EMA/CHMP/224365/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

AUBAGIO

International non-proprietary name: teriflunomide

Procedure No. EMEA/H/C/002514/II/0042

Note

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

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Winthrop Industrie submitted to the European Medicines Agency on 19 December 2022 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Submission of the final report from study EFC11759 listed as a category 3 study in the RMP. This is a two-year, multicenter, randomized, double-blind, 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 (MS) followed by an open-label extension.

The RMP version 8.0 has also been submitted.

The requested variation proposed amendments to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

With the current variation, the MAH provided the final study report of the open-label extension period of study EFC11759, a two-year, multicentre, randomised, double-blind, placebo-controlled, parallel group trial to evaluate efficacy, safety, tolerability and pharmacokinetics of teriflunomide administered orally once daily - at the dose of 7 mg or 14 mg adults equivalent - in paediatric patients with relapsing forms of MS followed by an open-label extension.

The open-label (OL) period that followed the double-blind (DB) period lasted until 192 weeks after randomisation. Its duration for a given patient depended on when the patient entered this period. The duration of the OL period was 96 weeks for participants who completed the 96-week DB 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.

Although specific objectives for the open-label extension were not pre-defined, the open-label period of study EFC11759 focussed on long-term safety and tolerability.

Interim analyses were performed while the study was ongoing. Results of the first interim analysis with the data cut-off date 27 November 2019 were presented in support of the line extension for Aubagio to include paediatric patients with RRMS. With regard to safety, these results were subsequently updated during the course of EMEA/H/C/002514/X/0031/G (second interim analysis with cut-off date 12 September 2020). Overall, paediatric subjects were exposed to teriflunomide for up to 1418 days during the combined double-blind and open-label period as per the final database lock on 13 October 2021.

The final clinical study report of the open-label period with teriflunomide in paediatric patients does not change the conclusions on clinical efficacy and safety assessed during the line extension.

With regard to efficacy the results of the updated and final long-term data of study EFC11759 suggest maintenance of effect of teriflunomide in paediatric patients with RMS. Efficacy findings are generally in line with the respective findings of the DB treatment period, as well as the preliminary long-term study data evaluated during the initial MAA for teriflunomide in the paediatric population.

No new or worsening of existing safety issues have been identified since the most recent open-label interim report of study EFC11759. As a consequence, no amendments to the product information have been proposed by the Applicant. This is agreed to.

A revised RMP version 8.0 was submitted as a result of the completion of study EFC11759. Taking into account that no new safety issues or worsening of existing ones have been identified, it is agreed that only general remarks have been added reflecting that teriflunomide has been well tolerated with a manageable safety profile during the open-label extension phase. However, it is noted that the section on the potential risk of teratogenicity has been completely revised in relation to data from the Sanofi Pharmacovigilance database with the new DLP. This is generally endorsed. However, the wording requires revision as detailed in section 11 below. As these required revisions are considered minor, they can be provided with the next RMP update (please also refer to section 9.7).

Following a request for supplementary information, a revised RMP version 8.1 was submitted. Since the open-label period of Study EFC11759/TERIKIDS has been completed and data on the long-term safety in children is now available, the missing information "long-term safety in paediatric patients" was removed from the summary of safety concerns in the RMP but will be further monitored within the PSURs.

The pharmacovigilance plan was updated to remove study EFC11759/TERIKIDS from the list of ongoing pharmacovigilance activities, as it has been completed, which is considered acceptable.

The benefit-risk balance of AUBAGIO remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Submission of the final report of the open-label extension period for study EFC11759, listed as a category 3 study in the RMP. This is a two-year, multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate efficacy, safety, tolerability and pharmacokinetics of teriflunomide administered orally once daily in pediatric patients with relapsing forms of multiple sclerosis (MS) followed by an open-label extension. The RMP version 8.1 has also been submitted.

☒ is recommended for approval.

Amendments to the marketing authorisation

The variation requires amendments to the Risk Management Plan.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Not applicable

Please refer to Scientific Discussion ‘Aubagio-H-C-002514-II-42’

5. Introduction

Aubagio (synonyms: teriflunomide, HMR 1726) is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS) and is distributed as film-coated tablets containing 7 mg or 14 mg of teriflunomide as active substance. In adults, the recommended dose of teriflunomide is 14 mg once daily. In paediatric patients (10 years of age and above), the recommended dose is dependent on body weight:

- Paediatric patients with body weight >40 kg: 14 mg once daily.

- Paediatric patients with body weight ≤40 kg: 7 mg once daily.

Paediatric patients who reach a stable body weight above 40 kg should be switched to 14 mg once daily.

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. Consequently, 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.

Aubagio received approval of marketing authorisation for the treatment of adult patients with relapsing remitting multiple sclerosis on 26 August 2013 (centralised procedure; EMEA/H/C/002514). Studies that have been conducted with teriflunomide in support of the indication in adult patients with RRMS included one phase 2 study (study 2001), and three phase 3 studies (TEMSO: a 2 year, placebo-controlled study; TOWER: a placebo-controlled, 48 to 152 weeks study; TENERE: active-controlled study, with a minimum duration of 48 weeks and a maximum duration of 118 weeks).

On 17 June 2021, a European Commission (EC) decision was issued for the extension of the indication to include treatment of paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS), rendering Aubagio the first oral first-line therapy for children and adolescents aged 10 to 17 years in the EU. Moreover, the EC granted an additional year of marketing protection in the EU. Reference is made to EMEA/H/C/002514/X/0031/G.

In support of the line extension procedure starting in 2020, the Applicant provided results of a single Phase 3 study EFC11759 (TERIKIDS), a two-year, multicenter, randomised, double-blind, 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. At the time of the MAA for Aubagio in paediatric patients, the open-label extension period of study EFC11759 was still ongoing. Results of the double-blind (DB) treatment period of up to 96 weeks (including a blinded PK run-in phase of 8 weeks) and interim results of the open-label (OL) treatment period of up to 192 weeks (original data cut-off 27 November 2019 with an additional safety data cut-off 12 September 2020) were submitted and assessed during EMEA/H/C/002514/X/0031/G.

The primary objective of the DB period in study EFC11759 was to assess the effect of teriflunomide in comparison to placebo on disease activity as measured by time to first clinical relapse after randomisation in children and adolescents 10 to 17 years of age with relapsing forms of MS. 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 safety and tolerability of teriflunomide compared to placebo and to evaluate the PK of teriflunomide. Exploratory objectives of the study were to assess the effect of teriflunomide in comparison to placebo on disease activity/progression measured by brain MRI and on cognitive function and to explore long-term treatment effects in teriflunomide/teriflunomide and placebo/teriflunomide group. Specific objectives for the open-label extension were not defined.

For the design details of study EFC11759, reference is made to the assessment reports/ EPAR of the Aubagio line extension (EMEA/H/C/002514/X/0031/G).

There were five global and 2 local amendments implemented subsequent to the original protocol (dated 30 May 2013) while study EFC11759 was ongoing. Global amendments 1 to 4 are described in detail in the assessment reports/ EPAR of the Aubagio line extension (EMEA/H/C/002514/X/0031/G). An additional amendment (No.5) to the protocol dated 10 December 2020. This amendment was made due to the emerging COVID-19 pandemic in order to implement changes to the conduct of the study for patients in the open-label period and optional extension period, to ensure continuation of patient treatment, while reducing personal contact with patients.

The Aubagio EU RMP version 7.3 has been updated by the MAH as a result of the completion of study EFC11759 to version 8.0. Please refer to section 9 for assessment of the proposed changes.

The data in the EU Summary of Product Characteristics are not affected by the final study results and therefore, no changes are proposed to the labelling.

6. Clinical Efficacy aspects

6.1. Methods – analysis of data submitted

As methods and results of the double-blind period of study EFC11759 as well as methods and preliminary long-term data (as of cut-off date of 27 November 2019) of the open-label extension have already been assessed during the initial MAA for Aubagio in the paediatric population, the general design of the study is only briefly described in the following.

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

The first patient has been enrolled in the open-label period: 02 April 2015

Study completion date: 06 October 2021 (last participant last visit)

An interim analysis regarding efficacy has been provided with cut-off date: 27 November 2019. The now presented final results are based on database lock date of 13 October 2021.

All subjects 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.

For subjects discontinuing study treatment or who were not interested to continue treatment with teriflunomide after study completion, teriflunomide was cleared from the body through an accelerated elimination procedure with either cholestyramine or activated charcoal.

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.

Study population

Participants of 10 to below 18 year of age, with relapsing form of multiple sclerosis meeting the criteria of MS based on McDonald criteria 2010 and IPMSSG criteria for paediatric MS, version of 2012 and had at least 1 relapse (or attack) in the 12 months preceding screening or at least 2 relapses (or attacks) in the 24 months preceding screening. Completed the double-blind period of the study and were below 18 years of age at open-label entry.

Dose regimen:

• During PK run-in period: 7 mg adult equivalent once daily dose of teriflunomide (1 tablet of 3.5 mg for participants with body weight of ≤40 kg or 1 tablet of 7 mg for participant with body weight >40 kg) for those previously in placebo arm and 14 mg adult equivalent (see below) for those who were previously in the teriflunomide arm during double-blind period.

• After PK run-in period: 14 mg adult equivalent once daily dose of teriflunomide based on the individual predicted PK parameters defined in the PK run-in period as follows:

- If individual predicted PK parameters ≤95th percentile of adult range of predicted PK parameters (repeated doses of 7 mg): 1 tablet of 7 mg for participants with a body weight of ≤40 kg or 1 tablet of 14 mg for participants with a body weight >40 kg.

- If individual predicted PK parameters > 95th percentile of the adult range of predicted PK parameters (repeated doses of 7 mg): 1 tablet of 3.5 mg for participants with a body weight of ≤40 kg or 1 tablet of 7 mg for participants with a body weight >40 kg.

Statistical methods:

Efficacy analyses for primary and secondary endpoints of the open-label period were of exploratory intent in principle to better understand treatment effects of teriflunomide monotherapy beyond the double-blind period in the paediatric population.

The first clinical confirmed relapse occurred from randomization in the double-blind period (including relapses during the PK run-in [8 weeks] phase) to the end of the open-label period was included for analysis. Treatment effect as measured by the hazard ratio and its associated 95% confidence interval (CI) was estimated using a Cox's proportional-hazards model with robust variance estimation. Cox's model included factors for treatment group, region, baseline pubertal status, age at study entry, and number of relapses in the year prior to randomization. The duration of time to the event was included in

the modelling to offset the lengths of individual observations. Kaplan-Meier estimates of probability of clinical relapse at Week 24, 48, 72, 96, 120, 144, 168 and 192 were estimated. The complementary log-log transformation was used to construct 95% CIs. Kaplan-Meier survival curves from randomization in double-blind period to the end of open-label period were presented. A stratified log-rank test with time to first clinical relapse as the dependent variable, treatment group as a test variable, region, and baseline pubertal status as covariates was provided as supportive. The proportion of participants with clinical relapse-free at Weeks 24, 48, 72, 96, 120, 144, 168 and 192 was estimated based on Kaplan-Meier methods.

The number of new or enlarged T2 lesions per MRI scan was analysed using a negative binomial regression model with robust variance estimation. The number of T1 Gd-enhancing lesions per MRI scan and the number of new T1 hypointense lesions per MRI scan were analysed using a similar negative binomial regression model as described above for T2 lesions. The proportion of participants free of new or enlarged T2 lesions at Weeks 48, 96, 144 and 192 was summarised based on all participants having an MRI at these time points. Kaplan-Meier method was used for estimation.

The change from baseline in Cognitive Battery tests and symbol digit modalities test (SDMT) was summarised descriptively. Box plot was provided as well.

The proportion of disease-free participant was summarised at Weeks 48, 96, 144 and 192 based on all participants having an MRI at these time points. Kaplan-Meier methods was used for estimation.

Adjusted annualized relapse rate (ARR) was performed using a Poisson regression model with robust error variance that would accommodate the potential over-dispersed data appropriately. The estimated relapse rates and 2-sided 95% CIs were provided for each treatment group.

6.2. Results

Study population

152 patients were enrolled in the OL period: 100 patients in the teriflunomide/teriflunomide group and 52 patients in the placebo/teriflunomide group.

Table 1 Participants disposition

	Placebo / Teriflunomide (N=52)	Teriflunomide / Teriflunomide (N=100)	All (N=152)
Randomized and treated in the double-blind period	52 (100)	100 (100)	152 (100)
Completed the double-blind period	52 (100)	100 (100)	152 (100)
Discontinued from the double-blind period	0	0	0
Enrolled in the open-label period	52 (100)	100 (100)	152 (100)
Enrolled but not treated in the open-label period	0	0	0
Completed the open-label treatment period	31 (59.6)	73 (73.0)	104 (68.4)
Discontinued from the open-label treatment period	21 (40.4)	27 (27.0)	48 (31.6)
Ongoing in the open-label treatment period	0	0	0
Reason for the open-label period treatment permanent discontinuation			
Adverse event	7 (13.5)	5 (5.0)	12 (7.9)
Lack of efficacy	10 (19.2)	14 (14.0)	24 (15.8)
Poor compliance to protocol	0	1 (1.0)	1 (0.7)
Other reason	4 (7.7)	7 (7.0)	11 (7.2)
Participant's decision to permanently discontinue the treatment in the open-label period	11 (21.2)	20 (20.0)	31 (20.4)

Note: Percentages are calculated using the number of enrolled participants in the open-label period as denominator.
Participant's decision to permanently discontinue the treatment indicates that number of participants who stopped the treatment by their own decision among all the permanently discontinued participants

Most of the 166 participants randomized in the double-blind period of the study entered the open-label period (100 [91.7%] participants in the teriflunomide group and 52 [91.2%] participants in the placebo group) to receive teriflunomide treatment.

Of the enrolled 152 participants, 104 (68.4%) participants completed the open-label period: 31 (59.6%) participants in the placebo/teriflunomide group and 73 (73.0%) participants in the teriflunomide/teriflunomide group.

Overall, 48 (31.6%) participants (21 [40.4%] participants in the placebo/teriflunomide group and 27 [27.0%] participants in the teriflunomide/teriflunomide group) discontinued from the open-label treatment period of the study; 19.2% in the placebo/teriflunomide group and 14.0% in the teriflunomide/teriflunomide group due to lack of efficacy and 13.5% in the placebo/teriflunomide group and 5.0% in the teriflunomide/teriflunomide group due to adverse events.

Efficacy results:

Table 2 Summary of Efficacy results – Efficacy population

	Placebo / Teriflunomide (N=52)	Teriflunomide / Teriflunomide (N=100)
Primary endpoint: Time to first confirmed clinical relapse[a] during combined double-blind and open-label treatment period		
KM estimate at Week 96	0.558 (0.413 ; 0.680)	0.400 (0.304 ; 0.494)
KM estimate at Week 192	0.635 (0.489 ; 0.749)	0.482 (0.381 ; 0.576)
Hazard Ratio (95% CI)[b]	-	0.617 (0.388 ; 0.983)
Stratified Log-Rank test p-value[c]	-	0.1058
Secondary endpoint: Time to first confirmed clinical relapse[d] during the open-label treatment period		
KM estimate at Week 96	0.284 (0.163 ; 0.419)	0.265 (0.180 ; 0.357)
KM estimate at Week 192	0.485 (0.269 ; 0.671)	0.288 (0.195 ; 0.388)
Hazard Ratio (95% CI)[b]	-	0.693 (0.370 ; 1.296)
Stratified Log-Rank test p-value[c]	-	0.4247
Secondary endpoint: Proportion of clinical relapse[a] free participants during combined double-blind and open-label treatment period		
KM estimate at Week 96	0.442 (0.305 ; 0.571)	0.600 (0.497 ; 0.688)
KM estimate at Week 192	0.365 (0.238 ; 0.494)	0.518 (0.416 ; 0.611)
Secondary endpoint: Number of new or enlarged T2-lesions per MRI scan during combined double-blind and open-label treatment period		
Adjusted number of new or enlarged T2 lesions per MRI scan[e]	11.087 (6.586, 18.662)	5.664 (3.417, 9.389)
Relative risk (95% CI)[e]	-	0.511 (0.343, 0.762)
P-value[e]	-	0.001
Secondary endpoint: Number of T1 Gd-enhancing lesions per MRI scan during combined double-blind and open-label treatment period		
Adjusted number of T1 Gd-enhancing lesions per MRI scan[f]	2.686 (1.263, 5.712)	1.532 (0.624, 3.762)
Relative risk (95% CI)[f]	-	0.570 (0.331, 0.983)
P-value[f]	-	0.0431
Secondary endpoint: Volume of T2 lesion (mL)		
Volume of T2 lesion (mL) at OL Week 96, Mean (SD)	15.5 (14.9)	13.0 (14.6)
Change from baseline[g] for volume of T2 lesion (mL) at OL Week 96, Mean (SD)	2.7 (8.1)	1.9 (4.0)
Volume of T2 lesion (mL) at OL Week 192, Mean (SD)	20.5 (11.7)	26.2 (25.9)
Change from baseline[g] for volume of T2 lesion (mL) at OL Week 192, Mean (SD)	0.4 (9.4)	-3.6 (30.6)
Secondary endpoint: Volume of T1 hypointense lesion (mL)		
Volume of T1 hypointense lesion (mL) at OL Week 96, Mean (SD)	2.9 (3.4)	3.3 (5.7)
Change from baseline[g] for volume of T1 hypointense hypointense lesion (mL) at OL Week 96, Mean (SD)	1.0 (2.0)	0.6 (1.9)
Volume of T1 hypointense lesion (mL) at OL Week 192, Mean (SD)	7.1 (7.8)	9.1 (11.7)
Change from baseline[g] for volume of T1 hypointense lesion (mL) at OL Week 192, Mean (SD)	4.0 (5.8)	2.5 (5.7)
Secondary endpoint: Number of new hypointense T1 lesions per MRI scan during combined double-blind and open-label treatment period		
Adjusted number of new hypointense T1 lesions per MRI scan[h]	3.315 (1.516, 7.251)	1.650 (0.831, 3.275)
Relative risk (95% CI)[h]	-	0.498 (0.296, 0.836)
P-value[h]	-	0.0083

Secondary endpoint: Proportion of participants free of new or enlarged T2-lesions during combined double-blind and open-label treatment period		
KM estimate at Week 96	0.154 (0.072 ; 0.264)	0.169 (0.103 ; 0.249)
KM estimate at Week 192	0.096 (0.035 ; 0.194)	0.116 (0.062 ; 0.188)
Secondary endpoint: Percentage change of brain volume		
Percentage change from baseline[g] of brain volume (%) at OL Week 96, Mean (SD)	-1.8 (1.9)	-1.4 (1.6)
Percentage change from baseline[g] of brain volume (%) at OL Week 192, Mean (SD)	-2.2 (1.2)	-3.0 (1.9)
Secondary endpoint: EDSS score		
EDSS score at OL Week 96, Mean (SD)	1.5 (1.3)	1.3 (1.1)
Change from baseline[g] for EDSS score at OL Week 96, Mean (SD)	0.2 (1.1)	0.0 (0.9)
EDSS score at OL Week 192, Mean (SD)	2.5 (NC)	0.9 (0.6)
Change from baseline[g] for EDSS score at OL Week 192, Mean (SD)	0.5 (NC)	-0.3 (0.5)
Secondary endpoint: Number of correct substitution measured by SDMT		
Number of correct substitution measured by SDMT at OL Week 96, Mean (SD)	56.2 (16.2)	57.8 (14.3)
Change from baseline[g] for number of correct substitution measured by SDMT at OL Week 96, Mean (SD)	7.6 (16.7)	8.0 (14.8)
Number of correct substitution measured by SDMT at OL Week 192, Mean (SD)	52.0 (NC)	58.3 (19.6)
Change from baseline[g] for number of correct substitution measured by SDMT at OL WEEK 192, Mean (SD)	12.0 (NC)	-0.3 (18.2)
Secondary endpoint: Number of completed items measured by SDMT		
Number of completed item measured by SDMT at OL Week 96, Mean (SD)	57.5 (15.7)	59.3 (12.5)
Change from baseline[g] for number of completed item measured by SDMT at OL Week 96, Mean (SD)	6.3 (16.6)	7.6 (12.5)
Number of completed item measured by SDMT at OL Week 192, Mean (SD)	53.0 (NC)	61.0 (15.1)
Change from baseline[g] for number of completed item measured by SDMT at OL Week 192, Mean (SD)	12.0 (NC)	-1.5 (18.3)
Secondary endpoint: BVMT-R - raw score 3 trials total[i]		
BVMT-R - raw score 3 trials total at OL Week 96, Mean (SD)	23.8 (8.4)	25.4 (7.5)
Change from baseline[g] for BVMT-R - raw score 3 trials total at OL Week 96, Mean (SD)	1.0 (6.9)	1.2 (5.4)
Secondary endpoint: BVMT-R - raw score delayed recall[i]		
BVMT-R - raw score delayed recall at OL WEEK 96, Mean (SD)	8.6 (2.8)	9.7 (2.3)
Change from baseline[g] for BVMT-R - raw score delayed recall at OL Week 96, Mean (SD)	-0.7 (2.6)	0.4 (1.6)
Exploratory endpoint: Proportion of disease-free participants[j] during combined double-blind and open-label treatment period		
KM estimate at Week 96	0.038 (0.007 ; 0.117)	0.120 (0.066 ; 0.192)
KM estimate at Week 192	0.038 (0.007 ; 0.117)	0.090 (0.044 ; 0.156)
Additional endpoint: Adjusted annualized relapse[d] rate during the open-label period		
Adjusted annualized relapse rate[k]	0.150 (0.076, 0.299)	0.134 (0.071, 0.254)

Relative risk (95% CI)[k]	-	0.892 (0.511, 1.559)
Risk difference (95% CI)[k]	-	-0.016 (-0.097, 0.065)
P-value[l]	-	0.6892
Additional endpoint: Time to disability progression sustained for 24 weeks[m] during combined double-blind and open-label treatment period		
Kaplan-Meier estimates of probability of sustained disability progression (95% CI) at Week 96	0.165 (0.077 ; 0.282)	0.094 (0.046 ; 0.163)
Kaplan-Meier estimates of probability of sustained disability progression (95% CI) at Week 192	0.323 (0.188 ; 0.466)	0.163 (0.096 ; 0.246)
Hazard Ratio (95% CI)[n]	-	0.465 (0.226 ; 0.959)

Abbreviations: BVMT-R, brief visuospatial memory test revised; CI, confidence interval; EDSS: expanded disability status scale; Gd, Gadolinium; KM, Kaplan-Meier; OL, open-label period; IMP, investigational medical product; MRI, magnetic resonance imaging; NC, not calculated; SD, standard deviation; SDMT, symbol digit modalities test.

a Clinical relapse that happened in the double-blind period was adjudicated by the relapse adjudication panel. If the relapse happened in the open-label period, then it was confirmed by objective signs on neurological examination (which is the basis for relapse adjudication panel confirming relapses).

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.

d Clinical relapse that happened in the open-label period was confirmed by objective signs on neurological examination (which is the basis for relapse adjudication panel confirming relapses).

e 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.

f 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.

g Baseline is defined as last non-missing value that was measured before or on the day of first administration of IMP in the double-blind period.

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

i This cognitive test only has test result up to OL Week 96.

j The disease-free participant was defined as participants with 1) No confirmed clinical relapse, 2) 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), 3) Free of MRI activity: No Gd-enhancing T1 lesions and no new/enlarging T2 lesions.

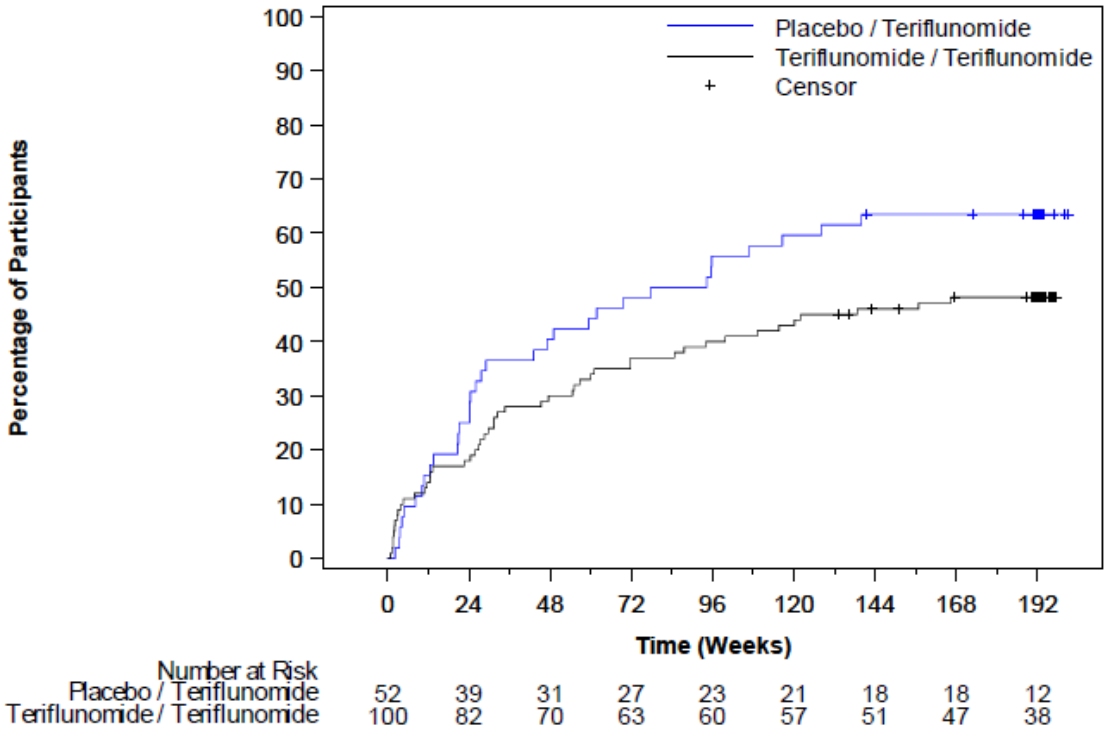
k Derived using Poisson model with robust error variance, with the total number of relapses onset between the open-label enrollment and last dose date of the open-label period as the response variable, treatment group, pubertal status, and region as covariates, and log-transformed standardized treatment duration in years as an offset variable.

l Chi-square test from estimating the rate ratios.

m The first sustained disability progression (ie, confirmed disability worsening) is defined as a sustained increase of at least 1.0 point (0.5 for participants with baseline EDSS >5.5) persisting for at least 24 weeks from baseline EDSS during combined double-blind and open-label treatment period.

n Derived using Cox proportional-hazards model with treatment group, region and pubertal status as covariate, offset by the lengths of individual observations.

Figure 1 Primary analysis: Kaplan-Meier (KM) plot of time to first confirmed clinical relapse during combined double-blind and open-label treatment period - Efficacy population



Note: Clinical relapse that happened in the double-blind period was adjudicated by the relapse adjudication panel. If the relapse happened in the open-label period, then it was confirmed by objective signs on neurological examination (which is the basis for relapse adjudication panel confirming relapses).

The participants who received teriflunomide since the start of the DB period had a numerically lower risk of confirmed clinical relapse over the combined DB and OL periods than the participants who received teriflunomide only from the start of the open-label period (relative risk reduction of 38.3%; hazard ratio (HR): 0.62; 95% CI (confidence interval): 0.39 to 0.98; p = 0.1058).

The estimated adjusted annualised relapse rates (ARR) in the open-label period were 13.4% and 15.0% in participants in the teriflunomide/teriflunomide group and placebo/teriflunomide group, respectively, which were close to the unadjusted relapse rates of 18.4% and 20.6% in participants in the teriflunomide/teriflunomide group and placebo/teriflunomide group, respectively, since enrolment of the open-label period as of the data cut-off.

The participants who received teriflunomide since the start of double-blind study had also a lower risk of disability progression sustained over the combined double-blind and open-label periods than the participants who received teriflunomide only from the start of the open-label (HR: 0.465; 95% CI: 0.226 to 0.959).

Regarding the MRI secondary endpoints, teriflunomide reduced the number of new or enlarged T2-lesion per scan and the number of Gd-enhancing T1 lesions per scan, when comparing participants previously treated with teriflunomide since the start of the double-blind period to participants treated with teriflunomide only from the start of the open-label period. Furthermore, teriflunomide reduced the number of new hypointense T1 lesions per scan, when comparing participants previously treated with teriflunomide since the start of the double-blind period to participants treated with teriflunomide only from the start of the open-label period.

There was a higher proportion of clinical relapse-free participants in the teriflunomide/teriflunomide group versus the placebo/teriflunomide group.

No meaningful difference between groups was observed for the cognitive tests. The number of participants evaluated at the end of the study was low and limited the interpretation of the results.

6.3. Discussion

Study EFC11759 (TERIKIDS) was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study (duration 96 weeks), followed by an open-label (OL) period that could last up to 192 weeks from randomisation to EOT. Efficacy data received from this long-term extension period support the efficacy results observed in the prior double-blind period of study EFC11759 and indicate maintenance of efficacy. 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.

7. Clinical Safety aspects

7.1. Methods – analysis of data submitted

For a detailed method description of study EFC11759, it should be referred to the assessment reports of the original application procedure (EMEA/H/C/002514/X/0031/G).

The safety analysis was conducted on the safety population defined as:

- all randomised patients exposed to study medication, during the DB period;
- all patients enrolled in the OL treatment period and who received any dose of teriflunomide.

Safety analyses were conducted according to the study treatment that the participants actually received in the DB period (placebo versus teriflunomide) and in the OL period (placebo/teriflunomide versus teriflunomide/teriflunomide, and, if applicable, overall).

Moreover, long-term safety analysis of Study EFC11759 focused on data of all teriflunomide-treated participants from randomisation in the DB period to the end of OL period. The safety results during this combined DB and OL period are summarised.

The safety information presented is based on TEAEs, SAEs, clinical laboratory data, vital sign measurements, ECGs, body weight, height and Tanner stage assessment with the following assessment schedule:

Table 3 Safety assessments study schedule

Variable	Visit
Clinical Laboratory	Transition, Weeks 4, 12, and then every 12 weeks up to the Week 192/EOT[a]
Vital signs	Transition, Weeks 4, 8, 12, and then every 12 weeks up to the Week 192/EOT[a]
ECG	Week 192/EOT[a] and after EOT[a] if abnormality on EOT
Immunoglobulins and TSH	Week 96 and Week 192/EOT[a] visit
Physical examinations	Weeks 12, 24, and then every 24 weeks up to the Week 192/EOT[a]
Tanner assessment	Every 24 weeks up to the Week 192/EOT[a] for all patients (until complete sexual maturity).

a Patients who complete the open-label treatment period or who prematurely discontinue, should complete EOT visit

ECG: electrocardiogram, TSH: thyroid stimulating hormone, EOT: end of treatment, PK: pharmacokinetic.

The following terms have been defined as adverse events of special interest (AESIs): *gastrointestinal disorders (nausea and diarrhoea), hepatic disorders, pancreatic disorders, bone marrow disorders, infections and infestations, hypersensitivity/severe skin disorders, malignancy, hypertension, cardiac arrhythmias, pulmonary disorders (interstitial lung disease), embolic and thrombotic events, haemorrhage, peripheral neuropathy, convulsions, alopecia and psychiatric disorders, and pregnancy*.

Tanner stages (scale of physical development in children, adolescents and adults) were assessed at baseline for each location (pubic hair and breasts in girls, pubic hair and testes in boys) by gender and treatment group, and every 24 weeks, and EOT or until complete sexual maturity (Tanner stage V).

7.2. Results

For the results of the DB period of study EFC11759, reference is made to the clinical assessment report and overview documents and the EPAR for EMEA/H/C/002514/X/0031/G.

The presentation of results in the following paragraphs pertains to the final data from the OL period with the data cut-off 13 October 2021.

Patient exposure

152 patients (52 patients in the placebo/ teriflunomide group and 100 patients in the teriflunomide/ teriflunomide group) were treated in the OL period of study EFC11759. Cumulative duration of treatment exposure from enrolment in the DB period to the final cut-off date in the OL period was 36.18 patient-years for the patients receiving 7 mg teriflunomide group and 265.82 patient-years for the patients receiving 14 mg teriflunomide (most of the patients received 14 mg). Median duration of study treatment was 683 days for the teriflunomide 7 mg group and 680 days for the 14 mg group. Most of the patients received IMP (62.5% in the 7 mg group and 62.9% in the 14 mg group) for more than 96 weeks.

*Table 4 Extent of exposure to investigational medicinal product in OL period - Safety population - Study EFC11759 OL period (**cut-off date 13 October 2021**)*

	Placebo / Teriflunomide (N=52)				Teriflunomide / Teriflunomide (N=100)				All (N=152)			
	3.5 mg (N=0)	7 mg (N=13)	14 mg (N=36)	Missing (N=3)	3.5 mg (N=0)	7 mg (N=3)	14 mg (N=96)	Missing (N=1)	3.5 mg (N=0)	7 mg (N=16)	14 mg (N=132)	Missing (N=4)
Cumulative duration of treatment exposure (participant years)		27.97	78.64	0.12		8.21	187.18	0.10		36.18	265.82	0.22
Duration of study treatment (days)												
Number	0	13	36	3	0	3	96	1	0	16	132	4
Mean (SD)		785.8 (232.6)	797.9 (352.4)	15.0 (13.5)		999.7 (143.5)	712.2 (277.9)	35.0 (NC)		825.9 (231.2)	735.5 (301.1)	20.0 (14.9)
Median		673.0	774.5	11.0		1041.0	677.5	35.0		683.0	680.0	20.5
Min ; Max		429 ; 1162	71 ; 1287	4 ; 30		840 ; 1118	92 ; 1283	35 ; 35		429 ; 1162	71 ; 1287	4 ; 35
Duration of study treatment by category [n(%)]												
>0 and ≤4 weeks	0	0	0	2 (66.7)	0	0	0	0	0	0	0	2 (50.0)
>4 and ≤12 weeks	0	0	1 (2.8)	1 (33.3)	0	0	0	1 (100)	0	0	1 (0.8)	2 (50.0)
>12 and ≤24 weeks	0	0	1 (2.8)	0	0	0	3 (3.1)	0	0	0	4 (3.0)	0
>24 and ≤48 weeks	0	0	4 (11.1)	0	0	0	7 (7.3)	0	0	0	11 (8.3)	0
>48 and ≤72 weeks	0	1 (7.7)	1 (2.8)	0	0	0	8 (8.3)	0	0	1 (6.3)	9 (6.8)	0
>72 and ≤96 weeks	0	5 (38.5)	4 (11.1)	0	0	0	20 (20.8)	0	0	5 (31.3)	24 (18.2)	0
>96 and ≤120 weeks	0	3 (23.1)	8 (22.2)	0	0	1 (33.3)	35 (36.5)	0	0	4 (25.0)	43 (32.6)	0
>120 and ≤144 weeks	0	1 (7.7)	2 (5.6)	0	0	0	5 (5.2)	0	0	1 (6.3)	7 (5.3)	0
>144 and ≤168 weeks	0	3 (23.1)	10 (27.8)	0	0	2 (66.7)	11 (11.5)	0	0	5 (31.3)	21 (15.9)	0
>168 and <192 weeks	0	0	5 (13.9)	0	0	0	7 (7.3)	0	0	0	12 (9.1)	0
≥192 weeks	0	0	0	0	0	0	0	0	0	0	0	0
Cumulative duration of study treatment by category [n(%)]												
>0 week	0	13 (100)	36 (100)	3 (100)	0	3 (100)	96 (100)	1 (100)	0	16 (100)	132 (100)	4 (100)
>4 weeks	0	13 (100)	36 (100)	1 (33.3)	0	3 (100)	96 (100)	1 (100)	0	16 (100)	132 (100)	2 (50.0)
>12 weeks	0	13 (100)	35 (97.2)	0	0	3 (100)	96 (100)	0	0	16 (100)	131 (99.2)	0
>24 weeks	0	13 (100)	34 (94.4)	0	0	3 (100)	93 (96.9)	0	0	16 (100)	127 (96.2)	0
>48 weeks	0	13 (100)	30 (83.3)	0	0	3 (100)	86 (89.6)	0	0	16 (100)	116 (87.9)	0
>72 weeks	0	12 (92.3)	29 (80.6)	0	0	3 (100)	78 (81.3)	0	0	15 (93.8)	107 (81.1)	0
>96 weeks	0	7 (53.8)	25 (69.4)	0	0	3 (100)	58 (60.4)	0	0	10 (62.5)	83 (62.9)	0
>120 weeks	0	4 (30.8)	17 (47.2)	0	0	2 (66.7)	23 (24.0)	0	0	6 (37.5)	40 (30.3)	0
>144 weeks	0	3 (23.1)	15 (41.7)	0	0	2 (66.7)	18 (18.8)	0	0	5 (31.3)	33 (25.0)	0
>168 weeks	0	0	5 (13.9)	0	0	0	7 (7.3)	0	0	0	12 (9.1)	0
≥192 weeks	0	0	0	0	0	0	0	0	0	0	0	0

Note: Participants are considered in the group of treatment they actually received at the end of the PK run-in period in the open-label period

The missing column shows participants who didn't reach the end of open-label PK run-in period

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

During the OL period, the demographic, medical history and disease characteristics at baseline of the population enrolled were similar to the randomised population demographic characteristics (DB period).

Adverse events

Common adverse events

During the OL period, the proportion of patients with any TEAEs, treatment emergent SAEs, and any TEAEs leading to permanent treatment discontinuation was lower in the teriflunomide/ teriflunomide group compared with the placebo/ teriflunomide group (Table 5).

Table 5 Overview of safety profile: TEAEs - Safety population – Study EFC11759 OL period

n (%)	Placebo/ Teriflunomide (n=52)	Teriflunomide/ Teriflunomide (n=100)	All (n=152)
Patients with any TEAE	47 (90.4)	81 (81.0)	128 (84.2)
Patients with any treatment emergent SAE	15 (28.8)	14 (14.0)	29 (19.1)
Patients with any TEAE leading to death	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	7 (13.5)	4 (4.0)	11 (7.2)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event, n (%) = number and percentage of patients with at least one TEAE

Long-term safety analysis

TEAEs and treatment-emergent SAEs with teriflunomide were reported for 95% and 22.4% of patients from the randomisation in the DB period to the end of the OL period. TEAEs leading to permanent treatment discontinuation were reported in 11.2% of participants. No participant died during the study.

Display of AEs

The following TEAEs at the SOC level were reported more frequently in the placebo/ teriflunomide group than in the teriflunomide/ teriflunomide group (with a difference of ≥5%): Psychiatric disorders (17.3% vs. 11%), Nervous system disorders (34.6% vs. 27%), Respiratory, thoracic and mediastinal disorders (23.1% vs. 11%), Gastrointestinal disorders (34.6% vs. 28%), Musculoskeletal and connective tissue disorders (19.2% vs. 11%), Investigations (28.8% vs. 20%), and Renal and urinary disorders (11.5% vs. 3%). The following TEAEs at the SOC level were reported more frequently in the teriflunomide/ teriflunomide group than in the placebo/ teriflunomide group (with a difference of ≥5% by decreasing order in the teriflunomide/ teriflunomide group): Infections and infestations (57% and 50%), and Blood and lymphatic system disorders (10% and 3.8%), respectively.

The following TEAEs at the PT level were reported more frequently in the teriflunomide/ teriflunomide group than in the placebo/ teriflunomide group (with a difference ≥5% by decreasing order in the teriflunomide/ teriflunomide group): upper respiratory tract infection (22% of participants in the teriflunomide/ teriflunomide group and 13.5% of participants in the placebo/ teriflunomide group) and accidental overdose (10% and 3.8%), respectively. The following TEAEs at the PT level were more frequently reported in the placebo/ teriflunomide group than in the teriflunomide/ teriflunomide group (with a difference of ≥5% by decreasing order in the placebo/ teriflunomide group): alopecia (17.3% and 10%), ALT increased (15.5% and 3%), dizziness (11.5% and 3%), micturition urgency (9.6% and none), depression (7.7% and 2%), acute sinusitis (5.8% and none), bronchitis (5.8% and none), and asthma (5.8% and none) (Table 6).

In both groups, the majority of the TEAEs were of mild or moderate intensity. Severe TEAEs were reported in 10% of patients in the teriflunomide/ teriflunomide group and 13.5% of patients in the placebo/ teriflunomide group.

Treatment-related TEAEs were reported by 42% of participants in the teriflunomide/ teriflunomide and 40.4% of participants in the placebo/ teriflunomide group. The most frequently reported TEAEs with an incidence of ≥5% in either treatment group were: alopecia (9% of participants on teriflunomide/ teriflunomide and 17.3% of participants on placebo/ teriflunomide) and ALT increased (none and 7.7%).

*Table 6 Number (%) of patients with TEAE(s) with a frequency ≥2% in any treatment group by primary SOC and PT in the OL period – Safety population (compiled by the Assessor; **cut-off date 13 October 2021**)*

Primary system organ class – Preferred term n (%)	**Placebo/ Teriflunomide (N=52)**	**Teriflunomide/ Teriflunomide (N=100)**	**All (N=152)**
Any class	47 (90.4)	81 (81.0)	128 (84.2)
Infections and infestations	**26 (50.0)**	**57 (57.0)**	**70 (54.6)**
Nasopharyngitis	8 (15.4)	20 (20.0)	28 (18.4)
Upper respiratory tract infection	7 (13.5)	22 (22.0)	29 (19.1)
Influenza	5 (9.6)	5 (5.0)	10 (6.6)
Rhinitis	2 (3.8)	6 (6.0)	8 (5.3)
Tonsillitis	3 (5.8)	4 (4.0)	7 (4.6)
Urinary tract infection	2 (3.8)	5 (5.0)	7 (4.6)
Gastroenteritis	2 (3.8)	5 (5.0)	7 (4.6)
Respiratory tract infection	1 (1.9)	5 (5.0)	6 (3.9)
Pharyngitis	1 (1.9)	4 (4.0)	5 (3.3)
Sinusitis	2 (3.8)	2 (2.0)	4 (2.6)
Bronchitis	3 (5.8)	0	3 (2.0)
Conjunctivitis	1 (1.9)	2 (2.0)	3 (2.0)
Ear infection	0	2 (2.0)	2 (1.3)
Otitis externa	0	2 (2.0)	2 (1.3)
Gastroenteritis	2 (3.8)	5 (5.0)	7 (4.6)
Tracheitis	2 (3.8)	0	2 (1.3)
Acute sinusitis	3 (5.8)	0	3 (2.0)
Cystitis	2 (3.8)	0	2 (1.3)
Tracheobronchitis	2 (3.8)	0	2 (1.3)
Coronavirus infection	0	2 (2.0)	2 (1.3)
Blood and lymphatic system disorders	**2 (3.8)**	**10 (10.0)**	**12 (7.9)**
Anaemia	0	6 (6.0)	6 (3.9)
Leukopenia	1 (1.9)	2 (2.0)	3 (2.0)
Neutropenia	0	2 (2.0)	2 (1.3)
Metabolism and nutrition disorders	**3 (5.8)**	**10 (10.0)**	**13 (8.6)**
Decreased appetite	0	3 (3.0)	3 (2.0)
Vitamin D deficiency	1 (1.9)	4 (4.0)	5 (3.3)
Vitamin B12 deficiency	1 (1.9)	2 (2.0)	3 (2.0)
Psychiatric disorders	**9 (17.3)**	**11 (11.0)**	**20 (13.2)**
Depression	4 (7.7)	2 (2.0)	6 (3.9)
Anxiety	1 (1.9)	2 (2.0)	3 (2.0)
Suicide attempt	0	2 (2.0)	2 (1.3)
Nervous system disorders	**18 (34.6)**	**27 (27.0)**	**45 (29.6)**
Headache	7 (13.5)	14 (14.0)	21 (13.8)
Dizziness	6 (11.5)	3 (3.0)	9 (5.9)
Hypoaesthesia	4 (7.7)	3 (3.0)	7 (4.6)
Paraesthesia	1 (1.9)	4 (4.0)	5 (3.3)
Syncope	3 (5.8)	1 (1.0)	4 (2.6)
Tremor	2 (3.8)	1 (1.0)	3 (2.0)
Uhthoff's phenomenon	0	3 (3.0)	2 (2.0)
Eye disorders	**4 (7.7)**	**9 (9.0)**	**13 (8.6)**
Eye pain	0	3 (3.0)	3 (2.0)
Visual impairment	2 (3.8)	1 (1.0)	3 (2.0)
Vision blurred	0	3 (3.0)	3 (2.0)
Ear and labyrinth disorders	**2 (3.8)**	**3 (3.0)**	**5 (3.3)**
Vertigo	1 (1.9)	2 (2.0)	3 (2.0)
Cardiac disorders	**1 (1.9)**	**2 (2.0)**	**3 (2.0)**
Palpitations	0	2 (2.0)	2 (1.3)
Vascular disorders	**2 (3.8)**	**4 (4.0)**	**6 (3.9)**
Hypertension	0	2 (2.0)	2 (1.3)
Varicose vein	0	2 (2.0)	2 (1.3)
Respiratory, thoracic and mediastinal disorders	**12 (23.1)**	**11 (11.0)**	**23 (15.1)**
Oropharyngeal pain	2 (3.8)	7 (7.0)	9 (5.9)
Asthma	3 (5.8)	0	3 (2.0)
Cough	2 (3.8)	1 (1.0)	3 (2.0)
Respiratory disorder	2 (3.8)	0	2 (1.3)

Primary system organ class – Preferred term n (%)	Placebo/ Teriflunomide (N=52)	Teriflunomide/ Teriflunomide (N=100)	All (N=152)
Any class	47 (90.4)	81 (81.0)	128 (84.2)
Gastrointestinal disorders	**18 (34.6)**	**28 (28.0)**	**46 (30.3)**
Diarrhoea	6 (11.5)	7 (7.0)	13 (8.6)
Abdominal pain	2 (3.8)	8 (8.0)	10 (6.6)
Abdominal pain upper	0	3 (3.0)	3 (2.0)
Nausea	3 (5.8)	4 (4.0)	7 (4.6)
Vomiting	2 (3.8)	1 (1.0)	3 (2.0)
Constipation	2 (3.8)	4 (4.0)	6 (3.9)
Aphthous ulcer	2 (3.8)	1 (1.0)	3 (2.0)
Mouth ulceration	2 (3.8)	2 (2.0)	4 (2.6)
Vomiting	2 (3.8)	1 (1.0)	3 (2.0)
Dyspepsia	1 (1.9)	2 (2.0)	3 (2.0)
Toothache	0	2 (2.0)	2 (1.3)
Pancreatitis acute	0	3 (3.0)	3 (2.0)
Hepatobiliary disorders	**2 (3.8)**	**2 (2.0)**	**4 (2.6)**
Hepatic function abnormal	2 (3.8)	1 (1.0)	3 (2.0)
Skin and subcutaneous tissue disorders	**12 (23.1)**	**22 (22.0)**	**34 (22.4)**
Alopecia	9 (17.3)	10 (10.0)	19 (12.5)
Acne	0	4 (4.0)	4 (2.6)
Eczema	0	3 (3.0)	3 (2.0)
Dry skin	2 (3.8)	0	2 (1.3)
Rash	2 (3.8)	2 (2.0)	4 (2.6)
Musculoskeletal and connective tissue disorders	**10 (19.2)**	**11 (11.0)**	**21 (13.8)**
Back pain	2 (3.8)	1 (1.0)	5 (3.3)
Arthralgia	2 (3.8)	1 (1.0)	3 (2.0)
Myalgia	1 (1.9)	2 (2.0)	3 (2.0)
Muscular weakness	2 (3.8)	0	2 (1.3)
Pain in extremity	0	3 (3.0)	3 (2.0)
Muscle spasms	2 (3.8)	0	2 (1.3)
Renal and urinary disorders	**5 (9.6)**	**3 (3.0)**	**8 (5.3)**
Micturition urgency	5 (9.6)	0	5 (3.3)
Pollakiuria	2 (3.8)	1 (1.0)	3 (2.0)
Reproductive system and breast disorders	**2 (3.8)**	**4 (4.0)**	**6 (3.9)**
Dysmenorrhoea	1 (1.9)	2 (2.0)	3 (2.0)
General disorders and administration site conditions	**8 (15.4)**	**15 (15.0)**	**23 (15.1)**
Fatigue	4 (7.7)	4 (4.0)	8 (5.3)
Pyrexia	1 (1.9)	3 (3.0)	4 (2.6)
Asthenia	2 (3.8)	1 (1.0)	3 (2.0)
Influenza-like illness	0	2 (2.0)	2 (1.3)
Oedema peripheral	0	2 (2.0)	2 (1.3)
Non-cardiac chest pain	0	2 (2.0)	2 (1.3)
Investigations	**15 (28.8)**	**20 (20.0)**	**35 (23.0)**
Alanine aminotransferase increased	8 (15.4)	3 (3.0)	11 (7.2)
White blood cell count decreased	2 (3.8)	5 (5.0)	7 (4.6)
Blood creatine phosphokinase increased	2 (3.8)	2 (2.0)	4 (2.6)
Lipase increased	1 (1.9)	2 (2.0)	3 (2.0)
Red blood cell count decreased	0	2 (2.0)	2 (1.3)
Neutrophil count decreased	1 (1.9)	2 (2.0)	3 (2.0))
Weight decreased	2 (3.8)	3 (3.0)	5 (3.3)
Amylase increased	0	2 (2.0)	2 (1.3)
Monocyte count decreased	1 (1.9)	3 (3.0)	4 (2.6)
Transaminases increased	1 (1.9)	1 (1.0)	2 (1.3)
Weight increased	0	2 (2.0)	2 (1.3)
Protein urine present	2 (3.8)	1 (1.0)	3 (2.0)
Blood immunoglobulin G decreased	0	2 (2.0)	2 (1.3)
Injury, poisoning and procedural complications	**9 (17.3)**	**18 (18.0)**	**27 (17.8)**
Accidental overdose	2 (3.8)	10 (10.0)	12 (7.9)
Skin laceration	0	3 (3.0)	3 (2.0)
Fall	2 (3.8)	1 (1.0)	3 (2.0)

Primary system organ class – Preferred term n (%)	Placebo/ Teriflunomide (N=52)	Teriflunomide/ Teriflunomide (N=100)	All (N=152)
Any class	47 (90.4)	81 (81.0)	128 (84.2)
Thermal burn	2 (3.8)	0	2 (1.3)
Ligament sprain	1 (1.9)	2 (2.0)	3 (2.0)
Intentional overdose	0	2 (2.0)	2 (1.3)

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term MedDRA 24.0
n (%) = number and percentage of patients with at least one TEAE

Long-term safety analysis

The most frequently reported TEAEs at the SOC level (≥20% of teriflunomide-exposed participants from the randomisation in the DB period to the end of the OL period) were: Infections and infestations (67.7%), Nervous system disorders (41%), GI disorders (43.5%), Skin and subcutaneous tissue disorders (37.9%), Investigations (32.3%), Respiratory, thoracic and mediastinal disorders (23.6%), Injury, poisoning and procedural complications (23.6%), and General disorders and administration site conditions (22.4%).

The most frequently reported TEAEs at the PT level (≥10% of teriflunomide exposed participants) were: nasopharyngitis (26.7%), alopecia (23%), upper respiratory tract infection (23%), headache (19.9%), abdominal pain (11.2%), influenza (11.8%), diarrhoea (12.4%), and dizziness (9.9%). The majority of the TEAEs were of mild or moderate intensity. 15.5% of teriflunomide-exposed participants reported TEAEs that were considered severe. All reported severe TEAEs occurred in less than 1% of participants except blood creatine phosphokinase increased (2.5%), headache (1.2%), and pancreatitis acute (1.2%).

Serious adverse event/deaths/other significant events

No deaths occurred during the study.

Serious adverse events

Overall, the proportion of participants with treatment-emergent SAEs was lower in the teriflunomide/ teriflunomide group (14% participants) than in the placebo/ teriflunomide group (28.8% participants).

The most frequently reported SAEs (≥2% by SOC level) in the teriflunomide/ teriflunomide group were Nervous system disorders (6%), Psychiatric disorders (3%), GI disorders (3%), Infections and infestations (2%), Investigations (2%), and Injury, poisoning and procedural complications (2%). For the placebo/ teriflunomide group, the most frequently reported SAEs by SOC included Investigations (5.8%), Infections and infestations (3.8%), Psychiatric disorders (3.8%), Nervous system disorders (3.8%), Respiratory thoracic and mediastinal disorders (3.8%), and General disorders and administration site conditions (3.8 %).

The most frequently reported SAEs by preferred terms in ≥2.0% of patients in either treatment group were blood creatine phosphokinase increased, suicide attempt, Uhthoff's phenomenon, pancreatitis acute, asthma, and ALT increased (Table 7).

*Table 7 Number (%) of patients with treatment-emergent SAEs by primary SOC and PT – Safety population - Study EFC11759 OL period (**cut-off date 13 October 2021**)*

Primary system organ class – Preferred term n (%)	**Placebo/ Teriflunomide (N=52)**	**Teriflunomide/ Teriflunomide (N=100)**	**All (N=152)**
Any class	15 (28.8)	14 (14.0)	29 (19.1)
Infections and infestations	**2 (3.8)**	**2 (2.0)**	**4 (2.6)**
Acute sinusitis	1 (1.9)	0	1 (0.7)
Bronchitis	1 (1.9)	0	1 (0.7)
Coronavirus infection	0	1 (1.0)	1 (0.7)
Encephalitis viral	0	1 (1.0)	1 (0.7)
Pneumonia	0	1 (1.0)	1 (0.7)
Tonsillitis	1 (1.9)	0	1 (0.7)
Upper respiratory tract infection	0	1 (1.0)	1 (0.7)
Blood and lymphatic system disorders	**0**	**1 (1.0)**	**1 (0.7)**
Neutropenia	0	1 (1.0)	1 (0.7)
Psychiatric disorders	**2 (3.8)**	**3 (3.0)**	**5 (3.3)**
Suicide attempt	0	2 (2.0)	2 (1.3)
Adjustment disorder	1 (1.9)	0	1 (0.7)
Depression suicidal	0	1 (1.0)	1 (0.7)
Emotional disorder of childhood	1 (1.9)	0	1 (0.7)
Nervous system disorders	**2 (3.8)**	**6 (6.0)**	**8 (5.3)**
Hypoaesthesia	1 (1.9)	1 (1.0)	2 (1.3)
Uhthoff`s phenomenon	0	2 (2.0)	2 (1.3)
Dizziness	0	1 (1.0)	1 (0.7)
Epilepsy	0	1 (1.0)	1 (0.7)
Headache	1 (1.9)	0	1 (0.7)
Multiple sclerosis	0	1 (1.0)	1 (0.7)
Syncope	0	1 (1.0)	1 (0.7)
Respiratory, thoracic and mediastinal disorders	**2 (3.8)**	**0**	**2 (1.3)**
Asthma	2 (3.8)	0	2 (1.3)
Gastrointestinal disorders	**1 (1.9)**	**3 (3.0)**	**4 (2.6)**
Pancreatitis acute	0	2 (2.0)	2 (1.3)
Constipation	0	1 (1.0)	1 (0.7)
Food poisoning	1 (1.9)	0	1 (0.7)
Pancreatic disorder	0	1 (1.0)	1 (0.7)
Hepatobiliary disorders	**1 (1.9)**	**0**	**1 (0.7)**
Hepatic function abnormal	1 (1.9)	0	1 (0.7)
Skin and subcutaneous tissue disorders	**0**	**1 (1.0)**	**1 (0.7)**
Drug eruption	0	1 (1.0)	1 (0.7)
Pregnancy, puerperium and perinatal conditions	**1 (1.9)**	**0**	**1 (0.7)**
Pregnancy	1 (1.9)	0	1 (0.7)
General disorders and administration site conditions	**2 (3.8)**	**1 (1.0)**	**3 (2.0)**
Asthenia	1 (1.9)	0	1 (0.7)
Gait disturbance	0	1 (1.0)	1 (0.7)
Pyrexia	1 (1.9)	0	1 (0.7)
Investigations	**3 (5.8)**	**2 (2.0)**	**5 (3.3)**
Blood creatine phosphokinase increased	1 (1.9)	2 (2.0)	3 (2.0)
Alanine aminotransferase increased	2 (3.8)	0	2 (1.3)
Injury, poisoning and procedural complications	**0**	**2 (2.0)**	**2 (1.3)**
Overdose	0	1 (1.0)	1 (0.7)
Skin laceration	0	1 (1.0)	1 (0.7)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event, SOC: System organ class PT: Preferred term MedDRA 24.0; n (%) = number and percentage of patients with at least one treatment emergent SAEs
Note: Table sorted by SOC internationally agreed order and by decreasing frequency of PT in overall group

Long-term safety analysis: Treatment-emergent SAEs were reported in 22.4% of teriflunomide-exposed participants from randomisation in the DB period to the end of the OL period, of which 6.8%

participants had SAEs that were considered related, by the Investigator. The frequency was low for each type of events. The most commonly reported SAEs (≥2% by SOC level) were from the Nervous system disorders (5.6%), GI disorders (3.7%), Investigation (3.7%), Infections and infestations (3.1%), Psychiatric disorders (3.1%), and Injury, poisoning and procedural complications (2.5%) SOCs. The related SAEs occurred in less than 1% of participants except ALT increased (1.3%), blood creatinine phosphokinase increased (1.2%), and pancreatitis acute (1.2%).

Adverse events leading to treatment discontinuation

4% of patients in the teriflunomide/ teriflunomide group and 13.5% of patients in the placebo/ teriflunomide group reported TEAE leading to treatment discontinuation (Table 8). In the teriflunomide/ teriflunomide group, two patients reported serious "pancreatitis acute" and one patient reported "amylase increased and lipase increased" (in a context of serious pancreatitis diagnosis). In the placebo/ teriflunomide group, one patient each discontinued due to neuropathy peripheral and pregnancy, and five patients discontinued due to ALT increased.

Table 8 Number (%) of patients with TEAE(s) leading to treatment discontinuation by primary SOC and PT - Study EFC11759 OL period – Safety population

Primary system organ class – Preferred term n (%)	**Placebo/ Teriflunomide (N=52)**	**Teriflunomide/ Teriflunomide (N=100)**	**All (N=152)**
Any class	7 (13.5)	4 (4.0)	11 (7.2)
Nervous system disorders	**1 (1.9)**	**0**	**1 (0.7)**
Neuropathy peripheral	1 (1.9)	0	1 (0.7)
Gastrointestinal disorders	**0**	**3 (3.0)**	**2 (2.0)**
Pancreatitis acute	0	2 (2.0)	2 (1.3)
Abdominal pain	0	1 (1.0)	1 (0.7)
Pregnancy, puerperium and perinatal conditions	**1 (1.9)**	**1 (1.0)**	**2 (1.3)**
Pregnancy	1 (1.9)	1 (1.0)	2 (1.3)
Investigations	**5 (9.6)**	**1 (1.0)**	**6 (3.9)**
Alanine aminotransferase increased	5 (9.6)	0	5 (3.3)
Amylase increased	0	1 (1.0)	1 (0.7)
Lipase increased	0	1 (1.0)	1 (0.7)

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term MedDRA 24.0, n (%) = number and percentage of patients with at least one TEAE leading to treatment discontinuation; Note: Table sorted by SOC internationally agreed order and by decreasing frequency of PT in overall group.

Long-term safety analysis: TEAEs leading to permanent treatment discontinuation were reported in 11.2% of teriflunomide-exposed participants, from randomisation in the DB period to the end of the OL period. The most commonly reported TEAEs (≥2 participants) leading to permanent treatment discontinuation by PT were: ALT increased (3.7%) and pancreatitis acute (2.5%). TEAEs of other PTs that led to treatment discontinuation were reported in one participant each.

Adverse events of special interest

Gastrointestinal disorders – nausea and diarrhoea

GI disorders reported as AESI (i.e. nausea and diarrhoea) were reported less frequently in the teriflunomide/ teriflunomide group than in the placebo/ teriflunomide group (9% vs. 15.4%). Of the 17 patients who experienced nausea or diarrhoea, 16 patients were recovered or recovering up to the last available report. All cases were non-serious and of mild or moderate intensity. No patient discontinued

due to nausea or diarrhoea events. In the placebo/ teriflunomide group, a majority of TEAEs of diarrhoea and nausea occurred between 24 and 36 weeks, and between 4 and 12 weeks, respectively. In the teriflunomide/ teriflunomide group, the incidence for both AESIs was similar for all time intervals. One patient experienced diarrhoea and two patients experienced nausea during the accelerated elimination period, all in the placebo/ teriflunomide group. Vomiting was reported by 1% of patients in the teriflunomide/ teriflunomide group and 3.8% in the placebo/ teriflunomide group (of which 1 patient also experienced nausea).

Long-term safety analysis: The incidence of teriflunomide-exposed participants with nausea or diarrhoea TEAEs from randomisation in the DB period until the end of the OL period was 19.3%.

Hepatic disorders (including liver function parameter)

Liver function

The mean ALT levels increased in both teriflunomide/ teriflunomide and placebo/ teriflunomide groups at the time of entry in the OL period. This increase was transient in the teriflunomide/ teriflunomide group. Then the ALT stabilized in both groups. No clinically relevant difference between groups were observed for the other parameters (ALP, AST, LDH, and GGT).

The proportion of patients with ALT >1x ULN in post-baseline visits was similar in both treatment groups. Other PCSA are depicted in (Table 9).

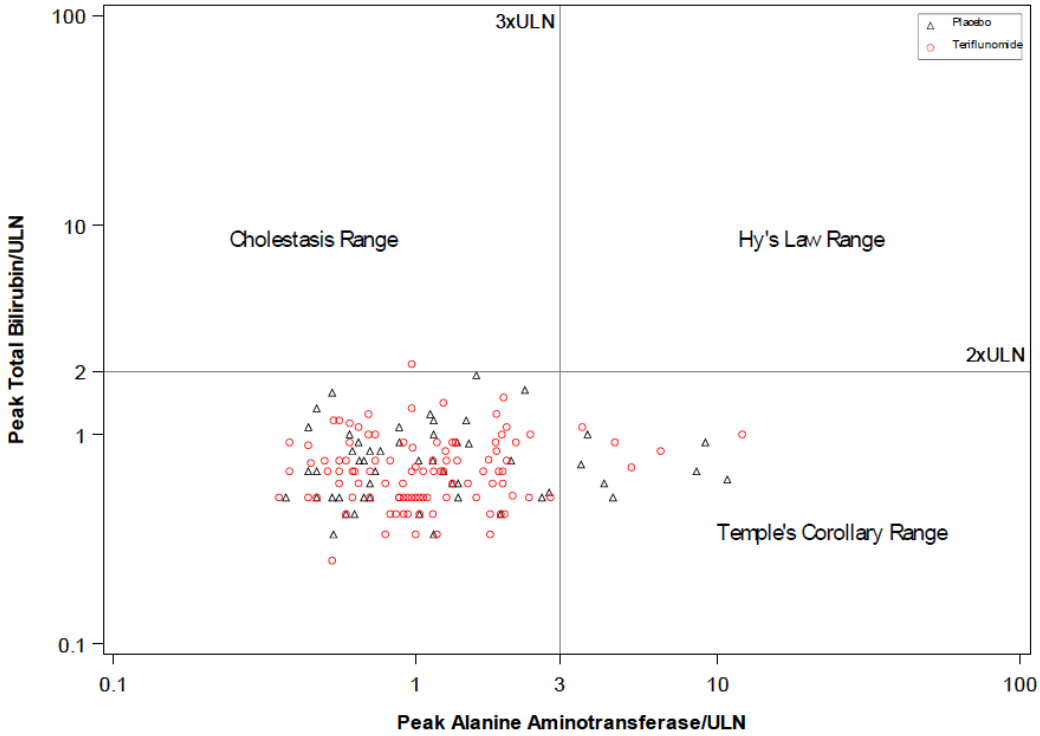
Table 9 Liver function - Number of patients with ALT >1 ULN in post-baseline visits – OL period - Safety population

	Placebo / Teriflunomide (N=52)	**Teriflunomide / Teriflunomide (N=100)**
ALT >20 ULN	0/52	0/100
ALT >10 ULN	1/52 (1.9%)	1/100 (1.0%)
ALT >8 ULN	3/52 (5.8%)	1/100 (1.0%)
ALT >5 ULN	3/52 (5.8%)	3/100 (3.0%)
ALT >3 ULN	7/52 (13.5%)	5/100 (5.0%)
ALT >2 ULN	11/52 (21.2%)	10/100 (10.0%)
ALT >1 ULN	27/52 (51.9%)	48/100 (48.0%)

Note: The number (n) represents the subset of the total number of participants who met the criterion in question at least once during the on-treatment period
The denominator (/N1) for each parameter within a treatment group is the number of participants for the treatment group who had that parameter assessed at post-baseline.

No patient had PCSA of ALT > 20 x ULN level. No patient experienced PCSAs that met the criteria of Hy's Law (the plot of distribution of peak values of ALT versus peak values of total bilirubin for the OL period was similar to the DB period; see Figure 2).

Figure 2 Plot of distribution of peak values of ALT versus peak values of total bilirubin – Safety population - OL period



Hepatic disorders

were less frequently reported in the teriflunomide/ teriflunomide group than in the placebo/ teriflunomide group (6.0% vs. 17.3%). All events were asymptomatic laboratory abnormalities. The most frequently reported treatment-emergent hepatic disorder (≥5% at PT level) was ALT increased (15.4% in the placebo/ teriflunomide group and 3% in the teriflunomide/ teriflunomide group) (Table 10).

Three patients in the placebo/ teriflunomide group had SAEs leading to treatment discontinuation (already been described and assessed during EMEA/H/C/002514/X/0031/G). For one patient, the final diagnosis was *drug induced liver injury due to IMP with a long half-life*.

Nine patients with treatment-emergent hepatic disorders experienced nonserious hepatic laboratory abnormalities (8 ALT increased and 1 transaminase increased): 5 patients in the placebo/ teriflunomide group and 4 patients in the teriflunomide/ teriflunomide group. Two patients discontinued from treatment because of hepatic laboratory abnormality TEAEs. All events were recovered up to the cut-off date of this report except for one event in the teriflunomide/ teriflunomide group (no information available).

The highest percentage of hepatic disorder TEAEs had an initial onset within the first week.

Table 10 Number (%) of patients with treatment-emergent hepatic disorder by primary SOC and PT in the OL period Study EFC11749 – Safety population

Primary system organ class – Preferred term n (%)	**Placebo/ Teriflunomide (N=52)**	**Teriflunomide/ Teriflunomide (N=100)**	**All (N=152)**
Any class	9 (17.3)	6 (6.0)	15 (9.9)
Hepatobiliary disorders	**2 (3.8)**	**2 (2.0)**	**4 (2.6)**
Hepatic function abnormal	2 (3.8)	1 (1.0)	3 (2.0)
Drug-induced liver injury	0	1 (1.0)	1 (0.7)
Hepatic steatosis	0	1 (1.0)	1 (0.7)
Investigations	**8 (15.4)**	**4 (4.0)**	**12 (7.9)**
Alanine aminotransferase increased	8 (15.4)	3 (3.0)	11 (7.2)
Transaminases increased	1 (1.9)	1 (1.0)	2 (1.3)

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term MedDRA 24.0 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 overall group

Long-term safety analysis: The incidence of teriflunomide-exposed participants with hepatic disorder TEAEs from randomisation in the DB period until the end of OL period was 11.8%. The most frequently reported treatment-emergent hepatic disorder (≥5% at PT level) was ALT increased (8.7%).

Pancreatic disorders and laboratory (pancreatic enzyme) parameters

Pancreatic enzymes

No clinically relevant differences between groups were observed for changes over time for mean lipase and amylase values.

Pancreatic disorders

Pancreatic disorders TEAEs were reported in 4 participants (4%) in the teriflunomide/ teriflunomide group and 1 participant (1.9%) in the placebo/ teriflunomide group; overall it concerned 5 patients (3.3% in total) (Table 11).

In the teriflunomide/ teriflunomide group, two patients experienced SAEs of pancreatitis and pancreatitis acute, leading to treatment discontinuation (and AEP). These cases have already been described and assessed during EMEA/H/C/002514/X/0031/G (two patients). Of note, one patient has been described in the interim report as experiencing acute pancreatitis with pancreatic nodules (pseudo-papilloma; coded as pancreatic neoplasm). The coding changed from pancreatic neoplasm to pancreatic disorder (now not recognized by CMQ grouping).

Another participant in the teriflunomide/ teriflunomide group experienced pancreatic disorders TEAEs (pancreatitis acute) during the accelerated elimination period after discontinuation from treatment due to nonserious amylase and lipase increased.

In the teriflunomide/ teriflunomide group, two Participants experienced nonserious increase in both amylase and lipase ≥2 × ULN and in the placebo/ teriflunomide group, one participant experienced nonserious lipase increase ≥ 2 × ULN.

All cases were recovered up to the cut-off date of this report.

No additional case of pancreatic disorders has been reported from the first interims report (safety data cut-off 12 September 2020) until the final data cut-off date 13 October 2021.

Table 11 Number (%) of patients with treatment-emergent pancreatic disorder by primary SOC and PT in the OL period Study EFC11749 – Safety population

Primary system organ class – Preferred term n (%)	**Placebo/ Teriflunomide (N=52)**	**Teriflunomide/ Teriflunomide (N=100)**	**All (N=152)**
Any class	1 (1.9)	4 (4.0)	5 (3.3)
Gastrointestinal disorders	**0**	**3 (3.0)**	**3 (2.0)**
Pancreatitis acute	0	3 (3.0)	3 (2.0)
Investigations	**1 (1.9)**	**2 (2.0)**	**3 (2.0)**
Lipase increased	1 (1.9)	2 (2.0)	3 (2.0)
Amylase increased	0	2 (2.0)	2 (1.3)

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term MedDRA 24.0 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 overall group

Long-term safety analysis: Overall, 8 (5%) of teriflunomide-exposed participants experienced pancreatic disorders from randomisation in the DB period until the end of OL period. Five participants (3.1%) experienced pancreatitis acute, two participants of whom were of severe intensity and two participants experienced pancreatitis of moderate intensity.

Bone marrow disorders

Bone marrow disorders were more frequently reported in the teriflunomide/ teriflunomide group than in the placebo/ teriflunomide groups (9% and 3.8%) during the OL period. The most commonly reported TEAEs derived from the investigations SOC and were white blood cell count decreased and monocyte count decreased (5% and 3% in the teriflunomide/ teriflunomide group). All cases were of mild or moderate intensity. One case of neutropenia was considered serious (Patient with a known pre-existing cyclic neutropenia) and no case led to treatment discontinuation.

Among the 11 patients who experienced bone marrow disorder TEAEs, one patient was not recovered from the event as of the cut-off date of this report.

The majority of TEAEs related to bone marrow disorders had an initial onset between 4 weeks and 12 weeks and 24 to 36 weeks of treatment.

For further details of abnormalities in haematology parameters see laboratory parameter section.

Long-term safety analysis: Overall, 15 (9.3%) of teriflunomide-exposed participants experienced bone marrow disorders TEAEs from randomisation in the DB period until the end of OL period, all mild or moderate in severity. The most commonly reported treatment-emergent bone marrow disorders (≥2% at PT level) were white blood cell count decreased (6.2%), neutrophil count decrease (3.1%) and monocyte count decrease (2.5%).

Infections and infestations

The incidence of patients with infections and infestations TEAEs was similar between the teriflunomide/ teriflunomide (57%) and the placebo/ teriflunomide group (51.9%). Most of the infections and infestations TEAEs were balanced between the two groups. The most frequently reported (≥5% in any treatment groups) TEAEs were: upper respiratory tract infections (teriflunomide/ teriflunomide and the placebo/ teriflunomide: 22% and 13.5%), nasopharyngitis (20% and 15.4%), rhinitis (6% and 3.8%), influenza (5% and 9.6%), gastroenteritis (5% and 3.8%), urinary tract infection (5% and 3.8%), respiratory tract infection (5% and 1.9%), tonsillitis (4% and 5.8%), acute sinusitis (none and 5.8%),

and bronchitis (0.0% and 5.8%). Overall, 4 patients experienced infections and infestations SAEs (already reported and assessed during EMEA/H/C/002514/X/0031/G), i.e. central nervous system infection (a similar infection of "viral encephalitis" was reported in the past medical history for this participant), upper respiratory tract infection and lung infection, bronchitis and tonsillitis, acute sinusitis and food poisoning. None of the TEAEs led to treatment discontinuation.

Long-term safety analysis: Overall, 110 (68.3%) of teriflunomide-exposed participants experienced bone marrow disorders TEAEs from randomisation in the DB period until the end of OL period, most of them of mild or moderate severity. The most commonly reported TEAEs (≥ 5% at PT level) were nasopharyngitis (26.7%), upper respiratory tract infection (23%), influenza (11.8%), tonsillitis (6.8%), pharyngitis (6.2%), rhinitis (6.2%), gastroenteritis (5.6%), urinary tract infection (5.6%), bronchitis (5%) and sinusitis (5%). Four events were of severe intensity (PT: upper respiratory tract infection, pilonidal cyst, pneumonia, and pulmonary tuberculosis).

Covid-19 related adverse events

Two participants (2%) experienced mild to moderate coronavirus infection in the teriflunomide/ teriflunomide group that did not lead to treatment discontinuation. One was a SAE, which was not considered related to the treatment by the Investigator. Both participants recovered from the events.

Hypersensitivity and severe skin reactions, malignancies and cardiac arrhythmias: were not reported in EFC11759.

Hypertension

Hypertension was only reported in the teriflunomide/ teriflunomide group (3%) (reference is made to EMEA/H/C/002514/X/0031/G).

Long-term safety analysis: The incidence of hypertension TEAEs in teriflunomide-exposed participants from randomisation in the DB period to the end of the OL period was 1.9%. All events were mild or moderate in intensity.

Pulmonary disorders

The proportion of patients who experienced pulmonary disorder TEAEs was similar between the teriflunomide/ teriflunomide and the placebo/ teriflunomide group (53% and 46.2%).

The most frequently (≥5% in any treatment groups) reported TEAEs by PT were upper respiratory tract infections (22.0% in the teriflunomide/ teriflunomide group and 13.5% in the placebo/ teriflunomide group), nasopharyngitis (20% and 15.4%), oropharyngeal pain (7% and 3.8%), rhinitis (6% and 3.8%), influenza (5% and 9.6%), respiratory tract infection (5% and 1.9%), tonsillitis (4.0% and 5.8%), acute sinusitis (none and 5.8%), asthma (none and 5.8%), bronchitis (0% and 5.8%).

Overall, 5 patients (one in the teriflunomide/ teriflunomide group and 4 in the placebo/ teriflunomide group) experienced SAEs already described and assessed during EMEA/H/C/002514/X/0031/G: lung infection and upper respiratory tract infection, acute sinusitis, bronchitis and tonsillitis, and two participants had asthma. No case of interstitial lung disorders was reported.

Long-term safety analysis: The incidence of pulmonary disorder TEAEs for teriflunomide-exposed participants from randomisation in the DB period to the end of the OL period was 63.4%. The most frequently (≥5%) reported TEAEs were: nasopharyngitis (26.7%), upper respiratory tract infection

(23%), influenza (11.8%), oropharyngeal pain (9.3%), tonsillitis (6.8%), pharyngitis (6.2%), rhinitis (6.2%), bronchitis (5%), cough (5%), and sinusitis (5%). Most of the events were of mild to moderate in severity, except for 3 cases of pneumonia, upper respiratory tract infection, and pulmonary tuberculosis of severe intensity.

Embolic and thrombotic events: were not reported during the OL period.

Haemorrhage

During the OL period, two (2%) patients in the teriflunomide/ teriflunomide group and one (1.9%) patient in the placebo/ teriflunomide group reported treatment-emergent, nonserious haemorrhage events (epistaxis and contusion). The events were of mild or moderate intensity.

Peripheral neuropathy

Three (3%) participants in the teriflunomide/ teriflunomide group and 2 (3.8%) participants in the placebo/ teriflunomide group experienced treatment-emergent peripheral neuropathy during the OL period. All events were non-serious including neuralgia of mild intensity and sensory loss of mild intensity in the teriflunomide/ teriflunomide group; neuralgia of mild intensity and neuropathy peripheral of moderate intensity in the placebo/ teriflunomide group. One patient discontinued treatment because of peripheral neuropathy. In this patient, electromyogram findings were consistent with polyneuropathic involvement characterized by mild loss of axons, predominantly in the lower extremities and sensory fibers. The event was rated related by the investigator. All cases have already been assessed during EMEA/H/C/002514/X/0031/G.

Long-term safety analysis: The incidence of peripheral neuropathy TEAEs for teriflunomide-exposed participants from randomisation in the DB period to the end of the OL period was 3.1%. A total of 4 teriflunomide-exposed participants experienced peripheral neuropathy disorders of mild or moderate intensity and 1 participant of severe intensity (PT: neuralgia). All events were nonserious. One event of peripheral neuropathy led to treatment discontinuation.

Convulsions

One event of epilepsy was reported in the teriflunomide/ teriflunomide group (not reported previously). The event was serious and moderate in intensity and led to hospitalisation. No medical history of epilepsy was reported. The event did not lead to treatment discontinuation and the patient recovered. It was not rated related to treatment by the investigator.

Long-term safety analysis: The incidence of convulsion TEAEs for teriflunomide-exposed participants from randomisation in the DB period to the end of the OL period was 1.9%, including two events of epilepsy of moderate and severe intensity and seizure of mild intensity.

Alopecia/ hair loss

During the OL period, alopecia/hair loss was less frequently reported in the teriflunomide/ teriflunomide group (10%) than in the placebo/ teriflunomide group (17.3%). All events were nonserious and did not lead to treatment discontinuation. All events were of mild or moderate intensity except one severe. Among the 19 participants, 13 participants recovered, 5 participants had not recovered and 1 participant was recovering at the end of the study.

Long-term safety analysis: The overall incidence of teriflunomide-exposed participants with alopecia TEAEs from the randomisation in the DB period to the end of the OL period was 23.6%. All events were mild or moderate in intensity except for one event that was of severe intensity. All the events were nonserious and did not lead to treatment discontinuation. During the DB period, one participant experienced a nonserious adverse event of alopecia areata of severe intensity. Corrective treatment was given. Participant wanted to continue IMP despite the event and finally decided to stop it during the OL period. The IMP was permanently discontinued due to non-recovery of the TEAE.

Psychiatric disorders

Psychiatric disorders were more frequently reported for patients from the placebo/ teriflunomide group as compared to those from the teriflunomide/ teriflunomide group (19.2% vs. 11%; Table 12). The most frequently reported TEAE was depression. Five participants experienced treatment-emergent SAEs of psychiatric disorders, including two SAEs of suicide. None of the events led to treatment discontinuation. Psychiatric disorders TEAEs were most frequently reported between from 12 to 24 weeks.

Table 12 Number (%) of patients with treatment-emergent psychiatric disorder by primary SOC and PT in the OL period – Safety population

Primary system organ class – Preferred term n (%)	**Placebo/ Teriflunomide (N=52)**	**Teriflunomide/ Teriflunomide (N=100)**	**All (N=152)**
Any class	10 (19.2)	11 (11.0)	21 (13.8)
Psychiatric disorders	**9 (17.3)**	**11 (11.0)**	**20 (13.2)**
Depression	4 (7.7)	2 (2.0)	6 (3.9)
Anxiety	1 (1.9)	2 (2.0)	3 (2.0)
Insomnia	1 (1.9)	1 (1.0)	2 (1.3)
Suicide attempt	0	2 (2.0)	2 (1.3)
Adjustment disorder	1 (1.9)	0	1 (0.7)
Affective disorder	0	1 (1.0)	1 (0.7)
Anxiety disorder	0	1 (1.0)	1 (0.7)
Attention deficit/hyperactivity disorder	1 (1.9)	0	1 (0.7)
Depression suicidal	0	1 (1.0)	1 (0.7)
Depressive symptom	0	1 (1.0)	1 (0.7)
Emotional disorder	1 (1.9)	0	1 (0.7)
Emotional disorder of childhood	1 (1.9)	0	1 (0.7)
Mood disorder due to a general medical condition	0	1 (1.0)	1 (0.7)
Obsessive-compulsive personality disorder	0	1 (1.0)	1 (0.7)
Poor quality sleep	0	1 (1.0)	1 (0.7)
Sleep disorder	1 (1.9)	0	1 (0.7)
Stress	0	1 (1.0)	1 (0.7)
Nervous system disorders	**1 (1.9)**	**0**	**1 (0.7)**
Somnolence	1 (1.9)	0	1 (0.7)
Injury, poisoning and procedural complications	**0**	**2 (2.0)**	**2 (1.3)**
Intentional overdose	0	2 (2.0)	2 (1.3)

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term MedDRA 24.0; 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 overall group.

2 SAEs of suicide (both occurred in the teriflunomide/ teriflunomide group) have been provided.

Long-term safety analysis: The overall incidence of psychiatric disorder TEAEs in teriflunomide-exposed participants from randomisation in the DB period to the end of the OL period was 21.1%. The most frequently reported (≥2% at PT level) TEAEs were depression (5.0%) and anxiety (4.3%). All events were of mild or moderate intensity except 3 events which were of severe intensity. One severe event (affective disorder) led to treatment discontinuation. Five participants experienced treatment-emergent SAEs of psychiatric disorders.

Pregnancies

One participant in the teriflunomide/ teriflunomide group became pregnant during the OL period (already reported during EMEA/H/C/002514/X/0031/G). No structural defect or functional abnormalities were reported to date for the newborn, who was breastfed.

In addition, one participant in the placebo/ teriflunomide group became pregnant during the OL period which was considered serious, and had a non-serious adverse event of vaginal bacterial infection of mild intensity. She underwent termination of pregnancy and recovered from the vaginal bacterial infection. The IMP was permanently discontinued due to the pregnancy.

Other significant adverse events – adverse events of pre-specified monitoring

Overdose

A total of 12 patients, 10 (10%) 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). None was associated with clinical symptoms. In one patient in the teriflunomide/ teriflunomide group, an SAE was reported related to suicide attempt in a patient who took a total of 18 tablets of teriflunomide leading to hospitalisation (see EMEA/H/C/002514/X/0031/G).

Long-term safety analysis: 9.3% of teriflunomide-exposed participants reported intake of 2 tablets in < 24 hours coded as accidental overdose, from the randomisation in the DB to the end of the OL period.

Laboratory findings

Haematology

Laboratory values over time

There was a decrease in mean platelet count in the placebo/ teriflunomide group from baseline when the patients entered the OL period and up to Week 8 thereafter, and no change for the teriflunomide/ teriflunomide group (plots can be derived from the CSR).

No clinically relevant difference between groups were observed for changes over time of haematocrit, erythrocyte count, prothrombin time and activated partial thromboplastin time during the on-treatment period.

A slight decrease in leukocyte counts, neutrophils and lymphocytes from baseline was observed in the teriflunomide/ teriflunomide group compared with placebo/ teriflunomide during the first 20 weeks in the DB period stabilising thereafter. No apparent differences between groups were evident after entering the OL period.

Individual participant changes and clinically abnormalities

Red blood cell, platelets and coagulation:

Overall, the proportion of participants with abnormalities in haemoglobin, erythrocytes, and platelet count was low and similar between groups from the randomisation up to the end of the OL period.

The proportion of PCSA values were higher in the teriflunomide/ teriflunomide group than in the placebo/ teriflunomide group for haematocrit (high abnormal values) and haemoglobin (haemoglobin decrease from baseline ≥20 g/L) during the on-treatment period.

The proportion of participants with erythrocytes value adults ≥6 $\times$ 10^{12}/L was higher in the teriflunomide/ teriflunomide group compared with the placebo/ teriflunomide group, while the overall incidence was low.

White blood cells

The proportion of participants with PCSAs of high leukocyte values was lower in the teriflunomide/ teriflunomide group than in the placebo/ teriflunomide group and was similar between groups of low leukocyte values during the on-treatment period. The proportion of participants with high neutrophils and eosinophils were lower in the teriflunomide/ teriflunomide group than in the placebo/ teriflunomide group. The proportion of participants with basophils value adults: >0.1 × 109/L was greater in the teriflunomide/ teriflunomide group compared with the placebo/teriflunomide group. The proportion of participants with abnormalities in lymphocytes and monocytes were similar between groups.

Three participants (2.0%) had leukopenia; 2 participants (1.3%) had neutropenia; and 1 participant (0.7%) had leukocytosis. Of these TEAEs, 1 event of neutropenia was considered serious and related to the treatment by the Investigator which was reported in the teriflunomide/ teriflunomide group.

Clinical chemistry

The mean phosphorus levels were stable.

No clinically relevant difference between groups were observed for electrolytes and metabolic function parameters. No participant reported any TEAEs related to abnormalities in electrolyte parameters including hypokalaemia, that were considered serious or leading to treatment discontinuation. Two (2.0%) participants in the teriflunomide/ teriflunomide and 1 participant in the placebo/ teriflunomide group reported a SAE of blood creatine phosphokinase increased.

Liver function (see AESI "hepatic disorders)

Renal function

During the OL period, mean uric acid in the placebo/ teriflunomide group dropped steadily through the first 12 weeks, and stabilised afterwards. No changes were observed in the teriflunomide/ teriflunomide group. No clinically relevant difference between groups were observed for the other parameters. One participant in the placebo/ teriflunomide group had serum creatinine >2 × baseline. No other clinically relevant abnormalities in renal function parameters were reported as TEAEs.

Regarding individual patient changes, the proportion of patients with renal function PCSAs for creatinine, glomerular filtration rate and urea nitrogen was similar between groups. The incidence of patients with creatinine clearance values indicative of mild renal impairment (adults: ≥60 - <90 mL/min) was lower in the teriflunomide/ teriflunomide group compared with placebo/ teriflunomide (14.6% and 25%).

The proportion of patients with creatinine value adults: ≥30% change from baseline was higher in the teriflunomide/ teriflunomide group compared with the placebo/ teriflunomide (14.6% and 8.3%).

Thyroid stimulating hormone

Mean TSH values were stable during the OL period.

Vital signs and other observations related to safety

Weight

From Week 24 in the DB period, body weight increased in both groups. Mean change (SD) from baseline to last on-treatment value was 3.6 (7.6) kg in the teriflunomide/ teriflunomide group and 1.3 (6.6) in the placebo/ teriflunomide group.

The proportion of participants with the on-treatment PCSA of ≥5% increase or ≥5% decrease in weight from baseline was similar between the teriflunomide/ teriflunomide group and the placebo/ teriflunomide group (19% versus 11.5% and 48% versus 53.8%, respectively).

Vital signs

The mean changes from baseline in SBP and DBP in standing and supine position were similar between treatment groups in the OL period and there were no clinically relevant changes observed from baseline across visits. The slight increase over time for SBP and DBP in supine position observed during the DB period became stable when entering the OL period.

Long-term safety analysis: Mean changes from baseline in DBP and SBP in standing and supine position were similar between treatment groups and there were no clinically relevant changes observed from baseline across visits. The same was observed for heart rate. The proportion of participants with on-treatment PCSAs in increased supine DBP and SBP was similar between the teriflunomide/ teriflunomide and the placebo/ teriflunomide group (57% vs. 57.7% and 39% vs. 25%, respectively). The proportion of participants with on-treatment PCSAs in decreased supine DBP and SBP was similar between the teriflunomide/ teriflunomide and the placebo/ teriflunomide group (9% vs. 13.5% and 2% vs. 7.7%, respectively). There were no PCSA values reported for heart rate.

Electrocardiogram

No clinically relevant changes were observed for ECG parameters during the OL period.

A few patients had PCSAs for ECG parameters. The proportion of patients with an increase in QTc interval was similar between groups during the OL period.

Tanner stage

A majority (more than 90%) of patients in both arms was Tanner stage >I (pubertal) at DB baseline. During the DB period, both treatment groups showed pubertal development (in patients not yet fully pubertal) 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 literature[1]. However, this is based on a rather small number of paediatric patients with less than Tanner Stage IV or V at baseline, who 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. No clinically relevant differences between groups were observed.

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

Safety in special populations

The incidences of any TEAEs, SAEs, TEAEs leading to treatment discontinuation, and AESIs for patients on placebo/ teriflunomide and teriflunomide/ teriflunomide were analysed based on:

- Intrinsic factors: Age group, Gender group (Male or Female), Race, Pubertal status, Pubertal status at disease onset, Weight group, MS subtypes, Number of relapses experienced overall, High disease activity (defined as 2 or more relapses in the past year, and 1 or more Gadolinium (Gd) enhancing lesions on baseline MRI).

  Some differences overall in both treatment groups were observed, in particular for infections and hepatic disorders regarding age, race, and weight. For example, regarding age (<13 years vs. ≥13 years) TEAEs from the following SOCs were reported more frequently in the younger versus the older paediatric subjects: infections and infestations (mainly seasonal infections), nervous system disorders (mainly headache), respiratory, and thoracic and mediastinal disorders (oropharyngeal pain). Moreover, it appears from the data that more male patients experienced TEAEs in line with hepatic disorders as compared to female patients. All pancreatic disorders were recorded in female patients. Interpretation of these differences is clearly hampered by the small number of patients in specific subgroups (e.g., patients <13 years, subgroups by race). In summary, no specific increase was noted in the teriflunomide group or teriflunomide/ teriflunomide group as compared to the placebo group or placebo/ teriflunomide group. The teriflunomide safety profile was generally consistent across subgroups.

- Extrinsic factors, i.e. region and previous MS treatment. The safety profile of teriflunomide was generally consistent across subgroups during the study.

Immunogenicity results

During the DB and the OL periods, a slight decrease in mean values of IgA, IgG, and IgM, was observed up to the end of the periods in the patients treated with teriflunomide.

Postmarketing experience

Reference is made to EMEA/H/C/002514/X/0031/G (postmarketing experience up to the cut-off date 17 January 2020 in paediatric patients up to 17 years of age).

An additional interval analysis in the Sanofi Global Pharmacovigilance Database has been performed to include data from 18 January 2020 to 22 July 2022. This search was performed to identify all cases from postmarketing sources (solicited and unsolicited cases) reported with teriflunomide as a suspect drug in patients up to 17 years of age. Cumulatively, a total of 43 unique case reports were retrieved in patients ranging from 10 to 17 years of age. 29 reports from solicited sources (non-interventional postmarketing studies) and 14 reports from unsolicited spontaneous sources. Among the 43 case reports, there were 10 cases reported as serious, and 33 reported as non-serious; the gender was female in 30 cases, male for 11 cases, and unknown in 2 cases. Among the 43 case reports, 41 were new cases and the remaining 2 were cases included in the initial submission, which received follow-up information during this interval.

8 of the 41 new cases were not related to an AE, and the remaining 33 cases included reporting of Aes. The Aes were related to MS in 6 cases and not related to MS in 27 cases. The 6 cases with Aes related to the underlying disease of MS (reported as Aes) included evocative signs such paraesthesia, gait disturbance, or MS relapse. Among the 27 cases with Aes not related to MS, there were 22 non-

serious cases and 5 serious cases. Based on individual case assessment, no likely or possible case was identified, among the 22 non-serious cases. All cases were unassessable due to limited information regarding medical history, concomitant medication or clinical course of adverse events.

Among the 5 SAEs not related to MS, 1 possible case was identified (neutropenia). The remaining cases were unassessable due to a lack of clinical background information.

Among the 41 new case reports, 15 cases reported off-label use. All of the off-label reported prescriptions were related to the effective treatment of MS in a young population with indication for oral treatment with teriflunomide, per neurologist prescription. Additionally, there were 3 new case reports for children below the age of 10 years. The reported age was 9 years in 2 cases and 8 years in 1 case. All cases were reported as non-serious. Among these, 1 case (Id: 2015SA009873) reported Aes (Affect lability, Diarrhoea, Gastroenteritis viral, Vomiting). The case was unassessable due to a lack of clinical background information.

7.3. Discussion

Study EFC11759 (TERIKIDS) was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study (duration 96 weeks), followed by an open-label (OL) period that could last up to 192 weeks from randomisation to EOT. The OL period focusses on the long-term safety and treatment effects in the placebo/ teriflunomide and in the teriflunomide/ teriflunomide group, for which results are based on the database lock 13 October 2021.

In the OL period, 132 of 152 patients (87%) received the 14 mg dose. Cumulatively, open-label data for teriflunomide 14 mg of more than 96 weeks are available for 83 (62.9%) paediatric patients. The highest cumulative duration of OL treatment with teriflunomide 14 mg was ~3.5 years for 12 patients.

TEAEs reported in the OL period of study EFC11759, their frequency, severity, and relation to treatment were found along expectations for teriflunomide in the double-blind period. No additional concerns or worsening of safety issues reported during the DB period have been identified in the OL period.

84.2% of patients reported at least 1 TEAE during the OL period. Most of the TEAEs in both treatment groups were mild or moderate in severity, with < 14% of TEAEs rated as severe. No deaths were reported. 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 common TEAEs (≥10% of teriflunomide exposed participants) from randomisation in the DB period to the end of the OL period were nasopharyngitis (26.7%), alopecia (23%), upper respiratory tract infection (23%), headache (19.9%), abdominal pain (11.2%), influenza (11.8%), diarrhoea (12.4%), and dizziness (9.9%).

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. 14% in the teriflunomide/ teriflunomide group. The most frequently reported treatment-emergent SAEs (≥2% of patients in either group) were blood creatine phosphokinase increased, suicide attempt, Uhthoff's phenomenon, pancreatitis acute, asthma, and ALT increased (1.9% and 2%, 0% and 2%, 0% and 2%, 0% and 2%, 3.8% and 0%, and 3.8% and 0% in the placebo/ teriflunomide group and teriflunomide/ teriflunomide group, respectively). SAEs that were rated related to teriflunomide were pancreatitis acute, two SAEs of blood CPK increased, headache, two SAEs of ALT increased, acute sinusitis, neutropenia, upper respiratory tract infection, and intentional overdose.

Discontinuations due to TEAEs in the OL period 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 [9.6%]).

Adverse events of special interest up to the final data cut-off date did not significantly change in incidence, severity, relationship to treatment, and discontinuations as compared to those reported in the open-label interim analysis during EMEA/H/C/002514/X/0031/G for GI disorders, hepatic disorders, bone marrow disorders, infections, hypertension, pulmonary disorders, peripheral neuropathy, alopecia.

For psychiatric disorders, two SAEs of suicidal attempt occurred in the teriflunomide/ teriflunomide group, one of which was already reported as "intentional overdose" in the interim report of the OL period. Both were not rated related to teriflunomide.

Pancreatic effects are an important identified risk with teriflunomide treatment based on nonclinical data, clinical adult studies, and from post-marketing reports. Mean amylase and lipase values did not show noticeable differences between treatment groups during the DB and OL period.

During EMEA/H/C/002514/X/0031/G, TEAEs related to pancreatic effects included isolated and asymptomatic pancreatic enzyme increases, that were found increased in paediatric patients treated with teriflunomide compared to placebo (3.7% vs. 1.8%). However, pancreatitis (acute) was reported in 5 teriflunomide-treated patients (2 during the DB and 3 during the OL treatment) confirmed by imaging data. No additional case of pancreatic disorders has been reported up to the final data cut-off date 13 October 2021.

No AESI related to hypersensitivity and severe skin reactions, malignancies and cardiac arrhythmias were not reported during the DB and OL period in EFC11759.

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). An additional TEAE of "epilepsy" was reported in the teriflunomide/ teriflunomide group during the OL period, which was a SAE of moderate severity and rated not related to teriflunomide, although, the narrative did not indicate an alternative explanation for the event.

Teriflunomide can cause serious birth defects when administered during pregnancy and is thus contraindicated (SmPC section 4.3). However, a total of 3 patients treated with teriflunomide became pregnant during the study. Two of them underwent termination of a pregnancy procedure 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 an enhanced pharmacovigilance process.

Accidental overdose and/or overdose was defined in the protocol as at least twice the intended dose (i.e. 2 tablets) within 24 hours. No increase in events was observed up to the data cut-off date in the OL period and all of them were asymptomatic except for a single TEAE that was related to attempted suicide (sensory disorders and tingling sensations for < 2 hours was reported).

No new concerns derived from *laboratory parameters* with regard to haematology, clinical chemistry, liver, pancreas and renal function.

There were no relevant changes or new findings in *vital signs* with regard to weight changes, blood pressure, heart rate, QTc interval or any other quantitative or qualitative ECG parameter changes.

As indicated during EMEA/H/C/002514/X/0031/G, special attention needs to be paid to TEAEs affecting sexual maturation, cognition, endocrine function and other aspects of development. 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). However, the small number of patients with Tanner Stages < IV and V at baseline having had a full course of 96-week DB treatment hampers interpretation of sexual maturation with teriflunomide treatment. Based on the final open-label data, patients in both treatment groups progressed to higher Tanner stages without relevant differences.

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. 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).

Postmarketing data for approximately 10 years of teriflunomide treatment have been presented and comprise off-label use data (prior to the approval of Aubagio in paediatrics) and 41 new cases reported after approval of the paediatric indication (EMEA/H/C/002514/X/0031/G). Of these, 5 SAEs were reported and only a single SAE was rated related (neutropenia). Interpretation of nonserious or serious AEs reported in the remaining cases is hampered by the lack of (medical) background information.

8. Risk management plan

The MAH submitted an updated RMP version 8.0 with this application. The (main) proposed RMP changes were the following:

8.1. Safety Specification

Identified and potential risks

In Part II Module SVII.3.1 the section on exposure to teriflunomide in the paediatric population was updated to include patients from the double-blind as well as the open-label treatment phases of Study EFC11759/TERIKIDS, which is acknowledged.

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

In Part II Module SVII.3.1 in the tables describing the identified risks as well as the potential risks the data lock point for analysis of cases from the Sanofi PhV database was updated to 12 September 2022, which is considered acceptable. No new relevant data is described as a consequence of the new date of analysis. With regard to Study EFC11759/TERIKIDS, only general remarks concerning the open-label extension phase were added such as "overall, teriflunomide was well-tolerated with a manageable safety profile, consistent with the experience observed in the double-blind period" and "no additional unexpected events were identified in the open-label period (for the identified risk infections and acute pancreatitis and the potential risks teratogenicity and serious opportunistic infections, including PML). Taking into account that no new safety issues or worsening of existing ones has been identified since

the most recent open-label interim report of study EFC11759, this is agreed to. However, it is noted that the section on the potential risk teratogenicity regarding data from the Sanofi Pharmacovigilance database was completely revised. In response to the RSI, the MAH explained that the information on the potential risk of teratogenicity was updated to reflect the information reported in the MAH Database with the updated DLP and the overall text was reviewed to improve the readability.

Missing information

Following completion of the open-label period of Study EFC11759/TERIKIDS, the following information was added to the section on missing information with regard to the safety concern long-term safety in paediatric patients:

> In children, the double-blind part and the open-label part of EFC11759/TERIKIDS with a maximum treatment duration of 8 years has been completed. No additional unexpected events were identified in the open-label period. Overall, teriflunomide was well-tolerated with a manageable safety profile, consistent with the experience observed in the double-blind period.

This wording is generally agreed. Since the open-label period of Study EFC11759/TERIKIDS has been completed and data on the long-term safety in children is now available, the missing information "long-term safety in paediatric patients" was removed from the summary of safety concerns in the RMP. Please also refer to section 9.2 below.

8.2. Summary of the safety concerns

In response to the RSI, the MAH submitted a revised RMP version 8.1 with the following summary of safety concerns:

Table SVIII.1: Summary of the Safety Concerns

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

PML: Progressive Multifocal Leukoencephalopathy.

The open-label period of Study EFC11759/TERIKIDS has been completed and data on the long-term safety in children is now available and no longer considered missing information. Study EFC11759/TERIKIDS was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study (duration 96 weeks), followed by an open-label period that could last up to 192 weeks from randomisation to EOT. Cumulatively, open-label data for teriflunomide 14 mg of more than 96 weeks are available for 83 (62.9%) paediatric patients. The highest cumulative duration of open-label treatment with teriflunomide 14 mg was approximately 3.5 years for 12 patients. As discussed in Section 7 (Clinical safety aspects) above, TEAEs reported in the open-label period of study EFC11759, including frequency and severity, were found along expectations for teriflunomide in the double-blind

period. No additional concerns or worsening of safety issues were reported during the open-label phase. An increased risk of pancreatic disorders in children as compared to adults had been identified during interim reports of the study (reports used in support of the line extension for Aubagio to include paediatric patients with RRMS). However, this risk is considered sufficiently minimised by extensive wording in the product information and no further information on this risk could be retrieved from the open-label period of Study EFC11759/TERIKIDS.

As requested in the RSI, the missing information "long-term safety in paediatric patients" was removed from the summary of safety concerns and all relevant Parts of the RMP. The MAH confirmed that "long-term safety in paediatric patients" will be retained in the PSUR summary of safety concerns in order to ensure regular analysis of all available data regarding this topic, so that potential changes in the safety profile, which might become visible when post-marketing exposure will increase, can be identified in a timely manner.

Considering the data in the safety specification, the safety concerns listed above are appropriate.

8.3. Pharmacovigilance plan

Study EFC11759 TERIKIDS was removed from the list of additional pharmacovigilance activities following the completion of the open-label period of the study (Parts III.2 and III.3), which is acceptable.

Overall conclusions on the PhV Plan

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

Routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

8.4. Risk minimisation measures

Reference to Study EFC11759 TERIKIDS has been removed from RMP Part V.3 Summary of risk minimization measures following completion of the open-label period of the study, which is acceptable.

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

8.5. Elements for a public summary of the RMP

The elements for a public summary of the RMP require revision following the conclusion of the procedure:

- Removal of "long-term safety in paeditaric patients" as missing information

8.6. Annexes

In Annex 2 Study EFC11759 was removed from Table 1 describing planned and ongoing studies and added to Table 2 describing completed studies, which is endorsed.

In Annex 3 Study EFC11759 was removed from Part C describing previously agreed protocols for ongoing studies, which is acceptable.

8.7. Overall conclusion on the RMP

☒ The changes to the RMP are acceptable.

The MAH should take the following points into consideration at the next RMP update:

The following conclusion on study EFC11759 with regard to the risk of teratogenicity in section SVII.3.1 is not appropriate and is to be deleted:

"Overall, teriflunomide was well tolerated with a manageable safety profile, consistent with the experience observed in the double blind period."

The statement on the relatedness between teriflunomide and congenital malformation should be revised as follows:

"Therefore, a total of 1274 cases of drug exposure via parent were retrieved. Of which, 30 pregnancies (considering a total exposure of 621 859 patient years as of DLP 12 Sep 2022) involved possible congenital malformations, for which causal relatedness ~~was not~~ **could neither be** established **nor denied**:"

9. Request for supplementary information

9.1. Major objections

Clinical aspects

None.

RMP aspects

None.

9.2. Other concerns

Clinical aspects

None.

RMP aspects

1.) It is noted that the section on the potential risk teratogenicity in Part II Module SVII.3.1 regarding data from the Sanofi Pharmacovigilance database was completely revised. The MAH is asked to explain why this revision was performed and to justify all changes in this section.

2.) The MAH should remove "long-term safety in paediatric patients" as missing information from the summary of safety concerns as well as all other Parts of the RMP.

3.) The MAH is asked to confirm that "long-term safety in paediatric patients" will be retained in the summary of safety concerns in PSURs in order to ensure regular analysis of all available data regarding this topic, so that potential changes in the safety profile, which might become visible when post-marketing exposure will increase, can be identified in a timely manner.

4.) In RMP Part III.2 information was added about an ongoing optional additional extension period of Study EFC11759 with teriflunomide offered to participants when they completed the study, to provide treatment until they are 18 years old and/or can switch to teriflunomide commercial product. However, it is not clear why this optional additional extension phase is needed, as teriflunomide is already approved in children 10 years and older in the EU. The MAH is asked to elaborate on this and to explain if submission of further data from this optional additional extension period of the study is planned, for example in PSURs. If this is not the case, it is not considered necessary to include the information about this optional extension in the RMP.

5.) In Annex 2 Study EFC11759 was added to Table 2 describing completed studies. This is generally endorsed, however, the new entry in Table 2 should not be restricted to the open-label period but to the complete study. The wording should be changed as follows:

> EFC11759: ~~Open label period of a~~ **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. […]

6.) The MAH is reminded to provide the complete RMP, including annexes, in track-changes-mode in all further steps of this procedure and any future procedures.

10. Assessment of the responses to the request for supplementary information

10.1. Major objections

N/A

10.2. Other concerns

Clinical aspects

N/A

RMP aspects

Question 1
It is noted that the section on the potential risk teratogenicity in Part II Module SVII.3.1 regarding data from the Sanofi Pharmacovigilance database was completely revised. The MAH is asked to explain why this revision was performed and to justify all changes in this section.

MAH's response
The previous RMP v7.3 had a DLP of 12 Sep 2020, all the tables of risks have been reviewed in the

RMP v 8.0 with an updated DLP of 12 Sep 2022. The Part II Module SVII.3.1 of RMP v8.0 regarding the potential risk of teratogenicity was updated to reflect the information reported in the MAH Database. The overall text was reviewed to improved readability and to update the potential risk of teratogenicity.

Assessment of the MAH's response
The information on the potential risk teratogenicity in RMP section SVII.3.1 was updated to reflect the information included in the MAH's database with the updated DLP and to improve the readability of the section. This is endorsed. However, the following conclusion on study EFC11759 with regard to the risk of teratogenicity is not appropriate and is to be deleted with the next RMP update (page 73 in tracked version):

~~"Overall, teriflunomide was well-tolerated with a manageable safety profile, consistent with the experience observed in the double-blind period."~~

The statement on the relatedness between teriflunomide and congenital malformation (page 73 of tracked version) should be revised as follows with the next RMP update:

"Therefore, a total of 1274 cases of drug exposure via parent were retrieved. Of which, 30 pregnancies (considering a total exposure of 621 859 patient years as of DLP 12-Sep-2022) involved possible congenital malformations, for which causal relatedness ~~was not~~ **could neither be** established **nor denied**:"

No detailed assessment of individual case reports was provided, however, it is doubted that a causal relationship between teriflunomide exposure during pregnancy and the congenital malformations reported can be excluded in the majority of the 30 cases.

The RMP should be revised accordingly, with the next RMP update.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 2

The MAH should remove "long-term safety in paediatric patients" as missing information from the summary of safety concerns as well as all other Parts of the RMP

MAH's response
The MAH acknowledges the Agency's comment and has modified the RMP accordingly.

Assessment of the MAH's response
The missing information 'long-term safety in paediatric patients' has been removed from the summary of safety concerns and all relevant sections of the RMP.

Issue resolved.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 3
The MAH is asked to confirm that "long-term safety in paediatric patients" will be retained in the summary of safety concerns in PSURs in order to ensure regular analysis of all available data regarding this topic, so that potential changes in the safety profile, which might become visible when post-marketing exposure will increase, can be identified in a timely manner.

MAH's response
The MAH confirms that long-term safety in paediatric patients will be retained in the summary of safety concerns in PSURs

Assessment of the MAH's response
The MAH confirmed to retain long-term safety in paediatric patients in the PSUR summary of safety concerns.

Issue resolved.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 4
In RMP Part III.2 information was added about an ongoing optional additional extension period of Study EFC11759 with teriflunomide offered to participants when they completed the study, to provide treatment until they are 18 years old and/or can switch to teriflunomide commercial product. However, it is not clear why this optional additional extension phase is needed, as teriflunomide is already approved in children 10 years and older in the EU. The MAH is asked to elaborate on this and to explain if submission of further data from this optional additional extension period of the study is planned, for example in PSURs. If this is not the case, it is not considered necessary to include the information about this optional extension in the RMP.

MAH's response
In the RMP Part III, in the paragraph informing on the removal of the completed pediatric clinical study (EFC11759) from the PV plan (both double-blind, and open-label periods), information related to an ongoing optional additional extension period was included for transparency reasons. The primary aim of this extension is not the collection of safety data but rather to provide access to the drug product to pediatric patients in countries outside of Europe, where it is not marketed yet.

The MAH acknowledges that this information related to the extension period of Study EFC11759 may convey some confusion; therefore the MAH proposes to remove it from the RMP. Cases reports related to patients enrolled in this optional extension phase will be reviewed as part of the routine PV surveillance process, as included in the PSUR.

Assessment of the MAH's response
Reference to the ongoing additional extension period of Study EFC11759 was removed from RMP section III.2. The MAH explained that this optional extension is aimed at providing access to

terflunomide for paediatric patients outside Europe, where it is not yet marketed. A deletion in the EU RMP is therefore considered justified. However, all safety-related information from this extension study will be reported as part of routine PhV monitoring.

Issue resolved.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 5
In Annex 2 Study EFC11759 was added to Table 2 describing completed studies. This is generally endorsed, however, the new entry in Table 2 should not be restricted to the open-label period but to the complete study. The wording should be changed as follows:

> EFC11759: ~~Open label period of a~~ **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. […]

MAH's response
The MAH agrees with the Agency's comment and has updated the Table 2 of Annex 2 accordingly.

Assessment of the MAH's response

Annex 2 has been revised as requested.

Issue resolved.

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 6
The MAH is reminded to provide the complete RMP, including annexes, in track-changes-mode in all further steps of this procedure and any future procedures.

MAH's response
The MAH acknowledges the request from the Agency and hereby provides the complete RMP, including annexes, in track-changes mode taking into account updates following the PRAC preliminary assessment report received on 28-Feb-2023.

Assessment of the MAH's response

The MAH provided the complete RMP in track-changes-mode, including annexes, as requested.

Issue resolved.

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance