22 April 2022
EMA/CHMP/260961/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

TECFIDERA

International non-proprietary name: dimethyl fumarate

Procedure No. EMEA/H/C/002601/II/0073

Note

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

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Table of contents

1. List of abbreviations 4

2. Background information on the procedure 5

2.1. Type II variation 5
2.2. Steps taken for the assessment of the product 6
2.1. Steps taken for the re-examination procedure 7

3. Scientific discussion 8

3.1. Introduction 8
3.1.1. Problem statement 8
3.1.2. About the product 10
3.1.3. The development programme/compliance with CHMP guidance/scientific advice 11
3.1.4. General comments on compliance with GLP, GCP 12
3.2. Non-clinical aspects 12
3.2.1. Introduction 12
3.2.2. Toxicology 12
3.2.3. Ecotoxicity/environmental risk assessment 13
3.2.4. Discussion on non-clinical aspects 14
3.2.5. Conclusion on the non-clinical aspects 16
3.3. Clinical aspects 16
3.3.1. Introduction 16
3.3.2. Pharmacokinetics 17
3.3.3. Pharmacodynamics 18
3.3.4. PK/PD modelling 19
3.3.5. Discussion on clinical pharmacology 19
3.3.6. Conclusions on clinical pharmacology 20
3.4. Clinical efficacy 20
3.4.1. Dose response study 20
3.4.2. Main study 20
3.4.3. Discussion on clinical efficacy 53
3.4.4. Conclusions on the clinical efficacy 58
3.5. Clinical safety 59
3.5.1. Discussion on clinical safety 75
3.5.2. Conclusions on clinical safety 81
3.5.3. PSUR cycle 81
3.6. Risk management plan 81
3.7. Update of the Product information 87
3.7.1. User consultation 87

4. Benefit-Risk Balance 87

4.1. Therapeutic Context 87
4.1.1. Disease or condition 87
4.1.2. Available therapies and unmet medical need 88
4.1.3. Main clinical studies 88
4.2. Favourable effects 88

4.3. Uncertainties and limitations about favourable effects 90
4.4. Unfavourable effects 90
4.5. Uncertainties and limitations about unfavourable effects 91
4.6. Effects Table 93
4.7. Benefit-risk assessment and discussion 95
4.7.1. Importance of favourable and unfavourable effects 95
4.7.2. Balance of benefits and risks 96
4.7.3. Additional considerations on the benefit-risk balance 97
4.8. Conclusions 97

5. Recommendations 97

6. Re-examination of the CHMP opinion of 27 January 2022 99
6.1. Detailed grounds for re-examination submitted by the MAH 99
6.2. Discussion and overall conclusion on grounds for re-examination 100

7. Recommendations following re-examination 108

8. EPAR changes 110

Appendix 110

1. List of abbreviations

ADEM	Acute Disseminated Encephalomyelitis
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
ARR	Annual Relapse Rate
AST	Aspartate Aminotransferase
$AUC_{0\text{-}inf}$	Area Under the Concentration-time curve from time 0 to infinity
$AUC_{0\text{-}12hr}$	Area Under the Concentration-time curve from time 0 to the concentration at hour 12
BID	twice a day
BL	baseline
BMI	Body Mass Index
BVMT-R	Brief Visuospatial Memory Test-Revised
CI(s)	confidence interval(s)
CHMP	Committee for Medicinal Products for Human Use
CNS	Central Nervous System
DB	Double-Blind
DBP	Diastolic Blood Pressure
DILI	Drug-Induced Liver Injury
DMF	Dimethyl Fumarate
DMT	Disease Modifying Therapy
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
ERA	Environmental Risk Assessment
GA	Glatiramer Acetate
GCP	Good Clinical Practices
Gd	Gadolinium
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GLP	Good Laboratory Practices
HCP	Health Care Professional
HR	Hazard Ratio
IPMSSG	International Paediatric Multiple Sclerosis Study Group
IFN β	Interferon Beta
IM	Intramuscular(ly)
ITT	Intent-To-Treat
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MMF	Monomethyl Fumarate
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
Nrf2	Nuclear factor (erythroid 2)-related factor 2
OR	Odds Ratio
PedsQL	Paediatric Quality of Life Inventory

PIP	Paediatric Investigational Plan
PK	pharmacokinetic(s)
PD	Postnatal Day; Pharmacodynamic(s)
PDCO	Paediatric Committee
PML	Progressive Multifocal Encephalopathy
PRAC	Pharmacovigilance Risk Assessment Committee
PSURs	Periodic Safety Update Reports
PT	Preferred Term
RMP	Risk Management Plan
RRMS	Relapsing-Remitting Multiple Sclerosis
SAEs	Serious Adverse Events
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard deviation
SDMT	Symbol Digit Modalities Test
SE	Standard error
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TEAEs	Treatment-Emergent Adverse Events
t_{max}	time to reach maximum observed plasma concentration
ULN	Upper Limit of Normal
WBC	White Blood Cells

2. Background information on the procedure

2.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Biogen Netherlands B.V. submitted to the European Medicines Agency on 2 June 2021 an application for a variation.

The following variation was requested:

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

Extension of indication to include treatment of relapsing remitting multiple sclerosis (RRMS) in paediatrics patients from 10 years of age and over; as a consequence sections 4.1, 4.2, 4.8, 5.1 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance.

Version 11.4 of the RMP has also been submitted to update the RMP (parts I-IV) based on Study 109MS306 data supporting the request for a paediatric indication and the Applicant took the opportunity to update the RMP with the most updated data (Part II modules SIV, SV and SVII).

The MAH is requesting an extension of the market protection of one additional year in line with the guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in accordance with Article 14(11) of Regulation (EC) No 726/2004.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0177/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0177/2020 was completed.

The PDCO issued an opinion on compliance for the PIP P/0177/2020.

Information relating to orphan market exclusivity

Similarity

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

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) No 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

2.2. Steps taken for the assessment of the product

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

Rapporteur: Martina Weise Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	2 June 2021
Start of procedure:	19 June 2021
CHMP Rapporteur Assessment Report	13 August 2021
PRAC Rapporteur Assessment Report	13 August 2021
PRAC Outcome	2 September 2021
CHMP members comments	6 September 2021
Updated CHMP Rapporteur Assessment Report	9 September 2021
Request for supplementary information (RSI)	16 September 2021
CHMP Rapporteur Assessment Report	16 November 2021
PRAC Rapporteur Assessment Report	16 November 2021
PRAC Outcome	02 December 2021
Request for supplementary information (RSI)	16 December 2021

Timetable	Actual dates
PRAC Rapporteur Assessment Report	30 December 2021
CHMP Rapporteur Assessment Report	11 January 2022
PRAC Outcome	13 January 2022
CHMP opinion	27 January 2022
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Tecfidera in comparison with existing therapies (Appendix 1)	27 January 2022

2.1. Steps taken for the re-examination procedure

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

Rapporteur: Daniela Philadelphy Co-Rapporteur: N/A

Evaluators: Christian Gartner

Timetable	Actual dates
Written notice to the EMA to request a re-examination of Tecfidera CHMP opinion of 27 January 2022	09 February 2022
Rapporteur's appointment	23 March 2022
Detailed grounds for the Re-examination (Appendix 2 of Final Opinion) submitted on	08 March 2022
Start of procedure:	09 March 2022
Rapporteur assessment report	06 April 2022
The <name of expert group> meeting considered the grounds for re-examination (Annex 3)	n/a
Rapporteur's updated assessment report circulated on:	n/a
An Oral explanation on the detailed grounds for re-examination took place on:	n/a
CHMP opinion:	22 April 2022

3. Scientific discussion

3.1. Introduction

3.1.1. Problem statement

Disease or condition

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

State the claimed the therapeutic indication

The therapeutic indication has been revised to exclude patients aged 10 to <13 years following the Applicant's responses to the request for supplementary information:

"*Tecfidera is indicated for the treatment of adult* ***and paediatric patients aged 13 years and older*** *with relapsing remitting multiple sclerosis (RRMS).*"

Epidemiology

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

Aetiology and pathogenesis

While the exact aetiology of MS remains unknown, it is generally assumed that MS is mediated by an immune-mediated inflammatory process that is triggered by environmental factors and superimposed on a genetic predisposition. The major contributors to this process are macrophages and microglia from the innate immune system, and T and B lymphocytes from the adaptive immune system. From the peripheral immune system, autoreactive T-helper cells are primed and stimulated to infiltrate the CNS where they target myelin antigens. Inflammation of the white and grey matter tissues in the CNS due to focal immune cell infiltration and release of cytokines are the incipient cause of tissue damage in MS not only to the myelin sheath but also to the underlying axons. This process happens over time and results in repeated attacks. Demyelination and axonal damage impairs or interrupts nerve transmission, giving rise to clinical signs and symptoms. B and T cells, monocytes, natural killer cells and dendritic

cells are all involved in any stage of MS. Neuropathology studies have found that the patterns of inflammation are very similar between relapsing and progressive MS.

Clinical presentation, diagnosis

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

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

Paediatric MS accounts for approximately 3% to 5% of MS cases[1][2][3][4][5][6][7][8] and the incidence increases with age (the majority of cases occur at or after the age of 10 years). The high number of relapses in the first years of the disease and the high frequency of paediatric patients with the relapsing-remitting

[1] Ghezzi A, Deplano V, Faroni J, Grasso MG, Liguori M, Marrosu G, et al. Multiple sclerosis in childhood: clinical features of 149 cases. Mult Scler. 1997;3(1):43-6.
[2] Boiko A, Vorobeychik G, Paty D, Devonshire V, Sadonick D, UBC MS Clinic Neurologists. Early onset multiple sclerosis: a longitudinal study. Neurology. 2002;59(7):1006-10.
[3] Chitnis T, Glanz B, Jaffin S, Healy B. Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. Mult Scler. 2009;15(5):627-31.
[4] Harding KE, Liang K, Cossburn MD, Ingram G, Hirst CL, Pickersgill TP, et al. Long-term outcome of paediatric-onset multiple sclerosis: a population-based study. J Neurol Neurosurg Psychiatry. 2013;84(2):141-7.
[5] Krupp LB, Tardieu M, Amato MP, Banwell B, Chitnis T, Dale RC, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immunemediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler. 2013;19(10):1261-7.
[6] Ness JM, Chabas D, Sadovnick AD, Pohl D, Banwell B, Weinstock-Guttman B. Clinical features of children and adolescents with multiple sclerosis. Neurology. 2007;68(Suppl 2):S37-45.
[7] Banwell B, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M. Multiple sclerosis in children: clinical diagnosis, therapeutic strategies, and future directions. Lancet Neurol. 2007;6(10):887-902.
[8] Waldman A, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M, Banwell B. Multiple sclerosis in children: an update on clinical diagnosis, therapeutic strategies, and research. Lancet Neurol. 2014;13(9):936-48.

course suggest that the inflammatory process is more pronounced in children with MS compared to adults[9][10][11].

In paediatric patients with MS, current consensus is to initiate pharmacological treatment shortly after diagnosis, even though the efficacy and safety of most therapies available for adults have not been formally demonstrated in children[12][13].

Management

As of the date of this document, only fingolimod and teriflunomide are explicitly approved in the EU for use in children 10 years of age and over. While fingolimod is restricted to patients with highly active relapsing remitting MS, teriflunomide is indicated for relapsing remitting MS without restriction.

Limited efficacy and safety data in the paediatric population have been collected for the use of conventional injectable therapies in adolescents ≥12 years of age. Three interferon-beta (IFN β) agents (two IFN β 1a and one IFN β 1b) and glatiramer acetate (GA) are allowed to be used in paediatric patients with MS according to the dosage and administration sections of the EU summary of product characteristics (SmPC).

3.1.2. About the product

Tecfidera (synonyms: dimethyl fumarate [DMF], BG00012) received approval of a European Union (EU) Marketing Authorisation Application (MAA) from the European Commission (centralised procedure) on 30 January 2014 for the treatment of adult patients with relapsing remitting multiple sclerosis. Tecfidera is distributed in 120 mg and 240 mg hard gelatine capsules. The starting dose is 120 mg two times a day orally. After 7 days, the Tecfidera dose is proposed to be 240 mg twice daily (BID) (480 mg DMF per day). Temporary dose reduction to 120 mg twice a day is foreseen and may reduce the occurrence of flushing and gastrointestinal (GI) side effects. Within 1 month, the recommended dose of 240 mg twice a day orally should be resumed.

In paediatric patients (13 years of age and above), the recommended dose is the same as in adults.

The mechanism by which DMF exerts therapeutic effects in MS is not fully understood. However, together with its active metabolite monomethyl fumarate (MMF), it acts to promote both anti-inflammatory and neuroprotective responses in peripheral and CNS resident cells and tissues. Non-clinical studies indicate that DMF pharmacodynamic (PD) responses appear to be mediated, at least in part, through stimulation of Nuclear factor (erythroid 2)-related factor 2 (Nrf2) transcriptional activity in the response to oxidative stress. DMF has been shown to up regulate Nrf2-dependent antioxidant genes in patients (e.g. NAD(P)H dehydrogenase, quinone 1; [NQO1]).

[9] Jancic J, Nikolic B, Ivancevic N, Djuric V, Zaletel I, Stevanovic D, et al. Multiple sclerosis in pediatrics: current concepts and treatment options. Neurol Ther. 2016;5(2):131-43.
[10] Benson LA, Healy BC, Gorman MP, Baruch NF, Gholipour T, Musallam A, et al. Elevated relapse rates in pediatric compared to adult MS persist for at least 6 years. Mult Scler Relat Disord. 2014;3(2):186-93.
[11] Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in pediatric onset compared with adult-onset multiple sclerosis. Arch Neurol. 2009;66(1):54-9.
[12] Waubant E, Banwell B, Wassmer E, Sormani MP, Amato MP, Hintzen R, et al. Clinical trials of disease-modifying agents in pediatric MS. Opportunities, challenges, and recommendations from the IPMSSG. Neurology 2019;92(22):e1-12.
[13] Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D, et al. ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. Mult Scler. 2018;24(2):96-120.

3.1.3. The development programme/compliance with CHMP guidance/scientific advice

The PIP for DMF (Tecfidera) was first approved by the EMA on 18 February 2011 (EMEA-000832-PIP01-10) for the indication targeted "*treatment of relapsing remitting forms of multiple sclerosis*". In the original PIP, a 24-week, double-blind (DB), placebo-controlled study (part 1), followed by a 24 week safety extension in which all patients will receive BG00012 (part 2) was chosen by the Applicant to demonstrate efficacy whilst minimizing the required number of patients due to expected recruitment difficulties. The proposed primary endpoint was "*the total number of new Gd-enhancing lesions over 4 MRI scans*". However, the Paediatric Committee (PDCO) requested modifications by the Applicant, amongst others, that the comparator should be an active control rather than placebo. Hereupon, the Applicant provided two new proposals with regard to the clinical study design.

However, neither of two study design options proposed by the Applicant were deemed acceptable by PDCO. A placebo-controlled design was rejected because a (albeit rather weak) standard of care existed in the form of the IFN β. With regard to the second proposal, an active-controlled, pre-post study design there were concerns regarding adequate demonstration of efficacy. The usefulness of a total number of 6 Gd- MRIs to be performed within a period of 7-8 months which would be needed to assess the primary endpoint was also felt to be ethically debatable.

Therefore, PDCO requested that the study to be conducted is a two year open-label, randomised, parallel-group study of DMF vs. IFN β 1a, with a primary endpoint of proportion of patients free of new/newly enlarging T2 MRI lesions at 24 months, and secondary efficacy endpoints being the proportion of patients free of new/newly enlarging T2 MRI lesions at 12 months, the proportion of patients free of new MRI activity (free of Gd-enhanced and free of new/newly enlarging T2 MRI lesions) at 12 and 24 months, time to first relapse, and proportion of patients free of relapse up to 24 months. Further safety follow-up of up to 5 years is to be foreseen.

Essential requests for modification of the agreed PIP were applied by the MAH and subsequently the PIP has been modified in agreement with the PDCO:

- Modification 01, issued 26 February 2013, decision No. P/0027/2013
- Modification 02, issued 10 July 2015, decision No. P/0144/2015
- Modification 03, issued 20 May 2016 decision No. P/0132/2016
- Modification 04, issued 30 June 2017 decision No. P/0167/2017
- Modification 05 issued 15 May 2020 decision No. P/0177/2020

PIP modifications 01 and 05 consisted of administrative changes to the timelines specified within the PIP. Modification 02 consisted of changes to the inclusion criteria in regard to the washout period required for treatments taken prior to the start of the study. Modification 03 consisted of separating Part 2 of the study, the follow-up extension study, from Part 1 of the study. Modification 04 was to remove the PK element of the PIP, as this aspect of the PIP was fulfilled separately within Study 109MS202. Further, the number of requested children aged 10 to less than 13 years was reduced from at least 20 to at least 10 children due to recruitment difficulties. The requirement was removed that a proportion of patients must be pre-pubertal at screening. Instead, the Applicant was requested to establish pubertal status of the patients at the time of the initiation of symptoms (retrospectively) and to perform an additional, separate efficacy analysis based on pubertal status at disease initiation. The 4-weeks washout period for GA and IFN β was removed. Instead, stratification of randomization of subjects by whether or not they had received therapy with IFN ß-1a or GA in the 4 weeks prior to study entry was added.

Two nonclinical studies of DMF in juvenile rats have been conducted to support the clinical studies and the paediatric indication. The MAH committed to include these studies in the application for a paediatric

indication (EMEA/H/C/2601/II/0061/G). Study P00012-14-02: An Oral (Gavage) Toxicity Study of Dimethyl Fumarate in Juvenile Rats, which was required as part of the PIP, and Study P00012-12-02: Toxicity Study of BG00012 when Administered Orally in Juvenile Male Rats (see Module 2.4 Nonclinical Overview).

The commercial formulation of Tecfidera, as used in adults, is proposed for dosing paediatric patients, and this formulation was used for the paediatric clinical studies. The PIP included the option of opening the capsules to facilitate the administration of the micro tablets on food as an alternative means of dosing for the paediatric participants. This option was not needed during the clinical studies; therefore, no changes to the adult commercial formulation were proposed for paediatric patients.

3.1.4. General comments on compliance with GLP, GCP

The two juvenile toxicity studies in rats, which had been previously evaluated by the CHMP and are discussed in this type II variation with regard to the proposed extension of the clinical indication to paediatric patients, complied with good laboratory practice (GLP) regulations (study nos. P00012-14-02 and P00012-12-02). It should be noted, however, that the bone densitometry performed in study no. P00012-14-02 was excluded from GLP compliance and only met general scientific standards.

The clinical trial was performed in accordance with good clinical practice (GCP) as claimed by the Applicant. It is stated that the study also meets the requirements of the Declaration of Helsinki, and/or, where applicable, the European Directive 2001/20 in relation to GCP in the conduct of clinical trials on medicinal products for human use and Directive 2005/28 on GCP for investigational medicinal products for human use. No serious breaches of GCP occurred during the study.

3.2. Non-clinical aspects

3.2.1. Introduction

In order to support the proposed extension of the indication of DMF to paediatric RRMS patients aged 10 years and above, the MAH had earlier conducted two toxicity studies in juvenile rats, which had been evaluated by the CHMP in type II variation procedures in 2016 (study no. P00012-1402; EMEA/H/C/2601/II/25) and 2019 (study no. P00012-1202; EMEA/H/C/2601/II/61/G), respectively. At the time of the evaluation of both investigations, CHMP had concluded that their outcome would have to be reconsidered upon extension of the clinical indication to paediatric patients. The essential findings of both studies are briefly reported below (please see assessment reports of the abovementioned variation procedures for further details).

3.2.2. Toxicology

Juvenile toxicity studies

Juvenile toxicity study of DMF in rats (study no. P00012-14-02)

DMF was administered once daily by oral gavage at doses of 5, 15, 50 and 140 mg/kg/day in vehicle (0.8 % hydroxypropylmethylcellulose) from postnatal day (PND) 28 to PND 93 to male and female juvenile rats (n=35/sex/group). One subset of animals of 15 males and females per group was sacrificed on PND 94, whereas the second subset of 20 males and females per group continued the study in an 8 week recovery period and were evaluated for reproductive capacity. The plasma exposure was

assessed by means of determination of the principal active metabolite MMF at the end of the treatment period (PND 93; 13 weeks of age) and, hence, concerned fully mature and adult, but not juvenile animals.

No effects of DMF on development, behaviour or reproductive performance of the F0 juvenile rats were noted. In addition, no effects on the male or female reproductive organs and no impact on the F1 offspring up to PND 4 were detected (litter size, gender proportion and postnatal survival/growth).

Prominent toxicities were observed in the non-glandular stomach and in the kidneys of the F0 generation as previously observed in other multiple dose toxicity studies in adult animals submitted for MAA of DMF.

Significant changes in bone densitometry in the vertebrae and femur (reduced bone mineral density and content) was evident in F0 juvenile male rats administered the 140 mg/kg/day DMF high dose, which was attributed to the diminished food consumption of these animals resulting in malnutrition due to the established non-glandular stomach toxicity of DMF.

Toxicity study of DMF in juvenile male rats (study no. P00012-12-02)

In view of the decreased weights of testes and epididymis, degeneration of seminiferous tubular epithelium and hypospermia in the epididymis in male dogs treated with 25 mg/kg/day in the chronic toxicity study (study no. P00012-05-05) as well as Leydig cell hyperplasia and adenoma at doses ≥100 mg/kg/day DMF in the 2 year carcinogenicity study in rats (study no. P00012-04-11), higher oral gavage doses of 50, 140 and 375 mg/kg/day DMF had been investigated in juvenile male rats from PND 28 to 92 as part of a PIP requirement of *"Tecfidera"* (EMEA/247744/2011). The dosing phase was followed by an 8 week recovery period. The dose-related plasma MMF exposure was confirmed after first DMF administration on PND 28 and at the end of the treatment phase on PND 90-92 without consistent evidence for accumulation.

The DMF-related adverse effects on food consumption/body weight, serum clinical chemistry and urinalysis parameters as well as stomach and kidneys mirrored those observed in male and female rats of the same age in the initial juvenile toxicity study (study no. P00012-14-02) as well as in adult rats. Moreover, no histopathological changes of male reproductive organs were found (testes, epididymis, pituitary, prostate or seminal vesicles). The observed delay of preputial separation in the juvenile animals was attributed to their reduced body weight/food consumption consequent to the adverse impact of DMF on the non-glandular stomach rather than a hormonal effect. The collected blood samples were therefore not analysed for inhibin-B, Luteinizing hormone, Follicle-stimulating hormone and testosterone as originally planned.

3.2.3. Ecotoxicity/environmental risk assessment

The MAH provided an updated Environmental Risk Assessment (ERA) based on the European guideline EMEA/CHMP/SWP/4447/00 and corresponding EMA Q&A document. The original ERA was submitted with the initial MAA. Due to the proposed extension of the target patient group to children from 10 years of age and older, the MAH updated the PECsurfacewater calculation and consequently the corresponding risk characterisations. No risks to the environment have been identified by the MAH due to the suggested more extensive clinical use.

For PEC refinement, the MAH adjusted the Fpen by consulting worst case prevalence data of RRMS from the MS International Federation (https://www.atlasofms.org/map/global/epidemiology/number-of-people-with-ms). Worst case prevalence for MS has been found in Germany with 303 cases per 100,000 inhabitants of which 85 % account for RRMS. The adjusted Fpen of 0.00258 is considered plausible.

According to the adjusted Fpen, the MAH calculated a refined PECsurfacewater of 0.93 µg/l. The refined PECsurfacewater exceeds the trigger of 0.1 µg/l for a Phase II Tier A assessment, which had already been conducted in the original ERA. Therefore, only recalculation of risk quotients was necessary for the update of the Phase II Tier A assessment.

Considering the updated, refined PECsurfacewater the RQs for surfacewater and microorganisms have shown to be <1. Therefore, no risk to the environment is to be expected from the proposed extension of the patient group to children from 10 years of age and older.

3.2.4. Discussion on non-clinical aspects

Two toxicity studies in juvenile rats with oral DMF administration up to 140 mg/kg/day (study no. P00012-14-02) or up to 375 mg/kg/day (study no. P00012-12-02) from PND 28 to PND92/93 had been earlier submitted by the MAH that were evaluated by the CHMP in 2016 and 2019, respectively (EMEA/H/C/2601/II/25; EMEA/H/C/2601/II/61/G). The age of the study animals corresponded to human children of approximately 3 years and older (see reviews by Kimmel CA and Buelke-Sam J. In Patty's Toxicology. J. Wiley & Sons, 5th Ed., Vol. I, Chap. 3, 2001; Kim NN *et al.*, *Int J Toxicol*. 2017; 36(4): 325-339). At the time of assessment of these juvenile toxicity studies, DMF therapy was restricted to adult RRMS patients. The CHMP had therefore concluded that the study outcomes would be evaluated anew upon extension of the MA to a paediatric study population.

In both juvenile toxicity studies, systemic DMF-related toxicities predominantly comprised dose-dependently impaired food consumption/body weight due to the impact of DMF on the non-glandular stomach. The adverse findings in the non-glandular stomach had been previously accepted by the CHMP as rodent-specific, because this organ lacks a clear anatomical counterpart in other species including humans.

In addition, nephrotoxicity was evident in in the juvenile animals, which had been earlier identified in other species (adult rats, mice, dogs and monkeys) and correlates with the common proteinuria known from DMF therapy of adult RRMS patients. Given the same dose regimen for paediatric RRMS patients as in adults and the lack of any safety margin with respect to human exposure at the recommended therapeutic dose, the warning for routine monitoring of renal function in section 4.4 of the current SmPC of *"Tecfidera"* is applicable for both adult and paediatric patient populations.

The second juvenile toxicity was performed to fulfil a PIP requirement, because diminished weights of testes and epididymides, degeneration of seminiferous tubular epithelia and hypospermia had been previously found in male dogs treated with 25 mg/kg/day DMF in the chronic toxicity study (study no. P00012-05-05) and Leydig cell hyperplasia and adenoma were unveiled at doses ≥100 mg/kg/day DMF in the 2 year carcinogenicity study in rats (study no. P00012-04-11). Consequently, higher DMF dosages up to 375 mg/kg/day were tested only in male juvenile rats-(study no. P00012-12-02). Still, no histological impairments of male reproductive organs were apparent. Nevertheless, the preputial separation was delayed in the juvenile rats, which was ascribed to their lower body weight/food consumption.

A direct hormonal effect of DMF seems unlikely given the normal fertility of adult male rats up to the same highest dose of 375 mg/kg/day and the lack of testis findings in the chronic toxicity study in monkeys (study nos. P00012-04-03 and P00012-05-08 assessed during MAA of *Tecfidera"*). Similar to the attenuated preputial separation in juvenile rats, the changes in testes and epididymis of male dogs of the chronic toxicity study had been therefore related to the reduced body weight due to lower food consumption of the study animals, considering additionally that dogs had required extra dietary supplementation. The testis findings in dogs developed at a 3-fold safety margin with respect to the recommended therapeutic administration in humans.

Changes in testicular Leydig cells were neither detected in both juvenile toxicity studies, nor in any other repeated-dose toxicity study of DMF. Nonetheless, increased incidences of Leydig cell adenoma in association with degenerations of seminiferous tubules in the testes and hypospermia in the epididymides were also determined in the 2 year carcinogenicity study of diroximel fumarate (DRF), a related fumarate ester of the same Applicant whose MAA is currently reviewed by the CHMP (EMEA/H/C/5437; *"Vumerity"*). As the pharmacological activity of both, DMF and DRF, is conveyed via MMF, a causal relationship of the testis changes with DMF treatment cannot be excluded. Accordingly, the testicular Leydig cell adenoma observed with DMF have been included in section 5.3 of the SmPC.

Moreover, significantly lower bone mineral density and content in vertebrae and femur was evident in juvenile male rats treated with the 140 mg/kg/day DMF high dose in study no. P00012-14-02. No bone effects were discovered in juvenile male rats at higher DMF doses up to 375 mg/kg/day (study no. P00012-12-02), which did not include bone densitometry scans. However, decreased bone mineralisation was similarly observed in both genders of juvenile rats at ≥150 mg/kg/day DRF administered from PND 25 to 63 (study no. AT-5108-38; EMEA/H/C/5437; *"Vumerity"*). The MAH attributed the reduced bone mineralisation to the potential malnutrition of the study animals due to the lower food consumption, although the decreased bone mass and density and/or bone geometry at the mid- or distal diaphysis in juvenile rats administered the 600 mg/kg/day DRF high dose indicated a direct effect on bone growth.

It should be noted that physeal dysplasia due to hypertrophy and disorganization of chondrocytes were detected in the proximal and distal femur as well as proximal tibia during necropsy in 5 out of 6 monkeys of the 91 days subchronic toxicity study of DRF at the 250 mg/kg/day high dose level (study no. AT 5108-14; EMEA/H/C/5437; *"Vumerity"*), which did not recover in one female. The physeal dysplasia developed dose- and time-dependently, because it was neither observed in monkeys during short-term administration of higher DRF doses, nor after chronic treatment of lower dosages. Furthermore, an age-dependency seems possible given that affected monkeys in the 91 days subchronic toxicity study were obviously of pre-pubertal age and consequently more susceptible for skeletal deficiencies than the adult and mature species of the DMF and DRF toxicology programs which lacked any bone defects.

Albeit adequate nutrition is certainly important for normal ossification (Cappon GD *et al. Birth Defects Res B Dev Reprod Toxicol*. 2005; 74(5): 424-30; Nitzsche D, *Regul Toxicol Pharmacol*. 2017; 90: 95-103), it appears questionable, if the defective bone mineralisation in juvenile rats and the physeal dysplasia in pre-pubertal monkeys can be simply disentangled.

In the course of the MA evaluation of DRF, an anti-angiogenic activity of DMF and DRF was hypothesized, but could not be confirmed for the main active metabolite MMF (García-Caballero M *et al. J Invest Dermatol*. 2011). Instead, another publication rather indicated a pro-angiogenic effect of the MMF effector Nrf2 (Li L *et al. Sci Rep*. 2016; 6: 37338).

At present, a direct role of Nrf2 in the regulation of bone homeostasis seems therefore more likely considering recently published literature data on the role of Nrf2 in bone metabolism. Increased osteoclast counts and differentiation, bone resorption and impaired formation of osteoblasts were determined at higher magnitude in juvenile compared to adult Nrf2-deficient mice (Rana T *et al. Free Radic Biol Med*. 2012; 53(12): 2298-307; Hyeon S *et al. Free Radic Biol Med*. 2013; 65: 789-799.; Kim *et al. Bone Res*. 2014; 2: 14033; Sun YX *et al. J Biomed Sci*. 2015; 22: 101). Conversely, the stimulation of Nrf2 signalling by DMF interfered with osteoclast formation *in vitro* and *in vivo*, induced osteocyte specific gene expression and reduced bone loss in a mouse model of osteoporosis (Yamaguchi *et al. J Cell Mol Med*. 2018; 22(2): 1138-1147; Sánchez-de-Diego *et al. Redox Biol*. 2021; 40: 101845). Still, comparative analyses of wildtype, homozygous and heterozygous Keap 1 mutant mice point towards the importance of balanced Nrf2 activation for normal bone formation: While moderate Nrf2 activity in heterozygous Keap $1^{+/-}$ mice was associated with increased bone formation and lower numbers of osteoclasts (Yin *et al. Sci Rep*. 2020; 10(1): 348), the increased Nrf2 activation in homozygous

Keap $1^{-/-}$ mice actually impaired osteoblast proliferation and induced bone hypoplasia (Yoshida E *et al. Genes Cells*. 2018; 23(5):386-392).

Thus, the impaired bone mineralisation in juvenile rats treated with either DMF or DRF and the physeal dysplasia detected in the 91 days subchronic toxicity study of DRF in pre-pubertal monkeys might be mechanistically related to the increased stimulation of Nrf2-mediated regulation of bone formation by MMF. It is obvious that juvenile animals are more vulnerable to perturbations of bone development. In addition, the toxicology data of DRF suggest that bone deficits are also impacted by the extent of MMF exposure and the study duration. The bone findings are considered of minor relevance for adult RRMS patients, whereas the limited data render the relevance for paediatric patients unknown (see Annex 3 and section 4.5 below). Considering these aspects, the MAH meanwhile agreed to restrict the paediatric population to the higher age range of 13 years or above. In addition, the defective bone development is delineated in section 5.3 of the SmPC of DMF.

With regard to the environmental risk of DMF, the PEC calculation and the assessment of the MAH for the proposed extension of the RRMS population to paediatric patients is considered acceptable. The risk characterisation is based on the PNECs from the initial ERA, which had been assessed as acceptable at that time. All risk quotients considering the new PEC value are below 1 and a risk is not indicated.

Although the correct Fpen of 0.00258 was used in the PEC calculation, the MAH inserted a wrong Pregion and calculated a wrong Fpen of 0.0014 on page 11 of the ERA. Since PECsw was calculated correctly, this has no influence on the risk characterisation.

Substance (INN/Invented Name): dimethyl fumarate (TECFIDERA)			
CAS-number (if available): 624-49-7			
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined (prevalence)	0.93	µg/L	> 0.01 threshold; Yes

The standard disposal advice has been adequately included in section 6.6 of the SmPC.

3.2.5. Conclusion on the non-clinical aspects

The proposed extension of the clinical indication of DMF to paediatric RRMS patients necessitated an updated assessment of the juvenile toxicity studies, which had been formerly concluded by the CHMP when the corresponding data were evaluated in 2016 (EMEA/H/C/2601/II/25) and 2019 (EMEA/H/C/2601/II/61/G), respectively. The essential findings of both investigations, and particularly the potential effect on bone growth has been adequately reflected in section 5.3 of the SmPC.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of dimethyl fumarate.

3.3. Clinical aspects

3.3.1. Introduction

The type II variation requests an extension of the indication for Tecfidera in RRMS to the paediatric population aged 10 years and older. Tecfidera is currently approved for the treatment of adult patients with RRMS. The approved starting dose is 120 mg two times a day orally. After 7 days, the Tecfidera dose is proposed to be 240 mg BID (480 mg DMF per day). Temporary dose reduction to 120 mg twice

a day is foreseen and may reduce the occurrence of flushing and GI side effects. Within 1 month, the recommended maintenance dose of 240 mg twice a day orally should be resumed.

The justification of the extension of the indication to paediatric patients aged 10 years and older is supported by one phase III study, study 109MS306 (Part 1) and two phase II studies, study 109MS202 and its extension, study 109MS311. Both studies have previously been submitted to the EMA via variation (EMEA/H/C/002601/II/0042 and EMEA/H/C/2601/II/0059) and are shortly described in section 4.4.2, supportive studies (reference is also made to section 4.3.2, PK/PD). Part 2 of study 109MS306, a 5 year optional open-label extension study for patients who completed Part 1 is ongoing and will be provided as separate Clinical Study Report. As agreed by PDCO, Part 2 is not included in the PIP for Tecfidera (EMEA-000832-PIP01-10-M03).

The proposed posology in the paediatric population aged 10 years and older is the same as in adults.

GCP

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

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

- Tabular overview of clinical studies

Table 1: Description of the pivotal study (109MS306 Part 1) of dimethyl fumarate in the paediatric RRMS population

Study ID	No. of study centres/ locations	Design	Study posology	Subjs by arm entered/ compl. treatment	Duration	Gender M/F Median Age	Diagnosis incl. criteria	Study objective/ Primary endpoint
109MS306 (Part 1)	44 centres (which randomised at least 1 patient) in 10 countries worldwide	Open-label, randomised, multicentre, active-controlled. Patients received Tecfidera 120 mg BID for the first 7 days, thereafter 240 mg BID or Avonex 30 µg i.m. once/wk (titrated during the first 4 wks starting at 7.5 µg and increased by 7.5 µg each week	Patients were randomised to Tecfidera or Avonex at 1:1 ratio Tecfidera: oral, twice daily Avonex: i.m.; once/wk	Avonex: 72 treated/ 42 compl. 96 wks Tecfidera: 78 treated/ 61 compl. 96 wks	96 wks	49/101 15.0 (10-17)	RRMS and at least 1 relapse in the 12 months or at least 2 relapses in the 24 months prior to Day 1, both with a prior brain MRI with MS lesions or Gd-lesions of the brain MRI 6 wks prior to Day 1	Safety, tolerability, efficacy proportion of patients free of new or newly enlarging T2 hyperint. lesions on brain MRI scans at Week 96

3.3.2. Pharmacokinetics

No new pharmacokinetic (PK) data have been provided as part of this variation procedure. The PK of Tecfidera is well established based on data from the clinical development programme for Tecfidera in adult participants with RRMS and healthy volunteers. The PK of the current formulation of Tecfidera was characterised in Study 109HV109, a bioequivalence study conducted in adult healthy volunteers.

The PK of Tecfidera in paediatric participants (age range 13-17 years) with RRMS was evaluated in Study 109MS202, which was assessed during EMEA/H/C/002601/II/0042 and which led to updates in the product information (SmPC sections 4.2, 4.8, 5.1, and 5.2). The MAH provided a summary of study

109MS202 and its extension study 109MS311 (assessed in variation procedure EMEA/H/C/002601/II/0059).

Study 109MS202 was a phase 2, 24-week, open-label, uncontrolled study to assess the effect of BG00012 on MRI lesions and PK in paediatric patients with RRMS aged 10 to 17 years (n=22).

The dose regimen was the same as the approved Tecfidera dosing regimen in adults with RRMS. Reference has been made to published data that suggest that the esterase activity is similar in children and in adolescents when compared with adults, suggesting that the relationship between body weight and exposure to the active metabolite of Tecfidera (MMF) is similar in the paediatric and adult populations[14]. Additional data derived from the pivotal Phase 3 clinical studies (Study 109MS301 and Study 109MS302) that included adult participants with RRMS with body weights as low as 34 kg and which lacked new or worsening safety issues. For these reasons, the approved dose in adults was chosen for study 109MS202. Data from the pivotal Phase 3 studies suggested that the variability in exposure did not affect safety and efficacy measures in adult participants with RRMS and suggested that Tecfidera 240 mg BID should be tolerable in the paediatric population.

Characterisation of the PK of Tecfidera in paediatric participants with RRMS was one of the secondary objectives of Study 109MS202. Overall, the PK parameters for Tecfidera in paediatric participants were similar to those observed in adults. As compared to adult healthy volunteers in Study 109HV109, the mean maximum observed plasma concentration values were similar in paediatric participants (1998.6 µg/L paediatric patients; 2121.2 µg/L adults). The mean calculated area under the concentration-time curve from time 0 to the concentration at hour 12 ($AUC_{0\text{-}12hr}$) values were comparable (3623.6 h*µg/L paediatric patients; 3504.6 h*µg/L adults), as were the mean area under the concentration-time curve from time 0 to infinity ($AUC_{0\text{-}inf}$) values (3630.5 h*µg/L paediatric patients; 3572.4 h*µg/L adults). Individual time to reach maximum time to reach maximum observed plasma concentration (t_{max}) in paediatric participants was variable (range: 1 to 8 hours), which is consistent with prior observations in adults. The t_{max} in paediatric participants was longer than in adult healthy volunteers receiving Tecfidera fasted (Study 109HV109) [4.2 and 2.6 hours, respectively], which is consistent with the food effect observed in adults.

When Tecfidera was administered to adult participants with RRMS with food (Study 109MS101), the time to reach t_{max} in paediatric and adult participants was comparable (4.2 and 4.6 hours, respectively). Mean apparent clearance values (74.45 L/h paediatric patients; 74.42 L/h adults [Study 109HV109]) were also similar. Elimination of MMF in paediatric participants was fast with an average elimination half-life of less than 1 hour, which is consistent with that previously observed in adult participants with RRMS and healthy volunteers. For 10 of 21 participants, MMF concentrations in plasma were below the limit of quantification at 10 hours post dose. The MAH concludes that in the paediatric population similar to adults no accumulation is expected to occur after 240 mg BID dosing.

Study 109MS311 was the 96-week extension of study 109MS202 to determine the long-term safety and efficacy of BG00012 in paediatric patients with relapsing-remitting multiple sclerosis (n =20). No PK data derived from this extension study.

3.3.3. Pharmacodynamics

No additional data on PDs have been provided.

[14] Zhu HJ, Appel DI, Jiang Y, Markowitz JS. Age- and sex-related expression and activity of carboxylesterase 1 and 2 in mouse and human liver. Drug Metab Dispos. 2009 Sep;37(9):1819-25.

3.3.4. PK/PD modelling

No data on PK/PD modelling have been provided.

3.3.5. Discussion on clinical pharmacology

For a detailed discussion of study 109MS202, reference is made to EMEA/H/C/002601/II/0042. Aspects regarding clinical efficacy and safety deriving from this study are also discussed in this variation report (section 2.4 and 2.5). Regarding the PK profile of Tecfidera, it can be concluded that the rate and extent of exposure in adolescent patients in study 109MS202 was found comparable to adult subjects. The PK analysis population included 21 subjects. The title of study 109MS202 "(…) *Pharmacokinetics in paediatric patients with RRMS aged 10 to 17 years (…)*" is misleading given that paediatric patients <13 years of age have not been included in this study. Hence, this conclusion relates to adolescents only. It should be noted that age distribution in this study was skewed towards older adolescents, i.e. only 6 of 21 evaluable patients were 13 to 15 years of age, and 15 of 21 patients were 16 and 17 years of age. The median age was 16 years and body weight ranged from 46 to 91 kg. Thus, the study sample of children reflects older adolescents, who are more representative of adults.

Regarding esterase expression and activity, a publication by Zhu et al. (2009) was referenced, which was found supportive in that adolescents aged 13 to 17 years exhibit a metabolic capacity comparable to adults. According to the MAH, supportive data regarding the same dose regimen applied in paediatric patients and adults derived from the pivotal phase 3 clinical studies (Study 109MS301 and Study 109MS302) that included adult patients with RRMS with body weights as low as 34 kg without eliciting a different safety profile. However, the exact number of subjects with a low body weight has not been presented and is considered to be rather small.

Overall, study 109MS202 is considered to provide supportive PK data in adolescents aged 13 to 17 years and therefore, in a subpopulation of the paediatric population studied in 109MS306.

In contrast, no PK data in paediatric patients aged 10 to <13 years derive from study 109MS202 and at the same time, only very limited clinical data are available for this paediatric subpopulation from study 109MS306 (i.e. 7 patients treated with Tecfidera and 8 patients treated with Avonex). Therefore, theoretical considerations by the MAH concerning this very young paediatric population including comparable esterase expression and activity, PK data in adults with very low body weight (down to 34 kg), and comparable clearance in paediatric participants and adults cannot be confirmed by data. From a clinical safety perspective, differences in the metabolic capacities between pre-pubertal patients aged 10 to <13 years compared to adolescents and adults cannot be excluded. Scientific knowledge also recently stressed the importance of balanced Nrf2 activation for normal bone homeostasis (see section 2.2 of this report). As such, while bone effects might not be of clinical relevance in the adult RRMS population, any implications in paediatric patients (especially in the very young and pre-pubertal children) remain unknown.

To conclude, the lack of PK data in the subpopulation of paediatric patients aged 10 to <13 years in study 109MS202 needs to be brought into context with limited or even missing clinical data from study 109MS306 in the same subpopulation. As such, relevant safety aspects (e.g. due to differences in metabolic capacities) in this age group need to be addressed by clinical data for which PK data would be considered supportive.

In this context, the MAH accepted to restrict the indication to paediatric patients aged 13 years and over.

3.3.6. Conclusions on clinical pharmacology

No new data have been submitted in the course of this variation procedure.

Available and previously assessed PK data from a small paediatric phase 2, open-label, uncontrolled study in 21 paediatric patients aged 13 to 17 years exhibit similar PKs as in adults and therefore provide supportive evidence for a subpopulation of the paediatric indication claimed.

3.4. Clinical efficacy

3.4.1. Dose response study

No dedicated dose response study in this population was conducted by the MAH.

The proposed posology in the paediatric population aged 10 years and older is the same as in adults.

The dose of the active comparator Avonex (titrated to 30 µg once weekly) was chosen because it was consistent with the recommended dose for the treatment of MS in adults and has been reported to be effective and well tolerated in paediatric patients with MS [Ghezzi 2005; Waubant and Chabas 2009].

3.4.2. Main study

To support the extension of indication in the paediatric population, the MAH conducted one phase III open-label, active-controlled study of 96 weeks duration, Part 1 of study 109MS306. This active-controlled phase was followed by a 4-week safety follow-up, where applicable, and a 5-year extension (Part 2).

Title of Study

Study 109MS306 (Part 1) (also referred to as study CONNECT):

An open-label, randomized, multicenter, multiple-dose, active-controlled, parallel-group, efficacy and safety study of BG00012 in children from 10 to less than 18 years of age with relapsing-remitting multiple sclerosis, with optional open-label extension

Methods

Study design

Part 1 of Study 109MS306/CONNECT was an open-label, randomised, multicenter, multiple-dose, active-controlled, parallel-group study.

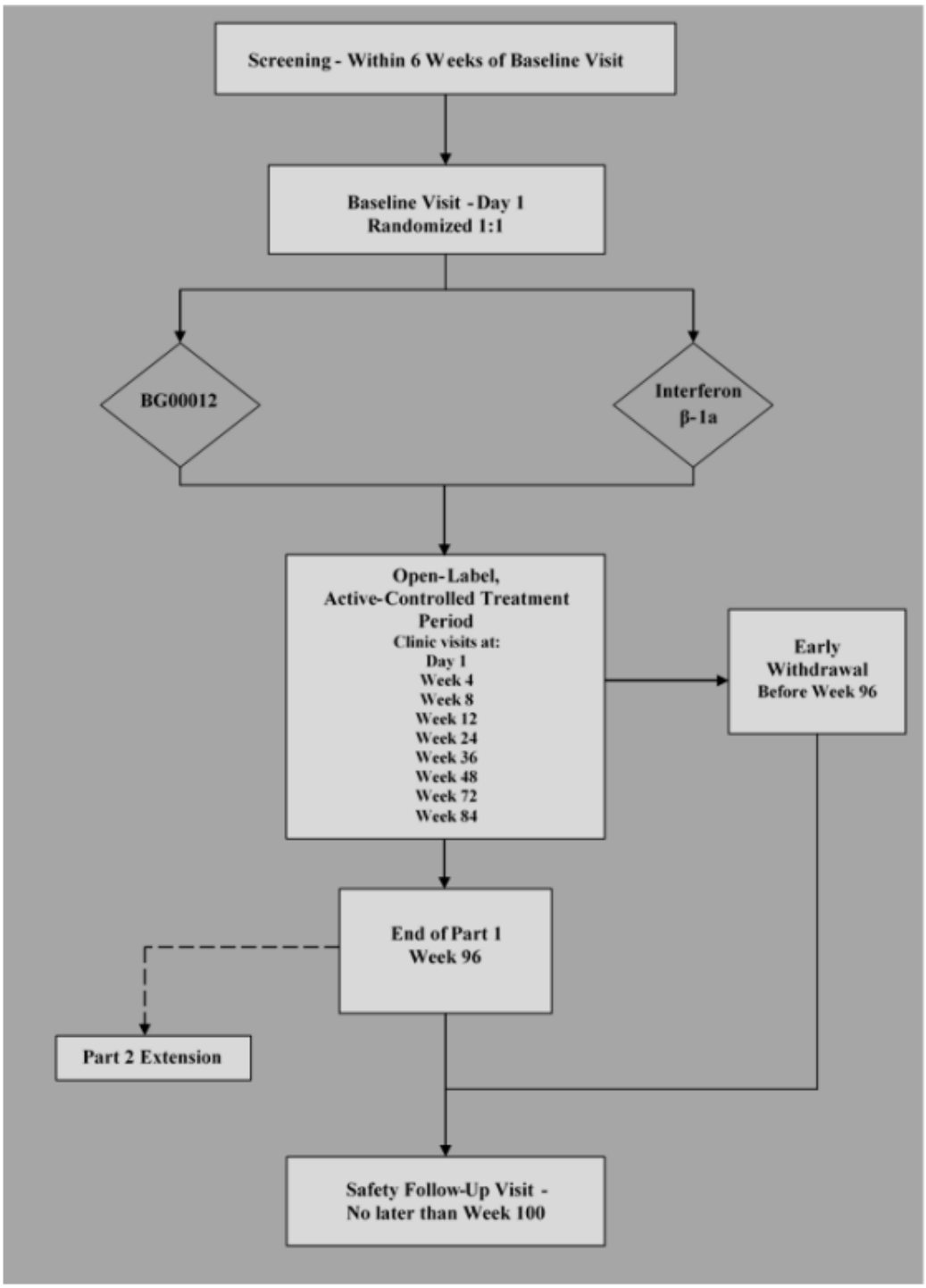
The study consisted of

- a screening period of up to 6 weeks,
- followed by a 96-week treatment period
- a safety follow-up period of approximately 4 weeks (for patients who did not continue into Part 2)

The maximum planned duration of Part 1 of the study for an individual participant was approximately 106 weeks. Patients who experienced MS relapse or disability progression during the study could

continue in the study. Patients who prematurely discontinued treatment could remain in the study and continue protocol-required tests and assessments. Patients who completed Week 96 in Part 1 and met the Part 2 entry criteria, were given the option to receive open-label Tecfidera 240 mg BID for 240 weeks in the optional Part 2 extension phase (up to approximately 5 years).

Figure 1: Study design 109MS306 Part 1



Study participants

Main inclusion criteria:

- Patients with relapsing-remitting multiple sclerosis according to the IPMSSG criteria for paediatric MS (2013 consensus definition for paediatric RRMS) [Krupp 2013] and had:
  - at least 1 relapse within the last 12 months prior to Day 1, with a prior brain MRI demonstrating lesions consistent with MS, or
  - at least 2 relapses within the last 24 months prior to Day 1, with a prior brain MRI demonstrating lesions consistent with MS, or
  - evidence of Gd-enhancing lesions of the brain on an MRI performed within the 6 weeks prior to Day 1.
- <18 years of age and ≥10 years of age at the time of informed consent or assent and a body weight ≥30 kg.
- Were ambulatory with a baseline EDSS score between 0 and 5.5, inclusive.

Main exclusion criteria:

- A MS relapse within 50 days prior to Day 1 and/or the participant had not stabilized from a previous relapse prior to Day 1.
- Disorders mimicking MS, such as other demyelinating disorders (e.g., ADEM), systemic autoimmune disorders, metabolic disorders and infectious disorders.
- Selected medical histories including clinically significant cardiovascular, pulmonary, GI, dermatologic, growth, developmental, psychiatric (including depression), neurologic (other than MS), and other diseases as well as history of abnormal laboratory results indicative of any significant endocrinologic, haematologic, hepatic, immunologic, metabolic, urologic, renal, and/or any other major disease that precluded participation in a clinical study.
- Any of the following abnormal blood test results at Screening: ALT (alanine aminotransferase), AST, (aspartate aminotransferase) or GGT (gamma-glutamyl transferase) ≥ 2 × upper limit of normal (ULN), leukocytes < 3500/mm3, eosinophils > 0.7 × 103/µL or > 0.7 giga/L, absolute lymphocyte count (ALC) < LLN (lower limit of normal); Proteinuria (1+ or greater) at Screening confirmed by a spot protein/creatinine ratio (with morning void) > 0.2 mg/mg approximately 2 weeks later. Note: documented benign proteinuria was not exclusionary or any of the following additional abnormal urine tests at Screening confirmed by a second urinalysis approximately 2 weeks later: haematuria, without known aetiology, glycosuria, without known aetiology.
- History of drug or alcohol abuse (as defined by the Investigator) within the 2 years prior to Day 1, contraindication for MRI, pregnant or breast-feeding female patients.
- Treated with: Fumaderm® or Tecfidera, total lymphoid irradiation, Cladribine, T-cell or T-cell receptor vaccination, any therapeutic monoclonal antibody, with the exception of rituximab or natalizumab at any time; mitoxantrone, cyclophosphamide, rituximab within the 12 months prior to Day 1; fingolimod, teriflunomide, natalizumab, cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, laquinimod, IV immunoglobulin, plasmapheresis or cytapheresis within 6 months prior to Day 1.
- Treatment with Steroids (IV or oral corticosteroid treatment, including agents that may act through the corticosteroid pathway), - 4-aminopyridine or related products (except participants on a stable dose of controlled-release fampridine for 3 months) within 30 days prior to Day 1.

Treatments

Investigational medicinal products (IMPs): Tecfidera (240 mg BID, oral) and Avonex (IFN β-1a) [30 µg once weekly, intramuscular injection]. Both groups received treatment for 96 weeks.

Patients took 1 capsule of Tecfidera orally at a dose of 120 mg BID for the first 7 days and 2 capsules orally at a dose of 240 mg BID thereafter.

Avonex was self-administered (or given via a proxy) once weekly beginning at Day 1/Baseline. Avonex doses were titrated during the first 4 weeks of the Study Treatment Period using the Avostartgrip™ titration kit. Avonex was started at a dose of 7.5 µg and increased by 7.5 µg each week for 3 weeks until the recommended dose of 30 µg was achieved to reduce the incidence and severity of flu-like symptoms that can occur when initiating Avonex therapy at a dose of 30 µg. At the discretion of the treating neurologist, dose titration may not have been necessary. Following titration, Avonex was administered once weekly by IM injection according to local prescribing information. Avonex doses were to be taken within 2 days of the scheduled dose. If a patient was unable to have the dose within 2 days, that dose was to be skipped, and the next dose taken as scheduled.

Modification of Tecfidera treatment schedule

Dose Reduction was allowed only for patients who were unable to tolerate Tecfidera due to flushing and/or GI disturbances. These patients reduced their dosage by taking 1 capsule (120 mg) BID for up to 4 weeks. Within 4 weeks at the reduced dose, patients resumed taking 2 capsules BID. If the patient was still unable to tolerate Tecfidera, the patient discontinued Tecfidera.

Dose Interruption: if a patient had any of the following laboratory test results: AST or ALT > 3 × ULN, creatinine > 1.2 × ULN, white blood cells (WBC) count < 2000/mm3, positive haematuria on microscopy without known aetiology. If these laboratory tests remained at these levels for 4 weeks or more, Tecfidera was permanently discontinued and the event was recorded as an adverse event (AE). Patients who subsequently developed the same abnormal laboratory value at any other time during the study permanently discontinued treatment with Tecfidera (i.e., only 1 dosing interruption was allowed for each patient for the same laboratory abnormality). However, patients who subsequently experienced a different laboratory abnormality could have study treatment with Tecfidera withheld again. However, only 2 dosing interruptions were allowed for each patient.

Dose Resumption: considered on a case-by-case basis and discussed with the Medical Monitor. Patients with abnormal laboratory values after Week 12 (after which clinic visits occurred once every 3 months) who were allowed to resume Tecfidera dosing following a 2- to 4-week interruption restarted dosing at a reduced dose of 1 capsule BID for 1 week. Patients also returned to the initial 4-weekly visit schedule for safety assessments for 2 consecutive normal laboratory assessments before reverting to the 3-monthly schedule. After 1 week at the reduced dose, patients took 2 capsules BID.

Concomitant medications

Symptomatic therapy, such as treatment for spasticity, depression, or fatigue, was not restricted, but had to be optimised as early as possible during screening in an attempt to maintain consistent treatment for the duration of the study. Patients were instructed not to start taking any new medications, including non-prescribed drugs, unless they had received permission from the Investigator. Any systemic steroid therapy, except for protocol-defined treatment of relapses, were not allowed. Steroids that were administered by non-systemic routes (e.g., topical, inhaled) were allowed.

The treatment for relapse was either 3 or 5 days with intravenous methylprednisolone up to 1000 mg/day, given once a day or in divided doses. Any changes to this treatment had to be first discussed

with the Sponsor Medical Director (or designee). Steroid retreatment of the same relapse was not allowed unless approved by the Sponsor Medical Director (or designee).

Objectives

Primary objective: To evaluate the safety, tolerability, and efficacy of BG00012 in paediatric subjects with RRMS, as compared with a disease-modifying treatment (DMT).

Secondary objectives: To assess health outcomes and evolution of disability.

Outcomes/endpoints

The following efficacy assessments were performed for Study 109MS306 Part 1:

- Brain MRI Scan ± Gd: at baseline, week 24 ± 14D, week 48 ± 14D, week 72 ± 14D, end of part 1/baseline part 2 visit, early withdrawal visit and at unscheduled relapse assessment visit.
- Clinical relapses: at unscheduled relapse assessment visit.
- EDSS: at screening, baseline, week 12 ± 5D, week 24 ± 5D, week 36 ± 5D, week 48 ± 5D, week 60 ± 5D, week 72 ± 5D, week 84 ± 5D, end of part 1/baseline part 2 visit, early withdrawal visit and at unscheduled relapse assessment visit.
- Brief Visuospatial Memory Test-Revised (BVMT-R) scores, Symbol Digit Modalities Test (SDMT) scores and school progression query: at baseline, week 48 ± 5D, end of part 1/baseline part 2 visit and at early withdrawal visit (not school progression query).
- PedsQL Multidimensional Fatigue Scale and PedsQL Quality of Life Scale: at baseline, week 24 ± 5D, week 48 ± 5D, week 72 ± 5D, end of part 1/baseline part 2 visit, early withdrawal visit and at unscheduled relapse assessment visit.

Outcome and assessment scales

Clinical relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurologic findings upon examination by the treating neurologist that were confirmed upon evaluation by the examining neurologist. New or recurrent neurologic symptoms that occurred less than 30 days following the onset of a protocol-defined relapse were considered part of the same relapse and were not treated with IVMP within the protocol. If a patient experienced new neurologic symptoms, they or their caregiver contacted the treating neurologist or treating nurse as soon as possible and within 48 hours of the onset of symptoms to complete a Telephone Questionnaire to determine the necessity of an Unscheduled Relapse Assessment Visit. If the visit was required, the participant was then evaluated in person by the treating neurologist at the Unscheduled Relapse Assessment Visit as soon as possible and within 72 hours of the onset of the potential relapse. If, in the opinion of the treating neurologist, an MS relapse may have occurred, the patient was also evaluated by the examining neurologist as soon as possible and within 5 days of the onset of the symptoms. The examining neurologist performed a detailed neurologic examination and obtained an EDSS score. New objective findings on the neurologic examination performed by the examining neurologist were required to confirm that a protocol-defined relapse had occurred. Unscheduled Relapse Assessment Visits did not modify or replace the patients' visit schedule. Treatment of an acute relapse could proceed at the discretion of the treating neurologist only after the completion of the examining neurologist's examination and only after a Gd-enhancing MRI of the brain had been performed.

The EDSS is a standardized method, widely accepted, ordinal scale used to evaluate disability in people with MS (Kurtzke, 1983). The EDSS is evaluated according to signs and symptoms observed during a standard neurological examination. These clinical observations are classified in 7 functional system scales, each of them grading signs and symptoms for different neurological functions: visual, brainstem, pyramidal, cerebellar, sensory, bowel or bladder, and cerebral. The score ranges from 0.0 (normal) to 10.0 (death due to MS). Disability progression was assessed using the EDSS. Confirmed EDSS progression was defined as at least a 1.0-point increase on the EDSS from a baseline EDSS $\geq$ 1.0 that was sustained for 12 weeks, or at least a 1.5-point increase on the EDSS from a baseline EDSS = 0 that was sustained for 12 weeks. A tentative EDSS progression was confirmed when this minimum EDSS change was present on the next study visit occurring after 74 days or longer from the initial observation. The 74-day interval was based on the visit windows allowed in the protocol around the target visit day. Time to EDSS progression was censored at the earlier of the first date of the alternative medication or the last EDSS assessment date, unless a patient was undergoing an unconfirmed progression at the last EDSS visit.

The BVMT-R is a measure of visuospatial memory used to document changes over time. This test was performed to assess learning/memory.

The SDMT is a valid and sensitive measure of cognitive processing speed that is easy to conduct and to follow by MS patients.

School progression query: If permitted by the local regulatory authority, the following question was posed to patients or caregivers: "During the past year, did [you/the participant] progress from one [class/grade level] to the next in school?"

The PedsQL Multidimensional Fatigue Scale and the PedsQL Quality of Life Scale: Both scales were measured by the participant's self-assessment and that of the parent/legal guardian. The PedsQL Multidimensional Fatigue Scale contains 18 questions in 3 fatigue dimensions (General Fatigue, Sleep/Rest Fatigue, and Cognitive Fatigue). The PedsQL Quality of Life Scale contains 23 questions in 4 dimensions (Physical Functioning, Emotional Fatigue, Social Fatigue, and School Fatigue). Scoring for each question was based on a 5-point Likert scale from 0 (Never) to 4 (Almost always). Each individual score was then reversed (subtracted from 4) and linearly transformed as follows: 0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0. For each dimension, the total score was calculated as the sum of all the items divided by the number of items answered. In the PedsQL Multidimensional Fatigue Scale, a higher total score indicated fewer problems, and in the PedsQL Quality of Life Scale, a higher score indicated a better quality of life.

Brain MRI: was not performed within 30 days of receiving a course of steroids, with the exception of MRIs obtained for the purpose of relapse assessment. The following Brain MRI parameters were performed: new or newly enlarging T2 hyperintense lesions, total Gd-enhancing lesions, new T1 hypointense lesions.

The MRI scans were forwarded to an independent, blinded, central MRI center for assessment.

Endpoints

Primary efficacy endpoint

- The proportion of subjects free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at week 96

Secondary efficacy endpoints

- Number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 24 and 96

- Proportion of subjects free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 24 and 48
- Proportion of subjects free of new MRI activity (i.e., free of Gd-enhancing and free of new or newly enlarging T2 MRI lesions on brain MRI scans) at Weeks 24, 48, and 96
- Time to first relapse
- Proportion of subjects free of relapse up to Week 96
- Annualized relapse rate (ARR) at Weeks 48 and 96
- Change from baseline to Week 96 in the EDSS score
- Fatigue as measured by the PedsQL Multidimensional Fatigue Scale scores
- Quality of Life as measured by the PedsQL

Exploratory Endpoints

- Number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 48 and 72
- Proportion of subjects free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Week 72
- Proportion of subjects free of new MRI activity (i.e., free of Gd-enhancing and free of new or newly enlarging T2 MRI lesions on brain MRI scans) at Week 72
- Number of new T1 hypointense lesions on brain MRI scans at Weeks 24, 48, 72, and 96
- Number of Gd-enhancing lesions on brain MRI scans at Weeks 24, 48, 72, and 96
- Time to progression of disability at 96 weeks as measured by at least a 1.0 point increase on the EDSS from baseline EDSS ≥1.0 that is sustained for 12 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS = 0 that is sustained for 12 weeks
- BVMT-R scores (to assess learning/memory) and SDMT scores (to assess processing speed), and school progression query at Weeks 48 and 96

Sample size

The sample size was primarily based on feasibility, with the goal of having 50 evaluable patients at the 96-week time-point of Part 1 for each treatment group. Therefore, the study was not powered for the Part 1 primary endpoint. Based on an estimated dropout rate of approximately 30% over 2 years, a total of 142 patients were needed to be enrolled to have at least 100 evaluable patients (50 patients per treatment group) after 2 years of treatment. With respect to the primary endpoint of Part 1, if the proportion of patients free from new or newly enlarging T2 hyperintense lesions was approximately 25%, the width of the 95% CI for the proportion would be approximately 0.24. If the proportion was around 40%, the width of the 95% CI would be approximately 0.28. This sample size provided approximately 82% power for the key secondary endpoint of Part 1 of number of new or newly enlarging T2 hyperintense lesions at Week 24. The assumptions were based on historical data on treatment effect for Avonex and Tecfidera on the number of T2 hyperintense lesions compared with placebo. It was assumed that the mean (SD) would be 3.5 (6.3) and 1.22 (2.92) for the number of new or newly enlarging T2 hyperintense lesions at Week 24 for the Avonex group and the Tecfidera group, respectively (a 65% reduction over the Avonex group). At Week 24, a 10% dropout rate was expected, resulting in about 63 evaluable patients per group. Based on these assumptions, the study had approximately 82% power to detect the difference between Tecfidera and Avonex. This power calculation was based on a negative binomial simulation.

Randomisation

Patients were randomly assigned to treatment by an interactive voice/web response system at the Baseline Visit (Day 1) to receive Tecfidera or Avonex in a 1:1 ratio and stratified according to whether

or not the participant received therapy with IFN β-1a or GA in the 4 weeks prior to study entry and in accordance with the following 3 age groups (10 to < 13 years: at least 10 evaluable patients, 13 to < 15 years: at least 20 evaluable patients, and 15 to < 18 years: at least 60 evaluable patients). Patients who withdrew from the study were not replaced.

Blinding (masking)

According to the clinical study report, page, 35, blinding has not been applicable as this was an open-label study.

Statistical methods

The statistical methods used in this study are further described in the statistical analysis plan (SAP), dated 06 December 2019.

Nominal p-values are presented for reference only and are not corrected for multiplicity.

Analysis populations:

Intent-to-Treat (ITT) Population: subjects who were randomised and received at least 1 dose of study treatment.

Completers Population: subjects from the ITT Population who completed Week 96 of the study and who have MRI data for Week 96.

ITT Population with week 96 MRI measurements

Primary endpoint analyses: Proportion of participants free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Week 96

The analysis of the primary endpoint included summary statistics and exact confidence intervals (CIs) (using the Clopper-Pearson method) for the proportion of participants free of new or newly enlarging T2 hyperintense lesions at Week 96 for each treatment group; it was performed on the Completers Population. Data were summarized using observed values. Sensitivity analyses of the primary endpoint were performed on the ITT Population (1] full ITT Population, 2] ITT Population including Week 96 MRI measurements (post hoc analysis)).

In both sensitivity analyses, a logistic regression model was used to analyse the proportion of participants free of new or newly enlarging T2 lesions, adjusted for age group and other baseline covariates, such as baseline T2 volume, sex, baseline EDSS and the number of relapses in a year prior to the study. In both analyses, the odds ratio (OR) for the odds of no new or newly enlarging T2 lesions in the Tecfidera treatment group, divided by the odds of the same event in the Avonex treatment group, was calculated. The p-value from the likelihood ratio test that the OR is 1 was given. An additional, separate efficacy analysis was carried out based on pubertal status at disease initiation (obtained from the Tanner staging at screening).

Secondary Endpoint Analyses:

Number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 24 and 96

A negative binomial regression model was used to analyse the number of new or newly enlarging T2 hyperintense lesions at both Week 24 and at Week 96, with treatment group in the model and adjusted for age group and baseline number of T2 lesions. Formal statistical testing was performed to compare the mean between the 2 treatment groups. These Week 24 and Week 96 analyses were based on

participants from the ITT Population who had observed data at Weeks 24 and 96, correspondingly. Analyses of the number of Gd-enhancing lesions and number of T1 hypointense lesions were performed similarly.

A sensitivity analysis compared the number of new or newly-enlarging T2 hyperintense lesions over 96 weeks relative to baseline between treatment groups using a negative binomial regression model on the observed number of new or newly enlarging T2 lesions at the participants' last visit prior to the Week 96. The logarithmic transformation of the last scan number (out of the 4 scheduled scans) was included in the model as the "offset" parameter. The model was adjusted for the baseline volume of T2 hyperintense lesions and baseline age group. Results of these models were exponentiated to transform back to lesion counts. In addition, a similar analysis was done using the last scan prior to alternative medication and up to Week 96.

The proportion of participants free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 24 and 48 and the proportion of participants free of new MRI activity (i.e., free of Gd-enhancing and free of new or newly enlarging T2 MRI lesions on brain MRI scans) at Weeks 24, 48, and 96 were analysed similarly as the primary endpoint without the corresponding sensitivity analyses. Participants were considered free of MRI activity if they were free of Gd-enhancing lesions at all post-baseline visits up to and including the specified visit and free of new or newly enlarging T2 lesions relative to Baseline.

Time to first relapse

Time to first relapse and estimated proportion of participants relapsed or relapse-free were presented based on the Kaplan-Meier method. If participants did not experience a relapse during Part 1 of the study, they were censored at their last visit in Part 1. Time to first relapse was also analysed using the Cox proportional hazards model, adjusted for baseline relapse rate, baseline EDSS score, and age group.

Proportion of participants free of relapse up to Week 96

The proportion of relapse-free participants up to Week 96 was summarized. In addition, for the ITT Population, the estimated proportion of participants who were relapse-free up to Week 96 was calculated based on the Kaplan-Meier method.

ARR at Weeks 48 and 96

ARR, calculated as the total number of relapses that occurred during the study divided by the total number of participant-years followed was presented by treatment group. Adjusted ARR, obtained from a negative binomial regression, adjusted for baseline relapse rate, baseline EDSS score and age group, was presented for each treatment group, along with the rate ratio for Tecfidera versus Avonex.

Fatigue as measured by the PedsQL Multidimensional Fatigue Scale scores and Quality of Life as measured by the PedsQL

At each scheduled visit, summary statistics were presented for each dimension for both scales by treatment group. Additionally, these endpoints were analysed using an analysis of covariance (ANCOVA) adjusted for baseline score and age group. Results for each scale were presented for the self-assessment and the parent assessment.

Summary statistics of change from baseline to Week 96 in EDSS score were presented for each treatment group. Time to progression of disability (based on EDSS) and estimated proportion of participants progressed at Week 96 were presented based on the Kaplan-Meier method and analysed using Cox regression.

BVMT-R and SDMT scores and changes from baseline were summarized using descriptive statistics.

Safety: All summary analyses of AEs referred to treatment-emergent AEs (TEAEs). TEAEs were defined as AEs occurring or worsening after beginning study treatment (after the first dose in this study). Analyses of TEAEs included all events through the end of a participant's follow-up. TEAEs were analysed based on incidence, defined as the proportion of participants who had at least 1 occurrence of an event out of the number of participants. The Medical Dictionary for Regulatory Activities (MedDRA) V23.1 was utilized to code and group TEAEs by system organ class (SOC) and preferred terms (PT). Summaries of TEAEs included the numbers and incidences/percentages of participants in the ITT population with a TEAE, a severe TEAE, a related TEAE, a treatment-emergent serious AEs (SAE), TEAEs leading to interruption or discontinuation of study treatment or withdrawal from study, and adverse events of special interest (AESIs).

Changes in the Planned Analyses

The SAP indicated that analyses would be adjusted for the use of IFN β-1a or GA in the 4 weeks before randomisation. However, this stratification factor was introduced in Protocol V5, and the majority of patients who were already in the study when this protocol version was implemented did not have this information collected at randomisation. When both MS treatment history and randomisation data were used to identify prior IFN β-1a or GA use in the 4 weeks before randomisation, only 4 patients met the criterion, so that factor was not used as a covariate in the final analyses.

Results

Participant flow

Disposition of patients is presented in Figure 2.

Figure 2: Disposition of subjects (ITT population)

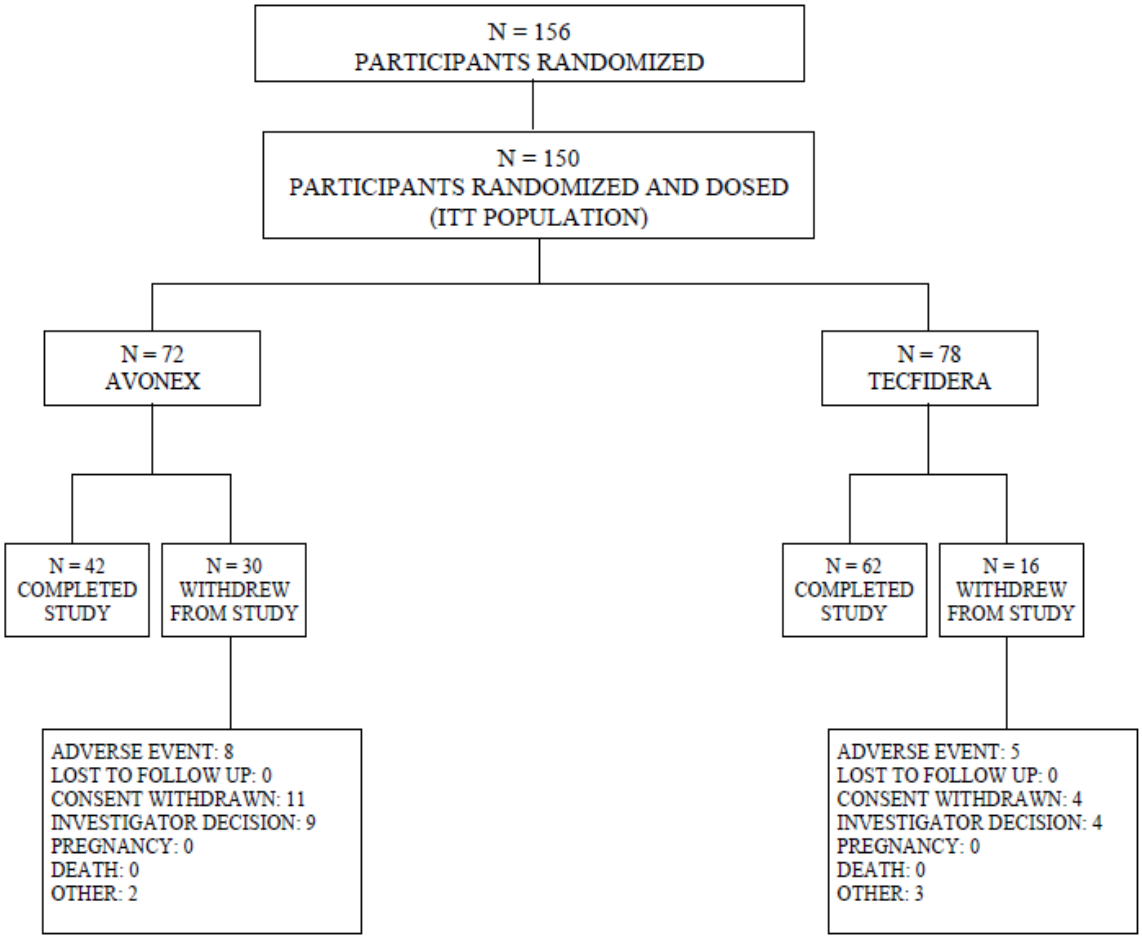


Table 2: Accounting of patients

	Avonex (N=77)	BG00012 240 mg BID (N=79)	Total (N=156)
Number of subjects randomised	77	79	156
Number of subjects randomised not dosed	5	1	6
Number of subjects dosed	72 (100)	78 (100)	150 (100)
Number of subjects who completed the treatment	42(58)	61 (78)	103 (69)
Number of subjects who completed the study	42 (58)	62 (79)	104 (69)
Number of subjects who discontinued study drug	30 (42)	17 (22)	47 (31)
End of treatment	0	0	0
Adverse event	8 (11)	6 (8)	14 (9)
Lost to follow-up	0	0	0
Consent withdrawn	11 (15)	4 (5)	15 (10)
Investigator decision	9 (13)	4 (5)	13 (9)
Death	0	0	0
Other	2 (3)	3 (4)	5 (3)
Number of subjects who withdrew from study	30 (42)	16 (21)	46 (31)
End of study	0	0	0
Adverse event	8 (11)	5 (6)	13 (9)
Lost to follow-up	0	0	0
Consent withdrawn	11 (15)	4 (5)	15 (10)
Investigator decision	9 (13)	4 (5)	13 (9)
Death	0	0	0
Other	2 (3)	3 (4)	5 (3)
Number of subjects entering Part 2	35 (49)	57(73	92 (61)

Numbers in parentheses are percentages based on number of subjects dosed.

Recruitment

This was a multicentre study with 44 study sites in 10 countries [Belgium (3 centres: randomised 3 patients), Czech Republic (4 centres: randomised 15 patients), Denmark (3 centres: randomised 1 patient), France (11 centres: randomised 37 patients), Hungary (2 centres: randomised 10 patients), Italy (9 centres: randomised 24 patients), Poland (6 centres: randomised 13 patients), Serbia (3 centres: randomised 12 patients), Sweden (2 centres: randomised 5 patients), United Kingdom (4 centres: randomised 5 patients of which 2 patients rolled over as adults in 2020), Argentina (1 centre: randomised 0 patients), Canada (1 centre: randomised 2 patients), Germany (4 centres: randomised 5 patients), Israel (3 centres: randomised 12 patients), Spain (5 centres: randomised 4 patients), Turkey (2 centres: randomised 4 patients), Bulgaria (1 centre: randomised 2 patients), Kuwait (1 centre: randomised 4 patients), United States (2 centres: randomised 0 patients)].

156 patients have been recruited. The countries with the largest numbers of subjects were France (37 patients), Italy (24 patients) and Czech Republic (15 patients).

The first patient has been treated on 28 August 2014 and the last patient completed Part 1 of the study on 12 November 2020.

Conduct of the study

Changes to the original protocol (dated 17 December 2013) included 4 global protocol amendments.

Amendment No 1 (resulting in protocol version 2 with date 10 February 2014), amongst others:

- Addition of blood sample volumes to address the 2008 EU Guidance for paediatric studies in which sample blood volume collection is recommended to be included in the protocol.

Amendment No 2 (resulting in protocol version 3 with date 16 January 2015), amongst others:

- To enable the early identification of subjects who are at risk for developing severe, prolonged lymphopenia, and to provide additional guidance on the management of such subjects.
- Inclusion criterion #6 has been revised for alignment with other paediatric MS studies: to include patients who had at least 2 relapses within the last 24 months prior to Day 1, rather than just patients who had at least 1 relapse within the last 12 months prior to Day 1.
- Modification of the treatment schedule for Avonex, section 10.1.2, that at the discretion of the treating neurologist, dose titration may not be necessary.

Amendment No 3 (resulting in protocol version 4 with date 08 February 2016), amongst others:

- The long-term extension study (part 2) was added required by PDCO.
- The follow-up period was extended from 24 weeks to 48 weeks for subjects who completed, temporarily withhold, or permanently discontinued study treatment for any reason and had a lymphocyte count less than the lower limit of normal (<LLN).
- Addition of BVMT-R scores, SDMT scores and school progression query at weeks 48 and 96 (exploratory endpoints) in Part 1 to align with the PIP requirements as well as to provide baseline measurements for these assessments in Part 2.
- Addition of Gd-enhanced brain MRIs for relapses.
- Inclusion criteria: Modification of the definition of relapsing-remitting multiple sclerosis (RRMS): *"Must have a diagnosis of RRMS* ***according to the International Paediatric Multiple Sclerosis Study Group criteria for paediatric MS (2013) [Krupp 2013]*** *(consensus definition for paediatric RRMS)* ~~*[Krupp 2007]).*~~*"* The definition of RRMS was updated to align with the most recent consensus definition for paediatric RRMS and as agreed to with PDCO.
- Exclusion criteria: To shorten the period between prior immunomodulatory treatment with glatiramer acetate or IFN β from 3 months to 4 weeks prior Day 1 of the study (a 4-week washout period is considered adequate to ensure that both IFN β-1a and GA have been eliminated, and no additional PDs effects would be expected).

Amendment No 4 (resulting in protocol version 5 with date 25 July 2017), amongst others:

- Removal of the PK/ PD sub-study due to recruitment difficulties and due to the fact that Study 109MS202, which evaluated the PK/PD of BG00012 in 22 paediatric subjects with RRMS, has recently been completed.
- Decreasing the required number of 10 to 12-year-old subjects from 20 evaluable subjects to 10 evaluable subjects and removal of the requirement for a minimum number of pre-pubertal subjects. Instead, the Applicant was requested to establish pubertal status of the patients at disease onset (retrospectively) and to perform an additional efficacy analysis based on pubertal status at disease initiation.)
- Removal of the washout requirement for IFN β-1a and GA.
- Addition of stratification of randomisation by whether or not the subject had received therapy with IFN β-1a or glatiramer acetate in the 4 weeks prior to study entry.

Protocol deviations

In total, 126 of 150 patients (84%) had at least 1 major protocol deviation: Avonex, 60 of 72 patients (83%); Tecfidera, 66 of 78 patients (85%).

Table 3: Summary of Major Protocol Deviations (ITT Population)

	Avonex (N=72)	BG00012 240 mg BID (N=78)	Total (N=150)
Number of subjects dosed	72 (100)	78 (100)	150 (100)
Number of subjects with at least one major deviation	60 (83)	66 (85)	126 (84)
STUDY PROCEDURES CRITERIA	44 (61)	40 (51)	84 (56)
INFORMED CONSENT	20 (28)	35 (45)	55 (37)
IP COMPLIANCE	12 (17)	33 (42)	45 (30)
LABORATORY ASSESSMENT CRITERIA	24 (33)	19 (24)	43 (29)
VISIT SCHEDULE CRITERIA	13 (18)	12 (15)	25 (17)
ADMINISTRATIVE CRITERIA	9 (13)	10 (13)	19 (13)
EFFICACY CRITERIA	9 (13)	7 (9)	16 (11)
ELIGIBILITY AND ENTRY CRITERIA	4 (6)	8 (10)	12 (8)
CONCOMITANT MEDICATION CRITERIA	3 (4)	7 (9)	10 (7)
SERIOUS ADVERSE EVENT CRITERIA	5 (7)	5 (6)	10 (7)
OTHER CRITERIA	3 (4)	6 (8)	9 (6)
SOURCE DOCUMENT CRITERIA	4 (6)	4 (5)	8 (5)
RA OR CEC APPROVALS CRITERIA	2 (3)	2 (3)	4 (3)
Number of subjects with at least one major deviation related to COVID-19 pandemic measures	3 (4)	7 (9)	10 (7)
STUDY PROCEDURES CRITERIA	1 (1)	4 (5)	5 (3)
VISIT SCHEDULE CRITERIA	2 (3)	3 (4)	5 (3)
LABORATORY ASSESSMENT CRITERIA	0	2 (3)	2 (1)

Major deviations: changes from the protocol that could affect data integrity or patient safety; e.g., errors in ICF signing, incorrect study treatment storage conditions, missed doses of study treatment, noncertified (EDSS/SDMT/BVMT-R) site staff performing assessments, and unscheduled relapse assessment visits occurring outside of the protocol-defined visit window.

Overall, the most common types of major protocol deviations (reported in > 25% of patients in either treatment group) were study procedures criteria (84 patients, 56%), informed consent (55 patients, 37%), IP compliance (45 patients, 30%), and laboratory assessment criteria (43 patients, 29%). A higher percentage of patients in the Tecfidera group than the Avonex group had IP compliance protocol deviations (Avonex: 12 patients, 17%; Tecfidera: 33 patients, 42%) and informed consent protocol deviations (Avonex: 20 patients, 28%; Tecfidera: 35 patients, 45%), and a higher percentage of patients in the Avonex group than the Tecfidera group had study procedures criteria protocol deviations (Avonex: 44 patients, 61%; Tecfidera: 40 patients, 51%) and laboratory assessment criteria protocol deviations (Avonex: 24 patients, 33%; Tecfidera: 19 patients, 24%).

According to the Applicant, there were no major protocol deviations that substantially impacted study findings or conclusions.

Protocol Deviations Due to COVID-19: Overall, 10 of 150 patients (7%) had at least 1 major protocol deviation related to COVID-19 pandemic measures (Avonex: 3 patients, 4%; Tecfidera: 7 patients, 9%). The only types of major protocol deviations related to COVID-19 pandemic measures that were reported in patients in both treatment groups were study procedures criteria (Avonex: 1 patient, 1%; Tecfidera: 4 patients, 5%) and visit schedule criteria (Avonex: 2 patients, 3%; Tecfidera: 3 patients, 4%). In addition, patients in the Tecfidera group had laboratory assessment criteria protocol deviations (2 patients, 3%) due to the pandemic.

Audits: A total of ten sites were audited during the study.

Baseline data

Baseline demographic characteristics

Demographic characteristics were generally similar in both treatment groups (Table 4).

ITT population: The mean (SD) age was 14.9 (1.62) years. Most (103 patients, 69%) were aged between 15 and 17 years, 32 patients (21%) were aged 13 or 14 years, and 15 patients (10%) were aged between 10 and 12 years. More than two-thirds of the patients were female (101 patients, 67%). Racial group was not collected for 53 patients (35%) because of confidentiality regulations and was missing or unknown for an additional 67 patients (45%). The mean (SD) weight was 63.88 (14.576) kg, mean (SD) height was 164.5 (8.68) cm, and mean (SD) BMI was 23.5 (4.42) kg/m2.

In the Completers Population (n =103) (evaluated for the primary endpoint), 36 of 103 patients (35%) were male. Most (70 patients, 68%) were aged between 15 and 17 years, 21 patients (20%) were aged between 13 and 14 years, and 12 patients (12%) were aged between 10 and 12 years.

Table 4: Demographics and patient characteristics at baseline (ITT population)

	Avonex (N=72)	BG00012 240 mg BID (N=78)	Total (N=150)
Age category (years)			
10-12	8 (11)	7 (9)	15 (10)
13-14	14 (19)	18 (23)	32 (21)
15-17	50 (69)	53 (68)	103 (69)
Age (years)			
n	72	78	150
Mean (SD)	15.0 (1.64)	14.9 (1.61)	14.9 (1.62)
Median	15.0	15.0	15.0
Q1,Q3	14.0, 16.0	14.0, 16.0	14.0, 16.0
Min, Max	10, 17	10, 17	10, 17
Sex			
Male	23 (32)	26 (33)	49 (33)
Female	49 (68)	52 (67)	101 (67)
Race			
White	14 (19)	11 (14)	25 (17)
Black or African American	0	0	0
Asian	1 (1)	1 (1)	2 (1)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific-Islander	0	0	0
Not Reported due to Confidentiality Regulations	26 (36)	27 (35)	53 (35)
Other	0	3 (4)	3 (2)
Unknown/Missing	31 (43)	36 (46)	67 (45)
Weight (kg)			
n	72	78	150
Mean (SD)	63.53 (14.021)	64.20 (15.154)	63.88 (14.576)
Median	62.50	63.00	63.00
Q1,Q3	53.00, 71.00	53.00, 72.60	53.00, 71.30
Min, Max	35.5, 101.2	36.6, 112.0	35.5, 112.0
Height (cm)			
n	72	77	149
Mean (SD)	165.0 (9.20)	164.0 (8.20)	164.5 (8.68)
Median	164.2	163.0	164.0
Q1,Q3	160.0, 171.5	159.2, 168.5	159.5, 170.0
Min, Max	143, 185	143, 180	143, 185

BMI (kg/m^2)			
n	72	77	149
Mean (SD)	23.2 (4.06)	23.7 (4.75)	23.5 (4.42)
Median	22.8	23.1	22.9
Q1,Q3	20.0, 26.0	19.8, 25.7	20.0, 26.0
Min, Max	16, 39	16, 35	16, 39

Numbers in parentheses are percentages.

Table 5: Summary of Tanner Staging of patients randomised and dosed (ITT Population)

	Avonex (N=72)	BG00012 240 mg BID (N=78)	Total (N=150)
Number of male subjects	23 (100)	26 (100)	49 (100)
Evaluation in male subjects			
Screening			
Testes and Scrotum tanner staging			
1 - Prepubertal	2 (9)	1 (4)	3 (6)
2 - Enlargement of scrotum and testes; scrotum skin reddens and changes in texture	2 (9)	3 (12)	5 (10)
3 - Enlargement of penis (length at first); further growth of testes	1 (4)	2 (8)	3 (6)
4 - Increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotum skin darker	3 (13)	3 (12)	6 (12)
5 - Adult genitalia	14 (61)	16 (62)	30 (61)
Pubic hair tanner staging			
1 - Prepubertal (can see velus hair similar to abdominal wall)	2 (9)	1 (4)	3 (6)
2 - Sparse growth of long, slightly pigmented hair, straight or curled, mainly on labia	3 (13)	5 (19)	8 (16)
3 - Darker, coarser and more curled hair, spreading sparsely over junction of pubes	0	1 (4)	1 (2)
4 - Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs	4 (17)	2 (8)	6 (12)
5 - Adult in type and quantity, with horizontal distribution	13 (57)	17 (65)	30 (61)
Number of female subjects	49 (100)	52 (100)	101 (100)
Evaluation in female subjects			
Screening			
Breast development tanner staging			
1 - Prepubertal	1 (2)	0	1 (<1)
2 - Breast bud stage with elevation of breast and papilla; enlargement of areola	2 (4)	1 (2)	3 (3)
3 - Further enlargement of breast and areola; no separation of their contour	6 (12)	5 (10)	11 (11)
4 - Areola and papilla form a secondary mound above level of breast	9 (18)	13 (25)	22 (22)
5 - Mature stage: projection of papilla only, related to recession of areola	25 (51)	23 (44)	48 (48)
Pubic hair tanner staging			
1 - Prepubertal (can see velus hair similar to abdominal wall)	1 (2)	0	1 (<1)
2 - Sparse growth of long, slightly pigmented hair, straight or curled, mainly on labia	1 (2)	1 (2)	2 (2)
3 - Darker, coarser and more curled hair, spreading sparsely over junction of pubes	8 (16)	3 (6)	11 (11)
4 - Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs	11 (22)	15 (29)	26 (26)
5 - Adult in type and quantity, with horizontal distribution	22 (45)	23 (44)	45 (45)

Numbers in parentheses are percentages.

Baseline disease characteristics

Overall disease characteristics at baseline were generally similar among the treatment groups.

Table 6: History of MS – ITT population

	Avonex (N=72)	BG00012 240 mg BID (N=78)	Total (N=150)
Number of subjects in ITT population	72 (100)	78 (100)	150 (100)
Time since first MS symptoms (years)			
n	72	77	149
Mean (SD)	1.2 (1.29)	1.7 (1.88)	1.5 (1.63)
Median	1.0	1.0	1.0
Q1,Q3	0.0, 2.0	1.0, 2.0	1.0, 2.0
Min, Max	0, 6	0, 10	0, 10
Time since diagnosis of MS (years)			
n	72	77	149
Mean (SD)	0.5 (0.69)	0.9 (1.55)	0.8 (1.22)
Median	0.0	1.0	0.0
Q1,Q3	0.0, 1.0	0.0, 1.0	0.0, 1.0
Min, Max	0, 4	0, 7	0, 7
Number of relapses within the past 12 months			
0	2 (3)	1 (1)	3 (2)
1	38 (53)	44 (56)	82 (55)
2	26 (36)	19 (24)	45 (30)
3	6 (8)	10 (13)	16 (11)
>=4	0	3 (4)	3 (2)
n	72	77	149
Mean (SD)	1.5 (0.69)	1.6 (0.96)	1.6 (0.84)
Median	1.0	1.0	1.0
Q1,Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0
Min, Max	0, 3	0, 5	0, 5
Number of relapses within the past 2 years			
0	2 (3)	1 (1)	3 (2)
1	26 (36)	27 (35)	53 (35)
2	33 (46)	35 (45)	68 (45)
3	8 (11)	10 (13)	18 (12)
>=4	3 (4)	4 (5)	7 (5)
n	72	77	149
Mean (SD)	1.8 (0.94)	1.9 (1.17)	1.9 (1.06)
Median	2.0	2.0	2.0
Q1,Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0
Min, Max	0, 6	0, 7	0, 7
Number of relapses within the past 3 years			
0	2 (3)	0	2 (1)
1	22 (31)	25 (32)	47 (31)
2	37 (51)	36 (46)	73 (49)
3	6 (8)	11 (14)	17 (11)
>=4	5 (7)	5 (6)	10 (7)
n	72	77	149
Mean (SD)	1.9 (1.01)	2.1 (1.19)	2.0 (1.11)
Median	2.0	2.0	2.0
Q1,Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0
Min, Max	0, 6	1, 7	0, 7
Time since most recent pre-study relapse in months			
n	71	77	148
Mean (SD)	4.7 (2.82)	5.3 (4.33)	5.0 (3.69)
Median	4.0	4.0	4.0
Q1,Q3	3.0, 6.0	3.0, 6.0	3.0, 6.0
Min, Max	1, 13	2, 34	1, 34

Baseline EDSS score			
0	23 (32)	24 (31)	47 (31)
1.0	16 (22)	25 (32)	41 (27)
1.5	17 (24)	6 (8)	23 (15)
2.0	9 (13)	14 (18)	23 (15)
2.5	4 (6)	5 (6)	9 (6)
3.0	1 (1)	2 (3)	3 (2)
3.5	0	0	0
4.0	2 (3)	0	2 (1)
4.5	0	0	0
5.0	0	2 (3)	2 (1)
>5.0	0	0	0
<=2.0	65 (90)	69 (88)	134 (89)
>2.0	7 (10)	9 (12)	16 (11)
n	72	78	150
Mean (SD)	1.1 (0.97)	1.2 (1.07)	1.1 (1.02)
Median	1.0	1.0	1.0
Q1,Q3	0.0, 1.5	0.0, 2.0	0.0, 2.0
Min, Max	0, 4	0, 5	0, 5
Dominant hand			
Left	8 (11)	5 (6)	13 (9)
Right	64 (89)	71 (91)	135 (90)
Missing	0	2 (3)	2 (1)

Numbers in parentheses are percentages.

Table 7: Summary of Baseline MRI Evaluation– ITT population

	Avonex (N=72)	**BG00012 240 mg BID (N=78)**	**Total (N=150)**
T1 lesion Volume (mL)			
n	72	77	149
Mean (SD)	1.45 (3.059)	1.31 (1.906)	1.37 (2.522)
Median	0.34	0.64	0.42
Q1,Q3	0.10, 1.15	0.11, 1.39	0.10, 1.29
Min, Max	0.0, 15.8	0.0, 8.8	0.0, 15.8
T2 lesion Volume (mL)			
n	72	78	150
Mean (SD)	8.01 (10.100)	8.67 (9.808)	8.36 (9.921)
Median	4.03	5.33	4.97
Q1,Q3	1.47, 11.04	2.46, 11.06	1.89, 11.06
Min, Max	0.0, 49.6	0.3, 47.1	0.0, 49.6
T2 lesion Count			
n	72	78	150
Mean (SD)	37.24 (32.023)	45.63 (36.304)	41.60 (34.460)
Median	26.50	35.50	30.50
Q1,Q3	17.00, 49.50	20.00, 66.00	18.00, 56.00
Min, Max	0.0, 152.0	5.0, 172.0	0.0, 172.0
Gadolinium-Enhancing Lesion Count			
n	72	77	149
Mean (SD)	3.58 (7.578)	2.35 (3.417)	2.95 (5.825)
Median	1.00	1.00	1.00
Q1,Q3	0.00, 3.00	0.00, 3.00	0.00, 3.00
Min, Max	0.0, 37.0	0.0, 16.0	0.0, 37.0

Prior medication

Table 8: MS Treatment History (ITT Population)

	Avonex (N=72)	BG00012 240 mg BID (N=78)	Total (N=150)
Number of subject who took any prior MS medication	23 (32)	23 (29)	46 (31)
Number of subjects who have taken the following medication prior to study entry	8 (11)	14 (18)	22 (15)
INTERFERON BETA-1A	4 (6)	10 (13)	14 (9)
GLATIRAMER ACETATE	3 (4)	3 (4)	6 (4)
INTERFERON BETA-1B	2 (3)	3 (4)	5 (3)
NATALIZUMAB	0	3 (4)	3 (2)
Other	16 (22)	11 (14)	27 (18)
METHYLPREDNISOLONE SODIUM SUCCINATE	5 (7)	7 (9)	12 (8)
CORTICOSTEROID NOS	6 (8)	2 (3)	8 (5)
PREDNISONE	1 (1)	4 (5)	5 (3)
METHYLPREDNISOLONE	2 (3)	1 (1)	3 (2)
DEXAMETHASONE	1 (1)	0	1 (<1)
PLASMAPHERESIS	1 (1)	0	1 (<1)
PREDNISOLONE	1 (1)	0	1 (<1)
STEROIDS	0	1 (1)	1 (<1)

Concomitant medication

The percentage of patients who took methylprednisolone sodium succinate was similar in each treatment group (Avonex: 18 patients, 25%; Tecfidera 18 patients 23%).

Numbers analysed

Table 9 includes the number of patient per analysis set.

Table 9: Number of Subjects by Analysis Populations

	Avonex (N=72)	BG00012 240 mg BID (N=78)	Total (N=150)
ITT population	72 (100)	78 (100)	150 (100)
Completers population	41 (57)	62 (79)	103 (69)

ITT population is defined as subjects who were randomized and received at least 1 dose of study treatment.
Numbers in parentheses are percentages based on ITT population.
Completers population is defined as subjects from ITT population who completed Week 96 of the study and had MRI data at Week 96.

The ITT Population with week 96 MRI measurements (n =104)

Outcomes and estimation

Primary efficacy endpoint: Proportion of participants free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Week 96

Primary analysis: Completers Population

Table 10: Proportion of subjects with no new or newly enlarging T2 hyperintense lesions at week 96 relative to baseline - Completers Population

	Avonex (N=41)	BG00012 240 mg BID (N=62)	Total (N=103)
Week 96			
Number of subjects included in analysis (a)	41	62	103
Subjects with no new or newly enlarging T2 lesions relative to baseline	2	10	12
Proportion of subjects with no new or newly enlarging T2 lesions relative to baseline	0.049	0.161	0.117
95% CI (b)	(0.006, 0.165)	(0.080, 0.277)	(0.062, 0.195)

CI = confidence interval.
(a)Subjects from the Completers population with baseline and post-baseline MRI measurements at Week 96.
(b)Clopper-Pearson exact 95% confidence interval.

Sensitivity analyses:

1) ITT Population

Table 11: Sensitivity analysis of proportion of participants with no new or newly enlarging T2 hyperintense lesions at week 96 relative to baseline, Logistic Regression - ITT Population

	Avonex (N=72)	BG00012 240 mg BID (N=78)	Total (N=150)
Week 96			
Number of subjects included in analysis	72	78	150
Subjects with no new or newly enlarging T2 lesions relative to baseline	2	10	12
Proportion of subjects with no new or newly enlarging T2 lesions relative to baseline	0.028	0.128	0.080
Odds Ratio (BG00012 vs. Avonex) (a) (b) (c)		6.99	
95% CI (a) (b) (c)		(1.63, 49.88)	
p-value (a) (b) (c)		0.0071	

(a) Based on logistic regression model, adjusted for age group, baseline T2 lesion volume, gender, baseline EDSS and the number of relapses in a year prior to the study.
(b) Odds ratio is the odds of the event (no new or newly enlarging T2 lesions) in the BG00012 group, divided by the odds of the event in the Avonex treatment group. P-value is from the likelihood ratio test that the odds ratio is 1. CI = Profile likelihood confidence interval. (c) One subject was excluded due to missing number of relapses in a year prior to the study.

2) ITT Population with Week 96 MRI measurements (excluding patients without MRI measurements)

Table 12: Sensitivity analysis of proportion of subjects with no new or newly enlarging T2 hyperintense lesions at weeks 24, 48, 72 and 96 relative to baseline, Logistic Regression - ITT Population excluding patients without MRI measurements

	Avonex (N=72)	BG00012 240 mg BID (N=78)	Total (N=150)
Week 24			
Number of subjects included in analysis (a)	64	75	139
Subjects with no new or newly enlarging T2 lesions relative to baseline	9	15	24
Proportion of subjects with no new or newly enlarging T2 lesions relative to baseline	0.141	0.200	0.173
Odds Ratio (BG00012 vs. Avonex) (b) (c) (d)		1.75	
95% CI (b) (c) (d)		(0.67, 4.78)	
p-value (b) (c) (d)		0.2525	
Week 48			
Number of subjects included in analysis (a)	57	73	130
Subjects with no new or newly enlarging T2 lesions relative to baseline	5	14	19
Proportion of subjects with no new or newly enlarging T2 lesions relative to baseline	0.088	0.192	0.146
Odds Ratio (BG00012 vs. Avonex) (b) (c) (d)		2.74	
95% CI (b) (c) (d)		(0.93, 9.33)	
p-value (b) (c) (d)		0.0685	
Week 72			
Number of subjects included in analysis (a)	46	67	113
Subjects with no new or newly enlarging T2 lesions relative to baseline	2	13	15
Proportion of subjects with no new or newly enlarging T2 lesions relative to baseline	0.043	0.194	0.133
Odds Ratio (BG00012 vs. Avonex) (b) (c) (d)		7.77	
95% CI (b) (c) (d)		(1.78, 55.64)	
p-value (b) (c) (d)		0.0047	
Week 96			
Number of subjects included in analysis (a)	42	62	104
Subjects with no new or newly enlarging T2 lesions relative to baseline	2	10	12
Proportion of subjects with no new or newly enlarging T2 lesions relative to baseline	0.048	0.161	0.115
Odds Ratio (BG00012 vs. Avonex) (b) (c) (d)		5.40	
95% CI (b) (c) (d)		(1.22, 38.79)	
p-value (b) (c) (d)		0.0251	

One subject in Avonex group had Week 96 MRI measurements but did not complete the study.
(a) Subjects with baseline and post-baseline MRI measurements at a given visit.
(b) Based on logistic regression model, adjusted for age group, baseline T2 lesion volume, gender, baseline EDSS and the number of relapses in a year prior to
the study.
(c) Odds ratio is the odds of the event (no new or newly enlarging T2 lesions) in the BG00012 group, divided by the odds of the event in the Avonex treatment
group. P-value is from the likelihood ratio test that the odds ratio is 1. CI = Profile likelihood confidence interval.

(d) One subject was excluded due to missing number of relapses in a year prior to the study.

Secondary efficacy endpoints:

MRI Secondary Efficacy Assessments

Number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 24 and 96

Table 13: Summary of number of new or newly enlarged T2 hyperintense lesions at Weeks 24, 48, 72, and 96 relative to baseline - ITT Population excluding patients without MRI measurements

Week 24			
Number of subjects included in analysis (a)	64 (100)	75 (100)	139 (100)
New lesions			
0	9 (14)	15 (20)	24 (17)
1	2 (3)	11 (15)	13 (9)
2	8 (13)	1 (1)	9 (6)
3	6 (9)	6 (8)	12 (9)
4	6 (9)	4 (5)	10 (7)
5-6	3 (5)	6 (8)	9 (6)
7-10	9 (14)	8 (11)	17 (12)
>=11	21 (33)	24 (32)	45 (32)
n	64	75	139
Mean (SD)	11.9 (20.16)	10.0 (14.61)	10.8 (17.35)
Median	5.5	5.0	5.0
Q1, Q3	2.0, 13.5	1.0, 13.0	1.0, 13.0
Min, Max	0, 121	0, 85	0, 121
Adjusted mean number of lesions (95% CI) (b)	9.79 (6.96, 13.78)	7.37 (5.19, 10.48)	
Lesion mean ratio (compared to Avonex) (95% CI) (b)		0.75 (0.50, 1.14)	
Percent reduction (compared to Avonex) (b)		24.71 (-13.57, 50.09)	
p-value (b)		0.1766	
Week 48			
Number of subjects included in analysis (a)	57 (100)	73 (100)	130 (100)
New lesions			
0	5 (9)	14 (19)	19 (15)
1	4 (7)	11 (15)	15 (12)
2	4 (7)	0	4 (3)
3	2 (4)	2 (3)	4 (3)
4	5 (9)	4 (5)	9 (7)
5-6	6 (11)	6 (8)	12 (9)
7-10	7 (12)	6 (8)	13 (10)
>=11	24 (42)	30 (41)	54 (42)
n	57	73	130
Mean (SD)	21.2 (48.20)	13.6 (18.96)	17.0 (34.98)
Median	8.0	6.0	7.0
Q1, Q3	3.0, 17.0	1.0, 16.0	1.0, 17.0
Min, Max	0, 314	0, 100	0, 314
Adjusted mean number of lesions (95% CI) (b)	15.64 (10.61, 23.04)	9.59 (6.74, 13.65)	
Lesion mean ratio (compared to Avonex) (95% CI) (b)		0.61 (0.40, 0.95)	
Percent reduction (compared to Avonex) (b)		38.66 (5.08, 60.36)	
p-value (b)		0.0290	

Week 72			
Number of subjects included in analysis (a)	46 (100)	67 (100)	113 (100)
New lesions			
0	2 (4)	13 (19)	15 (13)
1	2 (4)	9 (13)	11 (10)
2	2 (4)	2 (3)	4 (4)
3	0	1 (1)	1 (<1)
4	2 (4)	3 (4)	5 (4)
5-6	3 (7)	6 (9)	9 (8)
7-10	10 (22)	5 (7)	15 (13)
>=11	25 (54)	28 (42)	53 (47)
n	46	67	113
Mean (SD)	32.7 (68.69)	17.2 (23.67)	23.5 (47.80)
Median	11.5	6.0	9.0
Q1, Q3	7.0, 26.0	1.0, 25.0	2.0, 25.0
Min, Max	0, 359	0, 119	0, 359
Adjusted mean number of lesions (95% CI) (b)	24.06 (15.69, 36.89)	13.26 (9.15, 19.22)	
Lesion mean ratio (compared to Avonex) (95% CI) (b)		0.55 (0.34, 0.89)	
Percent reduction (compared to Avonex) (b)		44.87 (11.49, 65.66)	
p-value (b)		0.0139	
Week 96			
Number of subjects included in analysis (a)	42 (100)	62 (100)	104 (100)
New lesions			
0	2 (5)	10 (16)	12 (12)
1	3 (7)	10 (16)	13 (13)
2	1 (2)	3 (5)	4 (4)
3	0	2 (3)	2 (2)
4	2 (5)	3 (5)	5 (5)
5-6	0	3 (5)	3 (3)
7-10	6 (14)	5 (8)	11 (11)
>=11	28 (67)	26 (42)	54 (52)
n	42	62	104
Mean (SD)	32.1 (67.16)	19.4 (35.79)	24.5 (50.92)
Median	16.0	6.5	11.0
Q1, Q3	8.0, 28.0	1.0, 21.0	2.0, 26.0
Min, Max	0, 429	0, 233	0, 429
Adjusted mean number of lesions (95% CI) (b)	32.65 (20.97, 50.85)	12.42 (8.79, 17.54)	
Lesion mean ratio (compared to Avonex) (95% CI) (b)		0.38 (0.23, 0.62)	
Percent reduction (compared to Avonex) (b)		61.96 (37.91, 76.70)	
p-value (b)		0.0002	

Numbers in parentheses are percentages.
(a) Subjects with baseline and post-baseline MRI measurements at the specified visit.
(b) Estimated from a negative binomial regression model, adjusted for age group and baseline number of T2 hyperintense lesions

Table 14: Sensitivity analysis of number of new or newly enlarged T2 hyperintense lesions relative to baseline, Last Observation on/prior to the week 96 visit - ITT Population excluding patients without MRI measurements

	Avonex (N=72)	**BG00012 240 mg BID (N=78)**	**Total (N=150)**
Week 96			
Number of subjects included in analysis (a)	65	77	142
Adjusted mean number of lesions at Week 96	37.57 (25.70, 54.93)	20.75 (14.43, 29.84)	
Lesion mean ratio (compared to Avonex) (95% CI) (b)		0.55 (0.35, 0.86)	
Percent reduction (compared to Avonex) (95% CI)		44.77 (14.02, 64.53)	
p-value (b)		0.0092	

Only observed new or newly enlarging T2 lesions at the last visit of the subject up to Week 96 visit are used in this analysis.
(a) Subjects with baseline and at least one post-baseline MRI measurements.
(b) Estimated from a negative binomial regression model, adjusted for age group and baseline volume of T2 hyperintense lesions. To account for the timing of the MRI measurement, the logarithmic transformation of the scan number of the MRI assessment is included in the model as the offset parameter.

Table 15: Sensitivity analysis of number of new or newly enlarged T2 hyperintense lesions relative to baseline, Last Observation on/prior to the week 96 Visit, prior to the alternative medication - ITT Population excluding patients without MRI measurements

	Avonex (N=72)	BG00012 240 mg BID (N=78)	Total (N=150)
Week 96			
Number of subjects included in analysis (a)	65	76	141
Adjusted mean number of lesions at Week 96	37.99 (26.02, 55.49)	20.22 (14.09, 29.01)	
Lesion mean ratio (compared to Avonex) (95% CI) (b)		0.53 (0.34, 0.83)	
Percent reduction (compared to Avonex) (95% CI)		46.79 (17.26, 65.78)	
p-value (b)		0.0056	

Only observed new or newly enlarging T2 lesions at the last visit of the subject prior to the alternative medication and up to Week 96 visit are used in this analysis.
(a) Subjects with baseline MRI and at least one post-baseline MRI measurement prior to the alternative medication.
(b) Estimated from a negative binomial regression model, adjusted for age group and baseline volume of T2 hyperintense lesions. To account for the timing of the MRI measurement, the logarithmic transformation of the scan number of the MRI assessment is included in the model as the offset parameter.

Proportion of participants free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 24 and 48

Reference is made to Table 12 above.

At Week 24, the proportion of participants with no new or newly enlarging T2 hyperintense lesions was higher in the Tecfidera group (15 of 75 participants, 20.0%) than the Avonex group (9 of 64 participants, 14.1%).

At Week 48, the proportion of participants with no new or newly enlarging T2 hyperintense lesions was higher in the Tecfidera group (14 of 73 participants, 19.2%) than the Avonex group (5 of 57 participants, 8.8%).

Proportion of participants free of new MRI activity (i.e., free of Gd-enhancing and free of new or newly enlarging T2 MRI lesions on brain MRI scans) at Weeks 24, 48, and 96

Table 16: Proportion of participants free of new MRI activity at weeks 24, 48, 72, and 96 relative to baseline – ITT Population excluding patients without MRI measurements

	Avonex (N=72)	BG00012 240 mg BID (N=78)	Total (N=150)
Week 24			
Number of subjects included in analysis (a)	64	75	139
Subjects free of new MRI activity	9	15	24
Proportion of subjects free of new MRI activity	0.141	0.200	0.173
95% CI (b)	(0.066, 0.250)	(0.116, 0.308)	(0.114, 0.246)
Week 48			
Number of subjects included in analysis (a)	57	73	130
Subjects free of new MRI activity	5	13	18
Proportion of subjects free of new MRI activity	0.088	0.178	0.138
95% CI (b)	(0.029, 0.193)	(0.098, 0.285)	(0.084, 0.210)

Week 72			
Number of subjects included in analysis (a)	46	67	113
Subjects free of new MRI activity	2	12	14
Proportion of subjects free of new MRI activity	0.043	0.179	0.124
95% CI (b)	(0.005, 0.148)	(0.096, 0.292)	(0.069, 0.199)
Week 96			
Number of subjects included in analysis (a)	42	62	104
Subjects free of new MRI activity	2	9	11
Proportion of subjects free of new MRI activity	0.048	0.145	0.106
95% CI (b)	(0.006, 0.162)	(0.069, 0.258)	(0.054, 0.181)

Free of new MRI activity = free of Gd-enhancing lesions at all postbaseline visits up to and including the specified visit, and free of new or newly enlarging T2 MRI lesions relative to baseline at the specified visit.
(a) Subjects with baseline and post-baseline MRI measurements at the specified visit.
(b) Clopper-Pearson exact 95% confidence interval

Table 17: Proportion of subjects free of new MRI activity at week 96 relative to baseline, Logistic Regression – ITT Population excluding patients without MRI measurements

	Avonex (N=72)	**BG00012 240 mg BID (N=78)**	**Total (N=150)**
Week 96			
Number of subjects included in analysis (a)	42	62	104
Subjects free of new MRI activity	2	9	11
Proportion of subjects free of new MRI activity	0.048	0.145	0.106
Odds Ratio (BG00012 vs. Avonex) (b) (c) (d)		8.76	
95% CI (b) (c) (d)		(1.51, 81.44)	
p-value (b) (c) (d)		0.0138	

Free of new MRI activity = free of Gd-enhancing lesions at all postbaseline visits up to and including the specified visit, and free of new or newly enlarging T2 MRI lesions relative to baseline at the specified visit.
(a) Subjects with baseline and post-baseline MRI measurements at the specified visit.
(b) Based on logistic regression model adjusted for age group, baseline T2 lesion volume and number, and baseline Gd lesion number.
(c) Odds ratio is the odds of the event (no new MRI activity) in the BG00012 group, divided by the odds of the event in the Avonex treatment group. P-value is from the likelihood ratio test that the odds ratio is 1. CI = Profile likelihood confidence interval.
(d) One subject was excluded due to missing number of Gd lesions at baseline.

Time to first relapse

Proportion of participants free of relapse up to Week 96

Table 18: Table: Analysis of Time to First Relapse - ITT Population

	Avonex (N=72)	BG00012 240 mg BID (N=78)	Total (N=150)
Number of subjects who relapsed	30 (42)	25 (32)	55 (37)
Number of relapse-free subjects (a)	42 (58)	53 (68)	95 (63)
Time to first relapse (weeks) (b)			
10th percentile	8.7	21.3	11.4
25th percentile	30.4	48.4	40.1
50th percentile	NA	NA	NA
Estimated proportion of subjects who relapsed at (b)			
24 weeks	0.233	0.132	0.180
48 weeks	0.296	0.239	0.267
72 weeks	0.348	0.309	0.328
96 weeks	0.477	0.338	0.401
Estimated proportion of subjects relapse-free at (b)			
24 weeks	0.767	0.868	0.820
48 weeks	0.704	0.761	0.733
72 weeks	0.652	0.691	0.672
96 weeks	0.523	0.662	0.599
Hazard ratio (BG00012/Avonex) (c)(d)		0.574	
95% CI (c)(d)		(0.329, 1.001)	
p-value (c)(d)		0.0505	

Numbers in parentheses are percentages.
(a) Subjects who did not have a relapse, regardless of time in the study.
(b) Based on Kaplan-Meier product limit method.
(c) Based on a Cox proportional hazards model, adjusted for baseline relapse rate (the number of relapses in the 3 years prior to the study, divided by 3), age group and baseline EDSS.
(d) One subject in the BG00012 group was excluded due to missing number of relapses prior to the study

ARR at Weeks 48 and 96

The participant relapse rate was calculated as the number of relapses for each participant divided by the number of years followed in the study for that participant. At Week 48, the mean (SD) participant relapse rate for the Avonex group was 0.609 (1.3126), and for the Tecfidera group, it was 0.403 (1.0366). At Week 96, it was 0.697 (1.2685) for the Avonex group and 0.407 (1.0050) for the Tecfidera group.

Table 19: Summary of annualized relapse rate at weeks 48 and 96 - ITT Population

	Avonex (N=72)	BG00012 240 mg BID (N=78)	Total (N=150)
Week 0-48			
Number of subjects with relapses of			
0	52 (72)	60 (77)	112 (75)
1	14 (19)	14 (18)	28 (19)
2	4 (6)	4 (5)	8 (5)
3	1 (1)	0	1 (<1)
>= 4	1 (1)	0	1 (<1)
Total number of relapses	30	22	52
Total number of subject-years followed	58.65	68.38	127.03
Unadjusted annualized relapse rate (a)	0.511	0.322	0.409
Adjusted annualized relapse rate (b) (c)	0.564	0.324	
(95% CI) (b) (c)	(0.342, 0.931)	(0.188, 0.560)	
Rate ratio (compared to Avonex) (b) (c)		0.575	
(95% CI) (b) (c)		(0.301, 1.095)	
p-value (b) (c)		0.0941	
Subject relapse rate (d)			
n	72	78	150
Mean (SD)	0.609 (1.3126)	0.403 (1.0366)	0.502 (1.1777)
Median	0.000	0.000	0.000
Q1, Q3	0.000, 1.084	0.000, 0.000	0.000, 1.084
Min, Max	0.00, 7.45	0.00, 7.61	0.00, 7.61

Week 48-96			
Number of subjects with relapses of			
0	36 (50)	59 (76)	95 (63)
1	14 (19)	9 (12)	23 (15)
2	3 (4)	2 (3)	5 (3)
3	1 (1)	1 (1)	2 (1)
>= 4	0	0	0
Total number of relapses	23	16	39
Total number of subject-years followed	43.20	60.58	103.78
Unadjusted annualized relapse rate (a)	0.532	0.264	0.376
Adjusted annualized relapse rate (b) (c)	0.367	0.121	
(95% CI) (b) (c)	(0.160, 0.845)	(0.049, 0.301)	
Rate ratio (compared to Avonex) (b) (c)		0.331	
(95% CI) (b) (c)		(0.145, 0.753)	
p-value (b) (c)		0.0058	
Subject relapse rate (d)			
n	54	71	125
Mean (SD)	1.263 (4.0487)	0.335 (0.8747)	0.736 (2.7661)
Median	0.000	0.000	0.000
Q1, Q3	0.000, 1.087	0.000, 0.000	0.000, 0.000
Min, Max	0.00, 24.35	0.00, 4.84	0.00, 24.35
Week 0-96			
Number of subjects with relapses of			
0	42 (58)	53 (68)	95 (63)
1	17 (24)	16 (21)	33 (22)
2	8 (11)	6 (8)	14 (9)
3	3 (4)	2 (3)	5 (3)
>= 4	2 (3)	1 (1)	3 (2)
Total number of relapses	53	38	91
Total number of subject-years followed	101.85	128.96	230.81
Unadjusted annualized relapse rate (a)	0.520	0.295	0.394
Adjusted annualized relapse rate (b) (c)	0.528	0.240	
(95% CI) (b) (c)	(0.333, 0.836)	(0.147, 0.393)	
Rate ratio (compared to Avonex) (b) (c)		0.455	
(95% CI) (b) (c)		(0.260, 0.797)	
p-value (b) (c)		0.0063	
Subject relapse rate (d)			
n	72	78	150
Mean (SD)	0.697 (1.2685)	0.407 (1.0050)	0.546 (1.1445)
Median	0.000	0.000	0.000
Q1, Q3	0.000, 1.088	0.000, 0.543	0.000, 0.546
Min, Max	0.00, 7.45	0.00, 7.61	0.00, 7.61

Numbers in parentheses are percentages.
(a) Total number of relapses that occurred during the study divided by the total number of subject-years followed in the study.
(b) Estimated from a negative binomial regression model, adjusted for the baseline relapse rate, baseline EDSS score and age group. Baseline relapse rate is calculated as the number of relapses in three years prior to study entry divided by 3.
(c) One subject in the BG00012 group was excluded due to missing number of relapses prior to the study.
(d) Number of relapses for each subject divided by the number of years followed in the study for that subject.

Change from Baseline to Week 96 in the EDSS score

Results for the EDSS score were only descriptively summarised: the mean (SD) EDSS score at baseline was 1.12 (0.966) and 1.16 (1.074) for the Avonex and the Tecfidera treatment group, respectively, while at week 96 the mean (SD) EDSS score was 1.19 (1.101) and 1.17 (1.217), respectively, representing almost no changes in EDSS score for both treatment groups from study start until the end of the 96 weeks period.

Fatigue as measured by the PedsQL Multidimensional Fatigue Scale scores and Quality of Life as measured by the PedsQL

There were no trends in the mean or adjusted mean scores in any of the 3 fatigue dimensions (General Fatigue, Sleep/Rest Fatigue, and Cognitive Fatigue) during the study in either the participants' assessments or the parent/legal guardians' assessments. The mean and adjusted mean scores were

generally similar between the treatment groups and similar between participant and parent/legal guardian assessments.

There were no trends in the mean or adjusted mean scores in any of the 4 dimensions (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning) during the study in either the participants' assessments or the parent/legal guardians' assessments.

Exploratory efficacy endpoints:

Number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 48 and 72: Reference is made to table 13

Proportion of participants free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Week 72: Reference is made to table 12

Proportion of participants free of new MRI activity (i.e., free of Gd-enhancing and free of new or newly enlarging T2 MRI lesions on brain MRI scans) at Week 72: Reference is made to table 16

Number of new T1 hypointense lesions on brain MRI scans at Weeks 24, 48, 72, and 96 *(based on the ITT Population excluding patients without MRI measurements)*

Number of new T1 hypointense lesions at Week 96: Mean (SD): Avonex, 15.7 (38.17); Tecfidera, 9.7 (19.90), Adjusted mean (95% CI): Avonex, 18.82 (11.16, 31.75); Tecfidera, 7.83 (5.29,11.58), Percent reduction for Tecfidera compared to Avonex (95% CI): 58.41% (25.11,76.90), p-value: 0.0039, Participants with no new lesions: Avonex 4 (10%); Tecfidera 14 (23%)

Number of Gd-enhancing lesions on brain MRI scans at weeks 24, 48, 72 and 96

At all timepoints, the majority of participants in both treatment groups had no Gd-enhancing lesions; the proportion was higher in the Tecfidera group than the Avonex group at all timepoints. Based on an ordinal logistic regression adjusted for age group and number of Gd-enhancing lesions at baseline, there were no statistically significant differences in proportions between the treatment groups at any timepoint (based on OR). At Week 96, the OR of being in the group with higher Gd lesions in the Tecfidera group versus Avonex group was 0.43 (95% CI: 0.18, 1.03), p = 0.0596.

Table 20: Summary of Gd-Enhancing Lesion Count at Weeks 24, 48, 72, and 96 - ITT Population excluding patients without MRI measurements

	Avonex (N=72)	BG00012 240 mg BID (N=78)	Total (N=150)
Week 24			
Number of subjects included in analysis (a)	64 (100)	76 (100)	140 (100)
0	36 (56)	52 (68)	88 (63)
1-2	17 (27)	18 (24)	35 (25)
3-4	5 (8)	1 (1)	6 (4)
>=5	6 (9)	5 (7)	11 (8)
n	64	76	140
Mean (SD)	1.8 (4.58)	0.9 (2.49)	1.3 (3.61)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 1.5	0.0, 1.0	0.0, 1.0
Min, Max	0, 27	0, 13	0, 27
Odds ratio (compared to Avonex) (95% CI) (b) (c)		0.60 (0.29, 1.23)	
p-value(b) (c)		0.1627	

Week 48			
Number of subjects included in analysis (a)	57 (100)	73 (100)	130 (100)
0	38 (67)	55 (75)	93 (72)
1-2	11 (19)	10 (14)	21 (16)
3-4	3 (5)	3 (4)	6 (5)
>=5	5 (9)	5 (7)	10 (8)
n	57	73	130
Mean (SD)	1.5 (5.10)	0.8 (1.98)	1.1 (3.69)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 1.0	0.0, 0.0	0.0, 1.0
Min, Max	0, 36	0, 10	0, 36
Odds ratio (compared to Avonex) (95% CI) (b) (c)		0.75 (0.34, 1.69)	
p-value(b) (c)		0.4917	
Week 72			
Number of subjects included in analysis (a)	46 (100)	67 (100)	113 (100)
0	31 (67)	51 (76)	82 (73)
1-2	8 (17)	6 (9)	14 (12)
3-4	2 (4)	3 (4)	5 (4)
>=5	5 (11)	7 (10)	12 (11)
n	46	67	113
Mean (SD)	1.7 (5.15)	1.3 (3.32)	1.5 (4.14)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 1.0	0.0, 0.0	0.0, 1.0
Min, Max	0, 33	0, 17	0, 33
Odds ratio (compared to Avonex) (95% CI) (b) (c)		0.77 (0.32, 1.81)	
p-value(b) (c)		0.5434	
Week 96			
Number of subjects included in analysis (a)	42 (100)	62 (100)	104 (100)
0	25 (60)	47 (76)	72 (69)
1-2	13 (31)	9 (15)	22 (21)
3-4	1 (2)	2 (3)	3 (3)
>=5	3 (7)	4 (6)	7 (7)
n	42	62	104
Mean (SD)	1.3 (3.54)	1.4 (5.12)	1.3 (4.53)
Median	0.0	0.0	0.0
Q1, Q3	0.0, 1.0	0.0, 0.0	0.0, 1.0
Min, Max	0, 21	0, 35	0, 35
Odds ratio (compared to Avonex) (95% CI) (b) (c)		0.43 (0.18, 1.03)	
p-value(b) (c)		0.0596	

Numbers in parentheses are percentages.
(a) Subjects with MRI measurements at the specified visit.
(b) The odds ratio and the p-value are based on the ordinal logistic regression, adjusted for age group and the number of Gd-enhancing lesions at baseline. Gd lesion categories used in the ordinal logistic regression are: 0, 1-2, 3-4, >=5. Odds ratio is the odds of the event (being in a higher group for Gd lesions in the BG00012 treatment group), divided by the odds of the same event in the Avonex treatment group.
(c) One subject was excluded due to missing number of Gd lesions at baseline. Baseline number of Gd lesions was truncated at 20 for three subjects.

Time to progression of disability at Week 96

Few patients [4 patients (6%) in the Avonex group and 7 (9%) patients in the Tecfidera group] experienced a confirmed disability progression as defined during the 96-week treatment period.

BVMT-R scores, SDMT scores, and school progression query at Weeks 48 and 96

According to the Applicant, the mean BVMT-R scores at Baseline for each of the 3 trials and mean changes from baseline for each of the 3 trials over time were generally similar in the 2 treatment groups.

Mean SDMT scores at Baseline were similar in the 2 treatment groups. Mean changes from baseline over time were higher in the Tecfidera group than in the Avonex group.

At Week 48, the percentage of participants in both treatment groups who progressed to the next grade in school were the same (among those evaluated): Avonex, 38 of 41 participants (93%); Tecfidera, 56 of 60 participants (93%). At Week 96, 49 of 57 participants (86%) evaluated in the Avonex group and 68 of 74 participants (92%) evaluated in the Tecfidera group progressed to the next grade in school.

Ancillary analyses

Subgroup analyses were performed for the primary endpoint in the ITT Population based on pubertal status determined by Tanner Stage.

Table 21: Proportion of participants with no new or newly enlarging T2 hyperintense lesions at week 96 relative to baseline – participants' pre-pubertal status at onset of disease initiation

	Avonex (N=13)	BG00012 240 mg BID (N=16)	Total (N=29)
Week 96			
Number of subjects included in analysis (a)	9	15	24
Subjects with no new or newly enlarging T2 lesions relative to baseline	1	1	2
Proportion of subjects with no new or newly enlarging T2 lesions relative to baseline	0.111	0.067	0.083
95% CI (b)	(0.003, 0.482)	(0.002, 0.319)	(0.010, 0.270)

CI = confidence interval.
(a)Number of subjects prepubertal at onset of disease initiation.
(b)Clopper-Pearson exact 95% confidence interval.

Table 22: Proportion of participants with no new or newly enlarging T2 hyperintense lesions at week 96 relative to baseline – participants' pre-pubertal status at screening

	Avonex (N=5)	BG00012 240 mg BID (N=5)	Total (N=10)
Week 96			
Number of subjects included in analysis (a)	4	4	8
Subjects with no new or newly enlarging T2 lesions relative to baseline	1	0	1
Proportion of subjects with no new or newly enlarging T2 lesions relative to baseline	0.250	0.000	0.125
95% CI (b)	(0.006, 0.806)	(0.000, 0.602)	(0.003, 0.527)

CI = confidence interval.
(a)Number of subjects prepubertal at screening.
(b)Clopper-Pearson exact 95% confidence interval.

Comparison of clinical efficacy in the paediatric population and in young adults:

The Tecfidera studies DEFINE and CONFIRM (Study 109MS301 and Study 109MS302) included participants aged 18 to 55 years with a diagnosis of RRMS (McDonald criteria) and baseline EDSS score between 0 and 5.0, inclusive [Soman 2015]. Participants were randomised to Tecfidera 240 mg BID or three times a day, placebo, or GA (Study 109MS302 only) for up to 96 weeks. The integrated ITT Population included 771 participants receiving Tecfidera BID and 769 participants receiving placebo. Of these, 74 participants in the Tecfidera BID group and 87 participants in the placebo group were aged 18 to 25 years.

According to the Applicant, in young adults, Tecfidera BID was associated with a 71% reduction in the adjusted ARR at 2 years: the ARR was 0.2 for the Tecfidera BID group and 0.67 for the placebo group (rate ratio [95% CI] 0.29 [0.17, 0.51]; $p < 0.0001$). This compared favourably with the 49% reduction in the adjusted ARR observed with Tecfidera BID versus placebo in the overall integrated ITT Population (ARR 0.52 [0.43, 0.62]; $p < 0.0001$). The estimated proportion of participants aged 18 to 25 years who

relapsed was also significantly lower with Tecfidera BID (26.1%) than with placebo (58.4%), representing a 66% reduction; HR (95% CI) for Tecfidera/placebo, 0.34 (0.20, 0.59); p < 0.0001. Among young adults at 2 years, Tecfidera BID also demonstrated significant reductions in the number of new or newly enlarging T2 lesions (66% reduction vs. placebo; p < 0.0001) and Gd-enhancing lesions (73% reduction vs. placebo; p = 0.0027). The proportion of young adults with 12-week confirmed disability progression at 2 years was 3-fold lower in the Tecfidera BID group (6.3%) than the placebo group (18.9%), resulting in a 75% reduction (HR [95% CI] for Tecfidera BID/placebo, 0.25 [0.08, 0.77]; p = 0.0151).

Summary of main study

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

Table 23: Summary of Efficacy for trial 109MS306 Part1

Title: An open-label, randomized, multicenter, multiple-dose, active-controlled, parallel-group, efficacy and safety study of BG00012 in children from 10 to less than 18 years of age with relapsing-remitting multiple sclerosis, with optional open-label extension			
Study identifier	109MS306 Part1		
Design	open-label, randomised, parallel-group, active-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		96 weeks after randomisation up to 6 weeks Up to 5 years
Hypothesis	Exploratory: descriptive summary of primary endpoint by treatment arm		
Treatments groups	Dimethyl fumarate		Oral dimethyl fumarate capsules BID: 120 mg BID for the first days thereafter 240 mg BID n = 78 randomised and dosed
	Interferon ß-1 a		30 µg administered as intramuscular (im) injection once weekly. Start with a dose of 7.5 µg and increased by 7.5 µg each week for 3 weeks until 30 µg was achieved. n = 72 randomised and dosed
Endpoints and definitions	Primary endpoint	Proportion of subjects free of new or newly enlarging T2 hyperint. lesions on brain MRI scans at week 96	The analysis included summary statistics and exact CIs (using the Clopper-Pearson method) for the proportion of participants free of new or newly enlarging T2 hyperintense lesions at Week 96 for each treatment group. Data were summarized using observed values.
	Secondary endpoint	Number of new or newly enlarging T2 hyperint. lesions on brain MRI scans at weeks 24 and 96	A negative binomial regression model was used to analyse the number of new or newly enlarging T2 hyperintense lesions at both Week 24 and at Week 96, with treatment group in the model and adjusted for age group and baseline number of T2 lesions. Formal statistical testing was performed to compare the mean between the 2 treatment groups. Analyses of the number of Gd-enhancing lesions were performed similarly.
	Secondary endpoint	Proportion of subjects free of new MRI activity at weeks 24, 48 and 96	Analysed similarly as the primary endpoint. Participants were considered free of MRI activity if they were free of Gd-enhancing lesions at all post-baseline visits up to and including the specified visit and free of new or newly enlarging T2 lesions relative to Baseline.

	Secondary endpoints	Time to first relapse & proportion of subjects free of relapse up to week 96	Analyses were presented based on the Kaplan-Meier method. If participants did not experience a relapse during Part 1 of the study, they were censored at their last visit in Part 1. Time to first relapse was also analysed using the Cox proportional hazards model, adjusted for baseline relapse rate, baseline EDSS score, and age group. Several uncertainties remain whether the examining neurologist has sufficiently been blinded.
	Secondary endpoint	ARR	Reduction of the annualised relapse rate
	Secondary endpoint	EDSS score	Change from baseline summarised descriptively at each visit
	Exploratory endpoint	Number of Gd-enhancing lesions on brain MRI scans at weeks 24, 48, 72 and 96	See above
Database lock	unclear		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary analysis for the primary endpoint was based on the Completers population (Dimethyl fumarate: n = 62; IFN: n = 41) For all MRI based secondary endpoints, the primary analysis was based on the ITT Population excluding patients without MRI measurements at that visit (e.g.at week 96: Dimethyl fumarate: n = 62; IFN: n = 42) For ARR and EDSS scores the primary analysis was based on the ITT population (patients who were randomised and received at least 1 dose of study treatment) (Dimethyl fumarate: n = 78; IFN: n = 72)		
Descriptive statistics and estimate variability	Treatment group	Dimethyl fumarate	Interferon ß-1a (IFN)
	Primary endpoint: Proportion of participants free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Week 96	0.161	0.049
	95%CI	(0.080, 0.277)	(0.006, 0.165)
	Secondary endpoint: Number of new or newly enlarging T2 hyperint. lesions on brain MRI scans at week 96 adjusted mean number of lesions	12.42	32.65
	95%CI	(8.79, 17.54)	(20.97, 50.85)
	Secondary endpoint: Proportion of subjects free of new MRI activity at week 96 Proportion of subjects free of new MRI activity 95%CI	0.145 (0.069, 0.258)	0.048 (0.006, 0.162)
	Secondary endpoint: Proportion of subjects free of relapse up to week 96 (derived from time to first relapse analysis) Estimated proportion of subjects who relapsed at week 96 (Kaplan-Meier estimate)	0.338	0.477

	Secondary endpoint: ARR at week 96 Adjusted annualised relapse rate 95%CI	0.240 (0.147, 0.393)	0.528 (0.333,0.836)
	Secondary endpoint: Change from baseline in EDSS score (mean) (SD) at week 96	1.17 (1.217)	1.19 (1.101)
	Exploratory endpoint: Number of Gd-enhancing lesions at week 96 (mean) (SD)	1.4 (5.12)	(1.3 (3.54)

Effect estimate per comparison	Secondary endpoint: Number of new or newly enlarging T2 hyperint. lesions on brain MRI scans at week 96	Comparison groups	Dimethyl fumarate vs. IFN
		Percent reduction	61.96
		95% CI	(37.91, 76.70)
		P-value	0.0002*
	Secondary endpoint: Proportion of subjects free of new MRI activity at week 96	Comparison groups	Dimethyl fumarate vs. IFN
		Odds Ratio	9.76
		95% CI	(1.51, 81.44)
		P-value	0.0138*
	Secondary endpoint: Time to first relapse	Comparison groups	Dimethyl fumarate vs. IFN
		Hazard ratio	0.574
		95 %CI	(0.329, 1.001)
		P-value	0.0505*
	Secondary endpoint: ARR at week 96	Comparison groups	Dimethyl fumarate vs. IFN
		Rate ratio	0.455
		95% CI	(0.260, 0.797)
		p-value	0.0063*
	Secondary endpoint: Change from baseline in EDSS score Mean (SD)	Comparison groups	Dimethyl fumarate vs. IFN
		n.a.	Dimethyl fumarate: -0.03 (1.045) IFN: 0.13 (0.748)
	Exploratory endpoint: Number of Gd-enhancing lesions at week 96 (mean) (SD)	Comparison groups	Dimethyl fumarate vs. IFN
		Odds ratio	0.43
		95% CI	(0.18, 1.03)
		p-value	0.0596*
Notes	The primary analysis and several of the analyses of secondary endpoints were based on the Completers population (or patients with MRI data at the respective visit). This is not considered appropriate as the completer population is probably a selected population such that analyses based on these population are biased, as the outcomes in patients with missing data are expected to be different than for patients with observed data. Therefore, analyses based on the ITT population are considered of primary relevance. No comparison between treatment arms was planned for the primary analysis and no procedure for multiplicity adjustment was pre-specified. *All p-values should be considered as descriptive.		
Analysis description	**Sensitivity analysis of the primary endpoint in the ITT population (pre-specified)**		
Descriptive statistics and estimate variability	Treatment group	Dimethyl fumarate	IFN
	Proportion of participants free of new or newly enlarging T2 hyperintense lesions relative to baseline Week 96	0.128	0.028
Effect estimate per comparison	Comparison groups Odds ratio 95% CI p-value	Dimethyl fumarate vs IFN 6.99 (1.63, 49.88) 0.0071*	

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

N/A

Clinical studies in special populations

N/A

Supportive studies

Reference is also made to section 2.3.2 (Pharmacokinetics).

Study 109MS202 was a phase II, 24-week, open-label, uncontrolled study to assess the effect of BG00012 on MRI lesions and Pharmacokinetics in paediatric patients with RRMS aged 10 to 17 years (n =22).

Study 109MS311 was the 96 week extension of study 109MS202 to determine the long-term safety and efficacy of BG00012 in paediatric patients with relapsing-remitting multiple sclerosis (n =20).

3.4.3. Discussion on clinical efficacy

In support of efficacy of DMF (synonym: Tecfidera, BG00012) in paediatric RRMS patients aged 10 years and older, which has been updated during this procedure to '13 years of age and older', the Applicant submitted one pivotal study in line with the agreed PIP (EMEA-000832-PIP01-10).

Study 109MS306 Part 1 was an open-label, randomized, multicenter, multiple-dose, active-controlled, parallel-group, efficacy and safety study of BG00012 in children from 10 to less than 18 years of age with relapsing-remitting multiple sclerosis, with optional open-label extension.

No dedicated dose response study in this population was conducted by the MAH. Consistent with the treatment regimen in adult RRMS patients, the proposed starting dose for Tecfidera in the paediatric population is 120 mg BID, orally, to be increased to 240 mg BID after 7 days. This dosing regimen has also been chosen in a previous paediatric study, study 109MS202, that has been matter of assessment in 2017 (EMEA/H/C/002601/II/0042) (Reference is made to 3.3.). As of the date of the study conduct, the choice and the dose of the active comparator IFN ß-1a is considered adequate. It also has been used in the paediatric study for Gilenya (EMEA/H/C/002202/X/0044/G).

The population enrolled in study 109MS306 (n = 156; in a 1:1 ratio for IFN ß-1a and Tecfidera, stratified according to whether or not the participant received therapy with IFN β-1a or GA in the 4 weeks prior to study entry and in accordance with the following 3 age groups (10 to < 13 years: at least 10 evaluable patients, 13 to < 15 years: at least 20 evaluable patients, and 15 to < 18 years: at least 60 evaluable patients) was composed of males (33%) and females (67%) aged from 10 to 17 years with a median age of 15.0 years. There were 5 patients in the Avonex group who withdrew from the study before first treatment and 1 patient in the Tecfidera group who was randomised but not treated. According to the Applicant, this was due to the open-label nature of the trial: patients withdrew from the trial after realising what treatment they were assigned to.

After protocol version 5 (25 July 2017) has been completed, 34 patients were randomised to the Avonex arm and 34 patients were randomised to Tecfidera. The provided randomisation list shows, that several patients in the year 2018 still have been randomised based on protocol version 4 (not including the stratification according to whether or not the participant received therapy with IFN β-1a or GA in the 4 weeks prior to study entry). However, as none of these patients used IFN β-1a or GA in the 4 weeks prior to study entry, the delayed implementation of the protocol amendment did not affect the study outcomes.

The percentage of children <13 years was small (10%, as agreed by PDCO) and was also limited for those who were pre-pubertal (Tanner staging score of 1) at baseline [Avonex four patients (2 male and two female) vs. Tecfidera 1 male patient]. The mean number of relapses within the past year was comparable between the two treatment arms (mean = 1.6, median 1.0) as were the number of relapses within the past two years and the past three years (mean = 1.9, median 2.0 and mean = 2.0, median 2.0, respectively). Besides 2 patients under Avonex and 1 patient under Tecfidera, all patients

experienced relapses within the past 2 years. Regarding the disease progression stage, the study population consisted of rather newly diagnosed RRMS patients with a mean time since MS diagnosis of about 0.8 years (median = 0 years) and a mean time since first symptoms of MS of about 1.5 years (median = 1.0 years). The overall mean EDSS score at baseline was 1.1 representing almost no disability with only minimal signs in some functional systems. The mean number of T2 lesions at baseline was 37.24 (32.023) and 45.63 (36.304) in the Avonex and Tecfidera groups, respectively while the mean number of Gd-enhancing lesions was 3.58 (7.578) and 2.35 (3.417) in the Avonex and Tecfidera groups, respectively. Thus, the included patient population mainly consisted of early stage RRMS patients.

Around 69% of patients were naïve to previous MS treatment. Based on the overall study population, only 14 patients (9%) had taken IFN β-1a prior to study entry (Avonex group: 4 patients, 6%; Tecfidera group: 10 patients, 13%) and 6 patients (4%) had taken GA prior to study entry (3 patients, 4% in each treatment group). The imbalance across the two treatment arms with regard to IFN ß-1a pre-treatment might be caused by the number of patients who dropped out in the Avonex arm after they were aware that they had been randomised to IFN treatment.

The primary endpoint, the "proportion of subjects free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at week 96" was recommended by the PDCO (EMEA-000832-PIP01-10) and is considered appropriate although MRI endpoints are currently not recommended in the Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev.2) to demonstrate evidence of efficacy in confirmatory studies. Nevertheless, paediatric MS is dominated by inflammation and MRI can act as a marker for inflammatory activity. Typical MRI parameter for assessing the inflammatory component of MS are Gd-enhancing lesions and new/newly enlarging T2 lesions. Both have been widely used in clinical studies. Since they have been related to relapses, the most important clinical component of paediatric MS, they are considered important endpoints to reflect disease activity. Apart from that MRI endpoints played a key role in the assessment of efficacy for the paediatric indication of Aubagio (EMA/CHMP/289596/2021). With the responses, the Applicant clarified, that analyses of the primary endpoint, the "proportion of subjects free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at week 96" were based on all available MRI scans, including scheduled and unscheduled visits.

The secondary endpoints, e.g. the number of new or newly enlarging T2 hyperintense lesions on brain MRI scans, the proportion of subjects free of new MRI activity (i.e., free of Gd-enhancing and free of new or newly enlarging T2 MRI lesions on brain MRI scans) and the number of Gd-enhancing lesions on brain MRI scans (assessed as exploratory endpoint) are also supportive to reflect disease activity.

Other secondary endpoints included time to first relapse, proportion of subjects free of relapse, ARR, EDSS score, Fatigue and Quality of life. Cognition and time to disability progression as well as further MRI related endpoints were assessed as exploratory endpoints.

Statistical analyses included descriptive statistics and regression models for the comparisons between Tecfidera and Avonex (logistic regression for response endpoints, negative binomial regression for count data, time-to-event methods). Analyses were primarily performed based on the patients with non-missing data. As pre-specified primary analysis, providing descriptive statistics for the primary endpoint by treatment arm was specified. No confirmatory hypothesis test for comparing Tecfidera and Avonex was pre-planned, neither for superiority nor for non-inferiority. This includes that no procedure for multiplicity adjustment was specified. Furthermore, statistical analyses for primary and secondary endpoints were not specified in full details in study protocol or statistical analysis plan. The primary analysis of the primary endpoint and several of the analyses of secondary endpoints were based on the Completers population (or patients with MRI data at the respective visit). Analyses based on the patients with non-missing data is not according to usual standards as it may lead to a relevant selection bias. Sensitivity analyses based on the ITT-population were conducted but methods for missing data handling

in these analyses were not pre-specified and it is not clear in how far the results depend on the assumptions that were made for missing data.

In summary, the analyses should be considered descriptive and do not provide confirmatory evidence of efficacy for Tecfidera in the paediatric population.

The study has been conducted in an open-label design, which is comprehensible, as in case of the use of an injectable drug as comparator in a paediatric setting, a DB, double-dummy design to blind the two formulations (Tecfidera oral vs- e.g. IFN-ß) is not justified when Tecfidera treated patients would have been required to take additional placebo intramuscular injections once a week. As MRI scans were transferred electronically, read and interpreted by an independent blinded assessment centre, bias for the assessment of the primary endpoint can be excluded. Based on the Applicant´s responses to the RSI, it is considered that any potential bias from de-blinding the examining neurologist to the clinical endpoints, e.g. relapse confirmation, was limited. In addition, as the outcome on clinical relapses and data for new or newly enlarging T2 lesions, both representing disease activity, were concordant in the two treatment arms, the measures taken to maintain the blind for the assessment of the clinical endpoints are expected to have been sufficient, although no explicit information is given, whether e.g. injection sites had to be sufficiently covered, to maintain the blind as far as possible. Overall, also taking into consideration, that the ARR has been evaluated as a secondary endpoint in this open label study, the blinding could be considered acceptable.

Overall, the number of patients who had at least 1 major protocol deviation is considerably high with 126 out of 150 patients (84%). 16 patients (11%) had major "efficacy criteria"-related protocol deviations, 84 patients (56%) had major protocol deviations related to "study procedure criteria". However, the latter also might have been related to the efficacy outcome, e.g. incorrect order or wrong timespan for steroid-treatment and conduct of MRI after a relapse had occurred. With the response to the RSI, the Applicant clarified, that no sites or participants were excluded from the analyses due to protocol deviations based on internal protocol deviation review procedures. In addition, the Applicant provided post hoc per-protocol analyses for the primary endpoint, the key secondary endpoint and the ARR in line with those that have been performed in the adult studies for Tecfidera, study 109MS301 and study 109MS302. These per protocol analyses considered inclusion and compliance criteria to demonstrate that the amount of protocol deviations in study 109MS306 did not impact the efficacy results. Results of the provided analyses were overall consistent with those performed in the ITT population. Although the provided PP analyses considered only some specific categories of major deviations, it is not expected that further analyses would differ from the provided analyses. Therefore, the number of major protocol deviations in study 109MS306 is not expected to influence the overall efficacy results to a relevant extent, in addition, respective protocol deviations were well distributed across both treatment groups.

No subgroup analyses have been pre-specified. Given the overall small number of patients in both treatment arms, this is considered acceptable.

The Applicant also provided a comparison of clinical efficacy in the paediatric population against young adults, aged 18 to 25 years. Data for young adults are based on the pooled analyses for studies 109MS301 and 109MS302 in adults. Although neither the pooled analyses for studies 109MS301 and 109MS302 nor the subgroup analyses for young adults were pre-specified, they provide supportive information.

Efficacy data and additional analyses

Of the 156 randomised patients, 150 patients received at least 1 dose of study treatment (ITT Population): 72 patients under Avonex and 78 patients under Tecfidera treatment.

The completion rate of treatment at week 96 was 69% (n= 103 patients) in the ITT population (150 patients). More patients in the Tecfidera group (61 patients, 78%) than in the Avonex group (42 patients, 58%) completed treatment. The most common reasons for study treatment discontinuation were consent withdrawn (15 patients, 10%), AE (14 patients, 9%), and Investigator decision (13 patients, 9%). Treatment discontinuation due to "consent withdrawn" and "investigator decision" was higher in the Avonex treatment group when compared to Tecfidera treatment [11 (15%) versus 4 (5%), and 9 (13%) versus 4 (5%), respectively] while a comparable percentage of patients in both treatment groups discontinued treatment because of an "adverse event" (Avonex: 8 patients, 11%; Tecfidera: 6 patients, 8%). Treatment discontinuation due to the aspect "lack of efficacy" has not been assessed. However, according to the Applicant who referred to the free-text entries under the heading "reason for discontinuation of treatment" as part of "subject disposition and reasons for discontinuation of treatment and/or withdrawal from study", the following terms indicate medication ineffectiveness or disease progression: "MS relapse," "relapse(s)," "MS worsening," "progression of MS," "progression of disease," "ineffectiveness," "new lesions on MRI," "MRI progression," "lack of efficacy," "no efficacy," and "iconographic aggravation." Taken this into consideration, treatment discontinuation due to medication ineffectiveness or disease progression, both representing insufficient efficacy, was higher in the Avonex treatment group (12 patients, 17%) when compared to Tecfidera treatment (6 patients, 8%).

The proportion of patients who entered Part 2 of the study was considerably higher in the Tecfidera treatment group as compared to treatment with Avonex (57 (73%) vs. 35 (49%), respectively).

Demographic and disease characteristics overall were adequately balanced across the two groups and representative for the paediatric RRMS population.

With regard to the primary analysis of the primary endpoint that has been performed in the Completers Population, the proportion of patients with no new or newly enlarging T2 hyperintense lesions at week 96 relative to baseline was higher in the Tecfidera group (10 of 62 patients, 16.1% [95% Clopper-Pearson exact CI: 8.0%, 27.7%]) than in the Avonex group with 2 of 41 patients, 4.9% [95% Clopper-Pearson exact CI: 0.6%, 16.5%]. However, the primary analysis included a rather selected population, i.e., only patients who completed 96 weeks of treatment and who had a MRI at week 96. In particular, the differential drop-out (leading to imbalanced sample size of 41 under Avonex and 62 patients under Tecfidera) raises concerns on a relevant selection bias.

In a "sensitivity analysis", that has been performed in the ITT population, the proportion of patients with no new or newly enlarging T2 hyperintense lesions at week 96 relative to baseline was higher in the Tecfidera group with 10 of 78 patients (12.8%) than in the Avonex group (2 of 72 patients, 2.8%). The OR for the proportion of patients with no new or newly enlarging T2 hyperintense lesions at Week 96 in the Tecfidera group compared with the Avonex group was 6.99 (95% CI: 1.63, 49.88). This sensitivity analysis, including all randomised and treated patients without selection, is the analysis considered to be of most relevance. Missing data was replaced by non-response imputation in this analysis. The estimate of the proportion of patients with no new or newly enlarging T2 lesions relative to baseline under Tecfidera is conservative when using non-response imputation. However, for the comparison of Tecfidera vs Avonex, the non-response imputation may have led to bias in favour of Tecfidera because more data were missing for Avonex. Overall, while suggesting a trend in favour of Tecfidera, the results should be interpreted with caution. They should be considered descriptive and cannot be interpreted to confirm superiority of Tecfidera vs. Avonex because of methodological limitations (open-label design, no type 1 error control, methods not pre-specified in full details, particularly no method for missing data handling pre-specified).

With regard to secondary endpoints, the number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Week 96, the adjusted mean number of new or newly enlarging T2 hyperintense lesions was 32.65 (95% CI: 20.97, 50.85) for the Avonex group and 12.42 (95% CI: 8.79, 17.54) for the Tecfidera group, corresponding to a 61.96% reduction in the Tecfidera group compared to the Avonex group. However, as the analysis only included patients with MRI measurements at the given visit and excluded those without MRI measurements, these analyses have to be interpreted with caution, given that this is a selected population and bias due to differential selection in the two treatment arms cannot be excluded.

In addition, two sensitivity analyses (a) number of new or newly enlarged T2 hyperintense lesions relative to baseline, Last Observation on/prior to the week 96 visit, b) number of new or newly enlarged T2 hyperintense lesions relative to baseline, Last Observation on/prior to the week 96 Visit, prior to the alternative medication have been performed. These analyses are considered more appropriate than the analyses based on the completers, as only patients without post-baseline data were excluded, which is still not ideal but means that less patients were excluded than in the completer analysis. The analysis addresses the hypothetical effect if all patients completed treatment as planned (without taking alternative medications) under a missing at random assumption. Both analyses showed a trend in favour of Tecfidera as well, but the difference in favour of Tecfidera was smaller than in the completer analysis.

Overall, analyses on the number of new or newly enlarging T2 hyperintense lesions were consistent with the primary endpoint analysis. However, as the proportion of participants free of new or newly enlarging T2 hyperintense lesions on brain MRI scans is based on the number of new or newly enlarging T2 lesions, this outcome is not unexpected.

At week 96, the proportion of patients free of new MRI activity (i.e., free of Gd-enhancing and free of new or newly enlarging T2 MRI lesions on brain MRI scans) relative to baseline was higher in the Tecfidera group (9 of 62 patients, 14.5%) than in the Avonex group with 2 of 42 patients (4.8%) (OR for proportions: 8.76 (95% CI: 1.51, 81.44), indicating a better treatment effect for Tecfidera compared to Avonex. Overall, results were in line with those of the primary endpoint. However, again it has to be stressed, that the restriction of the analysis population to the patients who had an MRI at the given visit may result in a relevant selection bias that limits the overall conclusion.

The Kaplan-Meier estimate of the probability for clinical relapse was 34% in the Tecfidera group and 48% in the Avonex group during the 96-week open-label study period. The hazard ratio (HR) for relapse was 0.574 (95% CI: 0.329 to 1.001). In comparison to Avonex the time to first relapse was delayed in the Tecfidera treatment arm.

At Week 96, the adjusted ARR for the Avonex group was 0.528 (95% CI: 0.333, 0.836), and 0.240 (95% CI: 0.147, 0.393) for the Tecfidera group (rate ratio 0.46, 95% CI (0.26,0.78). Generally, there was an obviously low relapse rate across both treatment groups. Most of the patients in both treatment arms experienced 0 relapses (Avonex 58%, Tecfidera 68%) up to week 96.

As to be expected in the paediatric MS population with a generally rather low disability progression, no relevant changes in EDSS scores were seen from study start until the end of the 96 weeks period. Results for the EDSS score were only descriptively summarised: the mean (SD) EDSS score at baseline was 1.12 (0.966) and 1.16 (1.074) for the Avonex and the Tecfidera treatment group, respectively, while at week 96 the mean (SD) EDSS score was 1.19 (1.101) and 1.17 (1.217), respectively, representing almost no changes in EDSS score for both treatment groups.

There were no trends in the mean or adjusted mean scores in any of the 3 fatigue dimensions (General Fatigue, Sleep/Rest Fatigue, and Cognitive Fatigue) during the study in either the participants' assessments or the parent/legal guardians' assessments. The mean and adjusted mean scores were generally similar between the treatment groups and similar between participant and parent/legal

guardian assessments. There were no trends in the mean or adjusted mean scores in any of the 4 dimensions (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning) during the study in either the participants' assessments or the parent/legal guardians' assessments.

Chronic or persistent T1-hypointense lesions (black holes) in MRI have been related to irreversible tissue loss in MS patients. Tecfidera lead to nominal reduction in the mean number of new hypointense T1 lesions.

At all visits, most of the patients in both treatment groups had no Gd-enhancing lesions with a generally higher proportion in the Tecfidera group than in the Avonex group. At Week 96 the mean number of Gd-enhancing lesions was 1.3 under Avonex compared to 1.4 under Tecfidera. The OR of being in the group with higher Gd lesions in the Tecfidera group versus Avonex group was 0.43 (95% CI: 0.18, 1.03), reflecting the trend that patients in the Tecfidera group tended to be in the categories with less Gd lesions compared to Avonex. From baseline, the mean number of T1 Gd-enhancing lesions in the Avonex group declined from 3.58 to 1.3, the mean number of T1 Gd-enhancing lesions in the Tecfidera group declined from 2.35 to 1.4 at week 96.

A few patients experienced a confirmed disability progression as defined during the 96-week treatment period with 4 patients (6%) in the Avonex group and 7 (9%) patients under Tecfidera treatment.

According to the Applicant, the mean BVMT-R scores at Baseline for each of the 3 trials and mean changes from baseline for each of the 3 trials over time were generally similar in the 2 treatment groups. Mean SDMT scores at Baseline were similar in the 2 treatment groups. Mean changes from baseline over time were higher in the Tecfidera group than in the Avonex group. At Week 48, the percentage of participants in both treatment groups who progressed to the next grade in school were the same (among those evaluated): Avonex, 38 of 41 participants (93%); Tecfidera, 56 of 60 participants (93%). At Week 96, 49 of 57 participants (86%) evaluated in the Avonex group and 68 of 74 participants (92%) evaluated in the Tecfidera group progressed to the next grade in school.

Regarding the consistency of the efficacy outcome of dimethyl fumarate in the paediatric population and young adults the provided *post-hoc* analyses seem to be consistent with those from the overall adult patient population and in favour of Tecfidera. It may therefore be assumed, based on the known clinical efficacy in adults, that the clinical efficacy in children is also alike that observed in adults.

Additional expert consultation

N/A

Assessment of paediatric data on clinical efficacy

Study 109MS306 Part1 included paediatric patients aged 10 to 18 years of age and therefore, no further data are needed.

3.4.4. Conclusions on the clinical efficacy

In support of the extension of the indication of Tecfidera to paediatric patients aged 10 years and older (updated during the procedure to '13 years of age and older'), the Applicant has provided efficacy data from one open-label, active controlled study, study 109MS306 Part 1.

Due to methodological limitations (including open-label design, no type 1 error control, methods not pre-specified in full details, analyses generally not based on ITT-population), the results from study

109MS306 Part 1 are considered descriptive and do not provide stand-alone confirmatory evidence of efficacy for Tecfidera in the paediatric RRMS population.

However, results of the primary analysis for the primary endpoint, the "proportion of patients with no new or newly enlarging T2 hyperintense lesions at week 96", performed in a rather selected patient population, the Completers population, suggested a trend in favour of Tecfidera. This was supported by a sensitivity analysis based on the ITT population, including all randomised and treated patients without selection. Secondary MRI based endpoints, i.e. the number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Week 96, the proportion of patients free of new MRI activity (i.e., free of Gd-enhancing and free of new or newly enlarging T2 MRI lesions on brain MRI scans) and the mean number of Gd-enhancing lesions, indicated the same effect in favour of Tecfidera. Since these MRI parameters have been related to relapses, representing the most important clinical effect in this population and are often among the criteria chosen to reflect disease activity, they are considered to be of high importance in this context and extrapolation of efficacy based on these endpoints is accepted (reference is also made to the paediatric indication for Aubagio). In addition, the outcome on relapses, evaluated as secondary endpoints, was also indicative for an effect of Tecfidera in the paediatric population.

Regarding the consistency of the efficacy outcome of DMF in the paediatric population and young adults the provided analyses seem to be consistent with those from the overall adult patient population and in favour of Tecfidera.

Overall, it is considered that the natural history of MS is rather comparable in children and adults and therefore, an independent confirmation of efficacy in paediatric patients is not necessary in a situation where efficacy that has already been established in adult RRMS patients. Consequently, the use Tecfidera in paediatric patients has been adequately documented from a clinical efficacy perspective.

3.5. Clinical safety

Introduction

The safety profile of DMF deriving from clinical studies in adults at the time of marketing authorisation is detailed in the Tecfidera EPAR (EMEA/H/C/002601/0000/Rev 1). Moreover, no increased incidence in AEs has been observed during long-term treatment with Tecfidera, which was evaluated in the long-term study 109MS303. Results with a data cut-off 08 November 2019 were evaluated in a parallel procedure (EMEA/H/C/002601/II/0069/G).

Adverse events of special interest defined for Tecfidera are:

- Gastrointestinal AEs: the incidence of AEs associated with GI tolerability (mainly diarrhoea, nausea, abdominal pain upper, abdominal pain, and vomiting) was higher in DMF-treated subjects compared to placebo (31% placebo vs. 40% DMF 240mg BID; Pool A data).
- Flushing and related symptoms (assumed to be mediated by prostaglandins): the incidence of AEs associated with flushing (including hot flush) and/or flushing-like events was higher in DMF-treated subjects compared to placebo (9% placebo vs. 45% DMF 240mg BID; Pool A data). For both, GI tolerability and flushing AEs, these occur most frequently during the first month of treatment with DMF; these events may continue to occur intermittently throughout the treatment with Tecfidera. Temporary dose reduction (to 120 mg BID for up to 1 month) is advised in the SmPC to mitigate GI effects and flushing.

- Infections: similar rates for infections in DMF-treated subjects compared to placebo were reported in Pool A (56% placebo vs. 60% DMF 240mg BID). Serious infections were reported by 2% of patients treated with DMF 240mg BID and in 1% of patients on placebo. Additional analyses performed for DMF phase 3 studies could not confirm a relation between the occurrence of infections and the subject's minimum post-baseline lymphocyte counts. According to the SmPC, patients with serious infections should not start treatment with Tecfidera until the infection(s) is resolved.
- Cardiovascular disorders were not found different in patients on DMF and placebo during the phase 3 studies with Tecfidera.
- Hepatic disorders: The incidence of hepatic TEAEs was similar across treatment groups in Pool A (9% placebo vs. 9% DMF BID) and headed by elevations of liver transaminases. An increased incidence of elevated liver transaminases (≥3x ULN) with DMF compared to placebo was primarily due to differences that occurred early in the course of treatment, i.e. during the first 6 months.
- Renal disorders: Preclinical studies specified the kidney as a target for DMF-toxicity. However, the incidences of AEs in the renal and urinary disorders SOC were similar in DMF-treated subjects and those on placebo (18% placebo vs. 19% DMF BID). Small increases in the incidence of AEs of proteinuria, microalbuminuria, and albumin urine present were observed with DMF as compared to placebo in DMF safety pools, these events were mild to moderate in severity and did not lead to an increase in treatment discontinuations. No worsening in renal function was noted over time in DMF trials, including in the long-term study 109MS303 with DMF treatment of up to 12 years.
- Malignancies: the incidence of malignancies was low and balanced (<1% [3 subjects] placebo, <1% [2 subjects] DMF BID) in Pool A. The long-term risk for malignancies with DMF treatment has been further assessed in study 109MS303, with the overall incidence being 3%. Malignancies are a potential risk with DMF in the RMP.
- Suicide and depression: occurred in a low and similar incidence across treatment groups in Tecfidera clinical studies in adults. It should be noted that patients with multiple sclerosis have an increased prevalence of depression and an elevated risk of suicide.

A number of safety signals emerged for DMF after approval:

A safety signal for progressive multifocal encephalopathy (PML) has been identified early after approval of Tecfidera following the first confirmed and also fatal case of PML in a patient with severe prolonged lymphopenia (> 3.5 years) in a clinical study. The risk for PML has been taken up in a number of procedures either from a mechanistical perspective (lymphocytopenia) or based on additional confirmed cases (including EMEA/H/C/WS0689/G, EMEA/H/C/002601/II/0026, EMEA/H/C/002601/II/0030, EMEA/H/C/002601/R/0053, EMEA/H/C/002601/II/0030, EMEA/H/C/2601/II/54/G, EMEA/H/C/2601/II/58, and EMEA/H/C/2601/II/63). So far, 11 PML cases have been confirmed for Tecfidera, which all occurred in patients with lymphocyte counts below LLN (<0.91x10^9/L), and 10 of these cases occurred in the postmarketing setting. Substantial amendments have been introduced in the product information of Tecfidera, including a contraindication in patients with suspected or confirmed PML, detailed warnings (stopping rules, additional factors that might increase the risk for PML and demand increased vigilance), and description of study findings for lymphocyte subsets in section 4.8.

Lymphopenia seems to increase the risk for PML. Therefore, the mechanism of decreases in lymphocyte counts has been evaluated in nonclinical and clinical studies. While nonclinical investigations ruled out selective toxicity of DMF and MMF on human lymphocytes during Tecfidera treatment, a mechanistic

rational for the effect of DMF on lymphocytes could not be deduced from clinical studies. However, quantitative and qualitative changes within the lymphocyte subpopulations (specifically CD4+ and CD8+ T cells) in DMF - treated patients have been observed in study 109MS310, for which results are included in section 4.8 of the Tecfidera SmPC. Given the role of CD4+ and CD8+ T cells in the immunological defence against opportunistic infections, it is mechanistically plausible that loss of these subsets enhances the susceptibility for PML. In particular, the decline of CD8+ T cells has recently been related to the pharmacological activation of the Nrf2 pathway and also to the stimulation of phosphoinositide 3 kinase-Akt signalling by DMF[15][16].

A safety signal of drug-induced liver injury (DILI) related to Tecfidera treatment was reported in the postmarketing setting, including liver enzyme increase (≥ 3x ULN) and elevation of total bilirubin levels (≥ 2x ULN). The weighted cumulative evidence that derived from a review of data was deemed sufficient to support a causal association between hepatotoxicity and Tecfidera. Thus, a warning on these hepatic findings and monitoring requirements as well as respective ADRs have been included in sections 4.4 and 4.8 of the Tecfidera SmPC. DILI is further included as an important identified risk in the Tecfidera RMP.

Safety signals of overdose, anaphylaxis and thrombocytopenia were reported in the postmarketing experience and relevant information has been included in the Tecfidera product information.

Herpes zoster was reported as a postmarketing safety signal for Tecfidera and adequate warning and description of this ADR and its presentation has been added in the PI to also include that in a majority of patients concurrent lymphocyte counts met the criteria of moderate to severe lymphopenia. Recently, cases of Fanconi syndrome have been reported for a DMF-containing product in combination with other fumaric acid esters, while no such case derived from treatment with Tecfidera. However, given that MMF appears to be the component of interest, which derives from both drug products, this warning was deemed adequate for Tecfidera.

For DMF, two paediatric studies in patients aged 13 to <18 years have been conducted, i.e. a 24-week, open-label, prospective, uncontrolled study in 22 paediatric patients with RRMS (109MS202 with focus on pharmacokinetics) and its 96-week extension (109MS311). Study 109MS202 as well as study 109MS311 are not part of the Tecfidera PIP. Results from these two studies based on a limited number of subjects demonstrated an acceptable safety profile for paediatric patients with RRMS, which is consistent with the safety profile established in the adult population. Description of these data is included in the product information for Tecfidera.

Patient exposure

Disposition of patients

For detailed information, please see efficacy part of this AR in 3.4.2. (Table 2).

69% of patients (103 of 150 patients) in the ITT Population completed 96 weeks of treatment in Part 1 of the study: 78% of patients on Tecfidera (61 patients)and 58% of patients on Avonex (42 patients).

The most common reasons for study treatment discontinuation were consent withdrawn (10% in total, 15% on Avonex and 5% on Tecfidera), AEs (9% in total, 11% on Avonex and 8% on Tecfidera), and Investigator decision (9% in total, 13% on Avonex and 5% on Tecfidera).

Demographics

[15] Hammer A et al. Ann Clin Transl Neurol. 2018; 5(6): 668-676.
[16] Lückel C et al. Nat Commun. 2019; 10(1): 5722

The ITT Population (n=150) included all participants who were randomly assigned to a treatment group and received at least 1 dose of study treatment: Avonex, 72 patients; Tecfidera, 78 patients.

67% of patients were female (n=101). The mean (SD) age was 14.9 (1.62) years. Stratification of the ITT population was performed according to age:

- 10 to less than 13 years: 15 patients in total, 10% (8 patients [11%] on Avonex, 7 patients on Tecfidera [9%])
- 13 to less than 15 years: 32 patients in total, 21% (14 patients [19%] on Avonex, 18 patients on Tecfidera [23%])
- 15 to less than 18 years: 103 patients in total, 69% (50 patients [69%] on Avonex, 53 patients on Tecfidera [68%]).

Tanner staging is described in more detail under "*Vital signs, physical findings, and other observations related to safety*" below. Screening results are depicted in Table 5.

Mean body mass index (BMI) was 23.5 (4.42) kg/m² and mean body weight was 63.88 (14.576) kg.

Other baseline demographic and disease parameters are detailed in Table 4 and Table 6.

Extent of exposure

The mean (SD) exposure to study treatment overall was 78.6 (29.58) weeks, and higher in the Tecfidera (84.4 [26.01] weeks) than in the Avonex group (72.3 [32.02] weeks) (Table 24). The majority of patients were exposed to study treatment between 88 and 96 weeks (Avonex 58% and Tecfidera 65%).

The mean (SD) percentage of study treatment taken was similar in both groups: Avonex 87.4% (18.43) and Tecfidera 85.6% (15.45).

Table 24: Exposure to study drug during Part 1 of Study 109MS306 - ITT Population

	Avonex (N=72)	BG00012 240 mg BID (N=78)	Total (N=150)
Number of weeks on study drug			
0 to <= 8 wks	4 (6)	4 (5)	8 (5)
>8 to <= 16 wks	3 (4)	1 (1)	4 (3)
>16 to <= 24 wks	3 (4)	1 (1)	4 (3)
>24 to <= 32 wks	0	0	0
>32 to <= 40 wks	6 (8)	1 (1)	7 (5)
>40 to <= 48 wks	4 (6)	2 (3)	6 (4)
>48 to <= 56 wks	2 (3)	2 (3)	4 (3)
>56 to <= 64 wks	2 (3)	0	2 (1)
>64 to <= 72 wks	2 (3)	4 (5)	6 (4)
>72 to <= 80 wks	2 (3)	1 (1)	3 (2)
>80 to <= 88 wks	1 (1)	1 (1)	2 (1)
>88 to <= 96 wks	42 (58)	51 (65)	93 (62)
>96 to <= 104 wks	1 (1)	9 (12)	10 (7)
>104 to <= 112 wks	0	1 (1)	1 (<1)
> 112 wks	0	0	0
n	72	78	150
Mean (SD)	72.3 (32.01)	84.4 (26.01)	78.6 (29.57)
Median	95.0	96.0	95.0
Q1,Q3	47.0, 95.0	95.0, 96.0	70.0, 96.0
Min, Max	0, 98	1, 109	0, 109
Percentage of study drug taken (a)			
n	72	78	150
Mean (SD)	87.4 (18.43)	85.6 (15.45)	86.5 (16.91)
Median	95.3	91.6	92.1
Q1,Q3	81.5, 100.0	83.0, 94.5	82.6, 96.0
Min, Max	0, 100	4, 97	0, 100

NOTE 1: Numbers in parentheses are percentages.
NOTE 2: Subjects with missing data are excluded from the calculation. (a) Calculated as number of capsules or injections taken/number of capsules the subject is expected to take.

Patients who completed Week 96 in Part 1 and met the Part 2 entry could receive open-label Tecfidera 240 mg BID for 240 weeks in the Part 2 extension phase. 61% of patients (n=92) continued into Part 2 of the study (35 patients on Avonex [49%] and 57 patients on Tecfidera [73%]). Part 2 of Study 109MS306 is currently ongoing.

Adverse events

The following safety assessments were performed: AE monitoring, clinical laboratory analyses (haematology, blood coagulation, chemistry, urinalysis, endocrine, and urine cytology), physical examinations, vital signs, and electrocardiogram (ECGs).

Patient narratives were provided for SAEs (n=18) and TEAEs leading to discontinuation (n=8) and are discussed in the respective sections.

Common adverse events

Table 25: Overall Summary of Treatment Emergent Adverse Events - ITT Population

	Avonex (N= 72)	BG00012 240 mg BID (N= 78)	Total (N= 150)
Number of subjects with any event	69 (96)	74 (95)	143 (95)
Severity (a)			
Mild	27 (38)	29 (37)	56 (37)
Moderate	32 (44)	42 (54)	74 (49)
Severe	10 (14)	3 (4)	13 (9)
Related event (b)	59 (82)	67 (86)	126 (84)
Serious event	21 (29)	18 (23)	39 (26)
Related serious event	1 (1)	4 (5)	5 (3)
Events leading to drug withdrawal	8 (11)	5 (6)	13 (9)
Events leading to study discontinuation	8 (11)	5 (6)	13 (9)
Number of subjects who died	0	0	0

NOTE 1: Numbers in parentheses are percentages.
NOTE 2: A subject can appear in more than one category.
(a) Each subject counted once at maximum severity.
(b) Related as assessed by the investigator

The number of patients with at least one TEAE during Part 1 of the study was similar in the Avonex and Tecfidera group (96% and 95%, respectively). In a majority of patients from both groups, TEAEs were rated as related to treatment (Avonex: 82%, Tecfidera: 86%). Slightly more patients on Avonex as compared to Tecfidera experienced a treatment-emergent SAE (29% vs. 23%). Treatment-related SAEs were reported in more patients from the Tecfidera group as compared to Avonex (5% vs. 1%). Events leading to drug withdrawal or discontinuation from study were higher in the Avonex group as compared to Tecfidera (11% vs. 6%). No death occurred during the study.

Display of AEs

The most frequently reported TEAEs by SOC (≥25% of patients in either treatment group Avonex and Tecfidera) were: nervous system disorders (69% and 62%), infections and infestations (50% and 62%), gastrointestinal disorders (31% and 74%), general disorders and administration site conditions (78% and 27%), musculoskeletal and connective tissue disorders (38% and 26%), vascular disorders (8% and 46%), respiratory, thoracic and mediastinal disorders (11% and 32%), and skin and subcutaneous tissue disorders (6% and 33%).

The most common TEAEs (reported in > 5% of patients in either group) have been compiled in Table 26.

Table 26: TEAE(s) by SOC and PT in ≥ 5% in any treatment group sorted by decreasing frequency in study 109MS306 (compiled by the Assessor; moreover, comparative data from DMF 240 mg BID from Pool A in adults have been added)

System organ class – Preferred term n (%)	Avonex (N=72)	Tecfidera (N=78)	Pool A – DMF 240 mg BID
Any class	69 (96)	75 (95)	733 (95)
Nervous system disorders	**50 (69)**	**48 (62)**	**414 (54)**
Multiple sclerosis relapse	33 (46)	27 (35)	221 (29)
Headache	26 (36)	22 (28)	133 (17)
Paresthesia	5 (7)	6 (8)	56 (7)
Dizziness	1 (1)	4 (5)	33 (4)
Tremor	4 (6)	0	11 (1)
Infections and infestations	**36 (50)**	**48 (62)**	**463 (60)**
Nasopharyngitis	9 (13)	18 (23)	170 (22)
Gastroenteritis	5 (7)	9 (12)	42 (5)
Rhinitis	6 (8)	8 (10)	26 (3)
Upper respiratory tract infection	3 (4)	9 (12)	99 (13)
Influenza	3 (4)	8 (10)	54 (7)
Tonsillitis	6 (8)	5 (6)	9 (1)
Pharyngitis	4 (6)	5 (6)	31 (4)
Cystitis	0	4 (5)	11 (1)
Gastrointestinal disorders	**22 (31)**	**58 (74)**	**366 (48)**
Abdominal pain	5 (7)	32 (41)	73 (9)
Vomiting	6 (8)	18 (23)	65 (8)
Diarrhoea	4 (6)	15 (19)	107 (14)
Nausea	6 (8)	13 (17)	93 (12)
Abdominal pain upper	1 (1)	14 (18)	76 (10)
Dyspepsia	1 (1)	8 (10)	35 (5)
Constipation	2 (3)	5 (6)	23 (3)
General disorders and administration site conditions	**56 (78)**	**21 (27)**	**178 (23)**
Influenza-like illness	37 (51)	2 (3)	10 (1)
Pyrexia	17 (24)	8 (10)	27 (4)
Asthenia	6 (8)	4 (5)	24 (3)
Fatigue	7 (10)	2 (3)	94 (12)
Chills	4 (6)	0	4 (<1)
Non- cardiac chest pain	0	4 (5)	3 (<1)
Musculoskeletal and connective tissue disorders	**27 (38)**	**20 (26)**	**246 (32)**
Arthralgia	7 (10)	6 (8)	66 (9)
Back pain	6 (8)	6 (8)	94 (12)
Pain in extremity	8 (11)	4 (5)	58 (8)
Myalgia	9 (13)	2 (3)	13 (2)
Neck pain	4 (6)	1 (1)	27 (4)
Vascular disorders	**6 (8)**	**36 (46)**	**322 (42)**
Flushing	1 (1)	30 (38)	265 (34)
Hot flush	1 (1)	7 (9)	52 (7)
Respiratory, thoracic and mediastinal disorders	**8 (11)**	**25 (32)**	**117 (15)**
Oropharyngeal pain	4 (6)	14 (18)	37 (5)
Cough	2 (3)	11 (14)	38 (5)
Skin and subcutaneous tissue disorders	**4 (6)**	**26 (33)**	**245 (32)**
Rash	1 (1)	11 (14)	58 (8)
Erythema	0	8 (10)	36 (5)
Pruritus	0	6 (8)	62 (8)
Injury, poisoning and procedural complications	**6 (8)**	**18 (23)**	**103 (13)**
Ligament sprain	1 (1)	4 (5)	0
Eye disorders	**9 (13)**	**12 (15)**	**72 (9)**
Eye pain	5 (7)	2 (3)	13 (2)
Diplopia	0	5 (6)	5 (<1)
Reproductive system and breast disorders	**7 (10)**	**14 (18)**	**76 (10)**
Dysmenorrhoea	5 (7)	13 (17)	12 (2)
Ear and labyrinth disorders	**4 (6)**	**9 (12)**	**45 (6)**
Vertigo	1 (1)	4 (5)	22 (3)
Renal and urinary disorders	**7 (10)**	**4 (5)**	**146 (19)**
Proteinuria	4 (6)	2 (3)	67 (9)
Blood and lymphatic system disorders	**4 (6)**	**4 (5)**	**51 (7)**
Lymphopenia	0	2 (3)	18 (2)

NOTE 1: Numbers in parentheses are percentages.
NOTE 2: A subject was counted only once within each system organ class and preferred term.
NOTE 3: System organ class and preferred term are presented in decreasing frequency of the total column.

The most common TEAEs in the Tecfidera group were abdominal pain (41%), flushing (38%), MS relapse (35%), headache (28%), nasopharyngitis (23%), and vomiting (23%). The majority of patients experiencing TEAEs had events assessed as mild or moderate in severity. Severe TEAEs were reported in 9% of patients (14% in the Avonex group and 4% in the Tecfidera group). Severe TEAEs that occurred in > 1% of patients in either treatment group were MS relapse (4% in each treatment group), headache and influenza-like illness (3% each; only in the Avonex group).

Analysis of TEAEs by time interval (week 0-48 and week >48-96) revealed a similar incidence of GI disorders and nervous system disorders TEAEs in both intervals in the Tecfidera group, while flushing occurred with a higher incidence in the first year of treatment.

The most frequent treatment-related TEAEs overall were influenza-like illness (24%), flushing (20%), abdominal pain and headache (15% each), pyrexia (10%), and upper abdominal pain (8%), diarrhoea (6%), and erythema and rash (5% each). Of these, influenza-like illness (only in the Avonex group), headache, and pyrexia were reported in a higher percentage of patients in the Avonex group than the Tecfidera group. Flushing (reported only in the Tecfidera group), abdominal pain, upper abdominal pain (reported only in the Tecfidera group), diarrhoea, and erythema and rash (reported only in the Tecfidera group) were reported in a higher percentage of patients in the Tecfidera group than the Avonex group. The TEAEs of abdominal pain and upper abdominal pain in the Tecfidera group were all mild or moderate in severity. In the Tecfidera treatment group, no patient experienced GI-related AEs that led to study treatment discontinuation.

Post-hoc safety analysis - Overview of Paediatric - Adult Safety Outcomes in Tecfidera Studies

Table 27 summarises comparative safety events from Study 109MS306 Part 1 (paediatric data) and the controlled studies of Tecfidera in adults (PTs are based on the Tecfidera Investigator's Brochure, Version 17). In general, the frequencies of the events and the overall safety profiles were similar. An apparent increased frequency of some GI disorders (vomiting and dyspepsia) and skin and subcutaneous tissue disorders (rash and erythema) was seen in Study 109MS306 Part 1 compared with the controlled studies of Tecfidera in adults.

The numerical differences in the reported GI disorders TEAEs and TEAEs of rash or erythema between Study 109MS306 Part 1 and the placebo-controlled adult pivotal clinical studies are thought to reflect differences in study design and do not change the established safety profile for Tecfidera.

Table 27: Comparative Safety: Study 109MS306 Part 1 and Tecfidera Adult Data

SOC/PT	Tecfidera 109MS306 Part 1		Tecfidera Adult[2] Frequency Category[1]
	Tecfidera (N=78) n (%)	Frequency Category[1]	
Vascular Disorders	**36 (46)**		
Flushing	30 (38)	Very common	Very common
Hot flush	7 (9)	Common	Common
Gastrointestinal Disorders	**58 (74)**		
Diarrhoea	15 (19)	Very common	Very common
Nausea	13 (17)	Very common	Very common
Abdominal pain upper	14 (18)	Very common	Very common
Abdominal pain	32 (41)	Very common	Very common
Vomiting	18 (23)	Very common	Common
Dyspepsia	8 (10)	Very common	Common
Investigations	**7 (9)**		
Albumin urine present	0 (0)	-	Common
Aspartate aminotransferase increased	0 (0)	-	Common
Skin and Subcutaneous Tissue Disorders	**26 (33)**		
Pruritus	6 (8)	Common	Common
Rash	11 (14)	Very common	Common
Erythema	8 (10)	Very common	Common
Blood and Lymphatic Disorders	**4 (5)**		
Lymphopenia	2 (3)	Common	Common

Source: Study 109MS306 Part 1 clinical study report, Tecfidera Investigator's Brochure, Version 17
[1]Frequencies were defined as follows: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10).
[2]Includes pooled data from controlled adult studies in MS.

Adverse events of special interest

include *flushing and other related symptoms, GI tolerability (nausea, abdominal pain, diarrhoea, etc.), infections, including potential opportunistic infections, ischemic cardiovascular disorders, hepatic disorders, renal disorders, malignancies, and lymphopenia and leukopenia*.

Overall, 126 patients (84%; Avonex 74%; Tecfidera 94%) experienced at least 1 treatment-emergent AESI (see Table 28). Treatment-emergent AESIs occurred in a higher percentage in the Tecfidera group as compared to Avonex in the following SOCs: GI disorders (74% and 31%), infections and infestations (53% and 42%), vascular disorders (46% and 7%), respiratory, thoracic and mediastinal disorders (28% and 7%), skin and subcutaneous tissue disorders (28% and 1%), investigations (4% and 3%), blood and lymphatic system disorders (3% and 0%), and cardiac disorders (3% and 0%). Treatment-emergent AESIs occurred in a higher percentage in the Avonex group as compared to Tecfidera group in the following SOCs: general disorders and administration site conditions (42% and 19%), musculoskeletal and connective tissue disorders (13% and 3%), and renal and urinary disorders (10% and 5%).

Treatment-emergent AESIs by PT in >20% of patients and in a greater percentage of patients in the Tecfidera group than the Avonex group are: abdominal pain (Avonex 7%; Tecfidera 41%), flushing (Avonex 1%; Tecfidera 38%), nasopharyngitis (Avonex 13%; Tecfidera 23%), and vomiting (Avonex 8%; Tecfidera 23%). AESIs of pyrexia were reported in a greater percentage of patients in the Avonex (24%) than the Tecfidera group (10%).

Table 28: Treatment-emergent AESI(s) by SOC and PT sorted by decreasing frequency in study 109MS306 (compiled by the Assessor)

SOC/ PT n (%)	Avonex (N=72)	Tecfidera (N=78)
Number of patients with any AESI	53 (74)	73 (94)
Gastrointestinal disorders	**22 (31)**	**58 (74)**
Abdominal pain	5 (7)	32 (41)
Vomiting	6 (8)	18 (23)
Diarrhoea	4 (6)	15 (19)
Nausea	6 (8)	13 (17)
Abdominal pain upper	1 (1)	14 (18)
Dyspepsia	1 (1)	8 (10)
Constipation	2 (3)	5 (6)

SOC/ PT n (%)	Avonex (N=72)	Tecfidera (N=78)
Number of patients with any AESI	53 (74)	73 (94)
Toothache	3 (4)	1 (1)
Dental caries	2 (3)	1 (1)
Dry mouth	1 (1)	1 (1)
Abdominal pain lower	1 (1)	0
Frequent bowel movement	0	1 (1)
Gastritis	0	1 (1)
Gingival bleeding	1 (1)	0
Oesophagitis	0	1 (1)
Infections and infestations	**30 (42)**	**41 (53)**
Nasopharyngitis	9 (13)	18 (23)
Gastroenteritis	5 (7)	9 (12)
Rhinitis	6 (8)	8 (10)
Upper respiratory tract infection	3 (4)	9 (12)
Tonsillitis	6 (8)	5 (6)
Pharyngitis	4 (6)	5 (6)
Sinusitis	2 (3)	3 (4)
Urinary tract infection	2 (3)	3 (4)
Viral infection	2 (3)	3 (4)
Cystitis	0	4 (5)
Ear infection	1 (1)	3 (4)
Bronchitis	3 (4)	0
Laryngitis	0	3 (4)
Gastroenteritis viral	1 (1)	1 (1)
Oral herpes	0	2 (3)
Viral upper respiratory tract infection	2 (3)	0
Bacteriuria	0	1 (1)
Chronic sinusitis	1 (1)	0
Eye infection	1 (1)	0
Fungal skin infection	0	1 (1)
Gastrointestinal infection	1 (1)	0
Otitis externa	0	1 (1)
Otitis media	1 (1)	0
Otitis media acute	0	1 (1)
Pneumonia	0	1 (1)
Pneumonia pneumococcal	0	1 (1)
Respiratory tract infection	1 (1)	0
General disorders and administration site conditions	**30 (42)**	**15 (19)**
Pyrexia	17 (24)	8 (10)
Asthenia	6 (8)	4 (5)
Fatigue	7 (10)	2 (3)
Chills	4 (6)	0
Pain	3 (4)	0
Chest discomfort	0	1 (1)
Chest pain	0	1 (1)
Feeling hot	0	1 (1)
Generalised oedema	0	1 (1)
Oedema peripheral	1 (1)	0
Vascular disorders	**5 (7)**	**36 (46)**
Flushing	1 (1)	30 (38)
Hot flush	1 (1)	7 (9)
Hypotension	1 (1)	1 (1)
Hypertension	1 (1)	0
Orthostatic hypotension	1 (1)	0
Vasodilatation	0	1 (1)
Respiratory, thoracic and mediastinal disorders	**5 (7)**	**22 (28)**
Oropharyngeal pain	4 (6)	14 (18)
Cough	2 (3)	11 (14)
Dyspnoea	0	1 (1)
Pneumonitis	0	1 (1)
Tonsillar erythema	1 (1)	0
Skin and subcutaneous tissue disorders	**1 (1)**	**22 (28)**
Rash	1 (1)	11 (14)
Erythema	0	8 (10)
Pruritus	0	6 (8)
Dry skin	0	1 (1)
Ecchymosis	0	1 (1)
Rash erythematous	0	1 (1)
Rash pruritic	0	1 (1)
Musculoskeletal and connective tissue disorders	**9 (13)**	**2 (3)**
Myalgia	9 (13)	2 (3)
Renal and urinary disorders	**7 (10)**	**4 (5)**
Proteinuria	4 (6)	2 (3)

SOC/ PT n (%)	Avonex (N=72)	Tecfidera (N=78)
Number of patients with any AESI	53 (74)	73 (94)
Dysuria	1 (1)	1 (1)
Bladder discomfort	1 (1)	0
Renal cyst	0	1 (1)
Renal pain	1 (1)	0
Investigations	**2 (3)**	**3 (4)**
Alanine aminotransferase increased	1 (1)	1 (1)
Aspartate aminotransferase increased	1 (1)	0
Blood bilirubin increased	0	1 (1)
Blood glucose increased	0	1 (1)
Eosinophil count increased	0	1 (1)
Lymphocyte count decreased	0	1 (1)
Blood and lymphatic system disorders	**0**	**2 (3)**
Lymphopenia	0	2 (3)
Cardiac disorders	**0**	**2 (3)**
Palpitations	0	2 (3)
Hepatobiliary disorders	**1 (1)**	**1 (1)**
Hepatocellular injury	1 (1)	1 (1)
Nervous system disorders	**1 (1)**	**0**
Burning sensation	1 (1)	0

NOTE 1: Numbers in parentheses are percentages.
NOTE 2: A subject was counted only once within each system organ class and preferred term.
NOTE 3: System organ class and preferred term are presented in decreasing frequency of the total column.

TEAEs of lymphopenia were reported in 2 patients (3%) in the Tecfidera group. One of the cases was a severe SAE considered related to treatment by the Investigator (patient 100-004). The SAE of lymphopenia occurred at the same time as an SAE of tonsillitis (also considered severe and treatment-related); both events resulted in the patient being admitted to hospital. On the date of hospital admission, the patient's lymphocyte count was 400 cells/µL (reference range: 950 to 5250 cells/µL), and the following day the count was 300 cells/µL. Subsequent values were as follows, both within normal limits: 1400 cells/µL (3 days after hospital admission) and 2100 cells/µL (4 days after admission). Treatment was interrupted due to the SAEs (for approximately 14 days). On the fourth day after hospital admission both events were considered resolved and the patient was discharged from hospital. The patient's final lymphocyte count provided by the hospital (12 days after resolution of the SAE of lymphopenia) was 2000 cells/µL. Because the lymphocyte counts collected by the hospital were not part of a study visit, the results were not recorded in the patient's eCRF, and therefore the patient was not included in the set of patients with postbaseline lymphocyte counts $< 0.5 \times 10^9$/L. The patient's lymphocyte counts at all clinic visits during the study were within the normal range, including the value approximately 2 weeks before the onset of the SAEs (1.47×10^9/L).

No patient experienced a TEAE of leukopenia.

Resolution of 6 specific AESI PTs (flushing, nausea, abdominal pain, lower abdominal pain, upper abdominal pain, and diarrhoea) was of interest. A total of 69 of the 150 patients in the ITT Population (46%; Avonex: 17%; Tecfidera: 73%) experienced 1 or more of these PT events (Avonex: 27 events; Tecfidera: 256 events); all of the events in the Avonex group resolved during the study, except for a single event of flushing. More events in the Tecfidera group were not resolved by the end of the study, i.e. 8 events of flushing, 2 events of abdominal pain, and 2 events of abdominal pain upper.

Gastrointestinal disorders (and vascular disorders)

In Table 26, the most commonly reported TEAEs within the GI disorders SOC in the Tecfidera group were abdominal pain (41%), vomiting (23%), diarrhoea (19%), upper abdominal pain (18%), nausea (17%), dyspepsia (10%), and constipation (6%). All TEAEs in the GI disorders SOC in Study 109MS306 Part 1 were of (mainly) mild or moderate severity, and none resulted in treatment discontinuation.

The incidence of GI disorders and vascular disorders in the Tecfidera group decreased over time: the incidence of TEAEs within the GI disorders SOC tended to decrease from 25% of patients (Weeks 0 to

48) to 17% of patients (Weeks 48 to 96), and the incidence of vascular disorders decreased from 14% of patients (Weeks 0 to 48) to 2% of patients (Weeks 48 to 96).

Malignancies

No malignancies were reported during the study Part 1.

Pregnancies

No pregnancies were reported during the study Part 1.

Serious adverse event/deaths/other significant events

No deaths were reported during Part 1 of the study.

Serious adverse events occurred in 29% of patients in the Avonex group and in 23% of patients in the Tecfidera group (Table 29). The only treatment-emergent SAE reported by > 1% of patients in either treatment group was MS relapse (25% in the Avonex group and 17% in the Tecfidera group). 3% in total had an SAE that was considered related to study treatment: influenza-like illness in a single patient on Avonex (1%) and in 5% of patients on Tecfidera (lymphopenia and tonsillitis both in the same patient, and upper abdominal pain, MS relapse, and pruritic rash, each in 1 other patient).

The Applicant provided narratives of the SAEs.

Table 29: SAEs by System Organ Class and Preferred Term - ITT Population

	Avonex (N=72)	BG00012 240 mg BID (N=78)	Total (N=150)
Number of subjects with any serious event	21 (29)	18 (23)	39 (26)
Nervous system disorders	19 (26)	16 (21)	35 (23)
Multiple sclerosis relapse	18 (25)	13 (17)	31 (21)
Epilepsy	0	1 (1)	1 (<1)
Generalised tonic-clonic seizure	0	1 (1)	1 (<1)
Optic neuritis	0	1 (1)	1 (<1)
Paraesthesia	1 (1)	0	1 (<1)
Presyncope	0	1 (1)	1 (<1)
Relapsing multiple sclerosis	1 (1)	0	1 (<1)
Blood and lymphatic system disorders	1 (1)	1 (1)	2 (1)
Anaemia	1 (1)	0	1 (<1)
Lymphopenia	0	1 (1)	1 (<1)
Infections and infestations	0	2 (3)	2 (1)
Pneumonia pneumococcal	0	1 (1)	1 (<1)
Tonsillitis	0	1 (1)	1 (<1)
Gastrointestinal disorders	0	1 (1)	1 (<1)
Abdominal pain upper	0	1 (1)	1 (<1)
General disorders and administration site conditions	1 (1)	0	1 (<1)
Influenza like illness	1 (1)	0	1 (<1)
Hepatobiliary disorders	1 (1)	0	1 (<1)
Hepatocellular injury	1 (1)	0	1 (<1)
Injury, poisoning and procedural complications	0	1 (1)	1 (<1)
Fall	0	1 (1)	1 (<1)
Forearm fracture	0	1 (1)	1 (<1)
Musculoskeletal and connective tissue disorders	1 (1)	0	1 (<1)
Groin pain	1 (1)	0	1 (<1)
Psychiatric disorders	0	1 (1)	1 (<1)
Suicide attempt	0	1 (1)	1 (<1)
Skin and subcutaneous tissue disorders	0	1 (1)	1 (<1)
Rash pruritic	0	1 (1)	1 (<1)

Social circumstances	0	1 (1)	1 (<1)
Social problem	0	1 (1)	1 (<1)
Vascular disorders	1 (1)	0	1 (<1)
Hypertension	1 (1)	0	1 (<1)

NOTE 1: Numbers in parentheses are percentages.
NOTE 2: A subject was counted only once within each system organ class and preferred term.
NOTE 3: System organ class and preferred term are presented in decreasing frequency of the total column.

Laboratory findings

Haematology

including haemoglobin, haematocrit, red blood cell count, WBC count (with differential), and platelet count.

Mean haematology parameters over time

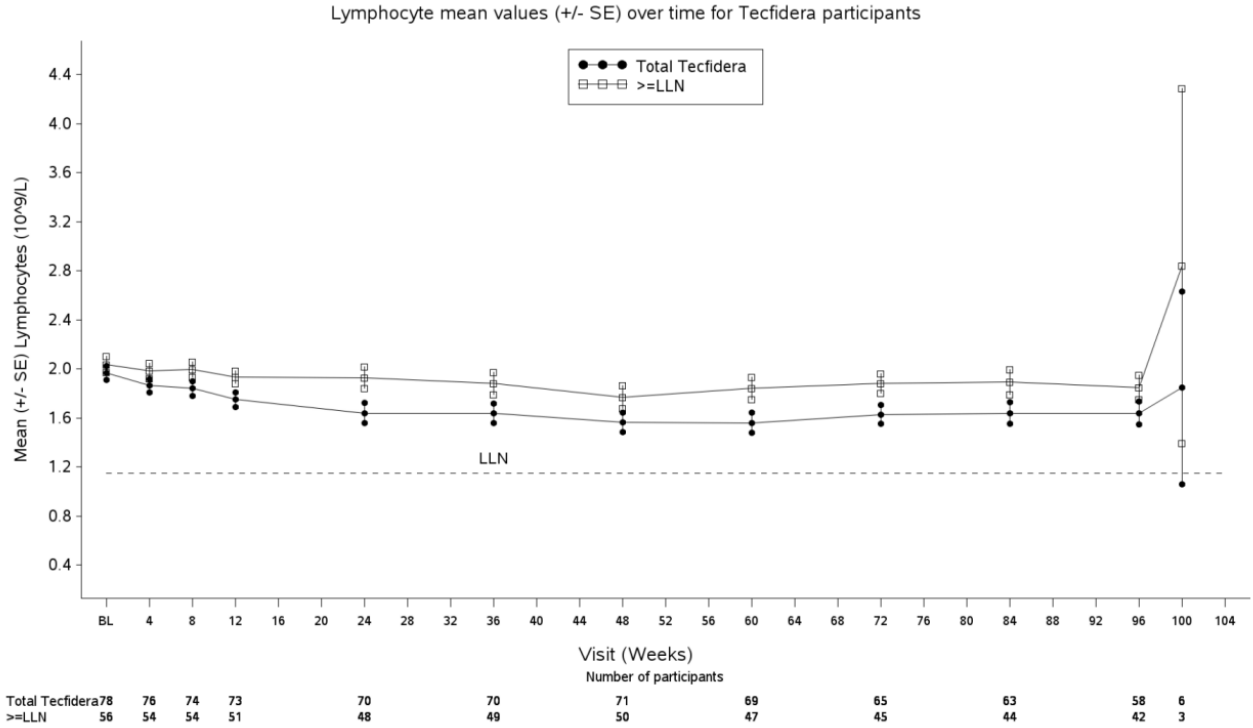
In the Tecfidera group, *mean leukocyte counts* decreased from baseline to Week 8. The decrease remained generally stable through Week 84; the mean increased at Week 96 (remaining below the baseline mean). Overall in both treatment groups, mean leukocyte counts were variable yet remained within normal range throughout the study.

Mean lymphocyte counts in the Tecfidera group decreased from baseline (~2.0 x 10^9/L) through Week 48 (1.6 × 10^9/L), plateauing through Week 60, and then increasing through Week 96 (but remaining below baseline mean); the mean returned to baseline at the follow-up visit at Week 100. Mean lymphocyte values in the Tecfidera group remained above LLN during Part 1 of the study (Figure 3). In the Avonex group, mean lymphocyte values postbaseline were slightly increased from baseline through Week 100.

Mean neutrophil values in the Tecfidera group decreased from baseline through Week 8; by Week 36 the mean had returned to within the normal range, plateauing through Week 84. The mean value increased again at Week 96 (the last visit of the treatment period), decreasing again at the follow-up visit at Week 100. In the Avonex group mean neutrophil values postbaseline were all below baseline levels through Week 96, returning to near baseline values at Week 100.

There were no trends in mean change from baseline values in erythrocyte counts, haemoglobin, haematocrit, or platelet counts or in coagulation parameters PTT, prothrombin time, or INR in either treatment group at Weeks 24, 48, or 96.

Figure 3: Lymphocyte Mean Values (± SE) Over Time for Paediatric Tecfidera Patients (Study 109MS306)



No participants experienced lymphocyte counts < 500 (x10^6/L), sustained for at least 6 months (24 weeks), or between 500 and 800 (x10^6/L), sustained for at least 6 months. All assessments, including unscheduled visits were used to classify participants in the above categories. LLN is lower limit in std unit. If there are multiple values of LLN for a give parameter, highest LLN is shown. SE= Standard Error; BL=Baseline; Lymphocyte < LLN: lymphocyte value recorded at visit was less than the lower limit of the normal range.

Clinically significant values

Notable potentially clinically significant haematology abnormalities in either treatment group were lymphocytes <0.8 × 10^9/L (Avonex 4%; Tecfidera 19%), lymphocytes <0.5 × 10^9/L (Avonex 1%; Tecfidera 4%), and total WBC < 3.0 × 10^9/L (Avonex: 0%; Tecfidera 13%).

Lymphocytes

A total of 4 patients experienced postbaseline lymphocyte counts < 0.5 x 10^9/L during the study (based on values collected at study visits only): 1 patient in the Avonex group and 3 patients in the Tecfidera group:

The patient in the Avonex group had 6 lymphocyte values < LLN between Weeks 24 and 72. Between the Week 48 and Week 72 visits there were 3 lymphocyte values < 0.5 × 10^9/L (0.37, 0.48, and 0.47× 10^9/L at the Week 48, 60, and 72 visits, respectively); other values in that time period ranged from 1.19 × 10^9/L to 1.38 × 10^9/L.

One patient on Tecfidera had a single value < 0.5 × 10^9/L (0.47 × 10^9/L) at the Week 100 (follow-up) visit (other values within normal range). The second patient had lymphocyte values < LLN from Week 12 through 96 (except for a single normal value). Between the Week 36 and Week 72 visits the patient had five values < 0.5 × 10^9/L (0.34 - 0.46 × 10^9/L); other values in that time period ranged from 0.51 × 10^9/L to 1.01 × 10^9/L. The third patient had lymphocyte values < LLN from Week 12 through 96. Between the Week 36 and Week 72 visits there were 3 lymphocyte values < 0.5 × 10^9/L (0.40 - 0.49 × 10^9/L); other values in that time period were 0.52 × 10^9/L and 0.54 × 10^9/L.

None of these 4 patients discontinued study treatment or withdrew from the study because of low lymphocytes, and no TEAEs of lymphopenia were reported for any of them. No patient experienced postbaseline lymphocyte counts < 0.5 × 10^9/L lasting for > 6 months.

Lymphocyte values over time and disposition from the study were evaluated for the subset of patients in the ITT Population who had a lymphocyte count < LLN sometime during the study and in addition 1) completed Part 1 of the study and did not enter Part 2, 2) permanently discontinued treatment during Part 1, and/or 3) had a dose interruption at least once during Part 1. Among this subset of patients, a total of 10 patients (Avonex: 3; Tecfidera: 7) experienced lymphocyte values < LLN at 1 or more postbaseline clinic visits during the study. Among the 7 patients in the Tecfidera group, 2 completed Part 1, 2 had a dose interruption, and 3 discontinued study treatment (1 of whom also had a dose interruption during treatment).

Post-hoc safety analysis - paediatric-Adult Lymphocyte Counts in Tecfidera Studies

The lymphocyte dynamics in the Study 109MS306 (Part 1) population were similar to those observed in the adult population (Pool B). Pool B represents the combined placebo-controlled and uncontrolled studies of Tecfidera in adults with MS, consisting of participants from the placebo-controlled Studies 109MS301, 109MS302, and C-1900 (Part 1), with added newly treated participants from the uncontrolled extension Studies C-1900 (Part 2) and Study 109MS303. In both, Study 109MS306 and Pool B, the mean baseline lymphocyte counts were approximately 2.0 × 10^9 cells/L, which decreased over the first 48 weeks with subsequent plateaus. In Study 109MS306, the mean lymphocyte counts decreased by about 20% but remained above the LLN during the study. In Pool B, the mean lymphocyte counts decreased by approximately 30%. Numerical differences between Study 109MS306 and Pool B (in %-decrease) are likely explained by the small numbers of patients in Study 109MS306 and are not thought to be meaningful. No patient in 109MS306 developed prolonged, severe lymphopenia or discontinued treatment due to prolonged lymphopenia; therefore, SmPC criteria remain appropriate for paediatric patients.

Analysis of shifts

A relevant *shift to high* values happened for eosinophils (Avonex 20%; Tecfidera 36%) and neutrophils (Avonex 14%; Tecfidera 12%). The parameters in which a *shift to low* values happened were monocytes (Avonex 73%; Tecfidera 70%), leukocytes (Avonex 28%; Tecfidera 41%), lymphocytes (Avonex 7%; Tecfidera 27%), erythrocytes (Avonex 14%; Tecfidera 23%), haemoglobin (Avonex 7%; Tecfidera 13%), and haematocrit (Avonex 16%; Tecfidera 22%).

Blood chemistry

Blood chemistry was performed: sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT, AST, GGT, blood urea nitrogen, creatinine, bicarbonate, calcium, magnesium, phosphate, uric acid, and glucose.

There were no trends in changes from baseline for any chemistry parameters in either treatment group, except for alkaline phosphatase. There was a decrease from baseline in mean alkaline phosphatase levels in both treatment groups, but the mean values did not go below normal levels.

Liver enzymes

The incidence of patients with ALT values > ULN by treatment group over time was as follows:

- Baseline: Avonex 6%; Tecfidera 5%
- Week 4: Avonex 10%; Tecfidera 16% (3% of patients had ALT > 3x ULN)
- Week 48: Avonex 5%; Tecfidera 3%
- Week 96: Avonex 5%; Tecfidera 0%

The incidence of patients with AST values > ULN by treatment group over time was as follows:

- Baseline: Avonex 7%; Tecfidera 1%
- Week 48: Avonex 4%; Tecfidera 1%
- Week 96: Avonex 3%; Tecfidera 0%

The incidence of patients shifting from normal at baseline to above normal postbaseline in liver enzymes were similar for Avonex and Tecfidera; shifts to ALT > ULN occurred most often (18% or 19%), followed by shifts to AST, alkaline phosphatase, and bilirubin > ULN (6% to 8%).

A total of 10 patients (5 in each of the treatment groups) experienced postbaseline ALT or AST ≥3x ULN, postbaseline bilirubin > 2x ULN, or postbaseline alkaline phosphatase > 1.5x ULN during the study. Three patients in the Avonex group and 2 patients in the Tecfidera group had postbaseline AST or ALT values > 3x ULN, and 1 patient in the Tecfidera group had postbaseline total bilirubin values > 2x ULN. Two patients in the Avonex group and 2 patients in the Tecfidera group had postbaseline alkaline phosphatase values > 1.5× ULN. One patient in the Tecfidera group experienced a TEAE of ALT increased and 1 patient experienced a TEAE of blood bilirubin increased. No patients in either treatment group had postbaseline ALT or AST values > 3× ULN and bilirubin > 2× ULN (Hy's Law criteria).

Other blood chemistry tests

No clinically notable changes in mean values for any other blood chemistry tests (sodium, potassium, chloride, urea nitrogen, creatinine, bicarbonate, calcium, magnesium, phosphate, glucose, and urate) over time. The parameters in which a shift to high values happened in > 25% of patients in either treatment group were calcium (Avonex 18%; Tecfidera 26%), magnesium (Avonex 57%; Tecfidera 59%), and glucose (Avonex 39%; Tecfidera 34%). The only parameters in which a shift to low values happened in > 25% of patients in either treatment group was glucose (Avonex 18%; Tecfidera 26%).

Urinalysis

Urinalysis was performed: colour, specific gravity, pH, protein, glucose, blood, ketones, and microscopy. There were no trends in changes from any urinalysis values in either treatment group.

A shift to high values occurred for the following parameters in > 25% of patients in either treatment group: ketones (Avonex 14%; Tecfidera 59%), occult blood (Avonex 40%; Tecfidera 44%), and protein (Avonex 81%; Tecfidera 92%). Proteinuria was reported as a TEAE in 3% of patients on Tecfidera (6% on Avonex).

Endocrinology

Endocrine tests were performed at baseline, Weeks 48 and 96, and Early Withdrawal (until patient had reached bone age of ≥ 16 years or until patient was postmenarche): insulin-like growth factor 1, insulin-like growth factor binding protein, FSH, LH, estradiol (E-2), and testosterone. Data were collected for 17 patients at Baseline, 12 patients at Week 48, and 9 patients at Week 96. No clinically relevant trends were observed.

Vital signs, physical findings, and other observations related to safety

Vital signs

Mean temperature, pulse rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and respiratory rate remained generally stable throughout the study, and there were no trends in (percent) changes from baseline measurements.

The most common clinically relevant vital sign abnormalities were high pulse rate (> 120 bpm or an increase from baseline of > 20 bpm) in 24% of patients on Avonex and 31% of patients on Tecfidera, low pulse rate (< 50 bpm or a decrease from baseline of > 20 bpm) in 17% and 18% of patients, respectively, and low DBP (< 50 mmHg or a decrease from baseline of > 20 mmHg) in 11% and 10% of patients, respectively. With the exception of high pulse rate (higher in the Tecfidera group), the percentages of patients experiencing each type of clinically relevant abnormality were generally similar across both treatment groups.

Clinically relevant abnormalities in vital signs were stratified by patient age < 13 years and ≥13 years. In both treatment groups, more patients < 13 years as compared to those ≥13 years had a pulse rate < 50 bpm or a decrease from baseline of > 20 bpm (Avonex: 25% and 16%; Tecfidera: 29% and 17%), and a SBP >130mmHg/ >140mmHg (Avonex: 25% and 5%; Tecfidera: 14% and 1%). More patients < 13 years as compared to ≥13 years, specifically in the Tecfidera group, had a DBP >80mmHg/ >90mmHg of > 20 bpm (14% and 4%).

ECGs

Most patients had normal ECG results throughout the study (ranging from 91% to 97% of patients evaluated across study visits, including follow-up). No patients had an abnormal ECG result that was considered to be an AE. A higher percentage of patients had an abnormal (not AE) ECG result at baseline in the Tecfidera group (12%) than the Avonex group (4%), but at other treatment period visits, the percentage of patients with an abnormal (not AE) ECG result was similar across treatment groups. No patient experienced a shift from normal ECG to abnormal, AE. A total of 11 of 135 patients (8%) experienced a shift from normal ECG to abnormal, not AE: Avonex, 4 of 68 patients, 6%; Tecfidera, 7 of 67 patients, 10%.

Growth parameters and Tanner staging

According to the study protocol, the following clinical assessments were performed to assess the safety profile of Tecfidera:

Physical examinations, including body weight, height, and Tanner Stage. Information regarding Tanner staging was collected at baseline for all male participants and for female participants who were premenarche until the participant's bone age reached ≥ 16 years or once the participant was postmenarche. According to study activities in the protocol, Tanner score was also assessed at Week 48 and at end of Part 1 of the study/ early withdrawal visit.

At screening, 3 out of 49 male subjects (6%; 2 patients on Avonex and 1 patient on Tecfidera) and 1 out of 101 female subject (<1%; patient was on Avonex) were pre-pubertal (i.e. Tanner Stage 1). In contrast, among 49 males, 30 (61%) had testes and scrotum Stage 5 (adult genitalia) and 30 (61%) had pubic hair Stage 5 (adult type and quantity). Among 101 females, 48 (48%) had breast development Stage 5 (mature) and 45 (45%) had pubic hair Stage 5 (adult type and quantity). The number of patients evaluated for Tanner Stage at Weeks 48 and 96 declined substantially from screening hampering evaluation of potential changes in any of the Tanner Stage measurements over time.

Discontinuation due to adverse events

TEAEs that led to study treatment discontinuation by SOC and PT (Table 30).

Narratives were provided for TEAEs that led to study treatment discontinuation.

Overall, 9% of patients had a TEAE that led to study treatment discontinuation: Avonex 11%; Tecfidera 6%. The TEAEs by PT that led to study treatment discontinuation (and subsequently also to withdrawal from study) in > 1% of patients in either treatment group were MS relapse and flushing. Of these, MS

relapse was reported in a similar percentage of patients in both treatment groups (Avonex 4%; Tecfidera 3%), and flushing was only reported in patients in the Tecfidera group (3%).

Table 30: TEAEs that led to discontinuation of study drug by SOC and PT (amended by the Assessor)

SOC/ PT n (%)	Avonex (N=72)	Tecfidera (N=78)
Number of patients with any event that led to discontinuation	8 (11)	5 (6)
Nervous system disorders	**5 (7)**	**2 (3)**
Multiple sclerosis relapse	3 (4)	2 (3)
Headache	1 (1)	0
Tremor	1 (1)	0
General disorders and administration site conditions	**2 (3)**	**0**
Asthenia	1 (1)	0
Influenza like illness	1 (1)	0
Vascular disorders	**0**	**2 (3)**
Flushing	0	2 (3)
Gastrointestinal disorders	**1 (1)**	**0**
Vomiting	1 (1)	0
Hepatobiliary disorders	**1 (1)**	**0**
Hepatocellular injury	1 (1)	0
Musculoskeletal and connective tissue disorders	**0**	**1 (1)**
Limb discomfort	0	1 (1)
Psychiatric disorders	**1 (1)**	**0**
Mood altered	1 (1)	0

NOTE 1: Numbers in parentheses are percentages.
NOTE 2: A subject was counted only once within each system organ class and preferred term.
NOTE 3: System organ class and preferred term are presented in decreasing frequency of the total column.

Post marketing experience

The Health Care Professional (HCP)-confirmed AEs and SAEs reported in the paediatric population are consistent with the experience in the total population in the postmarketing setting. As of 26 March 2021, a total of 4320 events (1099 confirmed by HCPs and 3221 reported by consumers) in paediatric patients reported in 1761 cases have been received since Tecfidera was first approved in the United States in March 2013. The majority of the events reported in paediatric cases were nonserious in nature (4057/4320 events). The most commonly reported events were product administered to patient of inappropriate age, off label use, flushing, MS relapse, nausea, and upper abdominal pain, and the most commonly reported serious event was MS relapse. This is consistent with the overall Tecfidera population.

3.5.1. Discussion on clinical safety

The safety profile of DMF in paediatric patients has been characterised based on the reporting of TEAEs, SAEs, TEAEs leading to discontinuation from treatment/ study, and TEAEs resulting in dose interruption or dose reduction during study 109MS306 Part 1. Open-label data from this part of the study are available up to 96 weeks. Longer-term safety data is expected from the ongoing Part 2 of the study, which aims to add an additional 5 years of treatment with DMF, with results presented in a separate CSR after completion (expected in 2025, with next interim results in Q3/4 of 2022).

The paediatric population included in the study was similar to those in other DMTs MS studies (i.e. Gilenya EMEA/H/C/002202/X/0044/G and Aubagio EMEA/H/C/002514/X/0031/G). However, a rather low number of paediatric patients (150 patients in total) was randomised, 78 patients in the DMF group and 72 patients in the Avonex group, which needs to be judged in the context of ongoing paediatric MS trials that are competing for patients. Mean (SD) age was 14.9 (1.62) years. The vast majority of patients belonged to the age group 15 to 17 years (69% in total). Few data are available regarding the age group 13 to 14 years (32 of 150 patients, 21%; 18 patients on Tecfidera and 14 patients on Avonex). The most

vulnerable subpopulation (paediatric patients <13 years and those with Tanner stage 1) is even less represented in study 109MS306, for which interpretability of safety data is severely limited:

- 3 of 150 patients (2%) were pre-pubertal, i.e. they were Tanner stage 1 at screening, i.e. had a Tanner staging of "1" in each of the two gender-specific Tanner subscales (including a single patient on Tecfidera and two patients on Avonex, all of them male). From this limited set of data, a conclusion on clinical safety in pre-pubertal patients is impossible.

- 15 of 150 patients (10%) were 10 to less than 13 years (7 on Tecfidera and 8 on Avonex); therefore, it is difficult to conclude on the safety profile in this age range.

The recommended DMF dose in paediatric patients is expected to be the same as in adults based on similar exposure: an initial dose of 120 mg BID over the first 7 days is followed by 240 mg BID as maintenance dose. Based on PK results from the open-label, multicentre, multidose study 109MS202 (EMEA/H/C/002601/II/0042), the rate and extent of exposure in adolescent patients 13 to 17 years of age was comparable to adult subjects. For paediatric patients <13 years of age, no PK data are available; therefore, it remains unknown whether the adult dose administered could lead to an increase in exposure to MMF and subsequently to an increased risk for adverse events. Available PK data in the paediatric population relate to adolescents only (median age of adolescents in study 109MS202 was 16 years) and cannot be extrapolated to very young children, for whom clinical data in study 109MS306 are also very limited. The limitation/ lack of data in the most vulnerable population, together with the uncertainty regarding bone effects in pre-pubertal/ very young paediatric patients (see further below), constituted a major concern regarding the age defined in the indication (…*aged 10 years and older*…). As a consequence, the Applicant agreed to restrict the indication to paediatric patients aged 13 years and older.

Extent of exposure

Mean duration of treatment during study Part 1 was shorter for Avonex as compared to Tecfidera (72.3 weeks vs.84.4 weeks). The imbalance is driven by a higher number of patients who discontinued study drug in the Avonex group as compared to the Tecfidera group (42% vs. 22%).

The majority of patients either treated with Tecfidera or Avonex were on study drug for >88 to ≤96 weeks (Tecfidera: 65% and Avonex: 58%). 12% of patients in the Tecfidera group had study drug treatment of >96 weeks to ≤104 weeks. Cumulative duration of study treatment for Avonex and Tecfidera was 100.18 subject-years and 126.69 subjects-years, respectively.

For the revised age range (paediatric patients 13 to 18 years of age), the cumulative exposure for time on treatment for Avonex and Tecfidera is 89.49 subject-years vs. 113.81 subjects-years.

TEAEs, SAEs, and TEAEs leading to permanent treatment discontinuation

No death was reported. A similar number of patients in both groups reported a TEAE, i.e. 96% on Avonex and 95% on Tecfidera, mainly mild to moderate in severity. A rather high proportion of paediatric patients reported SAEs in this study, which was higher in the Avonex group as compared to Tecfidera (29% vs. 23%). TEAE-related discontinuations from treatment/ from study were more frequently reported in the Avonex group as compared to Tecfidera (6% and 11%).

Common AEs associated with DMF treatment in adults are GI disorders (including diarrhoea, nausea, abdominal pain upper, abdominal pain and vomiting), flushing, skin and subcutaneous disorders (pruritus, rash, erythema), haematological abnormalities (lymphopenia and leukopenia), increased hepatic enzymes, and proteinuria (reference is made to EMEA/H/C/002601/0000/Rev 1).

The most frequently reported TEAEs during study 109MS306 (Tecfidera and Avonex group; >20% in either group) in paediatric patients were similar to those observed in adults and derived from the nervous

system disorders SOC, infections and infestations SOC, gastrointestinal disorders SOC, general disorders and administration site conditions SOC, musculoskeletal and connective tissue disorders SOC, vascular disorders SOC, respiratory, thoracic and mediastinal disorders SOC, and skin and subcutaneous tissue disorders SOC. Differences mainly pertain to a disproportional reporting for MS relapse (35% vs. 46%), seasonal infections (nasopharyngitis 23% vs. 13%; upper respiratory tract infection 12% vs. 4%; influenza 10% vs. 4%), and gastroenteritis (12% vs. 7%), any TEAEs from the GI disorders SOC (mainly abdominal pain, vomiting, and diarrhoea, which occurred in 19 to 41% of patients on Tecfidera and in 6 to 8% of patients on Avonex), flushing (38% vs. 1%), and rash/ erythema/ pruritus in 0 to 1% and 8 to 14% of patients from either group. Overall, the most common TEAEs with Tecfidera in 109MS306 were abdominal pain (41%), flushing (38%), MS relapse (35%), headache (28%), nasopharyngitis (23%), and vomiting (23%).

MS relapse was reported more frequently in patients on Avonex as compared to Tecfidera, in line with the reporting of SAEs (more frequently in the Avonex group as compared to Tecfidera, 25% vs. 17%).

Gastrointestinal disorder TEAEs are among the most frequently reported side effects of DMF-containing drug products, with incidences in adults between 33% (in study 109MS303) and 48% (in Pool A) for DMF 240 mg BID. An increased incidence of GI disorders in the Tecfidera group versus the Avonex group is thus expected (74% vs. 31%). However, in paediatric patients, the frequency is much higher as compared to adults, mainly driven by TEAEs of abdominal pain and vomiting. Gastroenteritis (in the infections and infestations SOC), was higher on Tecfidera as compared to Avonex, and higher as compared to adults. A single SAE of GI disorders (abdominal pain upper) was reported in study 109MS306, and no patient discontinued due to a GI event, while 14% of patients had treatment interruption and/ or dose reduction. Specifically in the paediatric population, compliance problems or early treatment discontinuations could pose an issue; however, neither for this study nor for study 109MS202 (n=22 patients) and its extension 109MS311 (n=20 patients) treatment discontinuations were reported despite the high frequency of GI disorder TEAEs.

TEAEs that occurred more frequently in the Tecfidera as compared to the Avonex group and, at the same time, more frequently in paediatric as compared to adult patients are, e.g. TEAEs from the GI disorders SOC, the respiratory, thoracic and mediastinal disorders SOC, and dysmenorrhoea. The latter is unlikely related to sexual dysfunction and might be expected in an adolescent and mainly female population around menarche. Moreover, the concomitant use of analgesics in the Avonex treatment group (due to flu-like symptoms) could have abated dysmenorrhoea reporting in this group.

Flushing and related symptoms, GI tolerability, infections (including potential opportunistic infections), ischemic cardiovascular disorders, hepatic disorders, renal disorders, malignancies, and lymphopenia and leukopenia have been defined adverse events of special interest, and were qualitatively found in line with the known safety characteristics of Tecfidera in adults:

Malignancies are a designated important potential risk of DMF treatment. In 109MS306, no malignancies were reported. *Flushing and flushing-related events* were neither rated severe or serious but led to treatment discontinuation in 2 patients (3%) and to dose interruption/ dose reduction in 5% of patients. No new concerns on *cardiac* safety could be deduced from DMF treatment in paediatric patients and did not emerge during treatment in adults. However, patients with significant cardiovascular conditions were excluded from participation in clinical trials.

Serious and opportunistic infections (other than PML and herpes zoster) constitute an important potential risk in the RMP of DMF and seems to be similar for paediatric and adult patients. Infections were reported as SAEs (pneumonia pneumococcal and tonsillitis) and 4 infections in the Tecfidera group (5% of patients; i.e. gastroenteritis, influenza, and tonsillitis) led to dose interruption/ dose reduction. Overall, the long-term risk to acquire serious and/ or opportunistic infections in the paediatric population cannot

be assessed based on the limited amount of long-term data. AESI in line with *renal and hepatic disorders* were neither rated severe, nor serious, nor led to discontinuation from treatment or interruption/ dose reduction in the Tecfidera group. A signal of *renal toxicity* derived from nonclinical studies with DMF. However, DMF in adults was not associated with an increased risk of renal or urinary events, neither in pivotal studies nor in the long-term extension study 109MS303. Proteinuria, haematuria, and microalbuminuria were each reported in < 10% of adult patients, mild to moderate in severity, and rarely led to treatment discontinuations. Fewer renal (and urinary) disorders TEAEs were reported in paediatric patients on Tecfidera as compared to Avonex (10% vs. 5%). One patient in each group experienced an AESI of hepatocellular injury. DILI is an identified risk for DMF. Monitoring of liver enzymes is recommended in the product information. Moreover, transient mean increases in liver transaminases with DMF typically develop within the first 4 weeks of treatment. There was no case of hepatitis or Hy's law in paediatric patients.

A reduction in lymphocyte counts, including the occurrence of *lymphopenia*, is an important identified risk with Tecfidera. Decreases in lymphocyte (and leukocyte) counts starting at Week 4 through Week 48 with a plateau up to Week 96 were noted in adults. Mean decreases in paediatric patients were slightly lower as compared to adults, i.e. ~21% and 9% (adults: 30% and 11%) for lymphocyte and leukocyte counts, respectively. Overall, 20 of 78 patients treated with Tecfidera (25.6%) were reported with ALC $< 0.91 \times 10^9$/L at any postbaseline visit, with 7 patients having an ALC <LLN at Week 96. PCS lymphocyte counts $<0.8 \times 10^9$/L and $<0.5 \times 10^9$/L were reported in 19% and 4% of patients in the Tecfidera group. Severe prolonged lymphopenia defined as ALC $< 0.5 \times 10^9$/L for >6 months was not reported. However, 4 patients had prolonged, mild-to-moderate lymphopenia (5.1%), and two patients (2.6%) had prolonged moderate-to-severe lymphopenia. During the DMF MAA, analyses were performed and showed evidence for slight recovery of lymphocytes 4 weeks post dose (after treatment discontinuation or completion). Nevertheless, these data were considered inconclusive, given that the observation period was short. Long-term study 109MS303 aimed to further address lymphocyte recovery with Tecfidera and results in adults were evaluated in EMEA/H/C/002601/II/0069/G. Time to recovery of lymphocyte counts has not been assessed given that patients with ALC counts <LLN at the end of treatment switched to the open-label extension (Part 2). *Lymphopenia* (lymphocyte count decreased) was reported in 3% (1%) of patients in the Tecfidera group, and rated as severe and serious in a single patient. This patient at the same time reported a SAE of tonsillitis. Both events led to hospitalisation and resolved upon interruption of treatment. Lymphopenia did not lead to discontinuation from Tecfidera treatment.

Serious AEs occurred in 39 patients, in 21 patients on Avonex and in 18 patients on Tecfidera. 3 of the 39 patients (two on Tecfidera [SAE of fall/ fracture and MS relapse] and one in the Avonex group [SAE of optic neuritis]) were <13 years. The most frequently reported SAE in both groups was MS relapse (17% of patients on Tecfidera vs. 25% on Avonex), which always led to hospitalisation and which was not rated related to study drug. In four patients on Tecfidera, MS relapse was reported as a SAE more than once during treatment (up to five SAEs of MS relapse were reported in patient 172-001), which could indicate a high disease activity. All other SAEs in either group were reported in single patients only. In the Tecfidera group these included epilepsy and generalised tonic-clonic seizure (one patient each), optic neuritis, presyncope, lymphopenia (related), pneumonia pneumococcal, tonsillitis (related), abdominal pain upper (related), fall/forearm fracture, suicide attempt and rash pruritic (related).

TEAEs leading to treatment discontinuation occurred in 6% of patients on Tecfidera and in 11% of patients on Avonex in line with the expected safety profile (i.e. MS relapse, flushing, and limb discomfort on Tecfidera). Temporary interruption of treatment and dose reduction were reported by more patients in the Tecfidera as compared to Avonex group (26% vs. 7%) and in line with known safety issues (most frequently due to GI disorders, flushing, gastroenteritis and pyrexia).

Clinical laboratory evaluations

Haematology results are basically in line with results from the phase 3 adult studies (see above). Eosinophil mean values transiently increased through Week 4 but returned to normal values by Week 12 in adults and this was found similar in paediatric patients.

In adult DMF clinical studies, hepatic transaminases ALT and AST increased compared to placebo, with a peak at Week 4, and returned to baseline values around Week 32. ALT and AST maximum post-baseline values were in a majority (>90%) of patients < 3x ULN and few patients had values ≥ 3x ULN in either treatment group. Hy`s law cases were not reported. Any shifts from baseline to abnormal postbaseline in hepatic enzymes in paediatric patients were similar or lower than in adults. In 9% of patients on Tecfidera, ALT increased was reported as TEAE and in 1%, a TEAE of blood bilirubin increased was reported. Hepatic enzyme increases are included as ADR in section 4.8 of the SmPC (frequency common).

No new safety concerns derive from administration of Tecfidera in paediatric patients regarding blood chemistry and urinalysis data.

There were no clinically relevant changes in *vital signs* or ECG parameters. Any potentially clinically significant values observed in paediatric patients were in line with the experience in adults.

Recent scientific data and preclinical experience with DRF (in the ongoing procedure EMEA/H/C/005437) suggest that Nrf2 (which is activated by DMF and DRF via their common major active metabolite MMF) could play a direct role in the regulation of bone homeostasis stressing the importance of balanced Nrf2 activation for normal bone development. Reference is made to 3.2.4. of this report. While the possible effect of DMF and DRF on bone homeostasis appears negligible for adult RRMS patients, the relevance and implications are more obvious in pre-pubertal children or those being in an early stage of puberty for whom the risk remains unknown.

In the paediatric population special attention should be paid to possible adverse effects on growth (e.g. height and weight), sexual maturation, cognition, and endocrine function in line with the provisions of the Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev. 2). This is of importance given that susceptibility to specific adverse reactions might change from pre- to post-pubertal status.

The MAH presented an integrated discussion on preclinical and clinical data with regard to paediatric growth and development in study 109MS306, which focused on height progression (versus standardised WHO height-for-age charts for male and female children and adolescents aged 5 to 19 years), bone age (versus chronological age), endocrine assessments, and sexual maturity as per Tanner staging.

The results need to be interpreted in the context of the age distribution in this study, i.e. 69% and 21% of the overall patients belonged to the age group 15 to 17 years and 13 to 14 years, respectively. Moreover, at baseline, a majority of these patients were already in an advanced stage of puberty indicated by a baseline Tanner stage 4 (approx. more than 75% in both groups). Therefore, the majority of patients in study 109MS306 might not have been affected by a potential impact of Tecfidera on growth and development.

With regard to bone homeostasis, the paucity of clinical data did not unveil a negative effect of Tecfidera. Presentation of progression in height from baseline in male and female paediatric patients per age groups (i.e. 10 to 12 years, 13 to 14 years, and 15 to 17 years) revealed no signs of delay in those treated with Tecfidera as compared to Avonex and as compared to healthy controls over a 96-week treatment course in this study. Few patients overall had bone age assessments by hand and wrist radiography (26 of 72 patients on Avonex and 34 of 78 patients on Tecfidera). Nevertheless, bone age and chronological age did not differ by more than 2 SD, the cut-off which would indicate abnormalities in bone

development. To follow-up the impact of Tecfidera on bone homeostasis, "Impaired bone development in paediatric patients" has been confirmed to be added to the summary of safety concerns in the Periodic Safety Update Reports (PSURs) to ensure regular specific review of the topic.

Only 14 patients on Tecfidera had endocrinological tests performed at baseline and even less at Week 48, and Week 96, respectively, based on the protocol provisions. Most of the estradiol and testosterone levels were only measured once during the study hampering determination of the hormonal state in these subjects over time and a potential influence of Tecfidera. However, abnormalities in these or other endocrine parameters (LH, FSH, IGF-1) were not found remarkably different between treatment groups.

Tanner staging was assessed at screening (and Week 48 and EOT Part 1) for all patients (for premenarche female patients, until bone age reached ≥ 16 years or until postmenarche), based on pubic hair and breast development in girls, and presentation of testes and scrotum and pubic hair in boys. This concerned assessment in 42 female and in 25 male patients. Almost half of the female and a majority of male patients presented with Tanner stage 5 at screening. Given that only a single (male) patient on Tecfidera was pre-pubertal, the safety profile in this subset of paediatric patients cannot be assessed. Tanner stage in the age group 10 to <13 years progressed in both treatment groups over the course of the study, with Avonex-treated paediatric patients having had a slightly lower increase as compared to Tecfidera-treated patients, probably due to a lower baseline Tanner stage in the Avonex group. Tanner stage progression in the age group 13 to <15 years was more even in both treatment groups and a similar trend for males and females treated with Tecfidera could be observed. In the age group 15 to 18 years, there were three deviations from age-expected Tanner stage scoring at baseline, one in the Avonex group and two in the Tecfidera group. The influence of Avonex or Tecfidera on sexual maturation in two of three patients remains unknown. Overall, no evidence for disruption of normal sexual maturation as a consequence of Tecfidera treatment can be derived from these data.

Overall, the MAH's proposal to restrict the indication to paediatric patients aged 13 years and older is considered adequate to handle the limitation and even absence of clinical data in those patients being in an early stage of puberty, where any impact of DMF could be more relevant.

Postmarketing data from international birth date of Tecfidera in the US to data cut-off (i.e. 26 March 2021; ~7 years) comprise off-label use data in paediatric patients. Cases for which AEs were reported were in a majority related to the known safety profile of Tecfidera and to the underlying disease. The most frequently mentioned SAE in paediatric patients in the postmarketing experience was MS relapse.

Assessment of paediatric data on clinical safety

The following safety data were also submitted and discussed by the MAH as part of the documentation for this variation procedure and are hence considered supportive (reference is also made to 3.3.2. of this AR):

Study 109MS202

Reference is made to EMEA/H/C/002601/II/0042 for detailed assessment of clinical safety.

Safety data for open-label treatment with Tecfidera for 24 weeks are available for 22 paediatric MS patients with a median age of 16 years and a body weight similar to adult subjects. Hence, this population is more representative of adults than of younger paediatric patients. Tolerability and safety issues (e.g. flushing and GI effects) were found in line with the known effects in adults. No new safety concerns emerged upon this limited dataset of paediatric patients having had a short duration of treatment. A high reporting of TEAEs from the nervous system disorders SOC (59%; mainly due to MS relapse in one-third of the patients, i.e. 32%) is of note, which complies with the data from 109MS306. SAEs were

reported in 5 patients (23%), with MS relapse reported in 4 of the 5 patients with SAEs. Dysmenorrhoea was reported in 2 patients (9%).

Study 109MS311

Reference is made to EMEA/H/C/002601/II/0059 for detailed assessment of clinical safety.

Safety data for the paediatric population from study 109MS202 comprise the extension of open-label treatment with Tecfidera for 96 weeks in 20 rollovers (median age of 17 years during the extension). Safety was generally in line with previous data (regarding GI disorders and flushing). MS relapse was reported in 20% of the patients. Dysmenorrhoea was reported in 3 patients (15%). 3 of 4 SAEs were MS relapse.

3.5.2. Conclusions on clinical safety

In support of the extension of the indication of Tecfidera to paediatric patients now revised to those aged 13 years and older, the Applicant has provided open-label, active-controlled safety data up to 96 weeks deriving from Part 1 of phase 3 study 109MS306. Long-term safety data for up to 5 years of open-label treatment with Tecfidera (Part 2) have been separated from the Tecfidera PIP and are not yet available to conclude on any potential impact of Tecfidera treatment during longer treatment duration. This is adequately reflected in the product information (section 4.4).

Available safety data for Tecfidera confirm the safety profile in paediatric patients to be qualitatively in line with that in the adult MS population. However, discrepancies have been noted in the incidence of events between paediatric and adult patients, i.e. a number of adverse events occurred with a higher frequency in paediatric patients as compared to adults. This has been dealt with by adequate labelling in the product information (section 4.8 of the SmPC). Moreover, recent scientific publications and preclinical data of DRF submitted in the ongoing MA procedure EMEA/H/C/005437 support a concern of a potential impact of DMF on bone homeostasis, which could be of relevance in the very young and pre-pubertal population for which pharmacological and clinical data are either lacking or very limited: Only 7 patients treated with Tecfidera were <13 years of age, and only a single patient treated with Tecfidera was pre-pubertal (Tanner stage 1). Restriction of the indication to paediatric patients aged 13 years and older is therefore adequate to reduce a potential but not clinically substantiated risk.

Approval of the revised indication is acceptable from a clinical safety perspective. Moreover, the product information has been revised as requested.

3.5.3. PSUR cycle

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

3.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 13 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

Table 31: Summary of safety concerns

Important identified risks	• PML • Decreases in leukocyte and lymphocyte counts • Drug-induced liver injury
Important potential risks	• Serious and opportunistic infections (other than PML and herpes zoster) • Malignancies • Effects on pregnancy outcome • Interaction with nephrotoxic medications leading to renal toxicity
Missing information	• Long-term efficacy and safety • Safety profile in patients over the age of 55 years • Safety profile in patients with moderate to severe renal impairment • Safety profile in patients with hepatic impairment • Safety profile in patients with severe active GI disease • Increased risk of infection in patients concomitantly taking anti-neoplastic or immunosuppressive therapies

Pharmacovigilance plan

Table 32: Ongoing and planned additional pharmacovigilance activities

Study name and description **Study Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
<u>Category 1</u> – ***Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation***				
• None				
<u>Category 2</u> – ***Imposed mandatory additional pharmacovigilance activities that are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances***				
• None				
<u>Category 3</u> – ***Required additional pharmacovigilance activities***				
Study 109MS401 (ESTEEM) A Multicenter, Global, Observational Study to Collect Information on Safety and to Document the Drug Utilization of Tecfidera (Dimethyl Fumarate) When Used in Routine Medical	*<u>Primary Objective:</u>* • To determine the incidence, type, and pattern of serious adverse events, including but not limited to serious infections (including opportunistic infections), hepatic	• Decreases in leukocyte and lymphocyte counts • Drug induced liver injury • Serious and opportunistic infections (other	Annual Progress Reports	Q2 Yearly
			Final CSR	Q4 2024

Study name and description Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Practice in the Treatment of Multiple Sclerosis • **Status:** Ongoing	events, malignancies, and renal events, and of AEs leading to treatment discontinuation in patients with MS treated with DMF. *Secondary Objectives:* • To determine DMF prescription and utilisation patterns in routine clinical practice in patients with MS. • To assess the effectiveness of DMF on MS disease activity and disability progression in routine clinical practice as determined by the EDSS score and MS relapse information. • To assess the effect of DMF on health-related quality of life, healthcare resource consumption, and work productivity.	than PML and herpes zoster) • Malignancies • Safety profile in patients over the age of 55 years • Safety profile in patients with moderate to severe renal impairment • Safety profile in patients with hepatic impairment • Safety profile in patients with severe active GI disease • Interactions with nephrotoxic medications leading to renal toxicity • Long-term efficacy and safety • Increased risk of infection in patients concomitantly taking anti-neoplastic or immunosuppressive therapies		
Study 109MS402 Biogen Multiple Sclerosis Pregnancy Exposure Registry • **Status:** Ongoing	*Primary Objective:* To prospectively evaluate pregnancy outcomes in women with MS who were exposed to a registry-specified Biogen MS product during the eligibility window for that product.	• Effects on pregnancy outcomes	Annual Progress Reports Final CSR	Q2 Yearly Q1 2022

Study name and description Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Study 109MS306 Part 2 Open-Label, Randomized, Multicenter, Multiple-Dose, Active-Controlled, Parallel-Group, Efficacy and Safety Study of BG00012 in Children From 10 to Less Than 18 Years of Age With Relapsing-Remitting Multiple Sclerosis, With Optional Open-Label Extension **Status:** Ongoing	*Primary Objective of Part 2:* • To evaluate the long-term safety of BG00012 in participants who completed Week 96 in Part 1 of Study 109MS306. *Secondary Objectives:* To describe the long-term MS outcomes of BG00012 in participants who completed Week 96 in Part 1 of Study 109MS306.	• Long-term safety and efficacy in paediatric participants aged 10 to < 18 years	Interim analysis	Q4 2022
			Final CSR	Q4 2025

Risk minimisation measures

Table 33: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
PML	***Routine risk minimisation measures:*** Information in SmPC Sections 4.3 (*Contraindications*), 4.4 (*Special warnings and precautions for use*), and 4.8 (*Undesirable effects*), and PL Section 4 (*Possible side effects*). ***Additional risk minimisation measures:*** The MAH distributed a DHPC in EU countries by 12 Nov 2020 to inform HCPs about cases of PML in the setting of lymphopenia (mild).	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** Targeted follow-up questionnaire ***Additional pharmacovigilance activities:*** None
Decreases in leucocyte and lymphocyte counts	***Routine risk minimisation measures:*** Information in SmPC Sections 4.4 (*Special warnings and precautions for use*) and 4.8 (*undesirable effects*) and PL Section 4 (*Possible side effects*). ***Additional risk minimisation measures*** No risk minimisation measures	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** Targeted follow-up questionnaire. ***Additional pharmacovigilance activities:*** Observational study (Study 109MS401, in adults)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Drug-induced liver injury	***Routine risk minimisation measures:*** Information in SmPC Sections 4.4 (*Special warnings and precautions for use*) and 4.8 (*Undesirable effects*) and PL Section 4 (*Possible side effects*). ***Additional risk minimisation measures*** No risk minimisation measures	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** Targeted follow-up questionnaire. ***Additional pharmacovigilance activities:*** Observational study (Study 109MS401)
Important potential risks		
Serious and opportunistic infections (other than PML and herpes zoster)	***Routine risk minimisation measures:*** Information in SmPC Section 4.4 (*Special warnings and precautions for use*) and PL Section 4 (*Possible side effects*). ***Additional risk minimisation measures*** No risk minimisation measures	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** Targeted follow-up questionnaire ***Additional pharmacovigilance activities:*** Observational study (Study 109MS401)
Malignancies	***Routine risk minimisation measures:*** Information in SmPC Section 5.3 (Preclinical safety data). ***Additional risk minimisation measures*** No risk minimisation measures	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** Targeted follow-up questionnaire ***Additional pharmacovigilance activities:*** Observational study (Study 109MS401)
Effects on pregnancy outcome	***Routine risk minimisation measures:*** Information in SmPC Sections 4.6 (*Fertility, pregnancy and lactation*) and 5.3 (*Preclinical safety data*), and PL Section 2 (*What you need to know before you take Tecfidera*). ***Additional risk minimisation measures*** No risk minimisation measures	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** Pregnancy registry (Study 109MS402)
Interaction with nephrotoxic medications leading to renal toxicity	***Routine risk minimisation measures:*** Information in SmPC Section 4.5 (*Interaction with other medicinal products and other forms of interaction*) and PL Section 2 (*What you need to know before you take Tecfidera*). ***Additional risk minimisation measures***	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** Observational study (Study 109MS401)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	No risk minimisation measures	
Areas of missing information		
Long-term efficacy and safety	***Routine risk minimisation measures:*** Text in SmPC Sections 4.8 (Undesirable effects) and 5.1 (Pharmacodynamic properties) ***Additional risk minimisation measures*** No risk minimisation measures	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** Observational study (Study 109MS401) Open-label extension (Part 2) of Study 109MS306 (in paediatric participants aged 10 to < 18 years)
Safety profile in patients over the age of 55 years	***Routine risk minimisation measures:*** Text in SmPC Sections 4.2 (*Posology and method of administration*) and 5.2 (*Pharmacokinetic properties*) ***Additional risk minimisation measures*** No risk minimisation measures	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** Observational study (Study 109MS401)
Safety profile in patients with moderate to severe renal impairment	***Routine risk minimisation measures:*** SmPC Section 4.4 (*Special warnings and precautions for use*) and PL Section 2 (*What you need to know before you take Tecfidera*). ***Additional risk minimisation measures*** No risk minimisation measures	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** Observational study (Study 109MS401)
Safety profile in patients with hepatic impairment	***Routine risk minimisation measures:*** Text in SmPC Section 4.4 (*Special warnings and precautions for use*) and PL Section 2 (*What you need to know before you take Tecfidera*). ***Additional risk minimisation measures*** No risk minimisation measures	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** Observational study (Study 109MS401)
Safety profile in patients with severe active gastrointestinal disease	***Routine risk minimisation measures:*** Text in SmPC Section 4.4 (*Special warnings and precautions for use*) and PL Section 2 (*What you need to know before you take Tecfidera*). ***Additional risk minimisation measures***	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** Observational study (Study 109MS401)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	No risk minimisation measures	
Increased risk of infection in patients concomitantly taking anti-neoplastic or immunosuppressive therapies	***Routine risk minimisation measures:*** Text in SmPC Section 4.5 (*Interactions with other medicinal products and other forms of interaction*) and PL Section 2 (*What you need to know before you take Tecfidera*). ***Additional risk minimisation measures*** No risk minimisation measures	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** Observational study (Study 109MS401)

3.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.3 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

3.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

4. Benefit-Risk Balance

4.1. Therapeutic Context

4.1.1. Disease or condition

With the present application, the Applicant originally sought approval of DMF for paediatric patients from 10 years to 17 years of age with RRMS. As a consequence of the concerns raised during the first round of this procedure based on the limited data in paediatric patients aged 10 to 12 years and those being pre-pubertal at study entry, the Applicant proposes to limit the indication for the paediatric population to patients aged 13 years and older.

Paediatric MS is a severe chronic, immune-mediated neurodegenerative disorder of the CNS, characterized by inflammation, demyelination, and axonal/neuronal destruction, with marked impact on patients' life and development, and leading to disability early in life. Although MS is predominantly a disease of young adults, approximately 3% to 5% of people with MS have their first symptoms in childhood. Genetic, serum, cerebrospinal fluid, and cell-based studies largely support a shared biology between paediatric-onset and adult-onset disease. Relapses are more frequent in patients with paediatric-onset compared with adult-onset MS and a greater number of MRI lesions is observed. One-

third of the paediatric MS patients experience cognitive impairment and MRI evidence of global and focal loss of age expected brain volume has been described.

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

Due to the clinical phenotype of paediatric MS with relapses as the most important clinical component reflecting disease activity, the most important endpoints relate to relapses (clinical) and MRI findings (representing inflammation).

4.1.2. Available therapies and unmet medical need

Fingolimod and teriflunomide are the only DMT as of yet that are explicitly approved in the EU for paediatric patients with RRMS aged 10 years and older. In addition, IFN β1a and GA can be used but efficacy and safety data in the paediatric population are limited. Corticosteroids are available for the symptomatic treatment of MS relapses.

4.1.3. Main clinical studies

In support of the extension of indication in the paediatric population, study 109MS306 Part 1 (also referred to as study CONNECT) was presented. Study 109MS306 Part 1 is a 96 week (two-year), open-label, multicenter, randomised, multiple-dose, active-controlled (against Avonex), parallel group trial to evaluate safety, tolerability, and efficacy of Tecfidera (also referred to as DMF; BG00012) (dosed: n = 78) vs. Avonex (dosed: n = 72) administered either orally BID (Tecfidera) or intramuscularly self-administered once weekly (Avonex) in paediatric patients with RRMS followed by an optional open-label extension (Part 2) up to approximately 5 years.

The study included children aged 10 to <18 years old suffering from RRMS according to the IPMSSG criteria for paediatric MS (2013 consensus definition for paediatric RRMS) [Krupp 2013] with an EDSS score ≤5.5.

With regard to disease activity, the following criteria had to be met:

- at least 1 relapse within the last 12 months prior to Day 1, with a prior brain MRI demonstrating lesions consistent with MS, or

- at least 2 relapses within the last 24 months prior to Day 1, with a prior brain MRI demonstrating lesions consistent with MS, or

- evidence of Gd-enhancing lesions of the brain on an MRI performed within the 6 weeks prior to Day 1.

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

4.2. Favourable effects

The primary endpoint was the "proportion of patients with no new or newly enlarging T2 hyperintense lesions at week 96 relative to baseline", performed in the Completer population. The proportion of patients with no new or newly enlarging T2 hyperintense lesions at week 96 relative to baseline was higher in the Tecfidera group (10 of 62 patients, 16.1% [95% Clopper-Pearson exact CI: 8.0%, 27.7%]) than in the Avonex group with 2 of 41 patients, 4.9% [95% Clopper-Pearson exact CI: 0.6%, 16.5%].

Results have been confirmed in a "sensitivity analysis" that has been performed in the ITT population. The proportion of patients with no new or newly enlarging T2 hyperintense lesions at week 96 relative to baseline was higher in the Tecfidera group with 10 of 78 patients (12.8%) than in the Avonex group (2 of 72 patients, 2.8%). The OR for the proportion of patients with no new or newly enlarging T2 hyperintense lesions at Week 96 in the Tecfidera group compared with the Avonex group was 6.99 (95% CI: 1.63, 49.88).

With regard to the secondary endpoint, the number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Week 96 performed in the ITT population excluding patients without MRI at that visit, the adjusted mean number of new or newly enlarging T2 hyperintense lesions was 32.65 (95% CI: 20.97, 50.85) for the Avonex group and 12.42 (95% CI: 8.79, 17.54) for the Tecfidera group, corresponding to a 61.96% reduction in the Tecfidera group compared to the Avonex group.

Two sensitivity analyses (a) number of new or newly enlarged T2 hyperintense lesions relative to baseline, Last Observation on/prior to the week 96 visit, b) number of new or newly enlarged T2 hyperintense lesions relative to baseline, Last Observation on/prior to the week 96 Visit, prior to the alternative medication have been performed. Both analyses showed a trend in favour of Tecfidera as well, but the difference in favour of Tecfidera was smaller than in the completer analysis.

At week 96, the proportion of patients free of new MRI activity (i.e., free of Gd-enhancing and free of new or newly enlarging T2 MRI lesions on brain MRI scans) relative to baseline was higher in the Tecfidera group (9 of 62 patients, 14.5%) than in the Avonex group with 2 of 42 patients (4.8%) (OR for proportions: 8.76 (95% CI: 1.51, 81.44).

The Kaplan-Meier estimate of the probability for clinical relapse was 34% in the Tecfidera group and 48% in the Avonex group during the 96-week open-label study period. The HR for relapse was 0.574 (95% CI: 0.329 to 1.001). In comparison to Avonex the time to first relapse was delayed in the Tecfidera treatment arm.

At Week 96, the adjusted ARR for the Avonex group was 0.528 (95% CI: 0.333, 0.836), and 0.240 (95% CI: 0.147, 0.393) for the Tecfidera group (rate ratio 0.46, 95% CI (0.26, 0.78). Most of the patients in both treatment arms experienced 0 relapses (Avonex 58%, Tecfidera 68%) up to week 96.

Descriptively summarised results for the EDSS score: the mean (SD) EDSS score at baseline was 1.12 (0.966) and 1.16 (1.074) for the Avonex and the Tecfidera treatment group, respectively, while at week 96 the mean (SD) EDSS score was 1.19 (1.101) and 1.17 (1.217), respectively, representing almost no changes in EDSS score for both treatment groups.

Exploratory endpoint: At all visits, most of the patients in both treatment groups had no Gd-enhancing lesions with a generally higher proportion in the Tecfidera group than in the Avonex group. At Week 96 the mean number of Gd-enhancing lesions was 1.3 under Avonex compared to 1.4 under Tecfidera. The OR of being in the group with higher Gd lesions in the Tecfidera group versus Avonex group was 0.43 (95% CI: 0.18, 1.03), reflecting the trend that patients in the Tecfidera group tended to be in the categories with less Gd lesions compared to Avonex. From baseline, the mean number of T1 Gd-enhancing lesions in the Avonex group declined from 3.58 to 1.3, the mean number of T1 Gd-enhancing lesions in the Tecfidera group declined from 2.35 to 1.4 at week 96.

The efficacy outcomes of DMF in the paediatric population and young adults seem to be consistent with those from the overall adult patient population and in favour of Tecfidera in the provided analyses. In study 109MS306, Tecfidera indicates an effect on typical MRI based parameters for assessing the inflammatory component of MS. Therefore, it may be assumed, based on the known clinical efficacy in adult patients, that the clinical efficacy in children is also alike that observed in adults.

4.3. Uncertainties and limitations about favourable effects

The proposed posology in the initially requested paediatric population aged 10 years and older is the same as in adults. PK bridging was performed based on already available and previously assessed PK data from a small paediatric phase 2, open-label, uncontrolled study in 21 paediatric patients aged 13 to 17 years. The data suggest similar exposure with the same dose of DMF in adolescent and adult patients. However, no PK data are available for patients < 13 years of age. It is unclear whether the adult dose is appropriate for these young patients. Potential overexposure is a safety rather than an efficacy issue. However, with the response to the RSI, the MAH proposed a restriction of the indication to adolescents ≥13 years of age, which is considered adequate to address this uncertainty.

One efficacy study has been provided in support of the claimed paediatric indication. Due to methodological limitations (including open-label design, no type 1 error control, methods not pre-specified in full detail, analyses generally not based on ITT-population), results are considered descriptive and do not provide confirmatory evidence of efficacy for Tecfidera in the paediatric population.

The study has been conducted in an open-label design. As MRI scans were transferred electronically, read and interpreted by an independent blinded assessment centre, bias for the assessment of the primary endpoint can be excluded. In addition, in reference to the description of the study report and based on the Applicant´s responses to the RSI, it is considered that a potential bias from de-blinding the examining neurologist to the clinical endpoints, e.g. relapse confirmation, was also limited. As the outcome on clinical relapses and data for new or newly enlarging T2 lesions, both representing disease activity, were concordant in the two treatment arms, the measures taken to maintain the blind for the assessment of the clinical endpoints are expected to have been sufficient, although no explicit information is given, whether e.g. injection sides had to be sufficiently covered, to maintain the blind as far as possible. Overall, also taking into consideration, that the ARR has been evaluated as a secondary endpoint in this open label study, the blinding could be considered acceptable.

4.4. Unfavourable effects

Treatment-emergent AEs after Tecfidera and Avonex administration were reported for 95% and 96% of paediatric patients in study 109MS306, respectively, with discontinuations due to TEAEs in 6% and 11% of patients and SAEs in 23% and 29% of patients (a majority of them being MS relapse). No death was reported. TEAEs with Tecfidera in study 109MS306 were qualitatively in line with those in adults. The SOCs with the highest proportions of subjects reporting TEAEs were nervous system disorders, infections and infestations, GI disorders, general disorders and administration site conditions, musculoskeletal and connective tissue disorders, vascular disorders, respiratory, thoracic and mediastinal disorders, and skin and subcutaneous tissue disorders. The most common TEAEs in the Tecfidera group included abdominal pain (41%), flushing (38%), MS relapse (35%), headache (28%), nasopharyngitis (23%), and vomiting (23%). Quantitative differences in the reporting of TEAEs in paediatric patients in excess of those in adults have been noted, e.g. for MS relapse, headache, GI disorders (mainly abdominal pain and vomiting), events from the respiratory, thoracic and mediastinal disorders SOC, and dysmenorrhoea.

Serious and opportunistic infections (other than PML and herpes zoster) are a potential risk with DMF treatment. In study 109MS306, two serious infections were reported (pneumonia pneumococcal and tonsillitis). None resulted in discontinuation from treatment.

Decreases in leukocyte and lymphocyte counts are an important identified risk with DMF, starting at Week 4 through Week 48 with a plateau up to Week 96. Mean decreases from baseline in paediatric patients were 9% and 21% for leukocyte and lymphocyte counts, respectively. In 109MS306, 7 patients in the Tecfidera group (i.e. approx. 9%) had at least one post-baseline lymphocyte count below LLN (<

0.91 × 10^9/L). Three of them permanently discontinued treatment (for other reasons), and three had dose interruption. Severe prolonged lymphopenia defined as ALC < 0.5 × 10^9/L for more than 6 months has not been reported due to protocol requirements for discontinuation. 3% and 1% of patients reported lymphopenia and lymphocyte count decreased as a TEAE. A single patient reported a SAE of lymphopenia. No patient discontinued treatment with Tecfidera due to lymphopenia.

Malignancies and cases of PML were not reported in paediatric patients but are potential and identified risks with DMF treatment in the RMP.

Increases in liver transaminases and related hepatic events have been reported in the adult DMF clinical programme and baseline and routine monitoring of liver enzymes is detailed in the SmPC. DILI is an important identified risk with DMF and is included as ADR in section 4.8 of the SmPC. Transient asymptomatic increases in liver transaminases with DMF were reported within the first 4 weeks of treatment in adult and likewise in paediatric patients. In a majority of paediatric patients on Tecfidera or Avonex, increases were in line with ALT and/ or AST of < 3x ULN. Laboratory abnormalities were reported as TEAE in a single patient each for ALT increased and blood bilirubin increased. One patient in each group experienced an AESI of hepatocellular injury. Cases of Hy's law were not observed in paediatric patients. The safety profile in patients with hepatic impairment is an area of missing information in the RMP.

There was no evidence for impaired renal function with Tecfidera treatment in paediatric patients. Abnormal urinalysis parameters were reported for urine protein, urine ketones and urine occult blood (in 92%, 59%, and 44% of Tecfidera patients and in in 81%, 14%, and 40% of Avonex patients in study 109MS306) without corresponding to renal TEAEs. Proteinuria was reported in 3% of paediatric patients. Proteinuria is included as common ADR with DRF and DMF in section 4.8 of the SmPC. DMF treatment of patients with moderate and/ or severe renal impairment is a missing information in the RMP. In addition, the interaction with nephrotoxic medications leading to renal toxicity is listed as an important potential risk in the Tecfidera RMP.

Vascular disorders (incl. flushing and flushing-related TEAEs) were reported by 46% and 8% of paediatric patients on Tecfidera and Avonex, respectively, and were neither rated severe or serious but led to treatment discontinuation in 2 patients (3%) and to dose interruption/ dose reduction in 5% of patients.

Gastrointestinal disorders TEAEs (mainly diarrhoea, nausea, and abdominal pain) are among the most frequently reported side effects of DMF-containing drug products, with incidences between 33% (in study 109MS303) and 48% (in Pool A) for DMF 240 mg BID and in line with data from the psoriasis indication (see EPAR of Skilarence EMEA/H/C/002157/0000). In 109MS306, 74% of patients on Tecfidera (31% on Avonex) reported GI disorders TEAEs, and in a single patient, abdominal pain upper was rated serious. No event led to treatment discontinuation. 14% of patients on Tecfidera had a dose reduction/ interruption due to GI events. Routine risk minimisation measures to improve GI tolerability with DMF include temporary dose reduction to half the maintenance dose and the intake with food.

4.5. Uncertainties and limitations about unfavourable effects

Overall, the safety profile of Tecfidera in paediatric patients is based on a limited dataset of 78 patients exposed to Tecfidera and 72 patients exposed to Avonex in study 109MS306. Cumulative duration of study treatment for Avonex and Tecfidera is 100.18 subject-years vs. 126.69 subjects-years. For the updated age range proposed by the MAH (paediatric patients 13 to 18 years of age), the cumulative exposure for time on treatment for Avonex and Tecfidera is 89.49 subject-years vs. 113.81 subjects-years, and for time on study it is 93.21 subject-years vs. 118.35 subjects-years.

Long-term data are available for 96 weeks of treatment during Part 1; however, only 78% of patients in the Tecfidera group completed the treatment (and 58% of patients on Avonex). Further long-term data from the open-label extension (Part 2) will not be presented within this procedure. The MAH committed to present interim data after the next interim analysis, which is scheduled for Q3/4 of 2022.

Few safety data are available regarding the most vulnerable subpopulations (i.e. children aged 10 to <13 years and pre-pubertal patients [Tanner stage 1]) for which interpretability of safety data is either difficult or impossible. No PK data is available for these paediatric subpopulations and it is unknown whether the proposed (adult) DMF dose (i.e. 240 mg BID) leads to an increased exposure to MMF and subsequently to the risk for an increase in side effects:

- Age: mean age was 14.9 (1.62) years. Only 7 patients on Tecfidera and 8 patients on Avonex (i.e. 15 out of 150 patients, 10%) were <13 years.

- Pubertal status: Only 3 patients were pre-pubertal (2%, reflected by Tanner Stage 1 at screening) of which one patient was treated with Tecfidera. Therefore, no safety conclusion in pre-pubertal patients can be drawn.

The Applicant proposed a restriction of the indication to adolescents ≥13 years of age, which is considered to adequately mitigate this uncertainty.

Uncertainty has been raised on a potential impact of Tecfidera on bone homeostasis in paediatric patients, in which Nrf2, the proposed main target of DMF action, was found to play a direct role. The mechanistic rationale has been discussed in detail in the ongoing MA procedure of DRF (EMEA/H/C/005437) and also applies to DMF, because both DMF and DRF exert their pharmacological activity via the common major active metabolite MMF. Detrimental effects on bone homeostasis, if any, are likely to especially affect younger patients with a growing skeleton. However, available data (i.e. bone age evaluation and laboratory parameters) suggest that Tecfidera does not pose a risk for impairment. In addition, it is reasonable to assume that the proposed restriction of the indication to adolescents aged 13 years and older will reduce the most vulnerable population. Additionally, the MAH confirmed that *"Impaired bone development in paediatric patients"* will be added to the summary of safety concerns in the PSURs to ensure regular specific review of the topic.

Uncertainty has also been raised with regard to potential effects on growth and sexual maturation. Growth parameters (e.g. height and weight) and Tanner staging assessments provide valuable information on a possible drug effect on physical development in paediatric MS patients and are thus to be assessed according to EMA/CHMP/771815/2011, Rev. 2. Upon request, the Applicant presented an integrated analysis on aspects of growth and development in paediatric patients treated in study 109MS306, including assessment of physical features (i.e. height), bone age assessment, endocrine laboratory parameters and Tanner staging. It should be noted that a majority of paediatric patients (more than 75% in both groups) enrolled in study 109MS306 had a baseline Tanner stage of 4, and were on average 15 years of age, thus limiting the informative value for the less physically progressed paediatric patients. Paediatric patients stratified by age groups (10 to <13 years, 13 to <15 years, and 15 to <18 years) similarly progressed in height and Tanner stage during 96 weeks of treatment with either Tecfidera or Avonex and as expected to background healthy reference populations. Moreover, bone age largely corresponds to chronological age in study 109MS306; however, far less than half of the patients in either group had measurements of bone age. The number of patients per age group with measurement of bone age is low as expected, especially in the lower age groups 10 to <13 years and 13 to <15 years (less than 10 patients per treatment group and time point). The informative value of endocrine tests is limited given that only few patients had serial measures of laboratory parameters. However, abnormalities in estradiol, testosterone or other endocrine parameters (LH, FSH, IGF-1) were not found remarkably different between treatment groups.

In this context it has been noted that dysmenorrhoea occurred more frequently in adolescent patients treated with Tecfidera as compared to Avonex and in excess of adult females. However, there is no evidence that dysmenorrhoea is related to sexual dysfunction caused by Tecfidera. Possible reasons for the different reporting in the Tecfidera and Avonex group could be related to different baseline Tanner stages (higher proportion of Tanner stage 4 in the Tecfidera group) and the more frequent use of analgesics in the Avonex group (due to flu-like symptoms). The difference in reporting between this study and in adults could be age-related given that dysmenorrhoea more frequently affects younger female patients as compared to older female patients. Adequate labelling is proposed in section 4.8 of the SmPC.

In addition, a disproportionate reporting of TEAEs was observed in paediatric as compared to adult patients (Pool A data of the Tecfidera clinical program in adults), including, for example, TEAEs from the GI disorders SOC and from the respiratory, thoracic and mediastinal disorders SOC. Patient compliance and early treatment discontinuations in the real-world setting have been discussed for GI disorders but there is at present no indication that this poses an issue in the paediatric population given the absence of treatment discontinuations due to GI-related TEAEs. The MAH added a description of TEAEs that occurred with a difference of 10% or more in paediatric patients compared to adults in section 4.8 of the SmPC. Moreover, the long-term risk to acquire serious and/ or opportunistic infections in the paediatric population seems not different from that in the adult population with more data collected during Part 2 of study 109MS306. At present, the language included in the PI is considered sufficient (recommending interruption of treatment with Tecfidera if a serious infection occurs).

With regard to the uncertainty on lymphopenia, it could be clarified that – despite the absence of patients with prolonged severe lymphopenia, there were 4 patients with prolonged, mild-to-moderate lymphopenia (5.1%), and two patients with prolonged moderate-to-severe lymphopenia (2.6%). No patient was included in the lymphocyte recovery monitoring period since patients with ALC<LLN at Week 96 either entered the open-label period or switched to another DMT. Despite limitations regarding the small data set, lymphopenia seems not worse in paediatric patients as compared to adults, rendering the current risk minimisation measures sufficient in paediatric patients.

4.6. Effects Table

Table 34: Effects Table for Tecfidera for the treatment of paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (MS) (study 109MS306 Part 1)

Effect	Short description	Unit	Tecfidera	Avonex	Uncertainties / Strength of evidence	References
Favourable Effects						
Proportion of participants free of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Week 96	Primary endpoint	%	Completers Population: 16.1 ITT Population: 12.8	Completers Population: 4.9 ITT Population: 2.8	Primary analysis was performed in a rather selected population, the Completers Population. Data were summarized using observed values.	(1)

Effect	Short description	Unit	Tecfidera	Avonex	Uncertainties / Strength of evidence	References
					Sensitivity analysis based on ITT population replaced missing values by non-response imputation, which may bias results in favour of Tecfidera	
Number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at week 96	Secondary endpoint	Adjusted Mean (SD)	12.42 (8.79,17.54)	32.65 (20.97,50.85)	Analysis has been performed in a selected population, i.e. excluding those patients without MRI at the given visit.	(1)
Proportion of subjects free of new MRI activity at week 96	Secondary endpoint	%	14.5	4.8	Analysed similarly as the primary endpoint.	(1)
Relapse probability until week 96 (derived from Time to first relapse analysis)	Secondary endpoint	Kaplan-Meier estimate, %	33.8	47.7		(1)
ARR at week 96	Secondary endpoint	No relapses /year	0.240	0.528	See above	(1)
EDSS score	Secondary endpoint, Week 96 change from baseline	Score from 0 to 10 (0=normal-10 =death)	-0.03 (1.045)	0.13 (0.748)	See above	(1)
Number of Gd-enhancing lesions at week 96	Exploratory endpoint	Mean (SD)	1.4 (5.12)	1.3 (3.54)		(1)
Unfavourable Effects						
Overall TEAEs	Number of patients with events	%	95	96		(1)
SAEs	Number of patients with events	%	23	29	SAEs were mainly due to MS relapse	(1)
Gastrointestinal disorders - abdominal pain - vomiting - diarrhoea - nausea - abdominal pain upper	Number of patients with events	%	74 41 23 19 17 18	31 7 8 6 8 1	More frequently reported in paediatric patients as in adults (48% overall in Tecfidera Pool A); at present, no evidence with regard to compliance problems and early discontinuations	(1)
MS relapse	Number of patients with events	%	35	46	More frequently reported in paediatric	(1)

Effect	Short description	Unit	Tecfidera	Avonex	Uncertainties / Strength of evidence	References
					patients as in adults (29% in Tecfidera Pool A)	
Dysmenorrhoea	Number of patients with events	%	17	7	More frequently reported in paediatric patients as in adults (2% in Tecfidera Pool A); adolescents are more frequently affected as adults; more frequent use of analgesics in the Avonex group as compared to Tecfidera	(1)
Respiratory, thoracic and mediastinal disorders	Number of patients with events	%	32	11	More frequently reported in paediatric patients as in adults (15% in Tecfidera Pool A)	(1)
Infections and infestations	Number of patients with events	%	62	50	Two infections reported as SAEs (pneumonia pneumococcal and tonsillitis)	(1)

Notes: (1) 109MS306 Part 1

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

The efficacy of DMF in the treatment of RRMS has already been established in adult patients. The Applicant is now seeking extension of the indication to paediatric RRMS patients 13 years and above.

In the paediatric study 109MS306 Part 1, DMF exerted the expected anti-inflammatory effects, as derived from MRI-based endpoints that appeared favourable compared to IFN β. The anti-inflammatory effects convey the benefit of DMF in the treatment of RRMS and eventually slow disease progression. Favourable effects with DMF were also observed regarding clinical relapses.

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

Overall, in the light of the given methodological limitations (including open-label design, no type 1 error control, methods not pre-specified in full details, analyses generally not based on ITT-population), the results from study 109MS306 Part 1 are considered descriptive and do not provide stand-alone confirmatory evidence of efficacy for Tecfidera in the paediatric RRMS population. However, in a situation where efficacy has already been established in adult RRMS patients, independent confirmation of efficacy in paediatric patients is not necessary.

Based on further *post-hoc* analyses including previous adult RRMS studies with DMF, the efficacy outcomes on the number of new or newly enlarging T2 lesions, Gd-enhancing lesions and relapse rate of dimethyl fumarate in the paediatric population and in young adults (up to 25 years of age) appear to

be consistent with those from the overall studied adult patients and in favour of Tecfidera compared to IFN β or placebo.

In addition, genetic, serum, cerebrospinal fluid and cell-based studies support a shared biology between paediatric-onset and adult-onset disease. Therefore, it can principally be assumed that a drug that has been proven to be effective in adult RRMS will likewise be effective in paediatric RRMS if an equivalent dose is administered.

Taking these considerations and the totality of the evidence together, efficacy of DMF with the proposed dose can be considered established for paediatric RRMS patients 13 years and older.

The safety profile of Tecfidera in paediatric patients is claimed to be similar to that in the adult RRMS population, for which adequate risk minimisation measures are in place. Safety in paediatric patients is based on a small dataset generated in a single open-label study against Avonex as active comparator. Owing to the rarity of childhood-onset RRMS, which resulted in recruitment problems, it is acknowledged that the age range of paediatric patients 10 to 17 years is not evenly distributed in the study (neither in the Tecfidera nor in the Avonex group). Moreover, supportive PK data in the lower age range 10 to less than 13 years are lacking and no such data have been generated in study 109MS306. Thus, the clinical study experience in children aged 10 to <13 years and in those being pre-pubertal (reflected by Tanner stage 1 at screening) and treated with Tecfidera is solely based on 7 and 1 patient(s), respectively, which does not allow to confirm that the safety profile in the very young children and in adolescents is similar, especially with regard to an effect on bone development for which pre-pubertal children are obviously more vulnerable than adolescents at more advanced age. This is further corroborated by the fact that it remains uncertain whether the same dose of DMF (i.e. 240 mg BID) applied to all paediatric patients independent of weight produces similar exposure to MMF. The Applicant thus accepted to restrict the indication to adolescents 13 years of age and older, which is acceptable from a clinical safety perspective.

The pattern of AEs with Tecfidera in paediatric patients observed in study 109MS306 is largely in line with that in the adult population reported in clinical studies and postmarketing.

However, comparison of clinical safety in paediatric and adult patients (from pivotal adult studies forming Pool A in the original Tecfidera submission) revealed an overall higher incidence in TEAEs at least from the nervous system disorders (driven by MS relapse), GI disorders, TEAES from the respiratory, thoracic and mediastinal disorders, and dysmenorrhoea, which are also more frequently reported in paediatric patients treated with Tecfidera compared to Avonex. Adequate labelling is proposed to be added to the product information. So far, no differences have been noted between paediatric and adult patients with regard to haematological changes, e.g. for lymphopenia. However, the consequences that derive from severe and/ or prolonged lymphopenia (i.e. serious and/ or opportunistic infections and PML) would not have been detected within this study due to its short duration and limited number of patients included.

The lack of long-term safety data beyond 96 weeks of treatment in paediatric patients is an uncertainty. However, the indication now precludes treatment in the most vulnerable paediatric population, i.e. in those aged <13 years and those being pre-pubertal, and data from the currently ongoing open-label extension Part 2 will shed more light on the long-term safety of DMF in adolescent patients. Physical and sexual development within 96 weeks of treatment has been analysed and addressed. Based on the limited data set, there is no evidence for a negative impact of Tecfidera on bone homeostasis, progression in growth, endocrine parameters, and sexual maturity by Tanner staging.

4.7.2. Balance of benefits and risks

Efficacy of Tecfidera has already been demonstrated in adult patients with RRMS. Similar efficacy can be concluded in the proposed paediatric patient population based on shared disease biology, similar drug

exposure (derived from PK studies), and similar anti-inflammatory effects. Re-establishing efficacy on its own is not necessary. Results for all relevant endpoints reflecting disease activity are indicative for an effect of dimethyl fumarate in the studied patient population comparable to that seen in adults, assuming that the clinical efficacy in children is also alike that observed in adults.

The MAH accepted to restrict the indication to paediatric patients 13 years of age and above; therefore, concerns on whether the adult dose is appropriate for patients <13 years (for whom no PK data are available) are no longer pursued and no additional data could be presented.

The safety profile of Tecfidera in the paediatric RRMS population generally presents with findings similar to adults, for whom the drug was approved in the European Union 7 years ago and for which risk minimisation measures proved efficacious. The incidence of some TEAEs with Tecfidera appears to be increased over Avonex and over those in adults but adequate labelling in section 4.8 of the SmPC is proposed. At present, a potentially negative impact of DMF on bone homeostasis based on mechanistic considerations and preclinical findings with DMF and DRF could not be substantiated from a clinical perspective based on the limited data set in study 109MS306.

Likewise, a thorough discussion on physical and sexual development in study 109MS306 was provided. Based on the limited dataset and available clinical assessments, no safety concern could be identified.

4.7.3. Additional considerations on the benefit-risk balance

N/A

4.8. Conclusions

The overall B/R of Tecfidera in the extension of the updated indication applied for, i.e. "*treatment of paediatric patients 13 years of age and older (…) with relapsing-remitting multiple sclerosis (MS)*" is positive.

5. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

C.I.6 (Extension of indication) type II Art.29 Extension of indication to include treatment of relapsing remitting multiple sclerosis (RRMS) in paediatrics patients from 13 years of age and over; as a consequence sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.3 and 6.6 of the Summary of Product Characteristics are updated. The Package Leaflet is updated accordingly.

The risk management plan (RMP) is updated to version 13 based on Study 109MS306 data supporting the request for a paediatric indication. The marketing authorisation holder took the opportunity to update

the RMP with the most updated data (Part II modules SIV, SV and SVII).

The MAH applied for an extension of the marketing protection of one additional year in accordance with Article 14(11) of Regulation (EC) No 726/2004.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0177/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet

Additional marketing protection

The CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and the "*Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period*",[17] and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).

However, by its Judgment of 5 May 2021 in Case T-611/18, *Pharmaceutical Works Polpharma v EMA*,[18] the General Court held that Tecfidera does not benefit from an independent global marketing authorisation. EMA has lodged an appeal against the General Court's ruling, and the appellate proceedings are pending. Nevertheless, for the purpose of implementing the General Court's ruling, but without prejudice to its position in the appellate proceedings, the Agency has conducted an ad hoc assessment relating to the therapeutic effect of monoethyl fumarate salts (MEF) within Fumaderm (in this respect, see the Opinion adopted by the CHMP on 11 November 2021[19] and appended as an Annex to the CHMP assessment report on the significant clinical benefit in comparison with existing therapies in accordance with Article 14(11) of Regulation (EC) No 726/2004).

In light of the scientific conclusions outlined in its Opinion of 11 November 2021, the CHMP is of the view that the totality of the available data cannot establish that MEF exerts a clinically relevant therapeutic contribution within Fumaderm. Those scientific conclusions and the Judgment of the General Court of 5 May 2021 in Case T-611/18 support the determination that Tecfidera does not benefit from an independent global marketing authorisation. This also entails that, following the General Court's reasoning, Tecfidera could not benefit, at the time of the submission of this type II variation application, from any marketing protection. As a result and without prejudice to the outcome of the above referenced appellate proceedings, the granting of an additional one-year of marketing protection period for Tecfidera cannot be recommended at this time.

17 In this respect, see: The "Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period". Adopted by the European Commission in November 2007; available at: https://ec.europa.eu/health/system/files/2016-11/guideline_14-11-2007_en_0.pdf.

18 In this respect, see: Judgment of the General Court of 5 May 2021 in *Pharmaceutical Works Polpharma v EMA*, T-611/18, EU:T:2021:241.

19 Opinion of the Committee for Medicinal products for Human Use on the ad hoc assessment relating to the therapeutic effect of monoethyl fumarate salts (MEF) within Fumaderm adopted on 11 November 2021.

6. Re-examination of the CHMP opinion of 27 January 2022

Following the CHMP conclusion that, the granting of an additional one-year of marketing protection period for Tecfidera could not be recommended, the MAH submitted detailed grounds for the re-examination of the grounds for refusal.

In that context, Biogen confirmed that the scope of its request for re-examination is limited to the section of the CHMP Opinion of 27 January 2022 insofar as it did not recommend the requested extension of marketing protection. In that regard, Biogen expressly noted that the request for re-examination is also directed against the CHMP Opinion of 11 November 2021.

As an initial remark, it is important to recall that the CHMP is a scientific body. As explained by Recital 23 of Regulation (EC) No 726/2004, the CHMP has been vested with exclusive responsibility for preparing EMA's opinions on all questions concerning medicinal products for human use. It follows from the provisions of Regulation (EC) No 726/2004, the CHMP is competent to provide scientific opinions and recommendations.

Turning to the grounds for re-examination submitted by Biogen, the MAH submitted the following three grounds: (i) "*Grounds in relation to the Ad Hoc Opinion and the appended ad hoc assessment*" (ii) "*Grounds in relation to the implications of the Variation* Opinion"; and (iii) "*Grounds in relation to the implications of the Ad Hoc Opinion in respect of whether the authorisation of Fumaderm was capable as commencing a GMA for Tecfidera*".

Based on a review of the above-mentioned grounds, it was noted that the scientific claims put forward by the marketing authorisation holder are contained under the section titled, "*Grounds in relation to the Ad Hoc Opinion and the appended ad hoc assessment*". Taking into account the legal framework governing the evaluation of medicinal products (including, an application for a type II variation) and the scientific competence of the CHMP, the focus of the re-examination procedure concerned the scientific claims contained under this section.

Further, it bears highlighting that certain claims and arguments relating to the "*Grounds in relation to the implications of the Variation* Opinion" and "*Grounds in relation to the implications of the Ad Hoc Opinion in respect of whether the authorisation of Fumaderm was capable as commencing a GMA for Tecfidera"* revolve around legal and regulatory considerations which do not need to be addressed by an EMA scientific committee, such as the CHMP.

6.1. Detailed grounds for re-examination submitted by the MAH

The applicant presented in writing arguments refuting the grounds for refusal. The detailed grounds for re-examination are structured and summarised as follows:

- **Grounds in relation to the Ad Hoc Opinion and the ad hoc assessment**

In this section Biogen has set out its concerns about the scientific evaluation of the contribution of MEF in Fumaderm in the ad hoc assessment report. Biogen's primary conclusion is that the nonclinical data, together with the consistency of findings across the clinical studies with no significant methodological limitations and the consistency across clinical endpoints (which show clinically relevant improved efficacy for DMF/MEF as compared to DMF alone), constitutes good scientific evidence that MEF contributes to the clinical efficacy of the DMF/MEF combination in Fumaderm. In this respect, Biogen relies upon a supporting expert report from a Professor. This Professor concludes that the available data from the two

key studies [Mrowietz 2017[20]; Nieboer 1990[21]] do not suffer from material methodological limitations and point clearly to a contribution of MEF. Furthermore, even if the CHMP disagrees with Biogen's interpretation of the data, it cannot properly be asserted that the data constitute good scientific evidence of the absence of any therapeutic contribution of MEF in Fumaderm. As the CHMP is aware, "absence of evidence" is not the same as "evidence of absence". This should be properly reflected in the Ad Hoc Opinion because, this has implications for the conclusions that can be drawn from the Ad Hoc Opinion with regard to applications to market generic Tecfidera as well as Biogen's type II variation application. Nor does the CHMP set out its reasoning for not recognising this difference, including its reasons for dismissing all the clinical studies as having material methodological limitations. Biogen does not believe that the final conclusion of the CHMP is correct; furthermore, the absence of full reasoning for the difference between the cautious conclusions on the individual studies and the unqualified nature of the final conclusion is striking, particularly so given the various ways in which the Ad Hoc Opinion and assessment are relevant to the integrity and consistent operation of the EU regulatory framework, and given the public health and other implications of their application. Biogen respectfully submits that even if the CHMP does not revise the Variation Opinion and the Ad Hoc Opinion to state (as Biogen contends that the CHMP should), that the available data demonstrate a clinically relevant therapeutic effect of MEF in Fumaderm, and that Tecfidera and Fumaderm therefore do not belong to the same GMA, the CHMP should at minimum revise the Variation Opinion and the Ad Hoc Opinion to state that the available data do not demonstrate that MEF does not have a clinically relevant therapeutic effect in Fumaderm, that the CHMP therefore cannot conclude that MEF does not have such an effect, and that Fumaderm and Tecfidera therefore do not belong to the same GMA.

6.2. Discussion and overall conclusion on grounds for re-examination

As explained *supra*, the CHMP has assessed the scientific grounds which are detailed under the MAH's request for re-examination. These scientific grounds revolve around "*the Ad hoc Opinion and the appended assessment report*".

The MAH submits that the nonclinical data, together with the supposed consistency of findings across the clinical studies with no significant methodological limitations and the consistency across clinical endpoints (which supposedly show clinically relevant improved efficacy for DMF/MEF as compared to DMF alone), constitutes good scientific evidence that MEF contributes to the clinical efficacy of the DMF/MEF combination in Fumaderm. Further, Biogen relies on a supporting expert report from a Professor. This Professor concludes that the available data from the two key studies [Mrowietz 2017; Nieboer 1990] do not suffer from material methodological limitations and point clearly to a contribution of MEF.

In this context, Biogen raises three elements that purportedly call for reconsideration of the ad hoc assessment that underlies the Ad Hoc Opinion. These elements are set out in detail in the expert report of 04 March 2022 of a Professor. These elements have been summarised by Biogen as follows:

a. The nature of what are claimed to be "severe methodological limitations" of the clinical studies, which is relevant to how much weight can be given the various clinical studies (for the purpose of the present report, this consideration will be referred to as Ground 1);

[20] Mrowietz U, Szepietowski JC, Loewe R, et al. Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: a randomized, double-blind, Fumaderm® - and placebo-controlled trial (BRIDGE). Br J Dermatol. 2017;176(3):615-623. Epub 2016/11/15.

[21] Nieboer C, de Hoop D, Langendijk PN, et al. Fumaric acid therapy in psoriasis: a double-blind comparison between fumaric acid compound therapy and monotherapy with dimethylfumaric acid ester. Dermatologica. 1990;181(1):33-37

b. The appropriateness, in a historical assessment of this nature, of focusing solely on "statistical significance" in concluding that MEF does not exert a clinically relevant therapeutic contribution (for the purpose of the present report, this consideration will be referred to as Ground 2); and

c. The manner in which direct assessments of clinical relevance were made and taken into account in reaching the opinion (for the purpose of the present report, this consideration will be referred to as Ground 3).

In summary, the MAH claims that the issues identified under Grounds 1, 2 and 3 have not been adequately considered and reasoned in the ad hoc assessment report that underlies the Ad Hoc Opinion and that, therefore, the CHMP should not have concluded, as it did, that the totality of the available evidence cannot establish a finding of a relevant contribution of MEF in Fumaderm.

Ground 1

The MAH concedes that two of the four clinical studies indeed had methodological limitations that limit their use in assessing the effect of MEF within Fumaderm. In this respect, the MAH focuses on the following two studies: Mrowietz et al (2017) and Nieboer et al (1990). According to the MAH, these two key studies did not suffer from material methodological weaknesses and support their position that MEF exerts a relevant therapeutic contribution within Fumaderm.

Nieboer et al (1990): While the CHMP recognises that a small sample size affects the precision of results and is not a concern per se, the principle remains that a relevant contribution of the active substance (as regards efficacy and/or safety) needs to be demonstrated. In that regard, in order to allow for a conclusion on possible existence of a demonstrated effect, the results must show an effect and it is insufficient to simply speculate on the existence of an effect by arguing that the trial was not large enough to elucidate it (see further the conclusion below). In that sense, a treatment effect must have been shown within the trial such that a trial with a small sample size can be convincing. A small sample size cannot be accepted as a methodological excuse in favour of a treatment effect. Nieboer et al. (1990) failed to demonstrate an effect of MEF within Fumaderm and therefore cannot lead to a conclusion of a relevant therapeutic effect.

Therefore, the CHMP disagrees that this trial has demonstrated an additional and clinically relevant therapeutic effect of MEF (see further below).

It is recognised by the CHMP that table 1 in Nieboer et al (1990) contains all randomized patients (of note, with regard to the complete case analysis, another analysis is referred to in the ad-hoc CHMP report, i.e. when only those patients were considered who could be evaluated after 16 weeks). The percentage of patients with an improvement of >50% is based on the full analysis set (FAS), and it can be said that 45% (10/22) vs 52% (12/23) were responders based on these assessments in the DMF vs the FAC (the combination) treatment arm in this study. However, the difference in these estimates goes back to an absolute difference of n=2 responders between the two treatment arms. This (small) numerical difference is not statistically significant and is a descriptive result. Further, it cannot establish a demonstrated true difference between the two treatments. As discussed above, the small sample size cannot be used as an excuse for a lack of demonstration of a treatment effect. Even the authors conclude that the treatment with the combination does not result in better therapeutic results than the DMF monotherapy.

Nieboer et al (1990) do not specify control for multiplicity. In any case, the overarching and crucial methodological limitation of this study revolves around the fact that it is not appropriate to conclude on a demonstrated effect based on numerical results, i.e. point estimates. Of note, it is even acknowledged by the MAH that "none of the endpoints reached conventional statistical significance".

In conclusion, a treatment benefit of MEF within Fumaderm cannot be concluded on (see also Ground 2).

Mrowietz et al (2017): This is considered to be the most relevant and recent study due to the controlled design, sample size and research question addressed. The non-completion rate is large with an amount of almost 40% in both, the LAS41008 (DMF) and Fumaderm arms, and handling of missing data and intercurrent events is always challenging to assess from publications. With regard to multiplicity, first superiority of DMF to placebo, and thereafter non-inferiority to the combination was tested, while a further superiority hypothesis of Fumaderm over DMF had not been pre-specified.

Nevertheless, these specific design aspects of the study are not the fulcrum of the discussion. The main "methodological limitation" is related with the way how interpretations are made in the submitted grounds for re-examination and as such, the study results do not allow for a conclusion of a demonstrated additional contribution of MEF in the combination product Fumaderm. The CHMP strongly disagrees with the MAH that point estimates and selected secondary endpoints allow a confirmatory conclusion of a demonstrated therapeutic effect as such an approach is methodologically inappropriate to demonstrate a treatment effect. An observed point estimate alone (2.8% difference in the PASI75 and 4.4% in PGA, CIs not presented) in the co-primary endpoints is not sufficient to conclude on the true existence of an effect, and also secondary endpoints cannot establish a confirmatory conclusion on efficacy. Notably, this is exactly what Mrowietz et al. (2017) conclude on, i.e. that "DMF is not significantly different from Fumaderm in clinical terms" and that "MEF salts not being essential to achieving a clinically relevant response".

In summary, the totality of the available data (including, Nieboer (1990) and Mrowietz (2017)) does not allow to establish that MEF has a clinically relevant therapeutic effect and further confirmatory data would be required to demonstrate such an effect. To that end, while there are some numerical differences in favour of the DMF/MEF combination vs. DMF alone, these differences do not demonstrate that MEF provides a therapeutic contribution as regards clinical efficacy in addition to DMF in the Fumaderm combination. Furthermore, as such conclusion on demonstrated efficacy cannot be drawn, it can also not be accepted that a clinically relevant therapeutic contribution of MEF within Fumaderm has been demonstrated.

Therefore, a re-evaluation of the available data has not altered the initial CHMP conclusion insofar as a clinically relevant therapeutic contribution of MEF within Fumaderm has not been demonstrated.

Regarding the expert report, according to the Professor, the CHMP presents no concrete reasons for dismissing the Nieboer 1990 and Mrowietz 2017 studies [Mrowietz 2017; Nieboer 1990] as they were well-controlled clinical trials with no severe methodological limitations affecting an assessment of the contribution of MEF in Fumaderm. Furthermore, the Professor finds that by dismissing the Mrowietz study on the grounds that "*the design of the study does not allow to demonstrate superiority of DMF/MEF versus DMF*" the CHMP fails to recognize two facts. First, because the conduct of the non-inferiority and superiority studies differs only in sample size, it is scientifically possible to draw superiority conclusions from a non-inferiority trial. Superiority in [Mrowietz 2017] was demonstrated in a secondary endpoint which reached statistical significance, and numerical superiority was reached in the remainder of primary and secondary endpoints except one. Second, for a study specifically designed to demonstrate superiority of DMF/MEF over DMF alone and to be adequately powered, as apparently requested by the CHMP, an enormous study randomizing almost 4700 patients would be required**.**

A detailed discussion on this topic is already provided above, as the specific points raised (under paragraph 6 of the request for re-examination) appear to correspond to Ground 1.

As also discussed above, the principal methodological flaw of the proposed conclusion on both studies is that point estimates and secondary endpoints do not suffice for the proposed conclusion of a therapeutic

contribution of MEF within DMF/MEF. For such demonstration, it is necessary that statistical significance of the primary endpoint(s) is shown. It is also reiterated by the CHMP, that further to this requirement of statistical significance, clinical relevance of an effect needs to be additionally justified.

The controlled design, especially of the clinical study in Mrowietz et al (2017), is agreed to as theoretically being appropriate and capable to demonstrate a potential treatment effect of MEF in Fumaderm. Nevertheless, while this is agreed the results of the trial do not allow a conclusion of a treatment effect of MEF within Fumaderm. As noted above from a design perspective a superiority hypothesis had not been specified (type I error control). While also conduct/analysis questions with regards to e.g. missing data handling generally need to be considered, it is in the light of the study results not necessary to discuss such in detail further, as the primary study results do not allow conclusion of a statistically demonstrated treatment effect of MEF in Fumaderm.

The MAH further argues that a sample size of 4700 patients would be needed to have 90% power to show superiority of the combination over DMF monotherapy when using the results observed in Mrowietz et al (2017). However, this is not considered an argument in favour of accepting the therapeutic contribution of MEF within Fumaderm; the fact that a large study would be needed to investigate the specific research question is not a reason to waive the need for the study. On the contrary, the large sample size is a function of the small numerical estimate observed and assumes this is the true effect.

It is concluded in summary, that a contribution of a clinically relevant therapeutic effect of MEF within Fumaderm has not been demonstrated**.**

Ground 2

Based on the data submitted, as part of the ad hoc assessment relating to the therapeutic effect of MEF within Fumaderm, the CHMP concluded that a clinically relevant contribution of MEF in Fumaderm has not been demonstrated.

Following the discussion in response to Ground 1, it is reiterated that statistical significance must be demonstrated in order to conclude that a treatment effect has been shown and as such statistical significance is essential to establish clinical relevance. This is particularly relevant for the primary endpoint(s) and a lack of such demonstration in the primary endpoint(s) render results in secondary endpoints as exploratory. In summary, it must be demonstrated that a statistically significant treatment effect exists. Only once it is established, it can be thereafter assessed whether the effect is clinically relevant.

In that line of argument, while it is noted that statistical significance is not the same as clinical relevance, the two notions corroborate and, based on the available data, it cannot be concluded that a clinically relevant effect of MEF within Fumaderm has been demonstrated. A clinically relevant effect cannot be concluded on without having demonstrated that an effect >0 exists.

While the meaning of p-values is well understood by the CHMP, the MAH´s conclusion that in the present case the point estimate can supersede non-significant results and can be interpreted as demonstrating a clinically relevant result is rejected. This presumption would treat the point estimate as demonstrative of the true effect and ignore the obvious uncertainties around the estimate. In any event, the results of the available clinical studies did not show that an effect exists, thereby obviating a conclusion of clinical relevance. Whilst it is acknowledged by the CHMP that the data do not prove the absence of an effect, of more relevance in the present context is that it cannot be concluded based on these data that an effect has been shown.

The MAH does not question in essence that a therapeutic effect of MEF in Fumaderm has not been demonstrated by the statistical tests associated with the primary endpoints. Rather the MAH relies on observations relating to several endpoints, and the assessment of relevance of point estimates. This

approach fundamentally deviates from appropriate evidence generation to demonstrate treatment effects. The consistency of effect estimates are not sufficient to support on its own a conclusion of a demonstrated effect. In the context of non-significant primary results such considerations are considered exploratory, but not confirmatory. If any, such results could motivate performing a confirmatory trial (see also, the response to Ground 2 below).

It is concluded in summary, that a contribution of a (clinically relevant) treatment effect of MEF within Fumaderm has not been demonstrated.

The Professor also explains that the CHMP was wrong to focus on statistical significance alone rather than on the consistency of the results within and across well-done clinical studies which support the conclusion that MEF contributes to the therapeutic efficacy of the Fumaderm combination**.**

In order to address this point raised by the Professor, reference is made to the statements on 'statistical significance' above.

First, it has to be reiterated again that the (descriptive) results from both the Mrowietz et al (2017) and the Nieboer et al (1990) studies are not appropriate to establish a difference between the two treatments (DMF&MEF combination and DMF alone). The conclusions set out under both studies (and indeed, in the context of other studies discussed within the course of the initial ad-hoc assessment) are consistent in that regard.

In terms of 'within-study consistency', it is again noted that endpoints in a clinical study are correlated, based on same patients, and cannot be regarded as independent replication.

As an additional remark, there were 'inconsistent' numerical results across Nieboer et al., 1990 and Nieboer et al., 1989; e.g., for the parameters redness and induration scores, scaling and itching. Mrowietz et al. (2017) showed 'inconsistent' trends for changes in PASI and PGA versus change in BSA.

It seems likely that some of these differences are attributed to chance alone.

An important aspect for assessments of 'consistency' is the availability of a balanced and complete literature dataset. To assess coherence of results across clinical trials, indirect comparison of data that have been generated from different studies is made. In that regard, it is worth highlighting that literature reviews have been conducted by several entities during the initial ad-hoc assessment. For the re-assessment, the expert report also refers to scientific literature. While not all entities have outlined their exact methodology for bibliographic research, some (e.g., BfArM) have provided many details on their search strategy. Taking into account the available data, including the data provided by the different entities, as well as results from a literature review performed during this procedure, the CHMP concludes with sufficient certainty that the most relevant accessible publications on the issue have been identified (and discussed at various time points during the process). For the present question, the two most relevant publications are indeed Nieboer et al., 1990, and Mrowietz et al (2017) due to the design of the respective studies and respective questions addressed.

There is no meta-analysis available on whether MEF exerts a clinically relevant effect in Fumaderm. However, a Cochrane Review from 2015 on oral fumaric acid esters (FAEs) has been reviewed for this application. The researchers from Cochrane, a well-established scientific community specialised in the assessment of meta-analyses and systematic reviews, selected randomised controlled trials with FAEs, including DMF monotherapy in the indication psoriasis. Six trials were included into the Cochrane Review: Altmeyer, 1994; Nugteren-Huying, 1990; Fallah Arani, 2011; Peeters, 1992; Langner 2004; Mrowietz 2006. The authors of the Cochrane review were unable to establish if the use of DMF alone has a similar efficacy and safety profile as the combination of DMF plus MEF. They furthermore concluded that "*the evidence provided in this review was limited, and it must be noted, that four out of six included studies were abstracts or brief reports, restricting study reporting"*.

It is acknowledged that some studies were not included in the Cochrane review (given that the Cochrane review was performed before Mrowietz et al. 2017 was published), but, based on the reported Mrowietz et al. 2017 results (and the discussion of the Mrowietz et al. 2017 study above), it is not expected that this conclusion would change.

The Mrowietz et al. 2017 data were included in the literature review on the topic by Landeck et al. 2018: *'Dimethyl fumarate (DMF) vs. monoethyl fumarate (MEF) salts for the treatment of plaque psoriasis: a review of clinical data'*. In the context of that review, the authors concluded that *'DMF as monotherapy for the treatment of psoriasis is as efficacious as in combination with MEF, making the addition of such fumarate derivatives unnecessary'***.**

Ground 3

The MAH criticizes the CHMP conclusions on clinical relevance in the ad-hoc assessment. The initial assessment concluded that a clinically relevant contribution of MEF within the MEF&DMF combination product has not been demonstrated. This conclusion is also maintained under the present re-examination procedure (see, the responses to Grounds 1, 2 and 3 and the conclusion).

As outlined above, data have been assessed and evaluated based on the principles of evidenced-based medicine and by looking at the totality of available data.

As the relevant studies failed to demonstrate a statistically significant effect, any assessment of clinical relevance of a (non-existing) effect becomes irrelevant.

The MAH's argument regarding claimed consistency of sufficiently favourable findings across clinical studies demonstrating a treatment effect of MEF can therefore not be followed. Lack of a statistically significant results have been consistently seen and as such, numerical differences of point estimates only cannot be regarded as a reliable basis to draw firm conclusions on a potential treatment effect.

The MAH submits that, by reference to the expert report, the CHMP Opinion does not evaluate whether the size of the differences between DMF/MEF and DMF seen in the [Nieboer 1990] and [Mrowietz 2017] studies constitute clinically relevant differences. According to the Professor, the two studies are broadly compatible with the CHMP Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis (2005). The Professor states that quantitative differences between DMF/MEF and DMF alone include the following:

a. In the BRIDGE Study [Mrowietz 2017], the odds of having a better outcome on the PASI scale were 1.3 times greater for Fumaderm than for DMF.

b. Success rates were 16%, 8%, and 22% greater for Fumaderm patients than for DMF monotherapy patients, using the PASI 50, PASI 75, and PASI 90 criteria, respectively. From a clinical perspective, this means that 22% more patients would achieve at least a 90% improvement using Fumaderm instead of DMF monotherapy—at least one additional success with Fumaderm for every four successful results that would have been achieved with DMF alone.

c. Success in achieving clear or almost clear results (PGA) was seen in 13% more patients receiving Fumaderm than in patients receiving DMF monotherapy.

d. In Nieboer 1990, for patients who tolerated their respective treatments, the odds of having a better outcome were 3.5 times greater for the combination than for DMF

e. In Nieboer 1990, the average total psoriasis score was lower for the combination than for DMF at every time point post-randomization.

f. In Nieboer 1990, the average subscale score was the same or lower for the combination than for DMF at every time point for four of the five subscales (induration, scaling, redness, and itching), and was virtually the same for the fifth scale (extent of eruption) at every time point except the last (which favored DMF) [Nieboer 1990], Figure 1].

g. The time course of these symptoms as reported indicates that even when the effectiveness of the combination and DMF were similar at the four-month endpoint, that effectiveness was achieved earlier for combination patients than for DMF patients. [Nieboer 1990], Figure 1].

It is again reiterated that numerical differences in point estimates cannot be interpreted as representing a true treatment effect (neither a confirmation that a true effect exists nor that this difference reflects the true difference). In fact, there is (large) uncertainty around point estimates and due to the insignificance of the results even a detrimental effect cannot be excluded. In consequence, the evaluation of clinical relevance, which is put forward on the basis of the existence of such numerical differences is rejected. Furthermore, it is not considered acceptable to draw conclusions based on selected (secondary) endpoints for which positive trends were observed. The above presented bullet points are considered data driven post hoc claims of selected outcomes. Therefore, any further comments on items a)-g) are irrelevant.

Based on the evidence from the two clinical studies, it is not possible to conclude that a therapeutic effect for MEF in Fumaderm has been demonstrated, as the point estimates and secondary outcome measures alone are not sufficient to support such a conclusion.

According to the Professor, physicians and patients would consider each of these improvements in clinically relevant efficacy measures to be themselves clinically relevant, and each of these improvements indicate that the presence of MEF contributes to the efficacy of the combination product.

The conceptual argument that physicians and patients would consider each of the purported improvements listed under items a. to g. as clinically relevant is considered to be exceedingly vague and unsubstantiated.

The totality of the available data neither showed a statistically significant result nor a clinically relevant effect (see also, the response to Grounds 1 and 3). The numerical differences shown cannot establish a difference between the two treatments (DMF alone and DMF & MEF combined). A relevant contribution of MEF within Fumaderm is not currently established and the above argument cannot be accepted. As explained, the study results do not support the conclusion that numerical differences can be considered a "true" difference and hence any considerations whether these numerical differences are clinically relevant or not are obsolete. The above argument under Ground 3 is therefore rejected.

On the basis of the above, the Professor concludes as follows:

"It is essential to recognize that statistical significance and clinical relevance are separate assessments, and that not exhibiting statistical significance is not grounds for concluding that that there is no effect, i.e., that MEF does not contribute to the therapeutic effect of DMF/MEF.

To the contrary, in view of the consistency of findings across studies as well as consistency across clinical endpoints, which show clinically relevant improved efficacy for DMF/MEF as compared to DMF alone, it is my opinion that MEF exhibits a clinically relevant therapeutic contribution within DMF/MEF therapy."

In order to address this point reference is made to the discussion on the other clinical grounds as presented above.

It is acknowledged that statistical significance and clinical relevance are different considerations, however, they are certainly interrelated/interdependent. For regulatory decision making, first it must be demonstrated that a "true" treatment effect exists, demonstrated by a statistically significant treatment effect. Thereupon it can be assessed whether the treatment is clinically relevant. Accordingly, as a first step, statistical demonstration of 'an' effect is necessary, which can thereafter in a second step be evaluated to be clinically relevant or not. In the present case neither a statistically significant nor a clinically relevant effect could be demonstrated for MEF that would contribute to the therapeutic effect of DMF/MEF.

Whilst it is acknowledged that the data do not prove the absence of an effect, it cannot be concluded that an effect exists. In that respect, it should be emphasised that scientific opinions are based on proven or actual evidence and not on missing evidence.

As regards the supposed existence of consistency of findings, this claim has been discussed under the response to Ground 2. Study results are rather consistent in that no difference between the two treatments could be established.

It is not agreed that across-study observations are capable of demonstrating a clinically relevant therapeutic contribution of MEF within DMF/MEF therapy.

Conclusion

As explained above, the CHMP examined whether MEF exerts a clinically relevant therapeutic contribution within Fumaderm in patients with psoriasis. The issue was assessed in the context of an ad hoc assessment relating to the therapeutic effect of MEF within Fumaderm (under procedure EMA/CHMP/260961/2022). By its Opinion on 11 November 2021, the CHMP concluded that the totality of the available data cannot establish that MEF exerts a clinically relevant therapeutic effect within Fumaderm.

The outcome of that assessment was of direct relevance when assessing the MAH's application for a type II variation for Tecfidera (EMEA/H/C/002601/II/0073). More particularly, it was of direct relevance for the MAH's accompanying request for an extension of marketing protection of one additional year for Tecfidera in accordance with Article 14(11) of Regulation (EC) No 726/2004, due to the claimed significant clinical benefit of the new indication.

While the CHMP considered that the benefit-risk balance was favourable and the type II variation to the terms of the marketing authorisation for Tecfidera could be granted, the additional year of marketing protection could not be recommended for the reasons set under Section 5 of the present report.

On 8 March 2022, the MAH submitted its detailed grounds for re-examination of the CHMP Opinion of 27 January 2022 relating to its type II variation application. That request for re-examination was also directed against the CHMP Opinion of 11 November 2021. The CHMP focused it's reassessment on the section concerning the "*Grounds in relation to the Ad Hoc Opinion and the appended ad hoc assessment*" of the request for re-examination. In particular, the CHMP examined the three elements raised by the MAH that purportedly call for reconsideration of the CHMP Ad Hoc Assessment Report of 11 November 2021. Those elements have been categorised as Grounds 1, 2 and 3 under the present report and focus, in particular, on the following clinical studies Nieboer et al. (1990) and Mrowietz et al. (2017).

The MAH questioned the initial assessment and raised objections in relation to:

- The assessment of study methodology
- The assessment of the quantitative differences observed in the two studies between DMF/MEF and DMF alone

- The assessment of statistical significance and clinical relevance
- The assessment of consistency of study results within the individual studies and across studies

The main point of discussion, raised in the grounds and re-assessed as part of this re-examination procedure, lay on the methodological limitations of the 2 main studies mentioned above and how the results have been interpreted by the MAH and CHMP. Having assessed all available data, the CHMP concluded that numerical results (i.e. point estimates and selected secondary endpoints) are not enough to demonstrate an effect of MEF. A treatment effect of MEF in Fumaderm, as claimed by the MAH, has not been demonstrated in either study.

In order to demonstrate the existence of a treatment effect, it is required that statistical significance is achieved. This is of particular importance when interpreting results for the primary endpoint(s); lack of such demonstration in the primary endpoint(s) render results in secondary endpoints as exploratory. Thereby the notion that regulators require statistically significant results for decision making to allow a conclusion on clinical relevance is correct. First, it must be demonstrated that a statistically significant treatment effect exists. Only once such is established, it can thereafter in a second step be assessed whether the observed results reach a size of clinical relevance or not.

In that sense, while it is agreed that statistical significance is not the same as clinical relevance, it cannot be concluded that a clinically relevant effect of MEF contribution in Fumaderm has been demonstrated. A clinically relevant effect cannot be concluded on without having demonstrated that an effect >0 exists.

The MAH's conclusion that in the present case the point estimate can supersede non-significant results and can be interpreted as demonstrating a clinically relevant result is strongly rejected. This presumption would take the point estimate as demonstrative of the true effect and ignore the obvious uncertainties around the estimate.

The conclusion that a clinically relevant therapeutic effect of MEF within Fumaderm has not been demonstrated is the same for both studies, and the results are consistent in that regard.

Overall conclusion:

The CHMP, having taken into consideration the scientific grounds raised by the MAH in relation to the scientific conclusions outlined in the CHMP Opinion of 11 November 2021, and the available data (including, Nieboer et al. (1990) and Mrowietz et al. (2017)) has not altered its initial conclusion insofar as a clinically relevant therapeutic contribution of MEF within Fumaderm has not been demonstrated. Therefore, the grant of one-year of additional marketing authorisation for Tecfidera cannot be recommended at this time.

7. Recommendations following re-examination

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

C.I.6 (Extension of indication) type II Art.29 Extension of indication to include treatment of relapsing remitting multiple sclerosis (RRMS) in paediatrics patients from 13 years of age and over; as a consequence sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.3 and 6.6 of the Summary of Product Characteristics are updated. The Package Leaflet is updated accordingly.

The risk management plan (RMP) is updated to version 13 based on Study 109MS306 data supporting the request for a paediatric indication. The marketing authorisation holder took the opportunity to update the RMP with the most updated data (Part II modules SIV, SV and SVII).

The MAH applied for an extension of the marketing protection of one additional year in accordance with Article 14(11) of Regulation (EC) No 726/2004.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0177/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Additional market protection

The CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and the "*Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period*",[22] and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).

However, by its Judgment of 5 May 2021 in Case T-611/18, *Pharmaceutical Works Polpharma v EMA*,[23] the General Court held that Tecfidera does not benefit from an independent global marketing authorisation. EMA has lodged an appeal against the General Court's ruling, and the appellate proceedings are pending. Nevertheless, for the purpose of implementing the General Court's ruling, but without prejudice to its position in the appellate proceedings, the Agency has conducted an ad hoc assessment relating to the therapeutic effect of monoethyl fumarate salts (MEF) within Fumaderm (in this respect, see the Opinion adopted by the CHMP on 11 November 2021[24] and appended as an Annex to the CHMP assessment report on the significant clinical benefit in comparison with existing therapies in accordance with Article 14(11) of Regulation (EC) No 726/2004).

In light of the scientific conclusions outlined in its Opinion of 11 November 2021, and based on the assessment of the scientific grounds raised by the MAH in relation to the scientific conclusions outlined in the CHMP Opinion of 11 November 2021, and a re-evaluation of the available data (including, Nieboer

22 In this respect, see: The "Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period". Adopted by the European Commission in November 2007; available at: https://ec.europa.eu/health/system/files/2016-11/guideline_14-11-2007_en_0.pdf.

23 In this respect, see: Judgment of the General Court of 5 May 2021 in *Pharmaceutical Works Polpharma v EMA*, T-611/18, EU:T:2021:241.

24 Opinion of the Committee for Medicinal products for Human Use on the ad hoc assessment relating to the therapeutic effect of monoethyl fumarate salts (MEF) within Fumaderm adopted on 11 November 2021.

et al. (1990) and Mrowietz et al. (2017), the CHMP is of the view that the totality of the available data cannot establish that MEF exerts a clinically relevant therapeutic contribution within Fumaderm. Those scientific conclusions and the Judgment of the General Court of 5 May 2021 in Case T-611/18 support the determination that Tecfidera does not benefit from an independent global marketing authorisation. This also entails that, following the General Court's reasoning, Tecfidera could not benefit, at the time of the submission of this type II variation application, from any marketing protection. As a result, and without prejudice to the outcome of the above referenced appellate proceedings, the CHMP having re-examined its initial opinion on the granting of an additional one-year of marketing protection period for Tecfidera and in its final opinion considers by consensus that the granting of one-year of additional marketing authorisation cannot be recommended at this time.

8. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-Var.No'

Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 27 January 2022.

Appendix

1. CHMP AR on the significant clinical benefit in comparison with existing therapies.
2. Statement indicating compliance with the agreed completed paediatric investigation plan.

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

EMA/CHMP/260961/2022

CHMP Assessment Report

Ad hoc assessment relating to the therapeutic effect of monoethyl fumarate salts (MEF) within Fumaderm

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Table of contents

List of abbreviations **114**

1. Background information **115**

2. Assessment **116**

2.1. Introduction 116

2.2. Assessment of the therapeutic contribution of MEF within Fumaderm 117

2.2.1. Non-clinical aspects 117

2.2.2. Clinical aspects 128

3. Submission of additional scientific observations by an interested entity **149**

4. Recommendations and next steps **150**

5. References **151**

List of abbreviations

DMF	Dimethyl fumarate
FA	Fumaric acid
FAE	Fumaric acid ester
Gclc	Glutamate-cysteine ligase catalytic subunit
GSH	Glutathione
Keap 1	Kelch-like erythroid cell-derived protein with cap-n-collar homology-associated protein 1
MEF	Monoethyl fumarate
MMF	Monomethyl fumarate
NQO1	NADPH dehydrogenase quinone 1
Nrf2	Nuclear factor erythroid 2-related factor 2
Osgin 1	Oxidative stress-induced growth inhibitor 1
SUDH	Succinate dehydrogenase
Srxn1	Sulfiredoxin 1

1. Background information

On 9 August 1994, the German National Competent Authority (the *Bundesinstitut für Arzneimittel und Medizinprodukte;* "BfArM") granted two marketing authorisations for two strengths of a combination medicinal product known as Fumaderm (comprised of the active substances monoethyl fumarate salts ("MEF") and dimethyl fumarate ("DMF")), for the treatment of psoriasis. On 13 June 2013, the marketing authorisations for Fumaderm were renewed. The marketing authorisations ("MA") are held by the Biogen group of companies.[25]

Fumaderm was authorised for the treatment of psoriasis in two strengths: (i) Fumaderm initial contains 30 mg of DMF, 67 mg of calcium MEF salt, 5 mg of magnesium MEF salt and 3 mg of zinc MEF salt ("Fumaderm initial"); and (ii) Fumaderm contains 120 mg of DMF, 87 mg of calcium MEF salt, 5 mg of magnesium MEF salt and 3 mg of zinc MEF salt ("Fumaderm"). The term "Fumaderm" will be used throughout the assessment report to refer indistinctively to both marketing authorisations.

On 30 January 2014, the European Commission granted a marketing authorisation ("MA") to the Biogen group of companies for the medicinal product Tecfidera (comprised of the active substance DMF).[26] Tecfidera is authorised for the treatment of adult patients with relapsing remitting multiple sclerosis.

Recital 3 of the Commission decision for Tecfidera stated that Tecfidera is not covered by the same global marketing authorisation ("GMA") as the previously authorised combination medicinal product Fumaderm. This was based on the conclusion (reached during the assessment of the marketing authorisation application ("MAA") for Tecfidera) that MEF and DMF are both active and are not the same active substance, since they do not contain the same therapeutic moiety.

On 27 June 2018, Pharmaceutical Works Polpharma ("Polpharma") submitted a MAA for a generic version of Tecfidera pursuant to Article 10(1) of Directive 2001/83/EC. By its decision of 30 July 2018, the EMA refused to validate Polpharma's application on the basis that Tecfidera was still subject to regulatory data protection. On 9 October 2018, Polpharma initiated court proceedings by submitting an application for annulment against EMA's decision to not validate its MAA. Polpharma also submitted a plea of illegality against Recital 3 of the Commission decision for Tecfidera that concluded that Tecfidera is entitled to a separate GMA to that of Fumaderm.[27]

On 23 July 2020, Mylan Ireland Limited ("Mylan") submitted a MAA for a generic version of Tecfidera pursuant to Article 10(1) of Directive 2001/83/EC. By its decision of 1 October 2020, EMA refused to validate Mylan's application. On 28 October 2020, Mylan commenced court proceedings by submitting an application for annulment against EMA's decision to not validate its application, as well as a plea of illegality against Recital 3 of the Commission decision for Tecfidera.[28]

By its Judgment of 5 May 2021, the General Court annulled EMA's decision to not validate Polpharma's MAA and concluded that the plea of illegality against the Commission decision for Tecfidera should be upheld. The General Court held that the Commission was not entitled to conclude that Tecfidera was covered by a different GMA to that of Fumaderm, without verifying or requesting the CHMP to verify whether and, if necessary, how the BfArM had assessed the role of MEF within Fumaderm, or without requesting the CHMP to verify the role played by MEF within Fumaderm.[29]

[25] For the purpose of the present report, Biogen Netherlands N.V and Biogen GmbH may be referred to as the Biogen group of companies.

[26] In this respect, see: Commission Implementing Decision of 30.01.2014 granting marketing authorisation under Regulation (EC) No 726/2004 of the European Parliament and of the Council for "Tecfidera - Dimethyl fumarate", a medicinal product for human use".

[27] In this respect, see: Case T-611/18, *Pharmaceutical Works Polpharma v EMA*.

[28] In this respect, see: Case T-703/20, *Mylan Ireland v EMA*.

[29] In this respect, see: paragraph 282 of the Judgment in Case T-611/18.

On 2 June 2021, Biogen submitted a type II variation application for the medicinal product Tecfidera, seeking at the same time the extension of the marketing protection of Tecfidera by one year (further to Article 14(11) of Regulation (EC) No 726/2004).

For the purpose of the implementation of the Judgment of the General Court of 5 May 2021 in Case T-611/18, *Pharmaceutical Works Polpharma v EMA,* and in connection to the above-mentioned three pending applications before the CHMP which concern DMF (two MAAs for a generic version of Tecfidera; and a type II variation for Tecfidera), **the CHMP is being asked to examine whether MEF exerts a clinically relevant therapeutic contribution within Fumaderm**.

In that connection, it may be pointed out that in the situation whereby the General Court annuls an act of an institution or body, it is required, in accordance with Article 266 of the Treaty on the Functioning of the European Union, to take measures necessary to comply with that judgment. The present *ad hoc* assessment is considered to conform to that requirement in view of the particular findings of the General Court in Case T-611/18.

In light of the above, the objective of this assessment is to support the determination as regards whether Tecfidera is covered by the same GMA as Fumaderm within the meaning of Article 6(1), second subparagraph, of Directive 2001/83/EC.

2. Assessment

2.1. Introduction

The aim of this assessment report ("AR") is to examine whether MEF exerts a clinically relevant therapeutic contribution within Fumaderm.

This AR is based on the original publications of the studies mentioned below. This AR has taken account of the European Public Assessment Reports ("EPARs") for Tecfidera and Skilarence and the responses to the LoQ, sent to the EMA by the following interested entities:

- German National Competent Authority (the *Bundesinstitut für Arzneimittel und Medizinprodukte;* BfArM)
- Biogen Netherlands B.V.
- Mylan Ireland Limited
- Pharmaceutical Works Polpharma

In addition, the assessment has taken account of an unsolicited submission from another company.

As indicated above, two strengths of Fumaderm were granted marketing authorisations as combination medicinal products on 9 August 1994. Those marketing authorisations came into force in Germany on 19 August 1994.

DMF and MEF are esters of fumaric acid. DMF is pre-systemically hydrolysed by ubiquitous esterases to its major active metabolite monomethyl fumarate (MMF), which is further degraded to fumaric acid (FA). Likewise, MEF is metabolized by esterases to FA.

Two types of Fumaderm have been licensed in Germany, which serve for titration during the initial three weeks of treatment (*"Fumaderm initial magensaftresistente Tabletten für Erwachsene"*, German MA number 27561.00.00) and in the subsequent weeks including maintenance of therapy (*"Fumaderm*

magensaftresistente Tabletten für Erwachsene", German MA number 27561.01.00; hereafter referred to as Fumaderm).

The following table compares the composition of the two authorised Fumaderm products:

Table 35: Composition of DMF and MEF in the two German Fumaderm medicinal products

Active substances	Fumaderm initial	Fumaderm
DMF	30 mg	120 mg
MEF, calcium salt	67 mg	87 mg
MEF, magnesium salt	5 mg	5 mg
MEF, zinc salt	3 mg	3 mg

Fumaderm initial (30 mg) is the starting dose, which is increased week by week to improve tolerability, particularly to decrease gastrointestinal side-effects, and Fumaderm (120 mg) is the higher-dosed tablet which is applied starting from week 4. The maximum dose of Fumaderm is 720 mg/day. The appropriate dose for most patients is 240-480 mg/day. Current German guidelines recommend a gradual increase in fumaric acid ester (FAE) dosage to determine optimal efficacy and tolerability for each patient.

Currently, two medicinal products containing DMF as gastro-resistant tablets are approved for psoriasis: Fumaderm, a fixed combination of DMF + MEF salts, and Skilarence, which contains only DMF.

To support the **Fumaderm** MA, a randomised, multi-center, double-blind study was submitted comparing Fumaderm to placebo (*Altmeyer et al., 1994).*

Skilarence (EMEA/H/C/2157), MA holder Almirall S.A., was approved on 21th April 2017 in a centralised procedure via Article 8(3) of Directive 2001/83/EC - full mixed application. The applicant indicated that DMF was considered to be a known active substance.

The only active substance in Skilarence is DMF (30 mg and 120 mg) and the DMF content is exactly the same as in Fumaderm initial and Fumaderm respectively. As part of the MAA for Skilarence, a pivotal phase III study comparing Skilarence to Fumaderm and placebo had been submitted.

Tecfidera, 120 mg and 240 mg, gastro-resistant hard capsules, which contains only the active substance DMF, has been approved for the treatment of adult patients with relapsing remitting multiple sclerosis. The legal basis for this MAA referred to Article 8(3) of Directive No 2001/83/EC (full mixed application). The clinical development programme consisted of one phase II placebo controlled study (Study C1900) and two phase III studies, one placebo controlled (Study 109MS301) and one placebo and active controlled - glatiramer acetate (Study 109MS302). In addition interim data from an ongoing extension study of the 2 phase III studies (Study 109MS303) were provided (Tecfidera, EPAR).

2.2. Assessment of the therapeutic contribution of MEF within Fumaderm

2.2.1. Non-clinical aspects

Pharmacodynamic activities of fumaric acid esters in relation to psoriasis

At the time of assessment of the MAA of Fumaderm in Germany, the mechanism of action of its DMF and MEF active substances was largely unknown considering also that relevant animal models reflecting human psoriasis were not available. For this reason, presumptive pharmacodynamic effects of these FAE were solely based on clinical experience in psoriasis patients and experimental findings gained in

pertinent cell culture systems *in vitro*, which were subsequently complemented by published scientific reports as further delineated below.

Early publications had described the concentration-dependent inhibition of nucleic acid synthesis at ≥10 µg/ml MEF in cultures of activated lymphocytes from healthy human subjects (Petres *et al*., 1975; Hagedorn *et al*., 1975). Based on these findings, another *in vitro* screen submitted during MAA of Fumaderm compared the activities of DMF and the calcium, magnesium and zinc salts of MEF on fibroblasts prepared from healthy as well as from uninvolved and involved psoriatic human skin (Sarheim *et al*., 1990). As fumarate is endogenously synthesized from succinate by succinate dehydrogenase (SUDH) in the citric acid cycle, the impact of the various FAEs was determined by means of succinate dehydrogenase activity in the different fibroblast preparations.

Compared to fibroblasts from healthy subjects, the basal SUDH activity was about 2- to 6-fold higher in uninvolved psoriatic fibroblasts, which additionally showed pronounced inter-individual variability (n=6-8 cultures of 5 different donors, respectively). When fibroblast preparations from uninvolved and involved skin from the same psoriasis patient were analysed, the SUDH activity was approximately 2.8- or 3.4-fold lower in the involved compared to uninvolved skin (n=2). Consequently, the influence of the various FAE on absolute SUDH activity in fibroblasts from the three sources cannot be directly compared. Instead, the comparison of relative magnitudes of the stimulatory/inhibitory effects in healthy and uninvolved psoriatic skin is more meaningful as depicted in Table 2.

In fibroblasts derived from healthy skin, SUDH activity was inhibited at low concentrations of FAE, but a concentration-dependent stimulation was noted at ≥0.03 mEq./l of DMF (Table 2). SUDH activation was lower at ≥0.3mEq./l for MMF and MEFs. In contrast, FA was rather inactive, which coincides with its poor penetration across cellular membranes (Nieboer *et al*., 1989).

In fibroblasts from uninvolved psoriatic skin, the stimulation of SUDH generally prevailed for all FAEs (Table 2). As in healthy skin, DMF and MMF revealed higher SUDH stimulation in uninvolved psoriatic skin than the MEF salts, but the magnitude of the activation was more pronounced (Table 2). Among MEF salts, calcium-MEF induced higher SUDH activity compared to the zinc and magnesium salts. Of note, the strongest SUDH stimulation was already evident at 0.03 mEq./l of all FAE, but declined at higher concentrations, which suggests a negative feedback effect of the accumulating fumarate leading to the inhibition of cellular proliferation due to blockade of the citric acid cycle.

Table 36: Effects of various FAE on relative SUDH activity in fibroblasts from healthy or uninvolved psoriatic skin

FAE	Concentration [mEq./l]						
	0.0003	**0.003**	**0.03**	**0.15**	**0.3**	**0.75**	**1.5**
Fibroblasts from healthy skin							
DMF	-41	-28	+38	+117	+102	+838	+956
MMF	+9	-13	-15	-33	+5	+2	+306
Ca-MEF	-42	+3	-6	-41	+1	-13	+53
Zn-MEF	-30	-21	-9	-37	+48	+107	+59
Mg-MEF	-45	-37	-32	-37	-51	-41	+30
FA	-5	-6	-5	+15	-26	0	-6
Fibroblasts from uninvolved psoriatic skin							
DMF	+1	-1	+295	+26	+21	+74	+128
MMF	+6	+160	+312	+80	+127	+112	+198
Ca-MEF	+40	+39	+147	+8	+10	+105	+135
Zn-MEF	+6	-19	+130	-14	+111	+68	+45
Mg-MEF	-56	-19	-20	+1	-15	-23	+37

+ = % stimulation; - = % inhibition; FA = fumaric acid; FAE = fumaric acid ester; DMF = dimethyl fumarate; MEF = monoethyl fumarate; MMF = monomethyl fumarate; n=6-8 cultures of 5 different donors each; adapted from the study of Sarheim BS *et al*., 1990.

The comparison of SUDH stimulation in fibroblasts from uninvolved and involved psoriatic skin of the same patient was limited to the strongest activators, i.e. DMF and Ca-MEF (Table 3). DMF significantly activated SUDH function at low concentrations of ≥0.03 mEq./l in uninvolved skin, whereas the magnitude of the stimulation was comparable at higher levels. In contrast, Ca-MEF did not induce relevant SUDH activation in fibroblasts of involved compared to the clear concentration-dependent effect in uninvolved psoriatic skin (Table 3). Thus, DMF and MEF apparently exert different grades of SUDH stimulation in skin fibroblasts with higher SUDH activity in psoriasis patients than in healthy subjects.

Table 37: Effects of DMF and Ca-MEF on SUDH activity in fibroblasts from uninvolved and involved psoriatic skin

FAE	Psoriatic skin	Concentration [mEq./l]						
		0.0003	**0.003**	**0.03**	**0.15**	**0.3**	**0.75**	**1.5**
DMF	Uninvolved	+70	-20	+194	+115	+329	+666	+700
	Involved	-14	-13	+47	+463	+326	+640	+958
Ca-MEF	Uninvolved	+43	+84	+69	+128	+179	+76	+1369
	Involved	-11	-10	+16	-2	+4	-21	-1

+ = % stimulation; - = % inhibition; FAE = fumaric acid ester; DMF = dimethyl fumarate; MEF = monoethyl fumarate; n=2 psoriasis patients; adapted from the study of Sarheim BS *et al*., 1990.

In line with these findings, DMF and the different MEF salts but not fumaric acid interfered with proliferation of immortal HaCaT keratinocytes as determined by inhibition of DNA and protein synthesis (Sebök *et al*., 1994). DMF was the most potent anti-proliferative agent at all test concentrations ≥0.4 µM, while Ca-MEF, Zn-MEF and Mg-MEF were less active at ≥1.3 µM, ≥35 µM and ≥35 µM, respectively. Accordingly, IC_{50} values for blockade of DNA and protein synthesis of 2.3 and 2.5 µM DMF,

133 µM and 145 µM Zn-MEF, 215 and 230 µM Ca-MEF, 275 µM and 270 µM Mg-MEF were derived. All FAE exerted significant cytotoxicity as measured by release of lactate dehydrogenase (LDH) of ≥12 µM DMF and Ca-MEF or ≥35 µM Zn-MEF or Mg-MEF each.

Subsequently, the same group reported that DMF significantly suppressed the expression of Intercellular Adhesion Molecule 1 (ICAM-1) at ≥4 µM and of the Human Leukocyte Antigen-DR (HLA-DR) on hyperproliferative HaCaT keratinocytes at ≥1.3 µM, i.e. two markers that are thought to induce leukocyte accumulation within psoriatic plaques (Sebök *et al*., 1998). In contrast, higher concentrations ≥106 µM Ca-, Zn- or Mg-MEF salts were required for ICAM-1 and HLA-DR down-regulation in HaCaT keratinocytes, while FA was ineffective. In normal human keratinocytes, even DMF concentrations up to 35 µM did not inhibit ICAM-1 and HLA-DR expression.

Another *in vitro* study indicated that DMF, MMF and MEF (not as salt with metal cation) induced a rapid but transient increase of calcium in cultures of normal human keratinocytes or simian virus 40-transformed immortal keratinocytes (SVK-14 cells) as measured spectrophotometrically with the calcium-binding fluorescent dye Fura-2 (Thio *et al*., 1994). Maximum calcium elevations were determined after 10 sec, were greater in normal compared to transformed keratinocytes and returned to basal levels within 90 to 120 sec. These calcium elevations were not blocked by pre-incubation with the bivalent cation chelator ethylenglycol-bis(aminoethylether)-N,N,N',N'-tetraacetic acid (EGTA) suggesting calcium release from intracellular stores. The calcium increase was concentration-dependent and reached its maximum at 0.2 mM MMF, 0.4 mM DMF and 0.2 mM MEF. Among the three FAE, the potency was MMF >DMF >MEF. In gross concordance with the aforementioned results of Sebök and colleagues (1994), higher concentrations of ≥10 µM DMF, ≥100 µM MMF or MEF, but not fumaric acid, were found to inhibit the proliferation of both types of keratinocytes. Contrary to Sebök *et al*. (1994), however, no direct cytotoxicity was observed by means of LDH increase at concentrations up to 0.2 mM DMF and 0.8 mM MMF or MEF.

Thus, DMF was clearly more potent than the MEF salts to inhibit the proliferation of keratinocytes.

Pharmacodynamic activity of MEF compared to DMF and MMF

In the dossier for the MAA of Tecfidera, DMF was shown to activate the ubiquitous transcription factor *"Nuclear factor erythroid 2-related factor 2"* (Nrf2) in primary cells of mice, rats and humans. Nrf2 regulates cellular antioxidant defence mechanisms. Under normal conditions, Nrf2 is repressed due to its interaction with *"Kelch-like erythroid cell-derived protein with CNC homology-associated protein 1"* (Keap 1), which leads to proteosomal degradation of Nrf2 in the cytoplasm. DMF and its primary active metabolite mono-methyl fumarate (MMF) both directly alkylate Keap 1, thereby releasing Nrf 2 from Keap 1 repression. Nrf 2 then translocates into the nucleus, where it activates expression of antioxidant and stress-associated genes by binding to the ARE sequence within their promoter regions (e.g. NADPH dehydrogenase quinone 1 (NQO1), glutathione reductase and aldo-keto reductase family 1 member B8 (Akr1b8)). This protection against oxidative stress was evident in astrocytes by increased cellular redox and mitochondrial membrane potentials, elevated glutathione and ATP levels and resistance against H_2O_2 treatment.

In vivo, tissue-dependent induction of Nrf2 target genes by DMF was shown in mice (NQO1 in lymphoid organs and Akr1b8 in gastrointestinal tissues). The dependency of oxidative protection on Nrf2 was confirmed by silencing of Nrf2 transcription with specific siRNA and *in vivo* by the lack of a pharmacodynamic response in $Nrf2^{-/-}$ knockout mice. Furthermore, DMF dose-dependently improved disease symptoms (demyelination and cell degeneration) and functional abilities in the EAE model of MS in rats. In addition, DMF significantly diminished excitotoxic lesions and improved neuronal survival as well as functional outcome evoked by the mitochondrial toxicant malonate in rats.

Moreover, DMF and MMF demonstrated anti-inflammatory activity by the suppression of lipopolysaccharide-mediated induction of inflammatory cytokines *in vitro* (TNFα, IL1β, CXCL10, CCL4). This anti-inflammatory effect relied on Nrf2 at low levels of DMF or MMF, but became independent at high concentrations, which was apparent in macrophages prepared from WT and Nrf2$^{-/-}$ mice. DMF also reduced pro-inflammatory cytokines in a collagen-induced arthritis model in rats and interfered with activation of astrocytes, microglia and macrophages as well as T-cell infiltration in an EAE model in rats. Thus, the apparent contribution of Nrf2-dependent and independent transcriptional regulation to the anti-inflammatory activities of DMF remains to be completely unravelled.

In investigations provided under the MAA of Tecfidera, MEF salts were tested in the range of 0 – 12 µg/ml, which encompasses its known peak plasma concentrations in humans. Of note, the median Cmax of MEF in psoriasis patients receiving two tablets of Fumaderm was 5.2 µM, which equates to approximately 0.75 µg/ml (Rostami-Yazdi *et al.,* 2010). However, plasma concentrations may not accurately reflect the exposure to MEF in certain tissues and locally in the intestinal mucosa, which would be expected to be much higher based on the site of absorption. Consequently, higher MEF concentrations were also tested *in vitro*.

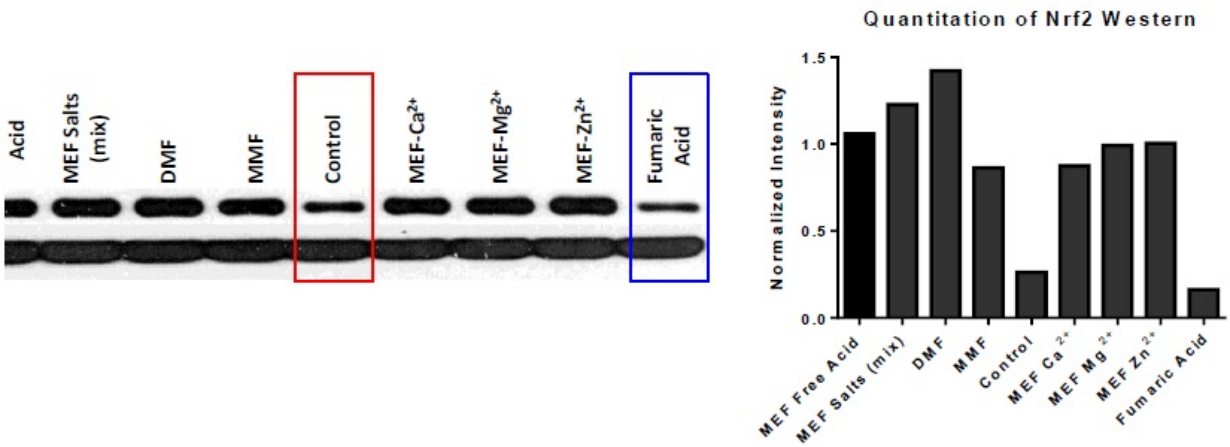
In all non-clinical investigations, the ratio of the calcium, magnesium, and zinc salts of MEF was 87:5:3 Ca-MEF, Mg-MEF, Zn-MEF, respectively, based on molecular weight. This reflects the ratio of these MEF salts in Fumaderm.

Overall, non-clinical results to corroborate a pharmacological activity of MEF indicate the following:

1.) The individual calcium, magnesium and zinc salts of MEF or a mixture of the three MEF salts induce Nrf2 in COS-1 cells *in vitro*.

The individual MEF salts, the free acid of MEF, DMF and MMF similarly increase Nrf2 concentrations as analysed by Western blotting, whereas FA was ineffective (Figure 1).

Figure 4: MEF salts increase Nrf2 protein in Cos-1 cells

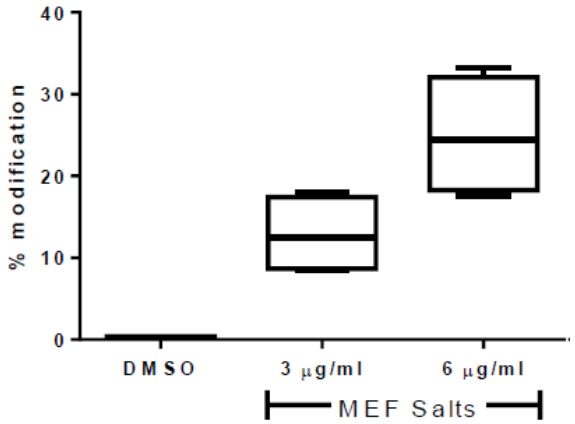


COS-1 cells were treated with 9 µg/ml of individual calcium, magnesium or zinc salts of MEF, with a mixture of MEF salts, the free acid form of MEF, DMF, MMF, FA or the vehicle control DMSO (boxed in red) to illustrate the basal Nrf2 level. Cells were harvested after 24 h and extracts analysed by Western blot with antibodies against Nrf2 or actin (loading control). Densitometry of Western blot signals reveals an approximate 5-fold increase in Nrf2 in samples treated with FAE compared to the vehicle control.

2.) The mixture of calcium, magnesium and zinc salts of MEF covalently modifies Keap1 at Cys151 *in vitro*.

Following incubation of transfected HEK293 cells with a mixture of the calcium, magnesium and zinc salts of MEF, the modification of Keap 1 was analysed by liquid chromatography and mass spectrometry (Figure 2). The same modification of Keap 1 at Cys151 had been previously demonstrated for DMF and MMF. As known for DMF, MEF is, hence, able to release Nrf2 from constitutive Keap 1 repression.

Figure 5: The mixture of MEF salts modifies Keap 1 at Cys151

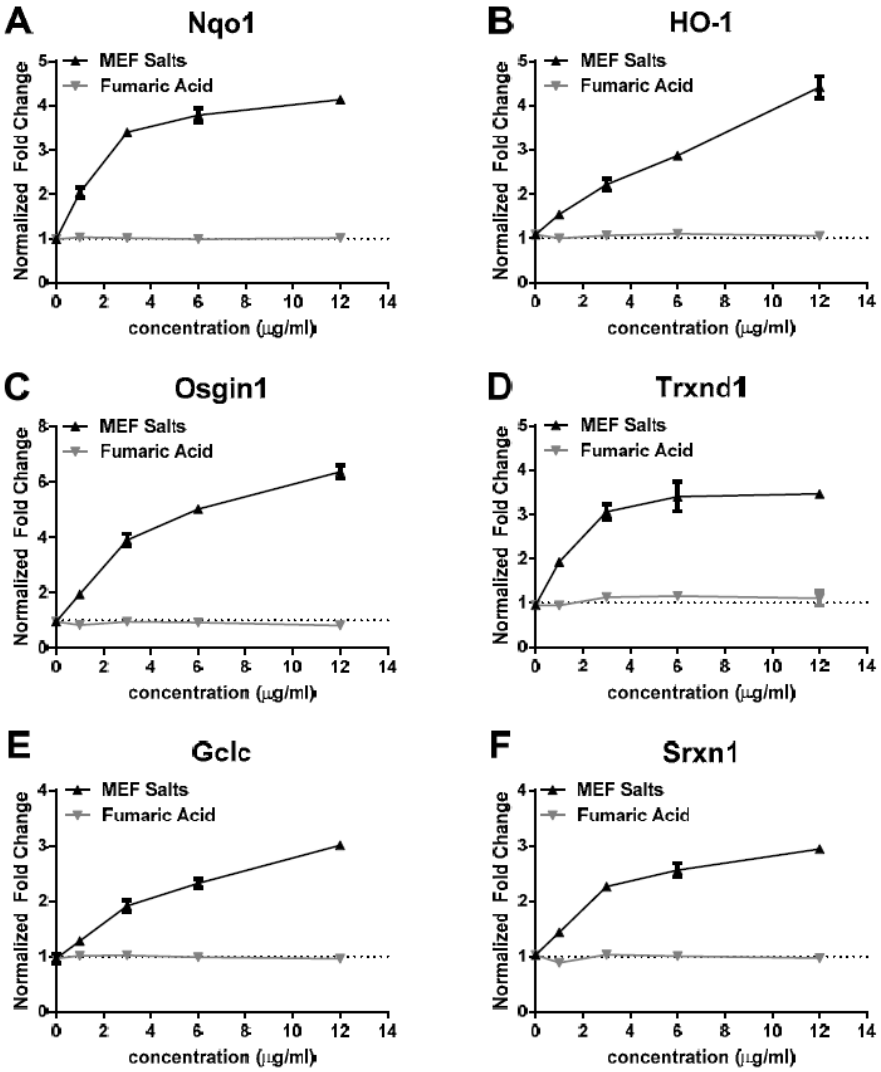


HEK293 cells were transfected with Keap1 and subsequently treated with either DMSO (control) or 3 or 6 µg/ml of calcium, magnesium and zinc salts of MEF. Keap1was immunopurified, fractioned by gel electrophoresis and then excised from the gel. The gel slice was reduced by DTT, alkylated by iodoacetamide, digested with trypsin, and then deglycosylated with PNGaseF. Resultant peptide pools were separated on a Dionex C18 column and analysed on a Thermo Fisher LTQ FT Ultra Hybrid mass spectrometer. SpectrumMill software was used to identify Keap1 peptides and cysteine modifications. The percentage of peptides containing a modification on Cys151 corresponding to the molecular weight of MEF was determined and is graphed on the Y-axis. Box-whisker plots demonstrate the means, quartiles, and max-min of quadruplicate determinations from two separate studies.

3.) The mixture of calcium, magnesium, and zinc salts of MEF concentration-dependently induces Nrf2-related gene expression in human astrocytes *in vitro*.

The transcriptional profiles obtained for the mixture of MEF salts differed for the individual genes: at a concentration of >3 µg/ml, the thioredoxin reductase 1 (Trxnd 1) response plateaued, while the slope (degree of relative increase) of NADPH dehydrogenase quinone 1 (NQO1) and sulfiredoxin 1 (Srxn1) responses decreased (Figure 3). In contrast, responses for haeme oxygenase-1 (HO-1), oxidative stress-induced growth inhibitor 1 (Osgin 1) and glutamate-cysteine ligase catalytic subunit (Gclc) exhibited a linear increase across the entire concentration range. These differential gene responses suggest that additional regulatory processes also govern expression or stability of these transcripts. Moreover, the pharmacological activity of the MEF salts appears to reside within the FAE as FA itself did not produce a response.

Figure 6: The mixture of MEF salts induces Nrf2-dependent gene expression

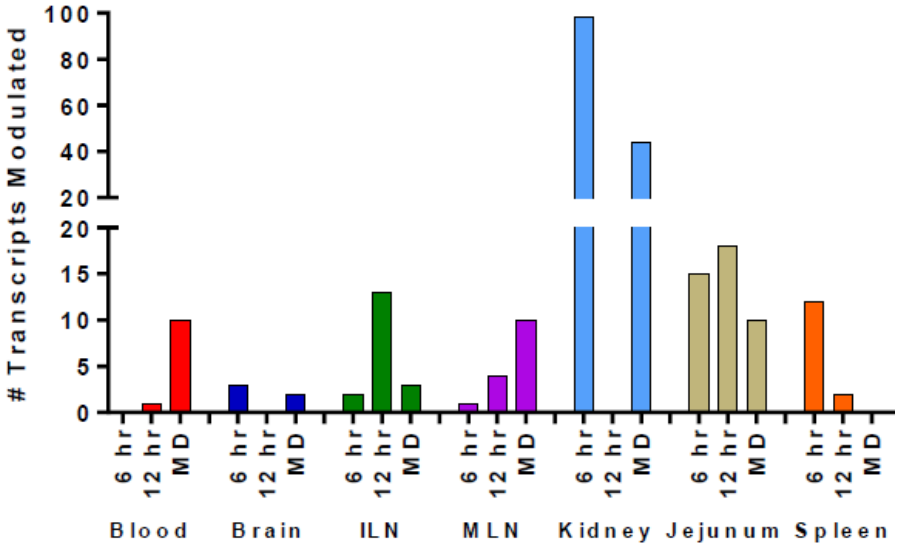


Human astrocytes were treated with a mixture of calcium, magnesium and zinc salts of MEF or fumaric acid. Transcriptional changes were evaluated by RT-PCR 24 h after treatment. (A) Nqo1, (B) HO-1, (C) Osgin 1, (D) Trxnd1, (E) (Gclc), (F) sulfiredoxin 1 (Srxn1). Responses have been normalised as a fold change relative to DMSO controls for each gene and probe set. Graph points represent averages of triplicate determinations; error bars represent standard deviations. Dotted line represents the basal level of transcription for each gene as assessed in vehicle treated cells, normalised to "1".

4.) The mixture of calcium, magnesium, and zinc salts of MEF modulated tissue-specific gene expression *in vivo*.

Transcriptional profiling revealed that the MEF salts significantly modified transcript levels in blood and all examined tissues of mice (brain, inguinal lymph node (ILN), mesenteric lymph node (MLN), kidney, jejunum and spleen) with the most prominent response in the kidney (Figure 4). MEF exposure in plasma and tissues was verified in a separate cohorts of animals.

Figure 7: The mixture of MEF salts significantly modulates tissue-specific transcription

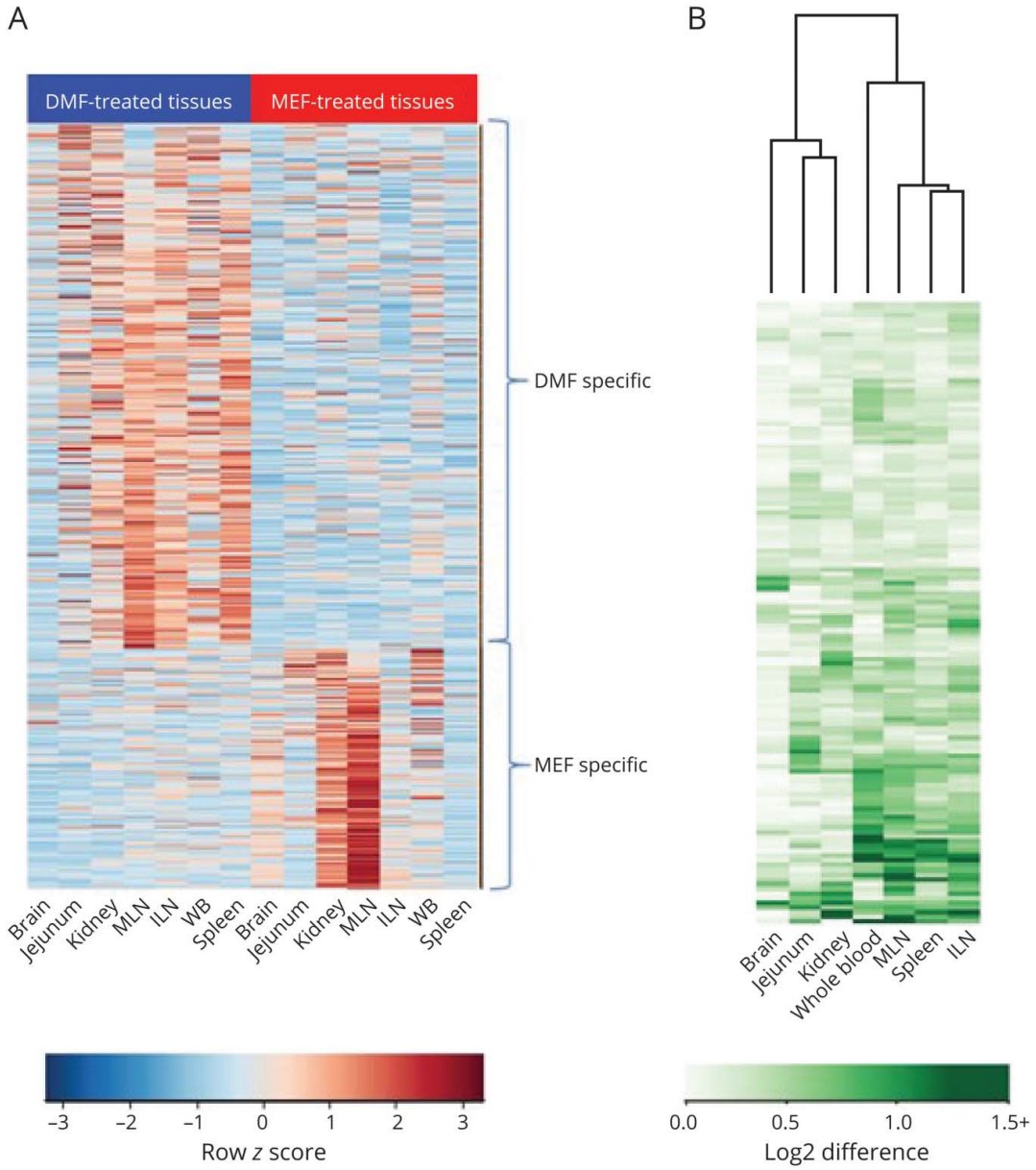


C57Bl/6 mice received single or repeated oral doses of 79.2 mg/kg MEF salts for 10 days (equivalent to 100 mg/kg DMF). Fumaric acid was not tested due to its lack of activity in previous investigations in vitro (see above). Transcriptional responses were evaluated by Affymetrix microarrays at 6 and 12 h after a single dose, and 12 h after the last dose following 10 consecutive days of once daily dosing (multiple dosing = MD).

Most recently, gene expression profiles were reported following repeated oral administration of 100 mg/kg DMF, a total dose of 79 mg/kg of the calcium, magnesium and zinc salt mixture of MEF or the DMF/MEF combination for 10 days in mice (Wipke *et al.*, 2021). The analyses were performed 12 h after the final dose and used Affymetrix microarray analyses that included tissues with preferential distribution of MMF and MEF (Figure 6). The expression of 487 genes was specifically altered in response to DMF treatment, which comprise the known Nrf2-mediated oxidative stress response, glutathione (GSH)-mediated detoxification and others (Figure 5A). These DMF-induced changes were particularly evident in mesenteric and inguinal lymph nodes, spleen and whole blood. For MEF, 224 gene expression changes were specifically noted that predominated in kidney and mesenteric lymph node. The MMF altered transcripts corresponded to apoptosis, death receptor and autophagy-related pathways.

Following dosing of the DMF/MEF combination, 132 genes demonstrated a significant interaction effect between DMF and MEF, which was most pronounced in immunological tissues, like whole blood, spleen, mesenteric and inguinal lymph node (Figure 5B).

Figure 8: Differential and overlapping gene expression profiles after administration of DMF, MEF salts or the DMF/MEF combination in mice



Gene expression profiles were determined by Affymetrix microarrays from tissues with preferential distribution of MMF and MEF at 12 h after the final repeated oral dose of either 100 mg/kg DMF, a total dose of 79 mg/kg of the calcium, magnesium and zinc salt mixture of MEF (ratio of 91.5 % : 5.2 % : 3.2 %) or the DMF/MEF combination for 10 days in mice. (A) Hierarchical clustering reveals 487 DMF-specific and the 224 MEF-specific probe sets after normalization (n = 7 biological sample sets each). DMF specificity is most pronounced in MLN, ILN, spleen, and whole blood, whereas MEF specificity is most evident in the kidney and MLN. (B) Hierarchical clustering shows 132 interaction probe sets, which is most pronounced in immunologic tissues: whole blood, MLN, ILN, and spleen. ILN = inguinal lymph node; MLN = mesenteric lymph node; WBC = white blood cell; (from Wipke *et al.*, 2021).

Evaluation comment

A sparse set of non-clinical data is provided for a comparison of the pharmacological effect of MEF in contrast to either DMF or fixed combination of MEF/DMF. Some of the comparative studies shows that in vitro the individual MEF salts, the free acid of MEF, DMF and MMF similarly increase Nrf2 concentrations as analysed by Western blotting, whereas FA was ineffective. Perhaps, the most relevant study for purpose of the comparison between DMF, MEF and their combination was recently published (Wipke et

al., 2021). Gene expression profiles were reported following repeated oral administration of 100 mg/kg DMF, a total dose of 79 mg/kg of the calcium, magnesium and zinc salt mixture of MEF or the DMF/MEF combination for 10 days in mice. The expression of 487 genes was specifically altered in response to DMF treatment, which comprise the known Nrf2-mediated oxidative stress response, glutathione (GSH)-mediated detoxification and others. These DMF-induced changes were particularly evident in mesenteric and inguinal lymph nodes, spleen and whole blood. For MEF, 224 gene expression changes were specifically noted that predominated in kidney and mesenteric lymph node. The MMF altered transcripts corresponded to apoptosis, death receptor and autophagy-related pathways. Following dosing of the DMF/MEF combination, 132 genes demonstrated a significant interaction effect between DMF and MEF, which was most pronounced in immunological tissues, like whole blood, spleen, mesenteric and inguinal lymph node

In addition to this data, the mixture of calcium, magnesium and zinc salts of MEF covalently modifies Keap1 at Cys151 in vitro. The same modification of Keap 1 at Cys151 had been previously demonstrated for DMF and MMF. As known for DMF, MEF is, hence, able to release Nrf2 from constitutive Keap 1 repression.

Exploratory studies provided for MEF can be considered as supportive for proof of concept in the indication of psoriasis. While a straightforward additive or synergistic effect of MEF in the combination cannot be concluded due to the limitations of the conducted non-clinical studies.

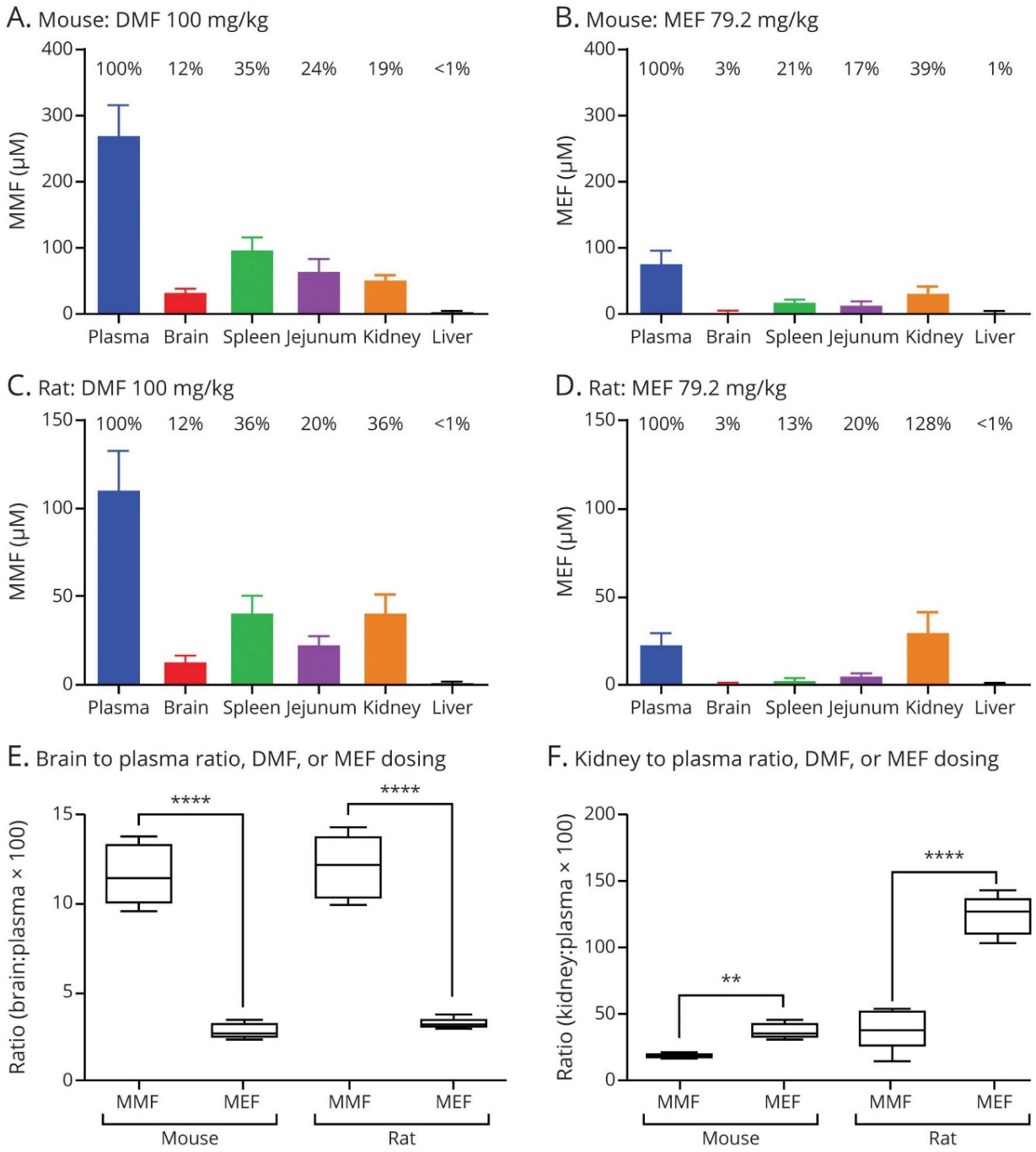
Pharmacokinetic properties of DMF and MEF

In pharmacokinetic (PK) investigations conducted in rats and dogs submitted during the MA of Tecfidera, DMF was rapidly absorbed from the gastrointestinal tract and converted pre-systemically to its active metabolite MMF. Quick absorption was also confirmed for MEF in these species. MMF was found to be further metabolised to fumaric acid, citric acid and glucose indicating initial DMF metabolism by esterases followed by the citric acid cycle. Accordingly, DMF was found to be predominantly eliminated as exhaled CO_2 (~60-65 %). About 21 % of the administered DMF dose was determined in urine, with cysteine and N-acetyl cysteine conjugates of mono- and dimethyl succinate as major urinary metabolites. MMF represented only up to 1.7 % of urinary metabolites, whereas the amount of unchanged DMF was negligible (< 0.2 %). The contribution of the faecal route to the elimination of DMF was small (≤ 4.4 %).

In addition, metabolism data obtained in rat and human hepatocyte suspensions indicated formation of glutathione (GSH) conjugates of DMF and MMF and a low amount of other minor metabolites excluding MEF. Analyses using liver microsomes or hepatocytes from rats and humans further confirmed that MEF does not convert to either DMF or MMF, and DMF or MMF are not transformed into MEF. In agreement with this finding, no MEF was detected in plasma or tissues of mice after oral administration of DMF, and, conversely, no DMF or MMF was identified in mice after oral administration of MEF. Thus, DMF and MEF are not metabolites of each other *in vivo*.

A recent publication reports the distribution of MMF and MEF after oral administration of either 100 mg/kg DMF or as total dose 79 mg/kg of the mixture of calcium, magnesium and zinc salts of MEF to mice and rats (Wipke *et al*., 2021). MMF widely distributed in both species and reached higher concentrations in brain and spleen than MEF (Figure 6). In contrast, MEF preferentially distributed into the kidney. Accordingly, the brain to plasma ratio is higher for MMF compared to MEF, while MEF demonstrates a higher kidney to plasma ratio than MMF. These data are in line with the higher excretion of intact MEF compared to MMF in rats (9-fold) and in Cynomolgus monkeys (26-fold; Wipke *et al*., 2021).

Figure 9: Distribution of MMF compared to MEF in mice and rats



After single oral administration of 100 mg/kg DMF or 79 mg/kg MEF salts in 0.8 % hydroxypropyl methylcellulose to C57Bl/6 mice (A, C) or Sprague-Dawley rats (B, D), plasma and tissue levels (brain, spleen, jejunum, kidney, and liver) of MMF and MEF were determined 30 min post dose. The relative tissue penetration in relation to plasma is given above each bar. Brain or kidney to plasma ratios of MMF and MEF in mice and rats highlight the significantly higher MMF brain exposure vs. MEF (E), whereas MEF reaches significantly higher levels in kidney than MMF (from Wipke *et al*., 2021).

Evaluation comment

Overall, the provided in vitro and in vivo PK non-clinical data shows that DMF and MEF are two different (to some extent) active moieties which share a similar metabolic pathway leading to the formation of fumaric acid (an inactive moiety). DMF and MEF are not metabolites of each other in vivo. In addition, in vitro data using liver microsomes or hepatocytes from rats and humans shows that MEF does not convert to either DMF or MMF, and DMF or MMF are not transformed into MEF. In the in vivo (mice and rats) study, MMF the active metabolite of DMF reached higher concentrations in the brain and spleen than MEF. In contrast, MEF is preferentially distributed into the kidney (Wipke et al., 2021).

Discussion on non-clinical aspects

The submitted pharmacodynamic and pharmacokinetic non-clinical data shows that DMF and MEF are two active moieties with pharmacological modes of action that are putatively different, but applicable for the indication of psoriasis. Nevertheless a straightforward additive or synergistic effect of MEF in the combination cannot be concluded due to the limitations of the conducted non-clinical studies.

2.2.2. Clinical aspects

- **Clinical pharmacology**

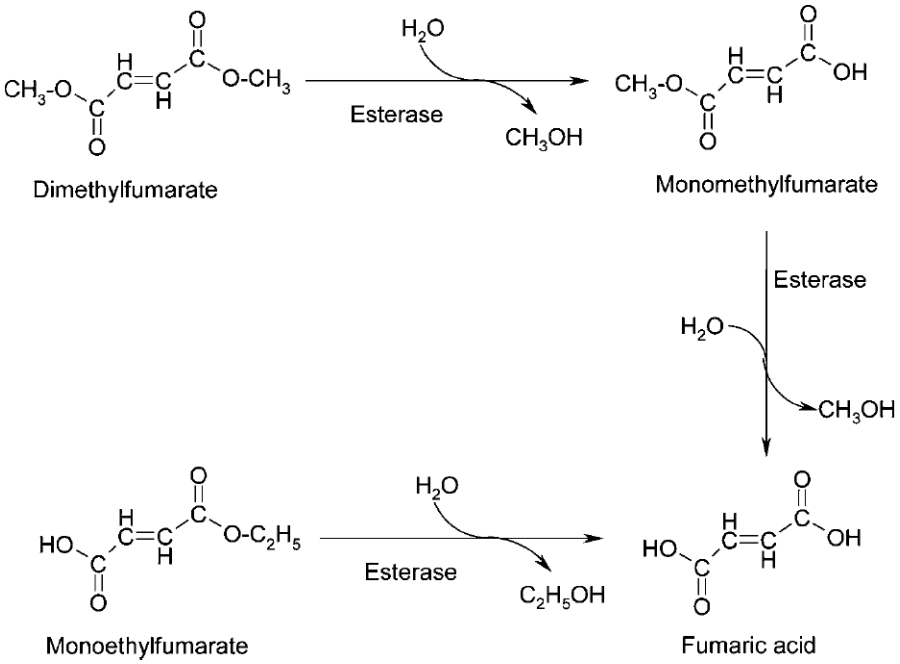
Pharmacological properties of DMF and the MEF salts

DMF and MEF are different esters of fumaric acid, which itself is inactive.

Pharmacokinetic properties

After oral administration, DMF is not detected in plasma because it is rapidly hydrolysed by esterases to its active metabolite MMF and/or interacts with GSH to form conjugates (Skilarence, EPAR). MMF is further degraded to fumaric acid (FA). Likewise, MEF is metabolized by esterases to FA (Rostami-Yazdi *et al*., 2010).

Figure 10: Presumptive metabolic pathway of DMF and MEF (Rostami-Yazdi et al., 2010)



MEF does not convert to either DMF or MMF, and DMF or MMF are not transformed into MEF. Thus, DMF and MEF are not metabolites of each other in vivo.

Pharmacodynamic properties

DMF, MMF and MEF are pharmacologically active

The main activity of DMF and MMF is considered to be immunomodulatory, resulting in a shift in T helper cells (Th) from the Th1 and Th17 profile to a Th2 phenotype and thus reducing inflammatory cytokine production with the induction of pro-apoptotic events, inhibition of keratinocyte proliferation, reduced expression of adhesion molecules, and diminished inflammatory infiltrate within psoriatic plaques.

In *in vitro* and *in vivo* studies MEF salts have been shown to: reduce IL-6 and TGF-alpha secretion in the psoriatic cocultures of KCs and T cells, suppress lymphocyte proliferation, induce early apoptotic effects on lympho-histiocytic cells and induce a rapid, transient Ca2+ increase in KCs and inhibit KC proliferation.

The mechanism by which dimethyl fumarate exerts therapeutic effects in multiple sclerosis is not fully understood. Preclinical studies indicate that dimethyl fumarate pharmacodynamic (PD) responses appear to be primarily mediated through activation of the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway. Dimethyl fumarate has been shown to up regulate Nrf2-dependent antioxidant genes in patients (e.g. NAD(P)H dehydrogenase, quinone 1; [NQO1]).

Effects on the immune system

In preclinical and clinical studies, dimethyl fumarate demonstrated anti-inflammatory and immunomodulatory properties. Dimethyl fumarate and monomethyl fumarate, the primary metabolite of dimethyl fumarate, significantly reduced immune cell activation and subsequent release of proinflammatory cytokines in response to inflammatory stimuli in preclinical models. In clinical studies with psoriasis patients, dimethyl fumarate affected lymphocyte phenotypes through a down-regulation of pro-inflammatory cytokine profiles (TH1, TH17), and biased towards anti-inflammatory production

(TH2). Dimethyl fumarate demonstrated therapeutic activity in multiple models of inflammatory and neuroinflammatory injury. In Phase 3 studies in MS patients, upon treatment with Tecfidera mean lymphocyte counts decreased on average by approximately 30% of their baseline value over the first year with a subsequent plateau (Tecfidera, SmPC).

- **Clinical Efficacy**

Most of the published clinical efficacy and safety studies in the indication psoriasis refer to Fumaderm (DMF/MEF) or other DMF/MEF combinations. In these studies, a therapeutic effect of Fumaderm (DMF/MEF) in psoriasis has consistently been described (e.g. *Altmeyer, 1994,* and *Gollnick, 2002).* Also, the therapeutic effect of DMF monotherapy in psoriasis has been described in clinical studies (*e.g. Langner 2004, Mrowietz 2006)*.

For the purpose of assessing whether MEF has a clinically relevant therapeutic contribution within Fumaderm from an efficacy standpoint, the following publications have been reviewed:

Altmeyer PJ, Matthes U, Pawlak F, Hoffmann K, Frosch PJ, Ruppert P, Wassilew SW, Horn T, Kreysel HW, Lutz G, Barth J, Rietzschel I, Joshi RK. Antipsoriatic effect of fumaric acid derivatives. J Am Acad Dermatol. 1994; 30: 977-81.

Atwan A, Ingram JR, Abbott R, Kelson MJ, Pickles T, Bauer A, Piguet V. Oral fumaric acid esters for psoriasis. Cochrane Database of Syst Rev. 2015.

Falkvoll S, Gerdes S, Mrowietz U. Switch of psoriasis therapy from a fumaric acid ester mixture to dimethyl fumarate monotherapy: results of a prospective study. J Dtsch Dermatol Ges. 2019; 17:906-912.

Gollnick H, Altmeyer P, Kaufmann R, Ring J, Christophers E, Pavel S, Ziegler J. Topical calcipotriol plus oral fumaric acid is more effective and faster acting than oral fumaric acid monotherapy in the treatment of severe chronic plaque psoriasis vulgaris. Dermatology. 2002; 205: 46-53.

Kolbach DN, Nieboer C. Fumaric acid therapy in psoriasis: results and side effects of 2 years of treatment. J Am Acad Dermatol. 1992;27: 769-71.

Landeck L, Asadullah K, Amasuno A, et al. Dimethyl Fumarate (DMF) vs. Monoethyl Fumarate (MEF) Salts for the Treatment of Plaque Psoriasis: a Review of Clinical Data. Arch Dermatol Res. 2018;310:475–483.

Langner A et al. Results of a phase II study of a novel oral fumarate, BG-12, in the treatment of severe psoriasis. J Europ Academ Dermatol Venereol. 2004; 18:798.

Lijnen R, Otters E, Balak D, Thio B. Long-term safety and effectiveness of high-dose dimethylfumarate in the treatment of moderate to severe psoriasis: a prospective single-blinded follow-up study. J Dermatolog Treat. 2016; 27: 31-6.

Mrowietz U, Reich K, Spellman MC. Efficacy, safety and quality of life effects of a novel oral formulation of dimethyl fumarate in patients with moderate to severe plaque psoriasis. Results of a phase 3 study. J Am Academ Dermatol. 2006: 54: AB202.

Nieboer C, de Hoop D, van Loenen AC, Langendijk PN, van Dijk E. Systemic therapy with fumaric acid derivates: new possibilities in the treatment of psoriasis. J Am Acad Dermatol. 1989; 20: 601-608.

Nieboer C, Langendijk PN, van Loenen AC, Gubbels J. Fumaric acid therapy in psoriasis: a double-blind comparison between fumaric acid compound therapy and monotherapy with dimethylfumaric acid ester. Dermatologica, 1990; 181:33-7.

Nugteren-Huying WM, van der Schroeff JG, Hermans J, Suurmond D. Fumaric acid therapy for psoriasis: a randomized, double-blind, placebo-controlled study. J Am Acad Dermatol. 1990; 22: 311-2.

Peeters AJ, Dijkmans BA, van der Schroeff JG. Fumaric acid therapy for psoriatic arthritis. A randomized, double-blind, placebo-controlled study. Br J Rheumatol 1992; 31: 502-4.

Walker F, Adamczyk A, Kellerer C, et al. Fumaderm® in Daily Practice for Psoriasis: Dosing, Efficacy and Quality of Life. Br J Dermatol. 2014;171:1197–1205.

Four publications, which compared the efficacy of DMF to DMF/MEF directly are considered the most relevant and are further described below.

These are the following:

- Kolbach DN, Nieboer C. Fumaric acid therapy in psoriasis: results and side effects of 2 years of treatment. J Am Acad Dermatol. 1992; 27: 769-71.

- Nieboer C, Langendijk PN, van Loenen AC, Gubbels J. Fumaric acid therapy in psoriasis: a double-blind comparison between fumaric acid compound therapy and monotherapy with dimethylfumaric acid ester. Dermatologica, 1990; 181:33-7.

- Mrowietz U, Szepietowski JC, Loewe R, et al. Efficacy and Safety of LAS41008 (Dimethyl Fumarate) in Adults with Moderate-to-Severe Chronic Plaque Psoriasis: a Randomized, Double-Blind, Fumaderm®- and Placebo-Controlled Trial (BRIDGE). Brit J Dermatol. 2017;176:615–623.

- Falkvoll S, Gerdes S, Mrowietz U. Switch of psoriasis therapy from a fumaric acid ester mixture to dimethyl fumarate monotherapy: results of a prospective study. J Dtsch Dermatol Ges 2019; 17: 906-912.

Moreover, study by Nieboer et al. (1989), which evaluated the efficacy and safety of MEF-Na is discussed below.

However, the non-randomised study of Kolbach and Nieboer (1992) is not suitable for a comparison, as the DMF-treatment group received only half of the DMF-dose in the Fumaderm-group. Moreover, this study was not randomized. Nevertheless, a short description of the study is provided below.

Kolbach and Nieboer, 1992

Efficacy and side effects of treatment with either DMF monotherapy or DMF/MEF salt combination in psoriatic patients were investigated over two years.

Group 1 (n=129) was treated with DMF, capsules filled with 60 mg of semi-enteric-coated. The dosage was increased weekly by 60 mg to a maximum of 240 mg DMF/day.

Group 2 (n=67) was treated with DMF/MEF (enteric-coated (Fumaderm) tablets): (1) *"Mite"*, containing 30 mg of DMF, 5 mg Mg^{2+}-, 3 mg Zn^{2+}-, and 56 mg Ca^{2+}-salts of MEF; or (2) *"Forte"*, containing 120 mg of DMF, 5 mg Mg^{2+}-, 3 mg Zn^{2+}-, and 87 mg Ca^{2+}-salts of MEF. Medication started with one *"Mite"* tablet per day to be increased weekly to three tablets per day. In the fourth week, medication was switched to one *"Forte"* tablet per day and this was increased weekly to a maximum of four tablets per day amounting to a maximum of 480 mg DMF + 380 mg MEF salts (i.e. 860 mg fumarate esters/day).

Results: The percentage of patients that continued the therapy was significantly higher in the DMF/MEF combination group than in the DMF group after 6 months. After 24 months, 55 % continued the DMF/MEF medication versus 16 % of the DMF users. Sufficient therapeutic results were obtained in approximately 50 % of the DMF/MEF-treated patients during the entire study. In the DMF group, the percentage of sufficient responders declined from 32 to 18 during the 24 months. These differences were statistically significant. The most important reason to discontinue the therapy was insufficient efficacy in the DMF group (36 %).

The study authors concluded that DMF/MEF combinatorial treatment was significantly superior to DMF monotherapy.

Evaluation comment

The efficacy and safety of DMF monotherapy in comparison to DMF/MEF salt combination was evaluated in 196 patients with nummular or plaque-type psoriasis. Numerical superiority of DMF/MEF salt combination over DMF was shown (after 24 months, 55% of patients continued on DMF/MEF salt combination therapy, compared to 16% of patients on DMF). Moreover, in the DMF group the percentage of sufficient responders declined from 32% to 18% during the 24-month study, while in the DMF/MEF salt combination group the percentage remained unchanged. However, there were significant shortcomings in this study, including the fact that the amount of DMF in the DMF/MEF combination was twice of the amount of DMF in the monotherapy arm. Therefore, patients in the DMF monotherapy group may have been treated with doses which were not sufficient for all patients and it is therefore difficult to assess any additive effects of the MEF esters.

There is no information on demographics and patients' disease features (e.g. severity of psoriasis, disease duration, previous treatment) across the groups. In the absence of randomization or any other method to control for baseline unbalance (the article established that the choice of the therapy was determined by a patient´s insurance), this is a critical shortcoming that prevents the interpretation on causal effects.

Moreover, mild topical corticosteroid was allowed during the study. However, no further information about the topical treatment was provided. No information about statistical analysis was found. Taking into consideration the evaluation of psoriasis, usage of topical corticosteroid might have distorted the results of the study. There are critical flaws in the study methods and statistical analysis, therefore no conclusion can be drawn from this study.

Furthermore, longer dose titration scheme was used in the DMF/MEF combination group compared to DMF group. Finally, differences in formulations (galenical formulation of the DMF/MEF combination and semienteric-coated DMF capsules) preclude the comparison of efficacy and safety of both products.

Overall, it is concluded that this study does not allow a comparison of DMF vs. MEF/DMF.

Nieboer et al., 1989

This study contains 6 studies, however, only 2, considering MEF could be considered relevant for this AR.

Study II: controlled study with MEFAE sodium (Na). In a double-blind study 240 mg MEFAE-Na was compared with placebo in 38 patients (22 women and 16 men). The treatment started with one capsule of 60 mg MEFAE-Na or placebo a day for a week. The dosage was increased in 3 weeks to a maximum of 240 mg. The observation time was 4 months.

Study IV: comparative study of 720 mg MEFAE-Na compared with 240 mg MEFAE-Na. This dose-finding study was performed because the daily 240 mg dosage of MEFAE was ineffective. It was performed in 20 patients, 12 women and 8 men: 10 had been treated with 240 mg MEFAE and 10 with placebo in the previous 4 months. The first group was given 720 mg daily, the latter 240 mg. The observation time was 3 months.

Table 38: Results of fumaric acid derivatives in psoriasis with the use of different treatment schedules (studies I-V)

Study	*n*	Improvement (%)• <25	25-50	>SO	Deteriorated;i:	Discontinued	
I: Open FACT studyt	36	4(11%)	6(17%)	23(64%)	0(0%)	3(8%)	
II: Double-blind study							
MEFAE-Na (240 mg)	19	9	6	1	3	1	
Placebo	19	8	5	2	4	1	
III: Double-blind study							
DMFAE (240 mg)	22	4	6	6	0	6	
Placebo	20	12	1	0	5	2	
IV: Comparative study							
MEFAE-Na (720 mg)	10	3	4	3	0	0	
MEFAE Na (240 mg)	10	6	1	3	0	0	
V: Open long-term study							
DMFAE (240 mg)	56	14(25%)	12(22%)	19(33%)	0(0%)	Early§ 11(20%)	Latell 4(7%)

Study II: double-blind study with 240 mg MEFAE-Na versus placebo

There was no difference between the numbers of improved, unimproved, or deteriorated cases in both groups. The average final score was the same in both groups, and so were the average final scores of each factor. Only the itching score showed a greater drop in the MEFAE-Na group than in the placebo group.

Study IV: comparative study 720 mg versus 240 mg MEFAE-Na

No difference was seen between the 720 mg versus the 240 mg regimen with regard to the number of improved patients. The average final scores of the total groups and the extent of the eruption, the redness and the thickness were the same, but significant differences ($p < 0.05$) were noted between the final scores of scaling and itching of both groups.

Evaluation comment

No difference between MEF-Na at the dose of 240 mg daily and placebo was observed in Study II.

Treatment with MEF-Na at the dose of 720mg or 240 mg daily resulted in comparable considerable improvements (>50% n=3 in both groups). Indeed, the same number of patients showed an improvement > 50% of the global score in both groups.

While the subscores for extent of the eruption, the redness and the thickness were not different between 720 mg – and 240 mg – treated patients, differences in favour of MEF-NA at the dose of 720mg – treated patients were observed in the final scores of scaling and itching in the study. The authors claimed these differences were statistically significant ($p<0.05$) and thus could be interpreted as supporting clinically relevant effects of MEF-Na. However, it should be noted that the average psoriasis severity score, established as efficacy endpoint in the section of methods in the article, was not different between both groups. Subscores were not presented as endpoints in this study and there was no evidence of adjustment for multiplicity. Therefore, the claim on statistical significance on scaling and itching scores could not be agreed. The small sample size is an additional limitation of the study.

Therefore, no conclusions on MEF-Na efficacy in psoriasis can be made based on this study. Moreover, no direct comparison to DMF was performed in these studies.

An *ad hoc* statistical analysis of Nieboer 1989 comparing the 240 mg Na-MEF data of Study IV, the 720mg MEF data of Study IV and a group including 240mg – and 720mg MEF data to the combined placebo data of Studies II and III was also taken into account. The patients in these groups were categorized as follows: "responders" who achieve at least 25% improvement, and "non-responders" who achieve less improvement or deterioration. The rate of response between the groups was compared using Fisher's Exact test (FET) or a chi-squared. Additionally, ordered logistic regression was applied considering 4 categories ("deteriorated," to < 25% improvement, to 25 to 50% improvement, and to > 50% improvement). In the context of that *ad hoc* statistical analysis, it was submitted that individually underpowered studies (Nieboer 1989) of the effect of MEF in the absence of DMF demonstrates statistically significant efficacy on the improvement of a psoriasis severity score compared to placebo when results are pooled to increase statistical power in an *ad hoc* statistical analysis.

While Nieboer 1989 used a global psoriasis score different than the one that is currently considered as a standard (PASI), it should be noted that in both cases the response is scored as a percentage of improvement with respect to the baseline value. In this regard, a 75% reduction in the PASI score with respect to baseline is the current standard of response assessment used for primary endpoints in most clinical trials of psoriasis. Lower level of responses (e.g. 50% reduction) have also been used as endpoints. However, responses below 50% are not considered as an acceptable demonstration of treatment response. This is in line with the CHMP guideline on clinical investigation of medical products indicated for the treatment of Psoriasis (CHMP/EWP/2454/02 corr).

Nieboer et al., 1990

The aim of this double-blind, 16 week trial was to assess the therapeutic effect of DMF monotherapy compared to DMF/MEF using the same DMF dosage and, thus, to assess the possible additional effect of MEF.

Treatment

Group 1 (n=22) received max. 480 mg DMF/day (max. 4 tablets/day of 120 mg each).

Group 2 (n=23) received max. 480 mg DMF/day + 380 mg MEF salts (max. 4 tablets/day of 120 mg DMF + 87 mg Ca^{2+}-MEF + 5 mg Mg^{2+}-MEF + 3 mg Zn^{2+}-MEF per tablet) for 4 months.

Patients
Randomization into two groups was made between 45 patients. 25 female, 20 male. Aged between 18 and 70 years. 22 were treated with DMFAE-E C. 23 with FAC-EC. At the end of the study 33 patients could be evaluated. 18 had been treated with DMFAE-EC and 15 with FAC-EC. At least 10% of the body surface was affected. At the beginning of the study 22 of these 33 patients showed the plaque type; 10 the macular type; and 1 the guttate type of psoriasis. 11 patients had joint complaints, 6 in the DM FAE-EC group and 5 in the FAC-EC group.

Results

The individual results are shown in Table 5. Compared to the initial population score, a considerable improvement (i.e. score more than halved) was observed in 45% of the patients treated with DMFAE-EC and in 52% of the treated with FAC-EC. This improvement was statistically significant.

In both groups 4 patients (18 and 15%) showed a full clearance. Considerable improvement occurred in 15 out of 22 (68%) patients with the plaque type and in 4 out of 10 (40%) of those with the macular type. The patient with the guttate type showed a full clearance after a treatment of 2 months with FAC-EC, but had an extensive relapse 1 month later even though the therapy had been continued. For 5 patients (22%) in the DMF AE-EC group and 1 patient (4%) in the FAC-EC group the psoriasis did not show any reaction to the therapy. The observed differences between the two groups appeared to be not significant. Deterioration, that is an increase of the score up to more than 125%, was not observed in either of the groups.

The course of the score in both groups with regard to the total average score and the separate parameters is shown in Figure 8 a, b. It covers the observations of those patients who could be evaluated after 4 months: 18 in the DMFA E- EC group and 15 in the FAC-EC group. The total average score in the DMFAE-EC group dropped from 9.7 to 4.1 and in the FAC-EC group from 10.5 to 4.1. The course of this score in both treatment groups was not significantly different at any time point (1- V). Subsequently, the separate parameters, too, did not show a significant difference in time course. The results after 4 months were not statistically different.

The joint complaints of the 6 patients in the DMFAE-EC group showed considerable improvement for 2 patients, and some improvement for 1, and deteriorated or remained unchanged for the other 3. In the 5 patients in the FAC-EC group a considerable improvement occurred in 2 cases and a slight improvement in 3 cases.

The general evaluation of the therapy by the patients usually corresponded with that of the investigators.

Figure 11: Course of the total psoriasis score and of the 5 parameters in patients treated with DMFAE-EC (n= 18) or FAC-EC (n= 15) during 4 months. a Total psoriasis severity score. b Percent decrease of the 5 parameters of the severity score

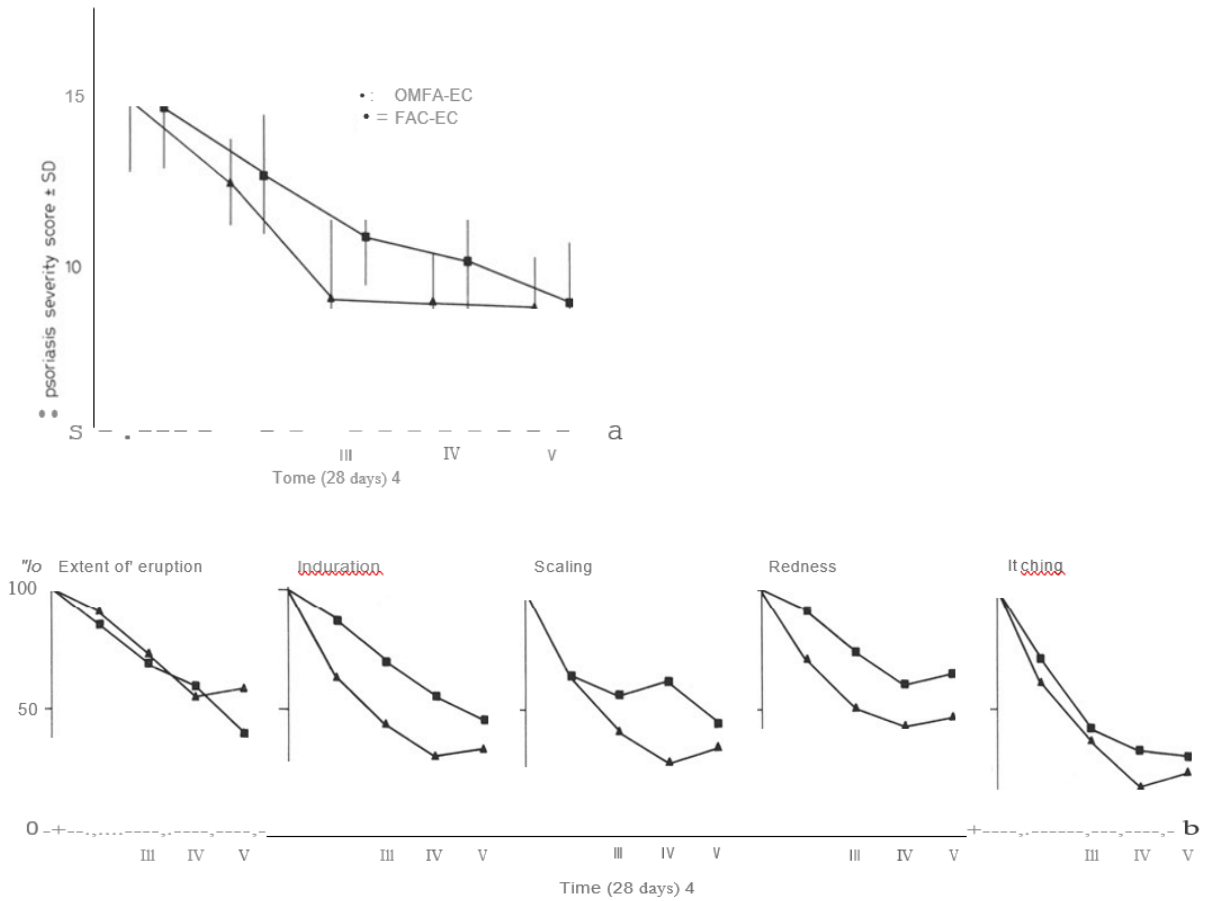


Table 39: Comparative study on the effects of DMFAE-EC (n = 22) and FAC-EC (n = 23) on 45 psoriasis patients

Medication	n	Improvement			Deter-ioration	Discon-tinuation
		<25%	25- 50%	>50%		
DMFAE-EC	22	5(22)	3 (14)	10 (45)	0	4(18)
FAC-EC	23	1 (4)	2 (9)	12 (52)	0	8(35)2

Discontinuations due to gastrointestinal side effects (gastralgia, diarrhoea, nausea) were reported for 3 of the 22 patients of the DMF group and for 7 or the 23 patients treated with the DMF/MEF combination. Moreover, one patient of the DMF/MEF combinatorial group discontinued due to the appearance of flushing symptoms, whereas another left the study, because his medication had been stolen.

In the EPAR for Skilarence, the results of Nieboer *et al*., 1990, and of the two sub-studies of Nieboer *et al*., 1989 are presented, as it is useful to compare the results of the same author, despite the different study designs:

Table 40: Percentage improvement of PASI after Treatment with DMF or DMF/MEF (Nieboer studies)

Author	Treatment Duration	Percentage of Patients		
		PASI >50% Improvement	PASI 25-50% Improvement	PASI <25% Improvement
Nieboer 1989 – Study III	16 weeks			
DMF 240 mg/day (n=22)		27%	27%	18%
Placebo (n=20)		0%	5%	60%
Nieboer 1990	16 weeks			
DMF 480 mg/day (n=22)		45%	14%	22%
DMF/MEF 480 mg/day (n=23)		52%	9%	4%
Nieboer 1989 – Study V (open label)	4-9 months			
DMF 240 mg/day (n=56)		33%	22%	25%

DMF=dimethyl fumarate, MEF=mono ethyl fumarate; n=number of patients evaluated, PASI=Psoriasis Area and Severity Index

As shown in Table 6, the anti-psoriatic effect, i.e. improvement of PASI with 240 mg DMF monotherapy was less pronounced than with 480 mg DMF resp. 480 mg DMF/MEF, which was administered in the Nieboer study (1990). This means, the DMF dose applied in the Nieboer 1989 studies (III and IV) was quite low (probably too low to achieve convincing results).

Evaluation comment

The aim of this double-blind study was to assess the therapeutic effect of DMF monotherapy compared to DMF/MEF using the same DMF dosage. There was a numerical difference in favour of DMF/MEF compared to DMF monotherapy in regard to the improvement of the psoriasis severity score. However, as acknowledged by the authors of the study, the difference is not statistically significant. Higher rate of discontinuations were observed in DMF/MEF group compared to DMF group. Overall, the evidence of this study is limited due to its small sample size, the short duration of treatment, and the absence of control for missing data (table 5 and figure 8 were based on a complete case analysis including 81% of patients in the DMFAE-EC [DMF] group and 65% of those in the FAC-EC [DMF/MEF] group). Subscores were not

presented as endpoints in this study so the course of these scores over time should be regarded as exploratory. In this study, the greatest differences were observed for redness and induration scores while a lower difference and no numerical difference were found for scaling and itching, respectively, as opposed to Study II and Study IV previously conducted by these authors (Nieboer et al., 1989).

Mrowietz et al., 2017

The objective of the BRIDGE study was to assess the efficacy and safety of a new formulation of DMF (LAS41008), compared with placebo and Fumaderm, in adults with moderate-to-severe chronic plaque psoriasis.

In this Phase III, double-blind, placebo-controlled, noninferiority trial, patients were randomized to receive LAS41008, Fumaderm, or placebo (2:2:1) for 16 weeks, up titrating to a maximum daily DMF dose of 720 mg, depending upon individual response.

The co-primary endpoints were the percentage of patients achieving ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75) and the percentage achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment (PGA) at Week 16. Secondary endpoints included PASI 75 at Weeks 3 and 8, PASI 50 and PASI 90 at Week 16, and scores of 0 to 1 in the PGA at Weeks 3 and 8 and BSA at weeks 3, 8, and 16.

Statistical analysis
The sample-size calculations were based on PASI 75 response rates of 50% and 10% for LAS41008 and placebo, respectively, and 'clear'/'almost clear' PGA response rates of 40% for LAS41008 and 10% for placebo. For the non-inferiority test of LAS41008 vs. Fumaderm® regarding PASI 75 at week 16, a zero difference was assumed and a noninferiority margin of 15% was set. An alpha level of 0.05 was defined and a dropout rate of 15% was factored into the calculations. A total of 690 patients (276 per active group and 138 in the placebo group) provided a power of > 99% for the two superiorities tests of LAS41008 vs. placebo, and 90% for the non-inferiority test of LAS41008 vs. Fumaderm.

In total, 671 patients were randomized and included in the full analysis set (n = 267, LAS41008; n = 273, Fumaderm; n = 131, placebo).

Figure 12: Trial design. BID, twice daily; QD, once daily; R, randomization; TID, three times daily. In the first 3 weeks, 30-mg dimethylfumarate tablets were used, and as the LAS41008 30-mg and Fumaderm Initial tablets differed in colour and size, a double-dummy technique was used, with each patient also receiving one placebo tablet per tablet of LAS41008 or Fumaderm. Subsequent uptitration was achieved using indistinguishable 120-mg tablets. a Trial-centre visits at weeks 12 and 16; Psoriasis Area and Severity Index (PASI), Physician's Global Assessment (PGA) and body surface area (BSA) at week 16 only

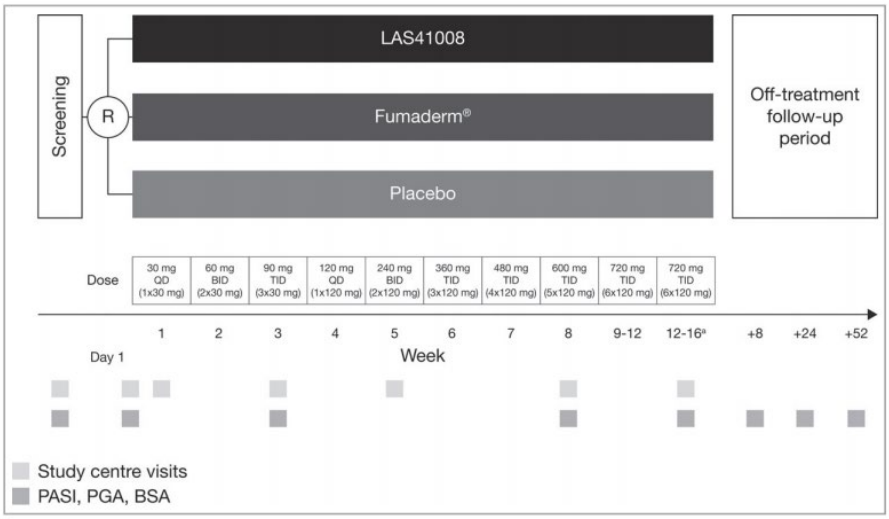


Figure 13: Participants flow

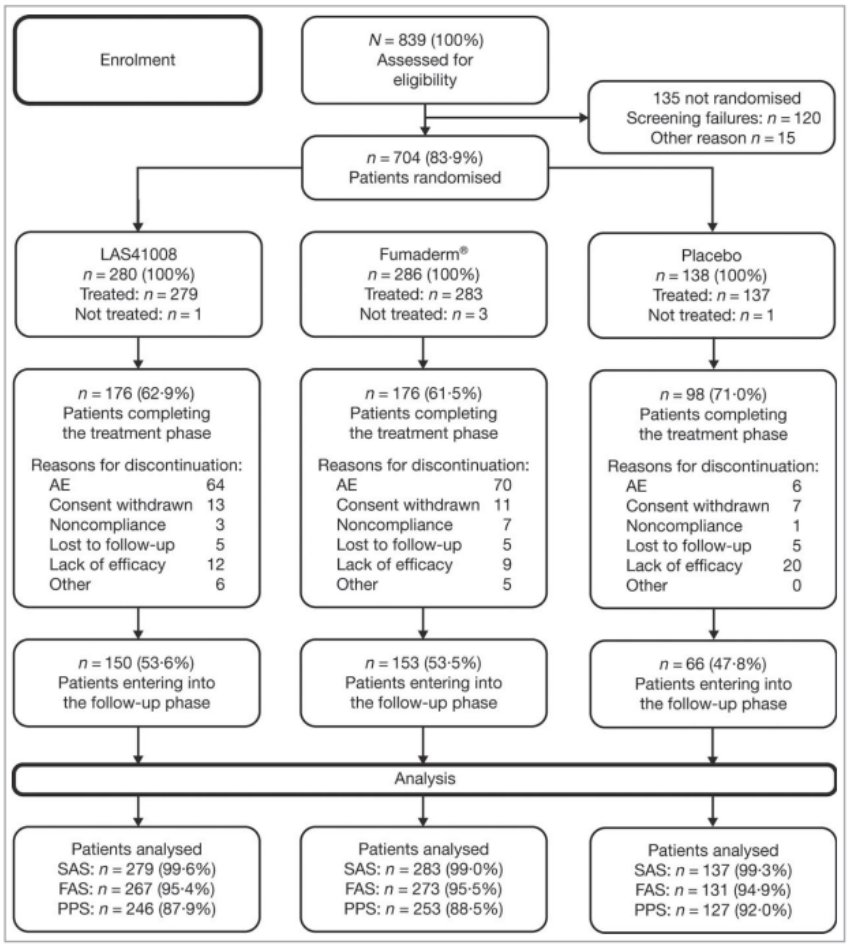


Table 41: Demographic and baseline patient characteristics (treated population)

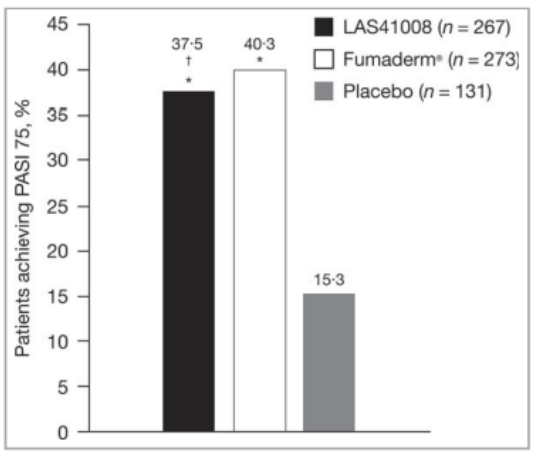
	LAS41008 (n = 279)	Fumaderm® (n = 283)	Placebo (n = 137)
Male, n (%)	174 (62·4)	185 (65·4)	93 (67·9)
Age (years)			
Mean ± SD	44·0 ± 15·2	45·0 ± 13·8	44·0 ± 14·3
Range	18–80	18–87	18–78
Race, n (%)			
White	275 (98·6)	280 (98·9)	137 (100·0)
Black/African American	1 (0·4)	0	0
Asian	1 (0·4)	3 (1·1)	0
Other	2 (0·7)	0	0
PASI total score, mean ± SD	16·3 ± 5·7	16·4 ± 6.79	16·2 ± 4·9
PGA group, n (%)[a]			
Moderate	162 (60·7)	164 (60·1)	79 (60·3)
Moderate to severe	93 (34·8)	94 (34·4)	49 (37·4)
Severe	12 (4·5)	15 (5·5)	3 (2·3)
Body surface area (%), mean ± SD	21·9 ± 11·6	21·3 ± 12·5	21·9 ± 12·3
Prior conventional systemic therapy, n (%)			
Methotrexate	20 (7·2)	39 (13·8)	14 (10·2)
Ciclosporin	12 (4·3)	8 (2·8)	8 (5·8)
Fumaderm®	9 (3·2)	11 (3·9)	4 (2·9)
Acitretin	8 (2·9)	15 (5·3)	9 (6·6)
Apremilast	1 (0·4)	1 (0·4)	0
Prior biological therapy, n (%)			
Interleukin inhibitors[b]	7 (2·5)	4 (1·4)	3 (2·2)
TNF-α inhibitors[c]	1 (0·4)	6 (2·1)	0
Prior nondrug therapy including phototherapy, n %	75 (26·9)	86 (30·4)	43 (31·4)

PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; TNF, tumour necrosis factor. [a]The PGA scale was defined as follows: 0, clear; 1, almost clear; 2, mild; 3, moderate; 4, moderate to severe; 5, severe. [b]Including secukinumab, ustekinumab and brodalumab. [c]Including adalimumab and etanercept.

Results

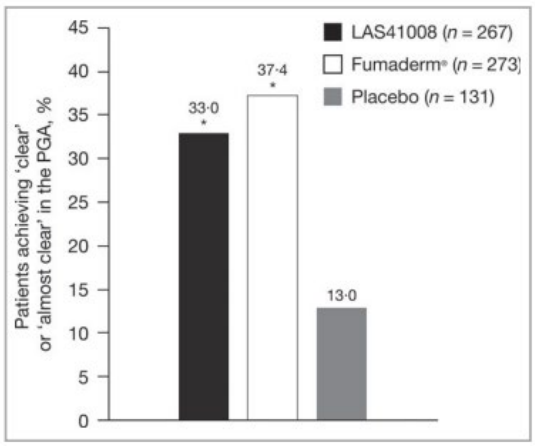
Co-primary endpoints: Significantly more patients achieved PASI 75 at week 16 following treatment with LAS41008 than with placebo [37.5% vs. 15.3%, P < 0.001; 99.24% confidence interval (CI) 10.7–33.7%]. Furthermore, LAS41008 was noninferior to Fumaderm at week 16 (37.5% vs. 40.3%, P < 0.001; 99.24% CI -14-0 to 8-4%) (Figure 11).

*Figure 14: Percentage of patients achieving ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75) at week 16 (full analysis set). *P < 0001 vs. placebo; † P < 0001 noninferiority vs. Fumaderm*



At week 16, 33%, 37.4% and 13% of patients had achieved a score of 'clear' or 'almost clear' in the PGA in the LAS41008, Fumaderm and placebo groups, respectively, and LAS41008 was significantly superior to placebo (P < 0.001; 99.24% CI 9–31%) (Fig.12). Concomitant intake of potentially nephrotoxic drugs (n = 108), such as angiotensin-converting enzyme inhibitors, angiotensin II inhibitors and/or statins, did not have a significant impact on the primary outcome measures or on the safety profile of LAS41008.

*Figure 15: Percentage of patients achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment (PGA) at week 16 (full analysis set). *P < 0.001 vs. placebo*



Based on the above results, the Authors concluded that the study has demonstrated the efficacy and safety of LAS41008 (DMF) for adults with moderate-to-severe chronic plaque psoriasis, showing it to be significantly superior to placebo and noninferior to the approved combination of FAEs (Fumaderm).

Evaluation comment

The objective of this double-blind placebo-controlled study was to assess the efficacy and safety of DMF compared with placebo and Fumaderm (DMF/MEF) in adult patients with moderate-to-severe chronic plaque psoriasis. Patients were randomized to receive DMF, Fumaderm, or placebo (2:2:1) for 16 weeks, up titrating to a maximum daily DMF dose of 720 mg, depending upon individual response.

The coprimary endpoints were the percentage of patients achieving ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75) and the percentage achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment (PGA) at Week 16. Secondary endpoints included PASI 75 at Weeks 3 and 8, PASI 50 and PASI 90 at Week 16, and scores of 0 to 1 in the PGA at Weeks 3 and 8 and BSA at weeks 3, 8, and 16. In total, 671 patients were randomized and included in the full analysis set.

Significantly more patients achieved PASI 75 at week 16 with either DMF or Fumaderm compared to placebo (37.5%, 40.3% and 15.3%, respectively). 33% of patients treated with DMF achieved 'clear' or 'almost clear' based on PGA at Week 16, compared with 13.0% receiving placebo and 37.4% receiving Fumaderm.

There was a small numerical difference in favor of Fumaderm in regard to the co-primary endpoints and most of the secondary endpoints. As stated in the EPAR "*The effects in regard to the co-primary endpoints were numerically slightly lower in the Skilarence group compared to Fumaderm although this could be due to variability, a limited PD and the efficacy effect of MEFs in Fumaderm may also be contributing to an anti-psoriatic effect*". Therefore, these differences although suggesting an additional therapeutic effect of MEF in Fumaderm may also appear due to variability or a limited PD. More importantly, it should be noted that this study was aimed to demonstrate superiority of DMF versus placebo and non-inferiority versus DMF/MEF. Consequently, the design of this study does not allow to demonstrate superiority of DMF/MEF versus DMF.

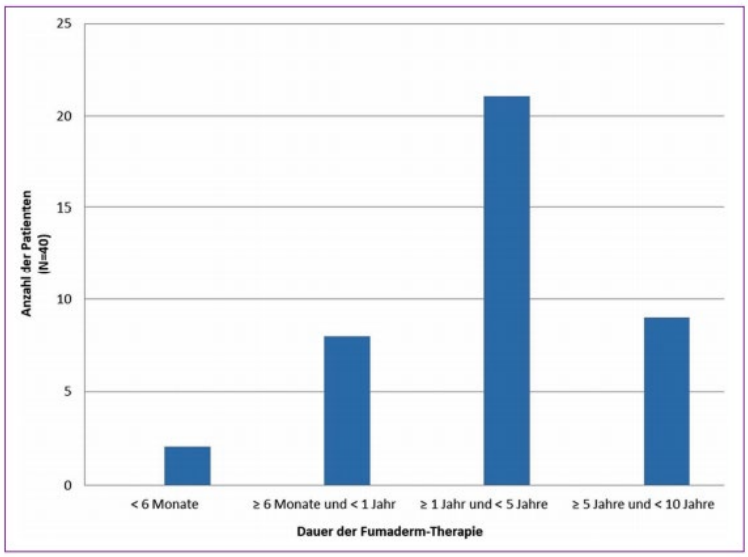
Falkvoll S et al., 2019

This was a prospective observational trial in patients who were treated with the FAE mixture. Patients whose psoriasis had improved and who could tolerate treatment with the FAE mixture were recruited. Treatment with the FAE mixture was switched to the DMF product without any interruption on the basis of the current DMF dose in the FAE mixture. Patients were then scheduled for the next regular check-up three months later. To assess psoriasis severity, the PASI index (psoriasis area and severity index) was used. When presenting for their first check-up after switching, patients were handed a questionnaire to investigate their views about tolerability and efficacy and to provide a global judgment of the switch.

Results

A total of 40 patients (24 male, 16 female) were prospectively and consecutively recruited to the study and underwent a check-up after switching treatments. The age of adult patients ranged from 18 to 74 years with a mean age of 46 years. One patient was 13 years old and received treatment off-label.

Figure 16: Number of patients related to the duration of continuous FAE therapy that they received before switching from the FAE mixture to the DMF product (n = 40)

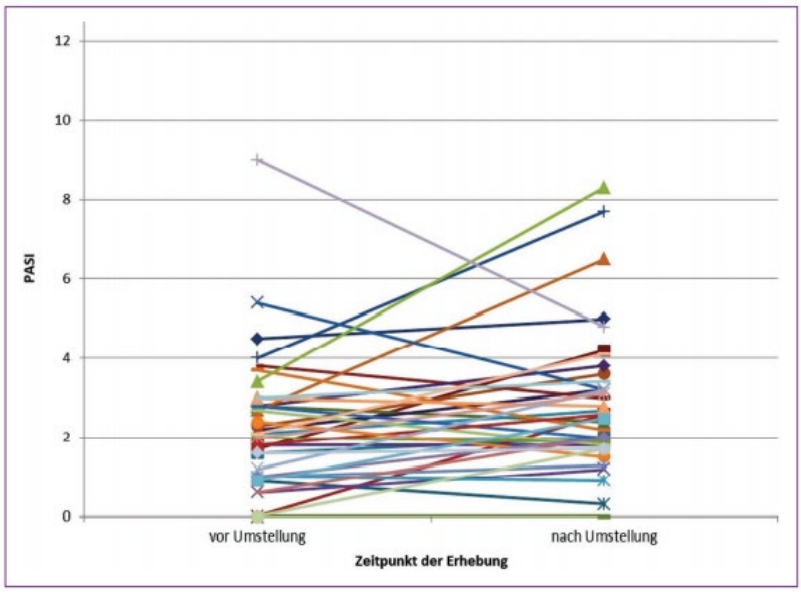


Most patients were treated with a daily DMF dose between 120 mg and 480 mg and had previously been treated with the FAE mixture for one to five years.

In general, the patients regarded the outcome of the switch to the DMF product as neutral or positive (18 positive, 18 neutral, 4 negative).

Efficacy as assessed with the PASI was equal or better in 34/37 patients, while 3/37 had a higher PASI severity after switching (Figure 14). A PASI estimate was not available at one of the visits in 3/40 patients.

Figure 17: Clinical course of PASI in patients treated with the FAE mixture before (t1) and after (t2) switching to the DMF product. The mean time between the two visits was 91.8 days (minimum 42 days, maximum 133 days; n = 37)



The Authors concluded that the results of this study showed that psoriasis patients can switch from the traditional FAE mixture to the same dose of DMF with similar clinical relief but without any washout period.

Evaluation comment

This prospective study was aimed to investigate the switch from the currently used DMF/MEF to DMF

monotherapy. The study was not designed to evaluate the treatment difference between DMF/MEF and DMF in the treatment of psoriasis. The objective of the study was to evaluate the clinical course of PASI in patients after switching to the DMF product.

Treatment with the DMF/MEF was switched to the DMF product without any interruption. Patients clinical state was evaluated after three months. To assess psoriasis severity, the PASI (psoriasis area and severity index) was used.

The patients regarded the outcome of the switch to the DMF product as neutral or positive (18 positive, 18 neutral, 4 negative). Efficacy as assessed with the PASI was equal or better in 34/37 patients, while 3/37 had a higher PASI severity after switching.

However, based on the presented data it is not possible to evaluate in how many patients PASI improved. Therefore, it is not possible to conclude on differences in efficacy between the two treatments.

Discussion on Efficacy

There are in a total 4 published studies which can be considered the most relevant for the evaluation of the clinical relevance of MEF in Fumaderm. However, the results of Kolbach & Nieboer (1992) were not included in the analysis due to severe limitations, described above.

Therefore, the assessment of the clinical relevance of MEF can be based on the results of 3 published studies:

In the Nieboer et al., study (1990), a numerical, but not statistically significant, difference in favour of DMF/MEF compared to DMF monotherapy (52% vs. 45%) was demonstrated in what regards the improvement of the psoriasis severity score.

When only patients who could be evaluated after 16 weeks were included in the analysis, the improvement percentage (i.e. a psoriasis severity score more than halved) was 55 % in the DMF group and 80 % in the DMF/MEF group. However, this complete case analysis may be biased. Except for the single patient for whom the tables were stolen, all other patients discontinued due to adverse events, an intercurrent event, likely informative that was completely disregarded by the investigators. Therefore, the comparison of 55% - 80% should not be considered a reliable estimate of the difference. Additionally, the evidence of this study is limited due to the small sample size and short duration of treatment.

In Falkvoll et al. (2019) study, efficacy as assessed with the PASI was equal or better in 34/37 patients, while 3/37 had a higher PASI severity after switching from DMF/MEF combination to DMF. However, it was not stated clearly in how many patients PASI improved. Therefore, it is not possible to conclude on differences in efficacy between the two treatments.

The most relevant study for this assessment appears to be study by Mrowietz et al. (2017), which was a pivotal study for the Skilarence MAA. The study was aimed to demonstrate superiority of DMF to placebo and non-inferiority to Fumaderm. Although both co-primary endpoints were met, the robustness of the demonstration of non-inferiority to Fumaderm was found questionable. As it was discussed in the EPAR for Skilarence, although the difference in proportion of patients achieving PASI 75 was -2.8 (99.24 CI =14.0 8.4; p-0.0003), and the lower limit of the confidence interval was within the prespecified non-inferiority limit of 15, given the absolute difference in proportion of responders by PASI 75 between DMF and placebo was 22%, the non-inferiority margin of 15% could not be appropriate.

The comparison between DMF and Fumaderm showed that Fumaderm consistently had a numerically higher response rate. In FAS population, 37.5% of the patients in the DMF group compared to 40.3% of the patients in the Fumaderm group achieved PASI 75 at Week 16. Moreover, the proportion of patients achieving PGA clear/almost clear was 33% and 37.4% in DMF and Fumaderm groups, respectively.

These data suggest that MEF may contribute to the efficacy in psoriasis to some extent. This assumption is supported by pharmacodynamic studies demonstrating MEF salts biological activities, including reducing IL-6 and TGF-alpha secretion in psoriatic cocultures of KCs and T cells, suppressing lymphocyte proliferation and inducing a rapid, transient [Ca2+] increase in KCs and inhibiting KC proliferation. However, and as stated in the EPAR for Skilarance, "*The effects in regard to the co-primary endpoints were numerically slightly lower in the Skilarence group compared to Fumaderm although this could be due to variability, a limited PD and the efficacy effect of MEFs in Fumaderm may also be contributing to an anti-psoriatic effect*". Therefore, reasons other than an additional therapeutic effect of MEF in Fumaderm could not be excluded. More importantly, the design of this study does not allow to demonstrate superiority of DMF/MEF versus DMF.

Overall, based on the available data, pharmacodynamic effects of MEF in psoriasis appear to be demonstrated. A numerical difference in favour of DMF/MEF combination reported in two independent randomized, double blind studies suggests that MEF could contribute to the efficacy of Fumaderm in the treatment of psoriasis. However, given the methodological limitations of the available clinical studies comparing directly DMF/MEF with DMF monotherapy in patients with psoriasis (small sample size, short duration of treatment, absence of methods to account for missing data, intercurrent events and multiple comparisons, absence of properly design studies to demonstrate superiority of DMF/MEF over DMF), a clinically relevant effect of MEF in Fumaderm has not been demonstrated.

- **Clinical Safety**

For the purpose of assessing whether MEF has a clinically relevant therapeutic contribution within Fumaderm from a safety standpoint, the following four publications have been reviewed.

Kolbach and Nieboer, 1992

In terms of tolerability, side effects were the most frequent reason to stop therapy in the DMF/MEF group (18%). For the DMF group, this percentage was 26%. In the first 6 months gastrointestinal complaints were the most frequent in both groups. However, the aforementioned difference was not significant and although the amounts of DMF in the DMF/MEF combination group were twice that of the DMF monotherapy, this is no sound proof that the MEF increased the tolerability.

Comparable to the studies from Nieboer *et al*. 1989, DMF in the DMF-monotherapy group was formulated as capsules filled with semi-enteric-coated granulate, whereas Fumaderm was formulated as enteric-coated tablets, which could have resulted in different drug release and hence affected the safety profile.

Evaluation comment

Although the amounts of DMF in the DMF/MEF combination were twice that of the DMF monotherapy, slightly higher discontinuation rate was reported in patients from DMF group compared to DMF/MEF group (16% vs 18%). However, it should be noted that differences in both formulations (semi-enteric coated vs enteric coated) could contribute to the overall tolerability.

Furthermore, taking into consideration different dose of DMF and different pharmaceutical formulation, no definite conclusion cannot be drawn from this study.

Nieboer et al., 1990

The subjective and objective side effects are shown in Table 8. The flushings started 3-4 h after the tablets were taken. They involved a feeling of tingling heat, accompanied by diffuse redness, which continued for about half an hour mainly localized in the face, arms and the upper part of the body. This symptom was not constantly present and in the course of the treatment its frequency decreased. More than half the patients were troubled by serious stomach complaints, involving gastralgia, but also nausea, vomiting and diarrhea. For 14% (n = 3) of the patients in the DMFAE-EC group and 30% (n = 7) in the FAC-EC group these complaints were a reason to discontinue the therapy. The abnormalities which were registered in the blood most generally were: leukopenia(< 3.0 x 10^9/1), lymphopenia (< 15%) and eosinophilia (> 5%). The former two developed in the course of the 3rd and 4th months. The eosinophilia usually began in the first 2 months and disappeared spontaneously in most of the cases.

Table 42: Side effects during treatment of psoriasis with DMFAE (n=22) or FAC-EC (n=23) over w period of 4 months

	DMFAE-EC (n = 22)		FAC-EC (n= 23)	
	11	0/0	n	0/0
Sy m pto m s				
Fl ushi n g	19	86	20	87
Dia rrh ea	12[2]	55	14[3]	61
Nausea/stomache	11[1]	50	14[3]	61
General malaise	2	9	1	4
Di zziness		5	0	0
Headac he		5		4
Laboratory				
Urine				
Albuminuria	0	0	2	9
Blood				
Leukopenia	3	14	3	13
Lympho pen ia	3	12	2	8
Eosinophilia	8	35	3	13
Increase of				
Creatinine/urea	0	0	0	0
Alkaline phosphatase	1	5	0	0
ASAT/A LAT	0	0		4

1 Patient discontinued the treatment as a result of this symptom.
2 3 Patients discontinued the treatment as a result of these symptoms.
3 7 Patients discontinued the treatment as a result of these symptoms.

Evaluation comment

In this study, higher discontinuation rate due to AEs (nausea, vomiting, diarrhoea) was reported in DMF/MEF group compared to DMF group (30% vs 14%). However due to small study size, no clear conclusion cannot be made.

Mrowietz et al., 2017

Treatment-emergent AEs (TEAEs) were reported in 83.9% and 84.1% of patients in the LAS41008 and Fumaderm® groups, respectively, and in 59.9% of patients in the placebo group. The majority were considered 'mild' in intensity (66.7%, 67.1% and 52.6% in the LAS41008, Fumaderm® and placebo groups, respectively). The most frequently reported TEAEs in both the LAS41008 (DMF) and Fumaderm® groups were gastrointestinal disorders (62.7% and 63.3%, respectively), including diarrhoea, abdominal pain, nausea and flatulence. Flushing was also commonly reported (18.3% and 16.3%, respectively) (Table 9).

Table 43: Adverse events (AEs) reported by ≥ 5% of the patients in any treatment group (safety population)

	LAS41008 (n = 279)	Fumaderm® (n = 283)	Placebo (n = 137)
At least one TEAE, n (%)	234 (83·9)	238 (84·1)	82 (59·9)
Preferred term, n (%)			
Diarrhoea	108 (38·7)	113 (39·9)	23 (16·8)
Upper abdominal pain	56 (20·1)	64 (22·6)	11 (8·0)
Abdominal pain	55 (19·7)	45 (15·9)	7 (5·1)
Nausea	30 (10·8)	24 (8·5)	5 (3·6)
Flatulence	15 (5·4)	16 (5·7)	7 (5·1)
Vomiting	13 (4·7)	19 (6·7)	2 (1·5)
Pruritus	24 (8·6)	28 (9·9)	15 (10·9)
Erythema	27 (9·7)	23 (8·1)	3 (2·2)
Skin burning sensation	22 (7·9)	20 (7·1)	3 (2·2)
Nasopharyngitis	18 (6·5)	23 (8·1)	13 (9·5)
Flushing	51 (18·3)	46 (16·3)	2 (1·5)
Lymphopenia	28 (10·0)	30 (10·6)	0
Eosinophilia	25 (9·0)	17 (6·0)	0
Headache	23 (8·2)	23 (8·1)	14 (10·2)

TEAE, treatment-emergent AE.

Lymphopenia was reported in 28 patients (10.0%) in the LAS41008 group, with three patients (1.1%) considered severe (< 0.5 x 10^9 cells L.1), and in 30 (10.6%) patients in the Fumaderm group, with two patients (0.07%) considered severe. Proteinuria was reported in four patients (1.4%) in the LAS41008 group and in six patients (2.1%) in the Fumaderm group. Overall, the frequency and type of the reported TEAEs were very similar and did not differ significantly between the LAS41008 and Fumaderm groups (Table 9).

Twenty-three serious TEAEs were reported in 22 patients (3.2%, 2.8% and 3.6% of patients in the LAS41008, Fumaderm and placebo groups, respectively). Only four of these serious TEAEs, occurring in three patients randomized to Fumaderm, were assessed by the investigator as related to treatment (erosive gastritis, gastritis, gastric ulcer and gastroduodenitis).

One death considered unrelated to the medication was reported in a patient receiving Fumaderm (subendocardial ischaemia). No relationship between blood abnormalities and the onset of infections was detected.

Laboratory investigations
At week 16 or upon early treatment discontinuation, the mean total lymphocyte counts had decreased from baseline by 0.52 x10^9 cells L^{-1} in both the LAS41008 and Fumaderm groups, and by 0.08 x 10^9 cells L^{-1} in the placebo group.

Similarly, the mean leucocyte counts had decreased from baseline by 0.73 x10^9 and 0.69 x 10^9 cells L^{-1} in the LAS41008 and Fumaderm groups, respectively, compared with 0.04 x 10^9 cells L^{-1} in the placebo group. Lymphocyte counts below 0.7 x 10^9 cells L^{-1} were observed during the trial in 22 patients in the LAS41008 group (7.9%), 21 patients in the Fumaderm group (7.4%) and one patient in the placebo group (0.7%). Based on the available follow-up data, white blood cell counts progressively recovered after treatment with either LAS41008 or Fumaderm was stopped.

Evaluation comment

The safety profile was evaluated based on data of 699 patients. Comparable frequency of adverse events was observed in DMF and Fumaderm groups. Most of adverse events were considered mild in severity. Lymphopenia was reported in 10% of patients treated with DMF and 10.6% of patients from Fumaderm group.

Falkvoll S et al. 2019

The majority of patients (27/40) did not experience any difference in GI complaints after switching from the FAE mixture to the DMF product. Gastrointestinal tolerability was judged as better for the DMF product by 7/40 patients and worse by 2/40 patients. No GI complaints were reported with either drug product by 4/40 patients. Flushing was unchanged in 24/40 patients, 8/40 reported less flushing and 6/40 reported more flushing. Flushing did not occur with either drug product in 2/40 patients. Regarding the question of overall tolerability, 28/40 patients reported similar tolerability, 8/40 reported better tolerability with the DMF product and 4/40 said that tolerability was worse after switching. In answer to the question about skin status in general, 27/40 patients reported that it was unchanged after switching from the FAE mixture to the DMF product, patients, 7/40 reported that it was better and 6/40 said it was worse.

Evaluation comment

Overall, no significant differences in AEs and overall tolerability were observed after switching from DMF/MEF to DMF. 31/40 and 26/40 patients did not notice differences between DMF and DMF/MEF with respect to gastrointestinal symptoms and flushing, respectively.

Discussion on Safety

The safety of DMF/MEF combination in comparison to DMF was evaluated in four studies (Kolbach and Niebor (1992); Niebor et al., (1990); Mrowietz et al., (2017) and Falkvoll et al., (2019)).

Although in Kolbach and Niebor (1992) study higher percentage of patients from DMF group discontinued the therapy compared to DMF/MEF group (16% vs 18%), differences in both formulations (semi-enteric coated vs enteric coated) could contribute to the overall tolerability. Nevertheless, it should be noted that the amounts of DMF in the DMF/MEF combination were twice that of the DMF monotherapy.

Contrary, in Niebor et al., (1990) study, 30% from DMF/MEF group and 14% from DMF group discontinued the study due to AEs (nausea, vomiting, diarrhoea).

In Mrowietz et al., (2017) study, frequency of adverse events reported in DMF and Fumaderm groups was comparable.

Similarly, no significant differences in AEs and overall tolerability were observed after switching from DMF/MEF to DMF in Falkvoll et al., (2019) study.

In summary, no significant differences in the safety profiles of DMF compared to DMF/MEF combination were observed in the available studies.

Unsolicited submission received during the evaluation

During the assessment of the therapeutic contribution of MEF in Fumaderm, on 8 September 2021, the CHMP received an unsolicited submission from a company.

The unsolicited submission has been considered by the CHMP and supports its recommendation as outlined below (3. Recommendations and next steps).

3. Submission of additional scientific observations by an interested entity

On 1 October 2021, an interested entity submitted additional observations to the CHMP in response to the Rapporteurs' preliminary assessment report ("PAR").

The additional observations included, in particular, previously unsubmitted information relating to a pre-clinical study. In support of that information, it has been claimed that the associated study demonstrates that MEF is capable of producing an additive, synergistic benefit to DMF in a non-clinical disease model.

The Rapporteurs reviewed those additional observations including the pre-clinical study. Further to that assessment, it was found that these observations were not capable of altering their conclusion that the totality of the available data has not established that MEF has a clinically relevant therapeutic contribution within Fumaderm. The reasons for this are as follows:

First, the Rapporteurs reviewed the different elements of evidence, which was listed in support of the finding that MEF has a clinically relevant therapeutic contribution within Fumaderm. It was noted that the different elements of evidence put forward mainly reproduced the findings (and claims) that had been previously submitted to the CHMP. The only new element of evidence pertained to the non-clinical study mEAE-012 (which will be discussed below).

Second, the results from the non-clinical study mEAE-012 were taken into account. These results stemmed from an experiment conducted in an experimental autoimmune encephalomyelitis (EAE) model, which was designed to compare the impact of treatment with DMF or MEF monotherapy with a combination of DMF+MEF on clinical and histopathological characteristics. Of note, neither the literature reference nor the study report was provided and as such details of the study are not available.

However, a number of shortcomings were identified in relation to the usefulness of this pre-clinical study.

The interested entity has neither provided a study protocol nor a statistical analysis plan. In the absence of this information, it is unclear whether this is a therapeutic non-clinical exploratory study or a therapeutic non-clinical confirmatory study.

However, the definitions of the primary and secondary endpoints for this study have not been provided.

Additionally, no information has been provided about how the entity addressed the inflation of the type I error rate as a result of multiple testing (multiplicity). In absence of a pre-specification of a primary endpoint and information on control of multiplicity, a conclusion on statistically significant effect cannot be reached and the statistically significant claims submitted for the aforementioned differences cannot be accepted.

Altogether considered, these results are considered exploratory and difficult to interpret. Consequently, clear conclusions could not be made based on the presented histopathological examination results.

Moreover, it is not clear how the doses used in mice correspond to the doses used in humans.

In conclusion, although the available non-clinical data could suggest a different impact of DMF+MEF combination on progression of EAE in mice, compared to DMF monotherapy, taking into account the

presented results and the above-described limitations, this data cannot be relied upon to establish the non-clinical efficacy of MEF within Fumaderm.

Without prejudice to the above, it also bears noting that, while it is true that (an) active substance(s) within a fixed combination medicinal product may have additive or synergistic effects, it is expected that clinical data is presented for the purpose of establishing its contribution to the overall effect in terms of efficacy. In particular, compelling mechanistic (in vitro data), preclinical and pharmacodynamic data could be adduced to support a claim of improved efficacy within the fixed combination medicinal product. That being so, improved efficacy over (an) individual active substance(s) that have established efficacy in the targeted indication (namely, DMF) needs to be shown. The design of the pivotal clinical studies should be according to specific clinical guidance, where placebo or standard of care – instead of those individual active substances - may be acceptable as comparators. A direct comparison against individual active substances with established efficacy in the targeted indication would however still be expected. More specifically, for the treatment of psoriasis, a three-armed, parallel-group studies with the active agent, placebo and comparative active treatment would be expected. Although the BRIDGE Study did take into account DMF, DMF+MEF and placebo, improved efficacy over DMF was not demonstrated.

The relevance of these non-clinical findings (either alone or in combination with the other elements of evidence presented) is limited in the context of the overall assessment, as these findings (account being taken of their above-outlined shortcomings) cannot suffice to establish the clinically relevant therapeutic contribution of MEF in the combination treatment. In that regard, the claim that MEF has an additive, synergistic effect within Fumaderm has not been demonstrated.

In light of all of the above and having taken into account all the available evidence (including the above-described non-clinical study), the additional observations submitted have not demonstrated that MEF has a clinically relevant therapeutic contribution within Fumaderm and the Rapporteurs' conclusion remains unchanged.

4. Recommendations and next steps

The CHMP reviewed all above-mentioned studies and data. The CHMP also considered all data submitted by the interested entities, including the data submitted by a company on 8 September 2021.

The available non-clinical data even if not extensive is not scarce and it suggests a potential PD effect and PK differences.

The available clinical data is not conclusive for the purpose of establishing that MEF has a clinically relevant therapeutic contribution within Fumaderm. Whilst said clinical data, including two clinical trials (Nieboer et al., 1990 and Mrowietz et al, 2017) showing numerical differences in favour of the DMF/MEF combination vs. DMF alone in psoriasis, may be indicative that MEF contributes to the efficacy of Fumaderm in the treatment of psoriasis to a small extent, this would need to be confirmed by appropriate data that demonstrate a clinically relevant therapeutic effect. In that respect, the evaluated data suffer, in part, from severe methodological limitations, including:

- Differences in DMF doses administered and differences in formulations (Kolbach and Nieboer, 1992);
- Small sample size and short duration (Nieboer, 1989; Nieboer, 1990);
- Lack of appropriate methods to account for missing data, intercurrent events and control for multiplicity (Nieboer, 1989 and Nieboer, 1990); and
- Lack of properly designed studies to demonstrate superiority of DMF/MEF over DMF (Kolbach and Nieboer, 1992; Mrowietz et al., 2017; Falkvoll S et al., 2019).

Taking into account the described results, including the severe methodological limitations of the clinical studies, it cannot be concluded based on these data that a clinically relevant therapeutic effect of MEF in Fumaderm has been demonstrated.

Therefore, the CHMP concludes that the totality of the available data cannot establish that MEF exerts a clinically relevant therapeutic contribution within Fumaderm.

Further to the above, the Rapporteurs recommend adoption of the opinion.

5. References

Altmeyer PJ, Matthes U, Pawlak F, Hoffmann K, Frosch PJ, Ruppert P, Wassilew SW, Horn T, Kreysel HW, Lutz G, Barth J, Rietzschel I, Joshi RK. Antipsoriatic effect of fumaric acid derivatives. J Am Acad Dermatol. 1994; 30: 977-81.

Atwan A, Ingram JR, Abbott R, Kelson MJ, Pickles T, Bauer A, Piguet V. Oral fumaric acid esters for psoriasis. Cochrane Database of Syst Rev. 2015.

Falkvoll S, Gerdes S, Mrowietz U. Switch of psoriasis therapy from a fumaric acid ester mixture to dimethyl fumarate monotherapy: results of a prospective study. J Dtsch Dermatol Ges. 2019; 17(9):906-912.

Gollnick H, Altmeyer P, Kaufmann R, Ring J, Christophers E, Pavel S, Ziegler J. Topical calcipotriol plus oral fumaric acid is more effective and faster acting than oral fumaric acid monotherapy in the treatment of severe chronic plaque psoriasis vulgaris. Dermatology 2002; 205(1): 46-53.

Hagedorn M, Kalkoff KW, Kiefer G, Baron D, Hug J, Petres J. Fumaric acid monoethylester: Effect on DNA-synthesis and preliminary findings in experimental studies in animals. 1975; 254(1): 67-73.

Kolbach DN, Nieboer C. Fumaric acid therapy in psoriasis: results and side effects of 2 years of treatment. J Am Acad Dermatol. 1992 Nov; 27(5 Pt 1): 769-71.

Landeck L, Asadullah K, Amasuno A, et al. Dimethyl Fumarate (DMF) vs. Monoethyl Fumarate (MEF) Salts for the Treatment of Plaque Psoriasis: a Review of Clinical Data. Arch Dermatol Res. 2018;310:475–483.

Langner A et al. Results of a phase II study of a novel oral fumarate, BG-12, in the treatment of severe psoriasis. J Europ Academ Dermatol Venereol 2004; 18(6):798.

Lijnen R, Otters E, Balak D, Thio B. Long-term safety and effectiveness of high-dose dimethylfumarate in the treatment of moderate to severe psoriasis: a prospective single-blinded follow-up study. J Dermatolog Treat. 2016; 27: 31-6.

Mrowietz U, Reich K, Spellman MC. Efficacy, safety and quality of life effects of a novel oral formulation of dimethyl fumarate in patients with moderate to severe plaque psoriasis. Results of a phase 3 study. J Am Academ Dermatol 2006: 54 (3) Suppl.: AB202.

Nieboer C, de Hoop D, van Loenen AC, Langendijk PN, van Dijk E. Systemic therapy with fumaric acid derivates: new possibilities in the treatment of psoriasis. J Am Acad Dermatol. 1989; 20(4): 601-608.

Nieboer C, Langendijk PN, van Loenen AC, Gubbels J. Fumaric acid therapy in psoriasis: a double-blind comparison between fumaric acid compound therapy and monotherapy with dimethylfumaric acid ester. Dermatologica, 1990; 181(1):33-7.

Peeters AJ, Dijkmans BA, van der Schroeff JG. Fumaric acid therapy for psoriatic arthritis. A randomized, double-blind, placebo-controlled study. Br J Rheumatol 1992; 31: 502-4.

Rostami-Yazdi M, Clement B, Mrowietz U. Pharmacokinetics of anti-psoriatic fumaric acid esters in psoriasis patients. Arch Dermatol Res. 2010; 302(7): 531-538.

Skilarence – EPAR.

Sarheim BS, Joshi RK, Speiser P. Psoriatic fibroblasts in cell culture. Contribution to the mode of action of fumarates in psoriasis treatment. Department of Pharmacy, Swiss Federal Institute of Technology. Zürich, 1990.

Sebök B, Bonnekoh B, Geisel J, Mahrle G. Antiproliferative and cytotoxic profiles of antipsoriatic fumaric acid derivatives in keratinocyte cultures. Eur J Pharmacol. 1994; 270(1): 79-87.

Sebök B, Bonnekoh B, Vetter R, Schneider I, Gollnick H, Mahrle G. The antipsoriatic dimethyl-fumarate suppresses interferon-gamma -induced ICAM-1 and HLA-DR expression on hyperproliferative keratinocytes. Quantification by a culture plate-directed APAAP-ELISA technique. Eur J Dermatol. 1998; 8(1): 29-32.

Tecfidera – EPAR.

Thio HB, Zomerdijk TP, Oudshoorn C, Kempenaar J, Nibbering PH, van der Schroeff JG, Ponec M. Fumaric acid derivatives evoke a transient increase in intracellular free calcium concentration and inhibit the proliferation of human keratinocytes. Br J Dermatol. 1994; 131(6): 856-861.

Walker F, Adamczyk A, Kellerer C, et al. Fumaderm® in Daily Practice for Psoriasis: Dosing, Efficacy and Quality of Life. Br J Dermatol. 2014;171:1197–1205.

Wipke BT, Hoepner R, Strassburger-Krogias K, Thomas AM, Gianni D, Szak S, Brennan MS, Pistor M, Gold R, Chan A, Scannevin RH. Different Fumaric Acid Esters Elicit Distinct Pharmacologic Responses. Neurol Neuroimmunol Neuroinflamm. 2021; 8(2): e950.