid organs. Hemorrhages in multiple organs (sometimes lethal) occurred secondary to the reduced platelet counts. Regenerative hemopoietic effects were sometimes seen (increased hemopoietic cells in bone marrow and extramedullary hemopoiesis in the spleen).

Other effects were not clearly associated with the pharmacologic activity of teriflunomide. Heinz bodies in erythrocytes and increased methemoglobin were indicative of an oxidative effect on red blood cells (RBCs) and may be associated with the aniline structure of the molecule. Pancreatic findings in dogs (acinar degeneration and individual acinar cell necrosis with loss of acini, fibrosis, and a minimal mononuclear inflammatory cell infiltrate) were not correlated with clinical signs or alterations in clinical pathology parameters (amylase, lipase or trypsin-like immunoreactivity).

The systemic exposure at the no-observed-adverse-effect-level (NOAEL) in rats and dogs was less than the human exposure at 14 mg teriflunomide. The pronounced species differences in the pharmacologic activity of teriflunomide (Table 8) may explain the fractional exposure ratios.

Table 8 - Species comparison of teriflunomide antiproliferative activity

	Human	Mouse	Rat
IC_{50} - Antiproliferative activity (μM teriflunomide)	12.5	3.5	0.086

IC_{50}: Half-Inhibitory Maximal Concentration.

In genotoxicity studies with teriflunomide, negative results were obtained in vitro for mutagenicity and in vivo for clastogenicity. A positive result observed in the in vitro chromosome aberration test in human lymphocytes (≥300 μg/mL) was likely related to the pharmacologic action of the drug; this conclusion is supported by the reduced cytotoxicity and clastogenicity that were observed with uridine supplementation. The highest concentration tested without an effect was 6 times greater than the mean human exposure at the 14 mg dose of teriflunomide.

No evidence of carcinogenicity was observed in a 2-year bioassay in rats up to the maximally tolerated dose of 4 mg/kg/day (approximately 1/2 the maximum human teriflunomide exposure based on area under the curve [AUC]) or mice up to the maximally tolerated dose of 12 mg/kg/day (approximately 5 times the maximum human teriflunomide exposure based on AUC).

4-trifluoro-methylaniline (4-TFMA), a minor metabolite of teriflunomide, was positive in genotoxicity studies conducted in vitro while negative results were observed in vivo. The 4-TFMA concentrations used in the in vitro genotoxicity studies are at least 1000 times higher than the mean plasma levels in patients exposed to 4-TFMA as a metabolite of teriflunomide. No neoplastic findings were observed in 2-year oral carcinogenicity studies of teriflunomide in rats and mice, which would have also evaluated the 4-TFMA metabolite.

Teriflunomide had no effect on mating performance or fertility in male or female rats. A slight decrease in epididymal sperm count (-12.5%) and effects on early embryonic and fetal development were seen in males and females, respectively, when treated separately. Teriflunomide is embryo-toxic and teratogenic in rats and rabbits when administered during organogenesis. Exposure ratios at the NOAELs were less than the human exposure at the 14 mg dose of teriflunomide. Administration of teriflunomide to pregnant rats during gestation and lactation also produced adverse effects in the offspring. However, no effects were observed in the offspring of pregnant rats that received teriflunomide during gestation only in order to avoid potential toxicity related to transfer of test article in the milk. ^{14}C-teriflunomide-derived radioactivity was excreted via lactation in rats at approximately 23.3%.

Juvenile rats were orally administered teriflunomide once daily for 7 weeks, beginning on Post-natal Day (PND) 21. Pharmacokinetic (PK) parameters and signs of toxicity were generally similar to adult rats. There were no adverse effects on growth, physical or neurological development, learning and memory, locomotor activity, sexual development, or fertility. Decreased body weight gain and food consumption, effects on erythron parameters (minimally decreased hemoglobin, red cell volume, packed cell volume; minimally increased reticulocytes and red cell distribution width), minimally decreased total protein and globulin concentrations, minimally increased cholesterol, and increased triglyceride concentrations were observed. Changes in immune function occurred (failure to mount an appropriate immune response after two antigen challenges, greatly reduced concentrations of IgM and IgG, and markedly increased B lymphocyte counts). Microscopic changes were observed in the spleen (increased incidence and/or severity of hemopoiesis and a very minor reduction of lymphoid hyperplasia), mesenteric and mandibular lymph nodes and Peyer's patches (minor reduction in germinal follicles). At the end of the 8-week recovery period, all findings partly or completely reversed.

Effects on the immune system were identified following 1-month oral administration of teriflunomide to adult rats. Decreased lymphocytes, WBC counts, CD3/CD4, CD3/CD8, and B cells were observed. Following Keyhole Limpet Haemocyanin (KLH) immunization, a dose-related decrease in IgM and IgG occurred, with effects on both the primary and secondary response. The secondary response was slightly greater than the primary response, except for the high dose female IgG, where the secondary response was less than the primary response. Effects were observed as low as 1 mg/kg/day.

The safety findings of teriflunomide identified in rodent and non-rodent species in the non-clinical studies are summarized in Table 9, with their toxicological relevance put into the perspective of human usage.

Table 9 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity • Key issues identified from acute or repeat-dose toxicity studies - **Pancreas**: Acinar degeneration and necrosis, with loss of acini, fibrosis, and minimal infiltration by mononuclear inflammatory cells; observed only in dogs (12 month NOAEL: 0.2 mg/kg/day, Day 364 mean AUC_{0-24} (area under the plasma concentration curve versus time from 0 to 24 hours) of 26.6 and 20.2 µg*h/mL for males and females, respectively). There were no clinical signs or alterations in clinical pathology parameters (amylase, lipase or trypsin-like immunoreactivity) that correlated with the light microscopic changes in the pancreas. - **Oral cavity/gastrointestinal tract**: Erosions, ulcers, bleeding, necrosis, and/or degeneration; observed in mice (3 month NOEL: 5 mg/kg/day, Day 85 mean AUC_{0-24} of 1660 and 1040 µg*h/mL for males and females, respectively) and dogs (3-month NOAEL: <0.8 mg/kg/day, Day 88 mean AUC_{0-24} of <107 and <118 µg*h/mL in males and females, respectively).	This effect identified pancreas as a target organ in dogs following chronic treatment. Association between the pharmacologic activity and pancreatic toxicity of teriflunomide has not been clearly established. This non-clinical finding prompted a close monitoring of potential pancreatic effects (via ultrasound imaging and pancreatic laboratory enzymes) in the Phase 2/3 clinical studies. In the postmarketing setting, cases of pancreatitis were observed with teriflunomide. Acute pancreatitis is an important identified risk with teriflunomide and is described in [Part II module SVII]. This observed effect may reflect • The immunomodulatory activity of the drug leading to the worsening status of certain infections (eg, herpetic or bacterial infections) or • An effect on rapidly dividing cells in the gastrointestinal tract due to the antiproliferative activity. In clinical studies, a low incidence of oral herpes was observed with teriflunomide 14 mg (3.4%) as compared to placebo (1.4%). Clinical complications such as infections and serious opportunistic infections have been considered as important risks and are described in [Part II module SVII].
- **Bone marrow**: Decreased erythropoiesis or granulopoiesis, resulting in anemia, leukopenia, lymphopenia, thrombocytopenia, and hemorrhages; observed in mice (3-month NOEL: 5 mg/kg/day, Day 85 mean AUC_{0-24} of 1660 and 1040 µg*h/mL for males and females, respectively) and dogs (3-month NOAEL: <0.8 mg/kg/day, Day 88 mean AUC_{0-24} of <107 and <118 µg*h/mL in males and females, respectively.	The effect on bone marrow is related to the exaggerated pharmacologic activity of the drug (inhibition of DNA synthesis), due to exposure/sensitivity of different species. The following was observed in patients treated with teriflunomide: • Decrease in WBC affecting the neutrophil and lymphocyte counts (observed decrease of about 15% for both). • Anemia observed in 1.2 to 2.4% patients. • Moderate decrease in platelet count (about 10%). Hematologic effects are considered as an important identified risk and is described in [Part II module SVII]. Hematologic effects are confirmed with clinical data with WBC.

Key Safety Findings	Relevance to human usage
- **Effects on Immune System and Lymphoid Organs:** Decreased WBC, lymphocytes, lymphocyte subpopulations CD3/CD4, CD3/CD8, and B cells in rats. Dose related decrease in IgM and IgG compared to controls following KLH immunization. Effects on both the primary and secondary response. The secondary response was generally slightly greater than the primary response. The NOAEL for effects on the immune system in rats was <1 mg/kg/day. **Spleen**: Follicular atrophy or hypoplasia; observed in mice (3-month NOEL: 5 mg/kg/day, Day 85 mean AUC_{0-24} of 1660 and 1040 µg*h/mL for males and females, respectively), rats (1-month NOAEL: 1.0 mg/kg/day IV, Day 28 mean AUC_{0-24} of 16.5 and 17.1 µg*h/mL for males and females, respectively), and dogs (3-month NOAEL: 2.5 mg/kg/day, Day 88 mean AUC_{0-24} of 680 and 590 µg*h/mL in males and females, respectively). **Thymus**: Thymic atrophy; observed in mice (3-month NOEL: 5 mg/kg/day, Day 85 mean AUC_{0-24} of 1660 and 1040 µg*h/mL for males and females, respectively) and rats (6-month NOAEL: 0.3 mg/kg/day, Day 181 mean AUC_{0-24} of 26.1 and 29.4 µg*h/mL for males and females, respectively).	This observed effect reflects the exaggerated pharmacologic activity of the compound (inhibition of DNA synthesis in rapidly dividing cells), impacting the immune system (decreased lymphocyte production). A 15% decrease in lymphocyte count was observed in clinical trials with teriflunomide. No signal (imbalance) for serious infection or serious opportunistic infection was observed in clinical studies. "Hematologic effects" and "Infections" have been considered as important identified risks and are described in [Part II module SVII]. "Serious opportunistic infections, including PML" has been considered as an important potential risk and is described in [Part II module SVII].
- **Red blood cells**: Heinz bodies, Howell-Jolly bodies, and/or increased methemoglobin; observed in mice (3-month NOEL: 5 mg/kg/day, Day 85 mean AUC_{0-24} of 1660 and 1040 µg*h/mL for males and females, respectively) and dogs (3-month NOAEL: 0.8 mg/kg/day, Day 88 mean AUC_{0-24} of 107 and 118 µg*h/mL in males and females, respectively).	These effects, unrelated to the pharmacologic activity of the drug, are indicative of an oxidative effect on RBC due to the aniline structure of the compound. However, the clinical impact appears limited as RBC and hemoglobin values remained stable over time with teriflunomide (change from baseline was <2% and <3% for RBC and hemoglobin, respectively).
• Reproductive/developmental toxicity studies - **Fertility**: In repeat dose toxicity studies, tubular degeneration of the testes and atrophy of the ovary were observed in mice (3-month NOEL: 5 mg/kg/day, Day 85 mean AUC_{0-24} of 147 and 97.5 µg*h/mL for males and females, respectively) and/or rats (1-month NOEL: 1 mg/kg/day IV, Day 28 mean AUC_{0-24} of 16.5 and 17.2 µg*h/mL for males and females, respectively). Two separate fertility studies were conducted, one in male rats and one in female rats. In males, a slight decrease in sperm count was observed. There was no effect on either male or female fertility. The NOAEL for fertility was 10 mg/kg/day in males and 8.6 mg/kg/day in females.	No effect on fertility was seen in male or female rats in separate studies. In clinical trials, pregnancies were observed in both pregnant women treated with teriflunomide as well as in pregnant partners of male patients treated with teriflunomide (see [Part II module SVII]).

Key Safety Findings	Relevance to human usage
- **Embryo-fetal Toxicity:** Effects observed in the offspring of female rats treated prior to mating up to gestation day 6: decreased fetal body weight, total post-implantation loss, increased early resorptions, decreased number of fetuses per litter, and isolated malformations. The NOAEL for early embryonic development was less than 0.84 mg/kg/day. Malformations observed in the offspring of pregnant rats treated during organogenesis: microophthalmia or anophthalmia, accompanied by aplasia lentis and decreased orbit size; hydrocephalus; edematous fetus; hematocyst on parietal bone; brachygnathia inferior; bent tarsal region of the hindpaw; fragmented, dysplastic and fused skull bones; multiple anomalies of the vertebral column; and alterations of ribs and pectoral girdle. Exposure at the NOAEL (1.0 mg/kg/day) for teratogenicity and embryolethality was less than the human exposure at 14 mg/day. Malformations observed in the offspring of pregnant rabbits treated during organogenesis: malformations of the forelimbs (short and misshapen ulna, absent radius, brachydactyly); absence of kidney, adrenal, and ureter; cleft lip and palate; growth retardation; hyperflexion of the forepaws; malpositioned branch of the carotid; anomalies of the lung lobes and sternebrae; and delayed ossification of several bones. Exposure at the NOAEL (1.0 mg/kg/day) for teratogenicity and embryolethality was less than the human exposure at 14 mg/day. Staged treatment at critical 3-day intervals during gestation in rats still resulted in embryo-fetal toxicity and teratogenicity, including total post-implantation loss or some degree of developmental toxicity consistent with the findings described above.	Pregnancy in treated women Although teriflunomide was not intentionally administered to pregnant women, pregnancy occurred in some women treated with teriflunomide during the clinical trial program. Teriflunomide was discontinued immediately after pregnancy was discovered and the patients were required to undergo an accelerated elimination procedure. No structural defects were reported in any of the newborn babies. Nevertheless, based on embryo-fetal toxicity observed in animal studies, teratogenicity has been considered as an important potential risk in pregnant women (see [Part II module SVII]). Pregnancy in female partners of male patients The risk of male-mediated embryo-fetal toxicity through teriflunomide treatment is considered low. The estimated female plasma exposure via the semen of a treated patient is expected to be 100 times lower than the plasma exposure observed at steady state after 14 mg of oral teriflunomide. There were no external malformations in the offspring of male rats administered teriflunomide for at least 10 weeks prior to mating with untreated female rats. Genotoxicity was not observed in vivo in 3 species. The highest concentration without an effect in the in vitro chromosome aberration test in human lymphocytes was 6 times greater than the mean human exposure at the 14 mg dose of teriflunomide. The risk of male-mediated embryo-fetal toxicity is mentioned in the labeling however the risk is not considered an important one. Teratogenicity not confirmed in human. Adequate prevention is needed and further risk documentation. Therefore, the risk has been considered as an important potential risk (see [Part II module SVII]).
- **Excretion into milk**: Milk excretion of 14C-teriflunomide in rats showed radioactivity excreted via lactation at approximately 23.3%. Adverse effects observed in the offspring of rats treated during gestation and lactation: limb defects and impaired coat growth sometimes associated with skin discoloration; corneal opacity, eye discharge, and negative pupillary reflex in a few pups; mean fetal weight per litter slightly decreased. Effects on coat growth resolved but limb defects persisted in a few pups after weaning. No effects on sexual maturation,	No clinical information is available in lactating women exposed to teriflunomide. Labeling information includes a statement that it is not known whether teriflunomide is excreted in human milk. Since, teriflunomide is excreted in milk in rats, many drugs are excreted in human milk and there is a potential for serious adverse reactions in nursing infants from teriflunomide, labeling also includes a statement not recommending continued teriflunomide treatment while nursing and that a decision should be made whether to discontinue nursing or discontinue the drug,

Key Safety Findings	Relevance to human usage
learning, memory, motor activity, startle response, reproductive ability, estrous cycles, mating behavior, fertility and fecundity, or early embryonic development. The NOAEL in the offspring was 0.10 mg/kg/day. Of importance, similar adverse findings were not seen in an exploratory study where teriflunomide was administered at 1.0 mg/kg/day during the gestation period and not during lactation to avoid transfer in the milk. Under those conditions, the NOEL in the offspring was 1.0 mg/kg/day.	taking into account the importance of the drug to the mother.
• Key findings in juvenile rats - Erythron parameters (minimally decreased hemoglobin, red cell volume, packed cell volume; minimally increased reticulocytes and red cell distribution width; increased incidence and/or severity of hemopoiesis in the spleen). Effects on erythropoiesis, including anemia, previously observed in repeat dose toxicity studies in sexually mature mice, rats, and dogs. - Immune function (failure to mount appropriate immune response after antigen, greatly reduced IgM and IgG concentrations, markedly increased B lymphocyte counts). Effects on immune function and microscopic findings in lymphoid tissues/organs previously see in sexually mature rats. Reason for increased B lymphocyte counts in juvenile rats compared to a slightly lower B lymphocyte count in sexually mature female rats is unknown but may be related to differences in treatment duration and/or exposure. - Lymphoid organs/tissues (minor reductions of lymphoid hyperplasia in the spleen; minor reduction in germinal follicles in the mesenteric and mandibular lymph nodes and Peyer's patches). - At the end of the 8-week recovery period, all findings partly or completely reversed. - Juvenile NOAEL: 0.3 mg/kg/day. Plasma exposures ($AUC_{0\text{-}24}$ hours) at the NOAEL were 16 100 ng.h/mL (males) and 20 500 ng.h/mL (females).	• The relevance of these results to humans is considered low given the available data from clinical trials and established clinical monitoring.
• Carcinogenicity - **Malignancy**: Teriflunomide was positive for genotoxicity in the in vitro chromosome aberration test in human lymphocytes. Supplementation with uridine reduced the cytotoxicity and the magnitude of the clastogenic effect. The highest concentration without an effect (250 µg/mL) was 6 times higher than the mean human	The positive response observed in the in vitro chromosome aberration test in human lymphocytes is likely related to the pharmacologic action of the drug (nucleotide pool imbalance due to DHO-DH inhibition). As such, it is considered a threshold effect. The 4-TFMA concentrations used in the in vitro genotoxicity studies are at least 1000 times higher than

Key Safety Findings	Relevance to human usage
exposure at the 14 mg dose. Teriflunomide was negative in all other genotoxicity studies. 4-Trifluoro-Methylaniline, a minor metabolite of teriflunomide, was positive for genotoxicity in vitro, and negative in vivo. Teriflunomide was non-carcinogenic in 2 rodent species up to the maximal tolerated dose. The exposure ratios at the NOEL for neoplasms (highest dose tested in both studies) was approximately 5 times in the mouse and <1X in the rat.	the mean plasma levels in patients exposed to 4-TFMA as a metabolite of teriflunomide. Although no signal was observed for malignancy in the clinical studies, since teriflunomide impacts the immune system, malignancies (including lymphoproliferative disorders) was listed in the RMP as an important potential risk till the RMP V7.0 and has been removed from RMP V7.2. It is being monitored through routine Pharmacovigilance activities.

4-TFMA: 4-Trifluoro-Methylaniline; AUC: Area Under the Curve; CD: Cluster of Differentiation; DHO-DH: Dihydroorotate Dehydrogenase; DNA: Deoxyribonucleic Acid; IgG: Immunoglobulin G; IgM: Immunoglobulin M; IV: Intravenous; KLH: Keyhole Limpet Haemocyanin; NOAEL: No-Observed-Adverse-Effect Level; NOEL: No-Observed-Event Level; PML: Progressive Multifocal Leukoencephalopathy; RBC: Red Blood Cell; RMP: Risk Management Plan; WBC: White Blood Cell.

No additional non-clinical data have been collected on the use of teriflunomide in any special populations. Teriflunomide is not intended for use in additional special populations.

RISK MANAGEMENT PLAN - PART II MODULE SIII: CLINICAL TRIAL EXPOSURE

Introduction

Monotherapy program

The clinical development program evaluating teriflunomide administered as monotherapy consisted of the following 5 studies in adult patients and 1 study in pediatric patients:

- Relapsing MS in adult patients
  - Study 2001: a completed, placebo-controlled Phase 2 study and its extension Study LTS6048 (a completed open-label long-term safety extension) evaluating 7 mg/day and 14 mg/day teriflunomide.
  - Study EFC6049/TEMSO (previously Study HMR1726/3001): a completed, placebo-controlled, Phase 3 pivotal study and its extension Study LTS6050 (a completed double-blind, long-term safety extension) evaluating 7 mg/day and 14 mg/day teriflunomide.
  - Study EFC10531/TOWER: a completed, placebo-controlled, Phase 3 pivotal study evaluating 7 mg/day and 14 mg/day teriflunomide, with a completed long-term extension study (under the same protocol code), with all patients receiving teriflunomide 14 mg regardless of the treatment received during the core study.
  - Study EFC10891/TENERE: a completed, active-controlled, Phase 3 core study evaluating 7 mg/day and 14 mg/day teriflunomide and subcutaneous interferon (IFN-β 1a [REBIF®]), with a completed long-term extension study (under the same protocol code), with all patients receiving teriflunomide 14 mg regardless of the treatment received during the core study.
- Clinically isolated syndrome (CIS) in adult patients
  - Study EFC6260/TOPIC: a completed, placebo-controlled, Phase 3 study evaluating 7 mg/day and 14 mg/day teriflunomide in CIS patients (long-term extension is completed under the same study).
- Relapsing MS in pediatric patients
  - Study EFC11759/TERIKIDS: a two year, multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate efficacy, safety, tolerability, and PKs of teriflunomide administered orally once daily - at the dose of 7 mg or 14 mg adults equivalent - in pediatric patients with relapsing forms of MS followed by an open-label extension. The double-blind, and open-label periods are completed.

Adjunctive therapy program

Additionally, a program has been conducted in order to evaluate the use of teriflunomide as an adjunct therapy and includes the following 3 studies:

- Two Phase 2 studies in patients with relapsing MS:

- PDY6045: a safety study of teriflunomide 7 mg/day and 14 mg/day as adjunct therapy to a stable dose of interferon-beta (IFN-β) compared to placebo and IFN-β, followed by an extension study LTS6047.
- PDY6046: a safety study of teriflunomide 7 mg/day and 14 mg/day as adjunct therapy to a stable dose of GA compared to placebo and GA, followed by an extension study LTS6047 (same extension protocol as for PDY6045).

- EFC6058/TERACLES: a placebo-controlled, Phase 3 study of teriflunomide 7 mg/day and 14 mg/day as adjunct therapy to a stable dose of IFN-β compared to placebo and IFN-β.

Clinical pharmacology

In adults:

The PKs and pharmacodynamics of teriflunomide were assessed in 20 clinical pharmacology studies in adult population. Two hundred and thirty-two (232) healthy subjects were exposed to a single oral dose from 7 to 70 mg. Among them, 6 subjects were exposed to a single 10 mg IV administration. In addition, 8 subjects with severe renal impairment and 17 subjects with mild and moderate hepatic impairment were exposed to a single dose of teriflunomide 14 mg.
Two hundred and forty-six (246) subjects were exposed to repeated doses of teriflunomide following a supratherapeutic regimen (repeated once daily oral doses of 70 mg up to 14 days) or a dosing regimen used to achieve concentrations in the therapeutic range (70 mg once daily for 3 to 4 days followed by 14 mg once daily for 8 to 11 days orally) or 2 consecutive doses of 100 mg/day.

At the end of all clinical studies, either cholestyramine or activated charcoal was administered to accelerate the elimination of teriflunomide.

In children:

In pediatric patients enrolled in the EFC11759/TERIKIDS study with body weight above 40 kg treated with 14 mg once daily, exposures are in the range to those observed in adult patients treated with the same dosage regimen. In addition, 98.6% of patients (145/147) weighing more than 40 kg needed 14 mg once daily to reach exposures similar to the steady state exposures in adults being treated with 14 mg once daily.

In pediatric patients enrolled in the EFC11759 TERIKIDS weighing 40 kg or less, 7 mg once daily dosing regimen led to exposures in the range to those observed in adult patients treated with 14 mg once daily. In addition, similar steady state exposures were documented in these pediatric patients after 14 mg every-other-day or 7 mg once daily dosing regimen.

Overall Clinical trial exposure

Overall teriflunomide exposure in the clinical program is detailed in Table 10 to Table 18 for adult population and Table 19 to Table 21 for pediatric population as follows:

Exposure in Adult Population

Pool A1 (placebo-controlled) consist of data from the 4 completed phase 2/3 monotherapy studies: phase 2 study 2001 (proof of concept), and phase 3 studies EFC6049/TEMSO, EFC10531/TOWER, and EFC6260/TOPIC. Follow up was 9 months for study 2001 and 2 years for TEMSO, and an average follow-up of 1.5 years and 1.3 years for TOWER and TOPIC, respectively.

Pool B (Active Treatment) consists of data from 2001 + LTS6048 (extension of 2001, the Placebo period of main study excluded for placebo switch patients), EFC6049/TEMSO+LTS6050 (extension of EFC6049/TEMSO), and EFC10891/TENERE. Average follow up is 6.3 years,4.7 years, and 1.2 years, respectively.

Exposure in Pediatric Population

A summary of the extent of exposure to the investigational medicinal product (IMP) during the combined double-blind and open-label treatment periods is presented in Table 20.

A total of 152 participants (100 participants in the teriflunomide/teriflunomide group and 52 participants in the placebo/teriflunomide group) were treated in the open-label period of the study. The cumulative duration of treatment exposure (the sum of all participants' duration of treatment exposure per treatment group) from enrollment to the open-label period was 36.18 participant-years for the teriflunomide 7 mg dose and 265.82 participant-years for the 14 mg dose Table 21.

Most of the participants (132 participants) received 14 mg teriflunomide. No participants received 3.5 mg in the open-label period. No difference in the duration of study treatment was noted between the 7 mg and 14 mg teriflunomide groups.

The median duration of study treatment was 683.0 days for the teriflunomide 7 mg group and 680.0 days for the 14 mg group. Most of the participants received the IMP (62.5% in the 7 mg group and 62.9% in the 14 mg group) for more than 96 weeks (Table 21).

Table 10 - Extent of exposure (Pool A1 and Pool B)

	Placebo	Teriflunomide		
		7 mg	14 mg	Total Teriflunomide
Pool A1				
Number of patients	997	1045	1002	2047
Duration of study treatment (days)				
Mean SD	552.29 (269.10)	543.63 (274.62)	533.07 (283.76)	549.27 (279.09)
Median	670	655	679	672
Minimum:Maximum	1.0:1183	1.0:1184	1.0:1214	1.0:1214
Cumulative duration of treatment (patient-years)	1507.56	1561.07	1517.26	3078.33

	Placebo	Teriflunomide		
		7 mg	14 mg	Total Teriflunomide
Pool B				
Number of patients		697	658	1355
Duration of study treatment (days)				
Mean SD		1609 (1247)	1607 (1286)	1608 (1265)
Median	Not applicable	1433	1361	1409
Minimum: Maximum		5.0:4678	1.0:4682	1.0:4682
Cumulative duration of treatment (patient-years)		3070	2895	5965

SD: Standard Deviation.

Table 11 - Exposure by duration (Pool B)

POOL B				
	Persons (N)		Person time (Patient-years)[a]	
Duration of exposure	**7 mg**	**14 mg**	**7 mg**	**14 mg**
Cumulative up to 1 week	695	657	53.03	50.13
Cumulative up to 4 weeks	685	649	156.16	146.87
Cumulative up to 12 weeks	666	619	302.31	281.58
Cumulative up to 24 weeks	632	588	434.16	403.06
Cumulative up to 36 weeks	614	560	561.45	512.08
Cumulative up to 48 weeks	586	529	789.31	712.64
Cumulative up to 72 weeks	502	456	913.34	829.08
Cumulative up to 96 weeks	457	413	1040.44	941.01
Cumulative up to 120 weeks	409	378	1123.46	1039.12
Cumulative up to 144 weeks	389	363	1249.08	1165.14
Cumulative up to 168 weeks	375	346	1377.14	1270.46
Cumulative up to 192 weeks	360	331	1485.08	1365.58
Cumulative up to 216 weeks	328	312	1504.94	1431.87
Cumulative up to 240 weeks	309	297	1559.84	1499.26
Cumulative up to 264 weeks	291	283	1598.84	1555.91
Cumulative up to 288 weeks	262	261	1562.39	1555.78
Cumulative up to 312 weeks	245	245	1571.16	1573.11
Cumulative up to 336 weeks	220	229	1515.05	1573.37
Cumulative up to 360 weeks	199	198	1456.99	1445.75
Cumulative up to 384 weeks	162	154	1261.02	1201.51

POOL B				
	Persons (N)		Person time (Patient-years)[a]	
Duration of exposure	7 mg	14 mg	7 mg	14 mg
Cumulative up to 408 weeks	137	141	1126.45	1161.05
Cumulative up to 432 weeks	107	113	885.88	935.56
Cumulative up to 456 weeks	84	89	734.09	777.79
Cumulative up to 480 weeks	55	50	505.95	459.96
Cumulative up to 504 weeks	48	41	463.64	396.02
Cumulative up to 528 weeks	42	36	425.00	364.29
Cumulative up to 552 weeks	34	33	359.69	349.11
Cumulative up to 576 weeks	30	31	331.17	342.21
Cumulative up to 600 weeks	25	24	287.47	275.98
Cumulative up to 624 weeks	16	19	191.34	227.22
Cumulative up to >624 weeks	6	9	75.68	113.55

Extracted from: PGM=PRODOPS/HMR1726/OVERALL/CSS_03/EXPLO/PGM/cdc_exposure_dur_s_t.sas OUT=EXPLO/OUTPUT/cdc_exposure_dur_s_t_ext_p2_i.rtf (25JUN2019 - 20:15)

a Patient-year exposure for 'cumulative up to 4 weeks' indicates the cumulative exposure up to 4 weeks for patients exposed for >1 week; 'cumulative up to 12 weeks' indicates the cumulative exposure up to 12 weeks for patients exposed for >4 weeks etc.

N: Number.

Table 12 - Exposure by age group and gender (Pool B)

POOL B				
	Persons (N)		Person time (Patient-years)	
Age by Gender	7 mg	14 mg	M	F
Female <38 years	220	224	892.18	948.16
Female ≥38 years	267	254	1304.01	1228.71
Male <38 years	103	95	398.49	320.16
Male ≥38 years	107	85	475.62	398.06

Extracted from: PGM=PRODOPS/HMR1726/OVERALL/CSS_03/EXPLO/PGM/cdc_exposure_subgrp_s_t.sas OUT=EXPLO/OUTPUT/cdc_exposure_subgrp_s_t_ext_p2_i.rtf (25JUN2019 - 20:14)

F: Female; M: Male; N: Number.

Table 13 - Exposure by ethnic origin (Pool A1)

POOL A1				
	Persons (N)		Person time (Patient-years)	
Ethnic origin	7 mg	14 mg	M	F
Caucasian/White	943	919	1425.62	1421.30
Black	11	13	14.27	12.53

POOL A1				
Asian/Oriental	72	59	95.41	69.01
Other	18	10	23.69	12.37

Extracted from: PGM=PRODOPS/HMR1726/OVERALL/SNDA_2013_CSS/REPORT/PGM/cdc_exposure_subgrp_s_t.sas OUT=REPORT/OUTPUT/cdc_exposure_subgrp_s_t_p1_x.rtf (13AUG2013 - 19:58)
F: Female; M: Male; N: Number.

Table 14 - Exposure by ethnic origin (Pool B)

POOL B				
	Persons (N)		Person time (Patient-years)	
Ethnic origin	7 mg	14 mg	M	F
Caucasian/White	679	638	2992.24	2819.76
Black	3	3	1.48	6.05
Asian/Oriental	8	11	27.32	44.77
Other	6	4	42.52	11.36

Extracted from: PGM=PRODOPS/HMR1726/OVERALL/CSS_03/EXPLO/PGM/cdc_exposure_subgrp_s_t.sasOUT=EXPLO/OUTPUT/cdc_exposure_subgrp_s_t_ext_p2_i.rtf (25JUN2019 - 20:14)
F: Female; M: Male; N: Number.

Table 15 - Exposure in renal impairment (Pool B)

POOL B				
	Persons		Person time (patient-years)	
Special population	7 mg	14 mg	7 mg	14 mg
Renal impairment (mild; ie, Cl_{cr}[a]≥50-≤80 mL/min)	96	84	500.49	433.83

Extracted from: PGM=PRODOPS/HMR1726/OVERALL/CSS_03/EXPLO/PGM/cdc_exposure_subgrp_s_t.sas OUT=EXPLO/OUTPUT/cdc_exposure_subgrp_s_t_ext_p2_i.rtf (25JUN2019 - 20:14)
a Creatinine clearance calculated from serum Creatinine
Cl_{cr}: Creatinine Clearance.

Table 16 - Exposure in placebo-controlled studies - Safety population - Pool A1

Study		Placebo (N = 997)	Teriflunomide	
			7 mg (N = 1045)	14 mg (N = 1002)
2001	N	61	61	57
	Patient-years	41.39	40.91	35.30
TEMSO	N	360	368	358
	Patient-years	622.13	639.58	614.21
TOWER	N	385	409	371
	Patient-years	601.64	617.80	576.18

Study		Placebo (N = 997)	Teriflunomide	
			7 mg (N = 1045)	14 mg (N = 1002)
TOPIC	N	191	207	216
	Patient-years	242.40	262.78	291.57
All placebo-controlled trials	N	997	1045	1002
	Patient-years	1507.56	1561.07	1517.26

Extracted from: PGM=PRODOPS/HMR1726/OVERALL/SNDA_2013_CSS/REPORT/PGM/cdc_exposure_pyr_s_t.sas OUT=REPORT/OUTPUT/cdc_exposure_pyr_s_t_p1_x.rtf (13AUG2013 - 19:36)
N: Number.

Table 17 - Exposure to Investigational Product - Safety population - Pool A1

	Placebo (N = 997)	Teriflunomide	
		7 mg (N = 1045)	14 mg (N = 1002)
Cumulative duration of treatment exposure (patient-years)	1507.56	61	57
Duration of study treatment (days)			
Number	997	1045	1002
Mean (SD)	552.29 (269.10)	545.63 (274.62)	553.07 (283.76)
Median	670.00	655.00	679.00
Minimum:Maximum	1.0:1183.0	1.0:1184.0	1.0:1214.0
Cumulative duration of study treatment by category [n (%)]			
>0 week	997 (100%)	1045 (100%)	1002 (100%)
>1 week	991 (99.4%)	1041 (99.6%)	997 (99.5%)
>4 weeks	978 (98.1%)	1025 (98.1%)	978 (97.6%)
>12 weeks	939 (94.2%)	971 (92.9%)	922 (92.0%)
>24 weeks	882 (88.5%)	897 (85.8%)	850 (84.8%)
>36 weeks	800 (80.2%)	820 (78.5%)	772 (77.0%)
>48 weeks	726 (72.8%)	757 (72.4%)	713 (71.2%)
>72 weeks	595 (59.7%)	627 (60.0%)	624 (62.3%)
>96 weeks	488 (48.9%)	500 (47.8%)	512 (51.1%)
>108 weeks	262 (26.3%)	267 (25.6%)	286 (28.5%)
>132 weeks	43 (4.3%)	42 (4.0%)	42 (4.2%)
>156 weeks	7 (0.7%)	7 (0.7%)	7 (0.7%)

Extracted from: PGM=PRODOPS/HMR1726/OVERALL/SNDA_2013_CSS/REPORT/PGM/cdc_exposure_s_t.sas OUT=REPORT/OUTPUT/cdc_exposure_s_t_p1_x.rtf (13AUG2013 - 19:33)
N: Number; SD: Standard Deviation.

Table 18 - Exposure to Investigational Product by intrinsic and extrinsic factors in patient-years - Safety population - Pool A1

			Placebo (N = 997)	Teriflunomide	
				7 mg (N = 1204)	14 mg (N = 1134)
Age	<37 years	N	453	513	484
		Patient-years	671.74	735.56	688.82
	≥37 years	N	544	532	518
		Patient-years	835.82	825.51	828.43
Gender	Female	N	716	734	710
		Patient-years	1083.29	1093.48	1067.42
	Male	N	281	311	292
		Patient-years	424.27	467.59	449.84
Age by gender	Age <37 years & Female	N	313	338	337
		Patient-years	460.11	478.38	470.56
	Age ≥37 years & Female	N	403	396	373
		Patient-years	623.18	615.10	596.86
	Age <37 years & Male	N	140	175	147
		Patient-years	211.63	257.18	218.26
	Age ≥37 years & Male	N	141	136	145
		Patient-years	212.63	210.41	231.57
Renal impairment (creatinine clearance at baseline)	<30 mL/min (moderate renal impairment)	N	0	0	1
		Patient-years	0	0	2.38
	≥30 - <50 mL/min (moderate renal impairment)	N	3	0	0
		Patient-years	1.88	0	0
	≥50 - ≤80 mL/min (mild renal impairment)	N	106	87	97
		Patient-years	156.58	117.71	134.86
	>80 mL/min (mild renal impairment)	N	883	956	899
		Patient-years	1340.98	1439.20	1371.46

Extracted from: PGM=PRODOPS/HMR1726/OVERALL/SNDA_2013_CSS/REPORT/PGM/cdc_exposure_subgrp_s_t.sas OUT=REPORT/OUTPUT/cdc_exposure_subgrp_s_t_p1_x.rtf (13AUG2013 - 19:58).

N: Number.

Table 19 - Exposure in the Completed Double-Blind Period of Study EFC11759/TERIKIDS - Safety Population

	Placebo (N = 57)	Teriflunomide			
		7 mg (N = 11)	14 mg (N = 97)	Missing (N = 1)	All (N = 109)
Cumulative duration of treatment exposure (patient-years)	56.53	14.59	131.04	0.01	145.64
Duration of study treatment (days)					
Number	57	11	97	1	109
Mean (SD)	362.2 (218.9)	484.5 (201.0)	493.4 (216.3)	4.0 (NC)	488.0 (218.0)
Median	273.0	539.0	665.0	4.0	660.0
Min; Max	1; 686	184; 675	83; 695	4; 4	4; 695
Duration of study treatment by category (n [%])					
>0 and ≤4 weeks	1(1.8)	0	0	1 (100)	1(0.9)
>4 and ≤12 weeks	2(3.5)	0	1(1.0)	0	1(0.9)
>12 and ≤24 weeks	7(12.3)	0	7(7.2)	0	7(6.4)
>24 and ≤48 weeks	23(40.4)	4 (36.4)	23(23.7)	0	27(24.8)
>48 and ≤72 weeks	6(10.5)	1 (9.1)	7(7.2)	0	8(7.3)
>72 and <96 weeks	8(14.0)	2 (18.2)	22(22.7)	0	24(22.0)
≥96 weeks	10(17.5)	4 (36.4)	37(38.1)	0	41(37.6)
Cumulative duration of study treatment by category (n [%])					
>0 week	57 (100)	11 (100)	97 (100)	1 (100)	109 (100)
>4 weeks	56 (98.2)	11 (100)	97 (100)	0	108 (99.1)
>12 weeks	54 (94.7)	11 (100)	96 (99.0)	0	107 (98.2)
>24 weeks	47 (82.5)	11 (100)	89 (91.8)	0	100 (91.7)
>48 weeks	24 (42.1)	7 (63.6)	66 (68.0)	0	73 (67.0)
>72 weeks	18 (31.6)	6 (54.5)	59 (60.8)	0	65 (59.6)
96 weeks	10 (17.5)	4 (36.4)	37 (38.1)	0	41 (37.6)

PGM=PRODOPS/HMR1726/EFC11759/CSR_02/REPORT/PGM/db_cdc_exposure_bytrt_s_t.sas
OUT=REPORT/OUTPUT/db_cdc_exposure_bytrt_s_t_i.rtf (12DEC2019 9:19)
Note: Patients are considered in the group of treatment they actually received at the end of the PK run-in period.
Missing column shows patients who drop out before they reached the end of the double-blind PK run-in period.
Duration of double-blind IMP exposure is defined as last double-blind dose date - first dose date + 1 day, regardless of unplanned intermittent discontinuations.
IMP: Investigational Medicinal Product; N: Number; PK: Pharmacokinetic; SD: Standard Deviation.

Table 20 - Extent of exposure to investigational medicinal product during combined double-blind and open-label treatment periods of Study EFC11759/TERIKIDS - Safety population

	Placebo/ Teriflunomide (N = 52)	Teriflunomide/ Teriflunomide (N = 100)	All (N = 152)
Cumulative duration of treatment exposure (participant years)	158.46	332.13	490.58
Duration of study treatment (days)			
Number	52	100	152
Mean (SD)	1113.0 (376.8)	1213.1 (296.3)	1178.8 (328.3)
Median	1344.0	1345.5	1344.0
Minimum; Maximum	192; 1407	217; 1418	192; 1418
Duration of study treatment by category (n [%]]			
>0 and 4 weeks	0	0	0
>4 and ≤12 weeks	0	0	0
>12 and ≤24 weeks	0	0	0
>24 and ≤48 weeks	3 (5.8)	3 (3.0)	6 (3.9)
>48 and ≤72 weeks	3 (5.8)	4 (4.0)	7 (4.6)
>72 and ≤96 weeks	3 (5.8)	3 (3.0)	6 (3.9)
>96 and ≤120 weeks	2 (3.8)	3 (3.0)	5 (3.3)
>120 and ≤144 weeks	5 (9.6)	5 (5.0)	10 (6.6)
>144 and ≤168 weeks	1 (1.9)	4 (4.0)	5 (3.3)
>168 and <192 weeks	8 (15.4)	20 (20.0)	28 (18.4)
≥192 weeks	27 (51.9)	58 (58.0)	85 (55.9)
Cumulative duration of study treatment by category (n [%])			
>0 week	52 (100)	100 (100)	152 (100)
>4 weeks	52 (100)	100 (100)	152 (100)
>12 weeks	52 (100)	100 (100)	152 (100)
>24 weeks	52 (100)	100 (100)	152 (100)
>48 weeks	49 (94.2)	97 (97.0)	146 (96.1)
>72 weeks	46 (88.5)	93 (93.0)	139 (91.4)
>96 weeks	43 (82.7)	90 (90.0)	133 (87.5)
>120 weeks	41 (78.8)	87 (87.0)	128 (84.2)
>144 weeks	36 (69.2)	82 (82.0)	118 (77.6)
>168 weeks	35 (67.3)	78 (78.0)	113 (74.3)
≥192 weeks	27 (51.9)	58 (58.0)	85 (55.9)

Duration of cumulative teriflunomide exposure is defined as last dose date in the open-label period - first dose date in the double-blind period + 1 day, regardless of unplanned intermittent discontinuations.

PGM=PRODOPS/HMR1726/EFC11759/CSR_02/REPORT/PGM/ol_cdc_exposure_all_s_t.sas
OUT=REPORT/OUTPUT/ol_cdc_exposure_all_s_t_i.rtf (17DEC2021 4:30)

N: Number; SD: Standard Deviation.

Table 21 - Extent of exposure to investigational medicinal product by dose at the end of the PK run-in period in the open-label period - Safety population

	Placebo/Teriflunomide (N = 52)				Teriflunomide/Teriflunomide (N = 100)				All (N = 152)			
	3.5 mg (N = 0)	7 mg (N = 13)	14 mg (N = 36)	Missing (N = 3)	3.5 mg (N = 0)	7 mg (N = 3)	14 mg (N = 96)	Missing (N = 1)	3.5 mg (N = 0)	7 mg (N = 16)	14 mg (N = 132)	Missing (N = 4)
Cumulative duration of treatment exposure (participant years)		27.97	78.64	0.12		8.21	187.18	0.10		36.18	265.82	0.22
Duration of study treatment (days)												
Number	0	13	36	3	0	3	96	1	0	16	132	4
Mean (SD)		785.8 (232.6)	797.9 (352.4)	15.0 (13.5)		999.7 (143.5)	712.2 (277.9)	35.0 (NC)		825.9 (231.2)	735.5 (301.1)	20.0 (14.9)
Median		673.0	774.5	11.0		1041.0	677.5	35.0		683.0	680.0	20.5
Min;Max		429;1162	71;1287	4;30		840;1118	92;1283	35;35		429;1162	71;1287	4;35
Duration of study treatment by category (n [%])												
>0 and ≤4 weeks	0	0	0	2 (66.7)	0	0	0	0	0	0	0	2 (50.0)
>4 and ≤12 weeks	0	0	1 (2.8)	1 (33.3)	0	0	0	1 (100)	0	0	1 (0.8)	2 (50.0)
>12 and ≤24 weeks	0	0	1 (2.8)	0	0	0	3 (3.1)	0	0	0	4 (3.0)	0
>24 and ≤48 weeks	0	0	4 (11.1)	0	0	0	7 (7.3)	0	0	0	11 (8.3)	0
>48 and ≤72 weeks	0	1 (7.7)	1 (2.8)	0	0	0	8 (8.3)	0	0	1 (6.3)	9 (6.8)	0
>72 and ≤96 weeks	0	5 (38.5)	4 (11.1)	0	0	0	20 (20.8)	0	0	5 (31.3)	24 (18.2)	0
>96 and ≤120 weeks	0	3 (23.1)	8 (22.2)	0	0	1 (33.3)	35 (36.5)	0	0	4 (25.0)	43 (32.6)	0
>120 and ≤144 weeks	0	1 (7.7)	2 (5.6)	0	0	0	5 (5.2)	0	0	1 (6.3)	7 (5.3)	0

	Placebo/Teriflunomide (N = 52)				Teriflunomide/Teriflunomide (N = 100)				All (N = 152)			
	3.5 mg (N = 0)	7 mg (N = 13)	14 mg (N = 36)	Missing (N = 3)	3.5 mg (N = 0)	7 mg (N = 3)	14 mg (N = 96)	Missing (N = 1)	3.5 mg (N = 0)	7 mg (N = 16)	14 mg (N = 132)	Missing (N = 4)
>144 and ≤168 weeks	0	3 (23.1)	10 (27.8)	0	0	2 (66.7)	11 (11.5)	0	0	5 (31.3)	21 (15.9)	0
>168 and <192 weeks	0	0	5 (13.9)	0	0	0	7 (7.3)	0	0	0	12 (9.1)	0
≥192 weeks	0	0	0	0	0	0	0	0	0	0	0	0
Cumulative duration of study treatment by category (n [%])												
>0 week	0	13 (100)	36 (100)	3 (100)	0	3 (100)	96 (100)	1 (100)	0	16 (100)	132 (100)	4 (100)
>4 weeks	0	13 (100)	36 (100)	1 (33.3)	0	3 (100)	96 (100)	1 (100)	0	16 (100)	132 (100)	2 (50.0)
>12 weeks	0	13 (100)	35 (97.2)	0	0	3 (100)	96 (100)	0	0	16 (100)	131 (99.2)	0
>24 weeks	0	13 (100)	34 (94.4)	0	0	3 (100)	93 (96.9)	0	0	16 (100)	127 (96.2)	0
>48 weeks	0	13 (100)	30 (83.3)	0	0	3 (100)	86 (89.6)	0	0	16 (100)	116 (87.9)	0
>72 weeks	0	12 (92.3)	29 (80.6)	0	0	3 (100)	78 (81.3)	0	0	15 (93.8)	107 (81.1)	0
>96 weeks	0	7 (53.8)	25 (69.4)	0	0	3 (100)	58 (60.4)	0	0	10 (62.5)	83 (62.9)	0
>120 weeks	0	4 (30.8)	17 (47.2)	0	0	2 (66.7)	23 (24.0)	0	0	6 (37.5)	40 (30.3)	0
>144 weeks	0	3 (23.1)	15 (41.7)	0	0	2 (66.7)	18 (18.8)	0	0	5 (31.3)	33 (25.0)	0
>168 weeks	0	0	5 (13.9)	0	0	0	7 (7.3)	0	0	0	12 (9.1)	0
≥192 weeks	0	0	0	0	0	0	0	0	0	0	0	0

Note: Participants are considered in the group of treatment they actually received at the end of the PK run-in period in the open-label period.
The missing column shows participants who didn't reach the end of open-label PK run-in period.
Duration of the open-label IMP exposure is defined as last dose date in the open-label period - first dose date in the open-label period + 1 day, regardless of unplanned intermittent discontinuations.
PGM=PRODOPS/HMR1726/EFC11759/CSR_02/REPORT/PGM/ol_cdc_exposure_bytrt_s_t.sas OUT=REPORT/OUTPUT/ol_cdc_exposure_bytrt_s_t_i.rtf (17DEC2021 4:30)
NC represent the only one participant and we cannot compute SD.
IMP: Investigational Medicinal Product; PK: Pharmacokinetic; N: Number; SD: Standard Deviation.

RISK MANAGEMENT PLAN - PART II MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 22 - Important exclusion criteria in pivotal studies in the development programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Patients with severe hepatic impairment (Child-Pugh class C).	Related to teriflunomide PK	No	Covered in contraindications section of the SmPC and in prescriber guide.
Pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with teriflunomide and thereafter as long as its plasma levels are above 0.02 mg/L.	Studies in animals have shown reproductive toxicity. Teriflunomide may cause serious birth defects when administered during pregnancy.	No	Covered in contraindications section of the SmPC and in prescriber guide.
Breast-feeding women	Animal studies have shown excretion of teriflunomide in milk.	No	Covered in contraindications section of the SmPC and in prescriber guide.
Patients with severe immunodeficiency states, eg, AIDS.	Related to immunomodulatory effect of teriflunomide	No	Covered in contraindications section of the SmPC and in prescriber guide.
Patients with significantly impaired bone marrow function or significant anemia, leucopenia, neutropenia or thrombocytopenia.	Related to immunomodulatory effect of teriflunomide	No	Covered in contraindications section of the SmPC and in prescriber guide.
Patients with severe active infection until resolution.	Related to immunomodulatory effect of teriflunomide	No	Covered in contraindications section of the SmPC and in prescriber guide.
Patients with severe renal impairment undergoing dialysis	Teriflunomide is eliminated through direct biliary excretion of unchanged drug and renal excretion of metabolites. AUBAGIO causes increases in renal uric acid clearance with mean decreases in serum uric acid of 20-30%.	No	Covered in contraindications section of the SmPC and in prescriber guide.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Patients with severe hypoproteinemia, eg, in nephrotic syndrome.	Related to teriflunomide PK effect via albumin	No	Covered in contraindications section of the SmPC and in prescriber guide.
Known history of chronic pancreatic disease or pancreatitis	Pancreatitis is part of the adverse event of pre-specified monitoring	No	Data available from clinical trial development program and covered by adverse event section of SmPC.
Concomitant use with other MS treatments	Concomitant use with other MS treatments could increase the risk of immunosuppression	No	Considered as missing information till the EU-RMP version 7.0 and has been removed from the LSC in EU-RMP update v 7.2 onwards.

AIDS: Acquired Immune Deficiency Syndrome; EU: European Union; LSC: List of Safety Concern; MS: Multiple Sclerosis; PK: Pharmacokinetic; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Given the large clinical development, including more than 4500 treated patients in clinical trials and 716 944 patient years in the postmarketing setting including almost 10 years of marketing experience, the limitation relative to frequent adverse drug reaction detection in clinical trials can be considered as no longer relevant.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 23 - Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant or breastfeeding women	Limited data were generated concerning use of teriflunomide in pregnant and lactating women, due to the contraception requirements during the clinical trials. In addition to the internal pharmacovigilance data (refer to [Part II SVII, Teratogenicity]), a publication with data cut-off Dec-2017 [70] brings information regarding the pregnancies of women exposed to teriflunomide from clinical trials and in the postmarketing setting as well as their outcomes. In the context of Post-Authorization Pregnancy Registries OBS13499 (US and Canada) and OBS12751 (EU and ROW), a total of 63 pregnancies occurred in 63 female patients who received teriflunomide (either 7 mg or 14 mg).

Type of special population	Exposure
Patients with relevant comorbidities • Patients with hepatic impairment • Patients with renal impairment	Patients with liver function impairment or persisting elevations of ALT, AST, or direct bilirubin greater than 1.5 x ULN were excluded from Phase 2/3 clinical studies. Patients with moderate or severe renal impairment (serum creatinine >133 μmol/L) were excluded from Phase 2/3 clinical studies.
Populations with relevant different ethnic origin	Enrollment in placebo-controlled studies within the teriflunomide group was mostly Caucasian. Non-Caucasian enrolled included: Asian/Oriental, Black, and "Other". Detailed figures are provided in the exposure tables in [Part II SIII].
Other • Children and adolescents	Multiple sclerosis is not infrequent in patients below 18 years of age. One hundred sixty six children and adolescents were included in the clinical studies performed to date. A placebo-controlled Phase 3 clinical study (EFC11759-TERIKIDS) assessing the efficacy, safety and tolerability, and teriflunomide administered to pediatric patients 10 to 17 years of age with relapsing MS, has been performed. The 166 patients randomized include 10 patients prepubertal (5 in the placebo and 5 in the teriflunomide group) and 26 patients under the age of 13 years old (10 in the placebo group and 16 in the teriflunomide group) at baseline. In the open-label period, all enrolled participants (100 participants in the teriflunomide/teriflunomide group and 52 participants in the placebo/teriflunomide group) were included in the analysis populations. The mean age of the study participants at baseline was 14.6 years (range of 10 to 17 years). Overall, 25 participants (16.4%) were below 13 years of age. Ten participants (6.6%) were prepubertal (Tanner Stage I). The completed clinical study report for double-blind, and open-label periods for study EFC11759/TeriKids is available. Overall, the LSC and known risks (both identified and potential) are similar in the Adult (above 18 years old) and Pediatric population (from 10 to 17 years old).
• Elderly patients (>65 years)	As is generally observed in MS clinical studies in order to ensure that relapsing forms of MS are targeted, no elderly patients (>65 years of age) were included in the teriflunomide clinical program.
• Pregnant partners of male patients	Overall, there were 162 cases reporting pregnancies in female partners of male patients exposed to teriflunomide (paternal exposure) during the course of phase 2, 3, or 4 monotherapy clinical trials or from postmarketing sources.
• Concomitant use with other MS treatments	Adjunct studies of teriflunomide were conducted: two with interferon - (study PDY6045 + LTS6047 with 75 patients exposed to the combination for up to one year and study EFC5068 in 534 patients exposed for an average of approximately 8 months [with a maximum of approximately 21 months]) and one with GA (study PDY6046 + LTS6047 with 83 patients exposed to the combination for up to one year).
• Concomitant use in patients receiving vaccine	No data

ALT: Alanine Transaminase; AST: Aspartate Transaminase; EU: European Union; GA: Glatiramer Acetate; LSC: List of Safety Concern; MS: Multiple Sclerosis; RMP: Risk Management Plan; ROW: Rest of the World; ULN: Upper Limit of Normal; US: United States.

Pregnant or breast-feeding women: Due to the embryo fetal toxicity observed in animals and since MS is highly prevalent in young women and that some treated women are likely to become pregnant even with strong contraception recommendations, teratogenicity is considered as an important potential risk, and is described in detail in [Part II SVII].

Patients with hepatic impairment: The PKs of teriflunomide in mild and moderate hepatic impairment was evaluated in Study POP6507 and showed no impact on the PK of teriflunomide. No specific study was conducted in patients with severe hepatic impairment. Product Labeling includes “severe hepatic impairment” as a contraindication.

Patients with renal impairment: Severe renal impairment had no impact on the PK of teriflunomide after a single oral dose of teriflunomide at 14 mg (Study POP11432). Therefore, no dose adjustment is anticipated in patients with mild or moderate or severe not undergoing dialysis renal impairment. Patients with severe renal impairment undergoing dialysis were not evaluated. Therefore, teriflunomide is contraindicated in this population.

Patients of different racial and/or ethnic origins: The population PK analysis identified race as a statistically significant covariate influencing teriflunomide PKs but leading to only small changes in predicted exposure in different races. The sample size was too small to draw any firm conclusions (Caucasians represented 96% of the analysis population), but Black, Asian, or other non-Caucasian race appears to have only small effects on PK parameters.

Children and adolescents: The efficacy and safety of teriflunomide have been established through the EFC11759/TERIKIDS study in patients 10-year-old and older.

- In the completed double-blind period, ten (10) patients (6.6%) of the study population of Study EFC11759/TERIKIDS were reported to be in Tanner Stage I at baseline, indicating that they were pre-pubertal (5 patients in each group).
- In the completed open-label period, the mean age of the study participants at baseline was 14.6 years (range of 10 to 17 years). Overall, 25 participants (16.4%) were below 13 years of age. Ten (10) participants (6.6%) were prepubertal (Tanner Stage I). Therefore, safety data in pre-pubertal patients is still limited and this subpopulation should be closely monitored (via routine pharmacovigilance activities).

Elderly patients (>65 years): Due to limited safety and efficacy data, teriflunomide should be used with caution in patients aged 65 years and over.

Pregnant partners of male patients: Seven (7) congenital anomalies were reported in partners of male patients treated with teriflunomide: a case of congenital flat feet, two cases of hip dysplasia, two cases of spinal bifida, one case of down syndrome and one case of alveolar capillary dysplasia were reported in full-term infants. All were assessed as unrelated to teriflunomide. In EU, teriflunomide is not contraindicated in male patients.

Concomitant use with other multiple sclerosis treatments: No new safety signal was observed in these teriflunomide adjunct studies as compared to the teriflunomide monotherapy studies. Concomitant use of teriflunomide with MS treatments (other than INF-β or GA) was considered as missing information till the EU-RMP version 7.0 and has been removed from the LSC in EU-RMP update version 7.2 onwards.

Concomitant use in patients receiving vaccine: Immunomodulating agents such as teriflunomide may impact the efficacy and safety of vaccines. Two clinical studies have shown that vaccinations to inactivated neo-antigen (first vaccination), or recall antigen (re-exposure) were safe and effective during AUBAGIO treatment. The use of live attenuated vaccines may carry a risk of infections and should therefore be avoided.

RISK MANAGEMENT PLAN - PART II MODULE SV: POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method used to calculate exposure

Internal sales data have been used as the source for teriflunomide exposure data retrieval. Sales figures for cumulative exposure can be retrieved from 12 September 2012 to 31 August 2023.

SV.1.2 Exposure

Teriflunomide was first approved in the US on 12 September 2012. The marketing authorization holder (MAH) made AUBAGIO available on the US market on 01 October 2012.

In addition to the countries where teriflunomide is authorized, patients received commercial teriflunomide via an International Charitable Access Program (ICAP).

Cumulative exposure was estimated at 264.99 million tablets, consisting of 258.74 million tablets of teriflunomide 14 mg and 6.25 million tablets of teriflunomide 7 mg. Based on the World Health Organization (WHO), defined daily dose of 14 mg, the patient exposure is estimated at 261.86 million patient days, corresponding to 716 944 patient years.

Table 24 - Exposure by dose and region (tablets)

	Teriflunomide		
REGION	**14 mg**	**7 mg**	**TOTAL**
AMESA	16 323 664		**16 323 664**
EUROPE	149 377 368	30 016	**149 407 384**
JAPAN PACIFIC ASIA	6 288 531		**6 288 531**
LATIN AMERICA	3 232 664		**3 232 664**
NORTH AMERICA	83 515 100	6 223 220	**89 738 320**
TOTAL	**258 737 327**	**6 253 236**	**264 990 563**

Source: Marco database (update Aug-2022).
AMESA: Africa, Middle East and South Asia; MARCO: Margin Consolidated.

RISK MANAGEMENT PLAN - PART II MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for misuse for illegal purposes

Teriflunomide possesses a unique mechanism of action for treating MS. Teriflunomide is shown to non-competitively and reversibly inhibit the mitochondrial enzyme DHO DH required for de novo synthesis of pyrimidines. Blockade of DHO DH by teriflunomide is believed to result in diminished numbers of activated lymphocytes in peripheral blood, that are available to enter the CNS leading to reduction or halting of CNS damage in patients with MS. It may not be required for it to cross the blood brain barrier to produce anti-inflammatory and immunomodulatory effects in the CNS.

An assessment of teriflunomide dependence and abuse potential was conducted based on the literature, chemistry, formulation, non-clinical and clinical data.

The pharmacological profile of teriflunomide, as assessed by binding and/or inhibition assays, is not similar to any known drugs of abuse. No information on behavioral effects related to the abuse potential of teriflunomide or its parent compound leflunomide was found in the literature. As indicated by its Tanimoto index of below 0.19, the chemical structure of teriflunomide does not present significant similarities with the chemical structures of representative known drugs of abuse, ie, morphine derivatives, CNS stimulants, hallucinogenic compounds, benzodiazepines, cannabinoid or nicotine compounds.

Available non-clinical data (safety pharmacology and toxicology) do not show any obvious drug dependence or abuse potential of teriflunomide.

No cases of abuse, dependence, or diversion were reported with the use of teriflunomide in clinical development program and the analysis of clinical data did not reveal teriflunomide potential for abuse and dependence. For the review, treatment emergent adverse events (TEAEs) were grouped in 3 pre specified categories, “euphoria related events”, “subjective response event” and “dissociative/psychotic events”. Across all clinical studies, the vast majority of “euphoria related events” consisted of nonspecific dizziness with a similar incidence across all treatment groups.

There were no reports of events suggestive of positive psychoactive effects of the drug. No case of abuse with teriflunomide has been reported in the medical literature. Review of case reports received in the postmarketing setting since International Birth Date (IBD) up to DLP did not indicate a new safety concern for potential misuse for illegal purposes.

In the pediatric population studied in EFC11759/TERIKIDS study, there were no events suggestive of a confirmed psychoactive effect of the drug, similarly to the results in the adult population.

In summary, teriflunomide demonstrated no signal of dependence and abuse potential after review of similarities to known drugs of abuse according to chemical structure, pharmacology and mechanism of action, non-clinical data, clinical trial data, and case reports from postmarketing experience.

RISK MANAGEMENT PLAN - PART II MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

Not applicable because it is not an initial RMP. The first RMP approved is v1.3.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable because it is not an initial RMP. The first RMP approved is v1.3.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable because it is not an initial RMP. The first RMP approved is v1.3.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

No new safety concerns or reclassification have been considered since RMP version 9.0.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following risks have been identified for teriflunomide and have been considered relevant for the RMP:

Important identified risks:

- Hepatic effects
- Hypertension
- Hematologic effects
- Infections
- Acute pancreatitis

Important potential risks:

- Teratogenicity
- Serious opportunistic infections, including PML

Missing information:

- None

SVII.3.1 Presentation of important identified risks and important potential risks

Exposure in adults:

The following pools were defined, one (Pool A) focusing on the placebo-controlled segments of studies and the other (Pool B) focusing on the active treatment, including the core and the extension segment of the studies and Study EFC10891/TENERE, in the initial submission. The pool A1 was defined in the TOPIC variation (procedure EMEA/H/C/002514/II/0003). They are described below, with pool A1 and pool B being the reference in the following risk tables:

Pool A (placebo-controlled) consist of data from the phase 2 study 2001 (Proof of Concept), and the phase 3 EFC6049/TEMSO study. Follow up period was of 9 months and 2 years, respectively.
Pool B (active treatment) consists of data from 2001 + LTS6048 (extension of 2001) and EFC6049/TEMSO + LTS6050[1] (extension of EFC6049/TEMSO). Average follow up is 6.3 years, 4.7 years, and 1.2 years, respectively.

Pool A1 (placebo controlled) consist of data from the 4 completed phase 2/3 monotherapy studies: phase 2 study 2001 (proof of concept), and phase 3 studies EFC6049/TEMSO, EFC10531/TOWER, and EFC6260/TOPIC. Follow up was 9 months and 2 years for the study 2001 and TEMSO, respectively, and an average follow up of 1.5 years and 1.3 years for TOWER and TOPIC, respectively.

In addition, when the analysis of elements of postmarketing Surveillance are confirming or amending the conclusions, a statement is added.

Exposure in children:

A summary of the extent of exposure to the IMP during the combined double-blind and open-label treatment periods is presented in Table 20.

A total of 152 participants (100 participants in the teriflunomide/teriflunomide group and 52 participants in the placebo/teriflunomide group) were treated in the open-label period of the study. The cumulative duration of treatment exposure (the sum of all participants' duration of treatment exposure per treatment group) from enrollment to the open-label period was 36.18 participant-years for the teriflunomide 7 mg dose and 265.82 participant-years for the 14 mg dose (Table 21).

Most of the participants (132 participants) received 14 mg teriflunomide. No participants received 3.5 mg in the open-label period. No difference in the duration of study treatment was noted between the 7 mg and 14 mg teriflunomide groups.

The median duration of study treatment was 683.0 days for the teriflunomide 7 mg group and 680.0 days for the 14 mg group. Most of the participants received the IMP (62.5% in the 7 mg group and 62.9% in the 14 mg group) for more than 96 weeks (Table 21).

[1] Placebo period of main study excluded for placebo switch patients.

Table 25 - Identified risk: Hepatic effects

<table>
<tr><th>Identified Risk</th><th>Hepatic effects</th></tr>
<tr><td>Potential mechanism</td><td>No hepatoxicity was observed in non-clinical studies performed with teriflunomide.
Hepatic effects were observed with leflunomide clinically.
Exploratory non-clinical studies have been performed with leflunomide and/or teriflunomide. Preliminary results suggest approximately 10-fold greater effects on mitochondrial function with leflunomide as compared to teriflunomide. However, no clear mechanism of hepatotoxicity has been identified at this time, including apoptosis, superoxide anion generation, or cytotoxicity in primary hepatocytes. Further exploratory studies are planned.</td></tr>
<tr><td>Evidence source(s) and strength of evidence</td><td>Literature, clinical data</td></tr>
<tr><td>Characterization of the risk</td><td><u>Frequency with 95% CI, Severity and nature of risk</u>
In Adults
Pool A1
As shown in Table 25a, based on laboratory data, the proportion of patients with mild transaminase increase (ALT≤3 ULN) was higher with both teriflunomide groups as compared to placebo, and without a dose-effect relationship observed. On the other hand, the incidence of patients with ALT elevations above 3 x ULN (3-5, 5-20 or >20 x ULN) was balanced across treatment groups. Among the 76 patients with ALT elevation >3 x ULN, complete return to normal (ALT<1 ULN or return to baseline) was recorded (on treatment or following treatment discontinuation) in most patients (69, 76 and 80% with placebo, teriflunomide 7 and 14 mg, respectively).
With respect to reported hepatic TEAEs, the proportion of patients with hepatic disorder TEAEs was higher in the teriflunomide treatment groups (19.8% and 21.5% in teriflunomide 7 and 14 mg, respectively) compared to the placebo group (15.2%).
Table 25a - Overview of hepatic disorder TEAEs and ALT increase (based on laboratory data) - Safety population - Pool A1
<table>
<tr><th></th><th></th><th colspan="2">Teriflunomide</th></tr>
<tr><th></th><th>Placebo
(N = 997)</th><th>7 mg
(N = 1045)</th><th>14 mg
(N = 1002)</th></tr>
<tr><td>Hepatic TEAE</td><td></td><td></td><td></td></tr>
<tr><td>Patients with any TEAE</td><td>152 (15.2%)</td><td>207 (19.8%)</td><td>215 (21.5%)</td></tr>
<tr><td>Patients with any serious TEAE</td><td>27 (2.7%)</td><td>22 (2.1%)</td><td>22 (2.2%)</td></tr>
<tr><td>Patients with any AE leading to death</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Patients with any TEAE leading to permanent treatment discontinuation</td><td>39 (3.9%)</td><td>47 (4.5%)</td><td>42 (4.2%)</td></tr>
<tr><td>ALT</td><td></td><td></td><td></td></tr>
<tr><td>Total</td><td>(N = 994)</td><td>(N = 1042)</td><td>(N = 999)</td></tr>
<tr><td>>3 ULN</td><td>66/994 (6.6%)</td><td>81/1042 (7.8%)</td><td>80/999 (8.0%)</td></tr>
<tr><td>>5 ULN</td><td>37/994 (3.7%)</td><td>30/1042 (2.9%)</td><td>31/999 (3.1%)</td></tr>
<tr><td>>10 ULN</td><td>16/994 (1.6%)</td><td>6/1042 (0.6%)</td><td>9/999 (0.9%)</td></tr>
<tr><td>>20 ULN</td><td>4/994 (0.4%)</td><td>1/1042 (<0.1%)</td><td>3/999 (0.3%)</td></tr>
</table></td></tr>
</table>

Identified Risk	Hepatic effects

ALT >3 ULN and TBILI >2 ULN (Hy's Law range)	5/994 (0.5%)	2/1042 (0.2%)	3/999 (0.3%)

Extracted from:
PGM=PRODOPS/HMR1726/OVERALL/CSS_EU_2014/REPORT/PGM/lab_pcsaliver_s_t.sas
OUT=REPORT/OUTPUT/lab_pcsaliver_s_t_p1_i.rtf (14MAR2014 - 22:38)
AE: Adverse Event; ALT: Alanine Transaminase; N: Number; TBILI: Total Bilirubin; TEAE: Treatment Emergent Adverse Event; ULN: Upper Limit of Normal.

Table 25b - Number (%) of patients with hepatic disorder TEAEs by Primary SOC and PT (for PTs occurring in ≥2 patients in teriflunomide) - Pool A1

		Teriflunomide	
Primary System Organ Class **Preferred Term n (%)**	**Placebo** **(N = 997)**	**7 mg** **(N = 1045)**	**14 mg** **(N = 1002)**
Any class	152 (15.2%)	207 (19.8%)	215 (21.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (1.2%)	10 (1.0%)	13 (1.3%)
Haemangioma of liver	11 (1.1%)	9 (0.9%)	12 (1.2%)
Focal nodular hyperplasia	0	1 (<0.1%)	1 (<0.1%)
Hepatobiliary disorders	29 (2.9%)	42 (4.0%)	28 (2.8%)
Hepatic steatosis	13 (1.3%)	18 (1.7%)	11 (1.1%)
Hepatic cyst	4 (0.4%)	6 (0.6%)	2 (0.2%)
Liver disorder	1 (0.1%)	1 (<0.1%)	2 (0.2 %)
Hepatic pain	0	2 (0.2%)	1 (<0.1%)
Hepatocellular injury	0	2 (0.2 %)	1 (<0.1%)
Hyperbilirubinaemia	1 (0.1%)	1 (<0.1%)	2 (0.2%)
Hepatomegaly	3 (0.3%)	10 (1.0%)	4 (0.4%)
Hepatitis toxic	0	0	2 (0.2%)
Liver injury	3 (0.3%)	2 (0.2%)	1 (0.1%)
Investigations	118 (11.8%)	168 (16.1%)	187 (18.7%)
Alanine aminotransferase increased	89 (8.9 %)	136 (13.0%)	150 (15.0%)
Aspartate aminotransferase increased	17 (1.7%)	29 (2.8%)	34 (3.4%)
Gamma-glutamyltransferase increased	9 (0.9%)	24 (2.4%)	24 (2.4%)
Hepatic enzyme increased	10 (1.0%)	9 (0.9%)	9 (0.9%)
Transaminases increased	10 (1.0%)	13 (1.2%)	16 (1.6%)
Blood bilirubin increased	6 (0.6%)	5 (0.5%)	3 (0.3%)
Bilirubin conjugated increased	3 (0.3%)	1 (<0.1%)	1 (<0.1%)
Liver function test abnormal	1 (0.1%)	3 (0.3%)	1 (<0.1%)
Blood bilirubin unconjugated increased	3 (0.3%)	2 (0.2%)	0

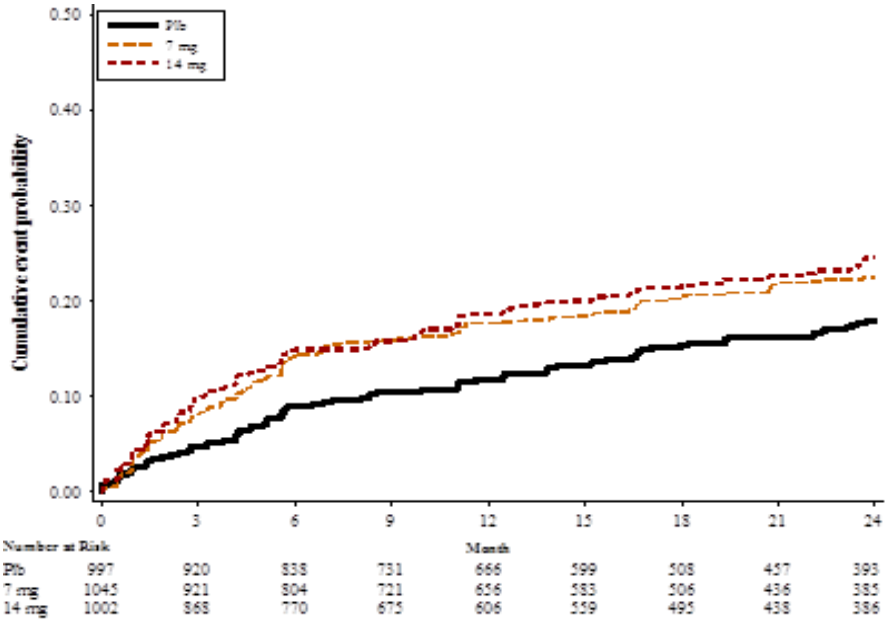
Identified Risk	Hepatic effects

Prothrombin time prolonged	3 (0.3%)	3 (0.3%)	1 (<0.1%)
International normalized ratio increased	2 (0.2%)	2 (0.2%)	0

n (%) = number and percentage of patients with at least one TEAE
Note: Table generally sorted by decreasing frequency of PTs in teriflunomide 14 mg group.
Extracted from:
PGM=PRODOPS/HMR1726/OVERALL/CSS_EU_2014/REPORT/PGM/ae_socpt_s_t.sas
OUT=REPORT/OUTPUT/ae_socpt_hepatic_s_t_p1_i.rtf (14MAR2014 - 23:08)
N: Number; PT: Preferred Term; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

The Kaplan-Meier plot (cumulative events) of time to onset of hepatic disorder TEAEs showed a higher probability of events with both teriflunomide treatment groups during the first 6 months compared to placebo. Most of the events were mild to moderate.

Figure F25a - Kaplan-Meier plot for time to onset of hepatic disorder TEAEs - Pool A1



a.PGM=PRODOPS/HMR1726/OVERALL/CSS_EU_2014/REPORT/PGM/ae_km_s_g.sasOUT=REPORT/OUTPUT/ae_km_hepatic_s_g_p1_i.rtf(15MAR2014 – 0:34)

Hepatic disorders were considered as severe in intensity in 23/997 (2.3%) patients with placebo, in 16/1045 (1.5%) patients with teriflunomide 7 mg, and in 21/1002 (2.1%) patients with teriflunomide 14 mg.

Alanine aminotransferase increased was overall the most common TEAE leading to treatment discontinuation (2.3%, 3.3%, and 2.6% in the placebo, teriflunomide 7 mg, and teriflunomide 14 mg group, respectively). Per study protocols, the treatment had to be discontinued for confirmed ALT increase above 3 x ULN.

Pool B: see Section “Seriousness/Outcomes”.

In children (EFC 11759/TERIKIDS study)

The incidence of hepatic disorders was similar in the teriflunomide and placebo groups.

Table 25c - Number (%) of patients with treatment-emergent hepatic disorders by primary SOC and PT - Safety population

Primary System Organ Class Preferred Term n (%)	Placebo (N = 57)	Teriflunomide (N = 109)
Any class	2 (3.5)	5 (4.6)
Hepatobiliary Disorders	1 (1.8)	0
Hyperbilirubinemia	1 (1.8)	0
Investigations	1 (1.8)	5 (4.6)
Alanine aminotransferase increased	1 (1.8)	3 (2.8)
Aspartate aminotransferase increased	0	1 (0.9)
Transaminases increased	0	1 (0.9)

MedDRA version: 22.0; n (%) = number and percentage of patients with at least one TEAE.
Note: Table sorted by SOC internationally agreed order and by decreasing frequency of PT in teriflunomide treatment group
Extracted from:
PGM=PRODOPS/HMR1726/EFC11759/CSR_02/REPORT/PGM/db_ae_socpt_s_t.sas
OUT=REPORT/OUTPUT/db_ae_hepatic_socpt_s_t_i.rtf (06FEB2020 9:39)
MedDRA: Medical Dictionary for Regulatory Activities; N: Number; PT: Preferred Term; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

The most frequently reported treatment-emergent hepatic disorder (≥5% at PT level) was alanine aminotransferase increased. Overall, teriflunomide was well-tolerated with a manageable safety profile, consistent with the experience observed in the double-blind period.

Sanofi Pharmacovigilance database

Cases of hepatic effects reported in the postmarketing setting were reviewed cumulatively, from Sep-2012 IBD to DLP 12-Sep-2023. In summary for this review, it was noted that the majority of patients were female, and the mean age was 48.9 years old. Confounding factors such as pre-existing history of hepatic disorders or elevated hepatic enzymes were reported. Time to event onset was missing in most cases and when available, the majority of cases reported onset within six months of initiating teriflunomide.

Case outcome was unknown in the majority of cases (40.4 %); 31% were reported to be resolved or resolving; and 27.3 % were not resolved.

This risk is reviewed on a regular basis in MAH's safety governance meetings and there was no change in the known hepatotoxicity profile. The cases were also reviewed to assess past medical history and current active disorder including hemangioma of liver, hepatic cancer, hepatitis, hepatic cirrhosis (with or without alcoholism), hepatic cyst, hepatic failure, and abnormal hepatic function.

The safety profile of teriflunomide regarding potential causes of hepatotoxicity remains similar to previous assessments and did not reveal any new or unexpected finding in the postmarketing setting.

EU-PASS OBS12753

In the PASS, in patients exposed to teriflunomide, the incidence rate of abnormal liver enzymes (>3 ULN) was 22.54 per 1000 person-years and the incidence rate of acute liver injuries was in 0.18 per 1000 person-years. These incidences were not different from incidences observed in other platform DMTs.

Seriousness/outcomes

In adults

All clinical studies (includes but is not limited to Pool A1 and Pool B)

Identified Risk	Hepatic effects
	In Pool A1 (the pool which composed the submitted EU SCS), serious hepatic disorders were reported with similar or lower frequency in teriflunomide groups compared to placebo group (see Table 25b). **Pool A1** In Pool A1, the proportion of patients with hepatic disorder TEAEs was higher in the teriflunomide treatment groups (19.8% [207/1045]) and 21.5% [215/1002] on teriflunomide 7 mg and 14 mg, respectively) compared to the placebo group (15.2% [152/997]). The main PT contributor was ALT increased. The median time to onset of hepatic disorders was 168.5 days in the placebo group, 127 days in the 7 mg teriflunomide group, and 115 days in the 14 mg teriflunomide group. Treatment emergent adverse events showed a higher probability of events in both teriflunomide groups compared to placebo, mainly during the first 6 months. Corrective treatment was given to 1.8% of patients on placebo, 3.0% of patients on teriflunomide 7 mg, and 2.4% of patients on teriflunomide 14 mg. Recovery was reported in 112 of 152 patients on placebo, 152 of 207 patients on teriflunomide 7 mg, and 183 of 215 patients on teriflunomide 14 mg during the observation period in Pool A1. Most of the events were mild to moderate. Hepatic disorders were considered as severe in 2.3% of patients on placebo, 1.5% of patients on teriflunomide 7 mg, and 2.1% of patients on teriflunomide 14 mg. The analysis of RR suggested an increased risk with both teriflunomide 7 mg (RR = 1.30; 95% CI: 1.07 to 1.57) and teriflunomide 14 mg (RR = 1.41; 95% CI: 1.17 to 1.70) compared to placebo. Throughout the EU clinical program, a total of 8 patients (4 on placebo, 4 on teriflunomide) were identified with hepatic enzymes level in the Hy's Law range (ALT >3 x ULN and total bilirubin >2 x ULN). All of these cases had plausible alternative explanation for the event. **Table 25d - Summary of cases of hepatic enzyme increase in Hy's Law range reported during the clinical program** | | | | | **Comments** | | TEMSO | Teriflunomide 7 mg | 4.5 months | [redacted] | • Gallbladder disease • Temporal dissociation of greater than 1 month between ALT increase and recovery and then the later rise of bilirubin with the values returning to normal while on treatment. | | TEMSO | Teriflunomide 14 mg | 9 months | [redacted] | • Increased ALT, AST and GGT, alkaline phosphatase, and total bilirubin accompanied by fever. • A CMV hepatitis infection was confirmed by positive testing for anti-CMV IgG and IgM antibodies. • An immune compromised state could be an acceptable alternative to a link to teriflunomide use. |

Identified Risk	Hepatic effects

TEMSO	Placebo	9 months	[redacted]	Hepatitis C infection
LT extension TEMSO	Teriflunomide 7 mg	2.9 years	[redacted]	History of gallbladder disease: diagnosed with gallstones resulting in a blocked bile duct evidenced by imaging; patient underwent a cholecystectomy.
LT extension TEMSO	Teriflunomide 14 mg	3.4 years	[redacted]	Hepatitis A (unrelated to study medication)
TES10852 (QT study)	Placebo	Not applicable	[redacted]	Diagnosed with Gilbert disease
ECF6260	Placebo	Discontinued treatment after ~1 year due to lack of efficacy	[redacted]	The patient was diagnosed with hepatitis C on Day 447. No corrective treatment was taken, and the liver enzymes returned to normal approximately 3 weeks later.
ECF6260	Placebo	Not applicable	[redacted]	Diagnosed with Gilbert syndrome. Discontinued study treatment on Day 520 due to progressive disease.

ALT: Alanine Transaminase; AST: Aspartate Transaminase; CMV: Cytomegalovirus; GGT: Gamma Glutamyl Transferase; IgG: Immunoglobulin G; IgM: Immunoglobulin M.

One additional clinically significant case of "toxic hepatitis" (with elevation of ALT up to 32.4 x ULN) requiring hospitalization was reported in a [redacted] patient in the TEMSO Study. Normalization in transaminases occurred about 5 months after discontinuation. Although the etiology of the hepatic event remained unclear, a causal role of teriflunomide in this case is possible.

In children (EFC 11759/TERIKIDS study)

Two patients in the teriflunomide group experienced serious hepatic disorders: one had alanine aminotransferase increased, and one had increased transaminases. Both events were asymptomatic, did not lead to permanent treatment discontinuation, and recovered with normalization of hepatic enzyme levels.

The 2 serious cases were graded as severe. The other events were of mild or moderate intensity.

One patient in the teriflunomide group experienced hepatic disorders (persisting alanine aminotransferase increased), diagnosed as drug-induced liver injury, leading to treatment discontinuation. The patient recovered with ALT normalization after teriflunomide discontinuation (and accelerated elimination procedure).

Background incidence/prevalence

Incidence of condition

There are no data in the literature on the incidence of liver injuries in the MS population.

Identified Risk	Hepatic effects
	In the general population, the acute liver failures or injuries are uncommon, the incidence of drug-induced hepatic injuries ranges from 13.9 per 100 000 inhabitants to 23.8 per 100 000 inhabitants. [71] Adult patients from placebo arms of clinical trials were at a greater than the expected 2.5% risk of presenting with an abnormal ALT. By year 1, 19% of patients increasing to 25% of patients at the end of year 2 had abnormal ALT. [72] A meta-analysis reported a significant increase of 30% in the odds of alteration in any liver function test in patients receiving interferon B compared to teriflunomide (OR: 1.3, 95% CI: 1.14-2.12), However, no significant difference were reported for liver failure and ALT elevation comparing Interferon B and teriflunomide. [73] Incidences of the above risk in patients under different treatment regimens during trials are: • Dimethyl fumarate (Clinical trial): 47%-56% increase in ALT >1 ULN and 6% had ALT ≥3 ULN, over 2 years. [74] • Glatiramer acetate (Clinical trial): 37% increase in ALT >1 ULN and 7% had ALT ≥3 ULN, over 2 years. [74] • Daclizumab HYP (Clinical trial): 47%-56% increase in ALT >1 ULN and 6% had ALT ≥3 ULN, over 2 years. [75] Alemtuzumab (Clinical trial): Any liver toxicity in 4% patients over 2 years. [76],[77] Mitoxantrone (retrospective review) 16% increased AST (grade > or = 1), over a median follow-up of 5 months. [78] • Oral fingolimod (clinical trial): 18.6% increase of any liver test and 6.9% to 8.4% had ALT ≥3 ULN, over 2 years. [79] • Interferons (longitudinal retrospective review): 37.6% of patients developed de novo ALT elevations >ULN and 12.4% developed de novo ALT >2 ULN over 39 months. [80] • Laquinimod (phase IIb clinical trial): increase of liver enzymes (ALT) in 23.4% in the 0.3 mg laquinimod group and 33.0% in the 0.6 mg laquinimod group, over 24 weeks. [81] • Natalizumab (Phase III clinical trial): abnormal liver-function results in 5% of patients over 2 years. [82] Overall, prevalence of liver disease ranged from 1.5% to 1.7%. In a survey of self-reported physical comorbidities in the NARCOMS participants, 1.5% reported having “liver disease”. [83] In a survey validating a self-report questionnaire of comorbidities against medical records, 1.2% of patients reported liver disease and 1.7% of patients had liver disease according to medical record. [84] **Impact on individual patient** Not applicable
Risk factors and risk groups	Mild and moderate hepatic impairment had no impact on the PK of teriflunomide (POP6507). Patients with severe hepatic impairment have been excluded from teriflunomide clinical trials. Other possible theoretical risk factors: concomitant treatment with hepatotoxic agents (including alcohol), viral infections (including viral hepatitis), gallbladder disease.
Preventability	The following can help prevent this risk: • Assess laboratory liver function tests (including ALT, bilirubin) at baseline before initiating treatment (to detect pre-existing liver disease), and periodically thereafter during treatment. • Contraindicate treatment in patients with severe hepatic impairment • Exercise caution in patients with pre-existing liver disease • Consider discontinuing treatment if liver enzyme increase (above 3 x ULN) is confirmed or if liver injury is suspected.

Identified Risk	Hepatic effects
	• Educate patient about signs and symptoms of liver injury, and to seek prompt medical attention if such signs/symptoms are present.
Impact on the benefit-risk balance of the product	The benefit-risk remains unchanged for teriflunomide.
Public health impact	Not evaluated

AE: Adverse Event; ALT: Alanine Transaminase; AST: Aspartate Transaminase; CI: Confidence Interval; CMV: Cytomegalovirus; DLP: Data Lock Point; DMT: Disease Modifying Therapy; EU: European Union; GGT: Gamma-Glutamyl Transferase; HYP: High-Yield Process; IBD: International Birth Date; IgG: Immunoglobulin G; IgM: Immunoglobulin M; MAH: Marketing Authorization Holder; MedDRA: Medical Dictionary for Regulatory Activities; MS: Multiple Sclerosis; N: Number; NARCOMS: North American Research Committee on Multiple Sclerosis; OR: Odds Ratio; PASS: Post-Authorization Safety Study; PK: Pharmacokinetic; PT: Preferred Term; RR: Relative Risk; SCS: Summary of Clinical Safety; SOC: System Organ Class; TEAE: Treatment-Emergent Adverse Event; TBILI: Total Bilirubin; ULN: Upper Limit of Normal.

Table 26 - Identified risk: Hypertension

Identified Risk	Hypertension
Potential mechanism	Unknown The analysis of vital signs showed no relevant change in heart rate in association with teriflunomide treatment, suggesting that blood pressure increases were not due to increased cardiac output or increased sympathetic activity. Significant vasoconstriction or changes in renal glomerular function which could have resulted in blood pressure elevation are not evident with teriflunomide; furthermore, there is no evidence for fluid retention.
Evidence source(s) and strength of evidence	Literature, clinical data.
Characterization of the risk	**Frequency with 95% CI** **In adults** **Pool A1** The analysis of the relative risk for hypertension events showed an increased risk with teriflunomide as compared to placebo with teriflunomide 7 mg, as shown below.

Table 26a - Hypertension / Blood pressure increase TEAEs - Relative risk as compared to placebo with 95% CI - Pool A1

	Relative Risk (compared to placebo)	95% CI
Teriflunomide 7 mg	1.66	1.04 to 2.64
Teriflunomide 14 mg	1.95	1.24 to 3.08

Extracted from:
PGM=PRODOPS/HMR1726/OVERALL/CSS_EU_2014/REPORT/PGM/ae_relrisk_s_t.sas
OUT=REPORT/OUTPUT/ae_relrisk_aesi_s_t_p1_i.rtf (14MAR2014 - 20:41)
CI: Confidence Interval; TEAE: Treatment Emergent Adverse Event.

Severity and nature of risk

Pool A1

The incidence of hypertension TEAEs of any class was greater in the teriflunomide groups compared to placebo (2.7%, 4.5%, and 5.3% for the placebo, 7 mg teriflunomide, and 14 mg teriflunomide groups, respectively).

Table 26b - Number (%) of patients with hypertension TEAEs by Primary SOC and PT - Safety population - Pool A1

Primary System Organ Class Preferred Term n (%)	Placebo (N = 997)	Teriflunomide 7 mg (N = 1045)	 14 mg (N = 1002)
Any class	**27 (2.7%)**	**47 (4.5%)**	**53 (5.3%)**
Cardiac disorders	**0**	**1 (<0.1%)**	**0**
Hypertensive heart disease	0	1 (<0.1%)	0
Vascular disorders	**20 (2.0%)**	**33 (3.2%)**	**45 (4.5%)**
Hypertension	18 (1.8%)	32 (3.1%)	43 (4.3%)
Blood pressure fluctuation	0	0	1 (<0.1%)
Essential hypertension	0	0	1 (<0.1%)
Hypertensive crisis	2 (0.2%)	1 (<0.1%)	1 (<0.1%)
Hypertensive angiopathy	1 (0.1%)	0	0
Investigations	8 (0.8%)	14 (1.3%)	8 (0.8%)
Blood pressure increased	8 (0.8%)	14 (1.3%)	7 (0.7%)
Blood pressure systolic increased	0	0	1 (<0.1%)

MedDRA version: 16.0; n (%) = number and percentage of patients with at least one TEAE.
Note: Table sorted by SOC internationally agreed order and decreasing frequency of PTs in teriflunomide 14 mg group.
Extracted from:
PGM=PRODOPS/HMR1726/OVERALL/CSS_EU_2014/REPORT/PGM/ae_socpt_s_t.sas
OUT=REPORT/OUTPUT/ae_socpt_hypertension_s_t_p1_i.rtf (14MAR2014 - 23:25)
MedDRA: Medical Dictionary for Regulatory Activities; N: Number; TEAE: Treatment Emergent Adverse Event; SOC: System Organ Class; PT: Preferred term.

Evaluation of blood pressure measurements showed that mean changes from baseline in SBP and DBP gradually increased over time with both treatment doses. A tendency to normalization of blood pressure with the cessation of study treatment was observed in the follow-up period.

The mean (SD) change from baseline to endpoint value for SBP was 2.3 (13.8), 2.7 (12.4), and -0.6 (12.7) mmHg for the 7 mg, 14 mg, and placebo groups, respectively. The mean (SD) change from baseline to endpoint value for DBP was 1.4 (10.1), 1.9 (9.9), and -0.3 (9.2) mmHg for the 7 mg, 14 mg, and placebo groups, respectively.

The increases in mean SBP and DBP compared to placebo started early after treatment initiation and were sustained over time.

Median time to onset of TEAEs potentially related to hypertension was 169 days on placebo, 251 days on teriflunomide 7 mg, and 203 days on teriflunomide 14 mg.

Patients who developed hypertension on teriflunomide treatment were usually well controlled with the introduction of or modification of antihypertensive treatment.

Pool B

Additional reports of hypertension/blood pressure increased were observed during the long-term extension. These included 3 cases of non-serious hypertensive crisis in patients with an underlying history of hypertension (1 at 7 mg, and 2 at 14 mg). The 3 patients recovered that same day with corrective treatment and continued the study. Overall, there was no clinical evidence for long-term complications due to hypertension.

In children (EFC 11759/TERIKIDS study)

No patient in the teriflunomide group and 1 patient (1.8%) in the placebo group experienced hypertension.

Table 26c - Number (%) of patients with TEAE(s) with a frequency ≥2% in any treatment group by Primary SOC, HLGT, HLT and PT - Safety population

Primary System Organ Class High Level Group Term, HLT, PT n(%)	Placebo (N = 57)	Teriflunomide (N = 109)
Cardiac disorders	1 (1.8)	5 (4.6)
High level group term: Cardiac disorders, signs and symptoms Necrotizing Enterocolitis	0	3 (2.8)
High level term: Cardiac signs and symptoms Necrotizing Enterocolitis	0	3 (2.8)
Palpitations	0	3 (2.8)
Vascular disorders	2 (3.5)	1 (0.9)
High-Level Group Term: Decreased and nonspecific blood pressure disorders and shock	2 (3.5)	0
High-Level Term: Vascular hypotensive disorders	2 (3.5)	0
Orthostatic hypotension	2 (3.5)	0

MedDRA version: 22.0; n (%) = number and percentage of patients with at least one TEAE.
Note: Table sorted by SOC internationally agreed order and HLGT, HLT, PT by alphabetic order
Only SOC with at least one PT with a frequency ≥2% in at least one group are presented.
Extracted from:
PGM=PRODOPS/HMR1726/EFC11759/CSR_02/REPORT/PGM/db_ae_hlgt_s_t.sas
OUT=REPORT/OUTPUT/db_ae_hlgt_2pct_s_t_i.rtf (06FEB2020 9:28)
HLGT: High Level Group Term; HLT: High Level Term; MedDRA: Medical Dictionary for Regulatory Activities; N: Number; PT: Preferred Term; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Sanofi Pharmacovigilance database

Cases of hypertension reported in the postmarketing setting at DLP 12-Sep-2023 were reviewed and were found to be consistent with the known safety profile of teriflunomide.

Seriousness/outcomes

In adults

Pool A1: There were no reports of hypertensive emergency (eg, malignant hypertension, hypertensive encephalopathy) and no other acute life-threatening complications secondary to increases in blood pressure. No increased risk of heart disease resulting from teriflunomide-induced hypertension became apparent during any study in Pool A1. Most of the TEAEs were mild in intensity. One event in the placebo group and 2 events in the teriflunomide 14 mg group were reported as severe in intensity.

Pool B: During the long-term exposure, there were 3 cases reported as hypertensive crisis in patients with underlying history of hypertension (1 at 7 mg and 2 at 14 mg). All 3 events were non-serious, recovered with corrective treatment, and did not lead to treatment discontinuation.

Patients who developed hypertension were usually well controlled with the introduction or modification of antihypertensive treatment.

Identified Risk	Hypertension
	Three patients with a diagnosis of hypertension experienced a cardiovascular event, all at 7 mg (one fatal MI, one non-fatal MI and one arrhythmia). **In children (EFC 11759/TERIKIDS study)** No case of hypertension was reported in the study in the teriflunomide group. **Background incidence/prevalence** **Incidence of condition** There are no data in the literature on the incidence of hypertension in the MS population. In the general population, the incidence of hypertension is 32 per 1000 person-years in Canada. [85] Incidences of hypertension in patients reported from clinical trials showed a cumulative incidence of 6.3% in patients treated with fingolimod over the 24 months follow-up. [79] Persistent hypertension is one of the risk factors for stroke, MI, heart failure and arterial aneurysm, and is a leading cause of chronic kidney failure. [86] Among pediatric MS patients (ie, 10 to <18 years of age) the incidence rate of hypertension is 10.12/1000 person-years (95% CI = 4.83-21.24). The hypertension rate among age, gender, and calendar-year matched controls (non-MS patients) was 2.09/1000 person-years (95% CI = 0.29-14.82). [87] **Prevalence of condition** In a survey of self-reported physical comorbidities in the NARCOMS participants, 30.1% reported having hypertension. [83] A cross-sectional study form the US reported age-, sex-, and race-adjusted prevalence of hypertension to be 33.0% (95% CI: 33.0-33.0) among MS patients and 26.4% (95% CI: 26.3-26.4) among people without MS with prevalence ratio of 1.25 (95% CI: 1.25-1.25). [88] In hospitalized MS patients age 65 or older, hypertension was the primary or secondary diagnosis for 5 out of every 100 discharges. [89] **Impact on individual patient** Not applicable
Risk factors and risk groups	Patients with prior history of hypertension, prior anti-hypertensive treatment or receiving concomitant drugs causing hypertension (eg, NSAID, OC). Presence of concomitant cardiovascular risk factors such as obesity, diabetes. [90] There was no evidence of an increased risk of hypertension regarding intrinsic (age, gender, race, BMI and extrinsic (region, territory, previous disease modifying MS therapy, selected concomitant medications) factors.
Preventability	Risk is preventable by: • Identifying patients with cardiovascular risk factors, pre-existing hypertension. • Periodic monitoring of blood pressure during treatment. • Initiation or adjustment of antihypertensive treatment, as necessary.
Impact on the benefit-risk balance of the product	The benefit-risk remains unchanged for teriflunomide.
Public health impact	Not evaluated

BMI: Body Mass Index; CI: Confidence Interval; DLP: Data Lock Point; HLGT: High Level Group Term; HLT: High Level Term; MedDRA: Medical Dictionary for Regulatory Activities; MI: Myocardial Infarction; MS: Multiple Sclerosis; N: Number; NARCOMS: North American Research Committee on Multiple Sclerosis; NSAID: Non-Steroidal Anti-inflammatory Drug; OC: Oral Contraceptive; PT: Preferred Term;

Identified Risk	Hypertension

SBP: Systolic Blood Pressure; SD: Standard Deviation; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event; US: United States.

Table 27 - Identified risk: Hematologic effects

Identified Risk	Hematologic effects
Potential mechanism	Pharmacological activity; contribution of central effect (bone marrow) versus peripheral effect (on circulating peripheral blood cells) is unknown.
Evidence source(s) and strength of evidence	Literature, non-clinical data and clinical data.
Characterization of the risk	**Frequency with 95% CI** **In adults** **Pool A1** The analysis of the relative risk of bone marrow disorder TEAEs suggested an increase risk with both teriflunomide 7 mg (RR = 2.10; 95% CI: 1.49 to 2.97) and teriflunomide 14 mg (RR = 2.33; 95% CI: 1.65 to 3.28) compared to placebo.

Table 27a - Bone Marrow Disorder TEAEs - Relative risk as compared to placebo with 95% CI-Pool A1

	Relative Risk (compared to placebo)	95% CI
Teriflunomide 7 mg	2.10	(1.49 to 2.97)
Teriflunomide 14 mg	2.33	(1.65 to 3.28)

Extracted from:
PGM=PRODOPS/HMR1726/OVERALL/CSS_EU_2014/REPORT/PGM/ae_relrisk_s_t.sas
OUT=REPORT/OUTPUT/ae_relrisk_aesi_s_t_p1_i.rtf (14MAR2014 - 20:41)
CI: Confidence Interval; TEAE: Treatment Emergent Adverse Event.

Severity and nature of risk

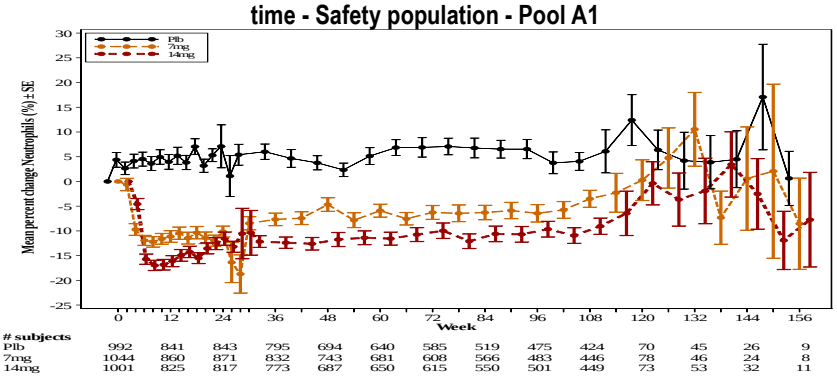
Pool A1

White blood cells

The analysis of laboratory CTCAE WBC decrease grade 1 (≥3 Giga/L and less than LLN, grade 2 (≥2 Giga/L to <3 Giga/L), and grade 3 (≥1 Giga/L to <2 Giga/L) showed that the proportion of patients with WBC decrease was higher in the teriflunomide groups compared to the placebo group with an apparent dose-effect relationship. There were no reports of CTCAE grade 4 WBC decreases.

Neutrophils

Figure F27a - Neutrophils (%) - plot of mean percent change from baseline over time - Safety population - Pool A1



PGM=PRODOPS/HMR1726/OVERALL/CSS_EU_2014/REPORT/PGM/lab_pctplot_s_g.sas
OUT=REPORT/OUTPUT/lab_pctplotneutro_s_g_p1_i.rtf (15MAR2014 - 0:43

As shown in Table 27b, the proportion of patients with CTCAE neutrophil count decrease grade 1 (≥1.5 Giga/L to <LLN) and grade 2 (≥1.0 Giga/L to <1.5 Giga/L) was higher on teriflunomide than on placebo. The proportion of patients with grade 3 (≥0.5 Giga/L to <1.0 Giga/L) neutrophil count decrease was 1.1% of patients on placebo versus 2.1% of patients on teriflunomide 7 mg and 2.3% of patients on teriflunomide 14 mg.

Reversibility of neutrophil count decreases was analyzed. Neutrophil counts returned to normal in the majority of patients before their last dose in all treatment groups.

Table 27b - White blood cells, Neutrophils, Lymphocytes - Number of patients with abnormalities CTCAE - Pool A1

Laboratory parameter by CTCAE criteria n/N1 (%)	Placebo (N = 997)	Teriflunomide 7 mg (N = 1045)	Teriflunomide 14 mg (N = 1002)
White blood cells			
Grade 1 (> 3 Giga/L and <LLN)	102/994 (10.3%)	210/1042 (20.2%)	258/999 (25.8%)
Grade 2 (>2 - <3 Giga/L)	37/994 (3.7%)	82/1042 (7.9%)	103/999 (10.3%)
Grade 3 (>1 - <2 Giga/L)	1/994 (0.1%)	3/1042 (0.3%)	6/999 (0.6%)
Grade 4 (<1 Giga/L)	0/994	0/428 0/1042	0/999
Neutrophils			
Grade 1 (>1.5 Giga/L and <LLN)	113/994 (11.4%)	216/1042 (20.7%)	259/999 (25.9%)
Grade 2 (>1.0 - <1.5 Giga/L)	55/994 (5.5%)	106/1042 (10.2%)	141/999 (14.1%)
Grade 3 (>0.5 - <1.0 Giga/L)	11/994 (1.1%)	22/1042 (2.1%)	23/999 (2.3%)
Grade 4 (<0.5 Giga/L)	2/994 (0.2%)	4/1042 (0.4%)	2/999 (0.2%)
Lymphocytes (decrease)			
Grade 1 (>0.8 Giga/L and <LLN)	68/994 (6.8%)	106/1042 (10.2%)	132/999 (13.2%)

Identified Risk	Hematologic effects

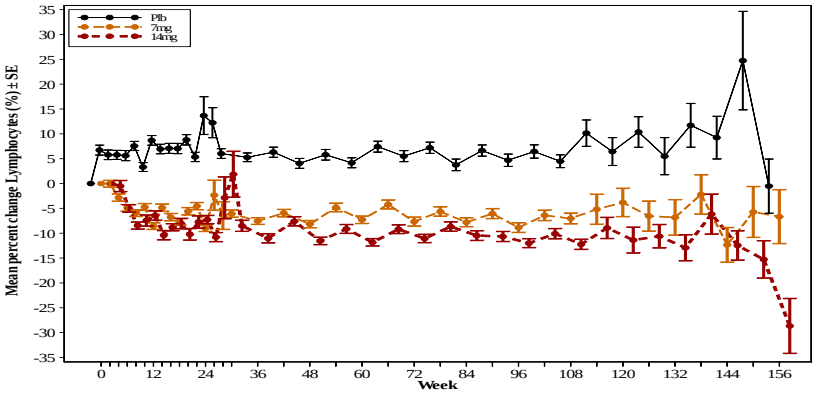
Grade 2 (>0.5 - <0.8 Giga/L)	51/994 (5.1%)	88/1042 (8.4%)	95/999 (9.5%)
Grade 3 (>0.2 - <0.5 Giga/L)	6/994 (0.6%)	11/1042 (1.1%)	20/999 (2.0%)
Grade 4 (<0.2 Giga/L)	0/994	2/1042 (0.2%)	1/999 (0.1%)

The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed post-baseline.
Extracted from:
PGM=PRODOPS/HMR1726/OVERALL/CSS_EU_2014/REPORT/PGM/lab_ctcaewbc_s_t.sas
OUT=REPORT/OUTPUT/lab_ctcaewbc_s_t_p1_i.rtf (15MAR2014 - 1:23)
CTCAE: Common Terminology Criteria for Adverse Event; N: Number; WBC: White Blood Cell.

Lymphocytes

The proportion of patients with CTCAE lymphocyte count decrease grade 1 (≥0.8 Giga/L to <LLN) and grade 2 (≥0.5 Giga/L to <0.8 Giga/L) was higher on teriflunomide than on placebo. The proportion of patients with grade 3 (≥0.2 Giga/L to <0.5 Giga/L) lymphocyte count decrease was 0.6% of patients on placebo compared to 1.1% of patients on teriflunomide 7 mg and 2.0% of patients on teriflunomide 14 mg. Additionally, 2 patients in the 7 mg teriflunomide group and 1 patient in the 14 mg teriflunomide group had a grade 4 lymphocyte count decrease (<0.2 Giga/L) versus none in the placebo group.

Figure F27b - Lymphocytes (%) - plot of mean percent change from baseline over time - Safety population - Pool A1



# subjects														
Plb	992	841	844	795	695	640	586	520	475	424	70	45	26	9
7mg	1044	860	872	832	743	681	609	566	483	447	78	46	24	8
14mg	1001	825	817	773	688	650	615	550	501	449	73	53	32	11

PGM=PRODOPS/HMR1726/OVERALL/CSS_EU_2014/REPORT/PGM/lab_meanplot_s_g.sas
OUT=REPORT/OUTPUT/lab_meanplolympho_s_g_p1_i.rtf (15MAR2014 - 5:02)

Pool B

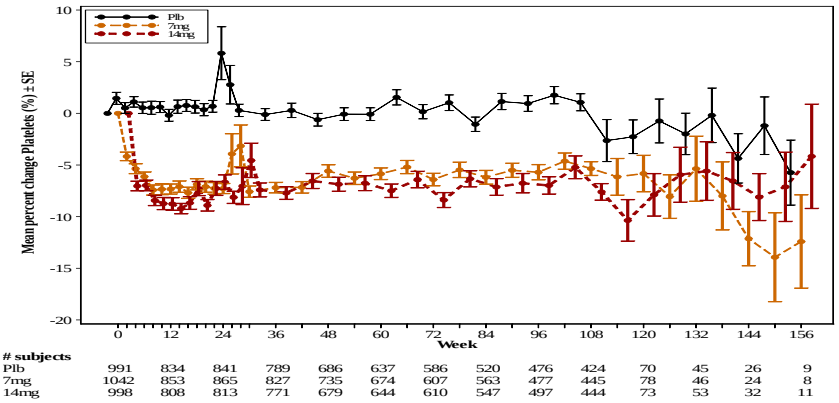
Neutrophil and lymphocytes: In Pool B, a higher incidence of patients had WBC decrease, neutrophil and lymphocyte counts decrease in teriflunomide 14 mg than in 7 mg. No additional cases of grade 4 neutropenia or grade 4 lymphopenia were reported.

The update of the pool B data did not change the analysis provided above.

Pool A1

Platelet count: The plot of mean changes in platelet count shows a slight decrease in platelet count that appears early after treatment initiation compared to placebo.

Figure F27c - Platelets (%) - plot of mean percent change from baseline over time - Safety population - Pool A1



PGM=PRODOPS/HMR1726/OVERALL/CSS_EU_2014/REPORT/PGM/lab_pctplot_s_g.sas OUT=REPORT/OUTPUT/lab_pctplotplat_s_g_p1_x.rtf (15MAR2014 - 0:42)

As shown in Table 27c, grade 1 thrombocytopenia was observed with an incidence of about 8% in the 7 mg group and 9% in the 14 mg teriflunomide group. There were two grade 2 thrombocytopenia cases observed in the 14 mg group and zero grade 3 thrombocytopenias, in either group.

Two subjects in the teriflunomide 7 mg group had a grade 4 thrombocytopenia.

Table 27c - Number (%) of patients with platelet abnormalities (CTCAE criteria) - Pool A1

Laboratory parameter CTCAE criteria n/N1 (%)	Placebo (N = 997)	Teriflunomide 7 mg (N = 1045)	Teriflunomide 14 mg (N = 1002)
Platelets			
Grade 1 (>75 Giga/L and <LLN)	46/994 (4.6%)	81/1042 (7.8%)	91/999 (9.1%)
Grade 2 (>50 - <75 Giga/L)	0/994	0/1042	2/999 (0.2%)
Grade 3 (>25 - <50 Giga/L)	1/994 (0.1%)	0/1042	0/999
Grade 4 (<25 Giga/L)	0/994	2/1042 (0.2%)	0/999

The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed post-baseline.
Extracted from:
PGM=PRODOPS/HMR1726/OVERALL/CSS_EU_2014/REPORT/PGM/lab_ctcaerbc_s_t.sas OUT=REPORT/OUTPUT/lab_ctcaerbc_s_t_p1_i.rtf (15MAR2014 - 0:46)
CTCAE: Common Terminology Criteria for Adverse Event; N: Number.

Hemorrhages: In Pool A1, the proportion of patients with hemorrhages was 6.6% of patients on placebo, 6.6% of patients on teriflunomide 7 mg, and 7.4% of patients on teriflunomide 14 mg. The main PT contributor across treatment groups was contusion. Of note, menorrhagia was reported in 0.8% and 1.6% of patients on teriflunomide 7 mg and 14 mg, respectively, versus 0.4% on placebo.

Pool B

Platelet count: In Pool B, 1 patient (teriflunomide 7 mg) had grade 4 platelet count decrease with normal value on retest performed 3 days later.

Hemorrhages: In Pool B, the proportion of patients with hemorrhages was similar in both treatment groups (13.5% and 12.8% on teriflunomide 7 mg and 14 mg, respectively). The update of the pool B data did not change the analysis provided above.

Identified Risk	Hematologic effects
	In children (EFC11759/TERIKIDS study) Bone marrow disorders were more frequently reported in the teriflunomide group (7.3%) than in the placebo group (1.8%) (Table 27d). **Table 27d - Number (%) of patients with treatment-emergent bone marrow disorders by primary SOC and PT - Safety population** **Primary System Organ Class Preferred Term n(%)** / **Placebo (N = 57)** / **Teriflunomide (N = 109)** Any class: 1 (1.8) / 8 (7.3) **Blood and lymphatic system disorders**: 0 / 4 (3.7) 0 / 3 (2.8) Neutropenia: 0 / 2 (1.8) Leukopenia: 0 / 2 (1.8) Monocytopenia **Investigations**: 1 (1.8) / 5 (4.6) White blood cell count decreased: 1 (1.8) / 4 (3.7) Neutrophil count decreased: 0 / 3 (2.8) Monocyte count decreased: 0 / 1 (0.9) MedDRA version: 22.0; n (%) = number and percentage of patients with at least one TEAE. Note: Table sorted by SOC internationally agreed order and by decreasing frequency of PT in teriflunomide treatment group. Extracted from: PGM=PRODOPS/HMR1726/EFC11759/CSR_02/REPORT/PGM/db_ae_socpt_s_t.sas OUT=REPORT/OUTPUT/db_ae_bone_socpt_s_t_i.rtf (06FEB2020 9:39) MedDRA: Medical Dictionary for Regulatory Activities; N: Number; PT: Preferred Term; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event. The most commonly reported TEAEs were neutropenia, leukopenia, and monocytopenia in the SOC Blood and lymphatic system disorders, and white blood cell count decreased, neutropenia and neutrophil count decreased in the SOC Investigations. **Sanofi Pharmacovigilance database** Cases of hematologic effects reported in the postmarketing setting at DLP 12-Sep-2023 were reviewed and were found to be consistent with the known safety profile of teriflunomide. **Seriousness/outcomes** **Neutrophils Pool A1** Four cases of grade 4 neutropenia were reported in the 7 mg teriflunomide group and 2 cases were reported in the 14 mg teriflunomide group. No case of febrile neutropenia was reported, and there was no evidence of a link between WBC decrease and the occurrence of infections. Isolated cases of more significant decreases predominantly of WBC were observed. Many of them had accelerated resolution and most of the patients continued treatment. **Pool A1** Platelet count: Platelet count decreased was reported by 0.6% and 0.5% of the patients in the 7 mg and 14 mg teriflunomide groups, respectively, versus 0.1% patient in the placebo group. Thrombocytopenia was reported by 0.6% of patients in each of the teriflunomide groups compared to 0.1% of patients in the placebo group. One case of significant thrombocytopenia, potentially related to an immune-mediated mechanism, was reported in the 14 mg teriflunomide group. A causal relationship with teriflunomide was considered possible. No other clinically significant complications to blood cytopenias were reported.

Identified Risk	Hematologic effects
	Hemorrhages: Hemorrhages were considered as serious in 2 patients in the placebo group, 5 patients in the 7 mg teriflunomide group, and 7 patients in the 14 mg teriflunomide group. Three patients on teriflunomide 14 mg discontinued due to hemorrhages. **Pool B** Platelet count: No additional case of serious thrombocytopenia was observed in Pool B. Hemorrhages: 6 patients in teriflunomide 7 mg and 1 in teriflunomide 14 mg had serious TEAEs related to hemorrhages. **Table 27e - Serious TEAEs of hemorrhages - Pool B additional events** **Teriflunomide 7 mg (6 events in 6 patients)** / **Teriflunomide 14 mg (1 event in 1 patient)** Upper gastrointestinal hemorrhage, metrorrhagia, gastric ulcer hemorrhage, hemorrhoidal hemorrhage, menorrhagia, and epistaxis. / gastroduodenal hemorrhage TEAE: Treatment Emergent Adverse Event. All observed cases of serious TEAEs of hemorrhage in Pool B recovered. The update of the pool B data did not change the analysis provided above. **In children (EFC11759/TERIKIDS study)** All events were of mild or moderate intensity. Overall, teriflunomide was well-tolerated with a manageable safety profile, consistent with the experience observed in the double-blind period. **Background incidence/prevalence** **Incidence of condition** A study conducted in the UK that compared 6932 MS patients with 68 256 non-MS patients reported a 25% increased risk of any infection in MS patients relative to non-MS patients (IRR: 1.25; 95% CI: 1.21-1.29) and a 100% increase in the risk of serious (hospitalized) infections in patients with MS compared to non-MS patients (IRR: 2.00; 95% CI: 1.84-2.17). [91] Similar results were observed in a US-based study that compared 7743 veterans with MS to 30 972 non-MS veterans and reported the nearly twice the incidence of serious infections in MS cohort compared to non-MS cohort (19.2/1000 person-years vs 10.3/1000 person-years). Furthermore, relative to non-MS population, having MS significantly increased the risk of fatal infection by 85% (HR: 1.85; 95% CI: 1.08-3.15), serious respiratory infections by 85% (HR: 1.85; 95% CI: 1.08-3.15), urinary tract infections by 344% (HR: 4.44; 95% CI: 3.59-5.51) and sepsis by 156% (HR: 2.56; 95% CI: 1.08-3.15). [42] In a Norwegian cohort, the crude mortality rate due to infections, mainly pulmonary and urinary tract infections is 1.73 per 1000 person-years [92] and the standardized mortality ratio of deaths due to infections is 9.75 in the MS population. There are no data in the literature on the incidence of platelet count decrease in the MS population. In the general population, the incidence of ITP was estimated to 3.3 per 100 000 adults/year. [93] Incidence of infection in patients treated • Cladribine: 48% of patients had infections over 96 weeks and 2.3% had herpes zoster. No relation was found between lymphocyte counts and herpes zoster. [94] • Natalizumab 79% of patients had infections over two years and 3.2% had serious infections. [82] • Dimethyl fumarate: 56% of patients had infections over 2 years. [74] • Glatiramer acetate: 50% of patients had infections over 2 years. [74]

Identified Risk	Hematologic effects
	• Daclizumab HYP: 65% of patients had infections over 2 years and 4% had serious infections. [75] • Interferon-β1a: 45% to 57% of patients had infections over 2 years, 2% had serious infections and 2% had herpes infections. [75,76,77] • Alemtuzumab: 67% of patients had infections over 2 years and 16% had herpes infections. [76,77] In treatment-naive relapsing MS patients, lymphopenia was reported to be present in 10.1% of the patients and 13.7% in controls. [95] Incidences of white blood cell decrease were described in patients under different treatment regimens are: • Mitoxantrone (retrospective review): 27% had reduced neutrophil count (grade≥1) and 18% had evident neutropenia over a median follow-up of 14 months. [78] • Fingolimod (clinical trial): 6.3% had leucopenia and 5.4% had lymphopenia over two years. [79] • Cladribine (clinical trial): 26.7% had lymphopenia, 7.1% had leucopenia and 2.0% had neutropenia over 96 weeks. [94] • Interferon-β1a: 16% to 23% had leucopenia and 14% to 17% had granulocytopenia. [96] **Prevalence of condition** In Maryland in the US, the age-adjusted prevalence rate of ITP was found to be 9.5 per 100 000 persons [97] and in patients with ITP the prevalence of MS was approximately 25 times the prevalence that would be expected in the general population. [98] **Impact on individual patient** Not applicable
Risk factors and risk groups	Patients with pre-existent neutropenia, combination with other neutropenic or lymphopenic drug. Patients with pre-existent thrombocytopenia. Combination with other thrombopenic drugs or drugs increasing the bleeding risk. There was no evidence of increased risk of hematologic effects or hemorrhages in patients treated with teriflunomide 7 or 14 mg compared to those receiving placebo regarding intrinsic (age, gender, race, BMI, baseline EDSS) and extrinsic (region, territory, previous disease modifying MS therapy, selected concomitant medications) factors.
Preventability	Decrease in WBC, neutrophil and lymphocytes are monitorable with assessment of blood cell count, before initiating teriflunomide treatment, and periodically throughout teriflunomide treatment. Decrease in platelet count is monitorable with assessment of platelets count before initiating teriflunomide treatment, and periodically thereafter during treatment with teriflunomide, or in case of hemorrhages.
Impact on the benefit-risk balance of the product	The benefit-risk remains unchanged for teriflunomide.
Public health impact	Not evaluated

AESI: Adverse Event of Special Interest; BMI: Body Mass Index; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Event; DLP: Data Lock Point; EDSS: Expanded Disability Status Cycle; HR: Hazard Ratio; HYP: High-Yield Process; IRR: Incidence Rate Ratio; ITP: Immune Thrombocytopenia; LLN: Lower Limit of Normal; MedDRA: Medical Dictionary for Regulatory Activities; MS: Multiple Sclerosis; N: Number; PT: Preferred Term; RR: Relative Risk; SOC: System Organ Class; TEAE: Treatment-Emergent Adverse Event; UK: United Kingdom; US: United States; WBC: White Blood Cell.

Table 28 - Identified risk: Infections

Identified Risk	Infections
Potential mechanism	Pharmacological activity; contribution of central effect (bone marrow) versus peripheral effect (on circulating peripheral blood cells) is unknown.
Evidence source(s) and strength of evidence	Literature, non-clinical data and clinical data.
Characterization of the risk	**Frequency with 95% CI** **In adults** **Pool A1** The analysis of RR for leucopenia, neutropenia, lymphopenia TEAEs grouped under 'bone marrow disorders' suggest an increased risk with teriflunomide 7 mg (RR = 2.10; 95% CI: 1.49 to 2.97) and 14 mg (RR = 2.33; 95% CI: 1.65 to 3.28) compared with placebo. However, this did not translate into an increased risk of infection (TEAEs of infections: RR with teriflunomide 7 mg as compared to placebo [RR = 0.99; 95% CI: 0.91 to 1.08]; RR with teriflunomide 14 mg as compared to placebo [RR = 0.99; 95% CI: 0.91 to 1.07]). Postmarketing experience: Cumulatively since the IBD, the MAH has received a total of 24 unique case reports (including 22 events of sepsis, 1 wound sepsis and 1 urosepsis). All events were assessed as serious. Five patients died due to sepsis and one patient experienced life-threatening sepsis. Seventeen patients experienced sepsis that led to hospitalization and in 1 patient the sepsis was a medically important event. Eight patients recovered or were recovering from sepsis at the time of the report. The 5 patients who died due to sepsis (4 due to urinary tract infection and 1 secondary to decubitus ulcers), all had advanced MS disease and multiple drug therapy. Sepsis is a known possible cause of death in patients with MS. **Severity and nature of risk** **Pool A1** Infections In Pool A1, as shown in Table 28a, infections were commonly reported (>50% in all 3 groups), with no observed imbalance among treatment groups. Infections were mainly of upper respiratory tract origin including nasopharyngitis. Infections leading to treatment discontinuation occurred in 0.5%, 0.8%, and 1.0%, with placebo, teriflunomide 7 and 14 mg, respectively. Serious infections and infestations TEAEs were observed in similar proportions of patients across the placebo and teriflunomide groups (2.2% on placebo, 2.2% on teriflunomide 7 mg, and 2.7% on teriflunomide 14 mg). Viral infections (in HLT Viral infections NEC) were reported with somewhat higher frequency in the teriflunomide 7 mg (5.3%) and 14 mg (4.8%) groups compared with placebo (3.5%), but with no clear trend in terms of a dose-effect relationship. The main PT contributors for viral infections in the 7 mg/14 mg teriflunomide treatment groups were viral gastroenteritis (1.7%/2.4%), viral infection (1.3%/0.9%) and respiratory tract viral infection (1.4%/0.7%). See Table 31 for description of opportunistic infections. **Table 28a - Number (%) of patients with infections and infestations TEAEs (only PTs with incidence ≥2% in teriflunomide groups are shown) - Pool A1** **Teriflunomide**

Identified Risk	Infections

Primary System Organ Class Preferred Term n (%)	Placebo (N = 997)	7 mg (N = 1045)	14 mg (N = 1002)
Any class	532 (53.4%)	553 (52.9%)	528 (52.7%)
Infections and infestations	532 (53.4%)	553 (52.9%)	528 (52.7%)
Nasopharyngitis	210 (21.1%)	184 (17.6%)	184 (18.4%)
Influenza	70 (7.0%)	71 (6.8%)	88 (8.8%)
Upper respiratory tract infection	96 (9.6%)	105 (10.0%)	99 (9.9%)
Urinary tract infection	86 (8.6%)	82 (7.8%)	88 (8.8%)
Bronchitis	50 (5.0%)	47 (4.5%)	47 (4.7%)
Sinusitis	42 (4.2%)	50 (4.8%)	53 (5.3%)
Gastroenteritis	34 (3.4%)	31 (3.0%)	38 (3.8%)
Pharyngitis	23 (2.3%)	25 (2.4%)	30 (3.0%)
Gastroenteritis viral	11 (1.1%)	18 (1.7%)	24 (2.4%)
Rhinitis	20 (2.0%)	29 (2.8%)	23 (2.3%)
Oral herpes	15 (1.5%)	23 (2.2%)	22 (2.2%)
Cystitis	16 (1.6%)	21 (2.0%)	21 (2.1%)
Respiratory tract infection	24 (2.4%)	20 (1.9%)	20 (2.0%)

Extracted from:
PGM=PRODOPS/HMR1726/OVERALL/CSS_EU_2014/REPORT/PGM/ae_socpt_s_t.sas
OUT=REPORT/OUTPUT/ae_socpt_infection_s_t_p1_i.rtf (14MAR2014 - 23:34)
N: Number; PT: Preferred Term; TEAE: Treatment Emergent Adverse Event.

Pool B

Infections: the proportion of patients with TEAEs related to infections and infestations was comparable across treatment groups (68.0% and 64.3% in the teriflunomide 7 mg and 14 mg groups, respectively). Few patients (0.4% and 1.1% of patients with teriflunomide 7 and 14 mg, respectively) discontinued treatment further to infection during the study period.

See frequency with 95% CI.

The update of the pool B data did not change the analysis provided above.

In children (EFC11759/TERIKIDS Study)

The proportion of patients with infections and infestations TEAEs was higher in the teriflunomide group (66.1%) than in the placebo group (45.6%) (Table 28b).

The most frequently occurring infections TEAEs (≥5% at PT level in any treatment groups) were nasopharyngitis, upper respiratory tract infection, influenza, and pharyngitis which were more frequently reported in the teriflunomide group, and gastroenteritis which was more frequently reported in the placebo group. No additional unexpected events were identified in the open-label period. Overall, teriflunomide was well-tolerated with a manageable safety profile, consistent with the experience observed in the double-blind period.

Table 28b - Number (%) of patients with treatment-emergent infections and infestations by primary SOC and PT - Safety population

Primary System Organ Class Preferred Term n(%)	Placebo (N = 57)	Teriflunomide (N = 109)
Any class	26 (45.6)	72 (66.1)
Infections and infestations	26 (45.6)	72 (66.1)
Nasopharyngitis	5 (8.8)	28 (25.7)
Upper respiratory tract infection	6 (10.5)	23 (21.1)
Influenza	4 (7.0)	10 (9.2)
Pharyngitis	1 (1.8)	7 (6.4)
Bronchitis	1 (1.8)	5 (4.6)
Respiratory tract infection viral	0	4 (3.7)
Rhinitis	2 (3.5)	4 (3.7)
Sinusitis	2 (3.5)	4 (3.7)
Tonsillitis	2 (3.5)	4 (3.7)
Gastroenteritis	3 (5.3)	3 (2.8)
Oral herpes	1 (1.8)	2 (1.8)
Urinary tract infection	1 (1.8)	2 (1.8)
Viral upper respiratory tract infection	1 (1.8)	2 (1.8)
Blastocystis infection	0	1 (0.9)
Conjunctivitis	0	1 (0.9)
Conjunctivitis viral	0	1 (0.9)
Cystitis	0	1 (0.9)
Ear infection	0	1 (0.9)
Folliculitis	0	1 (0.9)
Furuncle	1 (1.8)	1 (0.9)
Gastrointestinal infection	0	1 (0.9)
Herpes simplex	0	1 (0.9)
Myringitis	0	1 (0.9)
Paronychia	0	1 (0.9)
Pharyngotonsillitis	0	1 (0.9)
Pilonidal cyst	0	1 (0.9)
Pneumonia bacterial	0	1 (0.9)
Pulmonary tuberculosis	0	1 (0.9)
Respiratory tract infection	1 (1.8)	1 (0.9)
Tinea versicolor	2 (3.5)	1 (0.9)
Tonsillitis bacterial	0	1 (0.9)
Tooth infection	0	1 (0.9)
Vaginal infection	0	1 (0.9)

Vestibular neuronitis	0	1 (0.9)
Viral tonsillitis	0	1 (0.9)
Vulvovaginitis	0	1 (0.9)
Wound infection	0	1 (0.9)
Appendicitis	1 (1.8)	0
Helicobacter infection	1 (1.8)	0
Tracheobronchitis	1 (1.8)	0
Urogenital infection bacterial	1 (1.8)	0
Gastrointestinal disorders	0	1 (0.9)
Food poisoning	0	1 (0.9)

MedDRA version: 22.0; n (%) = number and percentage of patients with at least one TEAE.
Note: Table sorted by SOC internationally agreed order and by decreasing frequency of PT in teriflunomide treatment group
PGM=PRODOPS/HMR1726/EFC11759/CSR_02/REPORT/PGM/db_ae_socpt_s_t.sas
OUT=REPORT/OUTPUT/db_ae_infect_socpt_s_t_i.rtf (06FEB2020 9:39)
MedDRA: Medical Dictionary for Regulatory Activities; N: Number; PT: Preferred Term; SOC: System Organ Class, TEAE: Treatment-Emergent Adverse Event.

Sanofi Pharmacovigilance database

Cases of infections reported in the postmarketing setting at DLP 12-Sep-2023 were reviewed and were found to be consistent with the known safety profile of teriflunomide.

EU-PASS OBS12753

In the PASS, in patients exposed to teriflunomide, the incidence of serious infections was 4.77 per 1000 person-years, incidence of pneumonia ranged from 2.77 to 4.38 per 1000 person-years. These incidences were not different from incidences observed in other platform DMTs.

Seriousness/outcomes

In adults

Infections Pool A1

As shown in [Table 28c], a low and similar incidence of serious infections was reported (2.1%, 1.4%, and 2.2% with placebo, teriflunomide 7 and 14 mg, respectively). No febrile neutropenia was reported.

Table 28c - Serious TEAEs of infections - Pool A1

Placebo (24 events in 22 patients)	Teriflunomide 7 mg (27 events in 23 patients)	Teriflunomide 14 mg (29 events in 27 patients)
Pyelonephritis, cellulitis, abdominal abscess, abscess soft tissue, gastroenteritis (2 patients), acute hepatitis C, hepatitis C, cytomegalovirus infection, herpes zoster, influenza (2 patients), lower respiratory tract infection, lung infection, lung abscess, urinary tract infection	Appendicitis (3 patients), urinary tract infections (2 patients), gastroenteritis, peritonitis, bronchitis, cellulitis, Clostridium difficile colitis, enterococcal endocarditis, erysipelas, Escherichia bacteremia, infected bites, infected cyst, infectious mononucleosis, pelvic abscess, pilonidal cyst, pneumonia (3 patients), pulmonary	Bacteremia, CMV, hepatitis, gastroenteritis, pyelonephritis (4 patients), appendicitis (3 patients), renal abscess, and urinary tract infection (3 patients), acute sinusitis, appendiceal abscess, appendicitis perforated, bacterial sepsis, cystitis, diarrhea infectious, genital infection, neuroborreliosis,

Identified Risk	Infections

(3 patients), paronychia, post procedural infection, pyelonephritis acute, respiratory tract infection, staphylococcal bacteremia and skin infection	tuberculosis, pyelonephritis acute, respiratory tract infection, salpingo-oophoritis, Staphylococcal infection and wound infection	osteomyelitis, peritonitis, pneumonia bacterial, sinusitis, tonsillitis, tuberculosis gastrointestinal and urinary tract infection enterococcal

CMV: Cytomegalovirus; TEAE: Treatment-Emergent Adverse Event.

Infections Pool B

The incidence of serious TEAEs of infections in Pool B was comparable between the 2 teriflunomide doses (27 patients [3.9%] and 22 patients [3.3%] with teriflunomide 7 and 14 mg, respectively). The main contributor for serious TEAEs was urinary tract infections (3 and 4 patients for teriflunomide 7 and 14 mg, respectively).

Serious opportunistic infections for Pool B are discussed in Table 31.

In children (EFC11759/TERIKIDS Study)

Overall, 3 cases were serious: upper respiratory tract infection in one patient and pulmonary tuberculosis in another patient in the teriflunomide group and appendicitis in a patient from the placebo group. The case of upper respiratory tract infection related to a hospitalization for concomitant MS relapse, although it was not serious by itself. One infection led to treatment discontinuation (serious pulmonary tuberculosis). This patient was diagnosed at the occasion of a screening at school in the context of an epidemy of tuberculosis-[redacted]. The patient recovered from tuberculosis after IMP discontinuation and administration of anti-tuberculosis treatment.

Background incidence/prevalence

Incidence of condition

A study conducted in the UK that compared 6932 MS patients with 68 256 non-MS patients reported a 25% increased risk of any infection in MS patients relative to non-MS patients (IRR: 1.25; 95% CI: 1.21-1.29) and a 100% increase in the risk of serious (hospitalized) infections in patients with MS compared to non-MS patients (IRR: 2.00; 95% CI: 1.84-2.17). [91] Similar results were observed in a US-based study that compared 7743 veterans with MS to 30 972 non-MS veterans and reported the nearly twice the incidence of serious infections in MS cohort compared to non-MS cohort (19.2/1000 person-years vs 10.3/1000 person-years). Furthermore, relative to non-MS population, having MS significantly increased the risk of fatal infection by 85% (HR: 1.85; 95% CI: 1.08-3.15), serious respiratory infections by 85% (HR: 1.85; 95% CI: 1.08-3.15), urinary track infections by 344% (HR: 4.44; 95% CI: 3.59- 5.51) and sepsis by 156% (HR: 2.56; 95% CI: 1.08-3.15). [42]

In a Norwegian cohort, the crude mortality rate due to infections, mainly pulmonary and urinary tract infections is 1.73 per 1000 person-years [92] and the standardized mortality ratio of deaths due to infections is 9.75 in the MS population.

Incidence of infection in patients treated

- Cladribine: 48% of patients had infections over 96 weeks and 2.3% had herpes zoster. No relation was found between lymphocyte counts and herpes zoster. [94]
- Natalizumab 79% of patients had infections over two years and 3.2% had serious infections. [82]
- Dimethyl fumarate: 56% of patients had infections over 2 years. [74]

Identified Risk	Infections
	• Glatiramer acetate: 50% of patients had infections over 2 years. [74] • Daclizumab HYP: 65% of patients had infections over 2 years and 4% had serious infections. [75] • Interferon-β1a: 45% to 57% of patients had infections over 2 years, 2% had serious infections and 2% had herpes infections. [75,76,77] • Alemtuzumab: 67% of patients had infections over 2 years and 16% had herpes infections. [76,77] In treatment-naive relapsing MS patients, lymphopenia was reported to be present in 10.1% of the patients and 13.7% in controls. [95] Incidences of WBC decrease described in patients under different treatment regimens: • Mitoxantrone (retrospective review): 27% had reduced neutrophil count (grade ≥1) and 18% had evident neutropenia over a median follow-up of 14 months. [78] • Fingolimod (clinical trial): 6.3% had leucopenia and 5.4% had lymphopenia over 2 years. [79] • Cladribine (clinical trial): 26.7% had lymphopenia, 7.1% had leucopenia and 2.0% had neutropenia over 96 weeks. [94] • Interferon-β1a: 16% to 23% had leucopenia and 14% to 17% had granulocytopenia. [96] **Prevalence of condition** Prevalence of neutropenia in general adult population ranged from 0.5% to 0.66%. [99] In Maryland in the US, the age-adjusted prevalence rate of ITP was found to be 9.5 per 100 000 persons [97] and in patients with ITP the prevalence of MS was approximately 25 times the prevalence that would be expected in the general population. [98] **Impact on individual patient** Not applicable
Risk factors and risk groups	Patients with pre-existent neutropenia, concomitant treatment with other neutropenic or immunosuppressive agents, history of repetitive infections. The analysis of intrinsic or extrinsic factors did not identify any further particular risk group or risk factor for infections.
Preventability	Education of HCP and patient on risk of infection, and on signs and symptoms of infections, including seeking medical attention if they appear.
Impact on the benefit-risk balance of the product	The benefit-risk remains unchanged for teriflunomide.
Public health impact	Not evaluated

CI: Confidence Interval; CMV: Cytomegalovirus; DLP: Data Lock Point; DMT: Disease Modifying Therapy; EU: European Union; HCP: Healthcare Professional; HLT: High Level Term; HR: Hazard Ratio; IBD: International Birth Date; IRR: Incidence Rate Ratio; IMP: Investigational Medicinal Product; ITP: Immune Thrombocytopenia; MAH: Marketing Authorization Holder; MedDRA: Medical Dictionary for Regulatory Activities; MS: Multiple Sclerosis; N: Number; NEC: Not Elsewhere Classified; PASS: Post-Authorization Safety Study; PT: Preferred term; RR: Relative Risk; TEAE: Treatment-Emergent Adverse Event; UK: United Kingdom; US: United States.

Table 29 - Identified risk: Acute pancreatitis

Identified Risk	Acute pancreatitis
Potential mechanism	Unknown

Identified Risk	Acute pancreatitis
Evidence source(s) and strength of evidence	Literature, non-clinical data, clinical data, postmarketing experience.
Characterization of the risk	**Frequency with 95% CI** **In adults** **Pool A1** In Pool A1, the distribution of patients with pancreatic disorders TEAEs was similar across the treatment groups (2.8%, 2.6%, and 2.7% in the placebo, teriflunomide 7 mg, and teriflunomide 14 mg groups, respectively. The frequency of acute pancreatitis was similar across the treatment groups (0.1%, 0.1%, and 0.1% in the placebo, teriflunomide 7 mg, and teriflunomide 14 mg groups, respectively, corresponding to 1 case in each group). The analysis of the relative risk for pancreatic disorders is shown below.

Table 29a - Pancreatic Disorders TEAEs - Relative risk as compared to placebo with 95% CI - Pool A1

	Relative Risk (compared to placebo)	95% CI
Teriflunomide 7 mg	0.92	0.55 to 1.55
Teriflunomide 14 mg	0.96	0.57 to 1.62

Extracted from:
PGM=PRODOPS/HMR1726/OVERALL/CSS_EU_2014/REPORT/PGM/ae_relrisk_s_t.sas
OUT=REPORT/OUTPUT/ae_relrisk_aesi_s_t_p1_i.rtf (14MAR2014 - 20:41)
CI: Confidence Interval; TEAE: Treatment-Emergent Adverse Event.

Severity and nature of risk

Pool A1

The majority of the events were of mild intensity; 2 events in the placebo group, 2 events in the teriflunomide 7 mg group, and 1 event in the teriflunomide 14 mg group were considered as severe. Recovery during the observation period in Pool A1 was reported in 23 of 28 patients on placebo, 25 of 27 patients on teriflunomide 7 mg, and 25 of 27 patients on teriflunomide 14 mg. Pancreatic disorders were mainly asymptomatic, and pancreatic enzyme increases were reversible.

Median time to onset of pancreatic disorders was 175.5 days on placebo, 146 days on teriflunomide 7 mg, and 113 days on teriflunomide 14 mg.

Table 29b - Number (%) of patients with Pancreatic Disorders TEAEs by Primary SOC and PT - Safety population - Pool A1

		Teriflunomide	
Primary System Organ Class Preferred Term n (%)	Placebo (N = 997)	7 mg (N = 1045)	14 mg (N = 1002)
Any class	**28 (2.8%)**	**27 (2.6%)**	**27 (2.7%)**
Metabolism and nutrition disorders	0	1 (<0.1%)	0
Hyperlipasaemia	0	1 (<0.1%)	0
Gastrointestinal disorders	4 (0.4%)	1 (<0.1%)	2 (0.2%)
Pancreatitis acute	1 (0.1%)	1 (<0.1%)	1 (<0.1%)
Pancreatitis chronic	1 (0.1%)	0	1 (<0.1%)
Pancreatitis	2 (0.2%)	0	0

Identified Risk	Acute pancreatitis

Investigations	24 (2.4%)	25 (2.4%)	26 (2.6%)
Lipase increased	15 (1.5%)	15 (1.4%)	20 (2.0%)
Amylase increased	13 (1.3%)	15 (1.4%)	14 (1.4%)
Amylase abnormal	1 (0.1%)	0	0
Pancreatic enzymes increased	0	1 (<0.1%)	0

MedDRA version: 16.0. n (%) = number and percentage of patients with at least one TEAE.
Note: Table sorted by SOC internationally agreed order and decreasing frequency of PTs in teriflunomide 14 mg group. Extracted from:
PGM=PRODOPS/HMR1726/OVERALL/CSS_EU_2014/REPORT/PGM/ae_socpt_s_t.sas
OUT=REPORT/OUTPUT/ae_socpt_pancrea_s_t_p1_i.rtf (14MAR2014 - 23:43)
MedDRA: Medical Dictionary for Regulatory Activities; N: Number; PT: Preferred Term;
SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

Pool B

In Pool B, the proportion of patients with TEAEs potentially related to pancreatic disorders was 6.0% and 5.2% in the 7 mg and 14 mg teriflunomide groups, respectively.

In children (EFC11759/ TERIKIDS study)

Pancreatic disorders were reported in 4 patients (3.7%) in the teriflunomide group and 1 patient (1.8%) in the placebo group [Table 29c].

Table 29c - Number (%) of patients with treatment emergent pancreatic disorder by primary SOC and PT - Safety population

Primary System Organ Class Preferred Term n (%)	Placebo (N = 57)	Teriflunomide (N = 109)
Any class	1 (1.8)	4 (3.7)
Metabolism And Nutrition Disorders	0	1 (0.9)
Hyperlipasaemia	0	1 (0.9)
Gastrointestinal Disorders	0	2 (1.8)
Pancreatitis acute	0	2 (1.8)
Investigations	1 (1.8)	2 (1.8)
Amylase increased	0	1 (0.9)
Lipase increased	1 (1.8)	1 (0.9)

MedDRA version: 22.0; n (%) = number and percentage of patients with at least one TEAE.
Note: Table sorted by SOC internationally agreed order and by decreasing frequency of PT in teriflunomide treatment group.
PGM=PRODOPS/HMR1726/EFC11759/CSR_02/REPORT/PGM/db_ae_socpt_s_t.sas
OUT=REPORT/OUTPUT/db_ae_panc_socpt_s_t_i.rtf (06FEB2020 9:39
MedDRA: Medical Dictionary for Regulatory Activities; N: Number; PT: Preferred Term;
SOC: System Organ Class.

In children, no additional unexpected events were identified in the open-label period. Overall, teriflunomide was well-tolerated with a manageable safety profile, consistent with the experience observed in the double-blind period.

Sanofi Pharmacovigilance database

All cases of acute pancreatitis reported in the postmarketing setting at DLP 12-Sep-2023 were reviewed and were found to be consistent with the known safety profile of teriflunomide. No newly identified diagnostically confirmed case was reported at the paediatric age range (10 to 17 years old).

EU-PASS OBS12753

Identified Risk	Acute pancreatitis
	In the PASS, in patients exposed to teriflunomide, incidence rate of acute pancreatitis ranged from 0.31 to 16 per 1000 person-years according to definition used. This incidence was not different from incidence observed in other platform DMTs. **Seriousness/outcomes** **In adults** **Pool A1** The following Serious TEAEs were reported: in the placebo group: 2 pancreatitis, in the teriflunomide 7 mg group: 3 increased lipase and acute pancreatitis and in the teriflunomide 14 mg group: 2 increased lipase. In addition to these patients, 2 patients in the 14 mg teriflunomide group discontinued the treatment due to pancreatic disorder TEAEs. Recovery during the observation period in Pool A1 was reported in 23 of 28 patients on placebo, 25 of 27 patients on teriflunomide 7 mg, and 25 of 27 patients on teriflunomide 14 mg. Pancreatic disorders were mainly asymptomatic, and pancreatic enzyme increases were reversible. **In children (EFC11759/ TERIKIDS study)** The observed safety profile in pediatric patients (from 10 to 17 years-old) receiving teriflunomide daily was overall similar to that seen in adult patients. However, in the pediatric study (166 patients: 109 in the teriflunomide group and 57 in the placebo group), cases of pancreatitis were reported in 1.8% (2/109) of the teriflunomide-treated patients compared to none in the placebo group, in the double-blind phase. One of these events led to hospitalization and required corrective treatment. In pediatric patients treated with teriflunomide in the open-label phase of the study, 2 additional cases of pancreatitis (one was reported as a serious event, the other was a non-serious event of mild intensity) and one case of serious acute pancreatitis (with pseudo-papilloma), were reported. In two of these 3 patients, pancreatitis led to hospitalization. Clinical symptoms included abdominal pain, nausea and/ or vomiting and serum amylase and lipase were elevated in these patients. All patients recovered after treatment discontinuation and accelerated elimination procedure (see section 4.4) and corrective treatment. **Sanofi Pharmacovigilance database** Acute pancreatitis has been reported infrequently in the postmarketing setting with teriflunomide in adults, including cases of necrotising pancreatitis and pancreatic pseudocyst which were not fatal. Pancreatic events (acute pancreatitis) may occur at any time during treatment with teriflunomide, which may lead to hospitalization and/or require corrective treatment. **Background incidence/prevalence** There is no epidemiological data of pancreatitis in MS population in the literature. **Incidence of condition**: A comprehensive epidemiological analysis of data from the Truven Market Scan Research Databases found that the incidence of acute pancreatitis was 12.3/100 000 persons in children and 111.2/100 000 persons in non-elderly adults in 2014. [100] In a systematic review the global estimated incidence of acute pancreatitis was reported to be 33.7 cases (95% CI: 23.3 to 48.8) per 100 000 population-years. [101] The same study reported estimated incidence rates of 58.2 per 100 000 population-years in the US. For specific causes of acute pancreatitis, age standardized incidence rates were 5.4 per 100 000 for alcohol related and 5.7 per 100 000 for biliary tract disease related acute pancreatitis. Multiple sclerosis patients from 10 to <18 years of age have an acute pancreatitis incidence rate of 4.23 per 1000 person-years (95% CI: 1.37-13.13). Note than in the

Identified Risk	Acute pancreatitis
	matched comparison group of non-MS patients, no cases of acute pancreatitis were observed. [87] **Impact on individual patient** Acute pancreatitis may be life-threatening and fatal or may lead to disability.
Risk factors and risk groups	Patients with a pre-existing pancreatic disorder.
Preventability	In patients who develop signs or symptoms of pancreatic inflammation or disorder, consideration should be given to treatment discontinuation and to further investigation, as appropriate. Education of HCP and patient on risk of acute pancreatitis, and on signs and symptoms of pancreatitis, including advising patient to seek medical attention if the symptoms appear.
Impact on the benefit-risk balance of the product	The benefit-risk remains unchanged for teriflunomide.
Public health impact	Not evaluated.

CI: Confidence Interval; DLP: Data Lock Point; DMT: Disease Modifying Therapy; EU: European Union; HCP: Healthcare Professional; MedDRA: Medical Dictionary for Regulatory Activities; MS: Multiple Sclerosis; N: Number; PASS: Post-Authorization Safety Study; PT: Preferred Term; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event; US: United States.

Table 30 - Potential risk: Teratogenicity

Potential Risk	Teratogenicity
Potential mechanism	Teriflunomide inhibits DNA synthesis and crosses the placental barrier.
Evidence source(s) and strength of evidence	Literature, non-clinical studies with leflunomide and teriflunomide (embryo-fetal toxicity studies)
Characterization of the risk	**Frequency with 95% CI** Not applicable **Severity and nature of risk** **In adults**: This potential risk discussed in this table focuses on the fetal risk in women who enrolled in teriflunomide studies and became pregnant. (Note: Pregnancy in female partners of male patients is not considered as an important potential risk). Non-clinical studies conducted with teriflunomide showed embryofetal toxic effects in animals (rats and rabbits). All clinical studies in adults: A total of 76 pregnancies occurred in 76 female patients who received teriflunomide (either 7 mg or 14 mg) during the clinical development program. The pregnancy outcomes are as follows: 28 live births (which included 1 set of twins for a total 29 infants), 34 induced abortions (one of which was performed for an ectopic pregnancy), 12 spontaneous abortions, and 2 pregnancies with an unknown outcome as of the cut-off date (19-Apr-2019). **In children (EFC11759/TERIKIDS Study)**

[redacted] No additional unexpected events were identified in the open-label period.

Sanofi Pharmacovigilance database

A total of 1604 unique case reports were received from worldwide sources cumulatively from the IBD of 12-Sep-2012 through 12-Sep-2023. This includes clinical trial cases, post-marketing cases, and cases from non-interventional studies. Of the 1604, 224 clearly did not concern pregnancy and thus will not be further discussed. A discussion of the 1380 cases of drug exposure via parent follows below.

Therefore, a total of 1380 cases of drug exposure via parent were retrieved. Of which, 35 pregnancies (considering a total exposure of 716 944 patient years as of DLP 12-Sep-2023) involved possible congenital malformations, for which causal relatedness could neither be established nor denied:

Ventricular septal defect, polydactyly, fetal malformation, esophageal atresia, congenital nose malformation, vascular malformation, fetal chromosome abnormality, fetal disorder, syndactyly, fetal cystic hygroma, eyelid ptosis congenital, ductus venosus agenesis, persistent left superior vena cava, cryptorchism, congenital flat feet, congenital pyelocaliectasis, fetal macrosomia, congenital arterial malformation, atrial septal defect, Marcus Gunn syndrome, Amniotic cavity disorder, Talipes, ankyloglossia congenital, duodenal atresia, Congenital urethral anomaly, cystic lymphangioma, alveolar capillary dysplasia, spinal bifida, hip dysplasia, congenital choroid plexus cyst. In addition, trisomy 21 and pyloric stenosis were reported without exposure information available at the time of this report. One report of spina bifida occulta was reported with paternal exposure. Also, more than one congenital anomaly may be reported in more than one case.

Other birth defects included esophageal disorder, intrauterine growth and development retardation, heartbeat abnormal neonatal, mild pleural effusion, strabismus, eye movement disorder, developmental delay or immaturity, cerebral ventricle dilatation (minor ventriculomegaly) and abnormal development of the fetus.

Six cases reported fetal death; in one case the fetus died due to circular cord, in the other case, the patient (mother) developed breast cancer. At 6 weeks, the fetus was not viable. In one case, the mother was exposed to teriflunomide during eight weeks of pregnancy, following which the accelerated elimination was done and unspecified duration afterwards, it was reported that the fetus died due to unspecified reason. In one case, spontaneous abortion leading to fetal death. In two cases, the fetus died due to many congenital anomalies.

<u>Paternal Exposure:</u>

The GPV Database search retrieved 162 case reports (from IBD to 12-Sep-2023) of pregnant partner of male patients who were exposed to teriflunomide during pregnancy in the postmarketing setting, seven pregnancies (considering a total exposure of 716 944 patient-years as of DLP 12-Sep-2023) involved possible congenital malformations, for which causal relatedness was not established:

A case of congenital flat feet, two cases of hip dysplasia, two cases of spinal bifida, one case of trisomy 21 and one case of alveolar capillary dysplasia.

<u>Overall Summary:</u>

Among the total cumulative congenital anomaly cases, 15 were reported prospectively and 20 were reported retrospectively. Among the available information and expert assessment for 30 congenital anomalies, 24 were considered as major and 6 were considered as minor. In 4 cases more than one congenital anomaly was reported.

Exposed Pregnancies were early in the first trimester due to the accelerated elimination procedure done when the pregnancy was acknowledged. No specific pattern of defects was identified. The assessment of this risk did not reveal new or unexpected safety finding. The Product label indicates women of childbearing potential must use effective

Potential Risk	Teratogenicity
	contraception to avoid pregnancy while taking teriflunomide. If teriflunomide is stopped, women should continue contraception until teriflunomide plasma concentrations have been checked to be equal to 0.02 µg/mL or lower. Women, who are planning a pregnancy or are pregnant, should be advised that an accelerated elimination procedure can be used to quickly decrease the plasma concentration of teriflunomide. Without the accelerated elimination procedure, on average it takes eight months to reach plasma concentrations less than or equal to 0.02 µg/mL; however due to individual variation in drug clearance it may take up to two years. The accelerated elimination could be used at any time after discontinuation of teriflunomide. The evaluation of cases does not support an update of the characterization of this important potential risk. **Seriousness/outcomes** All delivered newborns to mothers treated with teriflunomide in clinical trials were healthy, except for a set of twins whose complications were attributed to prematurity. One of the twins presented with a major structural defect, ureteropyeloectasia (left sided). No other major structural or functional defects were observed in the Phase 3 clinical trials of teriflunomide. [100] **Background incidence/prevalence** **Incidence of condition** Overall incidence of pregnancy outcomes in patients with MS exposed or not exposed to disease modifying agents are described in different studies and was shown to be similar to the one observed in general population: A prospective observational study from the teratology information service in Germany from 1996 to 2007 analyzed pregnancy outcomes in women with MS treated with IFN-β, GA or untreated and a healthy comparative group. Spontaneous abortion rates were in normal range for all groups except the small subgroup of IFN-β1b. There were two major birth defects in the GA group (club feet and atrioventricular canal) and none in the IFN cohort. [103] A prospective cohort of 60 Finnish women with MS becoming pregnant in 2003-2005 there were no malformations or infant deaths. [104] Dahl and associates analyzed more than 2 million births registered in the Medical Birth Registry of Norway from 01-Jan-1967 to 31-Dec-2002. They reported that the proportion of neonates with birth defects did not differ between mothers with and without MS. [105] Another study analyzed data from the BERD, which was created by the Washington State Department of Health. This study reported that women with MS were no more likely to have infants with malformations (1.1% with MS compared with 2.0% without MS). [106] A retrospective study in MS centers in Argentina analyzed 141 pregnancies. Involuntary abortion was observed in 16% of pregnancies, and the rate of birth defects was 4.8%. [107] **Impact on individual patient** Not applicable.
Risk factors and risk groups	Pregnant women and WOCBP including adolescents.
Preventability	Communication/Education Plan in women of child-bearing potential: • Before treatment (investigate potential pregnancy and/or plan for pregnancy, emphasize need for contraception) • During treatment (continue to reinforce need for effective contraception, assess potential pregnancy or pregnancy intention) • If pregnancy occurs, need to alert physician immediately, assess benefit-risk, consider discontinuing treatment and performing accelerated elimination procedure.

Potential Risk	Teratogenicity
	Accelerated elimination procedure allows to quickly decrease the levels of teriflunomide in the blood and quickly reach plasma levels of less than 0.02 µg/mL, which is considered a non-teratogenic risk level for teriflunomide in humans.
Impact on the benefit-risk balance of the product	The benefit-risk remains unchanged for teriflunomide.
Public health impact	Not evaluated

BERD: Birth Events Record Database; CI: Confidence Interval; DLP: Data Lock Point; DNA: Deoxyribonucleic Acid; GA: Glatiramer Acetate; GPV: Global Pharmacovigilance; IBD: International Birth Date; IFN-β: Interferon Beta; MS: Multiple Sclerosis; WOCBP: Women of Child-Bearing Potential.

Table 31 - Potential risk: Serious opportunistic infections, including PML

Potential Risk	Serious opportunistic infections, including PML
Potential mechanism	Modulation of the cellular and humoral immune response.
Evidence source(s) and strength of evidence	Literature, non-clinical and clinical data.
Characterization of the risk	**Frequency with 95% CI:** See "Severity and nature of risk" and "Seriousness/Outcomes" below. **Severity and nature of risk** **In adults** **Pool A1** The proportion of patients with TEAEs related to opportunistic infections by primary SOC and PT was 7.0% of patients on placebo, 7.5% of patients on teriflunomide 7 mg, and 8.2% of patients on teriflunomide 14 mg. The main PT contributors were oral herpes (1.5%, 2.2%, and 2.2% on placebo, teriflunomide 7 mg, and teriflunomide 14 mg, respectively) and tinea pedis (0.4%, 0.6%, and 1.2% on placebo, teriflunomide 7 mg, and teriflunomide14 mg, respectively).

Table 31a - Number (%) of patients with infections and infestations TEAEs (only PTs occurring in ≥2 patients treated in a teriflunomide group are shown) - Pool A1

		Teriflunomide	
Primary System Organ Class Preferred Term n (%)	**Placebo (N = 997)**	**7 mg (N = 1045)**	**14 mg (N = 1002)**
Infections and Infestations	70 (7.0%)	78 (7.5%)	82 (8.2%)
Oral herpes	15 (1.5%)	23 (2.2%)	22 (2.2%)
Tinea pedis	4 (0.4%)	6 (0.6%)	12 (1.2%)
Herpes simplex	5 (0.5%)	2 (0.2%)	9 (0.9%)
Herpes zoster	10 (1.0%)	10 (1.0%)	9 (0.9%)
Vulvovaginal mycotic infection	4 (0.4%)	12 (1.1%)	6 (0.6%)
Fungal skin infection	4 (0.4%)	5 (0.5%)	5 (0.5%)
Herpes virus infection	3 (0.3%)	1 (<0.1%)	5 (0.5%)
Onchomycosis	4 (0.4%)	3 (0.3%)	5 (0.5%)
Oral candidiasis	1 (0.1%)	3 (0.3%)	3 (0.3%)
Candidiasis	1 (0.1%)	1 (<0.1%)	2 (0.2%)

Potential Risk	Serious opportunistic infections, including PML

Fungal infection	3 (0.3%)	3 (0.3%)	2 (0.2%)
Genital herpes	3 (0.3%)	2 (0.2%)	2 (0.2%)
Skin candida	2 (0.2%)	1 (<0.1%)	2 (0.2%)
Tinea versicolor	2 (0.2%)	3 (0.3%)	2 (0.2%)
Vulvovaginal candidiasis	5 (0.5%)	4 (0.4%)	2 (0.2%)
Oral fungal infection	2 (0.2%)	3 (0.3%)	0

Note: Table sorted by decreasing frequency of PTs in teriflunomide 14 mg group. Extracted from: PGM=PRODOPS/HMR1726/OVERALL/CSS_EU_2014/REPORT/PGM/ae_aesisumm_oppinfection_s_t.sas OUT=REPORT/OUTPUT/ae_aesisumm_oppinfection_s_t_p1_i.rtf (14MAR2014 - 20:53)

N: Number; PT: Preferred Term; TEAE: Treatment-Emergent Adverse Event.

Pool B

In Pool B, the number of patients with TEAEs related to opportunistic infections was 95 (13.6%) in teriflunomide 7 mg and 85 (12.9%) in teriflunomide 14 mg. These include but are not limited to: oral herpes, tinea pedis, and vulvovaginal mycotic infections.

All clinical studies

No case of PML was reported in the whole teriflunomide program.

The main opportunistic infections (eg, pneumocystis, toxoplasma, syphilis, mucocutaneous candidiasis, histoplasmosis, aspergillosis) did not occur in the teriflunomide studies.

In children (EFC11759/TERIKIDS Study)

One case of serious pulmonary tuberculosis was reported in the teriflunomide group. This patient was diagnosed in the context of an epidemy of tuberculosis. No additional unexpected events were identified in the open-label period. Overall, teriflunomide was well-tolerated with a manageable safety profile, consistent with the experience observed in the double-blind period.

Sanofi Pharmacovigilance database

As of DLP 12-Sep-2023, the reported cases of serious opportunistic infection, with the administration of teriflunomide were consistent in nature and severity with the known safety profile of teriflunomide. No diagnostically confirmed case of PML related to teriflunomide was retrieved from the Sanofi pharmacovigilance database.

EU-PASS OBS12753

In the PASS, in patients exposed to teriflunomide, the incidence of serious opportunistic infections in France was 0.36 per 1000 person-years. The adjusted HR was 2.4 (95% CI 1.2;4.8) compared to other platform DMTs without association to any pathogenic agent. In Belgium, in patients exposed to teriflunomide, incidence of patients receiving treatment for mycosis or tuberculosis was 2.80 and 8.92 per 1000 patient-years, respectively. The adjusted HR for tuberculosis was 1.7 (95% CI 1.1-2.6). No case of PML was observed in patients treated with teriflunomide in any study data source.

Seriousness/outcomes

In adults

Pool A1

Five serious TEAEs of opportunistic infections were reported: 2 in the placebo group (herpes zoster, hepatitis C and CMV infection), 1 in the 7 mg teriflunomide group (pulmonary tuberculosis), and 2 in the 14 mg teriflunomide group (tuberculosis gastrointestinal, acute hepatitis due to CMV).

Five patients had TEAEs related to opportunistic infections that led to study discontinuation: 2 patients had herpes zoster and 1 had tuberculosis in the

<table>
<tr><th>Potential Risk</th><th>Serious opportunistic infections, including PML</th></tr>
<tr><td></td><td>teriflunomide 7 mg group and 1 patient each had tuberculosis and CMV in the teriflunomide 14 mg group. In Pool B, the following additional serious TEAEs of opportunistic infections were observed:
<table>
<tr><th>Teriflunomide 7 mg (1 event)</th><th>Teriflunomide 14 mg (1 event)</th></tr>
<tr><td>Oral herpes (recovered in 9 days)</td><td>Suspected (unconfirmed) tuberculosis treated with a 6-month antituberculosis therapy</td></tr>
</table>
No TEAE related to opportunistic infection, other than the CMV hepatitis described above, led to study discontinuation.
In children (EFC11759/TERIKIDS Study)
One opportunistic infection led to treatment discontinuation (serious pulmonary tuberculosis). The patient recovered from tuberculosis after IMP discontinuation and administration of anti-tuberculosis treatment.
<u>Background incidence/prevalence</u>
Incidence of condition
The incidence of PML in patients with lymphoproliferative disorders is estimated to be 0.52% to 3.3%. [108] PML has also been seen in persons with autoimmune disorders (Systemic Lupus Erythematous, Rheumatoid arthritis, and nonspecific vasculitis). [109]
Incidence of PML is rare in MS patients.
In patients treated with natalizumab: PML risk was 1 in 1133 for patients treated for more than 24 months. [109]
Prevalence of condition
Opportunistic infections seen with use of immune modifying drugs for MS are likely to be similar to those seen with HIV infection and in organ and stem cell transplant patients, but knowledge is incomplete. A study conducted in 1984, prior to HIV infection, only 230 cases of PML were identified worldwide. With the AIDS pandemic, the prevalence increased dramatically because approximately 5% of all HIV-infected persons develop PML. [109]
<u>Impact on individual patient</u>
Serious opportunistic infections, including PML, may be life-threatening, fatal, or may lead to disability.</td></tr>
<tr><td>Risk factors and risk groups</td><td>In patients with rituximab-associated PML, most cases developed in patients with underlying disorders known to predispose toward development of PML, chiefly lymphoproliferative disorders, patients with HIV infection and autoimmune disorders.
With natalizumab, risk factors for PML include duration of treatment (number of natalizumab infusions) and prior use of immunosuppressive agents (eg, mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate).</td></tr>
<tr><td>Preventability</td><td>Based on the immunomodulatory effect of teriflunomide, if a patient develops a serious infection, consider suspending treatment and reassess the benefits and risks prior to re-initiation of therapy.
Accelerated elimination procedure with cholestyramine or charcoal may be considered. Instruct patients receiving teriflunomide to report symptoms of infections to a physician. Patients with active acute or chronic infections should not start treatment with teriflunomide until the infection(s) is resolved.</td></tr>
<tr><td>Impact on the benefit-risk balance of the product</td><td>The benefit-risk remains unchanged for teriflunomide.</td></tr>
</table>

Potential Risk	Serious opportunistic infections, including PML
Public health impact	Not evaluated, however the potential for systemic severe opportunistic infections needs to be carefully monitored.

AIDS: Acquired Immune Deficiency Syndrome; CI: Confidence Interval; CMV: Cytomegalovirus; DLP: Data Lock Point; DMT: Disease Modifying Therapy; GPV: Global Pharmacovigilance; EU: European Union; HIV: Human Immunodeficiency Virus; HR: Hazard Ratio; IMP: Investigational Medicinal Product; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PML: Progressive Multifocal Leukoencephalopathy; PT: Preferred Term; SOC: System Organ Class; TEAE: Treatment-Emergent Adverse Event.

SVII.3.2 Presentation of the missing information

Not applicable

RISK MANAGEMENT PLAN - PART II MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Summary of the safety concerns

Important identified risks	Hepatic effects
	Hypertension
	Hematologic effects
	Infections
	Acute pancreatitis
Important potential risks	Teratogenicity
	Serious opportunistic infections, including PML
Missing information	None

PML: Progressive Multifocal Leukoencephalopathy.

RISK MANAGEMENT PLAN - PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

The safety profile of teriflunomide is continuously monitored since product launch, using routine pharmacovigilance activities.

- Routine pharmacovigilance practices allowing a comprehensive, continuous and global overview of postmarketing safety profile and signal detection.
- Periodic assessment in periodic safety update report (PSURs)/periodic benefit-risk evaluation report (PBRER) for spontaneous reports related to identified and potential risks.
- Continued analysis of safety in clinical trials.

The following routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are in place, including:

- Specific adverse reaction follow-up questionnaire for liver injury (Drug induced liver injury form)
- Specific adverse reaction follow-up questionnaire for pancreatic effects (Pancreatic disorder form)
- Specific adverse reaction follow-up questionnaire for teratogenicity (Pregnancy reporting form)
- Specific adverse reaction follow-up questionnaire for serious opportunistic infections, including PML (PML form)
- In February 2023, [redacted] granted a [redacted] positive opinion for replacing pregnancy registries (OBS13499 and OBS12751) by an enhanced pharmacovigilance process.

  An enhanced pharmacovigilance process is used when identifying women with multiple sclerosis exposed to AUBAGIO (teriflunomide) during pregnancy to allow the evaluation of outcomes of pregnancy and infant up to one year. The overall objective of this pharmacovigilance process is to collect data for pregnancies exposed to teriflunomide, that the MAH becomes aware of via spontaneous reports to the MAH global pharmacovigilance database, that may allow for the assessment of adverse pregnancy outcomes and infant outcomes. Targeted follow-up questionnaires (drug exposure via parent [DEVP] forms) are used for follow-up of any pregnancy cases with exposure to teriflunomide, either during pregnancy or in the relevant time interval before conception, given the product's very long half-life, including reports of (pregnancy) exposure without outcome data or with a normal outcome. Structured analyses of all cases will be submitted regularly, every three years, currently synchronized with AUBAGIO PSUR submission requirements. Analyses will include a separate analysis of prospectively and retrospectively reported pregnancy cases as well as provision of details about time point of exposure to teriflunomide (before/during pregnancy, taking into account the long half-life and information on accelerated elimination procedure).

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable since there are no additional pharmacovigilance activities planned for this product.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 32 - Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Not applicable				

RISK MANAGEMENT PLAN PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No imposed post-authorization efficacy studies (PAES) as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for teriflunomide.

RISK MANAGEMENT PLAN - PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 33 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Hepatic effects	**Routine risk communication:** Labelled in section 4.8 of SmPC and section 4 of PIL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Contraindication for use in patient with severe hepatic impairment has been included in sections 4.2 and 4.3 of SmPC and in section 2 of the PIL. Advices on treatment monitoring in case of liver enzymes elevation (particularly in patients at risk with pre-existing liver disease or having a high level of alcohol consumption) are included in section 4.4 of SmPC and section 2 of PIL. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU).
Hypertension	**Routine risk communication:** Labelled in section 4.8 of SmPC and section 4 of PIL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Advice to appropriately monitor blood pressure before and during treatment is included in section 4.4 of SmPC and section 2 of PIL. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU).
Hematologic effects	**Routine risk communication:** Labelled in section 4.8 of SmPC and section 4 of PIL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Contraindications for patients with significantly impaired bone marrow function or any medically significant cytopenia are included in section 4.3 of SmPC and in section 2 of PIL. Advices on when to check complete blood cell count or perform accelerated elimination procedure are included in section 4.4 of SmPC and in section 2 of PIL. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU).
Infections	**Routine risk communication:** Labelled in section 4.8 of SmPC and section 4 of PIL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Contraindication for patient experiencing active infection or severe immunodeficiency states have been added to section 4.3 of SmPC and in section 2 of PIL.

Safety concern	Routine risk minimization activities
	Advices on suspending treatment or revaluating its benefit-risk in case of infection are included in section 4.4 of SmPC and in section 2 of PIL. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (Restricted medical prescription in EU).
Acute pancreatitis	**Routine risk communication:** Labelled in section 4.4 and 4.8 of SmPC and in sections 2 and 4 of PIL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** In pediatrics, pancreatic enzymes should be monitored if pancreatitis is suspected based on characteristic symptoms. If pancreatitis is confirmed, teriflunomide should be discontinued and an accelerated elimination procedure should be initiated as indicated in section 4.4 of SmPC and section 2 of PIL. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU).
Teratogenicity	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** Contraindications during pregnancy, breastfeeding and for WOCBP not using reliable contraception are included in section 4.3 of SmPC and in section 2 of PIL. Specific advices related to fertility, pregnancy and lactation are included in section 4.6 of SmPC and in section 2 of PIL. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU).
Serious opportunistic infections, including PML	**Routine risk communication:** Labelled in section 4.8 of the SmPC and section 4 of PIL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Contraindication for patient experiencing active infection or severe immunodeficiency states have been added to section 4.3 of SmPC and in section 2 of PIL. Advices on suspending treatment or revaluating its benefit-risk in case of infection are included in section 4.4 of SmPC and in section 4 of PIL. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU).

EU: European Union; MS: Multiple Sclerosis; PIL: Patient Information Leaflet; PML: Progressive Multifocal Leukoencephalopathy; SmPC: Summary of Product Characteristics; WOCBP: Women of Child-Bearing Potential.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

The following additional risk minimization tools have been implemented:

- Healthcare professional (HCP) education/discussion guide available in hard copy and web-based (depending on agreement with National Competent Authority) to educate HCPs and to facilitate (at the time of initiation of prescription with teriflunomide) a conversation

between the prescribing HCPs and the patient/legal representative around specific information pertaining to the following:

- Risk of hepatic effects
- Potential risk of teratogenicity
- Risk of hypertension
- Risk of hematologic effects
- Risk of infections/serious opportunistic infections

It also includes the following keys elements:

- A reminder to provide the Patient Card to the patient/legal representative and to discuss its content regularly during each consultation at least annually during treatment.
- A reminder to tell WOCBP including adolescents/their parents-caregivers that teriflunomide is contraindicated in pregnant women and in WOCBP not using an effective contraception during and after treatment.
- A reminder to assess regularly the potential for pregnancy in female patients including patients below 18 years old.
- A reminder to tell female children and /or parents/caregivers of female children about the need to contact the prescribing physician once the female child under teriflunomide treatment experiences menses. Counselling should be provided to the new patients of childbearing potential about contraception and the potential risk to the fetus.
- A reminder to report any pregnancy case to Sanofi, irrespective of adverse outcomes observed.
- A reminder to contact Sanofi for information regarding the measurement of teriflunomide plasma concentration.

- Patient education card will be given by the HCP to the patient/legal representative in hard copy at the time of treatment initiation of prescription and on an annual basis during the treatment (which the patient can keep, carry and share with other HCPs involved with their treatment). The HCP can download this card in countries, where available. The patient card helps the patient identify the following risks:
  - Risk of hepatic effects
  - Risk of teratogenicity
  - Risk of hypertension
  - Risk of hematologic effects
  - Risk of infections/serious opportunistic infections

  It also includes the following keys elements:
  - A reminder for both patients and all HCPs involved in their treatment that the patient is being treated with teriflunomide.
  - Information to educate the patient about signs/symptoms which could be indicative of risks and the need to report them to their HCP if these occur.
  - Encouragement for the patients to read the PIL thoroughly.

- Advice in case of pregnancy.
- In addition, in countries where the Patient Support Program (MS One to One) is available, patients have the option to access electronic information and opt for reminders.

Table 34 - Additional risk minimization measures

Healthcare professional education/discussion guide	
Objectives	To educate HCPs regarding some specific information pertaining to risks of hepatic effects; hypertension; hematologic effects; infections; teratogenicity; and serious opportunistic infections, including PML.
Rationale for the additional risk minimization activity	• The HCP education/discussion guide (hard copy/web-based) will be used at initiation of therapy. • To discuss need for liver function tests before treatment and periodically thereafter during treatment/To educate patient about signs and symptoms of liver disease/ To remind educate patient to inform doctor if he/she has hypertension/To educate HCPs about need for blood pressure check before treatment and periodically during treatment, and that blood pressure should be appropriately managed during treatment/To discuss need for complete blood cell counts before treatment and periodically during treatment based on signs and symptoms/To discuss need to contact doctor in case of signs/symptoms of infections, or if patient takes other medicines that affect the immune system/To educate female patients of child-bearing potential that they need to use effective contraception during and after treatment/To assess regularly the potential for pregnancy in female patients including patients below 18/To tell female children and/or parents/caregivers of female children about the need to contact the prescribing physician once the female child under teriflunomide treatment experiences menses for the first time of if otherwise required to get counselling about contraception and the potential risk to the fetus/To check pregnancy status before starting treatment in female patients of childbearing potential/To encourage prescribing HCPs to remind female patients of childbearing potential to contact their HCP if they stop contraception or prior to changing contraceptive measures/If female patients including adolescents become pregnant despite using contraceptive measures, they should discontinue teriflunomide and contact their doctor immediately who should inform them of the accelerated elimination procedure and report the pregnancy case to Sanofi irrespective of adverse outcome observed/To remind prescribing HCPs to contact Sanofi for information regarding the measurement of teriflunomide plasma concentration. • To facilitate a conversation between the prescribing HCPs and the patient about the information regarding the above risks. • To remind prescribing HCPs to provide the patient with a Patient Card regularly during each consultation at least annually during treatment, to be used as a tool to relay information to HCPs involved with their medical care (especially in case of medical emergencies and/or if new Doctors/HCPs are involved). • To encourage prescribing HCPs to remind patients to tell their HCP if they experience any of the signs and symptoms discussed in the Patient Education Card.
Target audience and planned distribution path	Audience: Prescribers (ideally MS Specialists, Physicians experienced in management of MS, Neurologists, pediatricians, neuro-pediatricians). Mechanism: Healthcare Professional education/discussion guide will be offered as a web-based tool (accessible and monitored via the product

Healthcare professional education/discussion guide	
	website) and a paper hard copy (tear-off sheet provided via direct mailing or by Sanofi Genzyme representatives, or downloadable and printable via the product website). Distribution of the materials is planned to be done post launch and then on an ad hoc basis. This specific approach will be tailored to the individual market to ensure optimum tool uptake and use. The HCP education/discussion guide will contain key information for the prescriber (ideally MS Specialist, Physicians experienced in the management of MS, Neurologists, specialized MS nurses) and HCPs to discuss with the patient and emphasize the need to thoroughly read the labeling information.
Plans to evaluate the effectiveness of the interventions and criteria for success	Routine pharmacovigilance and the following completed surveys: • Effectiveness of Minimization Measures of RMP: Analysis of distribution and use metrics of risk minimization tools. • Effectiveness of Minimization Measures of RMP: Behavior and Knowledge Survey in HCP Population. • Effectiveness of Minimization Measures of RMP: Behavior and Knowledge Survey in Treated Patient Population. <u>Criteria for judging the success of the proposed risk minimization measures</u>: • Number and severity of cases of interest reported. • Distribution: The MAH is tracking the distribution in the EU. It is noted that figures collected are underestimated as not including the downloads from websites leading to potentially multiple printings. • Behavior and Knowledge in HCPs: Knowledge with >70% of correct responses. Behavior: no pre-defined threshold. • Combined wave 1 and 2 effectiveness study results in HCPs were the following: - Overall results showed adequate knowledge and behavior of the HCPs around contraindications identification of potential risks, contraception and pregnancy. - It has to be mentioned that knowledge of the required liver function monitoring and the purpose/presence of the pregnancy registry was sub-optimal, which are considered as areas of interest/improvement. - Educational materials are overall effective in supporting HCP knowledge relating to the safe use of AUBAGIO. • To improve the effectiveness of the HCP Guide, the educational materials were refined to: - Increase the readability of the HCP Guide. - Include the name of the registry coordinator to the HCP guide to increase enrollment of patients in the pregnancy registries in countries where applicable.
Patient education card	
Objectives	To remind both patients/legal representatives and healthcare providers involved in their treatment that the patient is being treated with teriflunomide, a drug which may cause hepatic effects; hypertension; hematologic effects; infections; teratogenicity; and serious opportunistic infections, including PML.
Rationale for the additional risk minimization activity	To educate patient/legal representatives: • To pay attention to certain signs and symptoms (which might be indicate of liver disease or infections), and if these occur, to promptly contact their doctor/HCP. • To encourage the patients to thoroughly read the PIL or go to product website for comprehensive information on the benefit-risk of their treatment.

Healthcare professional education/discussion guide	
	• To remind WOCBP including girls and their parents/caregivers that teriflunomide should not be used in pregnant women and to use an effective contraception during and after treatment. • For WOCBP including girls and their parents/caregivers: to emphasize need for effective contraception during and after treatment with teriflunomide, and to stop teriflunomide and alert doctor immediately in case of pregnancy or if breastfeeding. • To remind both patients and HCP about the accelerated elimination procedure. • To remind WOCBP, that their doctor will provide counselling on the potential risks to the fetus and on the need for effective contraception. • To remind parents/caregivers of girls to contact the prescribing physician when the girls experiences menses for the first time in order to get counselling about the potential risk to the fetus and the need for contraception. • To remind patients to show the Patient Education Card to Doctors/HCPs involved with their medical care (especially in case of medical emergencies and/or if new Doctors/HCPs are involved). • To record the first date of prescription and the contact details of their prescriber (ideally MS Specialist, Physicians experienced in management of MS, Neurologists, specialized MS nurses).
Target audience and planned distribution path	Audience: Patients and their caregivers, HCPs Mechanisms: The following mechanisms are being proposed: • The Patient Education Card would be a credit-card size folded card carried by the patient. • The prescribing HCP (ideally MS Specialist, Physicians experienced in management of MS, Neurologists, specialized MS nurses) would be expected to fill-in their contact details and then give the card to the patient. • Replacement Patient Education Cards could be provided to patients by the HCPs and could also be accessible to patient electronically.
Plans to evaluate the effectiveness of the interventions and criteria for success	Routine pharmacovigilance and the following completed surveys: • Effectiveness of Minimization Measures of RMP: Analysis of distribution and use metrics of risk minimization tools. • Effectiveness of Minimization Measures of RMP: Behavior and Knowledge Survey in HCP Population. • Effectiveness of Minimization Measures of RMP: Behavior and Knowledge Survey in Treated Patient Population. Criteria for judging the success of the proposed risk minimization measures: • Number and severity of cases of interest reported. • Distribution: The MAH is tracking the distribution in the EU. It is noted that figures collected are underestimated as not including the downloads from websites leading to potentially multiple printings. • Behavior and Knowledge in HCPs: Knowledge with >80% of correct responses. Behavior: no pre-defined threshold. • Behavior and Knowledge in patients: >70% of correct responses. • Combined wave 1 and 2 effectiveness study results in patients were the following: - Overall, the results of the patient knowledge did not reach an acceptable level of correct responses, especially with respect to liver and infection symptoms. - Knowledge of risks in case of a pregnancy and the procedures to follow was near or above satisfactory which also applies to blood monitoring. - It has to be mentioned that results were influenced by the design of the study and the assumption of a certain level of prior medical knowledge.

Healthcare professional education/discussion guide	
	• To improve the effectiveness of the patient card, the educational materials were refined to: - Encourage patients to keep and refer to the materials as needed. - Increase the readability of the Patient Card. - Emphasize the need for HCPs to go through the materials with patients repeatedly and at least annually. - Remind patients that the educational materials are available on the MS One to One web site.

EU: European Union; HCP: Healthcare Professional; MAH: Marketing Authorization Holder; MS: Multiple Sclerosis; PIL: Patient Information Leaflet; PML: Progressive Multifocal Leukoencephalopathy; RMP: Risk Management Plan; WOCBP: Women of Child-Bearing Potential.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 35 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Hepatic effects	**Routine risk minimization measures:** SmPC: Sections 4.2, 4.3, 4.4 and 4.8 PIL: Sections 2 and 4 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). **Additional risk minimization measures:** Educational Materials (HCP education/discussion guide and patient education card).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted questionnaire (Drug induced liver injury form) **Additional pharmacovigilance activities:** None
Hypertension	**Routine risk minimization measures:** SmPC: Sections 4.4 and 4.8 PIL: Sections 2 and 4 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). **Additional risk minimization measures:** Educational Materials (HCP education/discussion guide and patient education card).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Hematologic effects	**Routine risk minimization measures:** SmPC: Sections 4.3, 4.4 and 4.8 PIL: Sections 2 and 4 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: Educational Materials (HCP education/discussion guide and patient education card).	
Infections	**Routine risk minimization measures:** SmPC: Sections 4.3, 4.4 and 4.8 PIL: Sections 2 and 4 Legal status Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). **Additional risk minimization measures:** Educational Materials (HCP education/discussion guide and patient education card).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Acute pancreatitis	**Routine risk minimization measures:** SmPC: Sections 4.4 and 4.8 PIL: Sections 2 and 4 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted questionnaire (pancreatic disorder form) **Additional pharmacovigilance activities:** None
Teratogenicity	**Routine risk minimization measures:** SmPC: Sections 4.3 and 4.6 PIL: Section 2 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). **Additional risk minimization measures:** Educational Materials (HCP education/discussion guide and patient education card).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Targeted questionnaire (pregnancy reporting form) • Pharmacovigilance enhanced process **Additional pharmacovigilance activities:** None
Serious opportunistic infections, including PML	**Routine risk minimization measures:** SmPC: Sections 4.3, 4.4 and 4.8 PIL: Sections 2 and 4 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). **Additional risk minimization measures:** Educational Materials (HCP education/discussion guide and patient education card).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted questionnaire (PML form). **Additional pharmacovigilance activities:** None

EU: European Union; HCP: Healthcare Professional; MS: Multiple Sclerosis; PIL: Patient Information Leaflet; PML: Progressive Multifocal Leukoencephalopathy; SmPC: Summary of Product Characteristics.

RISK MANAGEMENT PLAN - PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for AUBAGIO (Teriflunomide)

This is a summary of the Risk Management Plan (RMP) for AUBAGIO. The RMP details important risks of AUBAGIO how these risks can be minimized, and how more information will be obtained about AUBAGIO's risks and uncertainties (missing information).

AUBAGIO's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how AUBAGIO should be used.

This summary of the RMP for AUBAGIO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European public assessment report (EPAR).

Important new concerns or changes to the current ones will be included in updates of AUBAGIO's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

AUBAGIO is indicated for the treatment of adult and pediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS) (see SmPC for the full indication). It contains teriflunomide as the active substance and it is given by oral route.

Further information about the evaluation of AUBAGIO's benefits can be found in AUBAGIO's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/aubagio

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of AUBAGIO, together with measures to minimize such risks and the proposed studies for learning more about AUBAGIO's risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of AUBAGIO, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of AUBAGIO is not yet available, it is listed under "missing information" outlined in the next section.

II.A List of important risks and missing information

Important risks of AUBAGIO are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of AUBAGIO. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 36 - List of important risks and missing information

Important identified risks	Hepatic effects
	Hypertension
	Hematologic effects
	Infections
	Acute Pancreatitis
Important potential risks	Teratogenicity Serious opportunistic infections, including PML
Missing information	None

PML: Progressive Multifocal Leukoencephalopathy.

II.B Summary of important risks

Table 37 - Important identified risk with corresponding risk minimization activities: Hepatic effects

Hepatic effects	
Evidence for linking the risk to the medicine	Literature, clinical data
Risk factors and risk groups	Mild and moderate hepatic impairment had no impact on the PK of teriflunomide (POP6507). Patients with severe hepatic impairment have been excluded from teriflunomide clinical trials. Other possible theoretical risk factors: concomitant treatment with hepatotoxic agents (including alcohol), viral infections (including viral hepatitis), gall bladder disease.

Hepatic effects	
Risk minimization measures	Routine risk minimization measures: SmPC: Sections 4.2, 4.3, 4.4 and 4.8 PIL: Sections 2 and 4 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). Additional risk minimization measures: Educational Materials (HCP education/discussion guide and patient education card).

EU: European Union; HCP: Healthcare Professional; MS: Multiple Sclerosis; PIL: Patient Information Leaflet; PK: Pharmacokinetic; SmPC: Summary of Product Characteristics.

Table 38 - Important identified risk with corresponding risk minimization activities: Hypertension

Hypertension	
Evidence for linking the risk to the medicine	Literature, clinical data.
Risk factors and risk groups	Patients with prior history of hypertension, prior anti-hypertensive treatment or receiving concomitant drugs causing hypertension (eg, NSAID, OCs). Presence of concomitant cardiovascular risk factors such as obesity, diabetes. [90] There was no evidence of an increased risk of hypertension regarding intrinsic (age, gender, race, BMI) and extrinsic (region, territory, previous disease modifying MS therapy, selected concomitant medications) factors.
Risk minimization measures	Routine risk minimization measures: SmPC: Sections 4.4 and 4.8 PIL: Sections 2 and 4 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). Additional risk minimization measures: Educational Material (HCP education/discussion guide and patient education card).

BMI: Body Mass Index; EU: European Union; HCP: Healthcare Professional; MS: Multiple Sclerosis; NSAID: Non-Steroidal Anti-Inflammatory Drug; OC: Oral Contraceptive; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 39 - Important identified risk with corresponding risk minimization activities: Hematologic effects

Hematologic effects	
Evidence for linking the risk to the medicine	Literature, non-clinical data and clinical data.
Risk factors and risk groups	Patients with pre-existent neutropenia, combination with other neutropenic or lymphopenic drug. Patients with pre-existent thrombocytopenia. Combination with other thrombopenic drugs or drugs increasing the bleeding risk. There was no evidence of increased risk of hematologic effects or hemorrhages in patients treated with teriflunomide 7 or 14 mg compared to those receiving placebo regarding intrinsic (age, gender, race, BMI, baseline EDSS) and extrinsic (region, territory, previous disease modifying MS therapy, selected concomitant medications) factors.

Hematologic effects	
Risk minimization measures	Routine risk minimization measures: SmPC: Sections 4.3, 4.4 and 4.8 PIL: Sections 2 and 4 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). Additional risk minimization measures: Educational Material (HCP education/discussion guide and patient education card).

BMI: Body Mass Index; EDSS: Expanded Disability Status Scale; EU: European Union; HCP: Healthcare Professional; MS: Multiple Sclerosis; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 40 - Important identified risk with corresponding risk minimization activities: Infections

Infections	
Evidence for linking the risk to the medicine	Literature, non-clinical data and clinical data.
Risk factors and risk groups	Patients with pre-existent neutropenia, concomitant treatment with other neutropenic or immunosuppressive agents, history of repetitive infections. The analysis of intrinsic or extrinsic factors did not identify any further particular risk group or risk factor for infections.
Risk minimization measures	Routine risk minimization measures: SmPC: Sections 4.3, 4.4 and 4.8 PIL: Sections 2 and 4 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). Additional risk minimization measures: Educational Material (HCP education/discussion guide and patient education card).

EU: European Union; HCP: Healthcare Professional; MS: Multiple Sclerosis; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 41 - Important identified risk with corresponding risk minimization activities: Acute pancreatitis

Acute pancreatitis	
Evidence for linking the risk to the medicine	Literature, non-clinical data, clinical data, postmarketing experience.
Risk factors and risk groups	Patients with a pre-existing pancreatic disorder.
Risk minimization measures	Routine risk minimization measures: SmPC: Sections 4.4 and 4.8 PIL: Section 2 and 4 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). Additional risk minimization measures: None

EU: European Union; MS: Multiple Sclerosis; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 42 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Teratogenicity

Teratogenicity	
Evidence for linking the risk to the medicine	Literature, non-clinical studies with leflunomide and teriflunomide (embryo-fetal toxicity studies).
Risk factors and risk groups	Pregnant women and women of childbearing potential including adolescents.
Risk minimization measures	Routine risk minimization measures: SmPC: Sections 4.3 and 4.6 PIL: Section 2 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). Additional risk minimization measures: Educational Materials (HCP education/discussion guide and patient education card).

EU: European Union; HCP: Healthcare Professional; MS: Multiple Sclerosis; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 43 - Important potential risk with corresponding risk minimization activities: Serious opportunistic infections, including PML

Serious opportunistic infections, including PML	
Evidence for linking the risk to the medicine	Literature, non-clinical and clinical data.
Risk factors and risk groups	In patients with rituximab-associated PML, most cases developed in patients with underlying disorders known to predispose toward development of PML, chiefly lymphoproliferative disorders, patients with HIV infection and autoimmune disorders. With natalizumab, risk factors for PML include duration of treatment (number of natalizumab infusions) and prior use of immunosuppressive agents (eg, mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate).
Risk minimization measures	Routine risk minimization measures: SmPC: Sections 4.3, 4.4 and 4.8 PIL: Sections 2 and 4 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). Additional risk minimization measures: Educational Material (HCP education/discussion guide and patient education card).

EU: European Union; HCP: Healthcare Professional; HIV: Human Immunodeficiency Virus; MS: Multiple Sclerosis; PIL: Patient Information Leaflet; PML: Progressive Multifocal Leukoencephalopathy; SmPC: Summary of Product Characteristics.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of AUBAGIO.

II.C.2 Other studies in post-authorization development plan

There are no studies required for AUBAGIO.

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RISK MANAGEMENT PLAN - PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

TABLE OF CONTENTS

ANNEX 4.1 Specific adverse reaction follow-up questionnaire for liver injury (Drug induced liver injury form)

DILI (Drug Induced Liver Injury) check list Teriflunomide ***(HMR1726D) - To be attached to the corresponding completed SAE/ER and AE forms, concomitant treatment page and to all necessary reports (lab test, discharge summary)***

Sanofi Case ID- internal use only	Date of report	Study ID *if applicable*	Patient ID *if applicable*
Click here to enter Sanofi Case ID	Click here to enter a date.	Click here to enter Study ID	Click here to enter Patient ID Country of Origin Click here to enter Country of Origin
Reporter Name: Reporter Type: MD ☐Nurse ☐Pharmacist☐ ☐other, Please specify: ___	Reporter telephone	Reporter email	Country of case

PREVIOUS RELEVANT HISTORY AND CONCURRENT DISORDERS			
	NO	**YES**	*Specify details – ONSET Date DD/MM/YYYY*
Is the patient pregnant	☐	☐	
Hepato-biliary	☐	☐	
Allergic disease	☐	☐	
Allergy to drug	☐	☐	
Auto-Immune	☐	☐	
Heart/vascular disease	☐	☐	
Respiratory disease	☐	☐	
Cancer	☐	☐	
Surgical/Dental operation	☐	☐	
Alcohol consumption	☐	☐	*Number of drinks per day*
Acupuncture	☐	☐	
Occupational/toxic agent exposure	☐	☐	
Travels to Africa	☐	☐	
Travels to Asia	☐	☐	
Intravenous drug abuse	☐	☐	
Other	☐	☐	

DOCUMENTATION OF THE ADVERSE EVENT		
Main diagnosis:		**Start Date (DD/MM/YYYY)**
Are the following signs and symptoms associated?	*tick box if applicable* ☐	
Asthenia	☐	
Fever	☐	
Pruritus	☐	
Jaundice	☐	
Joint pain	☐	
Abdominal pain	☐	
Vomiting	☐	
Skin eruption	☐	**Type:**
Purpura	☐	
Hepatomegaly	☐	
Splenomegaly	☐	

Lymph nodes	☐	
Ascites	☐	
Asterixis	☐	
Coma	☐	
Malaise (with or without loss of consciousness)	☐	
INR>2 or prothrombin T.<50%	☐	
Dizziness	☐	
Hypotension	☐	
Arrhythmia	☐	

CENTRAL LABORATORY DATA *performed:* **NO** ☐ **YES** ☐ **Date:** Click here to enter a date.

LOCAL LABORATORY DATA *performed:* **NO** ☐ **YES** ☐ **Date:** Click here to enter a date.

ADDITIONAL TEST DATA (to be performed at local level)

	Not tested	Negative result	Positive result	Date of test DD/MM/YYYY	Titration
HBa Ag	☐	☐	☐		
Anti-Hbs Ab	☐	☐	☐		
Anti-Hbc Ab	☐	☐	☐		
Anti-Hbc/IgM Ab	☐	☐	☐		
Anti-HAV/IgM Ab	☐	☐	☐		
Anti-HCV Ab	☐	☐	☐		
PCR-C	☐	☐	☐		
Anti-CMV IgM Ab	☐	☐	☐		
Anti-EBV Ab	☐	☐	☐		
Anti-nuclear Ab	☐	☐	☐		
Antinative DNA Ab	☐	☐	☐		
Anti smooth muscle Ab	☐	☐	☐		
Anti mitochondrial AB	☐	☐	☐		

OTHER INVESTIGATIONS

Date DD/MM/YYYY	NATURE	RESULTS
Click here to enter a date.		
Click here to enter a date.		
Click here to enter a date.		

LIVER BIOPSY NO ☐ **YES** ☐ **DATE DD/MM/YYYY**
if YES is ticked a report needs to be attached

LIVER IMAGING *if YES is ticked a report needs to be attached*	DATE DD/MM/YYYY	BRIEF RESULTS
ULTRASONOGRAPHY NO ☐ YES☐		
CT SCAN NO ☐ YES ☐		
MRI NO ☐ YES ☐		

I. CONCOMITANT OR PREVIOUS DRUGS POSSIBLY SUSPECTED OF INDUCING Liver Injury					
Name	**Indication**	**Daily Dose**	**Route**	**Start Date**	**End Date**
				Click here to enter a date.	Click here to enter a date.
				Click here to enter a date.	Click here to enter a date.

Laboratory Tests	Date DD/MM/YYYY	Baseline Values	Result	Normal High / Low

ANNEX 4.2 Specific adverse reaction follow-up questionnaire for pancreatic effects (Pancreatic disorder form)

Teriflunomide - Pancreatic Disorder
Information to be transmitted to Global Pharmacovigilance & Epidemiology Dpt

*** To be attached to the corresponding completed AE/SAE form**

PROJECT:

Protocol N° if clinical trial: _____

Date of this report: ……/……/……..…
day month year

Patient ID: _____

INVESTIGATOR/REPORTER NAME:
……

Phone number:……

GPE case ID (for Sanofi internal use):

_____

1. PATIENT INFORMATION

Initials	**Age**	**DOB**	**Gender:** ☐ Male ☐ Female
Known allergies			

2. DRUG BEING REPORTED

Name: _____

3. SYMPTOMS

Were any of the following symptoms associated with the event:

Symptoms		**Date of Onset**	**Description**	**Outcome**
Abdominal Pain	☐ Yes ☐ No			☐ Recovered ☐ Recovering ☐ Continuing ☐ Not Recovered ☐ Recovered with Sequelae ☐ Fatal
Malaise	☐ Yes ☐ No			☐ Recovered ☐ Recovering ☐ Continuing ☐ Not Recovered ☐ Recovered with Sequelae ☐ Fatal
Nausea	☐ Yes ☐ No			☐ Recovered ☐ Recovering ☐ Continuing ☐ Not Recovered ☐ Recovered with Sequelae ☐ Fatal
Vomiting	☐ Yes ☐ No			☐ Recovered ☐ Recovering ☐ Continuing ☐ Not Recovered ☐ Recovered with Sequelae ☐ Fatal

Jaundice	☐ Yes ☐ No			☐ Recovered ☐ Recovering ☐ Continuing ☐ Not Recovered ☐ Recovered with Sequelae ☐ Fatal
Fever	☐ Yes ☐ No			☐ Recovered ☐ Recovering ☐ Continuing ☐ Not Recovered ☐ Recovered with Sequelae ☐ Fatal
Weight Loss	☐ Yes ☐ No			☐ Recovered ☐ Recovering ☐ Continuing ☐ Not Recovered ☐ Recovered with Sequelae ☐ Fatal
Abdominal bleeding	☐ Yes ☐ No			☐ Recovered ☐ Recovering ☐ Continuing ☐ Not Recovered ☐ Recovered with Sequelae ☐ Fatal

4. Any known results of genetic tests indicating an increased risk for pancreatitis?

☐ Yes, please provide details below ☐ No

_____

_____

5. Any anatomic anomalies potentially associated with pancreatitis?

☐ Yes, please provide details below ☐ No

_____

_____

6. PAST MEDICAL HISTORY

Please indicate if the patient had or has one or more of the following conditions

Condition		**Date diagnosed**	**Treatment (if available)**
Pancreatitis	☐ Yes ☐ No		
Cholelithiasis/ choledocholithiasis	☐ Yes ☐ No		

Hepatitis	☐ Yes ☐ No		
Abdominal tumor	☐ Yes ☐ No		
Abdominal surgery	☐ Yes ☐ No		
Abdominal trauma	☐ Yes ☐ No		
Condition		**Date diagnosed**	**Treatment (if available)**
Hypertriglyceridemia	☐ Yes ☐ No		
Hyperparathysoidism	☐ Yes ☐ No		
Hypercalcemia	☐ Yes ☐ No		
Human immunodeficiency virus	☐ Yes ☐ No		
Post-ERCP	☐ Yes ☐ No		
Malignancy Specify:_____	☐ Yes ☐ No		
Other suspected disorders Specify:_____	☐ Yes ☐ No		

7. SOCIAL HISTORY

Alcohol Consumption: ☐Yes ☐ No (if Yes, Drinks/day) _____
Tobacco user: ☐ Yes ☐ No _____ pack years

8. MEDICATION HISTORY

8.1. Please indicate if the patient has taken one or more of the following medications

Medication		**Start Date**	**End Date**	**Dose**	**Frequency**	**Reason for Discontinuation**	**Investigator Causality**[1]
Leflunomide	☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐
Azathioprine	☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐
Valproic Acid	☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐
Estrogen	☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐
Corticosteroids Specify:_____	☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐
Statins: Specify:_____	☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐

[1]Physician's assessment of relatedness to Pancreatitis

9. INVESTIGATIONS

9.1. Laboratory Tests

Investigation		**Date**	**Baseline Values**	**Result**	**Normal High / Low**
Red blood cell count	☐ Yes ☐ No				

WBC count	☐ Yes ☐ No				
Blood urea nitrogen	☐ Yes ☐ No				
Blood glucose	☐ Yes ☐ No				
Amylase	☐ Yes ☐ No				
Lipase	☐ Yes ☐ No				
Gamma GT	☐ Yes ☐ No				
Investigation		**Date**	**Baseline Values**	**Result**	**Normal High / Low**
Tripsinogen Activation Peptide	☐ Yes ☐ No				
Alanine aminotransferase (ALT)	☐ Yes ☐ No				
Aspartate aminotransferase (AST)	☐ Yes ☐ No				
Alkaline phosphatase	☐ Yes ☐ No				
Bilirubin	☐ Yes ☐ No				
Calcium	☐ Yes ☐ No				
Other Investigation		**Date**	**Baseline Values**	**Result**	**Normal High / Low**

9.2. Imaging studies

Investigation		**Date**	**Results**
Abdominal ultrasound	☐ Yes ☐ No		
Contrast enhanced abdominal CT	☐ Yes ☐ No		
Magnetic resonance imaging (MRI)	☐ Yes ☐ No		
Endoscopic Retrograde Cholangiopancreatogram (ERCP)	☐ Yes ☐ No		
Magnetic Resonance Cholangiopancreatogram (MRCP)	☐ Yes ☐ No		

10. Action taken with Aubagio as result of the adverse events:

Drug Withdrawn ☐ **Dose Reduced ☐** **Dose not changed ☐**

Was Aubagio re-administration? ☐ Yes ☐ No

Did the patient experience any adverse event, upon re-administration of Aubagio?

_____

11. MANAGEMENT

11.1. Causal relationship

Is there a reasonable possibility that the pancreatic disorder is associated with the use of the drug being reported?

☐ Yes ☐ No ☐ Unable to assess

11.2. Has any treatment been given to the patient to treat pancreatitis? ☐ Yes ☐ No

Medication	Dose	Frequency	RoA	Start date	End date

12. ABREVIATIONS

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ERCP	Endoscopic retrograde cholangiopancreatogram
MRCP	Magnetic resonance cholangiopancreatogram
RoA	Route of administration

ANNEX 4.3 Specific adverse reaction follow-up questionnaire for teratogenicity (Pregnancy reporting form)

TERIFLUNOMIDE

Targeted Follow-up Form (coversheet)

Please provide the below requested information in the dedicated sections of the support used to provide the data (i.e., safety collection form or Sanofi Portal). Information that has already been provided at previous times of reporting, and has not changed in the meantime, does not need to be provided again but any additional information in any sections will be very helpful.

- **Medical History/Risk Factors:**

  MS History**:**

  - Date of diagnosis
  - Number of relapses (please also detail number of relapses during pregnancy when applicable)
  - Date of last relapse
  - Most recent EDSS score / EDSS score prior to and during pregnancy if applicable
  - Day to day activity prior to event with regards to mobility, sensory and motor disturbances, blurred vision, and self-grooming.

- **Description of the Reported Event(s)/Clinical Course:**

  Which documents are available:

  - Hospital notes
  - Death certificate
  - Investigation results
  - Other

Discharge summary should be attached if needed/applicable.

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PREGNANCY / DRUG EXPOSURE VIA PARENT DATA COLLECTION FORM

Grey fields are for Sanofi use only

Information that has already been provided at previous times of reporting, and has not changed in the meantime, does not need to be provided again but any additional information in any sections will be very helpful.

1- DATE REPORT RECEIVED

COMPANY RECEIVED DATE:	☐ Initial ☐ Follow-up	DATE FORM COMPLETED BY REPORTER:
CASE NUMBER	**PRODUCT RECEIVED / PRODUCT CODE**	**SANOFI / CRO CONTACT**
LOCAL ID: GLOBAL PV ID:		NAME: TELEPHONE:
SOURCE	**STUDY INFORMATION (IF APPLICABLE)**	**WHO RECEIVED MEDICATION?**
SPONTANEOUS / UNSOLICITED ☐ (includes pregnancy registry) STUDY / SOLICITED (includes PSP/MRP) ☐	STUDY ID / REGISTRY ID: CENTER ID: PATIENT ID: TREATMENT ID:	☐ MOTHER ☐ FATHER INITIALS: INITIALS: (FIRST, MIDDLE, LAST) (FIRST, MIDDLE, LAST) Initials not to be collected for case report from clinical studies

2- REPORTER INFORMATION

NAME (first/last):	STREET:	
OCCUPATION: ☐ CONSUMER ☐ STUDY INVESTIGATOR ☐ LAWYER ☐ MEDICAL DOCTOR ☐ PHARMACIST ☐ OTHER HCP (HEALTHCARE PROFESSIONAL) ☐ OTHER	CITY/STATE/PROVINCE:	
PHONE: **EMAIL ADDRESS**: **EMAIL ADDRESS FOR PATIENT** (IF PATIENT IS NOT THE REPORTER):	POSTAL CODE:	COUNTRY:
PEDIATRICIAN CONTACT INFORMATION Name (first/ last):	PHONE:	EMAIL ADDRESS:

DOES MOTHER AGREE TO PROVIDE INFORMATION? YES ☐ NO ☐

DOES FATHER AGREE TO PROVIDE INFORMATION? YES ☐ NO ☐

3 - PARENT INFORMATION AT THE TIME OF THE PREGNANCY

	AGE/BIRTHDATE For clinical study, Year of birth to be collected only	RH (RHESUS) FACTOR	Height (HT) /UNIT	Weight (WT) /UNIT Record Mother's weight pre-pregnancy and gain during pregnancy	PAST AND CURRENT SIGNIFICANT MEDICAL CONDITIONS
MOTHER				Pre-pregnancy weight: Weight gain during pregnancy:	SMOKING HISTORY:_____CIGARETTES PER DAY** ALCOHOL:_____DRINKS PER DAY ** SUBSTANCE ABUSE **(specify):_____ HYPERTENSION: ☐NO ☐YES ☐UNK DIABETES: ☐NO ☐YES ☐UNK EPILEPSY: ☐NO ☐ YES ☐UNK **IF YES**, SPECIFY THE TYPE: _____ PSYCHIATRIC ILLNESS: ☐NO ☐YES **IF YES**, SPECIFY: _____ HIV seropositivity: ☐NO ☐YES ☐UNK HEPATITIS infection: ☐NO ☐YES ☐UNK **IF YES**, SPECIFY THE TYPE:_____ OTHER HISTORY* (including thyroid disorders, asthma or other respiratory conditions, allergic disease, heart disease, autoimmune disease, renal disease, malignancy, depression, sexually transmitted disease, learning difficulties, congenital malformations, environmental exposures):
FATHER					SMOKING HISTORY:_____CIGARETTES PER DAY ALCOHOL:_____DRINKS PER DAY SUBSTANCE ABUSE (specify):_____ HYPERTENSION: ☐NO ☐YES ☐UNK DIABETES: ☐NO ☐YES ☐UNK EPILEPSY: ☐NO ☐YES ☐UNK PSYCHIATRIC ILLNESS: ☐NO ☐YES ☐UNK HIV seropositivity: ☐NO ☐YES ☐UNK HEPATITIS infection: ☐NO ☐YES ☐UNK **IF YES**, SPECIFY THE TYPE: _____

3 - PARENT INFORMATION AT THE TIME OF THE PREGNANCY

	OTHER HISTORY* (including thyroid disorders, asthma, allergic disease, heart disease, autoimmune disease, depression, sexually transmitteddisease, learning difficulties, congenital malformations, environmental exposures):

*Include information on race, ethnicity, consanguinity or occupation if you consider it would contribute significantly to the investigation and evaluation of certain adverse findings in the pregnancy or its outcome or on the health of the fetus/child, per local privacy law.

**Mention if mother quit smoking stopped drinking and using substances or materially reduced her usage before or during pregnancy and when.

4 – SPECIFIC TO THE PREGNANCY PREVENTION PROGRAMME, IF APPLICABLE (e.g., valproate…)

WAS THERE A NEGATIVE PREGNANCY TEST AT TREATMENT INITIATION?	☐ NO	☐ YES	☐ UNK	☐ NA*
WAS THE PATIENT GUIDE RECEIVED?	☐ NO	☐ YES	☐ UNK	☐ NA*
WAS THE PATIENT CARD RECEIVED?	☐ NO	☐ YES	☐ UNK	☐ NA*
WAS AN ANNUAL REVIEW COMPLETED BY A SPECIALIST?	☐ NO	☐ YES	☐ UNK	☐ NA*
WAS THE ANNUAL RISK ACKNOWLEDGMENT FORM SIGNED?	☐ NO	☐ YES	☐ UNK	☐ NA*

*Not applicable

5- IMMUNIZATION / GYNECOLOGY

MATERNAL IMMUNE STATUS				GYNECOLOGICAL DETAILS			
RUBELLA:	☐ NO	☐ YES	☐ UNK	WERE CONTRACEPTIVE METHODS USED:	☐ NO	☐ YES	☐ UNK
TOXOPLASMOSIS:	☐ NO	☐ YES	☐ UNK	IF YES, SPECIFY: CONTRACEPTION TYPE:	☐ ORAL	☐ LOCAL	☐ IUCD
CMV:	☐ NO	☐ YES	☐ UNK				

CONTRACEPTION NAME: _____

CONTRACEPTION DOSE: _____

CONTRACEPTION START AND STOP DATES: _____

DETAILS OF POSSIBLE CAUSE TO CONTRACEPTION FAILURE: _____

5- IMMUNIZATION / GYNECOLOGY

NON-COMPLIANCE WITH PRIMARY METHOD (E.G HORMONAL/IUD): ☐ NO ☐ YES ☐ UNK
NON-COMPLIANCE WITH BARRIER METHOD: ☐ NO ☐ YES ☐ UNK
OTHER (EG., DRUG-DRUG INTERACTION, EPISODE OF GI DISORDER, …) ☐ NO ☐ YES ☐ UNK

RELEVANT GYNECOLOGIC HISTORY:

ABNORMAL MENSTRUAL CYCLES	☐ NO	☐ YES	☐ UNK	if YES, specify:
INFERTILITY	☐ NO	☐ YES	☐ UNK	if YES, specify:
HISTORY OF GYNECOLOGIC SURGERY	☐ NO	☐ YES	☐ UNK	if YES, specify:
SEQUELAE OF INFECTIONS	☐ NO	☐ YES	☐ UNK	if YES, specify:

6- PREGNANCY INFORMATION

DATE OF LAST MENSTRUAL PERIOD (LMP)
LMP _____ - _____ - _____ (DD-MMM-YY)

ESTIMATED DATE OF DELIVERY (EDD)
EDD _____ - _____ - _____ (DD-MMM-YY)

DATE OF POSITIVE PREGNANCY TEST (IF ANY)
_____ -_____-_____ (DD-MMM-YY)

DATE OF PREVIOUS NEGATIVE PREGNANCY TEST (IF ANY)
_____ -_____-_____ (DD-MMM-YY)

MEDICAL ASSISTANCE / HOSPITALIZATION DURING PREGNANCY?
☐ NO ☐ YES
DETAILS: _____

MULTIPLE FETUSES/CHILDREN? ☐ NO ☐ YES

IS THE OUTCOME OF CURRENT PREGNANCY KNOWN AT THE TIME OF THIS REPORT? ☐ NO ☐ YES

OBSTETRICAL HISTORY	NUMBER/ YEAR/ COMMENTS, INCLUDING ANY COMPLICATIONS
NUMBER OF PREVIOUS PREGNANCIES (including below obstetrical histories)	
LIVE BIRTHS, WITHOUT CONGENITAL ANOMALIES/ MALFORMATIONS/ NEURODEVELOPMENTAL DISORDERS/ AUTISM SPECTRUM DISORDERS (ASD)	
LIVE BIRTHS, WITH CONGENITAL ANOMALIES/ MALFORMATIONS/ NEURODEVELOPMENTAL DISORDERS/ AUTISM SPECTRUM DISORDERS (specify type of congenital anomalies/ developmental disorders/ ASD):	

6- PREGNANCY INFORMATION

ECTOPIC PREGNANCY	
SPONTANEOUS ABORTIONS PRIOR TO 20 WEEKS GESTATION (specify gestational age and identified cause, if any):	
ELECTIVE TERMINATION (FETAL DEFECTS) (specify gestational age and identified defects):	
ELECTIVE TERMINATION (NO FETAL DEFECTS OR UNKNOWN) (specify gestational age):	
FETAL DEATHS (>20 WEEKS GESTATION) (specify gestational age, cause(s)/ Post-Mortem findings):	

MATERNAL/PATERNAL/RELATIVES (including grandparents) **HISTORY**:

CONGENITAL MALFORMATION ☐NO ☐YES, SPECIFY RELATION/DETAILS: _____
CHILDREN DYING YOUNG ☐NO ☐YES, SPECIFY RELATION/DETAILS: _____
CHROMOSOMAL ABNORMALITY ☐NO ☐YES, SPECIFY RELATION/DETAILS: _____
DEVELOPMENTAL DELAY ☐NO ☐YES, SPECIFY RELATION/DETAILS: _____
HEREDITARY DISEASE ☐NO ☐YES, SPECIFY RELATION/DETAILS: _____
PERTINENT GYNECOLOGIC INFORMATION ☐NO ☐YES, SPECIFY RELATION / DETAILS: _____
CONSANGUINITY BETWEEN PARENTS ☐NO ☐YES, SPECIFY RELATION / DETAILS: _____
OTHER ☐NO ☐YES, SPECIFY: _____

7- ADVERSE EVENT (OTHER THAN ABNORMAL PREGNANCY OUTCOMES) INVOLVED DURING THE PREGNANCY?

☐NO ☐YES (please complete corresponding AE form(s))

THE AE OCCURRED IN THE ☐MOTHER ☐CHILD	GLOBAL PV DATABASE NUMBER FOR CHILD REPORT #

DESCRIBE ADVERSE EVENT(S) HERE AND INCLUDE CORRECTIVE TREATMENS IN SECTION 8:

8- MEDICATIONS: (include prescription & OTC medicines and pregnancy/food supplements e.g., folic acid and other vitamins, iron)

PRODUCTS* (LIST SANOFI-DRUG(S) FIRST)	CAUSAL RELATIONSHIP (YES / NO)	FETAL / NEONATAL EXPOSURE **	INDICATION	DOSE/ SCHEDULE / DOSE NUMBER	ROUTE	START DATE+ (DD-MMM-YY)	STOP DATE+ (DD-MMM-YY)	DURATION (DAYS)	BATCH NUMBER (mandatory) NA- if not available NO- if not obtainable at all	SITE OF ADMIN	SIDE OF ADMIN

*If any medications were possibly involved in the occurrence of the reported disorder; specify action taken & outcome

**Fetal exposure: select all the applicable numbers that apply for fetal exposure

1: PRIOR TO OR AT TIME OF CONCEPTION; **2**: DURING PREGNANCY; **3**: LABOR AND DELIVERY; **4**: BREAST FEEDING

+Stop and start dates: if exact dates are unavailable, provide gestation weeks of exposure or trimesters of exposure.

9- ADDITIONAL MEDICAL DATA

COMMENTS REGARDING MATERNAL HEALTH OR COMPLICATIONS DURING PREGNANCY: (E.G. EVIDENCE OF GESTATIONAL DIABETES, INFECTIONS, PREECLAMPSIA, DEPRESSION/ANXIETY)

10- PRENATAL TESTING

Specify below or check if none ☐

EXAMINATION	DATE (DD-MMM-YY)	NORMAL ✓	ABNORMAL ✓	SPECIFY ABNORMALITIES
AMNIOCENTESIS				
ALPHA FETAL PROTEIN (**AND OTHER SERUM MARKERS**)				
CHORIONIC VILLI SAMPLING				
FETAL NONSTRESS TEST				
UTERINE ULTRASOUND **(PLEASE DESCRIBE)**				
GENETIC SCREENING (**SPECIFY**:_____)				
OTHER (**SPECIFY**:_____)				

11- PREGNANCY OUTCOME

 # CHILDREN / FETUSES: ☐ **SINGLE** ☐ **MULTI (#____)**

CHILD/ FETUS	SEX	DATE OF DELIVERY, ABORTION, TERMINATION ORFETAL DEATH (DD-MMM-YY)	APGAR SCORE			DELIVERY MODE (✓)		WEEK OF GESTATION (WEEKS OF AMENORRHEA)	BIRTH WEIGHT & LENGTH	HEAD CIRCUM (cms)	OUTCOME**	CONGENITALANOMALY*** (malformations, genetic disorders, development disorder)		NEONATE DEATH (Age at death, specify cause)
			1 MIN	5 MIN	10 MIN (IF <7 AT 5 MIN)	VAG	C-SECT *					YES (specify)	NO	
						☐	☐		g cm					
						☐	☐		g cm					

11- PREGNANCY OUTCOME

* C-SECTION: IF YES, PLEASE PROVIDE REASON:

** OUTCOME: ENTER THE NUMBER APPROPRIATE TO THE PREGNANCY OUTCOME (ENTER ALL THAT APPLY)

1. LIVE BIRTH
2. SPONTANEOUS ABORTION (<20 WEEKS GESTATION)
3. ELECTIVE TERMINATION
4. ECTOPIC PREGNANCY
5. EARLY FETAL DEATH (20-27 WEEKS GESTATION)
6. LATE FETAL DEATH (AT LEAST 28 WEEKS GESTATION)
7. STILLBIRTH
8. MATERNAL DEATH (IF RESULTING IN FETAL DEATH, ADD APPROPRIATE NUMBER)

***ANY CONGENITAL ANOMALY OR DEVELOPMENTAL DISORDERS **IDENTIFIED AT BIRTH, SPECIFY HERE.**

Congenital anomaly identified at birth ☐ YES, SPECIFY HERE ☐ NO

IN CASE OF ANY CONGENITAL ANOMALY, OR DEVELOPMENTAL DISORDERS/AUTISM SPECTRUM DISORDERS **NOT IDENTIFIED AT BIRTH**

SPECIFY IN SECTION 12.

IN CASE OF ABORTION, STILL BIRTHS, FETAL DEATH OR MATERNAL DEATH, WAS AN AUTOPSY PERFORMED? ☐ NO ☐ YES ☐ UNK

IF YES, PROVIDE RESULTS FOR EACH WHERE APPLICABLE:

LABOR/DELIVERY:

ANY COMPLICATIONS OF LABOR AND/OR DELIVERY ☐ NO ☐ YES, SPECIFY:

MEDICATION DURING LABOR ☐ NO ☐ YES (if yes, complete in section 8)

CLEAR AMNIOTIC FLUID ☐ NO ☐ YES

NORMAL PLACENTA ☐ NO ☐ YES

ABNORMALITY OF UMBILICAL CORD VESSEL AND GASES ☐ NO ☐ YES, SPECIFY for each child/fetus:

Umbilical artery
pH:
PCO2:
PO2:

11- PREGNANCY OUTCOME

ADDITIONAL INFORMATION ABOUT THE NEWBORN CONDITION:

BREAST FEEDING ☐ NO ☐ YES IF YES, SPECIFY DURATION AND CAPTURE MATERNAL MEDICATIONS IN SECTION 8

NEONATAL ILLNESS ☐ NO ☐ YES, SPECIFY:

NEED FOR RESUSCITATION ☐ NO ☐ YES INTRAUTERINE GROWTH RESTRICTION OR IMMATURITY ☐ NO ☐ YES, SPECIFY:

HOSPITALIZATION ☐ NO ☐ YES

MEDICATIONS ☐ NO ☐ YES, SPECIFY:

CORRECTIVE TREATMENT RECEIVED BY NEWBORN ☐ NO ☐ YES, SPECIFY:

INTENSIVE CARE ☐ NO ☐ YES

TRANSFERRED TO INTENSIVE CARE UNIT OR PEDIATRIC DEPARTMENT ☐ NO ☐ YES DURATION:

ADDRESS OF DEPARTMENT

INFANT TO BE FOLLOWED UP BY (DOCTOR'S NAME AND ADDRESS)

12- PEDIATRIC ASSESSMENT

CHILD #	CHILD AGE AT THE TIME OF ASSESSMENT (with unit)	MOTOR DEVELOPMENT		NEUROLOGICAL AND BEHAVIOURAL DEVELOPMENT		GROWTH WEIGHT & LENGTH*	CONGENITALANOMALY NOT YET IDENTIFIED AT BIRTH		SPECIFY ABNORMALITIES*
		NORMAL	DELAYED	NORMAL	DELAYED		YES	NO	
						g cm			
						g cm			
						g cm			

*SPECIFY **MEDICAL EVENTS THAT LED TO MEDICAL OFFICE/ER VISIT OR HOSPITALIZATION** OR CONGENITAL ANOMALY **NOT IDENTIFIED AT BIRTH** OR DEVELOPMENTAL DISORDERS/AUTISM SPECTRUM DISORDERS

PRINTED NAME: **EMAIL ADDRESS**:

OCCUPATION:

SIGNATURE: _____ **DATE:**

ANNEX 4.4 Specific adverse reaction follow-up questionnaire for serious opportunistic infections, including progressive multifocal leukoencephalopathy (PML) (Progressive multifocal leukoencephalopathy form)

Teriflunomide - Progressive Multifocal Leukoencephalopathy (PML) check list*
Information to be transmitted to Global Pharmacovigilance & Epidemiology Dept.

***** To be attached to the corresponding completed AE/SAE Form**

PROJECT:

Protocol N° if clinical trial: _____

Date of this report: ……/……/……..…
Day month year

Patient ID: _____

INVESTIGATOR/REPORTER NAME:
……

Phone number: ……

GPE case ID (for Sanofi internal use):
_____

1. PATIENT INFORMATION

Initials	**Age**	**DOB**	**Gender:** ☐ Male ☐ Female

2. DRUG BEING REPORTED

Name: _____

3. PML-RELATED QUESTIONS

3.1. PML Diagnosis

3.1.1. Please indicate whether the diagnosis of PML is
☐ Suspected ☐ Confirmed ☐ Indeterminate

If indeterminate, what is the differential diagnosis?

_____

_____

3.1.2. Please indicate basis for diagnosis (check all that apply)
☐ Brain biopsy ☐ CSF PCR ☐ MRI

3.2. Causal relationship

Is there a reasonable possibility that PML diagnosis is associated with the use of the drug being reported?
☐ Yes ☐ No ☐ Unable to assess

3.3. Clinical symptoms

Symptoms		**Date of onset**
Recent changes in personality or mood	☐ Yes ☐ No	
Recent or sudden change in cognitive behaviour Example: confusion, disorientation	☐ Yes ☐ No	
Language or speech disturbances Example: aphasia or dysarthria	☐ Yes ☐ No	
Visual disturbances	☐ Yes ☐ No	
Ataxia/loss of motor coordination/progressive weakness	☐ Yes ☐ No	
New onset of seizures	☐ Yes ☐ No	
Other– if yes, please specify	☐ Yes ☐ No	

3.4. EDSS score

	Date	**Score**
Prior to the onset of symptoms		
After the onset of symptoms		

3.5. Laboratory and JCV information

Test*		Date	Results
JCV DNA Detection by PCR ☐ Yes ☐ No Laboratory used for detection (please provide name and location)	☐ CSF ☐ Plasma		
Brain biopsy ☐ Yes ☐ No Hospital facility (please provide name and location)			
CD4 count ☐ Yes ☐ No			
CD8 count ☐ Yes ☐ No			

*Please provide copies of test results

3.6. Other Investigation

Other Investigation	Date	Baseline Values	Result	Normal High / Low

3.7. Imaging information

	Date	Results
Was Brain MRI performed prior to the start of symptoms? ☐ Yes ☐ No		
Was Brain MRI performed for PML diagnosis? ☐ Yes ☐ No		
Was Brain CT performed prior to the start of symptoms? ☐ Yes ☐ No		
Was Brain CT performed for PML diagnosis? ☐ Yes ☐ No		

3.8. PML treatment

Has any treatment been given to the patient to treat PML? ☐ Yes ☐ No

Medication	Dose	Frequency	Route	Start date	End date

4. MEDICAL HISTORY

4.1. Please indicate if the patient had or has one or more of the following conditions

Relevant medical information		Date	Treatment (if available)
HIV or AIDS	☐ Yes ☐ No		
Leukemia/Lymphoma Other Malignancies	☐ Yes ☐ No ☐ Yes ☐ No		

Please specify:_____			
Opportunistic infection(s) (e.g CMV) Specify:_____	☐ Yes ☐ No		
Tuberculosis	☐ Yes ☐ No		
Organ transplant Please specify:_____	☐ Yes ☐ No		
Other autoimmune disease (e.g. SLE, Sjogren's, Behcet's, RA, psoriasis….) Please specify: _____	☐ Yes ☐ No		

4.2. Please indicate if the patient had prior JCV testing

Relevant investigations			**Date**	**Results**
JCV DNA testing before current illness (please provide the name of laboratory where the test was performed)	☐ Yes ☐ No	☐ CSF		
		☐ Plasma		
JCV Serology	☐ Yes ☐ No			

5. DRUG HISTORY

5.1. Please indicate any treatment the patient received/receiving for multiple sclerosis

Medication	**Date of 1st Course**	**Date of Last Course**	**No. of Courses**	**Dose/ Route**	**Reason for Discontinuation**	**Reporter Causality**[1]
Lemtrada™ (alemtuzumab) (if not the drug being reported) ☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐

Medication	**Start Date**	**End Date**	**Dose/ Route**	**Frequency**	**Reason for Discontinuation**	**Reporter Causality**[1]
Aubagio® (teriflunomide) (if not the drug being reported) ☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐
Tysabri® (natalizumab) ☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐
Gilenya® (fingolimod) ☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐
Tecfidera® (dimethyl fumarate) ☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐
Interferon beta (any product) ☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐
Copaxone® (glatiramer acetate) ☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐
Novantrone®, Elsep® (mitoxantrone) ☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐
Corticosteroids (most recent course) ☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐

Other MS Therapies ☐ Yes ☐ No Specify: _____							Related ☐ Unrelated ☐ Unknown ☐
Other MS Therapies ☐ Yes ☐ No Specify: _____							Related ☐ Unrelated ☐ Unknown ☐
Other MS Therapies ☐ Yes ☐ No Specify: _____							Related ☐ Unrelated ☐ Unknown ☐
Other MS Therapies ☐ Yes ☐ No Specify: _____							Related ☐ Unrelated ☐ Unknown ☐

[1]Physician's assessment of relatedness to PML

5.2. Please indicate if the patient has taken one or more of the following medications

Medication	**Start Date**	**End Date**	**Dose**	**Frequency**	**Reason for Discontinuation**	**Reporter Causality**[1]
Rituxan®, Mabthera® (rituximab) ☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐
Raptiva® (efalizumab) ☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐
Arava® (leflunomide) ☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐
Methotrexate ☐ Yes ☐ No						Related ☐ Unrelated ☐ Unknown ☐
Other immunosuppressive or chemotherapeutic agents (e.g., cyclophosphamide, tacrolimus, azathioprine, mycophenolate, cyclosporine) ☐ Yes ☐ No Please specify:						Related ☐ Unrelated ☐ Unknown ☐

[1]Physician's assessment of relatedness to PML

Abbreviations

AIDS	Acquired immunodeficiency syndrome
CMV	Cytomegalovirus
CT	Computed tomography
DNA	Deoxyribonucleic acid
EDSS	Expanded disability status scale
HIV	Human immunodeficiency virus
JCV	John Cunningham Virus
MRI	Magnetic resonance imaging
PCR	Polymerase chain reaction

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Proposed key messages of the additional risk minimization measures

1. **<u>Physician educational material:</u>**

- The Summary of Product Characteristics
- Healthcare professional (HCP) education/discussion guide

1.1 Healthcare professional education/discussion guide:

The educational material for HCP includes the following key elements:

- Healthcare professionals should discuss with their patients the specific safety concerns of AUBAGIO® detailed below including the tests and precautions needed for safe use, at first prescription, and regularly during treatment as follows:
  - Risk of hepatic effects:
    - Liver function tests are needed prior to the start of treatment and periodically during treatment.
    - To educate the patient about the signs and symptoms of liver disease and the need to report to their HCP if they experience any of them.
  - Potential risk of teratogenicity:
    - To remind women of child-bearing potential (WOCP) including adolescents/their parents-caregivers that AUBAGIO is contraindicated in pregnant women and in WOCP not using an effective contraception during and after treatment.
    - To assess regularly the potential for pregnancy in female patients including patients below 18 years old.
    - To tell female children and/or parents/caregivers of female children about the need to contact the prescribing physician once the female child under AUBAGIO treatment experiences menses. Counselling should be provided to the new patients of child-bearing potential about contraception and the potential risk to the fetus.
    - To check pregnancy status before starting treatment.
    - To educate female patients of child-bearing potential on the need for effective contraception during and after treatment with AUBAGIO.
    - To remind patients to inform their doctor immediately if they stop contraception, or prior to changing contraceptive measures.
    - If female patients become pregnant despite using contraceptive measures, they should stop AUBAGIO and contact their doctor immediately who should:
      - ~ Consider and discuss with the patient the accelerated elimination procedure,
      - ~ Report any pregnancy case to <marketing authorization holder> by calling <local number> or visiting <URL>, irrespective of adverse outcome observed.

    - Contact <marketing authorization holder> for information regarding the measurement of teriflunomide plasma concentration.
  - Risk of hypertension:
    - To check for a history of hypertension, and that blood pressure should be appropriately managed during treatment.
    - The need for blood pressure checks before treatment and periodically during treatment.
  - Risk of hematologic effects:
    - To discuss the risk of decreased blood cell counts (affecting mainly white blood cells) and the need for complete blood cell counts before treatment and periodically during treatment based on signs and symptoms.
  - Risk of infections/serious infections:
    - To discuss the need to contact the doctor in the event of signs/symptoms of infection, or if the patient takes other medicines that affect the immune system. If serious infection occurs, consider the accelerated elimination procedure.
- A reminder to provide patients/legal representative with a Patient Education Card, including filling-in their contact details, and to provide replacement Patient Education Cards as necessary.
- A reminder to discuss the content of the patient card with the patient/legal representative regularly at each consultation at least annually during treatment.
- To encourage patients to contact their multiple sclerosis (MS) physician and/or General Practitioner if they experience any of the signs and symptoms discussed in the Patient Education Card.
- Information on the optional service of a periodic reminder to patients on the MS One to One website about the continued need for effective contraception during treatment.
- At prescription renewal, adverse events are checked, ongoing risks and their prevention are discussed, and checks are made to ensure adequate monitoring is taking place.

2. <u>The patient information pack:</u>

- Patient Information Leaflet (PIL)
- Patient Education Card

2.1 Patient education card:

The educational card for the patients is aligned with labeling information and includes the following key elements:

- A reminder for both patients and all HCPs involved in their treatment that the patient is being treated with AUBAGIO, a drug which:
  - Should not be used in pregnant women.

  - Requires concomitant use of effective contraception in WOCP.
  - Requires a pregnancy status check before treatment.
  - Affects liver function.
  - Affects blood cell counts and the immune system.
- Information to educate the patient about important side effects and to pay attention to certain signs and symptoms which might indicate liver disease or infection, and if any of these occur, to contact their doctor/HCP promptly.
- To remind female patients to tell their doctor if breastfeeding.
- A reminder for WOCP including girls and their parents/caregivers:
  - To use an effective contraception during and after treatment with AUBAGIO.
  - That your doctor will provide counselling on the potential risks to the fetus and on the need for effective contraception.
  - To stop treatment with teriflunomide immediately if they suspect they might be pregnant and also to contact their doctor immediately.
- A reminder for parents / caregivers or girls
  - To contact your doctor when the girl experience menses for the first time in order to get counselling about the potential risk to the fetus and the need for contraception.
- If WOCP become pregnant:
  - To remind both patients and HCPs about the accelerated elimination procedure.
- To remind patients to show the Patient Education Card to Doctors/HCPs involved with their medical care (especially in the event of medical emergencies and/or if new Doctors/HCPs are involved).
- To record the first date of prescription and the contact details of their prescriber.
- To encourage the patients to read the PIL thoroughly.