



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 April 2021
EMA/CHMP/289596/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

AUBAGIO

International non-proprietary name: teriflunomide

Procedure No. EMEA/H/C/002514/X/0031/G

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



Table of contents

List of abbreviations	4
1. Background information on the procedure	6
1.1. Submission of the dossier	6
1.2. Steps taken for the assessment of the product	7
2. Scientific discussion	8
2.1. Problem statement	8
2.1.1. Disease or condition	8
2.1.2. Epidemiology	8
2.1.3. Aetiology and pathogenesis	8
2.1.4. Clinical presentation, diagnosis	9
2.1.5. Management	9
2.2. Quality aspects	11
2.2.1. Introduction	11
2.2.2. Active Substance	12
2.2.3. Finished Medicinal Product	12
2.2.4. Discussion on chemical, pharmaceutical and biological aspects	14
2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects	14
2.2.6. Recommendations for future quality development	14
2.3. Non-clinical aspects	14
2.3.1. Pharmacology	14
2.3.2. Pharmacokinetics	14
2.3.3. Toxicology	14
2.3.4. Ecotoxicity/environmental risk assessment	14
2.3.5. Discussion on non-clinical aspects	15
2.3.6. Conclusion on the non-clinical aspects	15
2.4. Clinical aspects	15
2.4.1. Introduction	15
2.4.2. Pharmacokinetics	17
2.4.3. Pharmacodynamics	18
2.4.4. Discussion on clinical pharmacology	18
2.4.5. Conclusions on clinical pharmacology	19
2.5. Clinical efficacy	19
2.5.1. Dose response study	19
2.5.2. Main study	19
2.5.3. Discussion on clinical efficacy	51
2.5.4. Conclusions on the clinical efficacy	58
2.6. Clinical safety	59
2.6.1. Discussion on clinical safety	75
2.6.2. Conclusions on the clinical safety	83
2.7. Risk Management Plan	83
2.8. Pharmacovigilance	91
2.9. Product information	91
2.9.1. User consultation	91

2.9.2. Quick Response (QR) code.....	91
3. Benefit-Risk Balance.....	92
3.1. Therapeutic Context	92
3.1.1. Disease or condition.....	92
3.1.2. Available therapies and unmet medical need	92
3.1.3. Main clinical studies	92
3.2. Favourable effects.....	93
3.3. Uncertainties and limitations about favourable effects	94
3.4. Unfavourable effects.....	95
3.5. Uncertainties and limitations about unfavourable effects	97
3.6. Effects Table	99
3.7. Benefit-risk assessment and discussion	102
3.7.1. Importance of favourable and unfavourable effects	102
3.7.2. Balance of benefits and risks.....	105
3.7.3. Additional considerations on the benefit-risk balance	106
3.8. Conclusions.....	106
4. Recommendations	106

List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ADEM	Acute Disseminated Encephalomyelitis
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
ARR	Annualized Relapse Rate
AST	Aspartate Aminotransferase
PBT	Persistent, Bioaccumulative and Toxic
BMI	Body Mass Index
BW	Body Weight
CDP-6M	6-Month Confirmed Disability Progression
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIS	Clinically Isolated Syndrome
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
CPK	Creatine Phosphokinase
CQA	Critical Quality Attribute
CSF	Cerebrospinal Fluid
DB	Double-Blind
DBP	Diastolic Blood Pressure
DHO-DH	Dihydroorotate Dehydrogenase
DILI	Drug-Induced Liver Injury
DMT	Disease-Modifying therapy
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EOT	End Of Treatment
EU	European Union
FDA	Food and Drug Administration
FSS	Functional System Scores
GCP	Good Clinical Practices
Gd	Gadolinium
GGT	Gamma-Glutamyl Transpeptidase
HPLC	High performance liquid chromatography
HR	Hazard Ratio
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFN- β	Interferon Beta
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
IPC	In-process control
IPMSSG	International Paediatric Multiple Sclerosis Study Group
ITT	Intent-To-Treat
IWRS	Interactive Web Response System
IVRS	Interactive Voice Response System
KF	Karl Fischer Titration
KM	Kaplan-Meier
LOCF	Last Observation Carried Forward
LS	Least Square
MA	Marketing Authorisation
MAR	Missing-at-Random Assumption

MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect Model with Repeated Measures
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NAWM	Normal Appearing White Matter
NB	Negative Binomial
OL	Open-Label
PASS	Post-Authorization Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PBT	Persistent, Bioaccumulative and Toxic
PCSA	Potentially Clinically Significant Abnormality
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PML	Progressive Multifocal Leukoencephalopathy
PND	Postnatal Day
PopPK	Population Pharmacokinetic
PP	Per Protocol
PSUR	Periodic Safety Update Report
PT	Preferred Term
PYE	Patient-Years of Exposure
RAP	Relapse Adjudication Panel
RMM	Risk minimisation measures
RMP	Risk minimisation plan
RMS	Relapsing Multiple Sclerosis
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SE	Standard Error
SMQ	Standardised MedDRA Queries
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPMS	Secondary Progressive Multiple Sclerosis
TEAE	Treatment-Emergent Adverse Event
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
US	United States
USP	United States Pharmacopoeia
USP/NV	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
WBC	White Blood Cell
WKS	weeks

1. Background information on the procedure

1.1. Submission of the dossier

Sanofi-Aventis groupe submitted on 28 April 2020 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation:

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of a marketing authorisation for Aubagio to add a new strength, 7 mg film-coated tablet, for use in paediatric patients from 10 years of age and older with relapsing remitting multiple sclerosis (MS). Extension of indication to include treatment of paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS) for Aubagio. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance.

The MAH is requesting an extension of the market protection of one additional year in line with the guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period.

Version 6.0 of the RMP has also been submitted.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (c) - Extensions of marketing authorisations

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0165/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0165/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Additional Data exclusivity/Marketing protection

The MAH requested consideration of one-year marketing protection in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) 726/2004.

Scientific advice

The Applicant received the following Scientific Advice (SA) on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
26 May 2016	EMA/H/SA/514/2/2016/PED/II	Fernando de Andrés Trelles Mario Miguel Rosa

EMA/H/SA/514/2/2016/PED/II seek advice regarding data to be submitted in support of a request to extend the current indication by adding treatment of paediatric patients. Further the Applicant asked for clarification how an additional year of market protection could be justified provided that an indication for the paediatric population was to be granted and considered a "new indication". A new indication would normally include an extended target population for the same disease, e.g. based on a different age range. As such, based on a positive benefit-risk balance, granting of an indication in 10-17 Years old RRMS patients would likely be regarded as a new indication. In order to benefit from an extended (11-year) marketing protection period a significant clinical benefit in comparison with existing therapies of a new therapeutic indication is needed. However, whether this is considered to be fulfilled can only be assessed at the time of submission, depending on the existence or non-existence of other approved products.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: N/A

The application was received by the EMA on	28 April 2020
The procedure started on	21 May 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	10 August 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	18 August 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	03 September 2020
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	17 September 2020
The MAH submitted the responses to the CHMP consolidated List of Questions on	19 December 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	26 January 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 February 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	25 February 2021

The MAH submitted the responses to the CHMP List of Outstanding Issues on	22 March 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	07 April 2021
The PRAC agreed on the PRAC Responses Assessment during the meeting on	9 April 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Aubagio on	22 April 2021
The CHMP adopted a report on the significant clinical benefit for Aubagio in comparison with existing therapies. (see Appendix 1)	22 April 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Paediatric MS is a severe chronic, immune-mediated neurodegenerative disorder of the central nervous system (CNS), characterized by inflammation, demyelination, and axonal/neuronal destruction, with marked impact on patients' life and development, and leading to disability early in life. Although MS is predominantly a disease of young adults, approximately 3% to 5% of people with MS have their first symptoms in childhood. Genetic, serum, Cerebrospinal fluid (CSF), and cell-based studies largely support a shared biology between paediatric-onset and adult-onset disease. Relapses are more frequent in patients with paediatric-onset compared with adult-onset MS. Cognitive impairment in paediatric patients with multiple sclerosis and magnetic resonance imaging (MRI) evidence of global and focal loss of age-expected brain volume have been described.

2.1.2. Epidemiology

Approximately 3-5% of all patients with MS experience their first attack before the age of 18 years (Belman et al. 2016). MS onset before 10 years of age is rare with less than 1% of MS patients experiencing their first attack before the age of 10. Hence, the overall prevalence estimates for paediatric MS are low, ranging from 0.07 to 2.9 per 100,000 (Gadoth 2003, Pohl et al. 2007, Renoux et al. 2007, Chitnis et al. 2009, Waldman et al. 2016).

2.1.3. Aetiology and pathogenesis

While the exact aetiology of MS remains unknown, it is generally assumed that MS is mediated by an immune-mediated inflammatory process that is triggered by environmental factors and superimposed on a genetic predisposition. The major contributors to this process are macrophages and microglia from the innate immune system, and T and B lymphocytes from the adaptive immune system. From the peripheral immune system, autoreactive T-helper cells are primed and stimulated to infiltrate the CNS where they target myelin antigens. Inflammation of the white and grey matter tissues in the CNS due to focal immune cell infiltration and release of cytokines are the incipient cause of tissue damage in MS not

only to the myelin sheath but also to the underlying axons. This process happens over time and results in repeated attacks. Demyelination and axonal damage impairs or interrupts nerve transmission, giving rise to clinical signs and symptoms. B and T cells, monocytes, natural killer cells and dendritic cells are all involved in any stage of MS. Neuropathology studies have found that the patterns of focal inflammation are very similar between relapsing and progressive MS.

2.1.4. Clinical presentation, diagnosis

As in adults, a diagnosis of MS in paediatric patients is made based on clinical and MRI features. According to the consensus definition proposed by the International Paediatric Multiple Sclerosis Study Group (IPMSSG), a diagnosis of MS in paediatric patients requires multiple episodes of CNS demyelination separated in time and space (Krupp et al 2013). Symptomatic overlap with Acute disseminated encephalomyelitis (ADEM) and the increased chance of leukodystrophies and metabolic disorders, complicates the differential diagnosis of paediatric-onset MS relative to adult onset MS (Venkateswaran and Banwell 2010, Krupp et al. 2013).

The initial course of MS is more often relapsing (-remitting) in paediatric onset MS (>98%) than in adult onset (approximately 85%) (Waldman et al. 2016). The relapse rate in paediatric MS is reported to be 2-3 times higher than in adult onset MS (Weinshenker et al. 1989a, Weinshenker et al. 1989b, Trojano et al. 2002, Yeh et al. 2009, Benson et al. 2014, Waldman et al. 2016). Although MRI features in paediatric MS are less well described, available data show that the underlying pathology is similar to adult relapsing MS (RMS). Children, however, tend to have a higher number of T2 lesions at the time of first event than adults (Waubant et al. 2009) and a lower propensity for lesions to enhance with gadolinium (Gd) (Banwell et al. 2007). A consistent finding in most of the paediatric cohort studies is lower disability scores in paediatric MS compared to adult MS, even when disease duration is taken into account. In the paediatric cohort described by (Renoux et al. 2007), the estimated median times from onset to the assignment of disability status scale scores of 4, 6 and 7 were 20 years, 29 years and 37 years, respectively. Compared to the adult-onset population, the time to expanded disability status scale (EDSS) scores of 4, 6 and 7 were approximately 10 years longer for patients with childhood onset MS. Similarly, and in line with this slower progression of disability, the conversion to secondary progressive MS (SPMS) took approximately 10 years longer in paediatric MS than in adult patients, occurring at a median of 28.1 years after the first attack of paediatric MS compared to 18.8 years for adult-onset patients. The median age of the person at SPMS onset was 41 years in paediatric patients with MS vs. 52 years in adult MS (~10 years earlier in paediatric patients vs adult MS).

Paediatric MS accounts for approximately 3% to 5% of MS cases¹⁻⁸ and the incidence increases with age (the majority of cases occur at or after the age of 10 years). The high number of relapses in the first years of the disease and the high frequency of paediatric patients with the relapsing-remitting MS (RRMS) course suggest that the inflammatory process is more pronounced in children with MS compared to adults⁹⁻¹¹.

In paediatric patients with MS, current consensus is to initiate pharmacological treatment shortly after diagnosis, even though the efficacy and safety of most therapies available for adults have not been formally demonstrated in children¹²⁻¹³.

2.1.5. Management

As of the date of this document, only fingolimod has been explicitly approved in the EU for use in children aged 10 years and older with highly active RRMS.

Conventional first-line therapies for the treatment of RRMS include interferon-beta (two interferon-beta 1a and one interferon-beta 1b) and glatiramer acetate, which are self-injectable disease-modifying therapies (DMTs). These are commonly used to treat paediatric MS as their indications (section 4.1 of the Summary of Product Characteristics [SmPC]) do not have an age limit and therefore formally include children. No controlled paediatric trials have been performed with interferons and glatiramer acetate and safety and efficacy solely rely on small retrospective observational studies.¹⁴⁻¹⁶

¹ Ghezzi A, Deplano V, Faroni J, et al. Multiple sclerosis in childhood: clinical features of 149 cases. *Mult Scler.* 1997;3(1):43-6.

² Boiko A, Vorobeychik G, Paty D, et al. Early onset multiple sclerosis: a longitudinal study. *Neurology.* 2002;59(7):1006-10.

³ Chitnis T, Glanz B, Jaffin S, Healy B. Demographics of paediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. *Mult Scler.* 2009;15(5):627-31.

⁴ Harding KE, Liang K, Cossburn MD, et al. Long-term outcome of paediatric-onset multiple sclerosis: a population-based study. *J Neurol Neurosurg Psychiatry.* 2013;84(2):141-7.

⁵ Krupp LB, Tardieu M, Amato MP, et al. International Paediatric Multiple Sclerosis Study Group criteria for paediatric multiple sclerosis and immunemediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult Scler.* 2013;19(10):1261-7.

⁶ Ness JM, Chabas D, Sadovnick AD, et al. Clinical features of children and adolescents with multiple sclerosis. *Neurology.* 2007;68(Suppl 2):S37-45.

⁷ Banwell B, Ghezzi A, Bar-Or A, et al. Multiple sclerosis in children: clinical diagnosis, therapeutic strategies, and future directions. *Lancet Neurol.* 2007;6(10):887-902.

⁸ Waldman A, Ghezzi A, Bar-Or A, et al. Multiple sclerosis in children: an update on clinical diagnosis, therapeutic strategies, and research. *Lancet Neurol.* 2014;13(9):936-48.

⁹ Jancic J, Nikolic B, Ivancevic N, et al. Multiple sclerosis in paediatrics: current concepts and treatment options. *Neurol Ther.* 2016;5(2):131-43.

¹⁰ Benson LA, Healy BC, Gorman MP, et al. Elevated relapse rates in paediatric compared to adult MS persist for at least 6 years. *Mult Scler Relat Disord.* 2014;3(2):186-93.

¹¹ Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in paediatric onset compared with adult - onset multiple sclerosis. *Arch Neurol.* 2009;66(1):54-9.

¹² Waubant E, Banwell B, Wassmer E, et al. Clinical trials of disease-modifying agents in paediatric MS. Opportunities, challenges, and recommendations from the IPMSSG. *Neurology* 2019;92(22):e1-12.

¹³ Montalban X, Gold R, Thompson AJ, et al.ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler.* 2018;24(2):96-120.

¹⁴ Banwell B, Reder AT, Krupp L, et al. Safety and tolerability of interferon beta-1b in paediatric multiple sclerosis. *Neurology.* 2006;66(4):472-476.

¹⁵ Tenenbaum SN, Banwell B, Pohl D, et al. Subcutaneous interferon Beta-1a in paediatric multiple sclerosis: a retrospective study. *J Child Neurol.* 2013;28(7):849-856.

¹⁶ Kornek B, Bemert G, Balassy C, et al. Glatiramer acetate treatment in patients with childhood and juvenile onset multiple sclerosis.

About the product

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), required for the *de novo* pyrimidine synthesis. As a consequence, teriflunomide blocks the activation and proliferation of rapidly dividing cells including activated lymphocytes which depend on *de novo* synthesis of pyrimidine to expand. Slowly dividing or resting cells which rely on the salvage pathway for pyrimidine synthesis are claimed to be unaffected by teriflunomide. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but likely includes the reduction of activated lymphocytes available to migrate into the CNS.

Teriflunomide is the active metabolite of leflunomide (Arava) indicated for rheumatoid arthritis and for psoriatic arthritis. *In vivo*, leflunomide is rapidly and almost completely metabolised to teriflunomide which is active *in vitro* and is presumed to be responsible for the therapeutic effect of Arava.

In this procedure, the Applicant proposed to extend the Aubagio indication as follows : "*treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS)*" and to add a new paediatric formulation as a new 7 mg strength film-coated tablet.

Type of Application and aspects on development

The Applicant submitted the following grouping of variations according to article 7.2 (b) of the variation regulation (cases for grouping variations listed in Annex III to Commission Regulation (EC) No 1234/2008):

- New strength: Extension of a marketing authorization under Annex I to Commission Regulation (EC) No 1234/2008 for teriflunomide 7 mg film-coated tablet
- New paediatric indication: Type II variation as defined in Article 2(3) of Commission Regulation (EC) No 1234/2008 for a new therapeutic indication. The Applicant is seeking approval for an indication in paediatric patients from 10 years of age and older with relapsing remitting multiple sclerosis indication under Article 8 of Paediatric Regulation 1901/2006.

The Applicant requested consideration of one-year marketing protection in regards of its application for a new indication in the framework of Aubagio procedure EMEA/H/C/002514/X/0031/G in accordance with Article 14(11) of Regulation (EC) 726/2004. The CHMP assessment report on the significant clinical benefit in comparison with existing therapies in accordance with Article 14(11) of Regulation (EC) No 726/2004 is appended in this CHMP AR.

Centralised scientific advice was given by the CHMP on 26 May 2016 (EMEA/H/SA/514/2/2016/PED/II) regarding the data to be submitted in support of a request to extend the current indication by adding treatment of paediatric patients. Further the Applicant asked for clarification how an additional year of market protection could be justified provided that an indication for the paediatric population was to be granted and considered a "new indication". A new indication would normally include an extended target population for the same disease, e.g. based on a different age range. As such, based on a positive benefit-risk balance, granting of an indication in 10-17 Years old RRMS patients would likely be regarded as a new indication. In order to benefit from an extended (11-year) marketing protection period a significant clinical benefit in comparison with existing therapies of a new therapeutic indication is needed. However, whether this is considered to be fulfilled can only be assessed at the time of submission, depending on the existence or non-existence of other approved products.

A pre-submission meeting was held with the Rapporteur on 03 February 2020, focussing on the acceptability of the data, e.g. the results for the primary endpoint and the role of sensitivity analyses (relapses and high MRI activity) in the context of a more frequent than anticipated switch from double-blind (DB) study drug to open-label (OL) treatment due to high MRI activity. Further discussions related to the dosage regimen in particular for paediatric patients ≤ 40 kg (14 mg tablet every-other-day, or 7 mg tablet every day), the justification for significant clinical benefit to obtain an extension of marketing protection (+1 year) and the risk management approach.

An additional pre-submission was held with the European Medicines Agency (EMA) on 05 February 2020 to obtain procedural and regulatory advices in anticipation of a submission planned on 4 May (extension and Type II) or 3 June 2020 (in the case of a Type II variation), e.g. due to the additional submission of the 7 mg dosage.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 7 mg of teriflunomide as active substance. The 7 mg strength is newly introduced with this line extension to the already approved 14 mg strength presentation together with an extension of the indication to paediatric patients.

Other ingredients are:

Tablet core: lactose monohydrate, maize starch, microcrystalline cellulose, sodium starch glycolate (Type A), hydroxypropylcellulose and magnesium stearate.

Tablet coating: hypromellose, titanium dioxide (E171), talc, macrogol 8000, indigo carmine aluminium lake (E132), iron oxide yellow (E172; only for the 7 mg strength).

The product is available in polyamide/aluminium/poly(vinyl chloride) -aluminium blisters inserted in wallets and packed in a carton as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The active substance (teriflunomide) is the same as for the authorised Aubagio 14 mg film-coated tablets. No new data on the active substance was provided with this line extension application.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The medicinal product is an immediate release film-coated tablet. The 7 mg tablet strength is presented as a very light greenish-blueish grey to pale greenish-blue, hexagonal film-coated tablet with imprint of dosage strength ('7') on one side and engraved with a corporate logo on the other side.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, except for the colourants which comply with the relevant Directive 2008/128/EC. The choice and the amount of colourant has been thoroughly justified with view of the paediatric indication. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The aim of formulation development was to manufacture an additional lower-strength film-coated tablet. The existing 14 mg strength and the new 7 mg and strength are both pharmaceutical forms for use in paediatric patients from 10 years of age or older.

The newly introduced 7 mg strength was developed together with the already approved 14 mg strength. The composition of the tablet core is qualitatively identical to the 14 mg strength.

The two tablet strengths are sufficiently visually distinguishable by their debossing and colour.

The development of the product, which included manufacturing process and dissolution method developments, has been described.

The same critical quality attributes (CQAs) as for the approved 14 mg strength apply.

Film-coating was developed for aesthetic reasons and to improve the patients' ability to swallow the tablet.

A detailed summary containing all formulation changes performed during development and their effect on the 7 mg and 14 mg film-coated tablets has been provided. The overview includes additional strength not intended for commercialisation.

The primary packaging consists of polyamide/aluminium/poly(vinyl chloride) -aluminium blisters and is the same as for the existing 14 mg tablets.

Manufacture of the product and process controls

The 7 mg film-coated tablets are manufactured by Sanofi Winthrop Industrie, France, using a batch manufacturing process which involves mixing, fluid-bed granulation, drying, sieving, mixing and lubrication, tableting and film-coating. The manufacturer used for the 7 mg strength is already approved for the 14 mg strength tablets and the manufacturing process is similar for the 7 mg and 14 mg strength. The batch size is identical for both strengths.

An adequate criticality analysis was performed as part of the pharmaceutical development. Sufficient information on the control of critical steps has been provided in the dossier and the in-process acceptance limits have been justified. The overall control strategy, process parameters and in-process

controls seem adequate in view of the available development data and in view of the standard nature of the manufacturing process.

Process validation results from three full scale batches indicate that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for appearance (visual), identification (HPLC, UV), assay (HPLC), degradation products (HPLC), dissolution (Ph. Eur.), uniformity of dosage units (HPLC), water content (KF) and microbial contamination (Ph. Eur.). The proposed specifications include all required tests relevant for this dosage form.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines and have shown to be stability-indicating. Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled. The limits for the dissolution test are justified.

A summary of the risk assessment for elemental impurities of the 7 mg strength has been provided. The outcome indicates that all findings were below the control threshold and therefore the existing control strategies are sufficient.

Batch analysis results are provided for three production-scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three production scale batches of finished product stored for up to 36 months under long-term storage conditions ($30\pm 2^{\circ}\text{C}/65\pm 5\%\text{RH}$) and for up to 6 months under accelerated storage conditions ($40\pm 2^{\circ}\text{C}/75\pm 5\%\text{RH}$) according to the ICH guidelines were provided. The stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Overall no significant tendencies in any of the parameters tested were observed.

Samples of production scale batches were exposed to light in line with the ICH Guideline on Photostability Testing of New Drug Substances and Products. No changes regarding the assay, the individual impurities as well as the total impurities occurred.

The stability results presented are satisfactory and support the proposed shelf life of 3 years without special storage conditions as stated in the SmPC (section 6.3).

Adventitious agents

The only excipient of animal origin used for the manufacture of the finished product is lactose monohydrate. It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The newly introduced 7 mg strength tablet is very similar to the already authorised 14 mg tablet strength in composition, way of manufacture, batch size and quality attributes.

The decreased amount of active substance is compensated by the amount of excipients, resulting in film-coated tablets of identical weight. Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

No new non-clinical data were provided with this application.

2.3.1. Pharmacology

Not applicable.

2.3.2. Pharmacokinetics

Not applicable.

2.3.3. Toxicology

As part of an earlier PIP requirement to support clinical development of teriflunomide in paediatric RRMS patients aged 10 years or above (EMA decision P/209/2011; EMA/643565/2011), a 2 weeks exploratory dose-range finding study in postnatal day (PND) 21 juvenile rats (study no. JUP0014) was assessed during original MA of teriflunomide, whereas the pivotal 7 weeks repeated-dose juvenile toxicity study in PND21 juvenile rats (study no. JUV0024) was more recently evaluated and approved by Type II variation on 26th April 2019 (EMA/H/C/2514/II/22).

2.3.4. Ecotoxicity/environmental risk assessment

Teriflunomide PEC_{surfacewater} value is below the action limit of 0.01 µg/L and is not a Persistent, Bioaccumulative and Toxic (PBT) substance as log K_{ow} does not exceed 4.5. Therefore, the environmental risk assessment stops in Phase I. It is assumed that teriflunomide is unlikely to represent a risk for the environment following its prescribed usage in patients.

Table 1: Summary of main study results for environmental risk assessment

Substance (INN/Invented Name): Teriflunomide/Aubagio			
CAS-number (if available): 163451-81-8			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K _{ow}	OECD107; U.S. FDA protocol 3.02	2.66 (pH 3)	Potential PBT: N
Phase I			
Calculation	Value	Unit	Conclusion
PEC surfacewater, refined (prevalence)	0.0068	µg/L	>0.01 threshold: N
Phase II Physical-chemical properties and fate			
Study type	Test protocol	Results	Remarks
Ready Biodegradability Test	OECD 301	1% degradation within 28 days	Not readily biodegradable

PBT: Persistent, Bioaccumulative and Toxic; FDA: Food and Drug Administration

2.3.5. Discussion on non-clinical aspects

The juvenile toxicity studies, which aimed to support the extension of the MA to paediatric RRMS patients aged 10 years and above, have been earlier performed and approved by the CHMP. Corresponding findings from these juvenile toxicity studies have been adequately implemented into section 5.3 of the SmPC. In addition, dedicated instructions regarding the use of teriflunomide by female adolescents becoming fertile have been implemented into the SmPC and PL in accordance with recent PRAC discussions.

Moreover, the proposed extension of the MA will not increase the environmental risk of teriflunomide following its prescribed usage in paediatric RRMS patients.

2.3.6. Conclusion on the non-clinical aspects

Approval of the extension of the MA of teriflunomide can be considered from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the Applicant

The Applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2: Description of the pivotal study EFC11759 TERIKIDS with teriflunomide in the paediatric RRMS population

Study ID	No. of study centres / locations	Design	Study Posology	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Study Objective / Primary Endpoint
EFC11759								
DB Period, completed	57 centers (which screened at least 1 patient) in 22 countries worldwide/ 54 centers randomized at least 1 patient	DB randomized, multicentre, placebo-controlled, with blinded PK run-in (8 wks): patients received placebo or a terifl. 7mg adult equivalent dose (BW ≤40kg: terifl. 3.5 mg, BW >40k: terifl. 7 mg) thereafter continuation with placebo or a terifl. 14mg adult equivalent dose (BW ≤40kg: terifl. 7 mg, BW >40k: terifl. 14 mg)	Patients were randomized to terifl. or placebo at 2:1 ratio oral; once daily	Placebo: 57 treated/ 53 compl. DB period Terifl.: 109 treated/ 102 compl. DB period	Variable, up to 96 weeks: patients who experienced after the PK run-in new disease activity (high MRI activity or a relapse) could switch earlier to the OL period	55/111 15.0 (10-17)	RRMS and at least 1 relapse in the 12 months prior screening or at least 2 relapses in the 24 months prior screening ≥10 years of age and <18 years of age	PK, efficacy and safety Time to first clinical relapse after randomization up to the end of the DB treatment period
OL period ongoing: data cut-off 27 November 2019	52 centers in 21 countries	Uncontrolled with PK run-in (8wks): pat. who were initially in the terifl. arm remained on adjusted 14 mg adult equivalent dose pat. who were initially in the placebo arm underwent PK run-in with 7mg adult equivalent dose thereafter continuation with terifl. 14mg adult equivalent dose	All patients were treated with terifl.	terifl/ terifl group: 100 patients placebo/ terifl. group: 52 patients	Up to a maximum of 192 weeks (including the remainder of the initial 96, where applicable, and 96 weeks extension)	50/102 15.0 (10-17)	See DB period	Long-term effect with focus on long-term safety

DB: Double-Blind; OL: Open-Label; PK: Pharmacokinetics; BW: Body Weight; RRMS: Relapsing-Remitting Multiple Sclerosis.

2.4.2. Pharmacokinetics

Pharmacokinetic (PK) data in children and adolescents 10 to 17 years of age (at the initial entry to the study) were collected during the completed DB period and the ongoing OL period of Study EFC11759/TERIKIDS. In this study, patients were treated with either 7 mg teriflunomide or 14 mg teriflunomide once daily, after they had completed an 8-week PK run-in phase, to reach steady state exposure similar to that seen in adults treated with the approved dose of teriflunomide 14 mg once daily.

In absence of prior PK data in children, patients who were to initiate teriflunomide treatment started the PK run-in phase on half the predicted dose with either 3.5 mg (body weight [BW] ≤ 40 kg) or 7 mg (BW >40 kg) teriflunomide once daily. Pre-dose PK samples were collected during PK run-in phase (at Week 2, 3, and 4), at Week 8 (end of PK run-in phase), 12, 24 and 36, and at end of treatment (EOT) for both the DB and OL periods. Only trough level plasma concentrations were measured.

At Week 36, mean (standard deviation (SD)) steady state plasma concentrations were 53.1 (25.3) µg/mL in the 7 mg teriflunomide group and 67.8 (41.7) µg/mL in the 14 mg teriflunomide group. Considering high variability and small numbers in the 7 mg group, no major differences in teriflunomide steady-state trough concentrations were observed after 7 mg and 14 mg once daily as expected due to dose adjustment to the 14 mg adult-equivalent dose at the end of the PK run-in phase.

The overall aim of the paediatric popPK model development was to support definition of the daily dose to be administered to reach similar exposure in paediatric patients as in adults being treated with 14 mg once daily. Model development was only performed on an interim paediatric database.

The goodness-of-fit plots showed a limited performance of the population model predictions with an important tendency to underpredict high concentration values. In addition, estimation of absorption rate constant was unrealistic thus leading to unreliable estimations of exposure parameters. Upon request, the dataset was enlarged with the five patients and 409 concentration-time points coming from the ongoing OL period. Therefore, the updated dataset was composed of 159 patients providing 1686 concentration-time points. In the popPK model the absorption rate constant was adjusted to the adult value as proposed. The proposed every-other-day dosing regimen was not supported since no data are available with this dosing regimen, the model could not support this recommendation and this kind of regimen is prone for medication errors. During the procedure, the Applicant presented detailed comparisons of observed data between paediatric populations and the whole target adult population. Additional information on the model development was provided and discussed and the appropriate depiction of the population prediction goodness-of-fit plot presented.

Comparisons of individual exposures over the whole BW range investigated as well as grouped per 5 kg BW bands in the BW range between 40 – 60 kg were compared to the whole target adult reference range. With the available dataset there is no clear pattern of higher exposure in the lighter BW bands in the range between 40 and 60 kg. Therefore, the proposed BW cut-off at 40 kg for the same dose as in adults is considered acceptable. In addition, the frequency of Treatment-Emergent Adverse Events (TEAEs), their maximum intensity and outcome after occurrence of TEAEs did not show any specific pattern with respect to height of exposure.

Additional information was given on the 13 paediatric patients BW >40 kg treated with 7 mg instead of 14 mg in the paediatric study. In a situation where they would have received 14 mg once daily, simulations showed that all would have had a steady state exposure included in the range observed in the adult patients under steady state with 14 mg once daily with only 1 patient who would have had C_{trough} exceeding the 95th percentile but below the maximum value. No demographic or baseline characteristic known to impact on PK parameters could explain the higher exposures in this patient.

Overall, the observed C_{trough} values are highly variable between paediatric individuals. They range between 3.9 to 232 $\mu\text{g/ml}$, comparable to the range seen in adults (range 0.68 to 239 $\mu\text{g/ml}$). There are some patients who exhibit very high trough concentrations. With the presented popPK analyses, some factors were identified which decreased clearance, such as high albumin, high bilirubin concentration, and female sex, thus leading to higher plasma concentrations. But no factor was considered to clinically relevantly influence PK. It might also be a combined influence of different factors.

As requested, the exposure in paediatric patients developing pancreatitis was further investigated. Exposure in these patients were within the ranges of exposure in the other paediatric patients and adults. No clear statement can be drawn with the few and variable data available. Nevertheless, it is considered that physicians should be made aware of the high variability in exposure. Therefore, an additional statement should be included in the SmPC section 5.2. in the subsection on Paediatric Population: *"Overall, observed trough concentrations were highly variable between individuals (C_{trough} range between 3.9 and 232 $\mu\text{g/ml}$)."*

Different points were provided and discussed in order to support dosing in paediatric patients below or equal to 40 kg BW. Bias for individual predictions (IPRED) was below 10%. The revised presentation of the population predictions versus observed concentrations showed that in the appropriate depiction, the regression line better suited the line of identity. This increases confidence in model performance. Comparison of individual observed exposures between paediatric subgroups (below and above 40 kg) and the whole adult reference group showed that paediatric exposure was in the same range as in the adult population. Simulations based on the updated paediatric model (including a "worst case scenario" of patients weighing 25 kg corresponding to the 5th percentile of 10-year-old children) confirmed the assumption that with the proposed dosing, exposure in paediatrics will match the adult reference range.

Overall, the BW cut-off of 40 kg for the same dose as in adults (14 mg) is accepted as well as the proposed dose of 7 mg in paediatric patients equal or below 40 kg. The proposed 14 mg every other day dosing for patients weighing below 40 kg has been withdrawn by the Applicant.

2.4.3. Pharmacodynamics

No new data were presented by the Applicant.

2.4.4. Discussion on clinical pharmacology

The PK of teriflunomide in children and adolescents 10 to 17 years of age was assessed using descriptive statistics on trough plasma samples collected in Study EFC11759/TERIKIDS. Additionally, a popPK analysis was conducted with data from DB and OL periods and compared paediatric exposures for patients with BW >40 kg and \leq 40 kg with exposures documented in adult patients.

No major differences in teriflunomide steady-state trough concentrations were observed after 7 mg and 14 mg once daily as expected due to dose adjustment to the 14 mg adult-equivalent dose at the end of the PK run-in phase.

The presented paediatric population PK model had been based on an interim paediatric database only, which had severe limitations. Upon request, the Applicant provided an updated popPK model, which now includes all available data. The newly provided evidence on the quality of the model further increases the confidence in the updated paediatric model. Overall, including all available data on PK and safety and support by the model, the proposed BW cut-off is considered acceptable as well as the proposed dose of 7 mg for patients equal or below 40 kg. Nevertheless, it is considered necessary to make physicians aware of the highly variable exposure, which, at present, cannot be explained by individual patient characteristics. In this respect, an additional SmPC statement is added.

2.4.5. Conclusions on clinical pharmacology

With the updated model and depiction of exposure in different BW bands, no clear pattern of higher exposure in patients with lower BW in the BW range between 40 and 60 kg could be retrieved. In addition, no clear correlation between exposure and safety issues was found. With the updated information on model quality, confidence in model performance was increased. Therefore, overall, proposed dosing in paediatrics is considered acceptable.

2.5. Clinical efficacy

2.5.1. Dose response study

No dedicated dose response study in the paediatric population was conducted.

Study EFC11759 included at beginning a blinded PK run-in for the first 8 weeks after randomization, during which patients received placebo, or half of their target dose, e.g. 3.5 mg teriflunomide daily for patients ≤ 40 kg, or 7 mg teriflunomide daily for patients >40 kg. It was anticipated that this would result in an exposure similar to adults being treated with 7 mg teriflunomide daily (the "7 mg adult equivalent dose"). After the end of the PK run-in phase, a 14 mg adult equivalent once daily dose (14 mg has been approved for the adult RRMS patient population) of teriflunomide based on BW or matching placebo was administered per day. According to a popPK analysis, the Applicant considered, that a dosage of 14 mg teriflunomide once daily would be appropriate for paediatric patients with a $BW > 40$ kg, and a dose of 7 mg teriflunomide once daily or 14 mg teriflunomide every-other-day for paediatric patients with a $BW \leq 40$ kg. No patient was adjusted to the 3.5 mg once daily dose during the PK run-in phase.

2.5.2. Main study

Study EFC11759 (study TERIKIDS)

Methods

A two-year, multicenter, randomized, DB, placebo-controlled, parallel group trial to evaluate efficacy, safety, tolerability, and PK of teriflunomide administered orally once daily in paediatric patients with RMS followed by an OL extension.

The study consisted of the following periods:

- a screening period up to 4 weeks,
- followed by a DB treatment period of up to 96 weeks total duration for each patient after randomization, that included a blinded PK run-in phase of 8 weeks. The PK run-in phase was intended to provide individual PK parameters to allow dose adjustment to ensure that patients randomized to receive teriflunomide would reach an exposure similar to that observed in adults treated with 14 mg once daily ("the 14 mg adult-equivalent dose") for the rest of the study from Week 8. Patients who experienced a relapse after the PK run-in phase (8 weeks) confirmed by the Relapse Adjudication Panel (RAP) had the option to switch to the OL period. Similarly, patients with high MRI activity according to strict definitions could switch to the OL period. Patients completing the 96-week DB period had the option to continue in the OL period.
- An OL period for the remainder of 192 weeks after randomization. The OL period that followed the DB period lasted until 192 weeks after randomization. Its duration for a given patient depended on

when the patient entered this period. The duration of the OL period was going to be 96 weeks for patients completing the 96-week DB period on treatment, and longer for patients switching to OL during the initial 96-week DB period at the occurrence of a confirmed relapse or in case of high MRI activity. All patients entering the OL period from the placebo arm or teriflunomide arm, repeated a second 8 weeks PK run-in phase. Placebo patients would initiate teriflunomide treatment when entering the PK run-in of the OL period, while patients previously treated with teriflunomide during the DB period continued with the same previously adjusted dose.

- A follow-up period for patients who discontinued.
- An optional additional extension period with teriflunomide offered to young patients when they completed the study to provide treatment until they were 18 years old and/or could switch to teriflunomide commercial product, whichever came first.

The implementation of the placebo arm was combined with switch criteria, i.e. patients who experienced new disease activity had the option to move early to the OL teriflunomide treatment arm. With regard to high MRI activity, the criteria were defined as follows: In case of at least 5 new/enlarged T2 lesions at the MRI of Week 24 an additional MRI was performed at Week 36. In case the follow-up MRI revealed at least 9 new/enlarged T2 lesions at Week 36, or at least 5 new/enlarged T2 lesions on each of the 2 consecutive MRI scans at Week 36 and Week 48, or, at Week 48 and Week 72 then the patient was qualified for early switch.

Study Participants

Main inclusion criteria relating to efficacy were RMS diagnosed based on the McDonald criteria 2010 and the IPMSSG criteria for paediatric MS, version of 2012, ages <18 years of age and ≥10 years of age at randomization, EDSS score ≤5.5, last relapse more than 30 days prior to randomization and meeting one of the following disease activity criteria:

- at least one relapse (or attack) in the 12 months preceding screening or,
- at least two relapses (or attack) in the 24 months preceding screening.

Subjects could be MS-treatment naïve or could have received prior MS DMT.

Treatments

Teriflunomide and placebo were taken orally as a single dose each day of the treatment periods. Investigational medical products (IMP) were taken with water and could be taken with or without food.

During the PK run-in period, patients randomized to the active treatment group who had a BW of 30 ± 10 kg received 1 tablet of 3.5 mg of teriflunomide daily, while patients with a BW of >40 kg received 1 tablet of 7 mg teriflunomide daily. It was anticipated that this would result in an exposure similar to adults being treated with 7 mg teriflunomide daily (the "7 mg adult equivalent dose").

After the end of the PK run-in phase, a 14 mg adult equivalent once daily dose of teriflunomide or matching placebo was administered per day as follows, based on exposures predicted from PK samples collected up to Week 4 using a PopPK model with allometric scaling adapted to the paediatric population.

Use of systemic corticosteroids for the treatment of MS relapse was allowed during the study in doses appropriate for the paediatric population based on the investigator's decision.

Objectives

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

Secondary objectives were

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

Outcomes/endpoints

Primary efficacy endpoint

- The time to first clinical relapse after randomization up to the end of DB treatment period.

Relapses were defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist and documented by the Functional System Scores (FSSs), i.e. an increase of at least 1 point on any FSS score. During the procedure, the Applicant was requested to discuss the discrepancy in relation to the definition for the extent of EDSS worsening required for relapse confirmation used in the studies performed in the adult population (2 points in one FSS or one point in two FSS). The Applicant clarified that this was justified by the chosen process of relapse confirmation performed by an external panel (RAP). Further, the Applicant argues that in the context of the study design also paediatric patients with an increase of only 1 FSS point were given the opportunity to switch to active treatment in the OL period. The Applicant's argumentation can be followed. New or recurrent symptoms that occurred less than 30 days following the onset of a relapse were considered part of the same relapse. Clinical relapses were reviewed for confirmation by an independent, trained RAP in a blinded fashion.

Secondary efficacy endpoints

- Proportion of clinical relapse-free patients at 24, 48, 72 and 96 weeks
- MRI endpoints based on central reading
 - Number of new/newly enlarged T2 lesions (key secondary endpoint)
 - Number of Gd-enhancing T1 lesions (key secondary endpoint)
 - Change from baseline in volume of T2 lesions
 - Change from baseline in volume of T1 hypointense lesions
 - Number of new hypointense T1 lesions
 - Proportion of patients free of new or enlarged MRI T2 lesions at 48 weeks and 96 weeks
 - Percentage change of brain volume.
- EDSS score
- Cognitive outcome measured by the symbol digit modalities test (SDMT) and Cognitive Battery Tests
- Teriflunomide PK
- Proportion of disease-free patients (exploratory endpoint)

MRI measurements were scheduled to be performed at Screening, and Weeks 24, 36 (optional for switch evaluation as needed), 48, 72 and 96/EOT in the DB period. For patients who experienced a relapse or high MRI activity during the DB period and switched to the OL teriflunomide extension, MRI assessments were scheduled at Weeks 48, 96, 144, and 192/EOT.

While the study was ongoing, the Applicant requested a modification of the agreed PIP in November 2018 parallel to interactions with the Food and Drug Administration (FDA) to propose to change the primary endpoint "time to clinical relapse". At that time the study was fully enrolled but was still ongoing and it was noted that more patients (21 patients) than anticipated were switching to the OL period, many of them (14 patients) due to high MRI activity. Given the anticipated impact of these switchers on the primary analysis, the Applicant discussed to include high MRI activity switches, along with the confirmed clinical relapses, in a composite primary endpoint, which corresponded to one of the pre-planned sensitivity analyses. However, PDCO and the FDA did not agree to change the primary endpoint during the ongoing study due to the study being far advanced and advised to take the pre-planned sensitivity analyses into account when assessing the efficacy data of the study. During the procedure the request for modification was withdrawn.

Sample size

Determination of sample size was based on the primary efficacy endpoint, time to first confirmed clinical relapse after randomization, and assumption were based on combined data from the completed Phase III monotherapy adult studies (EFC6049/TEMSO and EFC10531/TOWER).

Assuming 60% of placebo patients experience a relapse by 2 years, 165 children (110 teriflunomide and 55 placebo) were needed for 80% power to detect a hazard ratio (HR) (teriflunomide versus placebo) of 0.5 (2-sided alpha 0.05). The 2-year rate of relapse in the teriflunomide group would be 36.8% and the corresponding hazard rates (HR), assuming the time-to-relapse is exponentially distributed with a constant HR, would be 0.4581 for placebo and 0.2291 for teriflunomide. The sample size is adjusted assuming 20% of patients discontinue the study in 2 years due to reasons other than relapse.

Randomisation

Patients were randomized 1:2 to placebo and teriflunomide stratified by country in which the patient is being treated and patient pubertal status. This is considered appropriate, as according to the initially agreed PIP the study had to include pre-pubertal and pubertal MS patients. The randomization code list is generated by the interactive web response system and interactive voice response system (IWRS/IVRS) service provider. Patients fulfilling all inclusion and exclusion criteria at the Visit 1 (Day-28) and Visit 2 (Day 0) are qualified for randomization. Randomization occurs at Visit 2. The first dose of randomized IMP (either teriflunomide or placebo) will be taken the same day or the following day.

Blinding (masking)

There were 2 neurologists at each study center:

- The treating neurologist was responsible for patient eligibility evaluation, supervision of study medication administration, recording and treating of AEs and assessing relapses, and monitoring of safety assessments, including routine laboratory results and concomitant medications. Throughout the study, the treating neurologist was to remain unaware of the patient's treatment assignment. The same physician should, as best as possible, maintain the role of treating neurologist for a given patient throughout the study.

- The examining neurologist, independent from the treating neurologist, was responsible for conducting all FSS and EDSS score assessments. The examining neurologist was to be certified for EDSS rating prior any involvement in the study. Throughout the study, the examining neurologist was to remain unaware of the patient's treatment assignment and the safety profile of the patient (AEs, concomitant medications, and laboratory results).

All brain MRI scans were reviewed and interpreted independently by trained neuro-radiologists at a central facility with no access (ie, blinded) to treatment assignment thereby avoiding bias. An MRI manual explaining the instructions for standard image acquisition requirements, data transfer, archiving and shipping, and outlining the phantom data approval process was provided to all centers. According to the provided Imaging Review Charter, the Gd-enhancing lesion count measurement was performed manual by two qualified MRI readers. All other quantitative measurements were either computer generated quantitative analysis with full expert review and oversight or human interfaced analysis using a boundary finding segmentation algorithm.

Statistical methods

Analysis Population

Intent-to-treat population (ITT): all randomized patients analyzed according to the treatment group allocated by randomization.

Randomized population: all patients who had been allocated to randomized treatment regardless of whether the treatment kits were used. This was the population for analyses of demographics and baseline characteristics.

Safety population: all randomized patients exposed to DB study medication, regardless of the amount of treatment administered.

PK population: subset of the safety population containing patients who had at least one PK sample taken.

The ITT population was the primary analysis population for efficacy analysis. In addition, analyses based on the per-protocol (PP) population were requested and conducted for completeness post-hoc, although it is acknowledged, that such analyses should be considered with caution (potentially biased).

Analysis of primary efficacy endpoint

The primary endpoint 'time to first relapse' can be considered as a surrogate of the analysis of the relapse rate, which could be adequate assuming a constant individual relapse intensity over time. While this assumption may only be valid in case of adherence to study treatment, the analysis of time-to-first relapse can be considered as yielding the best available evidence on relapse, as patients were offered to switch to the active treatment following a relapse or high MRI activity.

The primary analysis was a stratified log-rank test (stratification: region, pubertal status) using a two-sided alpha level of 5%. The first confirmed clinical relapse occurring from randomization (including relapses during the PK run-in phase) to the end of the DB study period was included for analysis. Treatment effect as measured by the HR and its associated 95% confidence interval (CI) were estimated using a Cox's proportional-hazards model (factors: treatment, region, pubertal status, age, number of relapses in the year prior to randomization).

Patients were censored (1) at the time of permanent discontinuation of treatment/DB period, (2) at the time of discontinuing the DB period and switching to OL teriflunomide due to high MRI activity and (3) at week 96 (end of DB period) in case patients neither experienced a relapse nor high MRI activity. While the non-informative censoring assumption underlying the analysis may be valid for (3), validity of this

assumption is questionable in the other two cases, and additional analysis were required (see section on sensitivity analyses).

Furthermore, as the proportional-hazard assumption is not fulfilled in this study, the HR is not a reliable effect measure: Focus should be on estimates of relapse probability at different time points.

With regard to the mean times for time-to-event endpoints, restricted mean survival times (i.e. the mean time-to-event, "survival" is used as a technical term only), restricted to 96 weeks, were estimated.

Sensitivity Analyses for the primary efficacy endpoint

Six sensitivity analyses have been conducted using a similar analysis as for the primary endpoint. These analyses could have supported a significant primary analysis. However, given that the primary endpoint failed, formally no conclusions on efficacy can be made based on these analyses. All conclusions from this study must be considered as exploratory and descriptive.

- Time to first confirmed clinical relapse or high MRI activity meeting protocol criteria for switching into the OL period, whichever came first, after randomization before the treatment discontinuation/completion in the DB period.
Counting high MRI activity as an event addresses the issue that censoring at time of stopping the DB period due to high MRI activity is informative, since high MRI activity is related to a potential relapse. It can also be considered as addressing a composite endpoint.
- Time to first clinical relapse (ie, clinical relapse confirmed or not by the RAP) after randomization before the treatment discontinuation/completion in the DB period.
- Time to first confirmed clinical relapse occurring after the PK run-in (8 weeks) phase but before the treatment discontinuation/completion in the DB period.
For this analysis patients were censored at the time of relapse during titration/PK run-in (i.e. non-informative censoring is assumed), which is likely not valid. Regardless, this analysis provides little information on the use of teriflunomide without titration. Furthermore, no analysis to robustly derive this effect can reasonably be done.
- Time to first clinical relapse with objective signs on the examining neurologist's examination including relapses during the PK run-in phase and relapses reported after the study drug discontinuation and up to 96 weeks after randomization.
As the primary analysis employs a hypothetical estimand strategy for switching to OL teriflunomide in case of high MRI activity, this analysis supports the primary analysis by addressing an estimand based on the treatment policy strategy describing the effect of immediate application of Teriflunomide vs that after high MRI activity.
- *Post-hoc*: Time to high MRI activity for switching into the OL period.
Interpretation of this analysis is limited, as patients experiencing a relapse are censored, but (a) censoring at time of relapse is clearly informative and (b) patients experiencing a relapse may have had a high MRI activity prior to relapse that was not detected due to limited MRIs.
- *Post-hoc*: Time to first confirmed clinical relapse occurring after the PK run-in phase up to 96 weeks after randomization including relapses reported in both DB and OL periods.

The conducted sensitivity analyses do not address the issue of censoring patients at time of permanent and premature discontinuation of treatment/DB period, which may be informative, too. A sensitivity analysis using more reasonable assumptions to handle these discontinuations was therefore requested for the composite 'time to high MRI activity or relapse'. Additionally, interval censoring of the MRI component has been requested to be considered in an additional sensitivity analysis of the composite.

Subgroup Analyses for the Primary Endpoint

Pre-specified subgroup analyses were performed based: Age group at study consent (<13, ≥13 years), gender, race, pubertal status (at study consent and at disease onset), baseline BW group (≤40, >40 kg), MS subtypes (RRMS, other forms), number of relapses experienced within past 1 year (0, 1, 2 and ≥3), number of relapses experienced overall (0, 1, 2, 3 and ≥4), high disease activity at baseline (defined as 2 or more relapses in past year, and 1 or more Gd-enhancing lesions on baseline MRI (Yes, No)), Region (Europe, North America, Asia, Middle East, North Africa) and previous MS treatment (Yes, No).

Analysis of secondary endpoints

Imaging endpoints

The number of new/newly enlarged T2 lesions and the number of T1 Gd-enhancing lesions were defined as key secondary endpoints.

New/enlarged T2 lesion measurement:

The number of new/enlarged T2 lesions at each scan is counted with reference to the previous scan. In case a new lesion in the week 24 scan that would disappear in the week 48 scan and reappear in the week 72 scan (which is uncommon), it would be counted as new T2 at w72. A lesion that would appear in the week 24 scan and disappears in the last scan, would not be counted at the last scan. A significant enlargement (of at least 3 voxels) due to a new focal lesion (that overlaps an existing lesion) would be counted.

T1 lesion measurement:

Gd-enhancing T1 lesion count at each scan is assessed independently, with the capability of referring to the previous scan if needed. A lesion which would enhance on several scans would be counted on each scan if meeting the gad lesion criteria. However, contrast enhancing lesions in MS infrequently enhance for more than 4 to 6 weeks. For reference, please note the following Gd lesion criteria:

1. A Gd lesion must have 3 or more enhancing voxels that are contiguous and have at least 20% of intensity increase in the post-contrast T1C relative to Pre-contrast T1P.
2. The enhancing voxels must be totally or partially co-localized with the T2 lesions.
3. The enhancing voxels must be iso- / hyperintensity comparing to NAWM (normal appearing white matter).

Upon request, the Applicant clarified that the precise definition of the MRI endpoints “number of new/newly enlarged T2 lesions” and the “number of Gd-enhancing T1 lesions” were pre-specified in the SOP of the central reader NeuroRx. While the exact definition would have been expected to be described also in the clinical study report and in the statistical analysis plan (SAP) in order to be unambiguously pre-defined, this issue was not further pursued.

Primary analyses of MRI-based endpoints were only based on data from MRI scans performed during the DB period (i.e. prior to switching to OL teriflunomide treatment or prior to early treatment discontinuation due to other reasons). In case during the DB treatment period an additional MRI due to higher MRI activity at week 24 was performed at week 36, these data were also considered for the analyses.

The number of new or enlarged T2 lesions per MRI scan was analyzed using a negative binomial (NB) regression model with robust variance estimation for the individual treatment periods (factors/covariates: treatment, region, pubertal status, age; offset: log(number of MRIs)).

A similar NB regression model was used for the analyses on the number of T1 Gd-enhancing lesions and the number of new T1 hypointense lesions per MRI scan for the individual treatment periods.

The change from baseline in volume of T2 lesions and of T1 hypointense lesions, and the percentage change from baseline in brain volume were analyzed using a mixed-effect model with repeated measures (MMRM) approach (treatment, pubertal status, region, visit, visit*treatment, baseline) with appropriate transformation, if necessary (cubic root transformation for volume of T2 and T1 hypointense lesions). If significant violation from normality existed after transformation, rank analysis of covariance (ANCOVA) with last observation carried forward (LOCF) was used.

The proportion of patients free of new or enlarged T2 lesions at Weeks 48 and 96 of the DB-period was estimated with the Kaplan-Meier (KM) method.

Analysis of secondary endpoints is based on the missing-at-random (MAR) assumption (or similar aligned assumptions depending on the endpoint). Appropriateness of this assumption may be questionable for early and permanent treatment discontinuation and in case of switching due to high MRI activity. Consequently, robustness of results for secondary imaging endpoints regarding deviations from the MAR assumption was unclear and further analysis were required.

In particular, as restriction of evaluation to the DB period targets a hypothetical estimand, analysis using all available MRI assessments during the first 96 weeks following randomization regardless of switching was requested for secondary imaging endpoints. Furthermore, analysis based only on data from the DB period (i.e. prior to switching) was requested to multiply imputing missing MRI assessments during the first 96 weeks based on the placebo arm. For key secondary imaging endpoints tipping point analysis based on data of the DB period were requested as well.

In addition to these analyses, the key secondary endpoint "new/enlarged T2 lesions" was requested to be analysed accounting for the baseline number of lesions.

Additional secondary endpoints

EDSS score and the change from baseline in EDSS score were summarized descriptively at each visit by treatment group.

Cognitive outcome: The SDMT was analyzed by a MMRM model similar as done for volume of lesions and brain. The MMRM model included an additional covariate or age.

Disease-free patients were defined as patients 1) with no confirmed clinical relapse, 2) with no 24-week sustained disability progression (≥ 0.5 -point EDSS score increase if baseline EDSS score > 5.5 or ≥ 1 -point EDSS score increase from baseline if baseline EDSS score ≤ 5.5 , persisting for ≥ 24 weeks) and 3) free of MRI activity (No Gd-enhancing T1 lesions and no new/enlarging T2 lesions). The proportion of disease-free patients was summarized at Weeks 48 and 96 based on all patients having an MRI at these time points. KM methods were used for estimation.

Multiplicity control

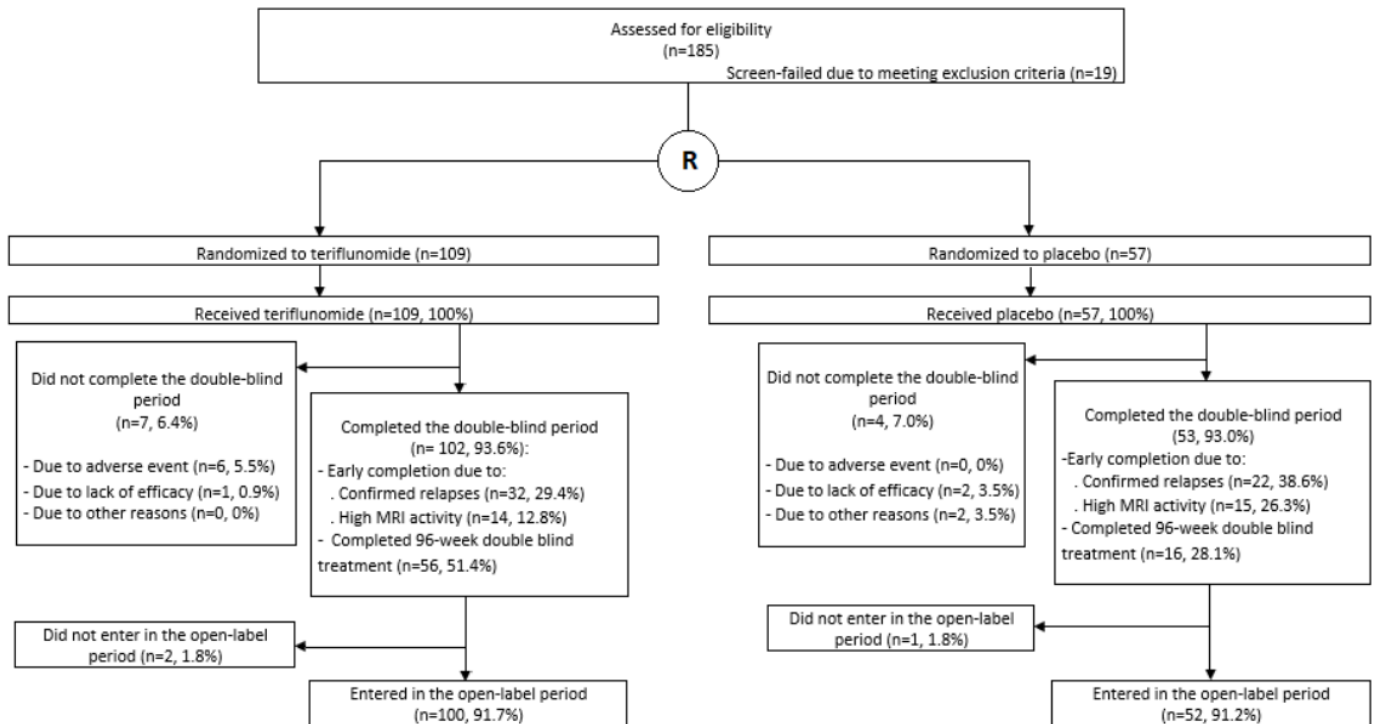
To allow confirmatory conclusions for the primary and the two key secondary imaging endpoints, multiplicity was planned to be controlled via hierarchical testing using the following sequence: 1) time to first relapse, 2) number of new/newly enlarged T2 lesions and 3) number of T1 Gd-enhancing lesion. Each hypothesis was to be formally tested, only if the preceding one was significant at 5% level. While the approach in principle properly controls the type 1 error in the strong sense, no confirmatory conclusions are possible for any of the endpoints as definition of secondary endpoints is unclear and as the study failed its primary endpoint. Consequently, all results of the study need to be considered to be exploratory and descriptive.

The database has been locked 27 November 2019 and randomization codes for treatment allocation of all randomized patients were released the following day.

Results

Participant flow

Figure 1: Disposition of subjects (ITT population)



Recruitment

This study was conducted in 57 centers in 22 countries.

- Study initiation date, DB phase: 16 July 2014 (date of first signed informed consent form)
- Study completion date, DB phase: 25 October 2019 (date of last patient last visit)

Conduct of the study

There were 4 global and 2 local (Russian) amendments made to the original protocol, dated 30 May 2013. Main changes in the global amendments were:

- Amendment 1 (18 December 2013) added MRI measures (weeks 24, 48 and 96) and MRI outcomes (change in T2 lesion volume, change in T1 hypointense lesion volume and new lesion number and brain atrophy) to the protocol.
- Amendment 2 (26 June 2014) extended the OL period to up 192 weeks, added a new MRI measurement (72 weeks) and further endpoints including proportion of patients free of new or enlarged MRI T2-lesions at Weeks 48 and 96 and proportion of disease-free patients.
- Amendment 3 (02 August 2018): Modification of total expected number of patients to include approximately 20% pre-pubertal patients or 10% of patients under the age of 13 years at time of inclusion into the study and at least 25% male patients.

- Amendment 4 (11 September 2019): addition of a biomarker research.

All randomized patients were treated with IMP and 93.6% and 93.0% of the randomized patients completed the DB period (e.g., patients who completed early due to first RAP-confirmed clinical relapse or high MRI activity or who reached week 96 of the double-blind treatment phase) in the teriflunomide and placebo groups, respectively. The main reason for permanent treatment discontinuation was AE in the teriflunomide group (5.5%) and lack of efficacy or other reason in the placebo group (3.5%).

Overall, there were 34 protocol deviation and 6 patients had critical or major efficacy-related protocol deviations, mainly IMP interruption exceeding 2 consecutive weeks reported in 3 patients (5.3%) in the placebo group.

Baseline data

Baseline demographic characteristics

The mean age of the overall study population was 14.6 years with a range from 10 to 17 years at study entry. Overall, 26 patients (15.7%) were below 13 years old at enrolment. The majority of patients were female (66.9%) but 33.1 % of patients were male paediatrics that is in accordance with the agreed PIP modification, February 2017 (EMA-001094-PIP01-10-M04).

Most subjects were Caucasian/White (70.5%) and 42.8% of the subjects were Europeans.

At baseline, 10 patients (6.0%) were pre-pubertal according to Tanner Stage I: 5 (4.6%) of the patients in the teriflunomide group and 5 (8.8%) patients in the placebo group. At disease (MS) onset, 34 patients (21.8%) were pre-pubertal, 21/99 (21.2 %) of the patients in the teriflunomide group and 13/57 (22.8 %) patients in the placebo group.

The mean BW was 58.0 kg. Eleven patients (6.6%) had a BW \leq 40 kg. The mean body mass index (BMI) was 22.1 kg/m².

Baseline disease characteristics

Overall disease characteristics at baseline were generally similar among the treatment groups. All patients were diagnosed with RRMS.

The study population consisted of relatively newly diagnosed RRMS patients with a comparable time since MS diagnosis (mean =1.40 years, median =0.69 years) and time since first symptoms of MS (mean =2.34 years, median =1.61 years). While in the placebo group, the mean time since the most recent relapse onset relative to randomization was 5.79 months, patients in the teriflunomide arm experienced their most recent relapse at a mean time of 4.97 months before randomization. The number of overall experienced relapses before study entry was comparable between the two treatment arms (mean = 2.8, median = 2.0) as were the number of relapses within the past year (mean = 1.5, median =1.0) and within the past 2 years (mean = 2.1, median =2.0). All patients experienced relapses within the past 2 years. EDSS scores at baseline were comparable with an overall mean EDSS score of 1.3 representing almost no disability with only minimal signs in some functional systems. This is considered typical for the patient population included with a slower disability progression over time as compared to adult MS patients.

The mean number of Gd-enhancing lesions at baseline was 3.9 for both treatment groups (median =1.0), while around half of the patients in both groups had \geq 1 T1 Gd-enhancing lesions on MRI. The number of new/newly enlarged T2 lesions is determined in reference to the MRI scans of the previous visit. Thus, it is not a value that is present at baseline. The mean (SD) number of baseline T2 lesions was slightly higher in the placebo group, 60.3 (40.8), than in the teriflunomide group, 51.3 (38.2). The number of

hypointense T1 lesions was not available for the baseline visit as this parameter request was not planned with the MRI reading center.

Approximately 19.9% of patients across both treatment groups had been previously treated with a DMT with the most common DMT being interferon beta-1-a (10.1% in the teriflunomide group and 17.5% in the placebo group). Around 80% of subjects were naïve to previous treatment with DMT.

With regard to descriptive purposes of primary symptoms, a total of 27.7% patients were included into the study with non-encephalopathic CNS clinical events, 6.6% with ADEM and 4.2% of the patients with other types of MS event that were not considered to contradict the final diagnosis of RRMS for these patients.

Numbers analysed

All 166 randomized patients were included in efficacy (ITT) and safety populations.

Table 3: Analysis population

	Placebo	Teriflunomide
Randomized population	57 (100)	109 (100)
Efficacy population (Intention-to-Treat)	57 (100)	109 (100)
Safety population	57 (100)	109 (100)
Pharmacokinetic (PK) population	56 (98.2)	109 (100)

The safety population and PK population are tabulated according to treatment actually received (as treated). For other populations, patients are tabulated according to their randomized treatment. The percentage is calculated as the number of patients in each population divided by the number of patients in randomized population per group.

Outcomes and estimation

Primary endpoint

Primary analysis: time to first confirmed clinical relapse

Confirmed clinical relapse occurred in 36.7% in the teriflunomide group and in 43.9% in the placebo group in the DB period, corresponding to a relative rate reduction of 34.3% (HR: 0.657; 95% CI: 0.388 to 1.113, p=0.2949). Patients in the placebo group experienced the first confirmed relapse after randomization earlier than patients in the teriflunomide group; the median duration was 39.14 weeks versus 75.29 weeks, respectively; the mean and SD were 49.25 (33.36) weeks versus 62.60 [36.12] weeks, respectively. The estimated probability of confirmed clinical relapse at Week 96, using the KM method was 0.531 in the placebo group and 0.389 in the teriflunomide group (Table 4).

Table 4: Primary analysis: Analysis of time to first confirmed clinical relapse after randomization during the DB treatment period (ITT population)

	Placebo (N=57)	Teriflunomide (N=109)
Number of patients with confirmed clinical relapse during the double-blind treatment period, N (%)	25 (43.9)	40 (36.7)
Number of patients who were censored, N (%)	32 (56.1)	69 (63.3)
Median survival time (95% CI)	95.57 (43.14, NC)	NC (NC, NC)
Mean survival time (95% CI)	63.21 (53.88, 74.64)	69.92 (63.33, 77.39)
Time to first confirmed clinical relapse (weeks)		
Number	57	109
Mean (SD)	49.25 (33.66)	62.60 (36.12)
Median	39.14	75.29
Min ; Max	0.1 ; 98.0	0.1 ; 98.7
Kaplan-Meier estimates of probability of confirmed clinical relapse during the double-blind treatment period (95% CI) at ^a		
24 Weeks	0.232 (0.132 ; 0.349)	0.183 (0.117 ; 0.261)
48 Weeks	0.391 (0.259 ; 0.521)	0.298 (0.214 ; 0.386)
72 Weeks	0.452 (0.305 ; 0.588)	0.364 (0.272 ; 0.456)
96 Weeks	0.531 (0.360 ; 0.676)	0.389 (0.293 ; 0.483)
Hazard Ratio (95% CI) ^b	-	0.657 (0.388 ; 1.113)
Stratified Log-Rank test p-value ^c	-	0.2949

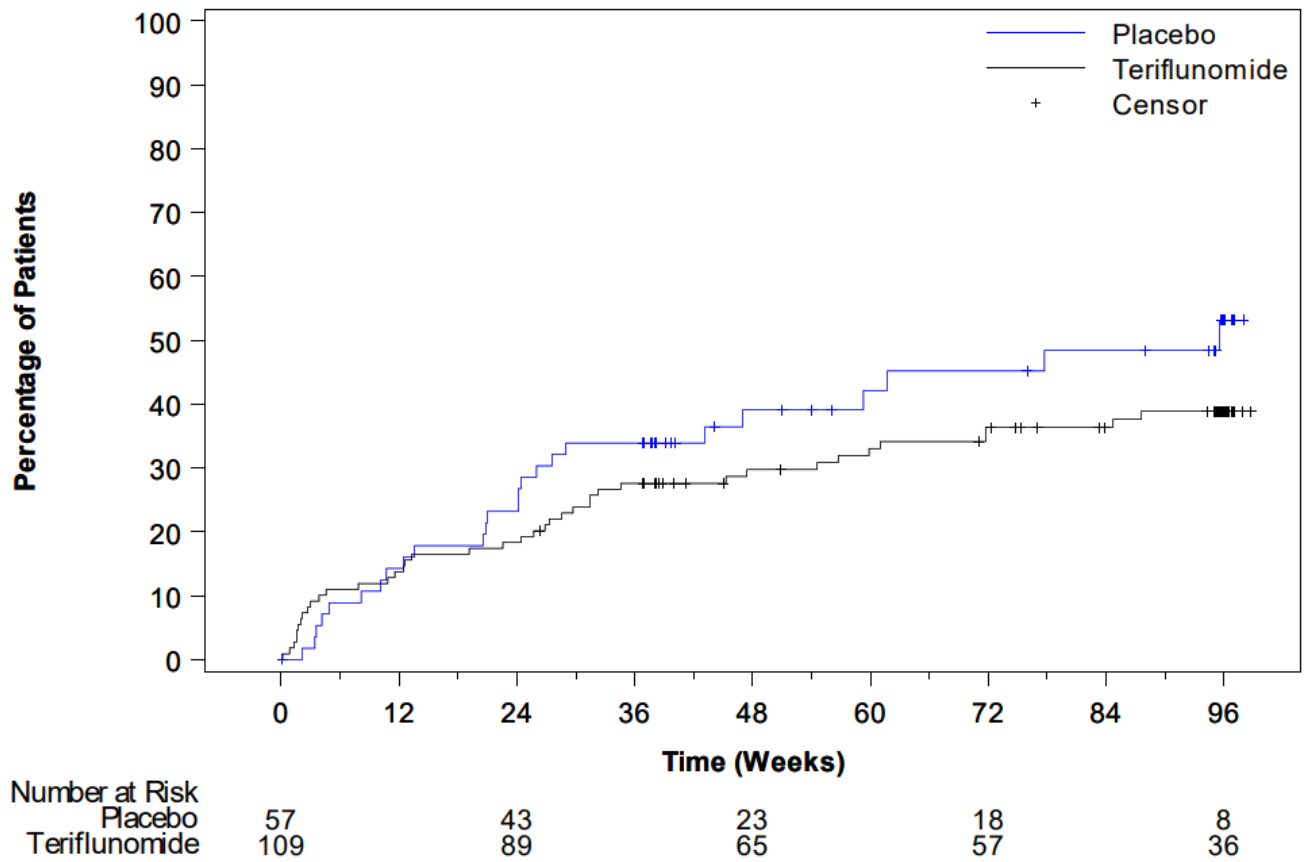
Note: Confirmed clinical relapse must have objective signs on the examining neurologist's examination confirming the event and must then be reviewed and confirmed by an independent relapse adjudication panel (RAP). Time to event is calculated as date of confirmed clinical relapse - randomization date + 1 day. The North Africa and North America were combined for region stratum due to small sample size.

a Derived from Kaplan-Meier estimates.

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

c Derived from log-rank test with stratification of region and pubertal status.

Figure 2: Primary analysis: Kaplan-Meier (KM) plot of time to first confirmed clinical relapse after randomization during the DB treatment period (ITT population)



Note: Confirmed clinical relapse must have objective signs on the examining neurologist's examination confirming the event and must then be reviewed and confirmed by an independent relapse adjudication panel (RAP). Time to event is calculated as date of confirmed clinical relapse - randomization date + 1 day.

Looking at the KM plot (Figure 2) of time to first confirmed relapse it directly becomes apparent that the proportional Hazards assumption is not fulfilled. Up to about 24 weeks there is almost no difference between estimated relapse rates (although up to week 12 relapses were slightly more frequent for teriflunomide) and from week 36/48 onwards, the curves are almost parallel (although numbers at risk are low at the end of the curves). Consequently, the power of the study to detect the observed difference in KM curves is reduced. The most informative part seems to be restricted to the time between 24 to 24/36 weeks. Furthermore, for this analysis patients are censored at time of high MRI activity (most at week 36) which is questionable given that censoring is highly informative. Sensitivity analysis counting high MRI activity as an event as discussed below would partly address this issue (in case the primary analysis were successful), though it should be noted that the design hampers an unbiased analysis of the primary endpoint.

Sensitivity analyses

Time to first confirmed clinical relapse or high MRI activity meeting criteria for switching into OL period, whichever came first

Teriflunomide reduced the rate of confirmed clinical relapse or high MRI activity, whichever came first, when compared to placebo by 43.4% (49.5% of patients in the teriflunomide group versus 68.4% of patients in the placebo group; HR: 0.566; 95% CI: 0.368 to 0.870, p=0.0409), representing significant differences for teriflunomide in comparison to placebo, however only nominally since the primary

analysis failed to show statistical significance. Patients in the placebo group relapsed earlier than in the teriflunomide group (median duration of 37.00 weeks and 72.14 weeks, respectively) (Table 5).

Table 5: Analysis of time to first confirmed clinical relapse or high MRI activity meeting criteria for switching into OL period during the DB treatment period (ITT population)

	Placebo (N=57)	Teriflunomide (N=109)
Number of patients with confirmed clinical relapse or high MRI activity meeting criteria, N (%)	39 (68.4)	54 (49.5)
Number of patients who were censored, N (%)	18 (31.6)	55 (50.5)
Median survival time (95% CI)	37.43 (35.86, 59.29)	87.57 (56.71, NC)
Mean survival time (95% CI)	51.10 (42.97, 61.26)	64.01 (57.55, 71.39)
Time to first confirmed clinical relapse or high MRI activity meeting criteria (weeks)		
Number	57	109
Mean (SD)	48.57 (33.72)	62.29 (36.20)
Median	37.00	72.14
Min ; Max	0.1 ; 98.0	0.1 ; 98.7
Kaplan-Meier estimates of probability of confirmed clinical relapse or high MRI activity meeting criteria (95% CI) at ^a		
24 Weeks	0.232 (0.132 ; 0.349)	0.183 (0.117 ; 0.261)
48 Weeks	0.558 (0.417 ; 0.677)	0.379 (0.288 ; 0.469)
72 Weeks	0.654 (0.511 ; 0.764)	0.466 (0.369 ; 0.557)
96 Weeks	0.720 (0.575 ; 0.823)	0.505 (0.407 ; 0.596)
Hazard Ratio (95% CI) ^b	-	0.566 (0.368 ; 0.870)
Stratified Log-Rank test p-value ^c	-	0.0409

Note: Confirmed clinical relapse must have objective signs on the examining neurologist's examination confirming the event and must then be reviewed and confirmed by an independent relapse adjudication panel (RAP). Time to event is calculated as date of confirmed clinical relapse or high MRI activity (whichever comes first) - randomization date + 1 day. The North Africa and North America were combined for region stratum due to small sample size.

a Derived from Kaplan-Meier estimates

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

c Derived from log-rank test with stratification of region and pubertal status

For the analysis of the above described composite endpoint "time to relapse or high MRI activity" addressed as part of the pre-specified sensitivity analyses for the primary endpoint, a *post-hoc* analysis using placebo-based multiple imputations (jump to reference) to handle early permanent discontinuation of treatment/DB period to assess deviations from the non-informative censoring assumption has been provided upon request. Results were consistent with the results of the pre-planned analysis, apparently due to the fact that only few patients discontinued without event (Table 6). An additional post-hoc analysis considering interval censoring of the MRI component supported the pre-planned analysis. Apparently, interval censoring seems less relevant for the actual data.

Table 6: Analysis of time to first composite endpoint during the DB treatment period using jump to reference multiple imputation approach until weeks 96 - ITT population

	Placebo (N=57)	Teriflunomide (N=109)
Without multiple imputation:		
Number of patients with confirmed clinical relapse or high MRI activity meeting criteria, N (%)	39 (68.4)	54 (49.5)
Number of patients who were censored, N (%)	18 (31.6)	55 (50.5)
Number of discontinued patients with no events of relapse or high MRI activity	4 (7.0)	6 (5.5)
Time to first confirmed clinical relapse or high MRI activity meeting criteria (weeks)		
Number	57	109
Mean (SD)	48.57 (33.72)	62.29 (36.20)
Median	37.00	72.14
Min ; Max	0.1 ; 98.0	0.1 ; 98.7
With multiple imputation:		
Nonparametric Kaplan-Meier estimates of probability of confirmed clinical relapse or high MRI activity meeting criteria (95% CI) at ^a		
Week 24	0.226 (0.125 ; 0.346)	0.174 (0.110 ; 0.251)
Week 48	0.566 (0.423 ; 0.687)	0.373 (0.281 ; 0.464)
Week 72	0.660 (0.516 ; 0.771)	0.452 (0.354 ; 0.545)
Week 96	0.717 (0.575 ; 0.819)	0.503 (0.400 ; 0.597)
Hazard Ratio (95% CI) ^b		0.514 (0.334 ; 0.789)
Stratified Log-Rank test p-value ^c		0.0380

Note: Confirmed clinical relapse must have objective signs on the examining neurologist's examination confirming the event and must then be reviewed and confirmed by an independent relapse adjudication panel (RAP).

Time to event is calculated as date of confirmed clinical relapse or high MRI activity (whichever comes first) - randomization date + 1 day for patient who completed the DB period. Follow-up time for patient who discontinued from the DB period was imputed based on Kaplan-Meier multiple imputation method. Imputation was performed 200 times.

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

a Derived from nonparametric Kaplan-Meier estimates

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

c Derived from log-rank test with stratification of region and pubertal status.

Kaplan-Meier multiple imputation approach was used based on placebo data only to implement jump to reference imputation.

PP analyses for the primary endpoint (including the sensitivity analysis counting also high MRI activity as an event) were in line with the primary analyses. With regard to the analysis counting also MRI activity as an event the probability of having an event by week 48 was 58.2% and 37.7% in the placebo and teriflunomide arm, respectively and therefore comparable to that of the primary pre-specified analysis although not statistically significant ($p = 0.0558$).

Secondary efficacy endpoints

Key secondary endpoints:

Number of new or enlarged T2-lesions

A (nominal) significant reduction in the rate of new or enlarged T2 lesions per MRI scan was demonstrated with teriflunomide, compared to placebo (4.7 and 10.5 lesions, respectively, ($p=0.0006$), corresponding to a 55% reduction over the DB treatment period (rate ratio [RR]: 0.450; 95% CI: 0.285 to 0.711) (Table 7).

Table 7: Analysis of number of new or enlarged T2-lesions per MRI scan (ITT population)

	Placebo (N=57)	Teriflunomide (N=109)
Patients with ≥ 1 new or enlarged T2 lesions, N(%)		
Yes	38 (84.4)	85 (85.0)
No	7 (15.6)	15 (15.0)
Patient level new and enlarged T2 lesions per MRI scan ^a		
Number	45	100
Mean (SD)	17.8 (26.3)	7.2 (9.3)
Median	5.0	4.1
Min ; Max	0 ; 134	0 ; 42
Total number of new or enlarged T2 lesions	1542	1800
Total number of MRI scans	123	339
Unadjusted number of new or enlarged T2 lesions per MRI scan ^b	12.537	5.310
Adjusted number of new or enlarged T2 lesions per MRI scan ^c		
Estimate (95% CI)	10.515 (4.705, 23.500)	4.735 (2.122, 10.567)
Relative risk (95% CI)		0.450 (0.285, 0.711)
P-value		0.0006

a The number of new and enlarged T2-lesions for each patient divided by the number of scans for that patient.

b The total number of new and enlarged T2 lesions divided by the total number of MRI scans during the DB treatment period

c Negative binomial regression model with robust variance estimation, with total number of new and enlarged T2-lesions as response variable, with treatment group, region, pubertal status and age as covariates and log-transformed number of scans a as an offset variable.

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

Number of Gadolinium-enhancing T1 lesions

A (nominal) significant reduction in the rate of Gd-enhancing T1 lesions was demonstrated with teriflunomide ($p < 0.0001$), compared to placebo (1.9 and 7.5 lesions, respectively), corresponding to a 75% reduction at the end of the DB treatment period (RR: 0.253; 95% CI: 0.126 to 0.505). While post-baseline, the mean number of T1 Gd-enhancing lesions in the teriflunomide group declined from 3.9 at baseline to 1.4, the mean number of T1 Gd-enhancing lesions in the placebo group increased from 3.9 at baseline to 5.1 (Table 8).

Table 8: Analysis of number of T1 Gd-enhancing lesions per MRI scan (ITT population)

	Placebo (N=57)	Teriflunomide (N=109)
Baseline		
Patients with ≥ 1 T1 Gd-enhancing lesions, N(%)		
Yes	31 (54.4)	57 (53.3)
No	26 (45.6)	50 (46.7)
Patient level T1 Gd-enhancing lesions per MRI scan ^a		
Number	57	107
Mean (SD)	3.9 (7.7)	3.9 (7.5)
Median	1.0	1.0
Min ; Max	0 ; 38	0 ; 39
Post-baseline		
Patients with ≥ 1 T1 Gd-enhancing lesions, N(%)		
Yes	32 (71.1)	55 (55.0)
No	13 (28.9)	45 (45.0)
Patient level T1 Gd-enhancing lesions per MRI scan ^a		
Number	45	100
Mean (SD)	5.1 (11.7)	1.4 (3.6)
Median	0.8	0.2
Min ; Max	0 ; 56	0 ; 26
Total number of T1 Gd-enhancing lesions	386	316
Total number of MRI scans	123	339
Unadjusted number of T1 Gd-enhancing lesions per MRI scan ^b	3.138	0.932
Adjusted number of T1 Gd-enhancing lesions per MRI scan ^c		
Estimate (95% CI)	7.505 (2.482, 22.695)	1.897 (0.656, 5.489)
Relative risk (95% CI)		0.253 (0.126, 0.505)
P-value		<0.0001

a The number of T1 Gd-enhancing lesions for each patient divided by the number of scans for that patient.

b The total number of T1 Gd-enhancing lesions divided by the total number of MRI scans during the DB treatment period

c Negative binomial regression model with robust variance estimation, with total number of T1 Gd-enhancing lesions as response variable, with baseline, treatment group, region, pubertal status and age as covariates and log-transformed number of scans as an offset variable-

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

As the study failed its primary endpoint and multiplicity was planned to be controlled across primary and secondary endpoints via hierarchical testing, none of these key secondary endpoints can be claimed "statistically significant".

Requested *post-hoc* analyses for the key secondary endpoints showed that at week 36, 21 scans were performed under placebo and 44 scans under teriflunomide. Ignoring these scans similar results were obtained as in the pre-planned analyses.

Additional *post hoc* analyses were provided upon request for all MRI endpoints that included all available MRI assessments performed within 96 weeks after randomization (including those obtained after the DB period due to early treatment discontinuation or switch to OL teriflunomide treatment). According to the provided analyses 44 additional scans were included for placebo and 35 additional scans were included for teriflunomide as compared to the analysis of the DB period. The number of additional scans included,

however, is relatively small as compared to the number of remaining missing scans until week 96. Hence, missing data imputation remains critical.

Considering 21+44 scans at week 36, in total $4 \times 57 + 21 = 249$ scans would have been expected for placebo and $4 \times 109 + 44 = 480$ for teriflunomide, leading to $249 - 123 = 126$ scans for placebo patients and $480 - 339 = 141$ for teriflunomide patients that were missing in the reported analysis, of which 44 and 35 scans were added in the analysis of the DB and OL phase, corresponding to 35% and 25%. Whereas results from the combined data of DB and OL phase could have been reassuring and even conservative due to the switch from placebo to the active treatment, the large amount of remaining missing scans does not allow for a confirming conclusion. During the procedure, the Applicant provided the number of missing scans. However, the Applicant confirmed that the additional value of the analyses including OL data is limited but still supportive due to a positive trend.

With regard to the requested sensitivity analysis for the number of new/newly enlarged T2 lesions the Applicant took the number of T2 lesions into account as the number of new/enlarged T2 lesions is assessed in reference to the MRI scans of the previous visit. Thus, it is not a value that could be presented at baseline. A (nominal) significant reduction in the rate of new or enlarged T2 lesions per MRI scan was demonstrated with teriflunomide, compared to placebo (3,6 and 5,4 lesions, respectively) ($p = 0.0446$), corresponding to a 33% reduction over the DB treatment period (rate ratio [RR]: 0.665; 95%CI: 0.447 to 0.990). The relative risk reduction in this analysis (with adjustment for baseline T2 lesion count) is lower compared to the 55% relative reduction in the pre-defined analysis (estimated without adjusting for baseline T2 lesion count). This might be due to some baseline imbalances in T2 lesions (mean of 51 vs 60) favouring placebo in the unadjusted analysis. Although both analyses showed a nominally significant effect, the adjusted analysis reduced considerably the effect size due to the reported considerable baseline differences. Due to these baseline differences, the adjusted analysis, even not pre-specified, is considered to yield a more accurate treatment effect estimate.

Further requested and provided *post hoc* analyses showed, that the results do not appear to be robust when relevant missing data imputation is applied in a setting with large proportion of missing data in the DB period. 70% of placebo patients and 47% of teriflunomide patients had MRI data to be imputed. Referring to the number of missing scans, this lack of robustness cannot be rebutted by an analysis on all MRI scans, including those taken in the OL period, since the number of additional scans in the OL period remains small compared to the number of remaining missing scans. Whereas the large amount of missing data itself raises concerns about the robustness of the data, the analyses with imputed data drastically reduce the treatment effect and, consequently, no significant treatment effect is given. Taking into account, that this reduction in effect is mainly due to the imputation in the active treatment group and considering the fact that missing data in most cases occurred after patients had switched to the OLE phase because of having experienced a relapse or a high MRI activity, obviously correlated with an unfavourable outcome in the key secondary endpoints, the requested reference-based imputation method appears justified as a conservative sensitivity analysis. Due to the large amount of missing data, it appears informative to use a missing data imputation method that is capable to model a vanishing effect difference in patients with missing MRI data, even if this can be considered as rather conservative. Applying this approach the effect is approximately halved and the nominal statistical significance disappears.

Table 9: Analysis of number of new or enlarged T2-lesions per MRI scan using jump to reference multiple imputation approach until weeks 96 - ITT population

	Placebo (N=57)	Teriflunomide (N=109)
Number of patients with imputed MRI data for early withdrawn in the double-blind period	40 (70.2)	51 (46.8)
Patient level new and enlarged T2 lesions per MRI scan with imputation data		
Number	57	109
Mean (SD)	18.5 (24.8)	12.3 (17.4)
Median	11.0	5.2
Min ; Max	0 ; 142	0 ; 81
Mean of total number of new or enlarged T2 lesions ^a	4821.845	6078.765
Mean of total number of MRI scans	249	479
Mean of unadjusted number of new or enlarged T2 lesions per MRI scan ^b	19.365	12.691
Adjusted number of new or enlarged T2 lesions per MRI scan ^c		
Estimate (95% CI)	11.803 (5.281, 26.381)	8.359 (3.381, 20.666)
Relative risk (95% CI)		0.708 (0.391, 1.282)
P-value		0.2541

a The number of new and enlarged T2-lesions for each patient divided by the number of scans for that patient. b The total number of new and enlarged T2 lesions divided by the total number of MRI scans from randomization up until 96 weeks after randomization.

c Negative binomial regression model with robust variance estimation, with total number of new and enlarged T2-lesions as response variable, with treatment group, region, pubertal status and age as covariates and log-transformed number of scans as an offset variable.

The North Africa and North America were combined for region stratum due to small sample size. Patients early withdrawn due to switch to the OL period or discontinuation in the DB period were imputed using jump to reference multiple imputations up to week 96 after randomization. Imputation was performed 200 times

Table 10: Analysis of number of T1 Gd-enhancing lesions per MRI scan using jump to reference multiple imputation approach until weeks 96 - ITT population

	Placebo (N=57)	Teriflunomide (N=109)
Number of patients with imputed MRI data for early withdrawn in the double-blind period	40 (70.2)	51 (46.8)
Baseline		
Patients with ≥ 1 T1 Gd-enhancing lesions, N(%)		
Yes	31 (54.4)	57 (53.3)
No	26 (45.6)	50 (46.7)
Patient level T1 Gd-enhancing lesions per MRI scan ^a		
Number	57	107
Mean (SD)	3.9 (7.7)	3.9 (7.5)
Median	1.0	1.0
Min ; Max	0 ; 38	0 ; 39
Post-baseline		
Patient level T1 Gd-enhancing lesions per MRI scan with imputation data		
Number	57	109
Mean (SD)	124.4 (898.1)	29.2 (219.9)
Median	1.2	0.4
Min ; Max	0 ; 6785	0 ; 2249
Mean of total number of T1 Gd-enhancing lesions ^a	28494.955	13052.065
Mean of total number of MRI scans	249	479
Mean of unadjusted number of T1 Gd-enhancing lesions per MRI scan ^b	114.438	27.249
Adjusted number of T1 Gd-enhancing lesions per MRI scan ^c		
Estimate (95% CI)	9.113 (3.292, 25.230)	5.781 (1.614, 20.706)
Relative risk (95% CI)		0.634 (0.247, 1.630)
P-value		0.3441

a The number of T1 Gd-enhancing lesions for each patient divided by the number of scans for that patient.

b The total number of T1 Gd-enhancing lesions divided by the total number of MRI scans from randomization up until 96 weeks after randomization.

c Negative binomial regression model with robust variance estimation, with total number of Gd-enhancing T1 lesions as response variable, with treatment group, baseline Gd-enhancing T1 lesion count, region, pubertal status and age as covariates and log transformed number of scans as an offset variable. The North Africa and North America were combined for region stratum due to small sample size. Patients early withdrawn due to switch to the OL period or discontinuation in the DB period were imputed using jump to reference multiple imputations up to week 96 after randomization. Imputation was performed 200 times.

PP analyses for the key secondary MRI based endpoints were in line with the primary analyses.

Other secondary endpoints

Proportion of clinical relapse-free patients: At week 96 59.4% of the patients in the teriflunomide treatment arm were relapse free compared to 45.5% under placebo.

Other MRI related endpoints

Analyses of these other MRI related endpoints are only exploratory and no confirmatory conclusions can be made based on the results for these endpoints.

Volume of T2 lesions: At Week 96, the mean change from baseline in volume of T2 lesions were 0.073 mL in the teriflunomide group and 0.201 mL in the placebo group with a least square (LS) mean (standard error [SE]) difference from placebo of -0.128 (0.049) mL ($p=0.0100$). The mean patient level volume (SD) of T2-lesions per scan was significantly lower in the teriflunomide group (13.8 [23.0] mL) when compared to the placebo group (15.7 [18.1] mL) ($p=0.0223$).

Volume of T1 hypointense lesions: No statistical difference was observed between the teriflunomide and the placebo treatment arm on the volume of T1 hypointense lesions per scan. The mean patient level total volume (SD) of T1 hypointense lesions per scan was similar in both groups: 2.8 [7.4] mL and 2.9 [6.4] mL in the teriflunomide and the placebo groups, respectively.

New hypointense T1 lesions: Teriflunomide significantly reduced the number of new hypointense T1 lesions per MRI scan by 49% compared to placebo (RR: 0.507; 95% CI: 0.281 to 0.913, $p=0.0236$). The observed mean of new T1 lesions per scan was lower in the teriflunomide group (3.7) than in the placebo group (8.1). The adjusted number of such T1 lesions was 1.2 in the teriflunomide group and 2.4 in the placebo group.

Proportion of patients free of new or enlarged T2 lesions: At Week 96, 10.1% of patients in the teriflunomide group and 3.5% of patients in the placebo group were free of new or enlarged T2-lesions.

Brain volume: A decrease in the brain volume has been observed in both treatment groups. No statistical difference was observed between the teriflunomide and placebo groups on the percentage change in brain volume. The mean percent changes in brain volume from baseline to Week 96 (MMRM data) were -0.529 in the teriflunomide group and -0.570 in the placebo group.

Change from baseline in EDSS: No relevant changes in EDSS scores were seen from study start until the end of the 96 weeks period. Results for the EDSS score were only descriptively summarized: the mean (SD) EDSS score at baseline was 1.4 (0.9) and 1.2 (0.9) for the placebo and the teriflunomide treatment group, respectively, while at week 96 the mean (SD) EDSS score was 1.7 (1.2) and 1.2 (0.9) respectively, representing a slight deterioration under placebo of 0.3. Requested *post hoc* analyses on 6-month confirmed disability progression (CDP-6M), both for the DB treatment period and for the first 96 weeks regardless of patients discontinuing the DB-period and switching to OL teriflunomide, showed that only few patients experienced a CDP-6M in the DB period with 2 (3.5%) patients in the placebo group and 5 (4.6%) patients under teriflunomide treatment. However, due to the switch to OL rescue treatment which was disproportionately higher in the placebo group compared to the teriflunomide group these results are difficult to interpret. During the 96-week period, better results were provided for CDP-6M in the active treatment arm with 8 (14.0%) patients in the placebo group and 9 (8.3%) patients in the teriflunomide group who experienced a CDP-6M.

Cognitive outcome

SDMT: No statistical difference was observed between the teriflunomide and placebo groups on the change in number of completed items and correct substitutions measured by SDMT.

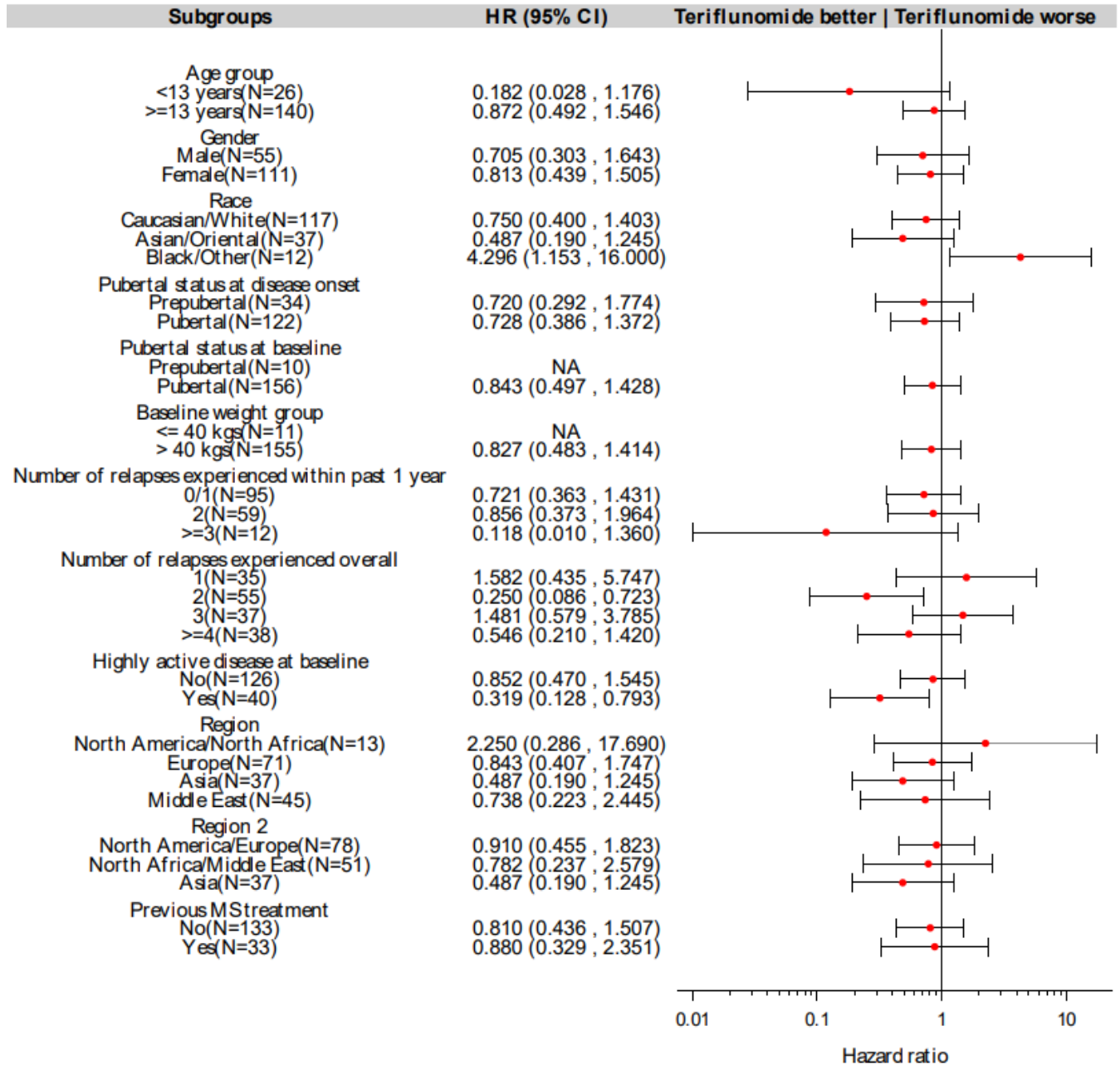
Cognitive Battery Tests: No meaningful differences between groups were observed for cognitive tests. These tests included BVMT-R, trail making test A and B, Beery VMI raw score, Wechsler abbreviated scale of intelligence II Vocabulary total raw score, D-KEFS letter fluency, category fluency and category switching total correct responses raw score, and selective reminding test.

Proportion of disease-free patients (exploratory endpoint): At Week 96, 6.4% of the patients in the teriflunomide group and 1.8% of the patients in the placebo group were disease free according to the defined criteria as stated in the statistical section. However, week 96 results are based on a very small number of patients that limit the overall conclusions.

Ancillary analyses

Subgroup analyses of the primary endpoint (pre-specified):

Figure 3: Subgroup analysis: Summary of time to first confirmed clinical relapse after randomization during DB treatment period by all subgroups (forest plot) (ITT population)



Note: Confirmed clinical relapse must have objective signs on the examining neurologist's examination confirming the event and must then be reviewed and confirmed by an independent relapse adjudication panel (RAP).

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

Hazard ratio for each subgroup is derived using Cox proportional-hazards model with treatment group, region and pubertal status as covariates and with robust variance estimation.

The North Africa and North America were combined for region stratum, the Black and Other were combined for race subgroup, the 0 and 1 were combine for number of relapse experienced within past 1 year due to small sample size.

For the region 2 subgroup analysis, the small region North America is combined with Europe, North Africa is combined with Middle East and Asia is analysed separately. Region 2 is not used as a stratum in the Cox proportional-hazards model for other subgroup analyses.

Results of the subgroup analyses were in favour of teriflunomide and overall consistent except for the subgroup of Black/Others patients, for the subgroup of patients from North America/North Africa region (these 2 different regions were pooled due to small numbers of patients and numbers of relapses experienced overall), and for the subgroup of patients who experienced 1 or 3 relapses overall. In the subgroup of patients with 2 relapses experienced overall before randomization teriflunomide significantly reduced the risk of a confirmed clinical relapse by 75.0% (HR: 0.250; 95% CI: 0.086 to 0.723). In the subgroup of patients with highly active disease at baseline teriflunomide significantly reduced the risk of a confirmed clinical relapse by 68.1% (HR: 0.319; 95% CI: 0.128 to 0.793).

Analyses with regard to dosing recommendations:

For the teriflunomide group, there was a process of dose adjustment in the paediatric population, based on BW, and with individual dose adjustment based on predicted exposure during the 8-week PK run-in phase, in which patients received half their target dose. The underlying assumption was that the appropriate exposure in children would be similar to that obtained in adults with the 14 mg once daily dose, which was shown to have the best benefit/risk. (Reference is made to the PK section).

Clinical relapses may have occurred before the therapeutic effect was developed, as indicated by the larger effect size and lower p value in the sensitivity analyses, excluding the clinical relapses observed during the PK run-in phase, compared to the primary analysis, which included all relapses since randomization: HR (95% CI): 0.657 (0.388 to 1.113); p=0.2949 for the primary analysis, and HR (95% CI): 0.507 (0.282 to 0.911), p=0.0815 for sensitivity analysis excluding the relapses. According to the Applicant, it is therefore probable that the 8-week half-dose phase had a negative impact on the study results, and it is therefore intended to start immediately teriflunomide treatment at the full dose.

From a statistical point of view, censoring patients at time of relapse in the PK run-in is questionable and therefore, this analysis should be considered with caution. However, no additional analysis can be recommended to robustly derive the efficacy for an application of teriflunomide without titration from the current study. From a clinical perspective, the analysis provides little information with regard to the benefit/ risk for use of teriflunomide without titration. However, overall the efficacy is not expected to be essentially impacted by starting with the adult equivalent dose.

Consistency of the efficacy of teriflunomide in the paediatric and adult RMS populations:

Key results of Study EFC11759/TERIKIDS are presented side by side with those of Study EFC6049/TEMSO and EFC6260/TOPIC, which were the 2 studies with both clinical and MRI evaluations over a similar duration. Only the information on the 14 mg daily dose is provided for the adult studies, as this is the basis for the 14 mg daily recommended dose for paediatric patients with RRMS based on BW, with which Study EFC11759/TERIKIDS was designed.

Table 11: Key efficacy results in paediatric and adult patients

	Study EFC11759/TERIKIDS ^a	Study EFC6049/TEMPO ^b	Study EFC6260/TOPIC ^c
Population and methods	RRMS 96 weeks or switch if confirmed clinical relapse or high MRI activity	RMS 108 weeks	CIS 108 weeks or switch if confirmed clinical relapse
Baseline characteristics			
Number of relapses in past year (Mean [SD])	1.5 (0.7)	1.4 (0.7)	NA
Number of Gd-enhancing lesions at baseline (Mean [SD])	3.9 (7.6)	1.66 (4.28)	1.3 (3.6)
Time to clinical relapse (HR, [95% CI])	0.657 (0.388, 1.113)	0.719 (0.577, 0.895)	0.574 (0.379, 0.869)
Time to clinical relapse or MRI activity (HR, [95% CI])	0.566 (0.368, 0.870)	NA	0.651 (0.515, 0.822)
Number of Gd-enhancing T1 lesions/scan (RR [95% CI])	0.253 (0.126, 0.505)	0.196 (0.120, 0.321)	0.415 (0.248, 0.694)
Number of new or enlarging T2 lesions	0.450 (0.285, 0.711)	0.306 (0.228, 0.411)	0.451 (0.305, 0.665)
Volume of lesions			
LS Mean difference from placebo (SE)	0.128 (0.049)	-0.089 (0.025)	0.091 (0.044)
95% CI	(-0.225 to -0.031)	(-0.137 to -0.041)	(-0.177 to -0.005)
p-value (versus placebo)	0.0100	0.0003, cubic root transformed	0.0374

Abbreviations: CI, confidence interval; CIS, clinically isolated syndrome; Gd, gadolinium; HR, hazard ratio; MRI, magnetic resonance imaging; MS, multiple sclerosis; NA, not applicable; RMS, relapsing multiple sclerosis; RR, relative risk; RRMS, relapsing remitting multiple sclerosis; SD, standard deviation.

a TERIKIDS study: clinical relapses confirmed by adjudication panel, high MRI activity threshold for the composite endpoint; volume of MRI lesions includes T2 lesions.

b TEMPO and TOPIC studies: volume of lesions include T1-enhancing lesions and T2 lesions, without double-counting (combined unique lesions).

c TOPIC study: relapses confirming clinical diagnosis of MS.

From Table 11, it is not possible to meaningfully compare effect sizes, i.e. for time to relapse, or number of Gd-enhancing lesions between the paediatric study and studies performed in adult patients as there were numerous specificities in the design of each study. However, since efficacy of teriflunomide has already been demonstrated in adult patients with RRMS, the Applicant was invited to consider and justify extrapolation of efficacy from the adult to the paediatric population with RRMS.

During the procedure, the Applicant provided data for the extrapolation of efficacy from the adult teriflunomide patient population to the paediatric patient population based on MRI endpoints taking the EMEA reflection paper on the use of extrapolation in the development of medicines for paediatric into account. The possibility to extrapolate efficacy from adults to children was justified based on arguments that genetic, serum, CSF and cell-based studies largely support a shared biology between paediatric-onset and adult-onset disease. However, the Applicant also mentioned "The PK results of EFC11759/TERIKIDS show overall consistency of PK profiles in children and adults which supports the efficacy extrapolation from adult patients to the paediatric population to determine the overall paediatric treatment effect." In our understanding, consistency of PK profiles between children and adults is not considered a justification for efficacy extrapolation nor needed as a prerequisite. Justification needs to be given for the assumption that similar exposure will lead to similar PD and efficacy outcome in children compared to adults. Subsequently, an optimal dose for the target paediatric population can be defined (with the help of a qualified PK model and observed paediatric PK data) to achieve same exposure in children compared to adults.

From the clinical studies performed in adult patients, Study TEMPO and TOPIC were considered relevant for the efficacy extrapolation due to the similar 2-year study duration compared to TERIKIDS and a similar frequency and MRI visit schedules in TERIKIDS.

The primary extrapolation was based on the adult RMS TEMPO data only since TOPIC was conducted in a CIS population, i.e. TEMPO data were used to derive an informative prior to analyze the TERIKIDS data with a Bayesian approach. Supportive analyses using data from both TEMPO and TOPIC to assess

the robustness of the extrapolation results were also provided. The patients enrolled in Study TOPIC included patients who could retrospectively be diagnosed as MS as per McDonald 2010 criteria applied retrospectively at study entry based on MRI information. However, as the classification was not possible in all patients based on the information available (295/618 not classified) and the numbers were small (78 met the diagnosis criteria [only 25 in the teriflunomide 14mg group], 245 did not meet the diagnosis), this classification has not been used for additional sensitivity analyses.

The efficacy extrapolation from the adult to the paediatric population was conducted for two MRI endpoints: 1) number of Gd-enhancing T1 lesions and 2) number of new or enlarging T2 lesions. Both endpoints are well established for assessing the inflammatory component of MS and have been widely used in MS clinical trials. Furthermore, both were prospectively defined as key secondary efficacy endpoints in TERIKIDS and were important secondary endpoints in the teriflunomide adult development program.

MRIs were performed approximately every 6 months in the 3 studies, based on a standardized acquisition in certified centers followed by central reading of the images. Methods between the adult and paediatric studies were essentially similar, with a few differences. In the 3 studies, the number of Gd-enhancing lesions was assessed independently on each scan, and the number of new and enlarged T2 lesions was assessed with respect to the previous scan. A difference between the adult studies and TERIKIDS was that the T2 lesions were measured separately of the Gd-enhancing lesions in TERIKIDS, whereas the key variable in the 2 adult studies was the unique active lesions, which was computed as the addition of T2 lesions with no Gd-enhancement and lesions with Gd-enhancement. As Gd-enhancing lesions generally appear as T2 lesions, the T2 variable in TERIKIDS and unique active lesion in the adult studies are similar, and in consequence the number of unique active lesions of Studies TEMSO and TOPIC was used as a proxy for the number of new or enlarging T2 lesions which is considered acceptable.

With regard to the statistical methods that were used, an informative prior derived from adult study TEMSO (and additionally from studies TEMSO and Topic) was used to analyse the TERIKIDS data with a Bayesian approach.

Table 12: Summary of extrapolation results for key secondary MRI endpoints: relative risk and risk difference for teriflunomide versus placebo (posterior probability of relative risk < 1: > 0.999 in all cases)

MRI Parameter/ Approach/ Effective Sample Size from Adult Data	TERIKIDS	TERIKIDS + Informative Prior from TEMSO (Primary)		TERIKIDS + Informative Prior from TEMSO+TOPIC (Sensitivity)	
	RR (95% CI) for teri 14 mg vs placebo	RR (95% CI) for teri 14 mg vs placebo in pediatric population	RD (95% CI) for teri 14 mg vs placebo in pediatric population	RR (95% CI) for teri 14 mg vs placebo in pediatric population	RD (95% CI) for teri 14 mg vs placebo in pediatric population
Gd-enhancing T1 lesions/scan	0.253 (0.126, 0.505)				
Approach 1					
ESS=40		0.271 (0.135, 0.545)	-2.909 (-5.893, -1.065)	0.297 (0.150, 0.604)	-2.626 (-5.223, -0.903)
ESS=80		0.284 (0.153, 0.536)	-2.743 (-5.198, -1.074)	0.326 (0.176, 0.613)	-2.361 (-4.545, -0.848)
ESS=120		--	--	0.351 (0.200, 0.617)	-2.143 (-3.988, -0.832)
Approach 2					
ESS=40		0.261 (0.131, 0.521)	-3.005 (-5.953, -1.130)	0.269 (0.133, 0.548)	-2.917 (-5.815, -1.056)
ESS=80		0.270 (0.145, 0.508)	-2.880 (-5.377, -1.204)	0.282 (0.152, 0.535)	-2.739 (-5.128, -1.118)
ESS=120		0.275 (0.154, 0.492)	-2.813 (-5.169, -1.252)	0.291 (0.163, 0.508)	-2.655 (-4.828, -1.175)
ESS=160		0.280 (0.163, 0.472)	-2.753 (-4.916, -1.320)	0.296 (0.173, 0.499)	-2.586 (-4.595, -1.200)
New/enlarging T2 lesions/scan	0.450 (0.285, 0.711)				
Approach 1					
ESS=40		0.479 (0.306, 0.744)	-8.294 (- 15.416, - 2.915)	0.506 (0.323, 0.781)	-7.595 (- 14.600, -2.447)

ESS=80		--	--	0.541 (0.366, 0.799)	-6.712 (-12.558, -2.145)
Approach 2					
ESS=40		0.435 (0.279, 0.674)	-9.614 (-17.376, -3.905)	0.440 (0.281, 0.687)	-9.457 (-17.327, -3.729)
ESS=80		0.429 (0.287, 0.635)	-9.771 (-16.598, -4.503)	0.439 (0.296, 0.648)	-9.440 (-16.173, -4.291)
ESS=120		0.422 (0.295, 0.598)	-9.962 (-16.180, -5.159)	0.436 (0.308, 0.623)	-9.510 (-15.495, -4.655)
ESS=160		0.420 (0.307, 0.578)	-10.010 (-15.656, -5.499)	0.437 (0.313, 0.604)	-9.427 (-15.282, -5.063)

Note: RR: relative risk; RD: risk difference; CI: credible interval; relative risk reduction = 100*(1- RR)

Whereas approach 1 uses the age distribution from TERIKIDS to derive a prior from the adult studies relevant for this age distribution, approach 2 did not take age into account. Using different weighing of the adult data corresponding to different effective sample sizes, results were obtained similar to the results from TERIKIDS study. Whereas approach 1 relies on the specific functional relation of the efficacy parameter to age, approach 2 prior relies on the assumption that efficacy is unrelated to age. Obviously, both assumptions are difficult to verify using adult data only, but similarity between the results of both approaches appears reassuring.

In conclusion, the Applicant has demonstrated that integration of the adult MRI data into the paediatric data in a Bayesian way does not change the results considerably.

Summary of main study

The following table summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13: Summary of efficacy for trial EFC11759

Title: A two-year, multicenter, randomized, DB, placebo-controlled, parallel group trial to evaluate efficacy, safety, tolerability, and pharmacokinetics of teriflunomide administered orally once daily in paediatric patients with relapsing forms of multiple sclerosis followed by an OL extension	
Study identifier	EFC11759; EudraCT no. 2011-005249-12
Design	Multicenter, randomized, DB, placebo-controlled, parallel group including a PK run-in phase to provide individual PK parameters for dose adjustment with the intention that patients randomized to teriflunomide would receive a 14 mg adult-equivalent dose from week 8 onwards Early switch: patients who experienced new disease activity (high MRI activity or a relapse) after the PK run-in could switch earlier to the OL period

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	variable; up to 96 weeks after randomization 8 weeks ongoing (data cut-off: 27 Nov 2019)	
Hypothesis	Superiority		
Treatments groups	Teriflunomide (terifl.)	Oral teriflunomide tablets once daily: PK run-in phase: patients received a terifl. 7mg equivalent adult dose: terifl. 3.5mg (BW ≤40 kg) or terifl. 7mg (BW >40kg); 8 weeks thereafter continuation with a terifl. 14mg adult equivalent dose: terifl. 7 mg (BW ≤40kg) or terifl. 14mg (BW >40kg); up to week 96 n = 109 randomized	
	Placebo	oral placebo tablets once daily, up to 96 weeks; n = 57 randomized	
Endpoints and definitions	Primary endpoint	Time to first clinical relapse	After randomization up to the end of DB treatment (based on confirmed protocol defined relapses)
	Key secondary endpoint	Number of new/newly enlarged T2 lesions	Step-down testing procedure was applied to ensure a strong control of the type-I error rate
	Key secondary endpoint	Number of Gd-enhancing T1 lesions	Step-down testing procedure was applied to ensure a strong control of the type-I error rate
	Secondary endpoint	EDSS score	Change from baseline summarized descriptively at each visit
	Secondary endpoint	SDMT	Change in number of completed item measured by SDMT and correct substitutions
Database lock	27 November 2019		

Results and Analysis

Analysis description	Primary Analysis		
Analysis population and time point	ITT (all randomized patients analysed according to the treatment group allocated by randomization); up to week 96		
Descriptive statistics and estimate variability	Treatment group	Teriflunomide (14 mg adult equivalent dose)	Placebo
	Number of subject	109	57
	Primary endpoint Time to first clinical relapse Median*	75.29 wks	39.14 wks
	Min; Max	(0.1; 98.7)	(0.1; 98.0)
	Key secondary endpoint: Number of new/newly enlarged T2 lesions (mean) (SD)	7.2 (9.3)	17.8 (26.3)
	Key secondary endpoint: Number of Gd-enhancing T1 lesions postbaseline (mean) (SD)	1.4 (3.6)	5.1 (11.7)

	Secondary endpoint: change from baseline in EDSS score (mean) (SD) at week 96	1.2 (0.9)	1.7 (1.2)
	Secondary endpoint: SDMT Mean (SD) Change from baseline at week 96 - Correct substitutions -Number of completed item	8.3 (11.1) 7.1 (11.1)	9.1 (10.9) 7.6 (11.0)
Effect estimate per comparison	Primary endpoint: time to first confirmed clinical relapse	Comparison groups	Teriflunomide vs. Placebo
		KM estimates of probability of confirmed clinical relapse: 48 / 96 weeks	Teriflunomide: 0.298 / 0.389 Placebo: 0.391 / 0.531
		95% CI (week 48 / 96)	Teriflunomide: (0.214; 0.386) (0.293; 0.483) Placebo: (0.259; 0.521) / (0.360, 0.676)
		Hazard ratio***	0.657
		95% CI	(0.388; 1.113)
		P-value (stratified Log-Rank test)	0.2949
	Key secondary endpoint: Number of new/newly enlarged T2 lesions	Comparison groups	Teriflunomide vs. Placebo
		Rate ratio	0.450
		95% CI	(0.285; 0.711)
		P-value	0.0006**
	Key secondary endpoint: Number of Gd-enhancing T1 lesions	Comparison groups	Teriflunomide vs. Placebo
		Rate ratio	0.253
		95% CI	(0.126; 0.505)
		P-value	0.0001**
	Secondary endpoint: Change from baseline in EDSS Week 96 change from baseline mean (SD)	Comparison groups	Teriflunomide vs. Placebo
		na	Teriflunomide: 0.0 (0.8) Placebo: 0.1 (0.8)
	Secondary endpoint: SDMT -Correct substitution -Number of completed item	Comparison groups	Teriflunomide vs. Placebo
		LS mean Difference from placebo (SE)	0.795 (2.668)
		95% CI	(-4.506;6.095)
		p-value	0.7361
		LS mean Difference from placebo (SE)	0.909 (2.687)
95% CI		(-4.431;6.248)	
p-value		0.7361	

Notes	<p>All analyses based on ITT population</p> <p>**Hierarchical testing was planned but key secondary endpoints cannot be considered statistically significant due to failed primary endpoint.</p> <p>***HR: proportional hazard assumption not fulfilled; focus instead on estimates of the probability for relapses at different time points</p> <p>Teriflunomide: 102/109 patients completed the DB period:</p> <ul style="list-style-type: none"> - early completion due to confirmed relapse (n = 32, 29.4%), or high MRI activity (n=14, 12.8%) - completed 96-weeks DB treatment (n=56, 51.4%) <p>Placebo: 53/57 patients completed the DB period:</p> <ul style="list-style-type: none"> - early completion due to confirmed relapse (n = 22, 38.6%), or high MRI activity (n=15, 26.3%) - completed 96-weeks DB treatment (n=16, 28.1%) 		
Analysis description	First Sensitivity analysis of the primary endpoint (pre-specified): Time to first confirmed clinical relapse or high MRI activity meeting criteria for switching into OL period, whichever came first		
Descriptive statistics and estimate variability	Treatment group	Teriflunomide (14 mg adult equivalent dose)	Placebo
	Number of subjects with switch criteria	54	39
	Median*	72.14 weeks	37.00 weeks
	Min; Max	(0.1; 98.7)	(0.1; 98.0)
Effect estimate per comparison	Comparison groups		Teriflunomide vs. Placebo
	KM estimates of probability of confirmed clinical relapse or high MRI activity: 48 / 96 weeks		Teriflunomide: 0.379 / 0.505 Placebo: 0.558 / 0.720
	95% CI (week 48 / 96)		Teriflunomide: (0.288; 0.469) / (0.407; 0.596)
	Hazard ratio***		0.566
	95%CI		(0.368;0.870)
	P-value (stratified Log-Rank test)		0.0409
Analysis description	Sensitivity analysis of the key secondary endpoint: Number of new/newly enlarged T2 lesions (post-hoc upon request): Analysis of number of new or enlarged T2 lesions per MRI scan using jump to reference multiple imputation approach until weeks 96		
Descriptive statistics and estimate variability	Treatment group	Teriflunomide (14 mg adult equivalent dose)	Placebo
	Number of patients with imputed MRI data for early	51 (46.8)	40 (70.2)
	Rate ratio		0.708
	95%CI		(0.391;1.282)
Effect estimate per comparison	P-value		0.2541
Analysis description	Sensitivity analysis of the key secondary endpoint: Number of Gd-enhancing T1 lesions (post-hoc upon request): Analysis of number of T1 Gd-enhancing lesions per MRI scan using jump to reference multiple imputation approach until weeks 96		
Descriptive statistics and estimate variability	Treatment group	Teriflunomide (14 mg adult equivalent dose)	Placebo
	Number of patients with imputed MRI data for early	51 (46.8)	40 (70.2)
	Rate ratio		0.634
	95%CI		(0.247;1.630)
Effect estimate per comparison	P-value		0.3441

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive study EFC11759 – ongoing open-label extension

Methods

The OL extension period of Study EFC11759 is an ongoing long-term phase of study EFC11759 to evaluate the long-term effect with focus on long-term safety of teriflunomide.

The first patient has been enrolled: 02 April 2015; an interim analysis regarding efficacy has been provided with cut-off date: 27 November 2019.

All patients who were previously treated with placebo or teriflunomide received teriflunomide. All patients started with a 8 weeks PK run-in phase. Those who were in the teriflunomide arm remained on their adjusted 14 mg adult equivalent dose and those who were in the placebo arm underwent the PK run-in with "7 mg adult equivalent to adjust the dose". The blinded PK run-in phase was intended to provide individual PK parameters to allow individual dose adjustment to ensure that patients would reach exposure similar to that seen in adults treated with 14 mg adult-equivalent dose (the "14 mg adult-equivalent dose") for the remainder of the study.

The duration of the OL period was 96 weeks for patients who completed the 96 week BD period on treatment, and longer for patients who switched to the OL period early during the initial 96 week DB period due to a confirmed relapse or in case of high MRI activity (for a total follow-up of 192 weeks).

Patient enrolled in the OL period were patients included in the DB period of the study who had the option to continue in the OL period because patients experienced a relapse after the DB period PK run-in phase (8 weeks) confirmed by the RAP; or patients had high MRI activity, meeting protocol criteria, during the DB period; or patients completed the 96-week DB period.

152 patients were enrolled in the OL period: 100 patients in the teriflunomide/teriflunomide group and 52 patients in the placebo/teriflunomide group. As of the data cut-off date, 30 patients had completed the OL period (21 patients in the teriflunomide/teriflunomide group and 9 patients in the placebo/teriflunomide group) and 88 patients were still ongoing (61 patients and 27 patients, respectively).

Results

From randomization in the DB period to the end of the OL period, confirmed clinical relapse occurred in 44.0% of patients in the teriflunomide/teriflunomide and 61.5% of patients in the placebo/teriflunomide group. Patients in the placebo/teriflunomide group experienced the first confirmed relapse after randomization earlier (mean [SD]: 82.44 [63.57] weeks) than in the teriflunomide/teriflunomide group (mean [SD]: 95.96 [62.96] weeks).

Patients who received teriflunomide since the start of the DB period had a numerically lower risk of confirmed clinical relapse over the combined BD and OL periods than the patients who received teriflunomide only from the start of the OL period (HR: 0.61; 95% CI: 0.38 to 0.98; p=0.098).

There was a higher proportion of clinical relapse-free patients in the teriflunomide/teriflunomide group (56%) compared to the placebo/teriflunomide (38.5%) group at week 192.

During the combined DB and OL periods, the percentage of patients with at least 1 new or enlarged T2-lesion was 84.8% in the teriflunomide/teriflunomide versus 88.5% in the placebo/teriflunomide group. The adjusted number of new or enlarged T2 lesions per MRI scan was 6.289 (95% CI: 3.656 to 10.819) in the teriflunomide/teriflunomide and 13.038 (95% CI: 7.638 to 22.255) in the placebo/ teriflunomide group.

During the combined DB and OL periods, the percentage of patients with at least 1 Gd-enhancing lesion increased more from baseline to post-baseline in the placebo/teriflunomide group (53.8% versus 75%) than in the teriflunomide/teriflunomide group (52% versus 57.6%). The adjusted number of Gd-enhancing lesion per MRI scan was 1.933 (95% CI: 0.701, 5.334) in the teriflunomide/ teriflunomide group and 4.195 (95% CI: 1.775 to 9.916) in the placebo/teriflunomide group, corresponding to a RR reduction of 53.9% (RR: 0.461; 95% CI: 0.254 to 0.835, p=0.0106).

Of the 152 patients, 21 patients (21.0%) in the teriflunomide/teriflunomide group and 13 patients (25.0%) in the placebo/teriflunomide group experienced at least 1 confirmed clinical relapse during the OL period. The adjusted annualized relapse rate (ARR) in the OL period was low and similar across the treatment groups (0.158 in the teriflunomide/teriflunomide group and 0.141 in the placebo/teriflunomide group).

During the combined DB and OL periods, disability progression sustained for 24 weeks occurred in 13.0% of patients in the teriflunomide/ teriflunomide group and 21.2% in the placebo/ teriflunomide group.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In support of efficacy of teriflunomide in paediatric patients from 10 years to 17 years of age with RRMS the Applicant submitted one pivotal study, study EFC11759 (TERIKIDS), in line with the agreed PIP (EMA- 001094-PIP01-10-M04).

Study EFC11759 was a two-year, multicentre (57 centers in 22 countries), randomized, DB, placebo-controlled, parallel group trial in paediatric patients (10 to <18 years old) with a confirmed diagnosis of RRMS and at least one relapse in the 12 months or at least two relapses in the 24 months preceding screening. The study also comprised an OL extension period for the remainder of 192 weeks after randomization in order to assess the long-term effect of teriflunomide with focus on long-term safety in this specific population.

The implementation of the placebo arm was combined with switch criteria, i.e. patients who experienced a confirmed relapse after the PK run-in phase (8 weeks) had the option to switch to the OL period. Similarly, patients with high MRI activity according to strict definitions qualified for early switch to the OL teriflunomide treatment arm. The criteria were defined as follows: In case of at least 5 new/enlarged T2 lesions at the MRI of Week 24 an additional MRI was performed at Week 36. In case the follow-up MRI revealed at least 9 new/enlarged T2 lesions at Week 36, or at least 5 new/enlarged T2 lesions on each of the 2 consecutive MRI scans at Week 36 and Week 48, or, at Week 48 and Week 72 then the patient was qualified for early switch. However, the option of switching to OL teriflunomide in case of high MRI activity prior to a relapse complicated the evaluation of the primary endpoint "time-to-first-clinical-relapse" as discussed below.

The population enrolled in this study (n=166; in a 1:2 ratio for placebo and teriflunomide, stratified by country and patient pubertal status) was composed of males (33.1%) and females (66.9%) aged from

10 to 17 years with a median age of 15.0 years. The percentage of children <13 years was small (15.7%) and was also limited for those who were pre-pubertal (Tanner staging score of I) at baseline [placebo 5 (8.8%) vs. teriflunomide 5 (4.6%)] and pre-pubertal with regard to disease onset [placebo 13 (22.8%) vs. teriflunomide 21 (21.2%)]. The mean number of relapses within the past year was 1.5 (median =1.0) and within the past 2 years 2.1 (median =2.0). All patients experienced relapses within the past 2 years. Regarding the disease progression stage, the study population consisted of relatively newly diagnosed RRMS patients with a mean time since MS diagnosis of about 1.40 years (median =0.69 years) and a mean time since first symptoms of MS of about 2.34 years (median =1.61 years). The overall mean EDSS score at baseline was 1.3 representing almost no disability with only minimal signs in some functional systems. Around 80% of patients were naïve to previous MS DT while the most common DMT was interferon beta 1-a. Thus, the included patient population mainly consisted of early stage and treatment naïve RRMS patients.

No dedicated dose response study in the paediatric population was conducted. Study EFC11759 included at the beginning a blinded PK run-in for the first 8 weeks after randomization, during which patients received placebo, or half of their target dose, e.g. 3.5 mg teriflunomide daily for patients ≤40 kg, or 7 mg teriflunomide daily for patients >40 kg. It was anticipated that this would result in an exposure similar to adults being treated with 7 mg teriflunomide daily (the “7 mg adult equivalent dose”). After the end of the PK run-in phase, a 14 mg adult equivalent once daily dose (14 mg has been approved for the adult RRMS patient population) of teriflunomide based on BW or matching placebo was administered per day. According to a population PK analysis, the Applicant considered, that a dosage of 14 mg teriflunomide once daily would be appropriate for paediatric patients with a BW >40 kg, and a dose of 7 mg teriflunomide once daily or 14 mg teriflunomide every-other-day for paediatric patients with a BW ≤40 kg. No patient was adjusted to the 3.5 mg once daily dose during the PK run-in phase.

The primary endpoint was the “time to first clinical relapse after randomization up to the end of the DB treatment period”. The primary endpoint is considered appropriate and is in accordance with the Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev. 2). The study duration of the DB phase was variable, i.e. event-driven. Consequently, it is not possible to evaluate the ARR, but the primary endpoint can be considered as a surrogate for the analysis of the relapse rate, which could be adequate assuming a constant individual relapse intensity over time. While this assumption may only be valid in case of adherence to study treatment, the analysis of time-to-first relapse can be considered as yielding the best available evidence on relapse, as patients were offered to switch to the active treatment following a relapse or high MRI activity. However, as defined for this study and in combination with the defined switch criteria, evaluation and interpretation of ‘time to first clinical relapse’ is hampered as the switch criteria bear the risk of ‘losing’ a high number of patients prior to experiencing a relapse. This is problematic as switching prior to relapse due to high MRI activity is informative.

The primary analysis was a stratified log-rank test (stratification: region, pubertal status) using a two-sided alpha level of 5%. The first confirmed clinical relapse occurring from randomization (including relapses during the PK run-in phase) to the end of the DB study period was included for analysis. Treatment effect as measured by the HR and its associated 95% CI were estimated using a Cox's proportional-hazards model (factors: treatment, region, pubertal status, age, number of relapses in the year prior to randomization). Patients were censored (1) at the time of permanent discontinuation of treatment/DB period, (2) at the time of discontinuing the DB period and switching to OL teriflunomide due to high MRI activity and (3) at week 96 (end of DB period) in case patients neither experienced a relapse nor high MRI activity. While the non-informative censoring assumption underlying the analysis may be valid for (3), validity of this assumption is questionable in the other two cases, and additional analyses were requested. Furthermore, as the proportional-hazard assumption is not fulfilled in this

study, the HR is not a reliable effect measure: focus should be on estimates of relapse probability at different time points.

Four sensitivity analyses were pre-defined in the SAP to show robustness of the primary analysis, amongst others “time to first confirmed clinical relapse or high MRI activity meeting protocol criteria for switching into the OL period, whichever came first, after randomization before the treatment discontinuation/completion in the DB period” and “time to first confirmed clinical relapse occurring after the PK run-in (8 weeks) phase but before the treatment discontinuation/completion in the DB period” as well as 2 *post-hoc* sensitivity analyses. However, the conducted sensitivity analyses do not address the issue of censoring patients at time of permanent and premature discontinuation of treatment/DB period, which may be informative, too. A sensitivity analysis using more reasonable assumptions to handle these discontinuations was therefore requested for the composite ‘time to high MRI activity or relapse’. Additionally, interval censoring of the MRI component has been requested to be considered in an additional sensitivity analysis of the composite.

The key secondary endpoints, i.e. the number of new/newly enlarged T2 lesions and number of Gd-enhancing T1 lesions are also endorsed since they have been related to relapses, the most important clinical component of paediatric MS, and are often among the criteria chosen to reflect disease activity. It was planned to control the type 1 error for these two endpoints via hierarchical testing. However, in the end, results for these endpoints need to be considered descriptive and exploratory only (see efficacy data). Other secondary endpoints included MRI related endpoints, cognition (SDMT and Cognitive Battery Tests), EDSS score or proportion of clinical relapse-free patients.

Analysis of secondary endpoints is based on the MAR assumption (or similar aligned assumptions depending on the endpoint). Appropriateness of this assumption may be questionable for early and permanent treatment discontinuation and in case of switching due to high MRI activity. Consequently robustness of results for secondary imaging endpoints regarding deviations from the MAR assumption was unclear and further analysis were required. In particular, as restriction of evaluation to the DB period targets a hypothetical estimand, analysis using all available MRI assessments during the first 96 weeks following randomization regardless of switching was requested for secondary imaging endpoints. Furthermore, analysis based only on data from the DB period (i.e. prior to switching) was requested to multiply imputing missing MRI assessments during the first 96 weeks based on the placebo arm. For key secondary imaging endpoints tipping point analysis based on data of the DB period were requested as well. In addition to these analyses, the key secondary endpoint “new/enlarged T2 lesions” was requested to be analysed accounting for the baseline number of lesions.

Overall, the number of protocol violations (n = 34) in the study was considered acceptable and does not seem to essentially impact the validity of the collected data. With regard to the analysis populations, the ITT population was the primary analysis population for efficacy analysis.

Pre-specified subgroup analyses were defined for the primary endpoint based on: age group at study consent (<13, ≥13 years), gender, race, pubertal status (at study consent and at disease onset), baseline BW group (≤40, >40 kg), MS subtypes (RRMS, other forms), number of relapses experienced within past 1 year (0, 1, 2 and ≥3), number of relapses experienced overall (0, 1, 2, 3 and ≥4), high disease activity at baseline (defined as 2 or more relapses in past year, and 1 or more Gd-enhancing lesions on baseline MRI (Yes, No)), Region (Europe, North America, Asia, Middle East, North Africa) and previous MS treatment (Yes, No).

While the study was ongoing, the Applicant requested a modification of the agreed PIP in November 2018 parallel to interactions with the FDA to propose to change the primary endpoint “time to clinical relapse”. At that time the study was fully enrolled but was still ongoing and it was noted that more patients (21 patients) than anticipated were switching to the OL period, many of them (14 patients) due to high MRI activity. Given the anticipated impact of these switchers on the primary analysis, the

Applicant discussed to include high MRI activity switches, along with the confirmed clinical relapses, in a composite primary endpoint, which corresponded to one of the pre-planned sensitivity analyses (see above). However, PDCO and the FDA did not agree to change the primary endpoint during the ongoing study and advised to take the pre-planned sensitivity analysis into account when assessing the efficacy data of the study. During the procedure the request for modification was withdrawn.

During the procedure, the Applicant provided data for the extrapolation of efficacy from the adult teriflunomide patient population to the paediatric patient population based on MRI endpoints. Actually, adult data were used to derive an informative prior to be used in a Bayesian analysis of the TERIKIDS data. From the clinical studies performed in adult patients, Study TEMSO and TOPIC were considered relevant for the efficacy extrapolation due to the similar 2-year study duration compared to TERIKIDS and a similar frequency and MRI visit schedules in TERIKIDS. The primary extrapolation was based on the adult RMS TEMSO data only since TOPIC was conducted in a Clinical Isolated Syndrome (CIS) population. Supportive analyses using data from both TEMSO and TOPIC to assess the robustness of the extrapolation results were also provided. The patients enrolled in Study TOPIC included patients who could retrospectively be diagnosed as MS as per McDonald 2010 criteria applied retrospectively at study entry based on MRI information. However, as the classification was not possible in all patients based on the information available (295/618 not classified) and the numbers were small (78 met the diagnosis criteria [only 25 in the teriflunomide 14mg group], 245 did not meet the diagnosis), this classification has not been used for additional sensitivity analyses. The efficacy extrapolation from the adult to the paediatric population was conducted for two MRI endpoints: 1) number Gd-enhancing T1 lesions and 2) number of new or enlarging T2 lesions.

Efficacy data and additional analyses

A total of 109 and 57 patients received teriflunomide and placebo, respectively, and were analysed in the ITT.

Completion rate was high in this DB study. 102 (93.6%) and 53 (93.0%) of the randomized patients in the teriflunomide and the placebo arm, respectively, completed the DB treatment period (e.g., patients who early completed due to first RAP-confirmed clinical relapse or high MRI activity or who reached week 96 of the DB treatment phase). Most patients, 100 (91.7%) patients in the teriflunomide treatment arm and 52 (91.2%) in the placebo arm entered the OL period. The proportion of patients who completed the DB period up to 96 weeks was considerably higher in the teriflunomide treatment group as compared to placebo [56 (51.4%) vs. 16 (28.1%), respectively]. In the placebo treatment arm a higher proportion of patients met the pre-requisites for an early switch to the OL period due to criteria for high MRI activity or confirmed clinical relapse (26.3% and 38.6%, respectively) compared to patients treated with teriflunomide (12.8% and 29.4%, respectively). This might be indicative of an effect of teriflunomide with regard to those endpoints reflecting disease activity.

Permanent treatment discontinuation due to "lack of efficacy" and "other reasons" was higher in the placebo group when compared to teriflunomide treatment [2 (3.5%) versus 1 (0.9%), and 2 (3.5%) versus 0%, respectively] while "AEs" as reason for discontinuation were higher in the teriflunomide treatment arm when compared to placebo (5.5% and 0%, respectively).

Demographic and disease characteristics overall were adequately balanced across the two groups (with the exception of the mean (SD) number of baseline T2 lesions that was slightly higher in the placebo group, 60.3 (40.8), than in the teriflunomide group, 51.3 (38.2)) and representative for the paediatric RRMS patient population.

Treatment with teriflunomide in comparison to placebo did not meet the primary objective. The "time to first relapse" was slightly prolonged for teriflunomide compared to placebo: relapse probability was higher for placebo from approximately week 12 onwards compared to teriflunomide with 29.8% of

patients that relapsed by week 48 in the teriflunomide arm compared to 39.1% in the placebo arm. Although in comparison to placebo the time to first confirmed clinical relapse was delayed in the teriflunomide treatment arm, representing an effect of teriflunomide on relapses in the paediatric RRMS population, the difference did not reach statistical significance ($p=0.2949$). Looking at the KM plot of time to first confirmed relapse it directly becomes apparent that the proportional Hazards assumption is not fulfilled. Up to about 24 weeks there is almost no difference between estimated relapse rates (although relapses were slightly more frequent for teriflunomide) and from week 36/48 onwards, the curves are almost parallel (although numbers at risk are low at the end of the curves). The most informative part seems to be restricted to the time between 24 to 24/36 weeks. Consequently, the power of the study to detect the observed difference in KM curves is reduced. Furthermore, for this analysis, patients are censored at time of high MRI activity (most at week 36) which is questionable given that censoring is highly informative. Sensitivity analysis counting high MRI activity as an event as discussed below would partly address this issue (in case the primary analysis were successful), though it should be noted that the design hampers an unbiased analysis of the primary endpoint.

With regard to the sensitivity analysis "time to first confirmed clinical relapse or high MRI activity meeting criteria for switching into OL period, whichever came first", teriflunomide prolonged the time to confirmed clinical relapse or high MRI activity, whichever came first, when compared to placebo ($p=0.0409$). While also for this analysis the probability of an event (confirmed relapse or high MRI activity, whichever came first) was consistently higher for placebo compared to teriflunomide from approximately week 12 onwards, the estimated probability of these events increased after week 24 as compared to the primary analysis. This is not unexpected taking into account, that high MRI activity is counted as an event for this sensitivity analysis. The probability of having an event by week 48 was 55.8% and 37.9% in the placebo and teriflunomide arm, respectively. While the issue of informative censoring due to high MRI activity for the primary endpoint analysis is addressed in this sensitivity analysis by counting high MRI activity as an event, the proportional hazards assumption is still clearly not fulfilled questioning the use of the HR as a valid effect measure. As for the primary time-to-first-confirmed-relapse analysis, the most informative part of the KM curve seems to be the time from week 24 to week 36/48.

The second sensitivity analysis, "time to first confirmed clinical relapse occurring after the PK run-in phase", that excluded clinical relapses that occurred during the PK run-in phase is considered of little value because censoring patients at time of relapse in the PK run-in is questionable from a statistical point of view. Additionally, from a clinical perspective, the analysis provides little information with regard to the benefit/ risk for use of teriflunomide without titration.

For the analysis "time to relapse or high MRI activity" addressed as part of the pre-specified sensitivity analyses for the primary endpoint a *post hoc* analysis using placebo-based multiple imputations (jump to reference) to handle early permanent discontinuation of treatment/DB period to assess deviations from the non-informative censoring assumption showed similar results to the pre-planned analysis, apparently due to the fact that only few patients discontinued without event.

An additional *post-hoc* analysis considering interval censoring of the MRI component supported the pre-planned analysis. Apparently, interval censoring seems less relevant for the actual data.

Overall, a number of sensitivity analyses were performed, that showed stronger results than the primary analysis. The sensitivity analyses in general and in particular the one, that comprised criteria of a composite endpoint by counting in addition to relapse also high MRI activity as an event I yielded significant results, although only nominally since the primary analysis failed to show statistical significance. However, especially this composite endpoint is considered to be of clinical relevance since switching patients to (another) active treatment when high disease activity is detected on MRI and not waiting for a relapse to occur reflects clinical practice.

With respect to the key secondary endpoints, number of new or enlarged T2 lesions and number of Gd-enhancing T1 lesions, a (nominal) significant reduction in the rate of new or enlarged T2 lesions per MRI scan was demonstrated with teriflunomide, compared to placebo (4.7 and 10.5 lesions, respectively, ($p=0.0006$), corresponding to a 55% reduction over the DB treatment period (rate ratio [RR]: 0.450; 95% CI: 0.285 to 0.711).

With regard to the requested sensitivity analysis the Applicant took the number of T2 lesions into account. A (nominal) significant reduction in the rate of new or enlarged T2 lesions per MRI scan was demonstrated with teriflunomide, compared to placebo (3,6 and 5,4 lesions, respectively) ($p=0.0446$), corresponding to a 33% reduction over the DB treatment period (rate ratio [RR]: 0.665; 95%CI: 0.447 to 0.990). The relative risk reduction in this analysis (with adjustment for baseline T2 lesion count) is considerably lower compared to the 55% relative reduction in the pre-defined analysis (estimated without adjusting for baseline T2 lesion count) but still nominally significant. Due to given baseline differences, the adjusted analysis, even not pre-specified, is considered to yield a more accurate treatment effect estimate.

Also, a (nominal) significant reduction in the rate of Gd-enhancing T1 lesions was demonstrated with teriflunomide ($p<0.0001$), compared to placebo (1.9 and 7.5 lesions, respectively), corresponding to a 75% reduction at the end of the DB treatment period (RR: 0.253; 95% CI: 0.126 to 0.505). While post-baseline, the mean number of T1 Gd-enhancing lesions in the teriflunomide group declined from 3.9 at baseline to 1.4, the mean number of T1 Gd-enhancing lesions in the placebo group increased from 3.9 at baseline to 5.1.

According to the study design, the effect of teriflunomide on relapses was planned to be corroborated by results on the number of new or enlarged T2 lesions as well as of Gd enhancing T1 lesions. Both of these endpoints indicate inflammatory activity and have been associated with relapses. Therefore, these endpoints were chosen to be estimated as key secondary endpoints. From the results of these analyses it can be interpreted that teriflunomide has a clear effect on inflammation in the targeted patient population. However, as the study failed its primary endpoint and multiplicity was planned to be controlled across primary and secondary endpoints via hierarchical testing, statistical significance was only achieved nominally. Requested *post-hoc* analyses for the key secondary endpoints showed that at week 36, 21 scans were performed under placebo and 44 scans under teriflunomide. When ignoring these scans, similar results were obtained as in the pre-planned analyses.

Additional *post-hoc* analyses were provided upon request for all MRI endpoints that included all available MRI assessments performed within 96 weeks after randomization (including those obtained after the DB period due to early treatment discontinuation or switch to OL teriflunomide treatment). According to the provided analyses 44 additional scans were included for placebo and 35 additional scans were included for teriflunomide as compared to the analysis of the DB period. The number of additional scans included, however, is relatively small as compared to the number of remaining missing scans until week 96. Hence, missing data imputation remains critical.

Considering 21+44 scans at week 36, in total $4 \times 57 + 21 = 249$ scans would have been expected for placebo and $4 \times 109 + 44 = 480$ for teriflunomide, leading to $249 - 123 = 126$ scans for placebo patients and $480 - 339 = 141$ for teriflunomide patients that were missing in the reported analysis, of which 44 and 35 scans were added in the analysis of the DB and OL phase, corresponding to 35% and 25%. Whereas results from the combined data of DB and OL phase could have been reassuring and even conservative due to the switch from placebo to the active treatment, the large amount of remaining missing scans does not allow for a confirming conclusion. The Applicant confirmed that the additional value of the analyses including OL data is limited. However, overall, results are still supportive of the efficacy of teriflunomide on the key secondary MRI endpoints of new and enlarged T2 lesions and T1 Gd-enhancing lesions per scan.

Further requested and provided *post-hoc* analyses suggest that the results do not appear to be robust when conservative missing data imputation is applied in a setting with large proportion of missing data in the DB period. 70% of placebo patients and 47% of teriflunomide patients had MRI data to be imputed. Referring to the number of missing scans, this lack of robustness cannot be rebutted by an analysis on all MRI scans, including those taken in the OL period, since the number of additional scans in the OL period remains small compared to the number of remaining missing scans. Whereas the large amount of missing data itself raises concerns about the robustness of the data, the analyses with imputed data considerably reduced the treatment effect and, consequently, nominal significance was lost. This imputation approach is however considered too conservative. In addition, results still showed a relevant numerical effect.

A further secondary endpoint was "the proportion of clinical relapse-free patients". At week 96 59.4% of the patients in the teriflunomide treatment arm were relapse free compared to 45.5% under placebo. However, the KM plots are almost parallel and as the time to relapse rate (primary endpoint) can be translated into relapse free rates, this outcome is not unexpected.

Results regarding the change from baseline in volume of T2 lesions seem to be in favour of teriflunomide. Results regarding unenhancing T1 lesions are difficult to interpret. Chronic or persistent T1-hypointense lesions (black holes) in MRI have been related to irreversible tissue loss in MS patients. However, while teriflunomide led to (nominal) significant reduction in the mean number of new hypointense T1 lesions, evaluation of change from baseline in volume of hypointense T1 lesions did not indicate any advantage of teriflunomide over placebo. A decrease in the brain volume has been observed in both treatment groups. No statistical difference was observed between the teriflunomide and placebo groups on the percentage change in brain volume. The mean percent changes in brain volume from baseline to Week 96 (MMRM data) were -0.529 in the teriflunomide group and -0.570 in the placebo group. With respect to these other secondary MRI related endpoints, analyses of these are only exploratory and no confirmatory conclusions can be made based on the results for these endpoints.

As to be expected in the paediatric MS population with a generally rather low disability progression, no relevant changes in EDSS scores were seen from study start until the end of the 96 weeks period. Results for the EDSS score were only descriptively summarized: the mean (SD) EDSS score at baseline was 1.4 (0.9) and 1.2 (0.9) for the placebo and the teriflunomide treatment group, respectively, while at week 96 the mean (SD) EDSS score was 1.7 (1.2) and 1.2 (0.9) respectively, representing a slight deterioration under placebo of 0.3. Requested *post-hoc* analyses on CDP-6M, both for the DB treatment period and for the first 96 weeks regardless of patients discontinuing the double DB and switching to OL teriflunomide, showed that only few patients experienced a CDP-6M in the DB period with 2 (3.5%) patients in the placebo group and 5 (4.6%) patients under teriflunomide treatment. However, due to the switch to OL rescue treatment which was disproportionately higher in the placebo group compared to the teriflunomide group these results are difficult to interpret. During the 96-week period, better results were provided for CDP-6M in the active treatment arm with 8 (14.0%) patients in the placebo group and 9 (8.3%) patients in the teriflunomide group who experienced a CDP-6M.

With respect to cognition, no statistical difference was observed between the teriflunomide and placebo groups on the change in number of completed items and correct substitutions measured by SDMT. No meaningful differences between groups were observed for the aforementioned cognitive battery tests.

At Week 96, 6.4% of the patients in the teriflunomide group and 1.8% of the patients in the placebo group were disease free according to the defined criteria as stated in the statistical section. However, week 96 results are based on a very small number of patients that limit the overall conclusions.

Results of the subgroup analyses were in favour of teriflunomide and overall consistent except for the subgroup of Black/Others patients, for the subgroup of patients from North America/North Africa region (these 2 different regions were pooled due to small numbers of patients and numbers of relapses

experienced overall), and for the subgroup of patients who experienced 1 or 3 relapses overall. In the subgroup of patients with 2 relapses experienced overall before randomization teriflunomide significantly reduced the risk of a confirmed clinical relapse by 75.0% (HR: 0.250; 95% CI: 0.086 to 0.723). In the subgroup of patients with highly active disease at baseline teriflunomide significantly reduced the risk of a confirmed clinical relapse by 68.1% (HR: 0.319; 95% CI: 0.128 to 0.793). Overall, it has to be kept in mind, that subgroup analyses were based on the HR which is considered to be a less suitable effect measure in this setting.

Subgroup analyses were also performed for the first sensitivity analysis "time to first confirmed clinical relapse or high MRI activity". Results of the subgroup analyses were also in favour of teriflunomide and overall consistent except for the subgroup of Black/Others patients, for the subgroup of patients from North America/North Africa and for the subgroup of patients who experienced 3 relapses overall.

152 patients were enrolled in the OL period: 100 patients in the teriflunomide/teriflunomide group and 52 patients in the placebo/teriflunomide group. As of the data cut-off date, 30 patients had completed the OL period (21 patients in the teriflunomide/teriflunomide group and 9 patients in the placebo/teriflunomide group) and 88 patients were still ongoing (61 patients and 27 patients, respectively). Limited efficacy data from this long-term extension period could be considered indicative, that the effect of teriflunomide as assessed on different endpoints during the maintenance period is comparable to that shown in the DB treatment period. However, due to the uncontrolled design of the OL period as well as due to the attrition bias, the extension period of study EFC11759 is generally of limited value with regard to efficacy.

Regarding the extrapolation exercise using data from the adult RMS population the Applicant has demonstrated that integration of the adult MRI data into the paediatric data population in a Bayesian way does not change the results considerably.

Whereas approach 1 uses the age distribution from TERIKIDS to derive a prior from the adult studies relevant for this age distribution, approach 2 did not take age into account. Using different weighing of the adult data corresponding to different effective sample sizes, results were obtained similarly to the results from TERIKIDS study. Whereas approach 1 relies on the specific functional relation of the efficacy parameter to age, approach 2 prior relies on the assumption that efficacy is unrelated to age. Obviously, both assumptions are difficult to verify using adult data only, but similarity between the results of both approaches appears reassuring.

Assessment of paediatric data on clinical efficacy

Study EFC11759 included paediatric patients aged 10 to 18 years of age and therefore, no further data are needed.

2.5.4. Conclusions on the clinical efficacy

In support of the extension of the indication of Aubagio to paediatric patients aged 10 to 17 years, the Applicant has provided efficacy data from one placebo-controlled study, study EFC11759, and its long-term, OL period.

The study failed its primary endpoint "time to first clinical relapse after randomization up to the end of the DB treatment period" and thus efficacy of teriflunomide in the paediatric population with RRMS has not been formally demonstrated.

However, with regard to the sensitivity analysis "time to first confirmed clinical relapse or high MRI activity meeting criteria for switching into OL period, whichever came first", which is of high clinical

relevance, teriflunomide yielded a nominally statistically significant result in comparison to placebo ($p=0.0409$).

For the two key secondary MRI endpoints, number of new/newly enlarged T2 lesions and number of Gd-enhancing T1 lesions nominal significant reductions have been shown. As the study failed its primary endpoint and multiplicity was planned to be controlled across primary and key secondary endpoints via hierarchical testing, none of these two key secondary endpoints can be claimed "statistically significant" in the confirmatory sense. However, since these MRI parameters have been related to relapses, representing the most important clinical effect in this population and are often among the criteria chosen to reflect disease activity, they are considered to be of high importance in this context and extrapolation of efficacy based on these endpoints can be accepted.

Since efficacy of teriflunomide has already been demonstrated in adult patients with RRMS (teriflunomide is approved for this population), extrapolation from the adult patient population to the paediatric population based on MRI based secondary endpoints is considered justified. Upon request, the Applicant provided analyses demonstrating that using adult data as an informative prior for a Bayesian analysis of the paediatric population based on MRI derived endpoints does not change the results considerably.

Therefore, in light of all provided efficacy data and the results received, despite that the primary endpoint itself was not met, extrapolation of the adult indication to the paediatric population is considered justified.

2.6. Clinical safety

The safety of teriflunomide was assessed against placebo in paediatrics aged 10 to 17 years (both inclusive) based on the results of the DB period in study EFC11759. Long-term safety data are so far limited and interim data derive from the ongoing OL period of this study with a data cut-off of 27 November 2019. Within this procedure, the Applicant provided an update of safety data for the OL period of the study summarised in a safety update report with a new data cut-off of 12 September 2020. Any numbers on exposure and safety data in the OL period in this report were updated accordingly.

Patient exposure

A total of 166 patients were randomized to study treatment in the DB period of study EFC11759: 109 patients in the teriflunomide group and 57 patients in the placebo group.

Initiation of teriflunomide in the DB and OL period was conducted with half the 14 mg adult equivalent dose as part of a PK run-in phase for the first 8 weeks, i.e. patients $BW \geq 40$ kg received 7 mg teriflunomide and patients $BW < 40$ kg received 3.5 mg teriflunomide. Patients were then to be switched to the 14mg adult equivalent dose after the first 8 weeks on teriflunomide, depending on the outcome of the PK run-in phase, i.e. to 14 mg teriflunomide for patients $BW \geq 40$ kg, and to 7 mg teriflunomide for patients $BW < 40$ kg.

Extent of exposure was presented by dose in the teriflunomide arm (3.5 mg, 7 mg, and 14 mg). A majority of subjects was exposed to 14 mg teriflunomide (97 patients resulting in 131 PYE [patient-years of exposure]) and only 11 patients were exposed to 7 mg teriflunomide (resulting in 15 PYE), resulting in a total of 145.6 PYE, and 57 PYE for the placebo group. The median duration of treatment during the DB period was shorter for placebo (273.0 days) as compared to teriflunomide (660.0 days), which is a consequence of the provision of the study protocol, i.e. allowing all patients to switch from the DB period to the OL period in case of a RAP-confirmed clinical relapse, or high disease activity on MRI, or when reaching 96 weeks of follow up. The number of early switches in the placebo arm was higher than in the teriflunomide arm. Overall, the difference in exposure to placebo and teriflunomide during the study has to be taken into account when interpreting the safety data.

Cumulatively, 100 (92%) and 73 (67%) of teriflunomide-treated paediatric patients were exposed to the drug (any dose) for more than six months and more than one year, respectively. Only 41 (38%) of teriflunomide-treated patients received the drug for more than two years, thus limiting the availability of controlled long-term safety data. The cumulative exposure to placebo was even smaller (only 10 patients for more than 2 years). Exposure data by age category <13 years and ≥13 years reveal that the median duration of treatment is similar in both age categories for patients on placebo (299.5 days and 273.0 days) and slightly higher in patients <13 years versus those ≥13 years treated with teriflunomide (669 days vs. 596 days). A similar percentage of patients in both age categories per treatment group had a cumulative duration of treatment more than six months and more than one year.

A total of 152 patients (approximately 92%) were enrolled in the OL period of the study: 52 patients in the placebo/teriflunomide group and 100 patients in the teriflunomide /teriflunomide group. The cumulative duration of treatment exposure from enrolment in the OL period to the updated data cut-off 12 September 2020 was 30.53 patient-years at the teriflunomide 7 mg dose and 233.18 patient-years at the 14 mg dose. Most of the patients (132 patients) received 14 mg teriflunomide once daily. Up to the updated data cut-off, 84.1% and 49.2% of patients received teriflunomide 14 mg for ≥48 weeks and ≥96 weeks, respectively, and 7 patients (5.3%) in the OL period were exposed to this dose for more than 168 weeks (i.e. 3.5 years).

Regarding demographics, these were reflective of the intended paediatric MS study population regarding gender distribution, which was 2:1 (female to male) in both treatment groups. However, limitations regarding the availability of data concern younger paediatrics and those being pre-pubertal thus hampering firm safety conclusions:

- Median age was 15 years. Only 16% (i.e. 26 of 166 patients, 16 on teriflunomide and 10 on placebo) were <13 years, which hampers interpretability of safety in this age group. A more detailed breakdown of ages reveals a majority of patients in both treatment groups being 16 to 17 years of age followed by patients aged 14 to 15 years.
- Only 10 patients (6 %) reflect Tanner Stage I, indicating that they were pre-pubertal (5 patients in each treatment group).

Adverse events

The overall presentation of safety data does not take into account the switch from half the adult equivalent dose to the full adult equivalent dose of 14 mg after the first 8 weeks of treatment with teriflunomide during the DB and OL period. Therefore, no data is available to rule out the occurrence of tolerability issues, such as nausea, diarrhoea, and alopecia, with a higher initial teriflunomide dose during the first 8 weeks of treatment. Upon request, the Applicant provided an overview of TEAEs in the DB period for the first 8 weeks of treatment (i.e., based on half the adult equivalent dose) compared to the second 8 weeks (i.e., based on the full adult equivalent dose). TEAEs in general and specifically the potential tolerability issues in line with nausea and alopecia were more frequently reported within the first 8 weeks of treatment. At present, there is no evidence for an increased incidence of such TEAEs or early discontinuations between Week 8 and Week 16 (based on the full adult equivalent dose) as compared to the first 8 weeks of treatment (half the adult equivalent dose). Moreover, based on the PK of teriflunomide (slow increase in concentration and long elimination half-life of 19 days) the 14 mg adult equivalent dose is not expected to substantially increase the risk for tolerability issues.

Slightly more patients in the teriflunomide group reported TEAEs as compared to those in the placebo group (88.1% vs. 82.5%) during the DB period.

During the OL period, slightly more patients who were treated with placebo during the DB period reported TEAEs (86.5% in the placebo/ teriflunomide group and 79% in the teriflunomide/ teriflunomide group).

Display of adverse events

The most frequently reported TEAEs derived from the following System Organ Class (SOCs) that were reported more frequently in the teriflunomide group than in the placebo group (difference of $\geq 5\%$) during the DB period:

- Infections and infestations (66.1% in the teriflunomide group and 45.6% in the placebo group), driven by respiratory tract preferred terms (PTs), i.e. nasopharyngitis (25.7% and 8.8%), upper respiratory tract infection (21.1% and 10.5%), pharyngitis and bronchitis.
- Skin and subcutaneous tissue disorders (35.8% and 22.8%), driven by alopecia (21% teriflunomide vs. 12% placebo).
- Gastrointestinal disorders (33% and 24.6%), driven by abdominal pain (11% vs. 1.8%)
- Investigations (24.8% and 14%), driven by laboratory abnormalities, i.e. blood creatine phosphokinase (CPK) increased (5.5% vs. 0%), white blood cell count decreased (3.7% vs. 1.8%), neutrophil count decreased (2.8% vs. 0%), and alanine aminotransferase (ALT) increased (2.8% vs. 1.8%).
- General disorders and administration site conditions (18.3% and 12.3%), and Musculoskeletal and connective tissue disorders (15.6% and 8.8%), and Metabolism and nutrition disorders (9.2% and 3.5%).

SOCs reported with a similar incidence in patients on teriflunomide and placebo were: nervous system disorders (33.9% and 33.3%; [headache occurred more frequently on placebo (22.8%) vs. teriflunomide (16.5%), while paresthesia occurred in 11% of subjects on teriflunomide vs. 1.8% of subjects on placebo]), respiratory, thoracic and mediastinal disorders (18.3% and 15.8%), injury, poisoning and procedural complications (15.6% and 19.3%), psychiatric disorders (11% and 14%), eye disorders (10.1% and 15.8%), and reproductive system and breast disorders (3.7% and 10.5%).

For other SOC, where an increased reporting was noted in patients on teriflunomide, PTs do not indicate a specific cluster.

TEAEs at the SOC level reported more frequently in the placebo/ teriflunomide group than in the teriflunomide/ teriflunomide group (with a difference of $\geq 5\%$) during the OL period were: Nervous system disorders (32.7% versus 24%), Gastrointestinal disorders (30.8% versus 26.0%), Respiratory, thoracic and mediastinal disorders (23.1% versus 11.0%), Investigations (28.8% versus 17%), Psychiatric disorders (17.3% versus 8.0%), and Renal and urinary disorders (11.5% versus 3.0%). No TEAEs at the SOC level were reported more frequently in the teriflunomide/ teriflunomide group than in the placebo/ teriflunomide group with a $\geq 5\%$ difference. TEAEs from the Infections and infestations SOC occurred in a similar magnitude in patients on teriflunomide/ teriflunomide (53.0%) and patients on placebo/ teriflunomide (48.1%).

PTs reported more frequently in the teriflunomide/ teriflunomide group than in the placebo/ teriflunomide group (with a difference of $\geq 5\%$ by decreasing order in the teriflunomide/ teriflunomide group) were: upper respiratory tract infection (19.0% and 13.5%), respiratory tract infection (5.0% and none), PTs reported more frequently in the placebo/teriflunomide group than in the teriflunomide/ teriflunomide group (with a difference of $\geq 5\%$ by decreasing order in the placebo/ teriflunomide group) were: alopecia (17.3% versus 10.0%), ALT increased (15.4% versus 3.0%), dizziness (11.5% versus 2.0%), depression

(7.7% and 1.0%), hypoesthesia (7.7% and 2.0%), micturition urgency (7.7% and none), bronchitis (5.8% and none), and asthma (5.8% and none).

Adverse events of special interest (AESI)

Gastrointestinal disorders – nausea and diarrhoea

During the DB period, the incidence of nausea as well as diarrhoea/ frequent bowel movements was similar in the teriflunomide and placebo group (8.3% and 7.3% versus 7% and 7%). No increase in nausea and diarrhoea TEAEs in neither group was noted during the OL period: placebo/ teriflunomide (5.8% and 9.6%) and teriflunomide/ teriflunomide (4% and 6%). During the DB period, nausea was most frequently reported within the first week while diarrhoea was most frequently reported after 4 to 12 weeks of treatment.

Hepatic disorders (including liver function parameter)

Liver function: No clinically relevant differences between groups during the DB and OL periods were observed for changes over time of aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase, gamma-glutamyl transpeptidase (GGT), total bilirubin, and indirect bilirubin. An increase in mean ALT was observed in the teriflunomide group compared to the placebo group starting at Week 4 during DB treatment. ALT > 1x upper limit of normal (ULN) (ALT > 3x ULN) was reported in 25.7% (3.7%) of patients on teriflunomide and 14% (0%) of patients on placebo. Mean ALT also increased in the placebo/ teriflunomide group over the first weeks of treatment during OL, but also initially in the teriflunomide/ teriflunomide group. The proportion of patients with ALT >1x ULN in postbaseline visits was lower in the teriflunomide/ teriflunomide group than in the placebo/ teriflunomide group (35% vs. 48.1%) but higher as compared to the teriflunomide group in the DB period.

Hepatic TEAEs: During the DB period, the incidence of hepatic disorders was similar in the teriflunomide and placebo group. The most frequently reported treatment-emergent hepatic disorder was ALT increased (2.8% in the teriflunomide group and 1.8% in the placebo group). Two patients in the teriflunomide group experienced serious but asymptomatic hepatic disorders of ALT increased (Day 171) and transaminases increased (Day 429; graded "severe") that did not lead to permanent treatment discontinuation, and recovered with normalization of hepatic enzyme levels. One patient in the teriflunomide group experienced hepatic disorders (ALT increased) after Day 138 that led to treatment discontinuation. The patient recovered with ALT normalisation after teriflunomide discontinuation and accelerated elimination procedure. The other patients with treatment-emergent hepatic disorders experienced nonserious hepatic events: 2 in the teriflunomide group (increases of hepatic enzymes) and 2 in the placebo group (hyperbilirubinaemia and ALT increased).

Most hepatic disorder TEAEs were recorded between 4 and 12 weeks in the teriflunomide group but also occurred later during treatment. Hepatic disorder TEAEs with teriflunomide occur dose-related. Therefore, it needs to be taken into account that patients received half the adult-equivalent dose during the first 8 weeks of treatment.

During the OL period, hepatic disorders were less frequently reported in the teriflunomide/ teriflunomide group than in the placebo/ teriflunomide group and the vast majority had TEAEs from the investigations SOC (ALT increased: 3.0% and 15.4%, respectively). The incidence of TEAEs in the latter treatment group was higher compared to teriflunomide in the DB period.

Three patients in the placebo/ teriflunomide group experienced serious hepatic disorders leading to treatment discontinuation: 1 patient had hepatic function abnormal of severe intensity and ALT increased (430 IU/L) of moderate intensity, 1 patient had serious ALT increased (391 UI/L) of moderate intensity and nonserious transaminases increased of moderate intensity, and 1 patient had serious ALT increased (278 UI/L) of moderate intensity. For the latter patient, the diagnosis was "drug-induced liver injury"

(DILI) as per the narrative. The patient was treated with minocycline until 1.5 months before onset of the ALT increase, however, the half-life of minocycline questions a contribution to this event. In addition, 2 patients discontinued due to non-serious hepatic disorder TEAEs. All patients recovered up to the cut-off date of the OL period.

No cases of Hy's law were reported throughout the study.

The potential of teriflunomide to induce DILI has been assessed in variation procedures EMEA/H/C/002514/II/0029 and EMEA/H/C/002514/II/0032. Based on the presentation and review of available nonclinical and clinical data summarised by the Applicant in a safety evaluation report, there is sufficient evidence to support a causal association. Severe cases of DILI including life-threatening cases of liver failure have occurred for which a causal role of teriflunomide is at least possible (or even likely). Thus, the approved changes in section 4.4 of the product information reflect cases of DILI, risk factors for liver enzyme increases and DILI, and monitoring algorithm. Given that the hepatic safety of teriflunomide was found similar in paediatrics in study EFC11759, hepatic enzyme monitoring "at least every four weeks during the first 6 months of treatment and regularly thereafter" is likewise acceptable in paediatrics in the absence of risk factors (i.e. patients with pre-existing liver disorder, concomitant treatment with other hepatotoxic drugs, and/or consumption of substantial quantities of alcohol).

Pancreatic disorders and laboratory (pancreatic enzyme) parameters

Pancreatic function

No relevant differences between groups were observed for changes over time of mean lipase and amylase values in the DB and OL period.

Pancreatic disorders TEAEs

included TEAEs in line with pancreatic enzyme increases but also cases of pancreatitis, and were reported in 4 patients (3.7%) in the teriflunomide group and 1 patient (1.8%) in the placebo group during the DB period (Table 14). Two of the TEAEs in the teriflunomide group were coded as "pancreatitis acute". Most of the events occurred between 60 and 84 weeks after treatment initiation with teriflunomide. In 3 of the 4 patients on teriflunomide, pancreatic TEAEs led to treatment discontinuation: one serious case of acute pancreatitis of moderate intensity in a patient with congenital anomaly of cystic duct requiring hospitalization, one nonserious case of acute (caudal) pancreatitis with autoimmune features of severe intensity and one nonserious case of hyperlipasaemia of mild intensity. The patients were recovered or recovering.

Table 14: Number (%) of patients with treatment-emergent pancreatic disorders by primary SOC and PT in the DB period - Study EFC11749- 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)
Hyperlipasemia	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)

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term MedDRA 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

During the OL period, 5 patients (5%) in the teriflunomide/ teriflunomide group, and 1 patient (1.9%) in the placebo/ teriflunomide group reported pancreatic disorders TEAEs; overall, it concerned 6 patients (3.9% in total). Two of these six patients, both in the teriflunomide/ teriflunomide group, experienced SAEs in line with pancreatitis that led to hospitalisation, corrective treatment and discontinuation of teriflunomide. Both were accompanied by symptoms and confirmed by imaging data:

- One patient was reported with *pancreatitis acute* (lipase increased at 16.15 x ULN) of severe intensity after approx. 1 year of teriflunomide treatment. In this patient, abdominal imaging revealed acute pancreatitis with pancreatic nodules (pseudo-papilloma) and inflammatory lesions of the pancreas. This inflammatory process was coded as pancreatic neoplasm but was not rated related to teriflunomide despite the lack of confirming data (e.g. biopsy results). Thus, contribution of teriflunomide to this condition can neither be confirmed nor ruled out.
- One patient with *pancreatitis* (abdominal pain with lipase and amylase increase) of moderate intensity after approx. 3 years of teriflunomide, which was reported to have been recovered.

Nonserious *pancreatitis* of mild intensity leading to treatment discontinuation (and accelerated elimination procedure) was reported in an additional patient. The event was associated with nonserious amylase >2x ULN and nonserious lipase >2x ULN. The patient presented an abdominal ultrasound revealing increased echogenicity. The event was stated as "recovering".

No case of pancreatitis was reported in the placebo/ teriflunomide group.

Other TEAEs in line with pancreatic disorders during the OL period were:

- One patient in the teriflunomide/ teriflunomide group experienced nonserious increase in both amylase and lipase $\geq 2x$ ULN of mild intensity after approx. 2.5 years of teriflunomide (considered related). The patient recovered. Another patient had nonserious amylase increased of mild intensity considered related to teriflunomide. The patient had not recovered at the time of the cut-off date of the report.
- A single patient in the placebo/ teriflunomide group was reported with nonserious asymptomatic lipase increase $\geq 2x$ ULN after approx. 2 years of treatment with teriflunomide in the OL period (not considered related). The patient was reinitiated on teriflunomide after temporary interruption. However, no information on re-challenge is available.

Comparison of pancreatic effects in adults and paediatrics – results from the safety evaluation report

A detailed safety evaluation report aimed to address the observed imbalance of pancreatic events detected in study EFC11759 and those seen in adult clinical trials on pancreatitis sources of information included epidemiological data on pancreatitis, review of nonclinical, clinical and postmarketing (safety

database, excluding paediatrics) data, literature review, and disproportionality analyses using external databases:

- Epidemiological data from the Real-World Evidence Database Optum Humedica indicate an increased incidence rate of pancreatitis per 1000 person-years in MS patients versus non-MS controls that is more pronounced in patients 10 to 18 years.
- Comparative epidemiological review of background rates in adults and paediatrics (using literature sources) and teriflunomide post-marketing data for adult patients with MS as well as clinical study data of MS paediatric patients in EFC11759 reveal that the incidence of pancreatitis in teriflunomide-treated adults is higher compared to adult background rates (74.9/100,000 vs. 45/100,000); moreover, in teriflunomide-treated paediatrics the incidence of pancreatitis is much higher compared to background paediatric rates (4/166, i.e. 3% vs. 1/10.000).
- Detailed review of the Sanofi GPV database found 276 cases (322 events) of which two-third were serious. The majority of cases (i.e. patients) are reports of pancreatitis (n=176) and n=100 cases are reports of pancreatic enzyme increases. In approx. half of the cases, teriflunomide was discontinued. Among pancreatitis events in the GPV database, there were 2 events coded as "pancreatic pseudocyst" and 1 event of "pancreatitis necrotising". Of the 322 events, 106 led to hospitalisation and 116 were rated as medically significant events. For one patient, the outcome was "disability"; however, this coding was probably not related to pancreatitis but to the description of MS. Recovery from events was irregularly reported. Median time-to-onset of events was 1.4 years. Causality analysis per WHO-UMC criteria of n= 176 cases revealed 2 cases rated as likely related (published case reports) and one case possibly related. 4 other cases that were rated as possibly related to teriflunomide have already been assessed previously during EMEA/H/C/PSUSA/00010135/201503 and led to labelling revision with regard to pancreatitis. Two fatal events were reported but causality assessed these events as unlikely related to teriflunomide.
- External database evaluation/ disproportionality

Analyses found a clear signal for the TEAEs of pancreatitis and lipase increased in both databases (VigiBase and FDA Adverse Event Reporting System-FAERS). Borderline signal derived from acute pancreatitis (standardised MedDRA queries [SMQ]) [narrow] and pancreatic enzymes increased.

Overall, the presentation of data on pancreatic effects in paediatrics cannot rule out that teriflunomide plays a contributing role in the occurrence of pancreatitis. Monitoring of pancreatic enzymes at treatment initiation and regularly during treatment in clinical practise is not based on a scientific rationale and thus not warranted; obtaining pancreatic enzymes and related laboratory parameters in patients with suspected pancreatitis appears to best address this identified risk. Information on the risk of pancreatitis in paediatric patients and respective recommendations have been included in the SmPC, section 4.4. Moreover, post-marketing follow-up of pancreatitis is in place by means of a dedicated targeted follow-up form. Specific questions include de- and re-challenge and any known results of genetic tests indicating an increased risk for pancreatitis as well as a question about any anatomic anomalies potentially associated with pancreatitis.

Bone marrow disorders

All events in both periods were of mild or moderate intensity. No discontinuations due to bone marrow disorders were reported during the study.

During the DB period, the incidence of bone marrow disorders was higher in the teriflunomide group (7.3%) than in the placebo group (1.8%) with the most frequently reported TEAEs being neutropenia (2.8%), leukopenia (1.8%), and monocytopenia (1.8%) in the SOC Blood and lymphatic system disorders, and white blood cell count decreased (3.7%), and neutrophil count decreased (2.8%) in the

SOC Investigations. The events and mainly occurred between 12 and 24 weeks after treatment initiation. One adolescent patient in the teriflunomide group with a known pre-existing cyclic neutropenia at baseline experienced serious neutropenia of moderate intensity on Day 137 (rated related to teriflunomide). Teriflunomide was temporarily interrupted. The patient recovered.

Bone marrow disorders were more frequently reported in the teriflunomide/ teriflunomide group than in the placebo/ teriflunomide groups (6.0% and 3.8%) during the OL period. The most commonly reported TEAE was white blood cell count decreased (3% and 3.8%) and neutrophil count decreased (2% and 1.9%). The patient with a known pre-existing cyclic neutropenia experienced serious neutropenia of moderate intensity. The patient recovered. However, 2 of 7 patients with non-serious bone marrow disorder TEAEs were not recovered by the data cut-off in the OL period.

Infections and infestations

The proportion of patients with infections and infestations TEAEs was higher in the teriflunomide group (66.1%) than in the placebo group (45.6%). The most frequently reported infection TEAEs ($\geq 5\%$ 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.

Two of three infection serious AEs (SAEs) occurred in the teriflunomide group. One of these SAEs was an opportunistic infection (pulmonary tuberculosis) in a patient from China during a tuberculosis epidemic and led to discontinuation from treatment. The patient recovered from tuberculosis after anti-infective treatment. The second SAE in the teriflunomide group was an upper respiratory tract infection reported as serious due to hospitalisation related to concomitant MS relapse, but it was not serious by itself. Most cases of infections and infestations were of mild to moderate intensity with a peak in reporting between Week 4 and 24. Four cases were severe (upper respiratory tract infection, pulmonary tuberculosis and pilonidal cyst in the teriflunomide group and appendicitis in the placebo group).

No increased occurrence of infections was reported during the OL period (53.0% in the teriflunomide/ teriflunomide group and 50% in the placebo/ teriflunomide group) with PTs similar to the DB period. 5 patients reported SAEs up to the updated data cut-off in the OL period, three of them in the placebo/ teriflunomide group being rather unspecific in nature (bronchitis/ tonsillitis, sinusitis, and food poisoning). The following SAEs were reported in the teriflunomide/ teriflunomide group:

- A patient for whom a SAE of upper respiratory tract infection was reported during the DB period. After approx. 20 months of teriflunomide treatment, the patient was reported with *two serious TEAEs of upper respiratory tract infection and central nervous system infection*, which was not further specified. The patient was in need for hospitalisation and corrective anti-infective treatment. The patient experienced an additional SAE (lung infection, "pneumonia") approximately 100 days after recovery from the CNS infection. None of the reported SAEs for this patient was rated related to teriflunomide.
- The same patient was reported with a further SAE of upper respiratory tract infection of mild intensity upon data cut-off 12 September 2020.
- Coronavirus infection of moderate intensity (in a patient who experienced evocative signs of Coronavirus Disease 2019 (COVID-19) infection and was tested positive; this patient recovered with symptomatic treatment while teriflunomide was continued as planned).

TEAEs related to opportunistic infections were similarly reported for patients on placebo and teriflunomide in the DB period, i.e. in 5.3% and 4.6% of patients, with the most frequently reported PT

being tinea versicolour (3.5% and 0.9% of patients), followed by oral herpes (1.8% of patients in each group). Pulmonary tuberculosis and herpes simplex each occurred in a single subject on teriflunomide.

Overall, 5 of the 152 patients (3.3%) treated with teriflunomide in the OL period experienced opportunistic infections, more frequently reported in the placebo/ teriflunomide group compared to the teriflunomide/ teriflunomide group (5.8% vs. 2.0%, respectively). Each of the reported PTs occurred in a single subject and included herpes virus infection, oral herpes, and varicella in the P/T group and herpes zoster in the T/T group. The mycoplasma infection and the CNS infection were reported in the T/T group. CNS infection was the only serious opportunistic infection in the OL period.

No infections and infestations TEAEs led to treatment discontinuation.

Hypersensitivity and severe skin reactions

No AE were reported in EFC11759 until data cut-off.

Malignancies

No cases of malignancies were reported during the DB period. During the OL period, one patient in the teriflunomide/ teriflunomide group experienced acute pancreatitis with pancreatic nodules (pseudo-papilloma; benign lesion) coded as pancreatic neoplasm of severe intensity. The patient had stabilised but not recovered from pancreatic neoplasm after treatment discontinuation and AEP initiation. Although, two tumour markers were reported to be negative (i.e. CA125 and CA 19-9), biopsy results are not available. Therefore, a malignant condition cannot be ruled out.

Blood pressure and hypertension

Blood pressure (BP): slight mean increases for (supine) systolic (SBP) and diastolic BP (DBP) were noted from baseline to EOT in the teriflunomide group (mean change 4mm Hg and 3 mm Hg, respectively). Slightly more patients reported high potentially clinically significant abnormalities (PCSAs) for supine DBP and SBP in the teriflunomide group. In the OL period, the changes in the placebo/ teriflunomide and in the teriflunomide/ teriflunomide group were small and similar between groups.

Hypertension: No hypertension TEAEs were reported in teriflunomide-treated patients during the DB period; one patient experienced non-serious hypertension in the placebo group.

During OL, hypertension was only reported in the teriflunomide/ teriflunomide group (3 patients, 3.0%). 2 of 3 patients with hypertension TEAEs received corrective treatment (calcium channel blocker in 1 patient and calcium channel blocker plus angiotensin 2 receptor inhibitor in 1 patient) and recovered. Initial onset of hypertension was within 24 weeks. None of the cases was serious or led to treatment discontinuation.

Cardiac arrhythmias

No cases of cardiac arrhythmias were reported in the DB and the OL periods.

Pulmonary disorders

The highest percentage of treatment-emergent pulmonary disorders had an initial onset between 12 to 24 weeks. No cases of interstitial lung disorders were reported during the study.

More patients in the teriflunomide group than in the placebo group reported pulmonary disorders (63.3% vs. 43.9%). Most frequently reported TEAEs ($\geq 5\%$ at PT level in any treatment groups) were *nasopharyngitis, upper respiratory tract infection, influenza, pharyngitis, oropharyngeal pain, and cough*. Three SAEs in total included two severe TEAEs in the teriflunomide group (upper respiratory tract infection and pulmonary tuberculosis (leading to treatment discontinuation)) and asthma in the placebo group. All other events were of mild or moderate intensity.

During the OL period, the reporting of TEAEs probably related to pulmonary disorders was similar between groups (51% in the teriflunomide/ teriflunomide group and 46.2% in the placebo/ teriflunomide group), which was lower as compared to the DB period and again driven by TEAEs from the infections and infestations SOC. Likewise, 3 out of 5 patients with pulmonary disorder SAEs reported events in line with (respiratory tract) infections (teriflunomide/ teriflunomide group: lung infection of severe intensity and upper respiratory tract infection of mild intensity; placebo/ teriflunomide group: acute sinusitis of moderate intensity and bronchitis and tonsillitis of mild intensity). Two patients reported asthma as SAE that led to hospitalisation and corrective treatment, while IMP was continued. Both patients recovered from asthma and in both of them IMP was not rated related to the SAE based on the medical history of the patients, i.e. asthma, or hyperexcitability syndrome and allergies.

Embolic and thrombotic events

One patient in the teriflunomide group experienced nonserious "weakened left side" on Day 610 of the study, which was coded as hemiparesis (rated not related to teriflunomide). The event was of mild intensity and resolved within approximately 2 months. No TEAEs were reported during the OL period.

Haemorrhage

TEAEs regarding haemorrhages from any SOC were similarly reported between placebo and teriflunomide (5.3% and 7.3%). The most frequently reported PT with teriflunomide was nonserious contusion (3.7% vs 0%) of mild intensity. Cases were all related to accidental fall or sport. None of them led to treatment discontinuation. One case of gastrointestinal haemorrhage (haemorrhage of lower digestive tract-mild) was reported in the teriflunomide group on Day 361. Prior laboratory results in this patient were decreases in white blood cell (WBC) and platelet counts. The event of gastrointestinal haemorrhage (considered not related to teriflunomide by the Investigator) resolved within 1 month without corrective treatment and with continuation of teriflunomide. A single event of non-serious contusion was reported during the OL period in a patient in the placebo/ teriflunomide group. The event was of mild intensity.

Peripheral neuropathy

One (0.9%) patient in the teriflunomide group and 1 (1.8%) patient in the placebo group experienced treatment-emergent peripheral neuropathy during the DB period none of them being serious. The event in the teriflunomide group was of severe intensity (arm neuralgic pain coded as neuralgia), occurred at Day 305, resolved within 32 days (with corrective treatment), and was not considered related to IMP. The event in the placebo group was of mild to moderate intensity (neuropathy peripheral). Nerve conduction was not performed in the two patients.

Two patients in the placebo/ teriflunomide group (3.8%) and 3 patients in the teriflunomide/ teriflunomide group (3%) experienced peripheral neuropathy during the OL period, all of them recovered. All events were non-serious including neuralgia of mild intensity and sensory loss of mild intensity as well as moderate sensory disturbance in the teriflunomide/ teriflunomide group, and neuralgia of mild intensity and neuropathy peripheral of moderate intensity in the placebo/ teriflunomide group. The peripheral neuropathy led to treatment discontinuation. In this patient, electromyogram findings were concordant with polyneuropathic involvement characterised by mild loss of axons, predominantly in the lower extremities and sensory fibres.

Convulsions

The incidence of convulsions was similar in both groups during the DB phase (1.8% in the teriflunomide and 3.5% in the placebo group). One SAE (2 episodes of epilepsy) in the teriflunomide group was rated as not related given that this patient had a medical history of epilepsy. This patient is still treated in the OL period. No convulsion events were reported during the OL period.

Alopecia/ hair loss

Alopecia, frequently reported as hair loss and mainly temporarily-occurring, was more frequently observed with teriflunomide as compared to placebo (22.0% vs. 12.3%) during the DB period. None of the cases was serious or led to treatment discontinuation. In the teriflunomide group, alopecia was reported to have had an initial onset within 12 and 24 weeks.

During the OL period, alopecia was more frequently reported in the placebo/ teriflunomide group (17.3%) as compared to the teriflunomide/ teriflunomide (10.0%). All the events were nonserious. A single event of alopecia areata led to treatment discontinuation in the teriflunomide/ teriflunomide group. A majority of events were recovered or were recovering at the cut-off date of this report. Among the 18 patients reporting alopecia as per the first data cut-off, hair loss was reported 7 times (4 times in the placebo/ teriflunomide group and 3 times in the teriflunomide/ teriflunomide group) and modification of hair quality (thinner) was reported once in the placebo/ teriflunomide group.

Psychiatric disorders

During the DB period of EFC11759, reports of TEAEs related to psychiatric disorders were similar in patients on teriflunomide and placebo (13.8% vs. 14%), the most frequently reported TEAE being anxiety (3.7% vs. 5.3%). No case was serious. One patient on teriflunomide discontinued IMP due to an event of affective disorder on the first day of dosing together with a MS relapse. Teriflunomide was rated related to this event, which is rather unlikely given the time course and MS relapse being a confounder. During the OL period, TEAEs related to psychiatric disorders were more frequently reported in the placebo/ teriflunomide as compared to the teriflunomide/ teriflunomide group (19.2% vs. 9%), and headed by depression (7.7% vs. 1%). Although, this frequency is higher than in both treatment groups during the DB period, the overall numbers of patients with depression TEAEs are small. A single SAE of affective disorder (emotional disorder of childhood) was reported together with self-harming tendencies after 8 months of treatment with teriflunomide during the OL period. Emotional disorder of childhood was confirmed by psychiatric consultation and required hospitalisation and corrective treatment, while teriflunomide was continued. The status of the patient was "not recovered". Although, this this event was rated as not related to teriflunomide by the investigator, a contributing role cannot be ruled out.

Pregnancies

During the DB period, a single pregnancy was reported in a patient, who underwent elective abortion. During the OL period, two pregnancies were reported: one patient after approximately 1 month of treatment with teriflunomide. At this time, the patient was within the first weeks of the pregnancy. No wash-out was followed and the patient delivered a healthy infant with no signs of malformations. Another patient in the placebo/ teriflunomide group became pregnant and underwent termination of pregnancy. The occurrence of undesired pregnancies is of special importance in adolescents and therefore, key elements were included in the HCP guide and in the patient card as risk minimisation measures (RMMs)

Overdose

Accidental overdose and/or overdose was defined in the protocol as at least twice the intended dose (i.e. 2 tablets) on a given calendar day (within 24 hours). Accidental overdose was reported in a total of 8 patients (4.6% in the teriflunomide group and 5.3% in the placebo group) during the DB period of the study. None was associated with clinical symptoms.

A total of 10 patients, 8 (8.0%) patients in the teriflunomide/ teriflunomide group and 2 (3.8%) patients in the placebo/ teriflunomide group reported accidental overdose (intake of 2 tablets in less than 24 hours) during the OL period. None was associated with clinical symptoms. In one patient in the teriflunomide/ teriflunomide group, an SAE was reported related to suicide attempt leading to

hospitalisation. This patient experienced sensory disorders and tingling sensations for less than 2 hours and recovered after temporary teriflunomide discontinuation.

Comparison of the safety of teriflunomide in paediatrics and adults (incl. laboratory abnormalities)

The key safety issues pertaining to teriflunomide 14 mg in paediatrics (from EFC11759) are compared to adult safety data (derived from Pool A1, including Studies 2001, EFC6049/TEMPO, EFC10531/TOWER and EFC6260/TOPIC) in Table 15. Data interpretation should consider the overall difference in subjects included and the difference in exposure to placebo in both populations. The exposure to placebo in the paediatric population was shorter given that patients were given the option to receive teriflunomide OL.

Table 15: Teriflunomide safety in paediatrics and adults

Treatment group	EFC11759/Terikids DB period		Pooled adult placebo-controlled studies (Pool A1)	
	Placebo	Teriflunomide 14 mg – eq	Placebo	Teriflunomide 14 mg
N	57	109	997	1002
Median exposure (days)	273	660	670	679
Identified risks				
<u>Hepatic effects</u>				
Hepatic disorder TEAEs (%)	3.5	4.6	15.2	21.5
<u>Hypertension</u>				
Hypertension TEAE (%)	1.8	0	2.7	5.3
<u>Haematological effects</u>				
TEAEs of bone marrow disorders (%)	1.8	7.3	4.4	10.3
<u>Infections</u>				
Infections and infestations TEAEs (%)	45.6	66.1	53.4	52.7
Nasopharyngitis*	8.8	25.7	21.1	18.4
Upper respiratory tract infection*	10.5	21.1	9.6	9.9
Interstitial lung disease	0	0	0	0
<u>Pancreatic effects</u>				
Pancreatic disorders TEAEs (%)	1.8	3.7	2.8	2.7
<u>Peripheral neuropathy</u>	1.8	0.9	4.0	4.0
Potential risks				
Teratogenicity		1 elective abortion in the DB period, 1 pregnancy with normal delivery, and 1 pregnancy with early termination in the OL period		
Serious opportunistic infections (including PML)	0	1 pulmonary tuberculosis		Similar frequencies were reported across treatment groups (include pulmonary tuberculosis, CMV hepatitis and gastrointestinal tuberculosis)
Malignancies (incl. lymphoproliferative disorders)	0	0	0.5	0.3
Renal failure	0	0	0	0
Other TEAEs of interest based on observations in Terikids				
Alopecia (%)*	12.3	22.0	5.1	13.9
Abdominal pain TEAE (%)*	1.8	11.0	4.3	4.1
Paresthesia (%)*	1.8	11.0	6.7	8.8
CPK increase (%)*	0	5.5	0.7	1.6
Effects on vital signs or laboratory tests based on known effects in adult patients				

Treatment group	EFC11759/Terikids DB period		Pooled adult placebo-controlled studies (Pool A1)	
	Placebo	Teriflunomide 14 mg – eq	Placebo	Teriflunomide 14 mg
Weight				
Mean change (SD) from baseline to Week 24 (kg)	0.1 (2.4)	0.5 (2.8)	0.13 (3.17)	-1.21 (3.01)
Blood pressure				
Mean (SD) change from baseline to last on-treatment value (mmHg)				
Supine SBP				
DBP**	-0.5 (10.5)	3.9 (12.5)	-0.5 (13.7)	2.6 (13.2)
	1.5 (10.1)	3.3 (9.8)	-0.6 (9.5)	1.7 (10.1)
Lymphocyte				
Change from baseline to last value on treatment**	-0.01 (0.60)	-0.18 (0.54)	0.03 (0.51)	-0.27 (0.46)
	Giga/L	Giga/L	Giga/L	Giga/L
Neutrophil				
Change from baseline to last value on treatment**	0.74 x (1.65)	-0.76 (1.95)	-0.10 (1.68)	-0.58 (1.67)
	Giga/L	Giga/L	Giga/L	Giga/L
Platelet				
Change from baseline to last value on treatment**	5.8 (50.3)	-23.2 (42.2)	0.7 (45.5)	-23.5 (47.3)
	Giga/L	Giga/L	Giga/L	Giga/L
ALT increase				
ALT>3xULN (%)	0	3.7	6.6	8.0
ALT>20xULN (%)	0	0	0.4	0.3
Uric acid				
Change from baseline to last value on treatment (µmol/L)	-7.5 (45.1)	77.4 (62.7)	-3.4 (48.0)	-74.8 (48.7)
Phosphorus				
Change from baseline to last value on treatment (mmol/L) **	-0.063 (0.169)	-0.121 (0.213)	-0.011 (0.187)	-0.115 (0.182)

* PT level reported more frequently in the teriflunomide group than in the placebo group, with a difference of $\geq 5\%$; **Week 108 for PoolA1; ALT: alanine aminotransferase, CMV: cytomegalovirus, DB: double-blind, CPK: creatine phosphokinase, DBP: diastolic blood pressure, SBP: systolic blood pressure, SD: standard deviation, TEAE: treatment-emergent adverse event.

A higher reporting was noted in paediatrics vs. adults for the following TEAEs in the teriflunomide vs. the placebo group:

- Pancreatic disorders TEAEs were reported in 3.7% (4 patients) in the teriflunomide and 1.8% (1 patient) in the placebo group in Study EFC11759 (DB period), and in 2.7% in the teriflunomide and 2.8% in the placebo group in adults. Events of (acute) pancreatitis included in these numbers amount to 1.8% (2 patients) in the teriflunomide and none in the placebo group in Study EFC11759, and to 0.2% (2 patients) in the teriflunomide and 0.4% (4 patients) in the placebo group in adults. Three additional cases of pancreatitis (acute) were reported during the OL period (see AESI section). Pancreatic TEAEs in adults were reported with a similar incidence (2.7% on teriflunomide vs. 2.8% on placebo). Cases of pancreatitis in adults on teriflunomide leading to labelling revision were reported post-marketing (see summary of the Safety Evaluation Report).
- An increased frequency of infections was observed in paediatrics on teriflunomide vs. placebo but not in adults. The increase was driven by an increased frequency of nasopharyngitis and upper respiratory tract infection.
- TEAEs reported more frequently in the teriflunomide group than in the placebo group in paediatrics with a difference $\geq 5\%$ vs. a more evenly distribution in adult treatment groups (except for alopecia): *nasopharyngitis, upper respiratory tract infection, alopecia, paresthesia, abdominal pain, and blood CPK increased*. Based on the almost identical teriflunomide median exposure (in days) in paediatrics and adults, reporting of these TEAEs is higher in children as compared to adults.

A lower reporting was noted in paediatrics vs. adults for hepatic disorders TEAEs and increases in ALT; hypothetical reasons for this observation are a less frequent monitoring of liver enzymes in Study

EFC11759 as compared to adult studies in the first 24 weeks (i.e. every 4 weeks vs. every 2 weeks), but could also be a consequence of half the adult equivalent 14 mg dose administered for the first 8 weeks of treatment (PK run-in phase) in all patients.

No relevant differences between paediatrics and adults were observed regarding hypertension, haematological effects, interstitial lung disease (ILD), hypersensitivity reactions, peripheral neuropathy, teratogenicity, serious opportunistic infections (including progressive multifocal leukoencephalopathy [PML]), malignancies, renal failure/ function parameters, and body weight changes.

Serious adverse event/deaths/other significant events

No fatal cases were reported in any treatment arm during the DB or OL period up to the data cut-off.

A similar proportion of patients in the DB period had at least 1 treatment-emergent SAE (11.0% of patients on teriflunomide and 10.5% of patients on placebo). Overall, 18 patients reported 25 SAEs. There was no increased incidence of SAEs in patients < 13 years.

The most frequent treatment-emergent SAEs ($\geq 1.0\%$ of patients in either treatment group) were syncope (1.8% in both groups), epilepsy (0.9% in the teriflunomide group and 1.8% in the placebo group) and blood CPK increased (1.8% versus none, respectively). All other SAEs were reported by 1 patient each. The majority of SAEs have not been considered related to IMP by the investigator. The SAEs rated to be related to teriflunomide were pulmonary tuberculosis, blood CPK increased, ALT increased, neutropenia, and pancreatitis acute. Cardiomyopathy in a single patient after 3 weeks on teriflunomide was related to pre-existing congenital cardiac abnormalities. The patient was hospitalized for a relapse. Teriflunomide was continued as planned.

During the OL period, the proportion of patients with treatment emergent SAEs was lower in the teriflunomide/ teriflunomide group than in the placebo/ teriflunomide group (13.0% and 28.8%). Overall, 28 patients reported 41 SAEs during the OL period. The most frequently reported SAEs by PTs in $\geq 2.0\%$ of patients in either treatment group were Uhthoff's phenomenon, asthma, ALT increased, and blood CPK increased (2% vs. 0, 0 vs. 3.8%, 0 vs. 3.8%, and 2.0 vs. 1.9% in the teriflunomide/teriflunomide group and placebo/ teriflunomide group, respectively). Other SAEs were reported by single patients only. The majority of SAEs have not been considered related to teriflunomide by the investigator. The SAEs rated to be related to treatment were pancreatitis (T/T), two SAEs of blood CPK increased (each from the T/T group), headache (P/T), two SAEs of ALT increased (each from the P/T group), acute sinusitis (P/T), neutropenia (T/T), upper respiratory tract infection (T/T), and MS (T/T).

Moreover, in the teriflunomide/ teriflunomide group, three SAEs in 2 patients were found noteworthy given that these were not considered related to teriflunomide:

The SAEs of central nervous system infection and pneumonia (and upper respiratory tract infection as of 12 September 2020) were reported in a patient, who was also reported with SAEs of epilepsy and upper respiratory tract infection during the DB period. This patient also had a relevant medical history (see AESI section on infections). The SAE of pancreatic neoplasm in a patient during the OL period is considered a medically significant event against the background of known pancreatic effects elicited by teriflunomide.

Laboratory findings

Haematology

Mean platelet count in the teriflunomide group dropped approx. 10 % from baseline up to Week 8 compared to the placebo group during the DB period and remained stable up to Week 96. At EOT in the

DB period, the mean platelets were $247.3 \times 10^9/L$ in the teriflunomide group and $269.7 \times 10^9/L$ in the placebo group. The decrease was similarly observed in the placebo/teriflunomide group at the beginning of the OL period and became similar between groups during the OL period.

A slight decrease in leukocytes from baseline to Week 20, mainly neutrophils and lymphocytes was observed in the teriflunomide group compared to the placebo group and remained stable thereafter. The decrease in leukocytes of approximately 15% (19% in neutrophils and 10% in lymphocytes) is in line with the adult population. However, mean decreases were delayed up to Week 20 in paediatrics as compared to adults (up to Weeks 6), which could be explained by the switch from half to full the adult equivalent dose at Week 8 in a majority of paediatrics. This might have caused additional decreases up to Week 20. At EOT in the DB period, the mean leukocytes were $5.78 \times 10^9/L$ in the teriflunomide group and $6.96 \times 10^9/L$ in the placebo group (neutrophils: $3.35 \times 10^9/L$ and $4.34 \times 10^9/L$, respectively and lymphocytes: $1.87 \times 10^9/L$ and $2.06 \times 10^9/L$, respectively).

A decrease in leukocytes from baseline to week 20, mainly neutrophils and lymphocytes, was observed in the teriflunomide/ teriflunomide group compared to the placebo/ teriflunomide group during OL stabilising thereafter.

No clinically relevant differences between groups were observed for changes over time of haemoglobin, haematocrit, erythrocytes mean corpuscular volume, prothrombin time, activated partial thromboplastin time, monocytes, basophils, and eosinophils.

The proportion of patients with PCSA during the DB period was slightly higher in the teriflunomide than in the placebo group for haemoglobin decrease from baseline ≥ 20 g/L and for platelets $< 100 \times 10^9/L$. 3.7% of subjects in the teriflunomide group vs. none on placebo reported platelets $< 100 \times 10^9/L$ (the lowest platelets value was $92 \times 10^9/L$). The proportion of patients with low PCSA for leukocytes and lymphocytes was higher in the teriflunomide group as compared to placebo group (64.2% vs. 39.3%).

There was no worsening of PCSA in any parameters in the OL period.

Clinical chemistry

Mean phosphorus levels decreased from Week 0 to Week 24 in the teriflunomide and placebo groups; however, the decrease in the teriflunomide group was approximately 10% from baseline relative to placebo, an effect already labelled in the SmPC. Mean creatine kinase values increased by $\sim 17\%$ until EOT with teriflunomide, although, the SD was very high at all visits. The plots of mean change from baseline in CPK over time in the DB and the OL period imply that there were outliers of mean changes from baseline at some time points only in the teriflunomide and in the teriflunomide/ teriflunomide group, respectively. The proportion of patients with high CPK abnormalities ($\geq 3x$ ULN) was slightly higher in the teriflunomide group as compared to the placebo group (8.3% versus 3.6%) during the DB period. Some of the elevated CPK reported in the teriflunomide group could be explained by alternative etiology (strenuous exercise or trauma).

For liver function parameters and pancreatic enzymes see AESIs.

Renal function

Mean uric acid levels decreased with teriflunomide but not with placebo within the first 24 weeks of treatment during the DB period and remained stable thereafter on a decreased level. A similar decrease was observed in the placebo/ teriflunomide group during the OL period within the first 12 weeks of treatment.

The proportion of patients with PCSA for uric acid ($< 120 \mu\text{mol/L}$ for adults) was higher in the teriflunomide group than in the placebo group (11.9% and 3.6%, respectively).

No relevant changes were observed for creatinine, creatinine clearance or blood urea nitrogen, neither during the DB or OL period.

Thyroid stimulating hormone (TSH)

Mean TSH values slightly decreased approximately over the first 48 weeks in the teriflunomide but not in the placebo group. Mean TSH values slightly decreased through first 48 weeks during DB period in the teriflunomide/ teriflunomide group and stabilised thereafter.

Vital signs, physical findings and other observations related to safety

Body Weight: A slight decrease in mean BW in patients on teriflunomide over placebo was observed during the first 24 weeks of treatment (0.5 kg vs. 0.1 kg). From Week 24 to Week 96, BW increased in both groups. The proportion of patients with a BW decrease $\geq 5\%$ was higher in the teriflunomide group compared to the placebo group (40.4% versus 26.8%). Mean change in BW slightly increased from baseline to Week 84 then returned to the baseline in the teriflunomide/ teriflunomide group, while it remained stable in the placebo/ teriflunomide group.

Electrocardiogram: No relevant changes were observed for electrocardiogram parameters, neither during the DB period nor with longer treatment in the OL period.

Tanner stage: The majority (more than 90%) of patients in both arms was Tanner stage $>I$ (pubertal) at baseline. During the DB period, and similar for both treatment groups, pubertal development in patients not yet fully pubertal was generally of no more than 2 stages, which is in line with the expectation of a progress rate in sexual maturation of approx. one Tanner stage per year retrieved from scientific literature¹⁷. This is, however, based on a rather small number of paediatric patients with less than Tanner Stage IV or V at baseline, who – at the same time – completed the 96-week DB period in study EFC11759. Moreover, variability in progression of Tanner Stages between treatment groups was observed during the combined DB and OL periods in either gender, which cannot be further clarified given the limited number of patients included in this additional analysis. In the OL period, patients in both treatment groups progressed to higher Tanner stages without relevant differences.

Safety in special populations

Intrinsic and extrinsic factors were analysed for their effects on the incidence of any TEAEs, SAEs, TEAEs leading to treatment discontinuation, and AESIs. Few differences overall in both treatment groups were observed, in particular for infections and hepatic disorders regarding age, race, and BW. Regarding race, there was a trend for a higher exposure in Asians compared to Caucasians (for patients receiving 14 mg adult equivalent, median $AUC_{0-24SS} = 1872 \mu\text{g.h/mL}$ for Asians and $1284 \mu\text{g.h/mL}$ for Caucasians). 12 and 25 patients on placebo and teriflunomide, respectively, were of Asian origin and all of them reported any TEAEs. With regard to Pubertal status (Tanner stage $\leq I$ vs. $>I$), all pre-pubertal subjects reported at least one TEAE, while there were no obvious differences in reporting of SAEs and TEAEs leading to discontinuation of treatment.

In general, no specific increase was noted in the teriflunomide group or teriflunomide/ teriflunomide group as compared to the placebo group or placebo/ teriflunomide group. Teriflunomide safety profile was generally consistent across subgroups. There were no new or unexpected safety findings.

¹⁷ Marceau K, Ram N, Houts RM et al. Individual Differences in Boys' and Girls' Timing and Tempo of Puberty: Modeling Development With Nonlinear Growth Models Dev Psychol. 2011; 47(5): 1389–1409

Safety related to drug-drug interactions and other interactions

No specific drug interaction studies were performed with teriflunomide in paediatric patients.

Discontinuation due to adverse events

Six (5.5%) patients in the teriflunomide group and no patient in the placebo group reported a TEAE leading to treatment discontinuation in the DB period: pancreatitis acute was reported in 2 patients and the other PTs were reported by 1 patient each and included pulmonary tuberculosis, hyperlipasemia, affective disorder and ALT increased.

Three (3.0%) of patients in the teriflunomide/ teriflunomide group and six (11.5%) of patients in the placebo/ teriflunomide group had to discontinue teriflunomide due to a TEAE in the OL period. In the placebo/ teriflunomide group, one patient reported neuropathy peripheral and five patients reported ALT increased. The reasons for discontinuation in the teriflunomide/ teriflunomide group were serious "pancreatitis", serious "pancreatitis acute", and "amylase increased and lipase increased" in a single patient (in the context of serious pancreatitis diagnosis).

AEs leading to discontinuation from treatment followed the known safety profile of teriflunomide as did TEAEs and SAEs leading to temporary treatment interruption in patients. Treatment interruption concerned solely but only few patients on teriflunomide, were often due to laboratory abnormalities and were limited to a few days in the majority of subjects (except for a 44 day interruption of teriflunomide in a patient with neutropenia).

Post marketing experience

A search from international birth date of 12 September 2012 through 17 January 2020 was performed in the Sanofi Global Pharmacovigilance Database in order to identify off-label post-marketing data in paediatrics (up to 17 years of age) from international birth date of Aubagio to data cut-off (January 2020). Cases for which AEs have been reported (36 out of 39 cases) were in a majority related to the underlying disease. Nonserious AEs in 4 patients were in line with the safety profile of teriflunomide. Two SAEs involved acute myocarditis following a viral infection and diarrhoea with traces of blood. While in the case of myocarditis, a causal relation seems to be present for the viral infection, the SAE of diarrhoea with traces of blood was not assessable due to a lack of background information. There were no case reports for children below the age of 11 years.

2.6.1. Discussion on clinical safety

The safety profile of teriflunomide in paediatrics has been characterized based on the results of study EFC11759: a single, multicenter, randomized, DB, placebo-controlled, parallel-group study in children and adolescents 10 to 17 years of age with RMS. Controlled safety data up to 96 weeks derives from the completed DB period of the trial, and followed by an ongoing OL period (up to 192 weeks). For the latter, interim results with the data cut-off 12 September 2020 are available to provide preliminary long-term safety experience. In the paediatric population special attention should be given to possible AE on sexual maturation, cognition, endocrine function and other aspects of development. This is of importance given that susceptibility to specific adverse reactions might also change from pre- to post-pubertal children. Tanner staging was assessed for each location (pubic hair and breasts in girls, pubic hair and testes in boys) by gender and treatment group, every 24 weeks, and at EOT or until complete sexual maturity (Tanner Stage V). The progress in sexual maturation in normal adolescents is expected to be 1 Tanner stage per year, which was likewise observed in paediatrics of both treatment groups in study EFC11759.

However, the small number of patients with Tanner Stages < IV and V at baseline and a full course of 96-week DB treatment needs to be considered when interpreting the data on sexual maturation.

Study EFC11759

A total of 166 patients were randomized, 109 patients in the teriflunomide group and 57 patients in the placebo group, which represents an acceptable number for a paediatric MS trial.

The recommended teriflunomide dose in paediatrics ≥ 40 kg should be 14 mg and in paediatrics < 40 kg it should be 7 mg, aiming at the same exposure as in adults. At the end of the PK run-in period, 11 of 109 patients received 7 mg teriflunomide and 97 of 109 patients (89%) received 14 mg teriflunomide. In the OL period, 126 of 152 patients (83%) received the 14 mg dose. No patient in study EFC11759 (neither during DB nor OL) was initiated on the 14 mg adult equivalent teriflunomide dose proposed in the SmPC. Even though, the 14 mg dose does not raise particular safety concerns beyond those in adults, tolerability issues, e.g. nausea, diarrhoea, and alopecia might be expected following treatment initiation with doses based on the adult exposure. Consequently, compliance problems or early treatment discontinuations might occur. No clinically relevant differences could be observed upon analysis of TEAEs in the DB period for the two time intervals of interest (i.e., for the first 8 weeks of treatment, when patients received half the adult equivalent dose, and the second 8 weeks, when patients received the full adult equivalent dose). In general, TEAEs were more frequently reported within the first 8 weeks of treatment. Nevertheless, it cannot be fully excluded that some of the tolerability TEAEs of interest (e.g. GI disorders TEAEs) might have been mitigated upon "titration" of teriflunomide from half to full the adult equivalent dose within 16 weeks of treatment. In addition, the numbers of subjects with TEAEs in this analysis are small hampering the evaluation of clear trends.

Extent of exposure was 131 PYE in the 14 mg dose group vs. 57 PYE in the placebo group during DB treatment. Moreover, median duration of treatment during the DB period was shorter for placebo as compared to teriflunomide (273.0 days vs. 660.0 days). The imbalance is acknowledged to be driven by the higher frequency of switches due to clinical relapses or high MRI activity in the placebo group as compared to the teriflunomide group. Exposure differences need to be considered for interpretation of the safety data, especially regarding TEAEs that consistently occurred throughout the study.

Cumulatively, 100 (92%) and 73 (67%) of teriflunomide-treated paediatric patients were exposed to the drug for ≥ 6 months and ≥ 1 year, respectively. Controlled safety data for more than 2 years of teriflunomide treatment are limited to 41 patients (38%) (and 10 [17.5 %] of placebo-treated patients). Interim data from the OL experience added a cumulative exposure of 263.71 PYE. Up to the new data cut-off, the highest cumulative duration of OL treatment with teriflunomide 14 mg was ~ 3.5 years for 7 patients.

Exposure data based on age was provided upon request. The median duration of treatment was similar in both age categories for patients on placebo (299.5 days and 273.0 days) and slightly higher in patients < 13 years versus those ≥ 13 years treated with teriflunomide (669 days vs. 596 days). A similar percentage of patients in both age categories per treatment group had a cumulative duration of treatment more than six months and more than one year. Thus, exposures in the two age categories in placebo- and teriflunomide-treated paediatric patients were similar.

The paediatric population included in the DB period was similar to that in other DMT MS studies (i.e. Gilenya EMEA/H/C/002202/X/0044/G). Few data are available regarding the most vulnerable subpopulations (< 13 years, Tanner stage I, $BW \leq 40$ kg) for which the interpretability of safety data is difficult:

- Age: median age was 15 years. Only 16 patients on teriflunomide and 10 patients on placebo (i.e. 26 out of 166 patients) were < 13 years. The vast majority of patients in the ≥ 13 years age group was aged 16 to 17 years, thus, more in line with the adult population.

- Physical development: only 10 patients were pre-pubertal (6 %; 5 patients per group) reflected by Tanner Stage I.
- Body Weight: only 5 patients on teriflunomide (and 6 patients on placebo) in the DB period had a BW of ≤ 40 kg. These patients were treated with a dose of 7 mg.

TEAEs, SAEs, and TEAEs leading to permanent treatment discontinuation

No deaths were reported as per the data cut-off. The number of patients with any TEAEs during the DB period was slightly higher in the teriflunomide group as compared to placebo (88.1% vs. 82.5%). A similar proportion of patients reported SAEs (11% vs. 10.5%), while TEAE-related discontinuations of treatment were only reported in the teriflunomide arm (5.5% of patients). During the OL period, more patients from the placebo/ teriflunomide group reported TEAEs, SAEs, and TEAEs leading to permanent treatment discontinuation as compared to those from the teriflunomide/ teriflunomide group. Thus, data imply that a majority of events occur early during treatment with teriflunomide.

The most frequently reported TEAEs during the DB period (>20 % in either group) in paediatrics were similar to adults and derived from the Infections and infestations SOC, Skin and subcutaneous tissue disorders SOC, Nervous system disorders SOC, Gastrointestinal disorders SOC, and Investigations SOC. Differences mainly pertain to a disproportional reporting (≥ 5 % with teriflunomide vs. placebo) of nasopharyngitis (25.7% vs. 8.8%), upper respiratory tract infection (21.1% vs. 10.5%), alopecia (21.1% vs. 12.3%), paresthesia (11.0% vs. 1.8%), abdominal pain (11.0% vs. 1.8%), and blood CPK increased (5.5% vs. 0%). For other SOCs, where an increased reporting was noted in patients on teriflunomide, PTs do not indicate a specific cluster.

During the OL period, the overall reporting of TEAEs by SOC was comparable to DB treatment and either similar or higher in the placebo/ teriflunomide group compared to the teriflunomide/ teriflunomide group.

25 serious AEs occurred in 18 patients during the DB period. 2 of the 18 patients (one in each group) were < 13 years. No pre-pubertal patient (Tanner stage I) experienced a SAE in the teriflunomide group. The most frequently reported SAEs were syncope (2 patients [1.8%] on teriflunomide vs. 1 patient [1.8%] on placebo), epilepsy (one patient in each group) and blood creatine phosphokinase increased (2 patients [1.8%] versus none, respectively). SAEs rated as being related to teriflunomide were pulmonary tuberculosis, neutropenia (re-challenge), pancreatitis acute, blood CPK increased, ALT increased.

SAEs during the OL period were basically in line with those from the DB period and were reported by a higher percentage of patients in the placebo/ teriflunomide group (28.8% vs. 13.0% in the teriflunomide/ teriflunomide group). Overall, 28 patients reported 41 SAEs during the OL period. 5 out of 28 patients with SAEs were < 13 years old. The most frequent treatment-emergent SAEs were Uhthoff's phenomenon, asthma, ALT increased, and blood CPK increased (2% and 0%, , 0% and 3.8%, 0% and 3.8%, and 2.0 and 1.9% in the teriflunomide/ teriflunomide group and in the placebo/ teriflunomide group, respectively). SAEs that were rated related to teriflunomide were pancreatitis, two SAEs of blood CPK increased, headache, two SAEs of ALT increased, acute sinusitis, neutropenia, upper respiratory tract infection, and MS.

In the DB period, TEAEs leading to permanent treatment discontinuation were solely reported by patients in the teriflunomide group (5.5%) in line with the expected safety profile (i.e. infections [pulmonary tuberculosis], pancreatic effects [hyperlipasemia and pancreatitis acute], and hepatic effects [ALT increased]). In the OL period, discontinuations due to TEAEs were similar to the DB period and driven by patients in the placebo/ teriflunomide group. TEAEs occurred in single patients only except for ALT increased (5 patients in the placebo/ teriflunomide group [10 %]).

Temporary discontinuations from treatment due to TEAEs or SAEs occurred in few patients only and were limited to a few days in most of the patients.

Adverse events of special interest

The incidence of gastrointestinal disorders (specifically nausea and diarrhoea) in paediatrics appears not different from adults. However, given that both events occur dose-related (based on the adult experience) and early during treatment (mainly within the first weeks to three months), the full adult equivalent dose (on which paediatrics have not been initiated in EFC11759) might cause tolerability and compliance issues in paediatrics, which cannot be clarified with the available data.

Hepatic toxicity is an important identified risk related to teriflunomide and mainly presents with elevation of ALT most frequently within the first 6 months of treatment. RMMs are in place and detailed in the adult SmPC in sections 4.3 (patients with Child-Pugh class C), 4.4 (baseline and routine monitoring of liver enzymes), and 4.8, which likewise apply to paediatrics. During the DB period, increases in mean ALT started at Week 4 and increased during the first 6 months. 26% patients on teriflunomide and 14% of patients on placebo had ALT > 1x ULN. ALT increases > 1x ULN were solely observed in the teriflunomide group (7 patients had ALT > 2x ULN, 6 %) but not in the placebo group; two of them had ALT > 5x ULN and 1 of them had ALT > 10x ULN. The incidence of hepatic disorders TEAEs from the hepatobiliary disorders SOC and the investigations SOC (mainly ALT increased) was similar in the teriflunomide and placebo group (4.6% and 3.5% [sum of TEAEs in both SOC]). Two patients in the teriflunomide group experienced serious hepatic disorders: ALT increased and increased transaminases, respectively. Both events were asymptomatic and accompanied by CPK increased. Both patients recovered without corrective treatment and with continuation of teriflunomide. During the OL period, an initial increase in mean ALT was observed in the placebo/ teriflunomide group over the first weeks of treatment but also in the teriflunomide/ teriflunomide group. The reporting of hepatic AEs in the placebo/ teriflunomide group was higher as compared to the teriflunomide/ teriflunomide group (15.4% vs. 3%) and even higher as reported in the teriflunomide group during the DB period (i.e. 4.6%), which could have been a consequence of concomitant (corticoid) medication in this treatment group (deriving from a switch from placebo to teriflunomide due to MS relapse). No increased incidence of hepatic SAEs was reported during the OL period. However, one patient (376003004) was diagnosed with "drug-induced liver injury". Upon request, the Applicant provided explanation on a possible confounder (i.e. minocycline treatment prior to the event). While it remains undetermined whether this case indeed presents DILI, this issue has been discussed in the two recent variation procedures EMEA/H/C/002514/II/0029 and EMEA/H/C/002514/II/0032. As an outcome of these variations, the frequency of hepatic enzyme monitoring has been revised and warning statements have been included in the SmPC. The recently approved liver enzyme monitoring schedule in adults, i.e. at least every four weeks during the first 6 months, and regularly thereafter, is likewise applicable to paediatrics given that the hepatic safety is considered similar in paediatrics and adults.

Slight differences in hepatic safety might be attributed to the different schedule of liver enzyme monitoring, i.e. every 4 weeks in paediatrics vs. every 2 weeks in adults. Moreover, the contribution of lower initial teriflunomide doses during the first 8 weeks of treatment in the paediatric trial to the incidence of liver enzyme increases, which are known to occur early during treatment, is unknown.

There were no cases of hepatitis or Hy's law in paediatric patients.

Pancreatic effects are an important identified risk with teriflunomide treatment that derives from the nonclinical experience, clinical adult studies, and most of all from post-marketing reports.

Mean amylase and lipase values (markers of pancreas function) did not show noticeable differences between treatment groups during the DB and OL period.

An increased reporting of TEAEs in line with pancreatic disorders was observed during the DB period, i.e. 4 patients (3.7%) in the teriflunomide group and 1 patient (1.8%) in the placebo group, all of them rated as related to teriflunomide. Three of four events led to treatment discontinuation in the teriflunomide group: one serious case of acute pancreatitis, one nonserious but severe case of acute caudal pancreatitis (both requiring hospitalisation), and one nonserious and asymptomatic case of hyperlipasemia. The incidence of pancreatic disorders TEAEs in paediatrics during the DB period contrasts the controlled pooled clinical data in adults, for which the incidence was similar in both groups (2.7% on teriflunomide and 2.8% on placebo). Moreover, TEAEs of pancreatitis were not reported in the teriflunomide groups in clinical studies in adults. During the OL period, pancreatic disorders TEAEs were reported in 6 patients, 5 patients (5.0%) in the teriflunomide/ teriflunomide group and 1 patient (1.9%) in the placebo/ teriflunomide group. The latter was a nonserious event of an asymptomatic lipase increased $\geq 2x$ ULN. Two patients experienced SAEs of pancreatitis and pancreatitis acute, leading to treatment discontinuation. The SAEs occurred after 1 and 3 years of teriflunomide treatment, respectively. Both SAEs presented with symptoms of pancreatitis and were accompanied by pancreatic enzyme elevations, led to hospitalisation and were treated with corrective treatments. The SAE of pancreatitis acute was severe in intensity and specifically concerning given that the patient presented with medically significant "pancreatic neoplasm" according to the narrative, and accompanied by symptoms (persistent epigastric pain, nausea, abdominal and back pain), and elevations in pancreatic enzymes and for which a surgery was indicated but refused. This case lacks biopsy results to confirm whether this is indeed a benign inflammatory process or a malignancy. Laboratory data and adverse events for this patient during the DB period have been provided and were unremarkable. The investigator did not consider teriflunomide to be related to the pseudo-papilloma of the uncinata process of the pancreas, which in consequence led to the event of pancreatitis. However, a contribution of teriflunomide remains likely. One additional patient upon the OL data cut-off of 12 September 2020 was reported with nonserious pancreatitis of mild intensity accompanied by elevations in pancreatic enzymes after more than 2.5 years of teriflunomide treatment, and confirmed by ultrasound. This event also led to treatment discontinuation and accelerated elimination procedure.

The risk for pancreatitis in paediatrics and adults was further taken up by the Applicant in a detailed review of cases from different sources, informed by postmarketing data, literature review and disproportionality analyses using external databases. Results of this review contribute to the results from study EFC11759. The incidence of pancreatitis in teriflunomide-treated adults was found higher compared to adult background rates (74.9/100,000 vs. 45/100,000); moreover, in teriflunomide-treated paediatrics the incidence of pancreatitis was found much higher compared to background paediatric rates (4/166 [3%] vs. 1/10,000). Specific events reported in adults, e.g. pancreatic pseudocyst and pancreatitis necrotising, are of general concern and should be taken into account when treating paediatrics.

Upon request, the Applicant proposed to include more detailed information regarding onset of pancreatic TEAEs, symptoms, diagnostic measures, and pancreatic enzyme monitoring in SmPC section 4.4. Discussion on feasibility and benefit of baseline and routine pancreatic enzyme monitoring, however, led to the conclusion that this would not reduce the risk of pancreatitis, even in patients receiving drugs with an established risk of pancreatitis. Therefore, the risk seems to be sufficiently covered by obtaining pancreatic enzymes in case of suspected pancreatitis and discontinuation of teriflunomide if pancreatitis is confirmed. In section 4.8, the Applicant included further refinement on the source data in the paediatric study. Furthermore, a paragraph on "*Gastrointestinal disorders*" in the section "*Description of selected adverse reactions*" has been added to include general information on pancreatitis in adults in the postmarketing setting. Overall, it remains important to increase awareness for such events in HCPs and patients to early identify those with a high risk for pancreatitis. Post-marketing follow-up of pancreatitis by means of targeted follow-up forms to the reporter of these events is considered to further address this issue in the real world setting.

Haematological effects are a designated identified risk with teriflunomide that causes anti-proliferative action on rapidly dividing cells leading to decreased erythropoiesis and granulopoiesis in the bone marrow. As indicated in the Aubagio EPAR, haematopoietic changes in bone marrow might result in development of anaemia, leukopenia, lymphocytopenia and thrombocytopenia, which can lead to impaired coagulation, haemorrhages, hemosiderosis and bacterial infections.

The proportion of patients with bone marrow disorders was higher with teriflunomide treatment compared to placebo in the DB period (7.3% vs. 1.8%) but not higher than in adults. The most frequently reported TEAEs derived from the blood and lymphatic system disorders SOC (neutropenia, leukopenia, and monocytopenia) and from the investigations SOC (WBC count decreased, and neutrophil count decreased were reported in 3.7% and 2.8% of patients on teriflunomide). One related SAE of neutropenia was confounded by a history of cyclic neutropenia (this was also the only patient with a SAE in the OL period). No increased incidence of events was observed during OL treatment.

Changes in haematology parameters were similar to adults: platelet counts decreased approx. 10 % from baseline to Week 8 with teriflunomide and remained stable thereafter. 4 subjects in the teriflunomide group vs. none on placebo had PCSA of low platelet counts (i.e. $< 100 \times 10^9/L$), which was either not confirmed upon repeat testing or falsely entered as PCSA despite being in the normal range. Platelet count reductions did not lead to an increase in haemorrhagic TEAEs during the DB period. Although, contusion was reported more frequently in the teriflunomide group as compared to placebo (3.7% vs.0%), events were related to sporting injury or accidental fall. One patient reported a gastrointestinal haemorrhage, which followed several occasions of haematological abnormalities, including reduced platelet counts. A contribution of teriflunomide to the gastrointestinal haemorrhage cannot be excluded.

A decrease of 15 % from baseline to Week 20 in leukocytes (mainly neutrophils and lymphocytes), similar to adults, was observed in the teriflunomide group. No clinically relevant differences between groups were observed for changes over time for other haematological parameters. RMM regarding the known identified haematological effects with teriflunomide in adults include regular monitoring of blood cell counts during treatment and a contraindication in patients with pre-existing impaired bone marrow function/ significant leukopenia are likewise adequate for the paediatric population.

Infections are an identified risk with teriflunomide, while serious opportunistic infections, including PML, are a potential risk. The Aubagio PI already includes a number of RMM to account for the risk of infections subsequent to immunomodulation/ immunosuppression from long-term treatment (in section 4.3 and 4.4). In adults, most of the reported infection and infestation TEAEs from clinical trials occurred with "common" frequency, except for severe infections including sepsis (section 4.8: not known, deriving from post-marketing experience). The incidence of infection SAEs with teriflunomide in adults was low and not different to placebo in clinical trials (~2.7%), with serious opportunistic infections reported with an incidence of 0.2%.

TEAEs from the infections and infestations SOC were reported more frequently on teriflunomide as compared to placebo (66.1% vs. 45.6%). The imbalance between teriflunomide and placebo is mainly driven by unspecific, seasonal and non-serious infections of the upper respiratory tract and nasopharyngitis. These events might also explain the slightly higher incidence in paediatrics as compared to adults. The incidence of infection SAEs was low and identical in both groups (1.8%): two SAEs occurred in the teriflunomide group, one of which was an opportunistic infection (pulmonary tuberculosis). No increased occurrence of infections or a difference in PTs was reported during the OL period. Opportunistic infections were similarly reported in the placebo and teriflunomide group and reporting in the OL period did not exceed that in the DB period. Except for pulmonary tuberculosis during the DB period, and CNS infection during OL teriflunomide, which both were rated serious, all other opportunistic infections were nonserious and mostly single TEAEs of herpes virus, herpes zoster, mycoplasma, and varicella.

Malignancies (incl. lymphoproliferative disorders) are a potential risk of teriflunomide. No malignancies were reported up to the data cut-off in paediatrics except for the report of a case of “pancreatic neoplasm” for which biopsy results are lacking in order to rule out a malignant condition.

Hypertension is an important identified risk with teriflunomide covered by appropriate routine RMMs: blood pressure is recommended to be measured prior to teriflunomide initiation and periodically during treatment. Any hypertensive condition needs to be managed before and during treatment. No new safety signals with respect to blood pressure changes emerged in paediatrics.

The designated AESI of pulmonary disorders derives from the identified risk of ILD that has been reported with the parent compound leflunomide and with teriflunomide in the postmarketing setting in adults but not in study EFC11759 until the data cut-off. More patients on teriflunomide reported TEAEs related to pulmonary disorders as compared to placebo (63.3% vs. 43.9%), the difference being caused by the imbalance in TEAEs from the infections and infestations SOC. The incidence of TEAEs coded under respiratory, thoracic and mediastinal disorders SOC was similar in both groups during the DB period. Notably, unspecific oropharyngeal pain and dyspnoea were reported with low incidence but more often in the teriflunomide group. Two SAEs in the teriflunomide group included upper respiratory tract infection and pulmonary tuberculosis (related to a school epidemic). The reporting of TEAEs related to pulmonary disorders was similar for both groups in the OL period and lower than in the DB period. Five patients experienced rather unspecific SAEs, including lung infection and upper respiratory tract infection, acute sinusitis, bronchitis and tonsillitis. Asthma was reported as SAE in 2 patients with a medical history that could have contributed to the events. Cautious wording is included in the product information and considered adequate.

A single paediatric patient experienced a non-serious, mild and transient “weakened left side” with teriflunomide (captured under “Embolic and thrombotic disorders”), which was coded as hemiparesis and rated as related to the underlying MS.

During the DB period, nonserious TEAEs in line with peripheral neuropathy were reported in a single patient per group. During the OL period, 3 patients (3.0%) in the teriflunomide/ teriflunomide group and 2 patients (3.8%) in the placebo/teriflunomide group experienced peripheral neuropathy. One patient in the placebo/teriflunomide group reported peripheral neuropathy of moderate intensity that was confirmed by electromyogram and led to discontinuation of teriflunomide. The patient recovered within approximately one year.

Teriflunomide is not considered to evoke convulsions, for which a signal has been raised during EMEA/H/C/PSUSA/00010135/201709 (finally not confirmed). The incidence of epilepsy was low and similar in both groups during the DB phase. The only SAE in the teriflunomide group was rated not related (patient had a medical history of epilepsy). No events were reported during the OL period.

Despite its non-life-threatening nature, alopecia is considered an important TEAE with regard to tolerability and compliance, as it can be socially debilitating, particularly for female subjects and paediatrics and might thus impair compliance. However, from the DB period safety data, no compliance issues could be deduced from the small number of paediatrics, and no early discontinuations due to alopecia were reported. Although undetermined in the paediatric study, it remains unlikely (based on the PK characteristics of teriflunomide) that the full adult equivalent dose poses an additional risk over half the adult dose studied in the first 8 weeks of teriflunomide treatment. Alopecia is included as ADR in section 4.8 of the SmPC with the frequency “very common”. Slightly more paediatrics reported alopecia with teriflunomide as compared to adults (i.e. 22% vs. 14%). The same difference applied to paediatrics and adults treated with placebo (12% vs. 5.1%), however, mean exposure (in days) to placebo was much lower in paediatrics. During the OL period, more patients from the placebo/ teriflunomide group reported alopecia TEAEs as compared to the teriflunomide/ teriflunomide group (17.3% vs. 10%), which is indicative of a rather early and temporary effect.

Although, there is no evidence for an increased risk for psychiatric disorders with teriflunomide (or leflunomide) in adults, there is scientific evidence that psychiatric disorders more frequently occur in paediatrics with demyelinating diseases. The proportion of patients with treatment-emergent psychiatric disorder was not different between teriflunomide and placebo during the DB period. During the OL period, depression was reported in 7.7% of patients in the placebo/ teriflunomide group vs. 1% in the teriflunomide/ teriflunomide group). The frequency is higher than in the treatment groups during the DB period but is based on a small number of patients with such events. A single SAE of emotional disorder of childhood (adolescent mood disorder) together with self-harming tendencies was reported after 8 months of treatment with teriflunomide during the OL period, which was not recovered at the time of data cut-off.

Teriflunomide can cause serious birth defects when administered during pregnancy and is thus contraindicated during pregnancy (SmPC section 4.3). However, a total of 3 patients treated with teriflunomide became pregnant during the study. Two of them underwent elective abortion and the third gave birth to a normal infant, without structural defect or functional abnormalities. Undesired pregnancies are of special importance in female adolescents and have been taken into account by an update of the educational material on teriflunomide. Adolescent pregnancies will also be monitored via the pregnancy registry.

None of the other safety parameters evaluated, incl. laboratory parameters (not previously mentioned), vital signs and physical development, gave rise to specific concern and were similarly reported in adults. No long-term implications on BW in paediatrics are expected based on the provided data. A small decrease over the first 24 weeks of treatment was not observed with longer teriflunomide duration.

No clinically relevant changes over time were observed for ECG parameters during the study.

Special populations have been studied, including intrinsic factors, i.e. age, gender, race, pubertal status, BW, and disease-related subgroups. Overall, there seems to be no specific subgroup for which the safety profile of teriflunomide is continuously worse than for the others taking into account the limitations that derive from very small numbers of patients included in subgroups (see above). The SOC depicting the highest variability in frequency of events in different subgroups is infections and infestations (generally the younger, pre-pubertal paediatrics and those with lower BW are more affected by PTs from this SOC).

Few postmarketing data (~7 years) comprise off-label use data in paediatrics. Cases for which AEs were reported were in a majority related to the underlying disease. Two SAEs were reported, one involved acute myocarditis following a viral infection (which is plausibly related to teriflunomide) and one SAE of diarrhoea with traces of blood (not assessable).

Comparison of the safety of teriflunomide in adults and paediatrics based on controlled study data

The difference in exposure to placebo in pooled adult studies (nearly identical exposure to teriflunomide and placebo in Pool A1) and in EFC11759 (exposure to placebo was less than half of teriflunomide exposure) needs to be taken into account for comparison of risks in paediatrics and adults. Reporting of recurrent events (e.g. seasonal respiratory infections) in EFC11759 probably inflates the incidence in the teriflunomide group in contrast to placebo. Nevertheless, the comparison between paediatrics and adults is based on a similar exposure to teriflunomide in controlled studies.

Reporting of alopecia, abdominal pain, paresthesia, and increased CPK was higher in paediatrics compared to adults. While no reason could be identified for abdominal pain and paresthesia, an increased awareness of hair loss in paediatrics as compared to adults might be the reason for increased reporting of alopecia. A more frequent reporting of increased CPK might be a consequence of exercising and trauma in a majority of paediatrics with these events. However, the contribution of teriflunomide remains uncertain and information on these differences has been included in section 4.8 of the SmPC.

No relevant differences between paediatrics and adults are anticipated for hypertension, haematological effects, ILD, hypersensitivity reactions, peripheral neuropathy, teratogenicity, serious opportunistic infections (including PML), malignancies, renal failure, and BW changes.

2.6.2. Conclusions on the clinical safety

In support of the extension of the indication of Aubagio to paediatrics aged 10 to 17 years, the Applicant has provided controlled safety data up to 96 weeks deriving from a Phase 3 study (EFC11759), including an ongoing long-term safety follow-up for up to an additional 96 weeks with a data cut-off of 12 September 2020.

Controlled as well as OL teriflunomide safety data confirm the safety profile in paediatrics to be largely in line with the AESI identified in the adult MS population. However, long-term safety in children remains an important missing information which warrants further characterisation given that extrapolation of safety from adult to paediatric patients is not straight forward. So far, only 41 (38%) of teriflunomide-treated paediatric patients received the drug for more than two years. Availability of controlled long-term safety data is therefore limited. Up to the data cut-off 12 September 2020, 152 patients were enrolled in the OL period of the study. It is expected that the long-term safety profile is further characterised by additional data collected in the OL period of study EFC11759.

Based on the so far available data it appears that the risk of pancreatic toxicity is increased in paediatric patients relative to adults. Detailed information on symptoms and actions upon suspicion and confirmation of pancreatitis has been described in the product information to increase clinical awareness for this event.

2.7. Risk Management Plan

Safety concerns

Table 16: Table SVIII.1: Summary of safety concerns

Important identified risks	Hepatic effects Hypertension Hematologic effects Infections Interstitial lung disease Acute pancreatitis Peripheral neuropathy
Important potential risks	Teratogenicity Serious opportunistic infections, including PML Cardiovascular effects Malignancies (including lymphoproliferative disorders) Potential off-label use in adults Renal failure ^a
Missing information	Use in combination with Multiple sclerosis treatments (other than IFN-β and glatiramer acetate) Long-term safety

^a This risk was identified as a potential risk with leflunomide.
IFN-B: Interferon Beta; PML: Progressive Multifocal Leukoencephalopathy

Pharmacovigilance plan

Table 17: Ongoing and planned required additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Prospective cohort study of long-term safety of teriflunomide in MS patients in Europe (EU-PASS) OBS12753 Ongoing (Cat. 3)	To characterize the long term safety profile of teriflunomide and determine the incidence of adverse events of special interest in a real life setting: acute liver injuries, infections, interstitial lung disease and pancreatic effects, notably pancreatitis, serious opportunistic infections including PML, malignancies, peripheral neuropathy, cardiovascular events, potential off-label use in adults, renal failure, and death and in patients receiving concomitant other MS treatments.	Hepatic effects, infections, interstitial lung disease, acute pancreatitis, serious opportunistic infections, including PML, cardiovascular effects, malignancies (including lymphoproliferative disorders), peripheral neuropathy, potential off-label use in adults, use in combination with MS treatments (other than IFN-β and glatiramer acetate), long term safety, and renal failure.	Final protocol in Yearly progress report Final study report	Apr-2015 Reported in PBRER/PSUR Jul-2021
Teriflunomide pregnancy exposure registry in the US/Canada OBS13499 Ongoing (Cat. 3)	To monitor reports of use and/or adverse events in pregnancy, and pregnancy outcomes.	Teratogenicity	Final protocol First patient First interim report Annual reports Final study report planned in	Feb-2013 Apr-2013 Sep-2014 Reported in PBRER/PSUR Dec-2023
International pregnancy exposure registry of teriflunomide OBS12751 (EU/ROW) Ongoing (Cat. 3)	To monitor reports of use and/or adverse events in pregnancy, and pregnancy outcomes.	Teratogenicity	Final protocol Amended protocol 1 Ready for enrollment in Annual periodic reports Final study report	Dec-2013 Oct-2014 Nov-2014 First progress report in Sep-2016, then annually reported in PBRER/PSUR. Dec-2023
Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates

<p>EFC11759 – Open label period of a multicenter, randomized, double blind, parallel group trial to evaluate efficacy, safety, tolerability and pharmacokinetics of teriflunomide in comparison to placebo followed by a long-term open label extension phase, in children and adolescents 10 to 17 years of age with MS with relapses</p>	<p>To characterize the safety profile of teriflunomide in children if use occurs in this age group.</p>	<p>Long term safety in children including hepatic effects, infections, hypertension, hematologic effects, interstitial lung disease, acute pancreatitis, serious opportunistic infections, including PML, cardiovascular effects, malignancies (including lymphoproliferative disorders), peripheral neuropathy and renal failure</p>	<p>Last patient Last Visit (OL): Interim Reports (OL) Final study report planned (OL)</p>	<p>Sep-2021 Mar-2020 Oct-2022</p>
<p>Ongoing (open label extension period) (Cat. 3)</p>				

EU: European Union; IFN-β: Interferon Beta; MS: Multiple Sclerosis; OL: Open Label; PASS: Post-Authorization Safety Study; PBRER: Periodic Benefit-Risk Evaluation Report; PML: Progressive Multifocal Leukoencephalopathy; PSUR: Periodic Safety Update Report; ROW: Rest of the World; US: United States.

Risk minimisation measures

Table 18: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Hepatic effects	<p>Routine risk minimization measures:</p> <p>SmPC: Sections 4.2, 4.3, 4.4 and 4.8 PIL: Sections 2 and 4</p> <p>Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU).</p> <p>Additional risk minimization measures:</p> <p>Educational Materials (HCP education/discussion guide and patient education card).</p>	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <p>Targeted questionnaire (drug induced liver injury form)</p> <p>Additional pharmacovigilance activities:</p> <p>Non-interventional long-term safety study: (EU-PASS) OBS12753 in adults. Pediatric clinical study (EFC11759) (open label extension period).</p>
Hypertension	<p>Routine risk minimization measures:</p> <p>SmPC: Sections 4.4 and 4.8 PIL: Sections 2 and 4</p> <p>Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU).</p> <p>Additional risk minimization measures:</p> <p>Educational Materials (HCP education/discussion guide and patient education card).</p>	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <p>None</p> <p>Additional pharmacovigilance activities:</p> <p>None in adults. Pediatric clinical study (EFC11759) (open label extension period).</p>
Hematologic effects	<p>Routine risk minimization measures:</p> <p>SmPC: Sections 4.3, 4.4 and 4.8 PIL: Sections 2 and 4</p> <p>Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU).</p> <p>Additional risk minimization measures:</p> <p>Educational Materials (HCP education/discussion guide and patient education card).</p>	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <p>None</p> <p>Additional pharmacovigilance activities:</p> <p>None in adults. Pediatric clinical study (EFC11759) (open label extension period).</p>

<p>Infections</p>	<p>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).</p>	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Non-interventional long-term safety study (EU-PASS) OBS12753 in adults. Pediatric clinical study (EFC11759) (open label extension period).</p>
<p>Interstitial lung disease</p>	<p>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</p>	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire (interstitial lung disease form) Additional pharmacovigilance activities: Non-interventional long-term safety study: (EU-PASS) OBS12753 in adults. Pediatric clinical study (EFC11759) (open label extension period).</p>
<p>Acute pancreatitis</p>	<p>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</p>	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire (pancreatic disorder form) Additional pharmacovigilance activities: Non-interventional long-term safety study (EU-PASS) OBS12753 in adults. Pediatric clinical study (EFC11759) (open label extension period).</p>

<p>Peripheral neuropathy</p>	<p>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</p>	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire (peripheral neuropathy reporting form) Additional pharmacovigilance activities: Non-interventional long-term safety study (EU-PASS) OBS12753 in adults. Pediatric clinical study (EFC11759) (open label extension period).</p>
<p>Teratogenicity</p>	<p>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).</p>	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire (pregnancy reporting form) Additional pharmacovigilance activities: International pregnancy exposure registry of teriflunomide OBS12751 (EU/ROW). Teriflunomide pregnancy exposure registry in the US/Canada OBS13499.</p>
<p>Serious opportunistic infections, including PML</p>	<p>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).</p>	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire (PML form) Additional pharmacovigilance activities: Non-interventional long-term safety study (EU-PASS) OBS12753 in adults. Pediatric clinical study (EFC11759) (open label extension period).</p>
<p>Cardiovascular effects</p>	<p>Routine risk minimization measures: SmPC: Section 4.8 PIL: Section 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</p>	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Non-interventional long-term safety study (EU-PASS) OBS12753 in adults. Pediatric clinical study (EFC11759) (open</p>

	measures: None	label extension period).
Malignancies (including lymphoproliferative disorders)	Routine risk minimization measures: SmPC: Section 4.8 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: None Additional pharmacovigilance activities: Non-interventional long-term safety study (EU-PASS) OBS12753 in adults. Pediatric clinical study (EFC11759) (open label extension period).
Potential off-label use in adults	Routine risk minimization measures: Risk not presented in Labeling 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: None Additional pharmacovigilance activities: Non-interventional long-term safety study (EU-PASS) OBS12753 in adults.
Renal failure^a	Routine risk minimization measures: SmPC: Sections 4.2 and 4.3 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: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Non-interventional long-term safety study (EU-PASS) OBS12753 in adults. Pediatric clinical study (EFC11759) (open label extension period).
Use in combination with Multiple sclerosis treatments (other than IFN-β and glatiramer acetate)	Routine risk minimization measures: SmPC: Section 4.4 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: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Non-interventional long-term safety study (EU-PASS) OBS12753 in adults.

<p>Long term safety</p>	<p>Routine risk minimization measures: Risk not presented in Labeling Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU).</p> <p>Additional risk minimization measures: None</p>	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None</p> <p>Additional pharmacovigilance activities: Non-interventional long-term safety study (EU-PASS) OBS12753 in adults. Pediatric clinical study (EFC11759) (open label extension period).</p>
--------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

a This risk was identified as a potential risk with leflunomide.
EU: European Union; HCP: Healthcare Professional; IFN- β : Interferon Beta; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PIL: Patient Information Leaflet; PML: Progressive Multifocal Leukoencephalopathy; ROW: Rest of the World; SmPC: Summary of Product Characteristics; US: United States.

Conclusion

The CHMP and PRAC considered that the risk management plan version 7.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the Applicant and has been found acceptable for the following reasons: No significant changes are proposed in the package leaflet. Thus, consultation with the target patient group is considered not required for the line extension and paediatric indication. The proposed new text is in line with the latest QRD template and is written in a language understandable by the patient.

2.9.2. Quick Response (QR) code

A request to include a QR code in the labelling and package leaflet for the purpose of accessing the most up to date version of the package leaflet and educational material has been submitted by the Applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code: approved package leaflet

and educational material for patients as outlined in the Risk Management Plan.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

With the present application, the Applicant seeks approval of teriflunomide for paediatric patients from 10 years to 17 years of age with RRMS.

Paediatric MS is a severe chronic, immune-mediated neurodegenerative disorder of the CNS, characterized by inflammation, demyelination, and axonal/neuronal destruction, with marked impact on patients' life and development, and leading to disability early in life. Although MS is predominantly a disease of young adults, approximately 3% to 5% of people with MS have their first symptoms in childhood. Genetic, serum, CSF, and cell-based studies largely support a shared biology between paediatric-onset and adult-onset disease. Relapses are more frequent in patients with paediatric-onset compared with adult-onset MS and a greater number of MRI lesions is observed. A third of the paediatric MS patients experience cognitive impairment and MRI evidence of global and focal loss of age expected brain volume has been described.

As for adult MS patients, treatment strategies in paediatric MS aim at the symptomatic treatment of acute relapses and MS symptoms as well as on disease-modification.

Due to the clinical phenotype of paediatric MS with relapses as the most important clinical component reflecting disease activity, the most important endpoints relate to relapses (clinical) and MRI findings (new or enlarging T2/FLAIR lesions and Gadolinium-enhancing T1 lesions), representing acute inflammation.

3.1.2. Available therapies and unmet medical need

In addition to treatments approved for the symptomatic treatment of MS including corticosteroids for the treatment of relapses, fingolimod is the only DMT as of yet explicitly approved in the EU for paediatric patients aged 10 years and older with highly active RRMS. Interferon-beta (interferon-beta 1a and interferon-beta 1b) and glatiramer acetate are widely used to treat paediatric MS as their indications do not have an age limit and therefore, formally include children. However, limited efficacy and safety data in the paediatric population have been collected for the use of these DMTs in paediatric patients.

3.1.3. Main clinical studies

In support of efficacy, study EFC11759 (also referred to as study TERIKIDS) was presented. Study EFC11759 is a two-year, multicenter, randomized, DB, placebo-controlled, parallel group trial to evaluate efficacy, safety, tolerability, and PK of teriflunomide (n = 109) vs. placebo (n = 57) administered orally once daily in paediatric patients with RMS followed by an OL extension.

The implementation of the placebo arm was combined with switch criteria, i.e. patients who experienced a confirmed relapse after the PK run-in phase (8 weeks) had the option to switch to the OL period.

Similarly, patients with high MRI activity according to strict definitions qualified for early switch to the OL teriflunomide treatment arm.

The study included children aged 10 to <18 years old suffering from RRMS, diagnosed based on the McDonald criteria 2010 and the IPMSSG criteria for paediatric MS, version of 2012 with an EDSS score ≤ 5.5 and last relapse more than 30 days prior to randomization. With regard to disease activity, the following criteria had to be met:

- at least one relapse (or attack) in the 12 months preceding screening or,
- at least two relapses (or attack) in the 24 months preceding screening.

Subjects could be MS-treatment naïve or could have received prior MS DMT.

3.2. Favourable effects

The primary endpoint was "time to first clinical relapse". Confirmed clinical relapse occurred in 36.7% in the teriflunomide group and in 43.9% in the placebo group in the DB period, corresponding to a relative risk reduction of 34.3% (HR: 0.657; 95% CI: 0.388 to 1.113, $p=0.2949$).

Patients in the placebo group experienced the first confirmed relapse after randomization earlier than patients in the teriflunomide group; the reported median duration was 39.14 weeks versus 75.29 weeks, respectively; the reported mean and SD were 49.25 (33.36) weeks versus 62.60 [36.12] weeks, respectively.

The "time to first relapse" was slightly prolonged for teriflunomide compared to placebo: relapse probability was higher for placebo from approximately week 12 onwards compared to teriflunomide with 29.8% of patients that relapsed by week 48 in the teriflunomide arm compared to 39.1% in the placebo arm.

Overall, treatment with teriflunomide in comparison to placebo did not meet the primary endpoint, however with regard to the sensitivity analysis "time to first confirmed clinical relapse or high MRI activity meeting criteria for switching into OL period, whichever came first", teriflunomide reduced the risk of confirmed clinical relapse or high MRI activity, whichever came first, when compared to placebo by 43.4% (49.5% of patients in the teriflunomide group versus 68.4% of patients in the placebo group; HR: 0.566; 95% CI: 0.368 to 0.870, $p=0.0409$). Patients in the placebo group experienced the first confirmed relapse or high MRI activity meeting criteria earlier than patients in the teriflunomide group (median duration of 37.00 weeks and 72.14 weeks, respectively).

Regarding the sensitivity analysis "time to first confirmed clinical relapse occurring after the PK run-in phase", that excluded clinical relapses that occurred during the PK run-in phase, the proportion of patients with clinical relapse was 32.7% in the teriflunomide group versus 51.0% in the placebo group (HR: 0.507; 95% CI: 0.282 to 0.911, $p=0.0815$).

The key secondary endpoints were the number of new/newly enlarged T2 lesions and the number of Gd-enhancing T1 lesions. A (nominal) significant reduction in the rate of new or enlarged T2 lesions per MRI scan was demonstrated with teriflunomide, compared to placebo (4.7 and 10.5 lesions, respectively), ($p=0.0006$) (unadjusted analysis, pre-specified), corresponding to a 55% reduction over the DB treatment period (rate ratio [RR]: 0.450; 95% CI: 0.285 to 0.711). With adjustment for baseline T2 lesion count, a (nominal) significant reduction in the rate of new or enlarged T2 lesions per MRI scan was demonstrated with teriflunomide, compared to placebo (3,6 and 5,4 lesions, respectively) ($p = 0.0446$), corresponding to a 33% reduction over the DB treatment period (rate ratio [RR]: 0.665; 95%CI: 0.447 to 0.990). Also, a (nominal) significant reduction in the rate of Gd-enhancing T1 lesions was demonstrated with teriflunomide ($p<0.0001$), compared to placebo (1.9 and 7.5 lesions,

respectively), corresponding to a 75% reduction at the end of the DB treatment period (RR: 0.253; 95% CI: 0.126 to 0.505). While post-baseline, the mean number of T1 Gd-enhancing lesions in the teriflunomide group declined from 3.9 at baseline to 1.4, the mean number of T1 Gd-enhancing lesions in the placebo group increased from 3.9 at baseline to 5.1.

Descriptively summarized results for the EDSS score: the mean (SD) EDSS score at baseline was 1.4 (0.9) and 1.2 (0.9) for the placebo and the teriflunomide treatment group, respectively, while at week 96 the mean (SD) EDSS score was 1.7 (1.2) and 1.2 (0.9) respectively, representing a slight deterioration under placebo of 0.3. Requested *post-hoc* analyses on CDP-6M, both for the DB treatment period and for the first 96 weeks regardless of patients discontinuing the DB-period and switching to OL teriflunomide, showed that only few patients experienced a CDP-6M in the DB period with 2 (3.5%) patients in the placebo group and 5 (4.6%) patients under teriflunomide treatment. During the 96-week period, better results were provided for CDP-6M in the active treatment arm with 8 (14.0%) patients in the placebo group and 9 (8.3%) patients in the teriflunomide group who experienced a CDP-6M.

Regarding the extrapolation exercise using data from the adult RMS population the Applicant has demonstrated that integration of the adult MRI data into the paediatric data population in a Bayesian way does not change the results considerably.

3.3. Uncertainties and limitations about favourable effects

No dedicated dose response study was conducted. A paediatric popPK model was developed to support definition of the daily dose to be administered to reach similar exposure in paediatric patients as in adults being treated with 14 mg once daily. The presented popPK model was based on an interim paediatric database only and had severe limitations (e.g. inadequate estimation of absorption rate constant, thus inadequate estimation of exposure, important underprediction of higher concentrations). Upon request, the Applicant updated the model during the procedure; however, uncertainties on model appropriateness remained. Further information was provided during the procedure and no clear pattern of higher exposure in patients with lower BW in the BW range between 40 and 60 kg (in steps of 5 kg BW bands) was visible, which would necessitate to increase the BW cut-off for same dose as in adults. With the updated information on model quality, confidence in the performance of the model has been increased. Simulations based on the updated paediatric popPK model, including a worst case scenario on patients weighing 25 kg (corresponding to the 5th percentile of 10-year-old children) confirmed that exposures in paediatric patients with the proposed dosing will be in the same range as seen in adults treated with 14 mg once daily.

Study EFC11759 failed its primary endpoint "time to first clinical relapse" ($p=0.2949$). With regard to the KM plot of time to first confirmed relapse the proportional Hazards assumption is not fulfilled. Up to about 24 weeks there is almost no difference between estimated relapse rates (although relapses were slightly more frequent for teriflunomide) and from week 36/48 onwards, the curves are almost parallel (although numbers at risk are low at the end of the curves). The most informative part seems to be restricted to the time between 24 to 24/36 weeks. Consequently, the power of the study to detect the observed difference in Kaplan-Meier curves is reduced. Furthermore, for this analysis, patients are censored at time of high MRI activity (most at week 36) which is questionable given that censoring is highly informative.

A number of sensitivity analyses were performed for the primary endpoint that showed consistent results in comparison to the primary analysis. The sensitivity analyses in general and in particular the one, that comprised criteria of a composite endpoint by counting in addition to relapse also high MRI activity as an event, could have supported a significant primary analysis. However, since hierarchical testing was foreseen in the SAP and the primary analysis failed to show statistical significance, formally, no

confirmatory conclusion can be drawn from this additional analysis, representing nominally significant differences for teriflunomide in comparison to placebo.

It was planned to control the type 1 error for the two key secondary endpoints via hierarchical testing. However, as the primary endpoint failed, statistical significance for downstream endpoints cannot be formally claimed.

With regard to the requested sensitivity analysis for the number of new/newly enlarged T2 lesions the Applicant took the number of T2 lesions into account as the number of new/enlarged T2 lesions is assessed in reference to the MRI scans of the previous visit. Thus, it is not a value that could be presented at baseline: A (nominal) significant reduction in the rate of new or enlarged T2 lesions per MRI scan was demonstrated with teriflunomide, compared to placebo (3,6 and 5,4 lesions, respectively) ($p = 0.0446$), corresponding to a 33% reduction over the DB treatment period (rate ratio [RR]: 0.665; 95%CI: 0.447 to 0.990). The relative risk reduction in this analysis (with adjustment for baseline T2 lesion count) is lower compared to the 55% relative reduction in the pre-defined analysis (estimated without adjusting for baseline T2 lesion count). This might be due to some baseline imbalances in T2 lesions (mean of 51 vs 60) favouring placebo in the unadjusted analysis. In sum, although both analyses showed a nominally significant effect, the adjusted analysis reduced considerably the effect size due to the reported considerable baseline differences. Whereas results from the combined data of DB and OL phase could have been reassuring and even conservative due to the switch from placebo to the active treatment, the large amount of remaining missing scans does not allow for a confirming conclusion. The Applicant confirmed that the additional value of the analyses including OL data is limited. Overall, results are still supportive of the efficacy of teriflunomide on the key secondary MRI endpoints of new and enlarged T2 lesions and T1 Gd-enhancing lesions per scan.

Further requested and provided *post-hoc* analyses showed, that the results do not appear to be robust when relevant missing data imputation is applied in a setting with large proportion of missing data in the DB period. 70% of placebo patients and 47% of teriflunomide patients had MRI data to be imputed. Referring to the number of missing scans, this lack of robustness cannot be rebutted by an analysis on all MRI scans, including those taken in the OL period, since the number of additional scans in the OL period remains small compared to the number of remaining missing scans. Whereas the large amount of missing data itself raises concerns about the robustness of the data, the conservative sensitivity analyses with reference-based imputed data considerably reduce the treatment effect and, consequently, nominal statistical significance is lost. Taking into account, that this reduction in effect is mainly due to the imputation in the active treatment group and considering the fact that missing data in most cases occurred after patients had switched to the OL phase because of having experienced a relapse or a high MRI activity, obviously correlated with an unfavourable outcome in the key secondary endpoints, the requested reference-based imputation method appears justified as a sensitivity analysis. Due to the large amount of missing data, it appears informative to use a missing data imputation method that is capable to model a vanishing effect difference in patients with missing MRI data, even if this can be considered as rather conservative. Applying this approach the effect is critically reduced (i.e. approximately halved) and the nominal statistical significance disappears.

Due to the switch to OL rescue treatment which was disproportionately higher in the placebo group compared to the teriflunomide group analyses on CDP-6M are difficult to interpret.

3.4. Unfavourable effects

The safety profile of teriflunomide in paediatrics 10 to 17 years of age has been examined in a single controlled phase 3 study including 166 patients, 109 of whom were treated with teriflunomide and 57 with placebo. Controlled safety data amount to 145.6 patient-years for the teriflunomide group. Up to

the cut-off date of 12 September 2020, uncontrolled duration of exposure added approximately 260 patient-years for teriflunomide (7 and 14 mg). Teriflunomide was well tolerated, with a low rate of discontinuations and temporary discontinuations from treatment due to TEAEs (5.5% each) and a similar incidence of SAEs in treatment groups (11%). The system organ classes with the highest proportions of subjects reporting TEAEs were Infections and Infestations, Skin and subcutaneous tissue disorders, Nervous System Disorders, Gastrointestinal disorders, and Investigations.

Hepatic adverse effects are an identified risk related with teriflunomide treatment and mainly present with asymptomatic increases in ALT starting at Week 4 and most frequently within the first 6 months of treatment. Abnormalities, i.e. ALT > 2x ULN up to > 10x ULN were reported for 7 patients in the teriflunomide group but in no subject on placebo. Of these 7 patients with hepatic abnormalities, two reported an SAE and one subject had to discontinue treatment. All of them recovered. Liver enzyme increases were generally not associated with hepatic TEAEs. No increased incidence of hepatic abnormalities was reported during treatment with teriflunomide in the OL period, with a total of 5 patients, who discontinued during this period. None of the patients treated with teriflunomide met the criteria for Hy's law. Treatment with teriflunomide is contraindicated in patients with severe hepatic impairment (Child-Pugh class C). Baseline and routine monitoring of liver enzymes is detailed in the SmPC.

Pancreatic effects/ disorders is an identified risk related to teriflunomide treatment in adults, a signal that initially derived from preclinical studies in dogs. TEAEs related to pancreatic effects include isolated and asymptomatic pancreatic enzyme increases, that were found increased in paediatric patients treated with teriflunomide compared to placebo (3.7% vs. 1.8%). Pancreatitis (acute) was reported in 5 teriflunomide-treated patients (2 during DB and 3 during OL treatment) confirmed by imaging data. Time-to-onset of these events was > 11 months and up to 3 years. The pancreatitis cases presented with epigastric pain, high lipase (and amylase) leading to hospitalisation and treatment discontinuation. All patients recovered/ were recovering from pancreatitis after teriflunomide discontinuation and AEP. In one of the patients with pancreatitis in the OL period, diagnosis was "pancreatic neoplasm". In one patient (DB period), isolated and asymptomatic high lipase values (hyperlipasemia) were reported as reason for discontinuation. The patient presented with normal imaging.

Haematological effects (bone marrow disorders) are an identified risk with teriflunomide presenting with decreases in leukocyte counts, mainly neutrophils and lymphocytes. The incidence of such TEAEs in paediatrics was higher for teriflunomide as compared to placebo (7.3% vs. 1.8%) but in line with adults and did not lead to discontinuation of treatment. A single patient with a SAE of cyclic neutropenia (pre-existing) was reported in the study. RMMs include regular monitoring of blood cell counts during treatment and a contraindication in patients with pre-existing impaired bone marrow function/ significant leukopenia.

The overall rate of infections in the DB period was higher for the teriflunomide group as compared to placebo (66.1% vs. 45.6%), driven by unspecific, seasonal and non-serious infections of the upper respiratory tract and nasopharyngitis. The incidence of infection SAEs was low and identical in both groups (1.8%): two SAEs occurred in the teriflunomide group, one of which was an opportunistic infection (pulmonary tuberculosis) which led to discontinuation of teriflunomide. Reporting of TEAEs during the OL period did not exceed DB incidences.

The designated AESI of pulmonary disorders derives from the identified risk of interstitial lung disease that has been reported with the parent compound leflunomide and postmarketing with teriflunomide in adults. No case of ILD has been reported in study EFC11759. Pulmonary disorders TEAEs were more frequently reported with teriflunomide as compared to placebo (63.3% vs. 43.9%) driven by TEAEs from the infections and infestations SOC.

Peripheral neuropathy was experienced by one patient in each treatment group during the DB period. During the OL period, 3.0% in the teriflunomide/ teriflunomide group and 3.8% in the placebo/ teriflunomide group experienced peripheral neuropathy. One of these patients discontinued teriflunomide due to a nonserious TEAE of peripheral neuropathy confirmed by nerve conduction testing.

The rate of gastrointestinal disorders (nausea and diarrhoea; 7 to 8% in both groups) in paediatrics appears not different from adults and events were most frequently reported during the first week(s) of treatment. TEAEs did not lead to discontinuation from treatment.

Reversible alopecia/ hair loss is commonly associated with teriflunomide in adults and was similarly reported in paediatrics early during treatment (within the first 6 months): 22% of patients on teriflunomide and 12% of placebo-treated patients.

No malignancies were reported in study EFC11759.

TEAEs in line with hypersensitivity reactions or hypertension, both of which are identified risks with teriflunomide, were not reported during the DB period.

Three pregnancies were reported while patients were treated with teriflunomide during study EFC11759, two of which resulted in termination of pregnancy, and the other resulted in delivery of a healthy infant with no signs of malformations.

3.5. Uncertainties and limitations about unfavourable effects

Overall, the safety profile in paediatrics is based on a limited controlled dataset of 109 patients exposed to teriflunomide in study EFC11759. Preliminary long-term data are available for an additional 2 years of OL teriflunomide treatment (data cut-off of 12 September 2020).

Few data are available regarding the most vulnerable subpopulations (< 13 years, Tanner stage I, BW ≤ 40 kg) for which interpretability of safety is difficult, especially with regard to long-term clinical safety:

- Age: mean age was 14.6 years. Only 16 patients on teriflunomide and 10 patients on placebo (i.e. 26 out of 166 patients) were < 13 years.
- Body Weight: only 5 patients on teriflunomide (and 6 patients on placebo) in the DB period had a BW of ≤40 kg. These patients were treated with a dose of 7 mg.
- Physical development: only 10 patients were pre-pubertal (6 %; 5 patients per group) reflected by Tanner Stage I at baseline. The progress rate in sexual maturation is scientifically based on approx. 1 Tanner stage per year (i.e. it is assumed that paediatrics do not progress more than 2 Tanner stages in a 96-week period). From the limited available data in paediatrics with a Tanner stages I, II, or III at baseline, who completed 96-week treatment during the DB period, teriflunomide was not found to affect sexual maturation.

Uncertainty has been raised with regard to the initial teriflunomide doses applied during the study, i.e. a 7 mg adult equivalent dose during the first 8 weeks followed by a 14 mg adult equivalent dose thereafter. Based on an indirect comparison of TEAEs and reporting of early discontinuations during the first 8 weeks and between Week 8 and Week 16 (after obtaining the full adult equivalent dose), there is no evidence for an increased risk of tolerability issues like gastrointestinal disorders (nausea and diarrhoea) and alopecia. These are known to emerge dose-related and early during treatment. Notwithstanding, it cannot be excluded that some of these tolerability TEAEs might have been mitigated upon "titration" of teriflunomide in the study from half the adult dose equivalent during the first 8 weeks to the full adult dose equivalent thereafter. In addition, the numbers of subjects with TEAEs in this analysis are small hampering the evaluation of clear trends. Of note, alopecia was more frequently

reported in paediatric patients compared to adult patients (based on controlled clinical data comparison) and also led to discontinuation in a single patient during the OL period (alopecia areata).

Moreover, adequacy of the dose in paediatrics has been questioned given that a number of paediatric patients with BW in line with adult subjects had higher AUC and minimum concentration values; therefore, a potential relation between exposure and occurrence of AEs, especially the 5 patients with events of pancreatitis, could have been claimed.

However, no clear correlation between exposure and safety issues could be retrieved based on the information given during the procedure.

Hepatic effects were reported with a lower incidence in paediatric patients as compared to adults in controlled trials (3.5% and 4.6% in the placebo and teriflunomide group in paediatrics versus 15.2% and 21.5% in adults). It remains elusive whether less frequent liver enzyme monitoring applied in the paediatric study (every 4 weeks instead of every 2 weeks in adult clinical trials) explains this difference. Moreover, given that liver enzyme abnormalities were reported as usually starting at Week 4, the implication of the reduced dose during the first 8 weeks on the reporting rate remains unclear. It remains undetermined whether a single case reported as DILI in the patient's narrative is confounded by previous minocycline treatment. Variation procedures EMEA/H/C/002514/II/0029 and EMEA/H/C/002514/II/0032 on the signal of DILI and implementation of warnings have meanwhile been approved. The outcome with regard to measurement of liver enzymes at least every four weeks during the first 6 months of treatment and regularly thereafter roughly complies with the schedule applied in EFC11759 and based on a similar hepatic safety in paediatrics and adults, this is likewise applicable to paediatric patients.

Uncertainties pertain to the occurrence of pancreatic effects, especially cases of (acute) pancreatitis, which were reported more frequently in the small paediatric population in EFC11759 (5 of 166 patients) as compared to adult patients in clinical trials, and for which an increased risk in the post-marketing setting cannot be excluded. At present, baseline and serial measurement of pancreatic enzymes is not scientifically justified based on the lack of specificity of lipase as a biomarker for pancreas toxicity. However, the Applicant agreed to implement information on obtaining pancreatic enzymes and related laboratory parameters in patients with suspected pancreatitis during treatment and discontinuation of teriflunomide if pancreatitis is confirmed.

Review of pancreatic events in the GPV database and summarised in a safety update report retrieved adult cases of pancreatitis necrotising and pseudocyst, known complications of pancreatitis, which have been included in the description of selected adverse drug reactions in section 4.8 of the product information. Although, these complications have not been reported in paediatrics, they remain of concern in the young patient population given that these presentations necessitate further intervention (e.g. surgery in case of pseudocyst) or could entail life-long functional impairment of the pancreas. In this context, one of the four patients presenting with pancreatitis was diagnosed with medically significant "pancreatic neoplasm" 317 days after initiation of teriflunomide, described as "pseudo papilloma and inflammatory lesions". Insufficient clarification of histology findings hampers classification of this neoplasia and determination of a causal relationship with teriflunomide, which could have had at least a contributing effect to this serious adverse event.

During the DB period, a serious opportunistic infection of pulmonary tuberculosis was reported in a patient on teriflunomide, which resolved with anti-infective treatment and discontinuation of teriflunomide. During the OL period, the only serious opportunistic infection was coded as CNS infection, for which viral encephalitis in the absence of a pathogen was reported. Additional nonserious opportunistic infections occurred during OL teriflunomide, i.e. herpes virus infection, herpes zoster infection, mycoplasma infection, and varicella infection (concerning 5.8% and 2% of patients in the placebo/ teriflunomide group and in the teriflunomide/ teriflunomide group). Based on additional analyses for opportunistic infections in paediatrics, the risk seems to be comparable to that in adults.

Teriflunomide elicits reproductive toxicity by inhibiting DNA synthesis and crossing the placental barrier and is thus contraindicated during pregnancy or in women of childbearing potential not using reliable contraception during treatment with teriflunomide. The occurrence of undesired pregnancies is of special importance in adolescents. Additional risk minimisation measures to specifically address the new population of girls becoming fertile, and teenagers will include additional key safety messages in the HCP guide and in the patient card, as well as development of a QR code for the patient card. In addition, pregnancies (including in patients <18 years) will be followed in the ongoing pregnancy registry.

Blood CPK increased was reported as TEAE in the teriflunomide group only (5.5% vs. 0% on placebo). Serious blood creatine phosphokinase increased AEs were reported in two patients on teriflunomide during the DB period. The proportion of patients with high creatine kinase abnormalities ($\geq 3x$ ULN) was higher in the teriflunomide group as compared to the placebo group (8.3% versus 3.6%) during the DB period. Based on similar exposures to teriflunomide in paediatric and adult clinical controlled studies, increases in CPK were more frequently observed in paediatrics (5.5% vs. 1.6%). In four narratives on SAEs in the DB and OL period, blood CPK increased was concomitantly reported with ALT increased. Although, the Applicant provided alternative causes for these concomitantly increased parameters in two patients, i.e. trauma and intensive bodybuilding, it remains uncertain to which extent teriflunomide contributed to these SAEs given its known hepatic profile.

3.6. Effects Table

Table 19: Effects Table for Aubagio in the treatment of paediatric patients aged ≥ 10 years with relapsing remitting multiple sclerosis (MS) (data cut-off for the OL period of EFC11759: 12 September 2020)

Effect	Short Description	Unit	Teriflunomide	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
Time to first clinical relapse	Primary endpoint, after randomization up to the end of DB treatment	Weeks (median) Kaplan-Meier estimates of probability of confirmed clinical relapse and 95% CI	75.29 wk 48: 0.298 (0.214; 0.386) wk 96: 0.389 (0.293; 0.483)	39.14 wk 48: 0.391 (0.259; 0.521) wk 96: 0.531 (0.360; 0.676)	Numerical superiority of teriflunomide vs placebo (not stat significant; $p=0.2949$), high number of switches (due to high MRI activity: terifl 15 pat (13.8%), placebo 15 pat (26.3%)) prior to reaching an endpoint event may have affected the results.	(1)

Effect	Short Description	Unit	Teriflunomide	Placebo	Uncertainties/ Strength of evidence	References
Number of new/newly enlarged T2 lesions	Key secondary endpoint	Mean (SD) Rate ratio	7.2 (9.3) 0.450 (0.285; 0.711)	17.8 (26.3)	Superiority of teriflunomide vs placebo (nominal stat. sign.) Hierarchical testing was planned but endpoint cannot be considered stat. sign. due to failed primary endpoint. Post-hoc sensitivity analysis using conservative jump to reference multiple imputation approach until weeks 96 reduces the treatment effect by approximately 50%, with lost nominal statistical significance. Although still showing nominal stat. sign., an adjusted analysis by baseline T2 lesions reduced considerably the effect size due to considerable baseline differences (relative risk 0.665)	(1)
Number of Gd-enhancing T1 lesions	Key secondary endpoint	Mean (SD) Rate ratio	1.4 (3.6) 0.253 (0.126; 0.505)	5.1 (11.7)	Superiority of teriflunomide vs placebo (nominal stat. sign.) See above Post-hoc sensitivity analysis using conservative jump to reference multiple imputation approach until weeks 96 reduces the treatment effect, no sign for treatment effect is given any more.	(1)
EDSS score	Other secondary endpoint, week 96 change from baseline	Score from 0 to 10 (0=normal-10 =death) CDP-6M	1.2 (0.9) 5 (4.6%)	1.7 (1.2) 2 (3.5)	Due to the switch to OL rescue treatment which was disproportionately higher in the placebo group compared to the terifl group these results are difficult to interpret.	(1)

Effect	Short Description	Unit	Teriflunomide	Placebo	Uncertainties/ Strength of evidence	References
Time to first confirmed clinical relapse or high MRI activity meeting criteria for switch into OL period, whichever came first	Key sensitivity analysis of primary endpoint	Weeks (median) Kaplan-Meier estimates of probability of clinical relapse or MRI activity and 95% CI	72.14 wk 48: 0.379 (0.288; 0.469) wk 96: 0.505 (0.407; 0.596)	37.00 wk 48: 0.558 (0.417; 0.677) wk 96: 0.720 (0.575; 0.823)	Superiority of teriflunomide (nominal stat. sign.; p=0.0409)	(1)
Unfavourable Effects						
Gastrointestinal disorders - nausea - diarrhoea	Number of patients with TEAEs	%	8.3 7.3	7.0 7.0	Tolerability issues that occur early during treatment; the initial 7 mg adult equivalent dose might have alleviated these events	(1)
Hepatic disorders (incl. hepatobiliary disorders and investigations)	Number of patients with TEAEs	%	4.6	3.5	Mainly ALT increases	(1)
Elevations of liver enzymes	ALT >1x ULN ALT >3x ULN	%	25.7 3.7	14.0 0	Lower in controlled paediatric vs. adult experience	(1)
Pancreatic disorders	Number of patients with TEAEs	%	3.7	1.8	2 of the 4 cases in the teriflunomide group were cases of "pancreatitis acute"	(1)
Bone marrow disorders	Number of patients with TEAEs	%	7.3	1.8	WBC count decreases (neutrophils, leukocytes, and monocytes)	(1)
Infections and infestations	Number of patients with TEAEs	%	66.1	45.6	Driven by infections of the respiratory system (nasopharyngitis, URT infection, influenza, pharyngitis, bronchitis)	(1)
Malignancies	Number of patients with TEAEs	n	0	0	Uncertainty on description of Pancreatic neoplasm (nodule in the uncinata process of the pancreas with nature of pseudo papilloma and inflammatory lesions)	(2)

Effect	Short Description	Unit	Teriflunomide	Placebo	Uncertainties/ Strength of evidence	References
Pulmonary disorders	Number of patients with TEAEs	%	63.3	43.9	Including TEAEs from the infections and infestations SOC; TEAEs from the respiratory, thoracic, and mediastinal disorders SOC were similar for both groups	(1)
Peripheral neuropathy	Number of patients with TEAEs	%	0.9	1.8		(1)
Alopecia/ hair loss	Number of patients with TEAEs	%	22.0	12.3	In controlled adult trials, the incidence of TEAEs was 14% for teriflunomide vs. 5.1% for placebo	(1)
CPK increases - TEAEs - SAEs - CPK >3x ULN	Number of patients with TEAEs	%	5.5 1.8 8.3	0 0 3.6	In controlled adult trials, the incidence of TEAEs was 1.6% for teriflunomide vs. 0.7% for placebo	(1)

SDMT: symbol digit modality test, stat. sign.: statistically significant, ALT: alanine aminotransferase, CPK: creatine phosphokinase, TEAE: treatment emergent adverse event, SAE: serious adverse event, SOC: system organ class, ULN: upper limit of normal, WBC: white blood cells

Notes: (1) DB period of study EFC11759, (2) OL period of study EFC11759 (with data cut-off 12 September 2020)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy of teriflunomide in the treatment of RRMS has already been established in adult patients. The Applicant is now seeking extension of the indication to paediatric RRMS patients (≥ 10 and < 18 years of age).

In the paediatric study EFC11759 (TERIKIDS) the primary endpoint “time to first clinical relapse” only numerically favoured teriflunomide in comparison to placebo ($p=0.2949$). TERIKIDS is therefore a formally failed study. The effect size has likely been influenced by the justified and adequately defined switch criteria for patients experiencing new MRI disease activity to the OL teriflunomide treatment arm.

In this context, the so-called sensitivity analysis “time to first confirmed clinical relapse or high MRI activity meeting criteria for switching into OL period, whichever came first”, is of high clinical relevance as it reflects clinical practise. Patients with high disease activity on MRI are usually started on (another) active treatment without waiting for a relapse to occur. The Applicant requested a PIP modification with the aim to change the primary endpoint into this composite endpoint, while, according to the Applicant, the study was still blinded. However, PDCO and the FDA did not agree to change the primary endpoint due to the study being far advanced and advised to take the pre-planned sensitivity analyses into account when assessing the efficacy data of the study.

This composite endpoint, counting in addition to relapse also high MRI activity as an event, yielded a nominally statistically significant result in favour of teriflunomide. However, since the primary analysis

failed to show statistical significance, no confirmatory conclusion can be made from this additional analysis.

The same pertains to the key secondary endpoints, the number of new/newly enlarged T2 lesions and the number of Gd-enhancing T1 lesions. A nominally statistically significant reduction in the rate of new or enlarged T2 lesions per MRI scan was demonstrated with teriflunomide, compared to placebo (unadjusted analysis: $p = 0.0006$; adjusted analysis by baseline T2 lesions (not pre-specified): $p = 0.0446$). Also, a nominally statistically significant reduction in the rate of Gd-enhancing T1 lesions was demonstrated with teriflunomide ($p < 0.0001$), compared to placebo. It was planned to control the type 1 error for the two key secondary endpoints via hierarchical testing. However, as the primary endpoint failed, results for these endpoints need to be considered only descriptive and exploratory.

As to be expected in the paediatric MS population with a generally rather low disability progression, no relevant changes in EDSS scores were seen from study start until the end of the 96 weeks period.

Regarding the extrapolation exercise using data from the adult RMS population treated with teriflunomide the Applicant has demonstrated that integration of the adult MRI data into the paediatric data population in a Bayesian way does not change the results considerably.

Overall, although the study failed, results in general are indicative of an effect of teriflunomide on inflammation in the paediatric MS population. Of note, genetic, serum, CSF, and cell-based studies support a shared biology between paediatric-onset and adult-onset disease. Therefore, it can principally be assumed that a drug that has been proven to be effective in adult RRMS will likewise be effective in paediatric RRMS if an equivalent dose is administered.

Uncertainties have been raised on the appropriate BW cut-off for dosing with the same dose as in adults. Regarding paediatric patients with a BW equal or below 40 kg, the revised presentation of the population predictions versus observed concentrations increases confidence in the performance of the model in that the proposed dosing provides an exposure in paediatrics matching the adult reference range. This could be confirmed by comparison of individual observed exposure between paediatric subgroups (below and above 40 kg) and the adult reference group as well as by simulations of a worst-case scenario of patients weighing 25 kg (corresponding to the 5th percentile of 10-year-old children). Moreover, no clear pattern of higher exposure in patients in the BW range between 40 and 60 kg was noted and a correlation between exposure and safety issues could not be established.

Nevertheless, the initially proposed every other day dosing of 14 mg for patients with $BW < 40\text{Kg}$ is not acceptable due to a lack of data in support of this regimen and the inability of the model to support this dosing regimen. During the procedure, the Applicant withdraw this proposal and therefore, the proposed posology for children with $BW < 40\text{kg}$ is 7mg daily.

Overall, the safety database in paediatric patients, especially in the youngest pre-pubertal patients is limited, owing to the rarity of childhood-onset RRMS and availability of such patients for clinical trials.

In addition, for interpretation of the paediatric safety data, the overall longer observation period in the teriflunomide compared to placebo arm due to the defined switch criteria needs to be considered, which is specifically relevant for TEAEs that occurred throughout the study, and for which the incidence in the placebo arm might be underestimated (e.g. recurrent seasonal infections of the respiratory tract). However, the pattern and incidences of adverse events with teriflunomide in paediatric RRMS patients observed in study EFC11759 are largely in line with those in the adult population reported in clinical studies and postmarketing. Therefore, RMM already in place likewise apply to treatment of adults and paediatrics.

No new safety issues have been identified, but the reporting of pancreatic effects in paediatrics was increased over that in adults: five patients presented with confirmed pancreatitis during DB and OL

teriflunomide treatment (no patient on placebo), which contrasts controlled clinical trial data in adults (no case of pancreatitis reported with teriflunomide). In paediatric patients, the most common causes for pancreatitis in adults, i.e. gallstones and alcoholism, can virtually be excluded. Autoimmune causes and genetic susceptibility probably responsible for the increased incidence of pancreatitis in paediatric patients can neither be refused nor be confirmed based on the narrative descriptions and given the lack of events in the placebo group. Together with the available experience in adults and presented data from the GPV database, it appears that the risk is higher in paediatric patients as compared to adult patients.

More information was provided on the paediatric patients developing pancreatitis or pancreatic events during therapy with teriflunomide. A wide range of exposures (range 39.3 to 190 µg/ml for C_{trough}) was noted in the 5 paediatric patients with pancreatitis and in a single patient with hyperlipasaemia. In five out of the six patients, trough concentrations were above the median C_{trough} in adult patients with values in three patients being above the 90% percentile of adult C_{troughs}. This database is too limited to draw conclusions on potential dose adjustment, but physicians should be made aware of the high interindividual exposure in patients by an SmPC statement. The Applicant provided reasonable justification for not recommending routine pancreatic enzymes monitoring during treatment with teriflunomide. Data in paediatrics are still limited to firmly conclude on a causality of the emergence of increased pancreatic enzymes and the complete clinical picture of pancreatitis. Nonetheless, in all of the pancreatitis cases reported in the paediatric teriflunomide clinical program, pancreatitis was accompanied with pancreatic enzyme increases (either or both, serum lipase and amylase) and confirmed by imaging techniques. It is agreed that baseline and serial pancreatic monitoring is not specifically recommended for other drugs for which pancreas toxicity is a known side effect. Nevertheless, further information on and presentation of pancreatitis for such drugs is detailed in the label. Diagnosis of pancreatitis is based on clinical symptoms, substantiated by pancreatic enzyme measurement. This has been adequately described in sections 4.4 and 4.8 of the SmPC also including the recommendation to discontinue teriflunomide in case of confirmation of pancreatitis. Post-marketing follow-up of pancreatitis by using targeted follow-up forms updated with specific questions on de- and re-challenge and any known results of genetic tests indicating an increased risk for pancreatitis as well as a question about any anatomic anomalies potentially associated with pancreatitis is considered acceptable.

The applied dose regimen, which included an 8-week PK run-in phase with a reduced dose, might have mitigated tolerability issues, i.e. gastrointestinal disorders and alopecia. In the absence of data for initiating teriflunomide at the full adult equivalent dose in paediatrics, an indirect comparison was presented on the incidence of TEAEs and early discontinuations in the first 8 weeks of treatment and in the subsequent 8 weeks. These data do not indicate an increase in tolerability events between Weeks 8 and 16 of treatment.

Comparison of controlled clinical study data in adults and paediatrics revealed a slightly lower but overall similar incidence in hepatic abnormalities in paediatrics as compared to adult patients. Differences could possibly be related to the different monitoring algorithm in clinical studies (every 4 weeks in paediatrics instead of every 2 weeks in adults) and/ or to an effect of the reduced teriflunomide dose during the first 8 weeks of treatment. With regard to the issue of drug-induced liver injury assessed in the meanwhile approved variation procedures EMEA/H/C/002514/II/0029 and EMEA/H/C/002514/II/0032, the outcome is likewise applicable to paediatrics, including extended monitoring intervals of at least every 4 weeks instead of every 2 weeks during the first 6 months of treatment and regularly thereafter, as proposed in SmPC section 4.4.

Long-term safety data for teriflunomide in paediatric patients, especially in those being underrepresented in EFC11759, i.e. paediatrics aged < 13 years, those being pre-pubertal, or those with a BW < 40 kg, are limited. Given that extrapolation of safety from adult to paediatric patients is not straight forward, it is expected that the long-term safety profile is further characterised by additional data collected in the

ongoing OL period of study EFC11759. Long-term safety is included as important missing information in the RMP.

3.7.2. Balance of benefits and risks

The Applicant has presented one placebo-controlled study in RRMS patients aged 10 to <18 years. The study failed its primary endpoint “time to first clinical relapse after randomization up to the end of the DB treatment period” and thus efficacy of teriflunomide in the paediatric population with RRMS has not been formally demonstrated.

However, efficacy has already been demonstrated in adult patients with RRMS and, based on shared biology, extrapolation to paediatric patients is in principle possible. Re-establishing efficacy on its own is not necessary. The totality of data and analyses provide clear evidence of efficacy of teriflunomide in paediatric patients with RRMS:

- The predefined “sensitivity analysis” “time to first confirmed clinical relapse or high MRI activity meeting criteria for switching into OL period, whichever came first” showed statistical significance, although only nominally, and is considered the clinically most relevant analysis.
- For the two key secondary MRI endpoints, number of new/newly enlarged T2 lesions and number of Gd-enhancing T1 lesions (nominal) significant reductions have been shown in the pre-specified analyses. Since these MRI parameters have been related to relapses and are often among the criteria chosen to reflect disease activity, they are considered to be important in this context.
- The *post-hoc* Bayesian analysis provided by the Applicant supports significant reductions in MRI lesions with teriflunomide vs. placebo in TERIKIDS by combining adult and paediatric data using different weights attributed to the adult data. However, a large proportion of paediatric MRI data (being an essential part of the Bayesian analysis) was missing after patients had switched from placebo to teriflunomide. When applying a conservative imputation method (imputation with placebo data) for these missing MRI data, the effect was considerably reduced and failed to show statistical significance. This imputation approach is however considered too conservative. In addition, results still showed a relevant numerical effect.

The totality of the provided and updated popPK data is now considered sufficient to support the proposed dosing regimen in paediatrics.

The safety profile of teriflunomide in the paediatric RRMS population generally presents with findings similar to adults, for whom the drug was approved in the European Union 7 years ago and for which risk minimisation measures proved efficacious. The limited number of paediatric patients belonging to the most vulnerable subpopulation, i.e. those aged < 13 years, being pre-pubertal, or with a BW of < 40 kg, is of general uncertainty, although, so far available long-term data from an additional two years treatment with teriflunomide in the OL period do not point towards an increased susceptibility to adverse effects in these patients. At the same time, the limited long-term safety data, especially in the vulnerable subpopulation of the younger and prepubertal paediatric patients, needs to be addressed postmarketing. Therefore, additional long-term data are expected after completion of the OL period of study EFC11759. Moreover, the occurrence of TEAEs/SAEs related to pancreatic toxicity in paediatrics appears to be increased over those in adults, which is now adequately reflected in the product information (sections 4.4 and 4.8). Given that pancreatitis events in the paediatric study occurred between >11 months and up to 3 years, reporting of such events might increase with long-term treatment.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Aubagio in the extension of the application to include the treatment of *paediatric patients 10 years of age and older with relapsing remitting multiple sclerosis (RRMS)* is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Aubagio 7mg is favourable in the following indication:

Aubagio is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS) (please refer to section 5.1 for important information on the population for which efficacy has been established).

The CHMP therefore recommends the extension of the marketing authorisation for Aubagio subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree an educational programme with the National Competent Authority.

The MAH shall ensure that, following discussion and agreement with the National Competent Authorities in each Member State where AUBAGIO is marketed, at launch and after launch, all healthcare professionals who are expected to use AUBAGIO are provided with the following items:

- Summary of Product Characteristics (SmPC)
- Educational material for Healthcare professionals
- Patient Education Card

The educational material for HealthCare Professionals (HCP) will include the following key elements:

1. HCPs 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 teriflunomide
 - 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,
 - Encourage them to enrol in a pregnancy registry (in countries where a pregnancy registry is on-going),
 - Contact the National Registry Coordinator in the respective country who manages the enrolment of patient in the pregnancy registry (in countries where a pregnancy registry is on-going).
- 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 haematologic 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.
2. 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;
 3. A reminder to discuss the Patient Education Card content with the patient/legal representative regularly at each consultation at least annually during treatment;
 4. To encourage patients to contact their MS physician and/or General Practitioner if they experience any of the signs and symptoms discussed in the Patient Education Card;
 5. 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;
 6. 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.

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

1. A reminder for both patients and all HCPs involved in their treatment that the patient is being treated with teriflunomide, a medicine which:
 - Should not be used in pregnant women
 - Requires concomitant use of effective contraception in women of child-bearing potential
 - Requires a pregnancy status check before treatment
 - Affects liver function
 - Affects blood cell counts and the immune system
2. Information to educate the patient about important side effects:
 - 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 breast-feeding
 - A reminder for women of child-bearing potential including girls and their parents/ caregivers
 - to use effective contraception during and after treatment with teriflunomide
 - 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 experiences menses for the first time in order to get counselling about the potential risk to the fetus and the need for contraception
 - If women of child-bearing potential become pregnant:
 - To remind both patients and HCPs about the accelerated elimination procedure
 - To remind both patients and HCP about the Pregnancy Registry (in countries where pregnancy registry is on-going)
 - 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
3. To encourage the patients to read the PIL thoroughly

Additional Marketing protection

Furthermore, the CHMP reviewed the data submitted by the sanofi-aventis groupe, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0165/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP did recommends the variation(s) to the terms of the marketing authorisation,

concerning the following change(s):

Variations requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include treatment of paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS) for Aubagio. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Annex II, labelling and Package Leaflet are updated in accordance. The MAH is requesting an extension of the market protection of one additional year in line with the guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period.

Version 7.0 of the RMP has also been agreed.

Appendix

1. CHMP AR on the significant clinical benefit in comparison with existing therapies.