EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 February 2022
EMA/150754/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dimethyl fumarate Polpharma

International non-proprietary name: dimethyl fumarate

Procedure No. EMEA/H/C/005955/0000

Note

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

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List of abbreviations

ANOVA	Analysis of variance
AAS	Atomic Absorption Spectrometry
AP	Applicant's Part (or Open Part) of a ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ARR	Annualized Relapse Rate
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AUCinf	Area under the plasma concentration-time curve from time zero to infinity
AUCt	Area under the plasma concentration-time curve from time zero to time t
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
Cmax	Maximum plasma concentration
CMS	Concerned Member State
CNS	Central Nervous System
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
CTD	Common Technical Document
CYP	Cytochrome P450
DMF	Dimethyl fumarate
DMT	Disease-Modifying Treatment
DP	Decentralised (Application) Procedure
DPM	Drug Product Manufacturer
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EP	European Pharmacopoeia

FT-IR	Fourier Transform infrared spectroscopy
GC	Gas chromatography
Gd(+)	Gadolinium enhancing lesion
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICP-OES	Inductively coupled plasma – optical emission spectroscopy
IMP	Investigational Medicinal Product
IPC	In-process control
IR	Infrared
ISR	Incurred Sample Reanalysis
IU	International Units
LC-MS/MS	Liquid Chromatography with tandem Mass Spectrophotometry
LDPE	Low Density Polyethylene
LLOQ	Lower Limit of Quantitation
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MEB	Medicines Evaluation Board
MEK	Methyl ethyl ketone
MMF	Monomethyl fumarate
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MS	Mass Spectrometry (Quality part)
MTBE	Methyl *tert*-Butyl Ether
ND	Not detected
NEDA	No Evidence of Disease Activity
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
Nrf2	Nuclear factor-like-2

NtA	Notice to Applicants
OC	Oral Contraceptive
OOS	Out of Specifications
OTC	Over the Counter
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PK	Pharmacokinetics
PL	Package Leaflet
PP	Polypropylene
PPMS	Primary Progressive Multiple Sclerosis
PVC	Poly vinyl chloride
QC	Quality Control
QOS	Quality Overall Summary
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of a ASMF
RRMS	Relapsing-Remitting Multiple Sclerosis
RRT	Relative retention time
RSD	Relative standard deviation
SmPC	Summary of Product Characteristics
SPMS	Secondary Progressive Multiple Sclerosis
T1/2	Elimination half-life
TGA	Thermo-Gravimetric Analysis
TEA	Triethylamine
Th	T helper cell
Tlag	Lag time
Tmax	Time to reach maximum plasma concentration
Tmax	Time to reach maximum plasma concentration following drug administration
TTC	Threshold of Toxicological Concern
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet

XRD	X-Ray Diffraction

* This is a general list of abbreviations. Not all abbreviations will be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Zaklady Farmaceutyczne Polpharma S.A. submitted on 30 May 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Dimethyl fumarate Polpharma, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 December 2017.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Treatment of adult patients with relapsing remitting multiple sclerosis.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and bioequivalence studies with the reference medicinal product Tecfidera instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Tecfidera, 120 mg and 240 mg hard capsules.
- Marketing authorisation holder: Biogen Netherlands B.V.
- Date of authorisation: 30-01-2014
- Marketing authorisation granted by:
  - Union
- Marketing authorisation numbers:
  120 mg: EU/1/13/837/001, 240 mg: EU/1/13/837/002, 003

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Tecfidera, 120 mg and 240 mg hard capsules.
- Marketing authorisation holder: Biogen Netherlands B.V.
- Date of authorisation: 30-01-2014
- Marketing authorisation granted by:
  - Union
- Marketing authorisation numbers:
  120 mg: EU/1/13/837/001, 240 mg: EU/1/13/837/002, 003

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Tecfidera, 240 mg hard capsules
- Marketing authorisation holder: Biogen Netherlands B.V.
- Date of authorisation: 30-01-2014
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation numbers: EU/1/13/837/002, 003
- Bioavailability study numbers: 2149 and 2150

Additional considerations in relation to the regulatory data protection period of Tecfidera

By its Judgment of 5 May 2021 in Case T-611/18, *Pharmaceutical Works Polpharma v EMA*,[1] 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 and assessment report adopted by the CHMP on 11 November 2021).[2]

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 generic application, from any marketing protection. This position is without prejudice to the outcome of the above referenced appellate proceedings.

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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.

[1] 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.

[2] In this respect, see: the Appendix to the present assessment report.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Ewa Balkowiec Iskra Co-Rapporteur: N/A

The application was received by the EMA on	30 May 2021
The procedure started on	17 June 2021
The ad hoc assessment relating to the therapeutic effect of monoethyl fumarate salts (MEF) within Fumaderm started on	24 June 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	6 September 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	19 September 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 October 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	10 November 2021
The CHMP concluded that the totality of the available data cannot establish that MEF exerts a clinically relevant therapeutic contribution within Fumaderm on	11 November 2021
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	13 December 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 January 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on.	27 January 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	31 January 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	9 February 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Dimethyl fumarate Polpharma on	24 February 2022

2. Scientific discussion

2.1. Introduction

This application concerns a generic application according to article 10(1) of Directive 2001/83/EC for Dimethyl fumarate Polpharma 120 and 240 mg hard capsules.

The reference product is Tecfidera 120 mg and 240 mg hard capsules. Tecfidera was approved in Europe on 30 January 2014 (MAA No: EU/1/13/837/001-003, Biogen Netherlands B.V.).

The proposed indication for Dimethyl fumarate Polpharma is the same as for the reference product Tecfidera: treatment of adult patients with relapsing remitting multiple sclerosis.

To support the application the Applicant submitted two pivotal bioequivalence studies between Dimethyl fumarate Polpharma 240 mg hard capsules and reference product Tecfidera 240 mg hard capsules in order to assess the bioequivalence between the products. A biowaiver for the additional 120 mg strength was requested.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard gastro-resistant capsules containing 120 mg and 240 mg of dimethyl fumarate as active substance.

Other ingredients are:

Capsule content: croscarmellose sodium, silica, colloidal anhydrous, sodium stearyl fumarate, methacrylic acid - methyl methacrylate copolymer (1:1), methacrylic acid - ethyl acrylate copolymer (1:1) dispersion 30 per cent, talc, triethyl citrate, polysorbate 80, and glycerol monostearate 40-55;

Capsule: gelatin, titanium dioxide (E171), yellow iron oxide (E172), brilliant blue FCF (E133);

Capsule ink: shellac glaze, black iron oxide (E172), propylene glycol (E1520), ammonium hydroxide 28%.

The product is available in aluminium/PVC/PVDC blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of the active substance is dimethyl (E)-but-2-enedioate corresponding to the molecular formula $C_6H_8O_4$. It has a relative molecular weight of 144.13 and the following structure:

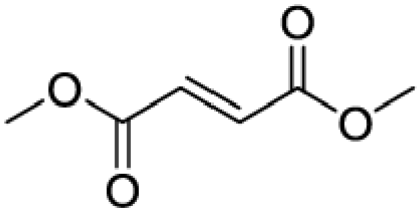

Figure 1: Active substance structure

The chemical structure elucidated by a combination of thermal analysis by DSC, UV study, FT-IR study, NMR Study (^{1}HNMR and ^{13}CNMR), mass spectra, X-ray powder diffraction, and elemental analysis.

The active substance is a non-hygroscopic, white to off-white powder, highly soluble in buffer solutions of pH 1.2, 4.5 and 6.8 at room temperature (25 °C).

Two geometric isomers/stereoisomers *Cis* and *Trans* exist. *Trans* isomer is thermodynamically stable and is the desired isomer. Undesired isomer (cis-isomer) is not possible in the active substance.

Polymorphism has not been observed for active substance.

Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturer. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Dimethyl fumarate is synthesized in 1 main step using well-defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for starting materials and reagents have been presented.
A discussion concerning possible organic and inorganic impurities, potential genotoxic impurities, nitrosamine impurities, elemental impurities and residual solvents have been presented. Further details concerning potential impurities, control strategy, supporting analytical data and analytical methods validation reports were provided in the restricted part (RP) of the ASMF documentation. Impurities originating from starting material, or from solvents (benzene) are provided in the RP ASMF.

The characterisations of the active substance and its impurities are in accordance with the EU guideline.

Potential and actual impurities were well-discussed with regards to their origin and characterised.

Specification

The active substance specification , includes tests for description (visual), solubility (Ph. Eur.), identification (IR, HPLC), water content (Ph. Eur.), sulphated ash (Ph. Eur.), related substance (HPLC), assay (HPLC), and residual solvents (GC).

The active substance specification covers all required parameters and is acceptable. The impurity levels are within the qualification threshold according to ICH Q3A and this was considered satisfactory.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data on 3 commercial scale batches of non- micronized and micronized of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of the non-micronised active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

Stability data from 3 commercial scale batches of the micronised active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions (5 ºC) and for up to 6 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* description, identification, water, related substances and assay (on anhydrous basis)*.* The analytical methods used were the same as for release and were stability indicating.

The stability results indicate that the unmicronised and micronised active substance manufactured by the proposed supplier is sufficiently stable.

The stability results justify the proposed retest period of 48 months stored at temperature 2-8 °C for the unmicronised active substance and 36 months for micronised material in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The 120 mg strength finished product is presented as a hard gelatin capsules, length: 19 mm, with white body and light-green cap, with overprint on the body 120 mg.

The 240 mg strength finished product is presented as a hard gelatin capsules, length: 23 mm, light-green, with overprint on the body 240 mg .

The primary goal of the development was to formulate a finished product that could be easily manufactured, that would be stable in the proposed packaging and that would be essentially similar to the reference medicinal product Tecfidera. The reference product is a multiparticulate dosage form – hard gelatin capsule filled with enteric coated minitablets. It was decided that the developed product should have similar (multiparticulate) design, however the form of the capsule filling will be different from the reference medicinal product. A product in form of hard gelatin capsules filled with granules coated with gastroresistant polymers has been developed.

Compatibility tests of the active substance with the prosed excipients were performed in order to detect potential incompatibilities, which could be observed in final formulation. No remarkable interactions between dimethyl fumarate and the excipients selected for the final formulation were found.

The selection of excipients was made mainly based on the composition of the reference medicinal product as well as based on the development experiments. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Two pivotal bioequivalence studies with the 240 mg strength under fast and fed conditions have been carried out between the generic and the reference medicinal product. The results of the studies confirmed bioequivalence of the developed generic product with the reference product.

A detailed description of the manufacturing process development has been provided.

The primary packaging is Al/PVC/PVDC blister packs. Primary packaging materials comply with the requirement of Commission Regulation (EU) no. 10/2011 of 14 January 2011 as amended and with the Ph. Eur. (chapter 3.1.11. "Materials based on non-plasticized poly (vinyl chloride) for containers for dry dosage forms for oral administration"). The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by two manufacturing sites.

The manufacturing process consists of 16 main steps.

Holding time for the in-bulk product has been established by appropriate stability studies discussed below in this report.

Major steps of the manufacturing process have been validated by a number of studies in 3 commercial scale batches per strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing

Product specification

The finished product release specifications, shown in **Error! Reference source not found.**, include appropriate tests for this kind of dosage form: appearance (visual), appearance of capsule content (visual), capsule average net weight (weight), uniformity of dosage units (Ph. Eur.), identification of titanium dioxide (chemical identification), identification of yellow iron oxide (E172) (chemical identification), identification of brilliant blue FCF –FD&C Blue 1 (E133) (UV/VIS), water content in filling of capsule (KF), identification of dimethyl fumarate (HPLC, GC), related substances (HPLC), assay of dimethyl fumarate (HPLC), content of 2-propanol (GC), dissolution test, microbiological tests (Ph. Eur.), total aerobic microbial count (TAMC) (Ph. Eur.), total yeast / moulds count

The potential presence of elemental impurities in the finished product has been assessed by a risk-assessment in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product (requested as Major Objection) has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control is needed.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 3 commercial band pilot batches per strength manufactured by the two manufacturing sites confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 commercial batches per strength and per manufacturing site of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH), stored up to 12 months under intermediate conditions (30 ºC / 65% RH) for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, appearance of capsule content, capsules average net weight, water content in filling of capsules, related substances, assay, dissolution, total aerobic microbial count (TAMC), total yeasts/ moulds count (TYMC) and Escherichia coli. The analytical procedures used are stability indicating.

No significant changes have been observed under long term conditions. In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is considered as photo-stable. The product does not require any special protection form light.

Holding time studies were performed for the finished product to establish the in-bulk storage period before packaging in the immediate package. The batches were packed in PET-Al-PE multilayer bag and in PE bag and stored for up to 6 months under long term conditions (25 ºC / 60% RH). Based on the available data the total holding time should not take more than 6 months and is calculated from the first day of combining active ingredient with other ingredients according to CPMP/QWP/072/96 Guideline.

Based on available stability data, the proposed shelf-life of 24 months and the storage conditions "Do not store above 30 °C" as stated in the SmPC (section 6.3 and 6.4) are acceptable.

Adventitious agents

The hard capsules used in the product manufacturing contain gelatine obtained from bovine sources . Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. One issue was raised by CHMP as Major Objection (MO) related to nitrosamine risk assessment. The issue was resolved satisfactorily by the applicant as described above. The biowaiver for the 120 mg strength is in line with the Guideline on the Investigation of Bioequivalence and thus accepted. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment (ERA) has been submitted.

According to the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1), the Applicant estimated the PEC*surfacewater* for Dimethyl fumarate at 2.4 µg /L and phase II environmental effect analysis was performed.

Substance (INN/Invented Name): Dimethyl fumarate			
CAS-number (if available):			
PBT screening		***Result***	***Conclusion***
Bioaccumulation potential- log K_{ow}	OECD107 or …	0.82	Potential PBT (Y/**N**)
PBT-assessment			
PBT-statement :	The compound is considered as PBT		

Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	2.4	µg/L			> 0.01 threshold (**Y**/N)
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	37	µg/L	species
Daphnia sp. Reproduction Test	OECD 211	NOEC	55.9	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	45.7	µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	2000	µg/L	

In addition, it is noted that the introduction of Dimethyl fumarate Polpharma is unlikely to result in any significant increase in the combined sales volumes and exposure of the environment to dimethyl fumarate.

It is agreed that Dimethyl fumarate Polpharma does not present a risk to the environment.

2.3.3. Discussion on non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided and is adequate. The pharmacology, pharmacokinetics and toxicology data of dimethyl fumarate are well known, and thus new non-clinical data are not required. The impurity profile has been discussed and was considered acceptable.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

2.3.4. Conclusion on the non-clinical aspects

The CHMP considers the non-clinical aspects adequate to support this application.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for a generic product consisting of gastro-resistant hard capsules containing 120 mg and 240 mg of Dimethyl fumarate. To support the marketing authorisation application, the applicant conducted 2 bioequivalence studies with the 240 mg strength based on cross-over designs under fasting and fed conditions.

The applicant also provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of dimethyl fumarate based on published literature. The Product Information is in line with the SmPC of the reference product.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98), the 'Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms' (EMA/CHMP/EWP/280/96 Rev1), the 'Guideline on quality of oral modified release products' EMA/CHMP/QWP/428693/2013 and the EMA dimethyl fumarate gastro-resistant capsules 120 mg and 240 mg product-specific bioequivalence guidance (EMA/CHMP/421315/2017) are of particular relevance.

GCP aspect

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

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

Exemption

This application is for Dimethyl fumarate Polpharma 120 mg and 240 mg gastro-resistant hard capsules.

Bioequivalence was demonstrated for the 240 mg strength and a biowaiver for the additional 120 mg strength was requested. In line with the Guideline, this exemption required that the composition is proportional, the formulations contain identical granules and are produced by the same manufacturing process, and the dissolution profiles are similar.

The 2 strengths of Dimethyl fumarate Polpharma are manufactured by the same process and the same manufacturer (Pharmaceutical Works Polpharma SA). The qualitative composition is the same and the composition is proportional.

The dissolution tests were conducted with Dimethyl fumarate 240 mg and 120 mg on 12 capsules each.

The similarity of the dissolution profiles was shown and bioequivalence studies for additional 120 mg strength are not required.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study 2149

Title: A Single-Dose, Randomized, Open-Label, Four-Way, Fully Replicate, Pivotal, Bioequivalence Study of Dimethyl fumarate 240 mg Gastro-Resistant Hard Capsules (Pharmaceutical Works Polpharma S.A.) and TECFIDERA® (dimethyl fumarate) 240 mg Gastro- Resistant Hard Capsules (Biogen Idec Ltd.) in Healthy Male and Non-Pregnant Female Volunteers under Fasting Conditions.

Methods

- **Study design**

This was a pivotal, single-dose, randomized, open-label, four-period, two-sequence, two treatment, single-Centre, fully replicate study designed to evaluate the comparative bioavailability of monomethyl

fumarate from Dimethyl fumarate 240 mg gastro-resistant hard capsules and Tecfidera® 240 mg gastro-resistant hard capsules administered to healthy male and non-pregnant female subjects under fasting conditions. Subjects were randomly assigned to one of the two dosing sequences.

Duration of treatment:

The study consisted of four study periods. Each study period included a single-dose drug administration of either the Test product or the Reference product.

Drug Concentration Measurements

Blood samples were collected from 22 time points in each study period.

Treatments Administered:

In each study period, subjects were dosed according to the randomization scheme with one of the following treatments: Treatment A (1 x 240 mg Dimethyl fumarate gastro-resistant hard capsules) or Treatment B (1 x 240 mg Tecfidera® gastro-resistant hard capsules)
Each subject was scheduled to receive a total of two treatments (each treatment twice) by the end of the study.

	Period 1	Period 2	Period 3	Period 4
Sequence 1	A	B	A	B
Sequence 2	B	A	B	A

The washout interval between drug administrations was 3 days.

- **Population(s) studied**

Healthy volunteers were enrolled and dosed in Period 1 and completed the study in its entirety. The data were included in the pharmacokinetic and statistical analysis.

- **Analytical methods**

An analytical method, using a high-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS), was developed for analysing the metabolite monomethyl fumarate in human plasma.

Validation:

The validation report for the analytical method was provided. The acceptance criteria were met for the relevant parameters such as specificity, sensitivity, precision, accuracy, linearity, matrix effect, and dilution integrity.

- **Pharmacokinetic variables**

The following parameters were calculated:

AUCinf: Area under the concentration-time curve from time zero to infinity

AUCt: Area under the concentration-time curve from time zero until the last measurable concentration or last sampling time t, whichever occurs first.

Cmax: Maximal observed plasma concentration.

Residual Area or AUC(res%) Extrapolated area under the curve, (AUCinf - AUCt)/AUCinf.

T1/2: Terminal elimination half-life.

Tmax: Time when the maximal plasma concentration is observed.

λ: Terminal elimination rate constant.

- **Statistical methods**

The 90% confidence intervals of the Test/Reference ratios for AUCt, AUCinf, and Cmax were calculated. Power for treatment comparisons for the pharmacokinetic parameters was calculated as the probability (type I error fixed at the 5% level) of detecting a difference at least equal to 20% of the reference treatment mean.
The following standards were used to determine bioequivalence for monomethyl fumarate:
1. The Geometric Mean Ratio (GMR) of the test to reference product and associated 90% CI of the AUCt should be within 80% - 125% regardless of its variability.
2. The GMR of the test to reference product of the Cmax should be within 80% - 125%.
3. The 90% CI for the GMR of the test to reference product of the Cmax should be within the following limits, depending on the calculated SWR (within subject standard deviation of the reference product) of the ln-transformed Cmax. As per EMA guidance, the extent of the widening is defined based upon the within subject variability seen in the bioequivalence study using scaled-average bioequivalence according to [U, L] = exp (± k × SWR), where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760.
a) Lower limit of 80.00% to upper limit of 125.00%, if SWR ≤ 0.294 (i.e., CV ≤ 30%)
b) Lower limit of exp (-0.760 × SWR) × 100.00% to upper limit of exp (0.76×SWR)×100.00%, if 0.294 <SWR<0.472 (30% < CV <50%).
c) Lower limit of 69.84% to upper limit of 143.19%, if SWR ≥ 0.472 (CV≥50%)

Results

Table 3.3.2.1. Bioequivalence results of plasma monomethyl fumarate

Bioequivalence Results of Plasma- Monomethyl Fumarate

TREATMENT A vs TREATMENT B

Parameter (N_A/N_B)#	Geometric Means Arithmetic Means (CV %) TRT A		TRT B		Ratio of Geometric Means	90% Confidence Interval	Intra-Subject CV (%)
AUCt (ng.h/mL)	3861.98 3968.09	(22.08)	3962.89 4076.01	(22.41)	97.45	95.40 - 99.55	
AUCinf (ng.h/mL)	3941.93 4048.34	(21.61)	4011.69 4148.69	(22.37)	98.26	96.16 - 100.41	
Cmax (ng/mL)	2188.38 2342.27	(28.92)	2159.25 2295.22	(36.63)	101.16	96.23 - 106.34	
Tmax* (h)	2.33 (1.33 - 7.00)		2.33 (1.00 - 7.00)				
Lambda** (1/h)	1.0854 (30.25)		1.1745 (24.95)				
T1/2** (h)	0.73 (48.96)		0.65 (47.88)				
AUCt/AUCinf**	0.9885 (1.18)		0.9886 (1.87)				
AUC(res%)**	0.0115 (101.23)		0.0114 (161.88)				

** Presented as arithmetic mean (CV%) only
* Presented as median and range
# N_A: Number of observations for Treatment A; N_B: Number of observations for Treatment B

The final bioequivalence analysis results, based on the revised data to include the revised dilution factor (1:1), are included below:

Table 3.3.2.2. Bioequivalence results of plasma monomethyl fumarate (after inclusion of dilution factor 1:1)

Bioequivalence Results of Plasma- Monomethyl Fumarate (After Including Dilution Factor 1.1)

TREATMENT A vs TREATMENT B

Parameter (N_A/N_B)#	Geometric Means Arithmetic Means (CV %) TRT A	 TRT B	Ratio of Geometric Means	90% Confidence Interval	Intra-Subject CV (%)
AUCt (ng.h/mL)	3862.53 3969.36 (22.11)	3963.80 4076.88 (22.39)	97.45	95.37 - 99.56	
AUCinf (ng.h/mL)	3944.25 4051.58 (21.63)	4015.78 4156.37 (22.33)	98.22	96.10 - 100.39	
Cmax (ng/mL)	2191.35 2290.56 (28.93)	2159.72 2295.84 (36.62)	101.46	96.48 - 106.70	
Tmax* (h)	2.33 (1.00 - 7.00)	2.33 (1.00 - 7.00)			
Tlag* (h)	0.67 (0.33 - 3.67)	0.67 (0.33 - 4.67)			
Lambda** (1/h)	1.1373 (27.85)	1.1822 (27.09)			
T1/2** (h)	0.67 (37.32)	0.66 (55.69)			
AUCt/AUCinf**	0.9879 (1.25)	0.9875 (1.95)			
AUC(res%)**	0.0121 (101.76)	0.0125 (153.83)			

** Presented as arithmetic mean (CV%) only
* Presented as median and range
# N_A: Number of observations for Treatment A; N_B: Number of observations for Treatment B

- **Safety data**

A total of 102 mild AEs was experienced by the subjects after treatment with the Test product. A total of 117 mild AEs was experienced by the subjects after treatment with the Reference product.
The safety profiles of the Reference and the Test Product were comparable.

Study 2150:

Title: A Single-Dose, Randomized, Open-Label, Two-Way, Crossover, Pivotal, Bioequivalence Study of Dimethyl fumarate 240 mg Gastro-Resistant Hard Capsules (Pharmaceutical Works Polpharma S.A.)

and Tecfidera® (dimethyl fumarate) 240 mg Gastro-Resistant Hard Capsules (Biogen Manufacturing ApS) in Healthy Male and Non-Pregnant Female Volunteers under Fed Conditions.

Methods

- **Study design**

This was a pivotal, single-dose, randomized, open-label, two-period, two-sequence, two-treatment, single-centre, crossover study designed to evaluate the bioequivalence of monomethyl fumarate from Dimethyl fumarate 240 mg gastro-resistant hard capsules and Tecfidera® 240 mg gastro-resistant hard capsules administered to healthy non-smoking, male and non-pregnant female subjects under fed conditions. Subjects were randomly assigned to one of the two dosing sequences.

Duration of treatment:

The study consisted of two study periods. Each study period included a single-dose drug administration of either the Test product or the Reference product.

Drug Concentration Measurements
Blood samples were collected from 24 time points in each study period.

Treatments Administered:
In each study period, subjects were dosed according to the randomization scheme with one of the following treatments: Treatment A (1 × 240 mg Dimethyl fumarate Polpharma gastro-resistant hard capsules) or Treatment B (1 × 240 mg Tecfidera® gastro-resistant hard capsules).
Each subject was scheduled to receive a total of two treatments by the end of the study. The washout interval between drug administrations was 3 days.

	Period 1	Period 2
Sequence 1	A	B
Sequence 2	B	A

- **Population(s) studied**

Healthy volunteers were enrolled and dosed in Period 1 and completed the study in its entirety. The data were included in the pharmacokinetic and statistical analysis.

- **Analytical methods, pharmacokinetic variables and statistical methods**

Similar to the Study 2149 (see above).

Results

Table 3.3.2.4. Bioequivalence results of plasma monomethyl fumarate

Bioequivalence Results of Plasma Monomethyl Fumarate:

TREATMENT A vs TREATMENT B

Parameter (N_A /N_B)	Geometric Means Arithmetic Means (CV %) TRT A		TRT B		Ratio of Geometric Means	90% Confidence Interval	Intra-Subject CV (%)
AUCt (ng.h/mL)	3468.81 3545.86	(21.09)	3509.22 3601.21	(22.52)	98.85	95.62 - 102.19	
AUCinf (ng.h/mL)	3703.23 3780.10	(20.45)	3745.12 3805.26	(19.16)	98.88	95.07 - 102.85	
Cmax (ng/mL)	1372.61 1469.81	(37.04)	1528.82 1649.22	(36.72)	89.78	80.79 - 99.77	
Tmax* (h)	7.50 (5.00 - 10.50)		7.26 (4.50 - 10.63)				
Lambda** (1/h)	0.9089 (37.82)		1.1126 (40.68)				
T1/2** (h)	0.92 (50.61)		0.83 (76.47)				
AUCt/AUCinf**	0.9840 (1.14)		0.9799 (3.05)				
AUC(res%)**	0.0160 (70.36)		0.0201 (148.44)				

Note: N_A /N_B are the number of observations for Treatment A and B , respectively
*: Presented as median and range
**: Presented as arithmetic mean (CV%) only
** Presented as arithmetic mean (CV%) only
* Presented as median and range
# N_A: Number of observations for Treatment A; N_B: Number of observations for Treatment B

The final bioequivalence analysis results, based on the revised data to include the revised dilution factor (1:1), are included below:

Table 3.3.2.5. Bioequivalence results of plasma monomethyl fumarate (including dilution factor 1:1)

Bioequivalence Results of Plasma- Monomethyl Fumarate (After Including Dilution Factor 1.1)

TREATMENT A vs TREATMENT B

Parameter (N_A / N_B)	Geometric Means Arithmetic Means (CV %) TRT A		TRT B		Ratio of Geometric Means	90% Confidence Interval	Intra-Subject CV (%)
AUCt (ng.h/mL)	3447.27 3527.44	(21.55)	3485.86 3575.36	(22.43)	98.89	95.81 - 102.07	
AUCinf (ng.h/mL)	3699.86 3779.87	(20.64)	3750.33 3811.29	(19.36)	98.65	94.83 - 102.63	
Cmax (ng/mL)	1372.61 1469.81	(37.04)	1534.91 1659.44	(37.44)	89.43	80.46 - [illegible]	
Tmax* (h)	7.50 (5.00 - 10.50)		7.26 (4.50 - 10.63)				
Tlag* (h)	4.00 (1.00 - 7.52)		5.00 (1.00 - 7.52)				
Lambda** (1/h)	0.9080 (40.03)		1.1051 (41.11)				
T1/2** (h)	0.93 (51.17)		0.84 (75.87)				
AUCt/AUCinf**	0.9830 (1.09)		0.9790 (3.02)				
AUC(res%)**	0.0170 (62.88)		0.0210 (140.62)				

The Test/Reference ratio of geometric means and the corresponding 90% confidence intervals for the ln-transformed AUCinf, AUCt and Cmax parameters were entirely contained within the acceptance range of 80.00% to 125.00%.

- **Safety data**

A total of 25 AEs was experienced by the subjects after treatment with the Test product. A total of 35 AEs was experienced by the subjects after treatment with the Reference product. The safety profiles of the Reference and the Test Product were comparable

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.2.3. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.3. Discussion on clinical aspects

Two separate bioequivalence studies under fasting and fed conditions were provided to demonstrate that Dimethyl fumarate Polpharma gastro-resistant hard capsules, 240 mg, is bioequivalent to the reference product Tecfidera.

Generally, the design of the bioequivalence studies is considered acceptable:

The choice of analyte (monomethyl fumarate) is in line with product-specific bioequivalence guidance (EMA/CHMP/421315/2017) and is endorsed.

The chosen study population (healthy volunteers) is appropriate. The validation method was performed according to the procedure recommended in the guidelines.

The point estimates and 90% confidence intervals for the ln-transformed pharmacokinetic variables Cmax and AUC were within the predefined bioequivalence range of 80% - 125% in both studies.

Dimethyl fumarate Polpharma gastro-resistant 240 mg hard capsules can therefore be considered bioequivalent with Tecfidera gastro-resistant 240 mg hard capsules.

The safety profiles of the both products were comparable, and no serious adverse events were reported.

According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) and the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1), the biowaiver criteria are met and the CHMP agreed that the results of the bioequivalence studies can be extrapolated to the additional 120 mg strength.

2.4.4. Conclusions on clinical aspects

Based on the bioequivalence studies and in line with the Guideline on the Investigation of Bioequivalence, Dimethyl fumarate Polpharma 240 mg is considered bioequivalent with Tecfidera 240 mg.

In addition, considering that the criteria for a biowaiver are met, the CHMP agreed that no additional *in vivo* bioequivalence study with the remaining strength 120 mg was needed. Dimethyl fumarate Polpharma 120 mg and 240 mg gastro-resistant capsules were thus considered essentially similar to the reference product Tecfidera.

Taken together, the CHMP concluded that the available clinical data were adequate to support the application for Dimethyl fumarate Polpharma 120 mg and 240 mg gastro-resistant capsules as a generic medicinal product to Tecfidera.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Progressive Multifocal Leukoencephalopathy (PML) Decreases in leukocyte and lymphocyte counts Drug-induced liver injury
Important potential risks	Serious and opportunistic infections (other than PML)

Summary of safety concerns	
	Malignancies Effects on pregnancy outcome Interaction with nephrotoxic medications leading to renal toxicity
Missing information	Safety profile in patients over the age of 55 years Safety profile in patients with renal impairment Safety profile in patients with hepatic impairment Safety profile in patients with severe active GI disease Long term efficacy and safety Increased risk of infection in patients concomitantly taking anti-neoplastic or immunosuppressive therapies

2.5.2. Pharmacovigilance plan

The following routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are included:

Specific adverse reaction follow-up questionnaires for risk of progressive Multifocal Leukoencephalopathy (PML), drug-induced liver injury, serious and opportunistic infections (other than PML) and malignancies.

No additional pharmacovigilance activities are deemed necessary.

2.5.3. Risk minimisation measures

It is agreed that routine risk minimisation measures are considered sufficient. The safety information in the Product Information is aligned to the reference product.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

It is however noted that an updated RMP for the reference product was agreed in January 2022, including additional specific adverse reaction follow-up questionnaires for the safety concerns Moderate Lymphopenia and Severe Lymphopenia (Decreases in leukocyte and lymphocyte counts). The applicant agreed to update the RMP via a variation procedure promptly following the approval of the MAA in order to include the additional questionnaires.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

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

2.6.2. Periodic Safety Update Reports submission requirements

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

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Atorvadyina (5mg and 10 mg coated tablets). The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of dimethyl fumarate gastro-resistant hard capsule. The reference product Tecfidera is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis. No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

Two pivotal bioequivalence studies were performed. The studies (single dose, randomised, cross-over, under fasting and fed conditions) were considered adequate to evaluate the bioequivalence of Dimethyl fumarate Polpharma and were in line with the respective European requirements and the product specific guidance in terms of design, analyte (metabolite) and parameters for bioequivalence assessment. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Dimethyl fumarate Polpharma 240 mg gastro-resistant hard capsule met the protocol-defined criteria for bioequivalence when compared with the Tecfidera 240 mg gastro-resistant hard capsule. The point estimates and their 90% confidence intervals for the parameters AUCinf, AUCinf and Cmax were all contained within the protocol-defined acceptance range of 80 to 125% in fasting and fed conditions. Bioequivalence of the two formulations was demonstrated.

In addition, the criteria for a biowaiver are met and the CHMP agreed that no additional *in vivo* bioequivalence study with the additional 120 mg strength was needed. Dimethyl fumarate Polpharma 120 mg and 240 mg gastro-resistant capsules were thus considered essentially similar to the reference product Tecfidera.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Dimethyl fumarate Polpharma is favourable in the following indication:

Dimethyl fumarate Polpharma is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (see section 5.1 for important information on the populations for which efficacy has been established).

The CHMP therefore recommends the granting of the marketing authorisation, subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

5. Appendix

5.1. CHMP Opinion on the ad hoc assessment relating to the therapeutic effect of monoethyl fumarate salts (MEF) within Fumaderm and CHMP ad hoc Assessment Report, as adopted on 11 November 2021

EMA/CHMP/304446/2022

CHMP Assessment Report

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

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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.[3]

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).[4] 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.[5]

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.[6]

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.[7]

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

[4] 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".

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

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

[7] 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 1: 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 2: 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 3: 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*.

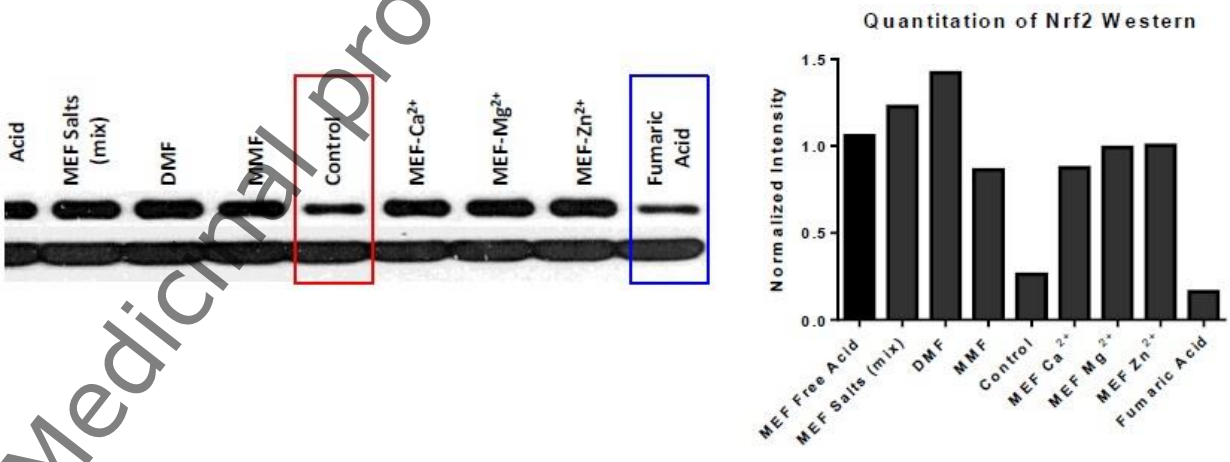
In all non-clinical investigations, the ratio of the calcium, magnesium, and zinc salts of MEF was 87:5:3 Ca-MEF, Mg-MEF, Zn-MEF, respectively, based on molecular weight. This reflects the ratio of these MEF salts in Fumaderm.

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 2).

Figure 2: MEF salts increase Nrf2 protein in Cos-1 cells

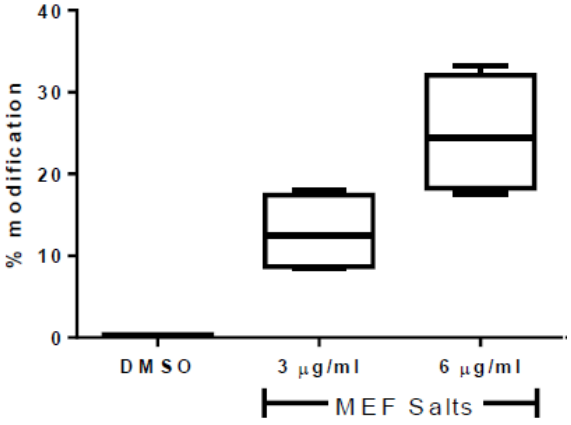


COS-1 cells were treated with 9 µg/ml of individual calcium, magnesium or zinc salts of MEF, with a mixture of MEF salts, the free acid form of MEF, DMF, MMF, FA or the vehicle control DMSO (boxed in red) to illustrate the basal Nrf2 level. Cells were harvested after 24 h and extracts analysed by Western 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 3). 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 3: The mixture of MEF salts modifies Keap 1 at Cys151

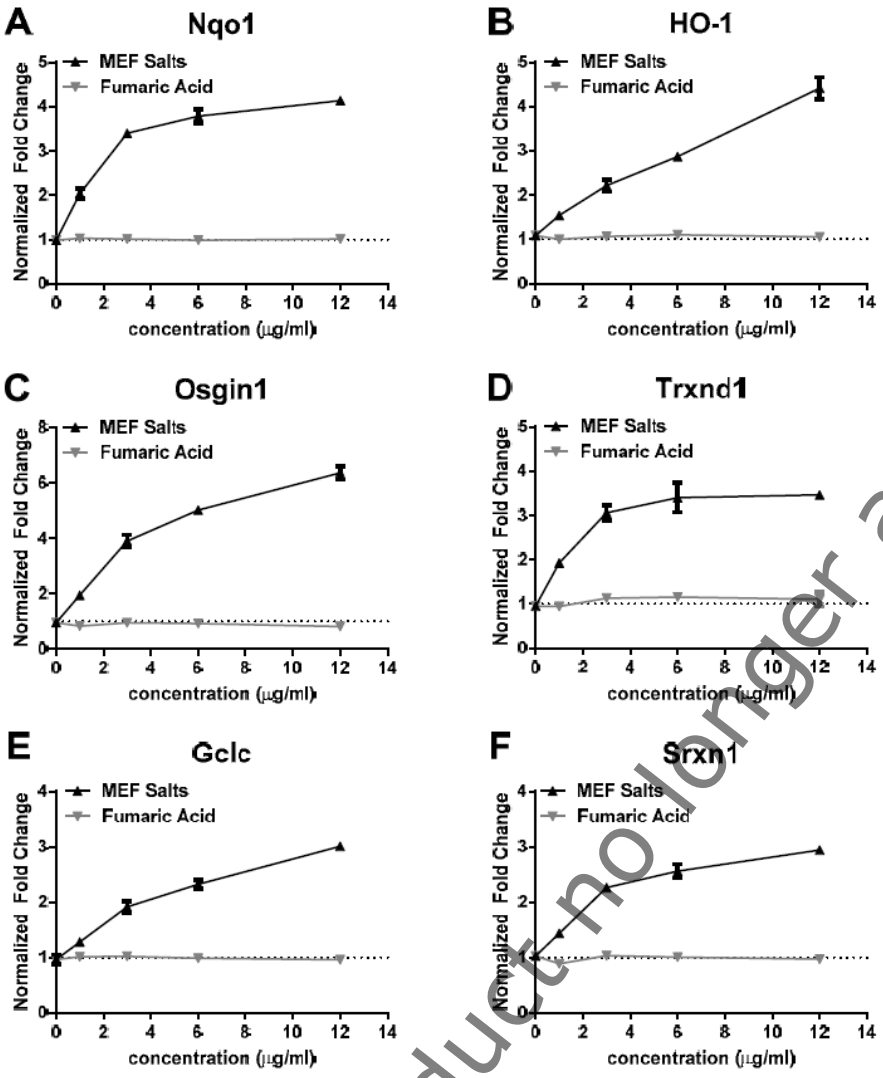


HEK293 cells were transfected with Keap1 and subsequently treated with either DMSO (control) or 3 or 6 µg/ml of calcium, magnesium and zinc salts of MEF. Keap1was immunopurified, fractioned by gel electrophoresis and then excised from the gel. The gel slice was reduced by DTT, alkylated by iodoacetamide, 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 4). 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 4: The mixture of MEF salts induces Nrf2-dependent gene expression

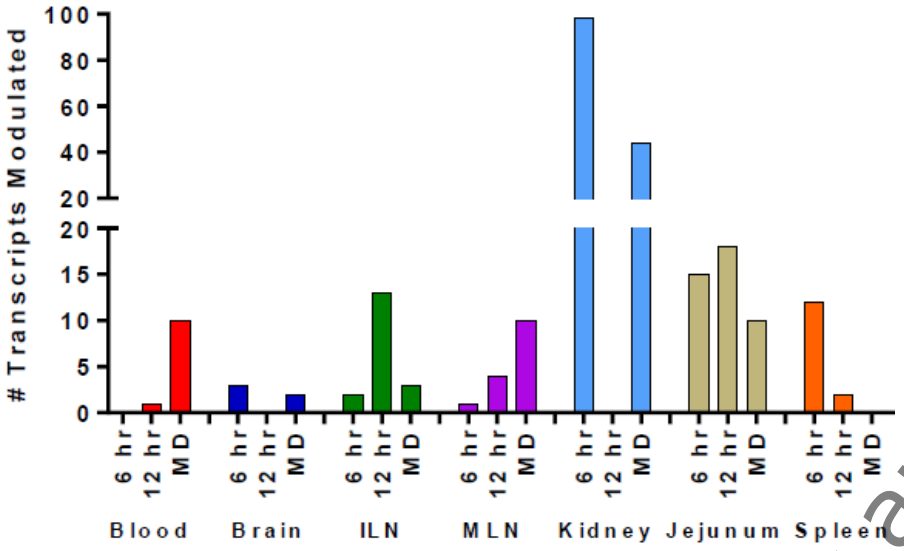


Human astrocytes were treated with a mixture of calcium, magnesium and zinc salts of MEF or fumaric acid. Transcriptional changes were evaluated by RT-PCR 24 h after treatment. (A) Nqo1, (B) HO-1, (C) Osgin 1, (D) Trxnd1, (E) (Gclc), (F) sulfiredoxin 1 (Srxn1). Responses have been normalised as a fold 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 5). MEF exposure in plasma and tissues was verified in a separate cohorts of animals.

Figure 5: The mixture of MEF salts significantly modulates tissue-specific transcription

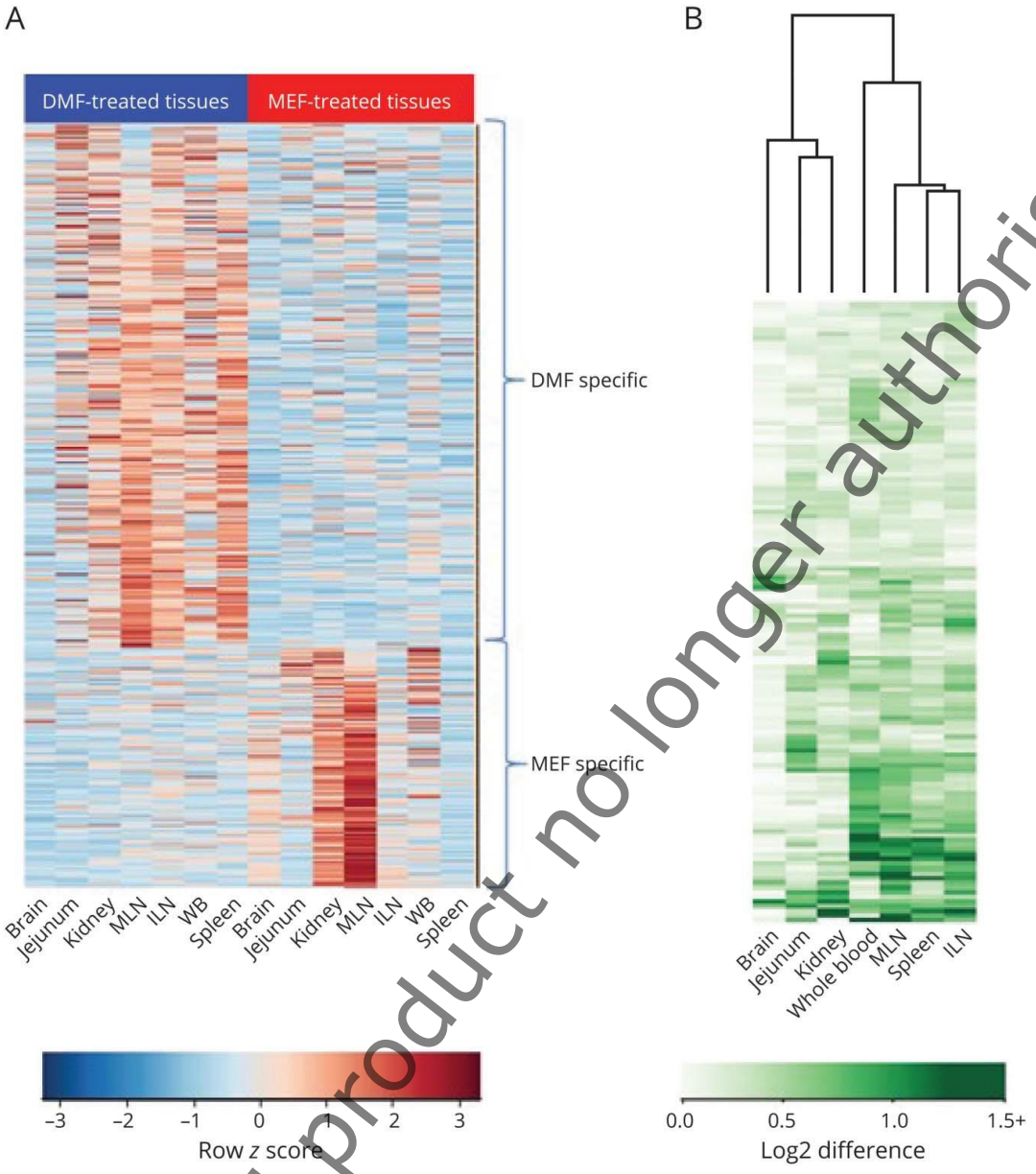


C57Bl/6 mice received single or repeated oral doses of 79.2 mg/kg MEF salts for 10 days (equivalent to 100 mg/kg DMF). Fumaric acid was not tested due to its lack of activity in previous investigations in vitro (see above). Transcriptional responses were evaluated by Affymetrix microarrays at 6 and 12 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 7). 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 6A). 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 6B).

Figure 6: 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.

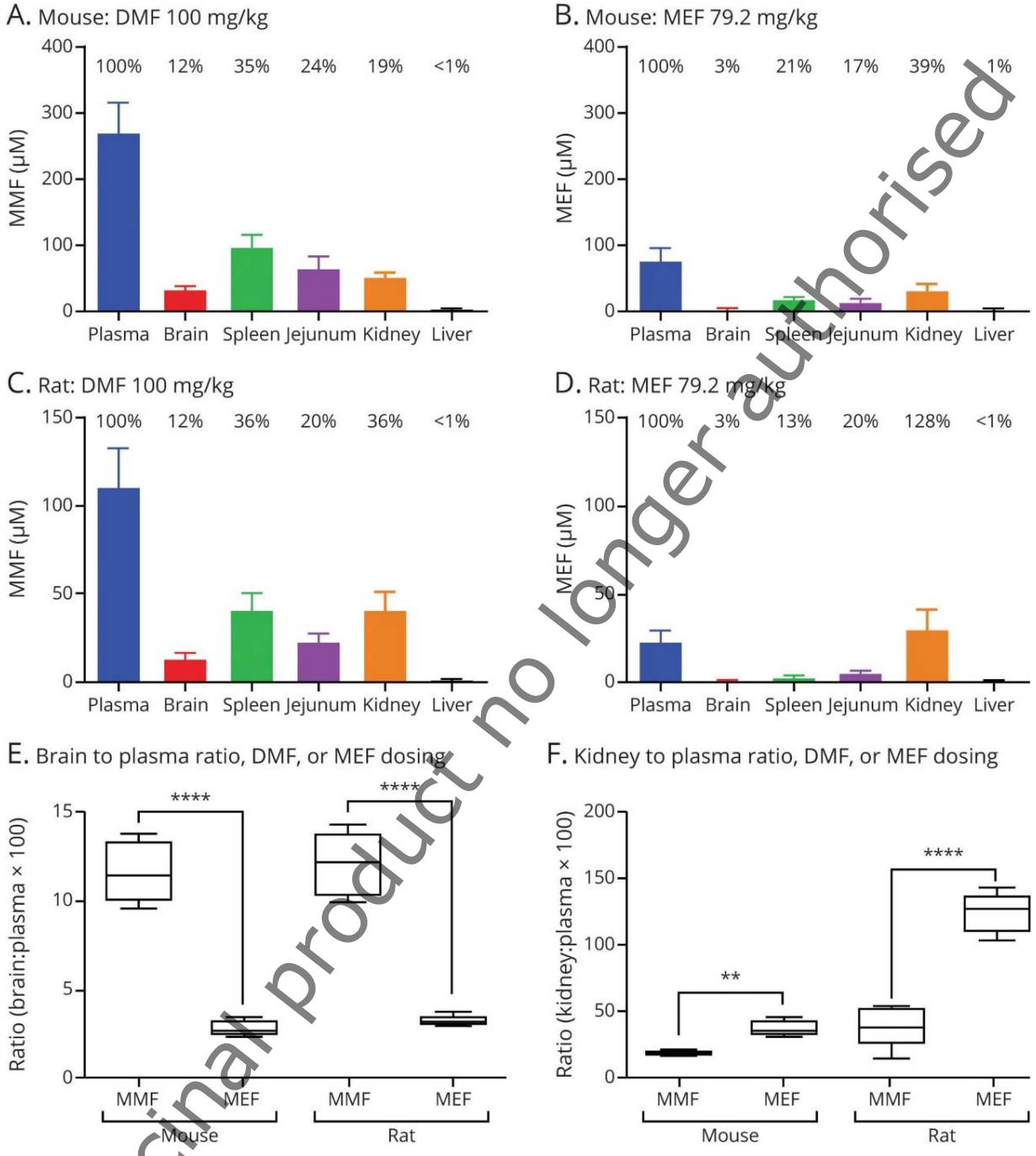
Pharmacokinetic properties of DMF and MEF

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 7). 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 7: 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**

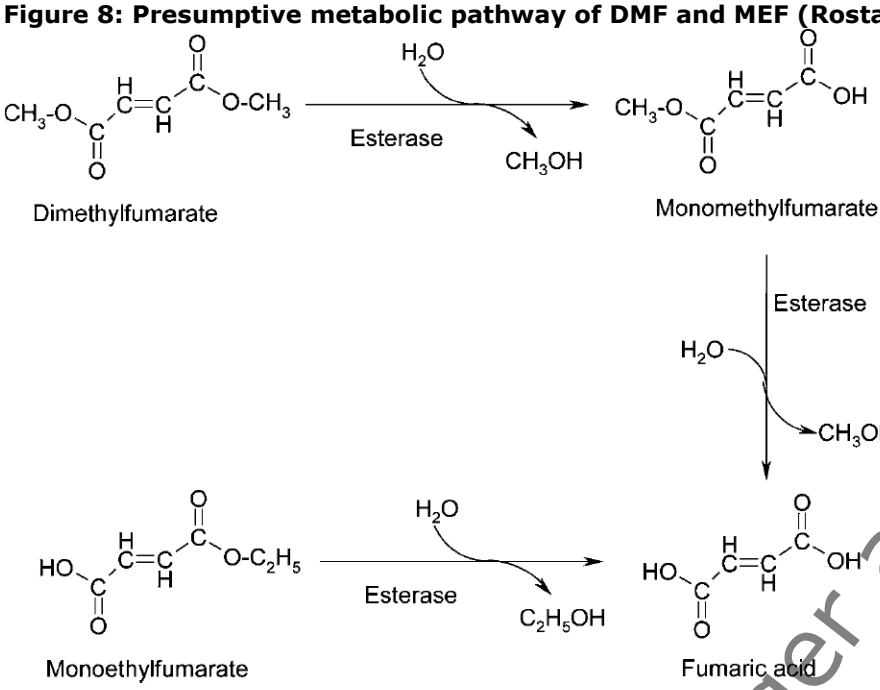
Pharmacological properties of DMF and the MEF salts

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 8: 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.

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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 4: 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 9 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 9: 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

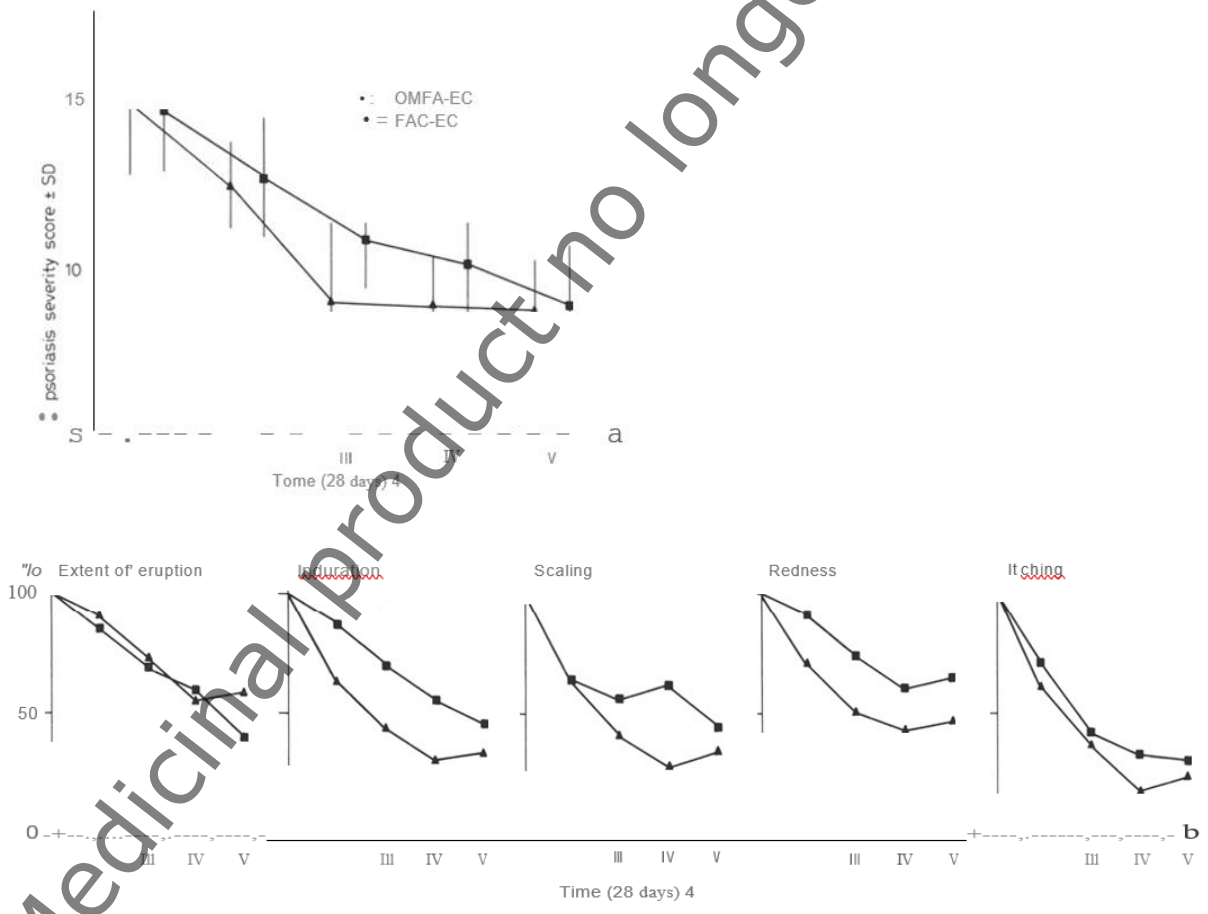


Table 5: Comparative study on the effects of DMFAE-EC (n = 22) and FAC-EC (n = 23) on 45 psoriasis patients

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 6: 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 10: 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

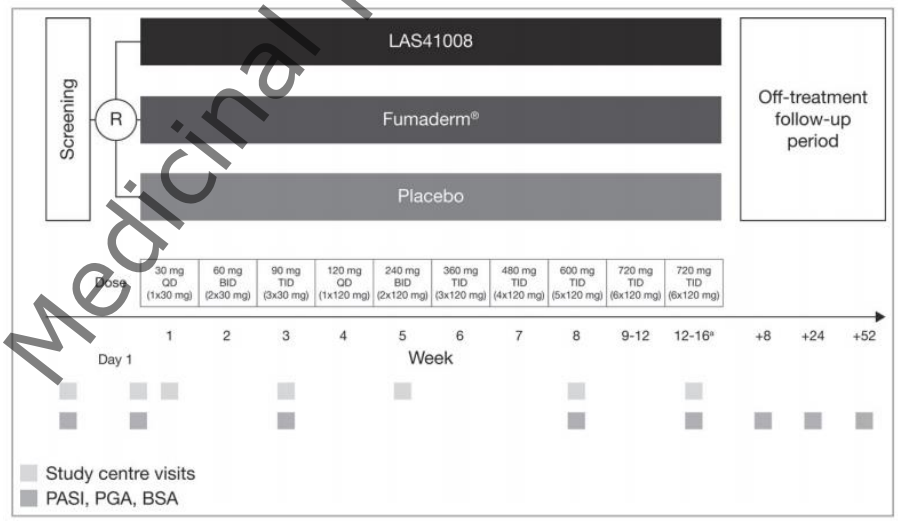


Figure 11: Participants flow

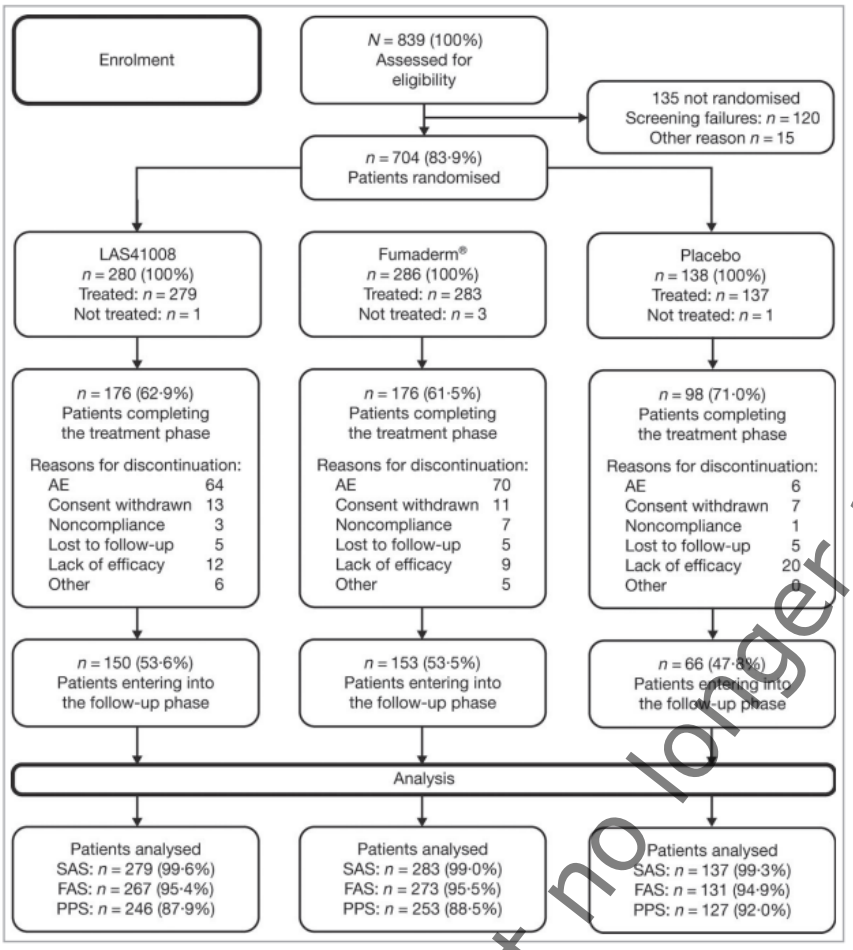


Table 7: Demographic and baseline patient characteristics (treated population)

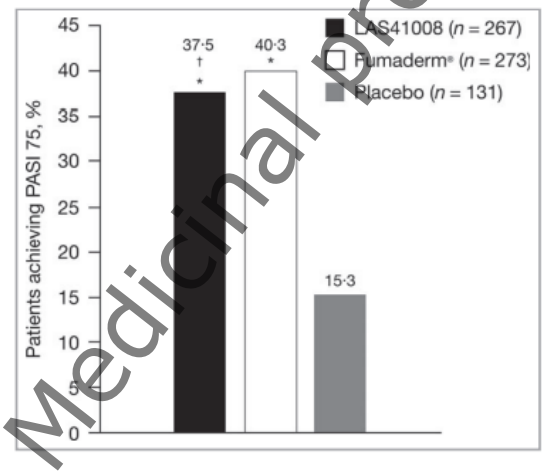
	LAS41008 (n = 279)	Fumaderm® (n = 283)	Placebo (n = 137)
Male, n (%)	174 (62·4)	185 (65·4)	93 (67·9)
Age (years)			
Mean ± SD	44·0 ± 15·2	45·0 ± 13·8	44·0 ± 14·3
Range	18–80	18–87	18–78
Race, n (%)			
White	275 (98·6)	280 (98·9)	137 (100·0)
Black/African American	1 (0·4)	0	0
Asian	1 (0·4)	3 (1·1)	0
Other	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 12).

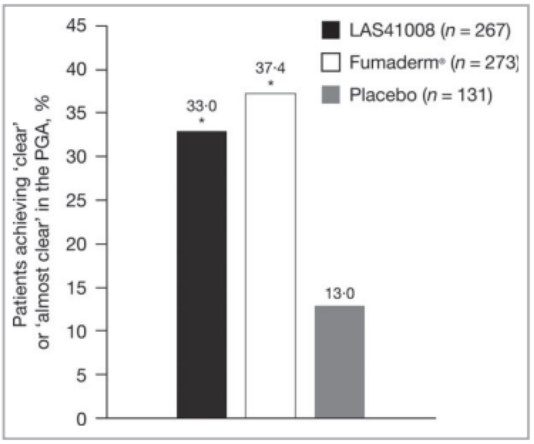
Figure 12: Percentage of patients achieving ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75) at week 16 (full analysis set). *P < 0001 vs. placebo; † P < 0001 noninferiority vs. Fumaderm



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 13: 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.

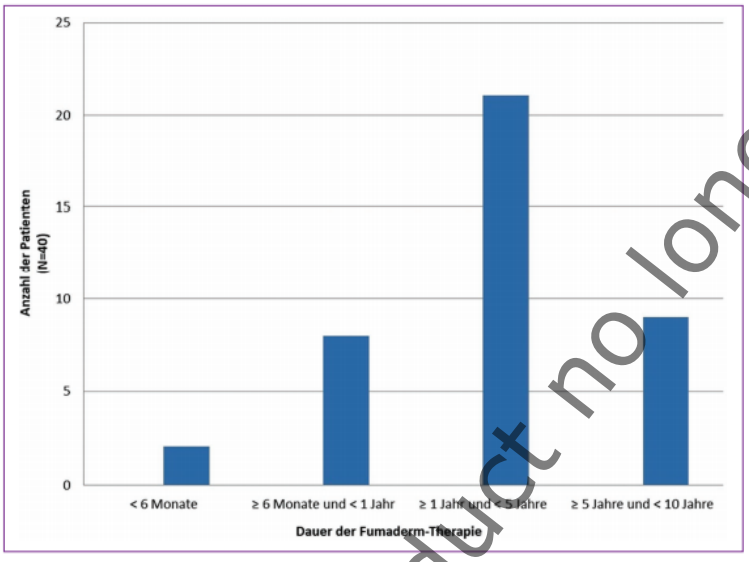
Falkvoll S et al., 2019

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 14: 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)

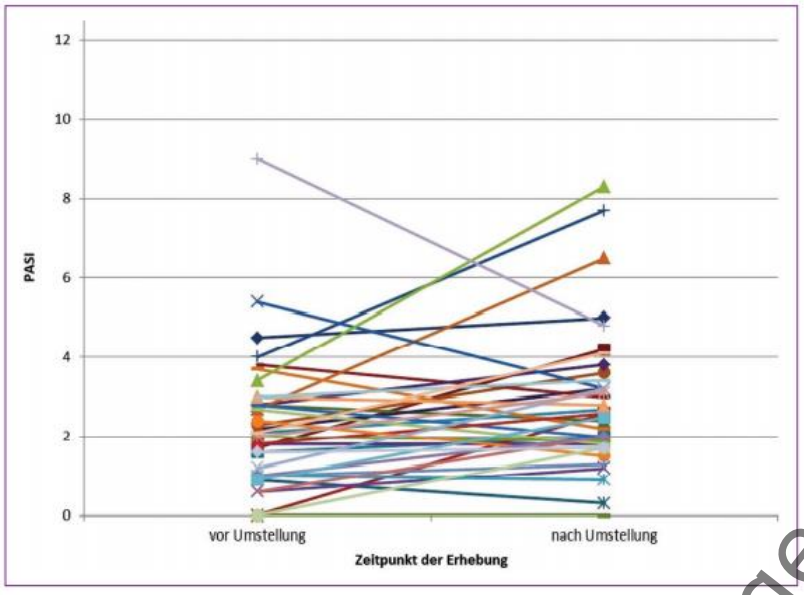


Most patients were treated with a daily DMF dose between 120 mg and 480 mg and had previously been treated with the FAE mixture for one to five years.

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 15). A PASI estimate was not available at one of the visits in 3/40 patients.

Figure 15: 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 8: 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 9: 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.

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