EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 October 2022
EMA/CHMP/790960/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dimethyl fumarate Teva

International non-proprietary name: dimethyl fumarate

Procedure No. EMEA/H/C/005963/0000

Note

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

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List of abbreviations

API	Active Pharmaceutical Ingredient
AP	Applicant's Part of an ASMF
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
CEP	Certificate of Suitability of the Ph.Eur.
CMS	Concerned Member State
CoA	Certificate of Analysis
CQA	Critical Quality Attribute
CRS	Chemical Reference Substance (official standard)
DCP	Decentralised Procedure
DD	Delivered Dose
DR	Delayed Release
DSC	Differential Scanning Calorimetry
DPI	Dry Powder Inhaler
EDQM	European Directorate for the Quality of Medicines
ERP	European Reference Product
FTIR	Fourier-transform infrared spectroscopy
GC	Gas Chromatography
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HPLC	High Pressure Liquid Chromatography
ICH	International Conference on Harmonisation
IPC	In-process control test
IR	Infrared
KF	Karl Fisher
LDPE	Low Density Polyethylene
LOD	(1) Limit of Detection, (2) Loss on Drying
LOQ	(1) Limit of Quantification, (2) List of Questions
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MO	Major Objection
MRI	Magnetic Resonance Imaging
MS	Mass Spectrometry
ND	Not detected
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
PDE	Permitted Daily Exposure
PE	Polyethylene
PET	Polyethylene terephthalate
Ph.Eur.	European Pharmacopoeia
PP	Polypropylene
ppb	parts per billion
PVdC	Polyvinylidene chloride
PVC	Polyvinyl chloride
QOS	Quality Overall Summary
QTPP	Quality Target Product Profile
RH	Relative Humidity
RMS	Reference Member State
RRMS	Relapsing remitting multiple sclerosis
RP	Restricted Part of an ASMF
RRT	Relative retention time
RSD	Relative standard deviation
TAMC	Total Aerobic Microbial Count
TGA	Thermo-Gravimetric Analysis
TSE	Transmissible Spongiform Encephalopathies
TYMC	Total Combined Yeast/Mould Count
UPLC	Ultra High Performance Liquid Chromatography
UV	Ultraviolet
XRPRD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant TEVA GmbH submitted on 13 September 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Dimethyl fumarate Teva, 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 24 June 2021.

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 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:

Dimethyl fumarate Teva 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).

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 a bioequivalence study 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 gastro-resistant hard capsule,
  Tecfidera 240 mg gastro-resistant hard capsules
- Marketing authorisation holder: Biogen Netherlands B.V.
- Date of authorisation: 31-01-2014
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/13/837/001-003

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

[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.

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.

1.5. 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: Hrefna Gudmundsdottir

The application was received by the EMA on	13 September 2021
The procedure started on	30 September 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 December 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	30 December 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 January 2022

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

The applicant submitted the responses to the CHMP consolidated List of Questions on	18 February 2022
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	28 March 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	7 April 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	22 April 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	21 June 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	6 July 2022
The CHMP agreed on a second list of outstanding issues to be sent to the applicant on	21 July 2022
The applicant submitted the responses to the second CHMP consolidated List of Outstanding Issues on	13 September 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the second List of Outstanding Issues to all CHMP and PRAC members on	27 September 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 Teva on	13 October 2022

2. Scientific discussion

2.1. Introduction

Dimethyl fumarate Teva is indicated for the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS).

Mechanism of action

The mechanism by which dimethyl fumarate exerts its therapeutic effects in multiple sclerosis (MS) is not fully understood. Preclinical studies indicate that dimethyl fumarate pharmacodynamic 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]).

Pharmacodynamic effects

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 pro-inflammatory 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 (DEFINE, CONFIRM and ENDORSE), upon treatment with dimethyl fumarate mean lymphocyte counts decreased on average by approximately 30% of their baseline value over the first year with a subsequent plateau. In these studies, patients who discontinued dimethyl fumarate therapy with lymphocyte counts below the lower limit of normal (LLN, 910 cells/mm^3) were monitored for recovery of lymphocyte counts to the LLN.

Paediatric population

The safety and effectiveness of dimethyl fumarate in paediatric RRMS was evaluated in a randomised, open-label, active-controlled (interferon beta-1a) parallel group study in patients with RRMS aged 10 to less than 18 years of age. One hundred and fifty patients were randomised to dimethyl fumarate (240 mg twice per day (BID) oral) or interferon beta-1a (30 µg IM once a week) for 96 weeks. The primary endpoint was the proportion of patients free of new or newly enlarging T2 hyperintense lesions on brain magnetic resonance imaging (MRI) scans at week 96. The main secondary endpoint was the number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at week 96. Descriptive statistics are presented as no confirmatory hypothesis was pre-planned for the primary endpoint.

The proportion of patients in the intention to treat (ITT) population with no new or newly enlarging T2 MRI lesions at week 96 relative to baseline was 12.8% for dimethyl fumarate versus 2.8% in the interferon beta-1a group. The mean number of new or newly enlarging T2 lesions at Week 96 relative to baseline, adjusted for baseline number of T2 lesions and age (ITT population excluding patients without MRI measurements) was 12.4 for dimethyl fumarate and 32.6 for interferon beta-1a.

The probability for clinical relapse was 34% in the dimethyl fumarate group and 48% in the interferon beta-1a group by the end of the 96 week open-label study period.

The safety profile in paediatric patients (aged 13 to less than 18 years of age) receiving dimethyl fumarate was qualitatively consistent with that previously observed in adult patients (see further in the SmPC).

2.2. Quality aspects

2.2.1. Introduction

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

Other ingredients are:

Capsule content: cellulose microcrystalline, croscarmellose sodium, silica colloidal anhydrous, magnesium stearate, methacrylic acid and methyl methacrylate copolymer, methacrylic acid and ethyl acrylate copolymer dispersion, talc, triethyl citrate;

Capsule shell: gelatin, titanium dioxide (E171), brilliant blue FCF (E133);

Capsule ink: shellac, black iron oxide (E172), propylene glycol, potassium hydroxide.

The product is available in PVC/PE/PVdC/-aluminium blister packs and white HDPE bottle, polypropylene cap with heat induction sealing, as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of dimethyl fumarate is Dimethyl (E)-butenedioate, (E)-2-butenedioic acid dimethyl ester corresponding to the molecular formula $C_6H_8O_4$. It has a relative molecular mass of 144.13 g/mol and the following structure:

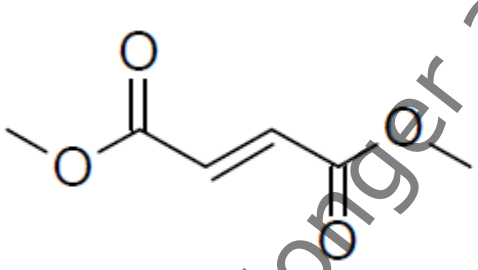


Figure 1: Active substance structure

The chemical structure of dimethyl fumarate was elucidated by a combination of the following techniques: IR (FTIR and Raman), X-ray powder diffraction (XRPRD), NMR (1H and 13C), MS, and UV spectroscopy, in addition to elemental analysis.

The active substance is a white crystalline powder, non-hygroscopic, soluble in acetone and ethyl acetate, slightly soluble in ethanol and sparingly soluble in methanol. It is slightly soluble in aqueous media.

Dimethyl fumarate is not chiral but Z isomer is possible.

2.2.2.2. Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for starting material and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

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

The active substance is packaged into PE bag as primary packing, placed inside a PET/Al/PET/LDPE bag and introduced into carton drum which complies with EC 10/2011 as amended.

2.2.2.3. Specification(s)

The active substance specification includes tests for: description (visual), Identification (by IR and by HPLC), sulphated ash (Ph. Eur.), water (KF), assay (HPLC), chromatographic purity (HPLC), residual solvents (GC), particle size (laser diffraction) and potency (calculation).

The proposed specification complies with ICH Q3A and Q3C.The proposed limits for related substances are acceptable and in line with ICH Q3A. The limit for residual solvents is in accordance with ICH Q3C.

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 assay and impurities testing has been presented.

Batch analysis data for commercial size batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

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

The following parameters were tested: description, water, identity, assay, related substances (purity). The analytical methods used were the same as for release and were stability indicating.

At both long term and accelerated conditions there is no change to the measured parameters. There are no trends and there is no impurity found above the reporting threshold at any of the measured time-points.

Photostability testing following the ICH guideline Q1B was performed. Results on stress conditions (basic, acid, oxidation, UV, heat) were also provided.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months when stored in the proposed container.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and pharmaceutical development

Dimethyl fumarate Teva 120 mg gastro-resistant capsules, hard, are size 0 capsules with white opaque body and blue opaque cap, and marking 'D120' printed in black ink on cap and body.

Dimethyl fumarate Teva 240 mg gastro-resistant capsules, hard, are size 0 capsules with blue opaque body and blue opaque cap, and marking 'D240' printed in black ink on cap and body.

These capsules contain white to off-white round tablets of about 6 mm diameter, plain on both sides. Each tablet has a weight of about 112 mg, contains 60 mg of active substance, and is coated with gastro-resistant coating. The 120 mg capsules contain 2 tablets, and the 240-mg capsules contain 4 tablets.

Dimethyl fumarate Teva has been developed to be a generic equivalent to the reference medicinal product TECFIDERA® (Dimethyl Fumarate delayed-release) capsules, for oral use, manufactured by

Biogen Netherlands B.V. Consequently, the objective was to prepare a delayed-release product being essentially similar to the reference medicinal product.

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.

The choice of excipients in the formulation of dimethyl fumarate delayed release capsules was based on reference product characteristics/composition, drug-excipient compatibility studies, suitability for the manufacturing processes, type of dosage form and on prior experience in the development of delayed release solid oral dosage forms. A summary of the drug-excipient compatibility studies was provided, and the selection of excipient and their grade was justified. No incompatibilities were recorded.

The proposed product contains similar excipients as the reference product. However, in the reference product also simethicone (30% emulsion), sodium lauryl sulphate and polysorbate 80 are used. In addition to the excipients used by the reference product, the proposed product also contains microcrystalline cellulose.

Initially, the Quality Target Product Profile (QTPP) was defined (Table 1) based on the properties of the active substance, characterisation of the reference product, consideration of the European Reference Product (ERP) label, and intended patient population. Identification of the Critical Quality Attributes (CQAs) was based on the intended safety and efficacy of the finished product and severity of harm to a patient resulting from failure to meet the quality attributes of the finished product.

Table 1: Finished product Quality Target Product Profile

QTPP Element	Target	Justification
Dosage form	Capsule	Pharmaceutical equivalence requirement (same dosage form)
Route of administration	Oral	Pharmaceutical equivalence requirement (same route of administration)
Dosage design	Delayed-Release Capsules	Delayed-Release design needed to meet label claims
Dosage strength	120 mg and 240 mg	Pharmaceutical equivalence requirement (same strengths)
Pharmacokinetics	Meets bioequivalence criteria to ERP – 240 mg (fasting and fed studies)	Bioequivalent requirement to meet the efficacy and safety requirement of the ERP.
Container closure system	PVC/PE/PVDC/Al Blisters and HDPE bottles with appropriate closure system.	Suitable container closure system to achieve the target shelf-life and to ensure capsule integrity during shipping
Drug product quality attributes	Physical attributes	Pharmaceutical equivalence requirement:
	Identification	
	Assay	Meeting the same compendial or other applicable (quality) standards (i.e., identity, assay, purity and quality)
	Content uniformity	
	Degradation products	
	Residual solvents	
	Drug release (less than 10% in acid media and rapid release in buffer pH 6.8)	
	Water content	
Stability	At least 24 months shelf-life at room temperature	Need for commercial requirement
Administration / concurrence with labeling	Capsules to be swallowed whole and intact. Not to be crushed, chewed, or capsule contents be sprinkled on food. Can be taken with or without food	Information is provided in the ERP labeling
Alternative methods of administration	None	None are listed in the ERP labeling

ERP: Eropean Reference Product

The pharmaceutical development focused on those CQAs that could be impacted by a change to the finished product formulation or manufacturing process. For generic Dimethyl Fumarate DR Capsules, these CQAs included assay, content uniformity dissolution and degradation products. Also, alcohol-induced dose dumping was assessed, as the drug release profile in presence of alcohol is critical to patient safety.

As dimethyl fumarate is a BCS Class-I molecule, particle size of active substance, does not have significant effect from dissolution or in-vivo bioequivalence point of view. The particle size of the active substance was chosen on basis of manufacturability, i.e. to achieve a blend with good flow properties during compression.

Based on outcome of preliminary bioequivalence studies as well as manufacturability and stability considerations, mini tablets were selected.

The applicant developed an in-house dissolution method which complies with Ph.Eur. 2.9.3, except for the vessel shape, which was adequately justified. The discriminatory power of the dissolution method has been demonstrated.

Results from alcohol induced dose dumping studies are provided. Results show that the proposed product does not release active substance in the presence of alcohol beyond the performance of the reference product.

The applicant conducted a bioequivalence study under fasting conditions and a bioequivalence study under fed conditions to compare the 240 mg test product to the 240 mg ERP and presented comparative dissolution studies between both. Although bioequivalence was demonstrated in the pivotal bioequivalence studies, dissolution was a review issue, but any differences were adequately justified by the applicant.

After the production of the batch for the bioequivalence study, a manufacturing site transfer was performed. A strength-based biowaiver has been applied for the 120 mg capsule, the justification of which is based on the following considerations:

- The 120- and 240-mg strengths are manufactured to the same manufacturing process
- The qualitative composition of the strengths is the same and the composition of the strengths is quantitatively proportional as the capsules of both strengths contain identical tablets. The capsule of strength 240 mg contains 4 tablets while the capsule strength 120 mg contains 2 tablets
- The *in vitro* dissolution profiles of all strengths are similar
- The active substance exhibits linear pharmacokinetics over the range of 120 mg to 360 mg according to the reference SmPC.

Due to some variability observed in dissolution results, the data supporting the site transfer and the biowaiver of strength for the 120 mg was a review issue.

By the end of the procedure, the applicant provided dissolution similarity data between the bio batch and the site transfer batches within the same strength (240mg) and to the additional strength (120mg) in two media (pH 1.2 for 2 hours followed by pH 6.8 phosphate buffer for 1 hour (Medium 1) and pH 4.5 acetate buffer for 2 hours followed by pH 6.8 phosphate buffer for 1 hour (Medium 2). Similarity was concluded using Bootf2BCA in compliance with Q&A 3.11 of the PKWP.

The responses, justifications and additional controls committed by the applicant (implementation of additional dissolution method, and shortening of the shelf life of the finished product to 24 months) were considered sufficient to demonstrate that the manufacturing process as applied in both manufacturing

sites lead to a product with similar dissolution profile, and to support the biowaiver for the 120 mg strength.

The primary packaging is PVC/PE/PVdC/-aluminium blister packs and white HDPE bottles with polypropylene cap. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The manufacturing process consists of the following main steps: dispensing, blending, tablet compression, coating, encapsulation of the delayed release tablets into empty capsule shells, and packaging. The process is considered to be a non-standard manufacturing process.

Scheme 1: Finished product manufacturing process

Bulk hold times are proposed and these are acceptable.

Major steps of the manufacturing process have been validated by a number of studies. Process validation has been performed on commercial-scale batches of Dimethyl Fumarate Delayed-Release 60 mg Tablets, Dimethyl Fumarate Teva 120 mg Capsules and Dimethyl Fumarate Teva 240 mg.

It has been demonstrated that the manufacturing process is capable of producing finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.2.3.3. Product specification(s)

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identification (UV, UPLC), uniformity of dosage units (Ph. Eur., mass variation), water content (Ph. Eur.), assay and related substances (UPLC), dissolution (Ph. Eur.), residual solvents (GC), microbiological quality (Ph. Eur.).

The proposed release and shelf-life specifications are acceptable. A review issue was raised due to some variability observed in dissolution results. During the procedure, the applicant had adequately proposed implementing additional controls for dissolution (additional method) at release and stability, as well as a shelf-life of 24 months to address concerns raised during review.

The limits for residual solvents are in accordance with ICH Q3C.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product 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 there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

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 both strengths confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.2.3.4. Stability of the product

Stability data from three full-scale batches of finished product of both strengths, 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. Bracketing was implemented for the HDPE bottle sizes, where only the smallest and largest container sizes are used; this is acceptable.

Samples were tested for description, water content, dissolution, assay, related substances, and microbiological quality. The analytical procedures were the same as for release and are stability indicating.

In addition, a photostability study was performed, results of which demonstrated that the product is not sensitive to light.

The in-use stability study for 180 days at 25°C/60%RH was performed at the start of shelf-life and after 18 months of storage. Neither show any degradation. Thus, there is no need to adopt an in-use shelf-life.

In response to the review issue raised on some variability observed in dissolution results, the applicant committed to a shelf-life of 24 months. Based on available stability data, the proposed shelf-life of 24 months with no special storage conditions, as stated in the SmPC (section 6.3 and 6.4), are acceptable.

In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.2.3.5. Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

No other excipients derived from animal or human origin have been used.

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. A review issue was raised due to some variability observed in dissolution results. During the procedure, the applicant has adequately proposed implementing two additional controls (additional dissolution method at release and stability, as well as a shelf life of 24 months).

Overall, the results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation: none.

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.

Pharmacodynamic, pharmacokinetic and toxicological properties of dimethyl fumarate are well known. As dimethyl fumarate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

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

2.3.2. Ecotoxicity/environmental risk assessment

Consumption data were provided by the applicant. Overall, the introduction of the generic product Dimethyl fumarate Teva with the same indication, population and dosage to the market will not lead to an increase in environmental exposure.

2.3.3. Discussion on non-clinical aspects

The CHMP considered that the non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. The application contains an adequate review of published non-clinical data.

The non-clinical sections of the SmPC are identical to that of the reference medicinal product.

2.3.4. Conclusion on the non-clinical aspects

The CHMP concluded that the non-clinical information submitted as part of this application supports the use of Dimethyl fumarate Teva in the approved indication.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for gastro-resistant capsule containing Dimethyl fumarate, 240 mg and 120 mg. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fasting conditions and one bioequivalence study with cross-over design under fed conditions. Both studies were done with the 240 mg strength.

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

Relevant for the assessment are the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1), guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Rev. 1) and dimethyl fumarate, gastro-resistant capsule, 120 mg, 240 mg, product-specific bioequivalence guidance (EMA/CHMP/421315/2017) as well as the guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1).

No formal scientific advice by the CHMP was given for this medicinal product.

GCP aspect

The Clinical trials were performed in accordance with good clinical practices (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

A strength based biowaiver has been applied for the additional capsule strength 120 mg based on the *in vivo* data of capsule strength 240 mg. The justification for the strength based biowaiver is presented below:

- The strengths are manufactured to the same manufacturing process
- The qualitative composition of the strengths is the same and the composition of the strengths is quantitatively proportional as the capsules of both strengths contain identical tablets. The capsule of strength 240 mg contains 4 tablets while the capsule strength 120 mg contains 2 tablets
- The *in vitro* dissolution profiles of all strengths are similar
- The active substance exhibits linear pharmacokinetics over the range of 120 mg to 360 mg according to the reference SmPC

240 mg (test product) vs. 120 mg (additional strength) and site transfer

Due to some variability observed in the dissolution results, the data supporting the site transfer and the biowaiver of strength for the 120 mg was a review issue.

By the end of the procedure, the applicant provided dissolution similarity data between the bio batch and the site transfer batches within the same strength (240mg) and to the additional strength (120mg) in two media (pH 1.2 for 2 hours followed by pH 6.8 phosphate buffer for 1 hour (Medium 1) and pH 4.5 acetate buffer for 2 hours followed by pH 6.8 phosphate buffer for 1 hour (Medium 2). Similarity was concluded using Bootf2BCA in compliance with Q&A 3.11 of the PKWP.

The responses, justifications and additional controls committed by the applicant (implementation of

additional dissolution method, and shortening of the shelf life of the finished product to 24 months) were considered sufficient to demonstrate that the manufacturing process as applied in both manufacturing sites lead to a product with similar dissolution profile, and to support the biowaiver for the 120 mg strength.

Tabular overview of clinical studies

To support the application, the applicant has submitted 2 bioequivalence studies as follows:

Study BE-1752-16	An open labeled, randomized, single dose, full replicate crossover, bioequivalence study of the Dimethyl fumarate delayed-release capsules, 240 mg in healthy human, adult subjects under fasting conditions.
Study BE-1753-16	An open labeled, randomized, single dose, full replicate crossover, bioequivalence study of the Dimethyl fumarate delayed-release capsules, 240 mg in healthy human, adult subjects under fed conditions.

The package of bioequivalence studies complies with the product-specific bioequivalence guidance on dimethyl fumarate, gastro-resistant capsule, 120 mg and 240 mg which recommends one single dose bioequivalence study of subjects under fasting conditions (study BE-1752-16) and one single dose bioequivalence study of subjects under fed conditions (study BE-1753-16).

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study BE-1752-16: An open labeled, randomized, single dose, full replicate crossover, bioequivalence study of the Dimethyl fumarate delayed-release capsules, 240 mg in healthy human, adult subjects under fasting conditions.

Methods

- **Study design**

This study was an open-label, single-dose, four-period, two-treatment, two-sequence, fully replicated cross-over bioequivalence study under fasting conditions with a washout period of 2 days between the four periods. Dimethyl fumarate 240 mg was administered in each period.

Following an overnight fast of at least 10 hours the subject was administered a single dose of the test product or the reference product with 240 ml of water. The subject fasted 4 hours after dosing.

Blood samples were collected pre-dosing (within 60 minutes of dosing) and at 0.500, 0.750, 1.000, 1.250, 1.500, 1.750, 2.000, 2.250, 2.500, 2.750, 3.000, 3.250, 3.750, 4.000, 4.500, 5.000, 5.500, 6.000, 7.000, 8.000, 10.000 and 12.000 hours post administration of a single dose dimethyl fumarate 240 mg, gastro-resistant capsule with 240 ml of water for the analyses of metabolite monomethyl fumarate in each period.

Clinical Phase	Dosing
Period 1	August 2017 (60 subjects dosed)
Period 2	August 2017 (60 subjects dosed)
Period 3	August 2017 (59 subjects dosed)
Period 4	August 2017 (57 subjects dosed)

- **Test and reference products**

The treatments were as follows:

Treatment	
Test product (T)	Dimethyl Fumarate Delayed-Release Capsules, 240 mg, Teva GmbH
Reference product (R)	Tecfidera Gastro-Resistant Hard Capsules, 240 mg, Biogen Idec Ltd.

- **Population(s) studied**

Healthy Asian (presumably Indian) male subjects (31.9 years (mean), body mass index (BMI): 23.3 kg/m2) participated in the study.

Subjects completed at least two periods with the reference product received in one of the completed periods of the study and were included in the statistical and pharmacokinetic analyses of monomethyl fumarate in line with the protocol.

Drop-outs:

One subject was withdrawn from the study due to adverse events (fever, cough without expectoration) in period 3 before dosing with the reference product.

Two subjects were withdrawn from the study due to adverse events (fever) in period 4 before dosing with the test product.

One subject was withdrawn from the study due to adverse events (abdominal pain) in period 4 with the reference product.

- **Analytical methods**

An analytical method was developed for the determination of metabolite monomethyl fumarate in human plasma.

The study samples were analysed by an LC method with MS/MS detection after solid-phase extractionfor the detection of monomethyl fumarate.

The method was fully and partially validated in human plasma The analytical method for monomethyl fumarate is generally adequately validated (pre-study and within study).

- **Pharmacokinetic Variables**

Method of assessment of pharmacokinetic parameters:

The pharmacokinetic and statistical evaluations were performed using Phoenix WinNonlin and PROC GLM of SAS® in order to make provisions for missing data and is able to deal with unbalanced designs more properly than the straightforward ANOVA, respectively.

Choice of primary variables and secondary PK variables:

The parameters calculated were AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, K_{el} and $t_{½}$.

Primary variables: AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}

Linear up/ log down trapezoidal (Linear Interpolation) method was used for AUC calculations, as indicated in the protocol.

- **Statistical methods**

ANOVA was performed on the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of monomethyl fumarate. The ANOVA model included *treatment* received, the *period* at which it was given along with the *sequence* in which each treatment being received and the *subject effect* (nested within the sequence). The treatment, period, sequence and subject effects were set as fixed effects and tested at 5% level of significance.

Criteria for conclusion of bioequivalence (full text according to the protocol):

Bioequivalence assessment will be based on Monomethyl fumarate pharmacokinetic data from the Test and Reference formulations.

The 90% confidence interval of the Test/Reference geometric mean ratios for log-transformed C_{max} and AUC_{0-t} of Monomethyl fumarate must fall within 80.00 – 125.00%.

However, if the true value of within subject co-efficient of variation of the log-transformed values of C_{max} of the reference product obtained in the current study [i.e., with justification that the obtained estimate of S_{WR} (within-subject standard deviation of the log-transformed values of C_{max} of the reference product) is reliable, and it is not as a result of outliers] is >30%, then the BE acceptance criteria for C_{max} can be widen to a maximum of 69.84%-143.19%.

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 [$\pm k \cdot s_{WR}$], 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 and S_{WR} is the within-subject standard deviation of the log-transformed values of C_{max} of the reference product. The table below gives examples of how different levels of variability lead to different acceptance limit using methodology.

Table 2: Levels of variability and corresponding acceptance limit

Within-Subject CV (%)	Lower Limit	Upper Limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
50	69.84	143.19

The geometric mean ratio (GMR) of Test/Reference Product of log-transformed C_{max} should lie within the conventional acceptance range 80.00 - 125.00% regardless of variability.

The possibility to widen the acceptance criteria based on high intra-subject variability does not apply to AUC where the acceptance range should remain at 80.00 – 125.00% regardless of variability.

Results

Table 3: Pharmacokinetic parameters for monomethyl fumarate (non-transformed values)

Pharmacokinetic parameter	Test	Replicate Test	Reference	Replicate Reference
	arithmetic mean ± SD	arithmetic mean ± SD	arithmetic mean ± SD	arithmetic mean ± SD
$AUC_{(0-t)}$	3706.67 ± 1107.31	3450.73 ± 1076.26	3681.75 ± 1101.74	3736.98 ± 1062.60
$AUC_{(0-\infty)}$	3848.58 ± 1179.31	3528.62 ± 1037.63	3721.91 ± 1106.87	3776.35 ± 1058.80
C_{max}	2138.12 ±888.50	1949.56 ±694.56	2074.80 ± 681.56	2200.80 ± 771.31
T_{max}*	2.875 (1.250-7.000)	2.750 (1.000 – 5.500)	3.000 (1.250-5.000)	2.750 (1.500 – 5.000)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 4: Statistical analysis for monomethyl fumarate (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	
$AUC_{(0-t)}$	95.25%	91.41-99.24%	
$AUC_{(0-\infty)}$	97.00%	93.05-101.12%	
C_{max}	92.88%	87.44-98.66%	

- ***Safety data***

A total of 12 adverse events were reported in the study. The adverse events were considered not related to the study treatments.

Study BE-1753-16: An open labeled, randomized, single dose, full replicate crossover, bioequivalence study of the Dimethyl fumarate delayed-release capsules, 240 mg in healthy human, adult subjects under fed conditions.

Methods

- **Study design**

This study was an open-label, single-dose, four-period, two-treatment, two-sequence, fully replicated cross-over bioequivalence study under fed conditions with a washout period of 2 days between the four periods. Dimethyl fumarate 240 mg was administered in each period.

Following an overnight fast of at least 10 hours apart from the high calorie, high fat meal (150 kcal from proteins, 250 kcal from carbohydrates, 555 kcal from fats) that was served 30 minutes prior to dosing

the subject was administered a single dose of the test product or the reference product with 240 ml of water. The subject fasted 4 hours after dosing.

Blood samples were collected pre-dosing (within 60 minutes of dosing) and at 1.000, 2.000, 2.500, 3.000, 3.500, 4.000, 4.333, 4.667, 5.000, 5.333, 5.667, 6.000, 6.333, 6.667, 7.000, 8.000, 9.000, 10.000, 11.000, 12.000, 14.000, 16.000 and 24.000 hours post administration of a single dose dimethyl fumarate 240 mg, gastro-resistant capsule with 240 ml of water for the analyses of metabolite monomethyl fumarate in each period.

Clinical Phase	Dosing
Period 1	August 2017 (60 subjects dosed)
Period 2	August 2017 (60 subjects dosed)
Period 3	August 2017 (58 subjects dosed)
Period 4	August 2017 (58 subjects dosed)

- **Test and reference products**

Treatment	
Test product (T)	Dimethyl Fumarate Delayed-Release Capsules, 240 mg, Teva GmbH
Reference product (R)	Tecfidera® Gastro-Resistant Hard Capsules, 240 mg, Biogen Idec Ltd.

- **Population(s) studied**

Healthy Asian (presumably Indian) male subjects (30.4 years (mean), BMI: 23.5 kg/m^2) participated in the study. Subjects completed at least two periods with reference product received in one of the completed periods of the study and were included in the statistical and pharmacokinetic analyses of monomethyl fumarate in line with the protocol.

Drop-outs:

Two subjects were withdrawn from the remainder of study (period 3 and 4) due to adverse events (vomiting) in period 1 and 2.

- **Analytical methods**

An analytical method was developed for the determination of metabolite monomethyl fumarate in human plasma.

The study samples were analysed by an LC method with MS/MS detection after solid-phase extraction. for the detection of monomethyl fumarate. The method was fully and partially validated in human plasma.

The analytical method for monomethyl fumarate is generally adequately validated (pre-study and within study).

- **Pharmacokinetic Variables**

Method of assessment of pharmacokinetic parameters:

The pharmacokinetic and statistical evaluations were performed using Phoenix WinNonlin and PROC GLM of SAS® in order to make provisions for missing data and is able to deal with unbalanced designs more properly than the straightforward ANOVA, respectively.

Linear up/ log down trapezoidal method was used for AUC calculations, as indicated in the protocolChoice of primary variables and secondary PK variables:

The parameters calculated were AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, K_{el}, $t_{½}$ and NK_{el} (number of points used in the calculation of the terminal rate constant).

Primary variables: $AUC_{0-t,}$ $AUC_{0-\infty}$ and C_{max}

- **Statistical methods**

ANOVA was performed on the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of monomethyl fumarate. The ANOVA model included *treatment* received, the *period* at which it was given along with the *sequence* in which each treatment being received and the *subject effect* (nested within the sequence). The treatment, period, sequence and subject effects were set as fixed effects and tested at 5% level of significance.

Criteria for conclusion of bioequivalence (full text according to the protocol):

Bioequivalence assessment will be based on Monomethyl fumarate pharmacokinetic data from the Test and Reference formulations.

The 90% confidence interval of the Test/Reference geometric mean ratios for log-transformed C_{max} and AUC_{0-t} of Monomethyl fumarate must fall within 80.00 – 125.00%.

However, if the true value of within subject co-efficient of variation of the log-transformed values of C_{max} of the reference product obtained in the current study [i.e., with justification that the obtained estimate of S_{WR} (within-subject standard deviation of the log-transformed values of C_{max} of the reference product) is reliable, and it is not as a result of outliers] is >30%, then the BE acceptance criteria for C_{max} can be widen to a maximum of 69.84%-143.19%.

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·s_{WR}], 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 and S_{WR} is the within-subject standard deviation of the log-transformed values of C_{max} of the reference product. The table below gives examples of how different levels of variability lead to different acceptance limit using methodology.

Table 5: Levels of variability and corresponding acceptance limit

Within-Subject CV (%)	Lower Limit	Upper Limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥50	69.84	143.19

* $CV(\%) = 100\sqrt{e^{s^2_{WR}} - 1}$

The geometric mean ratio (GMR) of Test/Reference Product of log-transformed C_{max} should lie within the conventional acceptance range 80.00 - 125.00% regardless of variability.

The possibility to widen the acceptance criteria based on high intra-subject variability does not apply to AUC where the acceptance range should remain at 80.00 – 125.00% regardless of variability.

Results

Table 6: Pharmacokinetic parameters for monomethyl fumarate (non-transformed values)

Pharmacokinetic parameter	Test	Replicate Test	Reference	Replicate Reference
	arithmetic mean ± SD	**arithmetic mean ± SD**	**arithmetic mean ± SD**	**arithmetic mean ± SD**
$AUC_{(0-t)}$	4166.80 ± 1121.45	4026.28 ± 958.82	4531.71 ± 1011.18	4100.52 ± 907.90
$AUC_{(0-\infty)}$	4577.56 ± 2055.98	4152.95 ± 919.08	4660.03 ± 1084.83	4220.20 ± 937.58
C_{max}	2130.94 ± 797.49	2200.96 ± 818.03	2321.29 ± 776.43	2248.85 ± 852.89
T_{max}*	5.667 (3.000-24.000)	5.333 (2.500–12.000)	5.500 (3.000-8.000)	5.333 (2.500–9.000)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 7: Statistical analysis for monomethyl fumarate (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	
$AUC_{(0-t)}$	94.24%	91.35-97.21%	
$AUC_{(0-\infty)}$	97.23%	93.99-100.58%	
C_{max}	93.42%	87.48-99.76%	

- ***Safety data***

A total of 13 adverse events of mild severity were reported in the study. The adverse events were considered not related to the study treatments.

2.4.2.2. Pharmacodynamics

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

2.4.3. Discussion on clinical aspects

The pivotal bioequivalence studies were conducted in line with the product specific guidance (EMA/CHMP/421315/2017) on dimethyl fumarate gastro-resistant capsule, 120 mg and 240 mg in terms of design, population (healthy subjects), analyte (metabolite monomethyl fumarate) and parameters (AUC0-t, AUC0-∞ and Cmax) for bioequivalence assessment. According to the guidance mentioned above pre-treatment of aspirin could be considered in order to reduce the most common adverse flushing event during fasting conditions. This aspect was not considered. However, the studies confirmed that flushing was not observed as an adverse event during fasting and fed conditions.

The test product was compared to an EU reference product under fasting and fed conditions.

The alternative replicate study design is acceptable to demonstrate bioequivalence between the test product and reference product given the expected high intra-subject CV of Cmax of the latter providing the possibility of widening the acceptance criterion of Cmax. Widened acceptance criteria were not necessary. The results of bioequivalence studies BE-1752-16 and BE-1753-16 indicate that the test product is bioequivalent with the EU reference product under fasting and fed conditions as the 90% CI of the ratio for geometric least square means of log-transformed data of AUC0-t, AUC0-∞ and Cmax for metabolite monomethyl fumarate of the test product and reference product fall within the conventional acceptance criterion of 80.00-125.00% for subjects in the fasting and fed conditions.

With regards to the extrapolation of the *in vivo* data of 240 mg to the additional strength 120 mg, similarity has been demonstrated for the additional strength.

The clinical and analytical site of the studies have been inspected by an EU inspectorate before. No triggers for study-specific inspection were considered necessary.

2.4.4. Conclusions on clinical aspects

The CHMP considered that this application contains an adequate review of published clinical data.

Bioequivalence has been shown between the test product and EU reference product in subjects under fasting conditions (study BE-1752-16) and in subjects under fed conditions (study BE-1753-16) in line with the product-specific bioequivalence guidance (EMA/CHMP/421315/2017) for dimethyl fumarate 120 mg, 240 mg, gastro-resistant capsule.

The results of studies BE-1752-16 and BE-1753-16 with 240 mg formulation can be extrapolated to the additional strength 120 mg according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6 as the similarity has been demonstrated between the 240 mg and the 120 mg strength.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 8: 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 and herpes zoster) Malignancies Effects on pregnancy outcome Interaction with nephrotoxic medications leading to renal toxicity

Summary of safety concerns	
Missing information	Long term efficacy and safety Safety profile in patients over the age of 55 years Safety profile in patients with moderate to severe renal impairment Safety profile in patients with hepatic impairment Safety profile in patients with severe active GI disease Increased risk of infection in patients concomitantly taking anti-neoplastic or immunosuppressive therapies

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

The safety information in the proposed product information is aligned to the reference medicinal product, which is considered adequate.

No additional risk minimisation measures are considered warranted, in line with the reference product.

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

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

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.

For dimethyl fumarate, PSURs are currently not required for products referred to in Articles 10(1), 10a, 16a of Directive 2001/83/EC as amended.

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 the leaflet for "Dimethyl Fumarate Teva 120mg Gastro-resistant capsules hard and Dimethyl Fumarate Teva 240mg Gastro-resistant capsules, hard" and the leaflet for "Rosuvastatin/Ezetimibe 5mg/10mg, Rosuvastatin/Ezetimibe 10mg/10mg, Rosuvastatin/Ezetimibe 20mg/10mg, Rosuvastatin/Ezetimibe 40mg/10mg". 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 Capsules, hard 120 mg and 240 mg. The reference product Tecifidera is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis.

This application contains an adequate review of published clinical data. Bioequivalence has been shown between the test product and EU reference product in subjects under fasting conditions (study BE-1752-16) and in subjects under fed conditions (study BE-1753-16) in line with the product-specific bioequivalence guidance (EMA/CHMP/421315/2017) for dimethyl fumarate 120 mg, 240 mg, gastro-resistant capsule.

The results of studies BE-1752-16 and BE-1753-16 with 240 mg formulation can be extrapolated to the additional strength 120 mg according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6 as the similarity has been demonstrated between the 240 mg and the 120 mg strength.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. The application contains an adequate review of published non-clinical data.

The quality of this product is considered 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.

The RMP version 1.3 is acceptable.

4. Recommendations

Outcome

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

Dimethyl fumarate Teva is indicated for the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS).

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: CHMP Opinion on the ad hoc assessment relating to the therapeutic effect of monoethyl fumarate salts (MEF) within Fumaderm

5.1. CHMP ad hoc Assessment Report, as adopted on 11 November 2021

CHMP Assessment Report

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

Table of contents

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 metabolised 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-centre, 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 21 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 synthesised 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*.

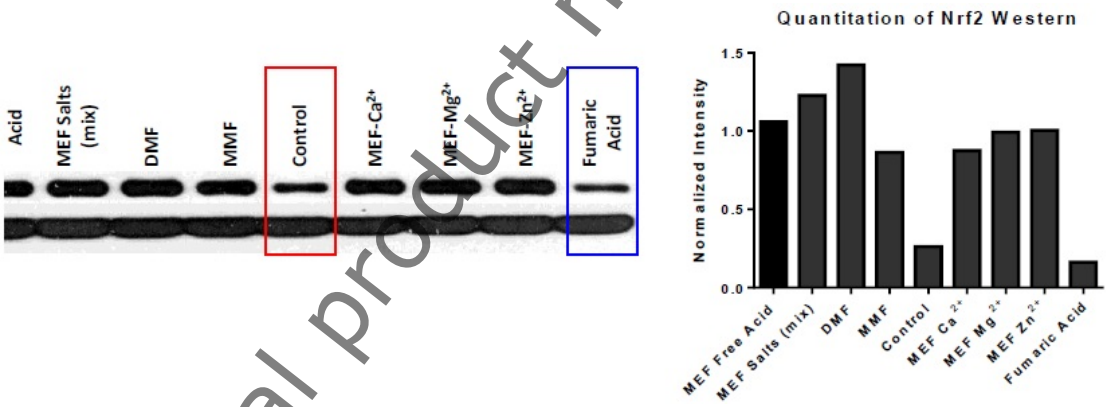
In all non-clinical investigations, the ratio of the calcium, magnesium, and zinc salts of MEF was 87:5:3 Ca-MEF, Mg-MEF, Zn-MEF, respectively, based on molecular weight. This reflects the ratio of these MEF salts in Fumaderm.

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 1).

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



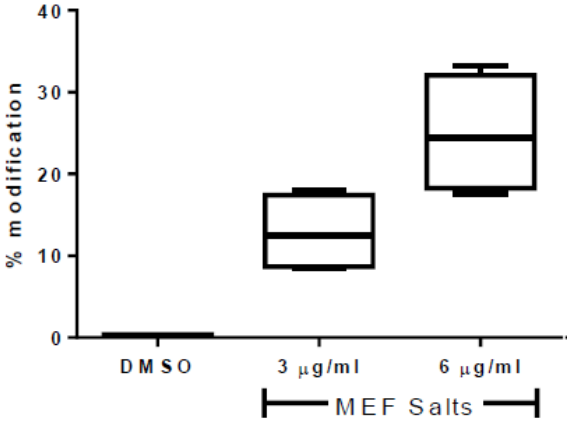
COS-1 cells were treated with 9 µg/ml of individual calcium, magnesium or zinc salts of MEF, with a mixture of MEF salts, the free acid form of MEF, DMF, MMF, FA or the vehicle control DMSO (boxed in red) to illustrate the basal Nrf2 level. Cells were harvested after 24 h and extracts analysed by Western 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 2). The same modification of Keap 1 at Cys151 had been previously

demonstrated for DMF and MMF. As known for DMF, MEF is, hence, able to release Nrf2 from constitutive Keap 1 repression.

Figure 3: The mixture of MEF salts modifies Keap 1 at Cys151

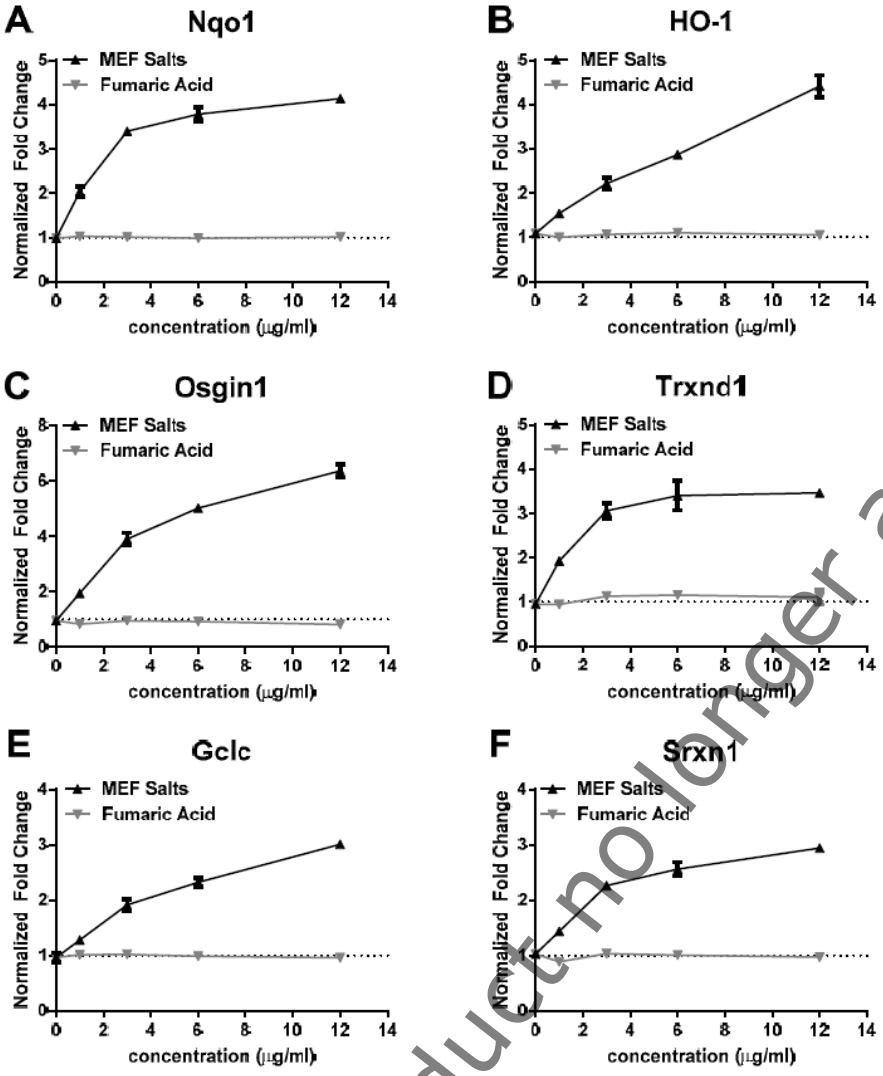


HEK293 cells were transfected with Keap1 and subsequently treated with either DMSO (control) or 3 or 6 µg/ml of calcium, magnesium and zinc salts of MEF. Keap1was immunopurified, fractioned by gel electrophoresis and then excised from the gel. The gel slice was reduced by DTT, alkylated by iodoacetamide, 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 3). In contrast, responses for haeme oxygenase-1 (HO-1), oxidative stress-induced growth inhibitor 1 (Osgin 1) and glutamate-cysteine ligase catalytic subunit (Gclc) exhibited a linear increase across the entire concentration range. These differential gene responses suggest that additional regulatory processes also govern expression or stability of these transcripts. Moreover, the pharmacological activity of the MEF salts appears to reside within the FAE as FA itself did not produce a response.

Figure 4: The mixture of MEF salts induces Nrf2-dependent gene expression

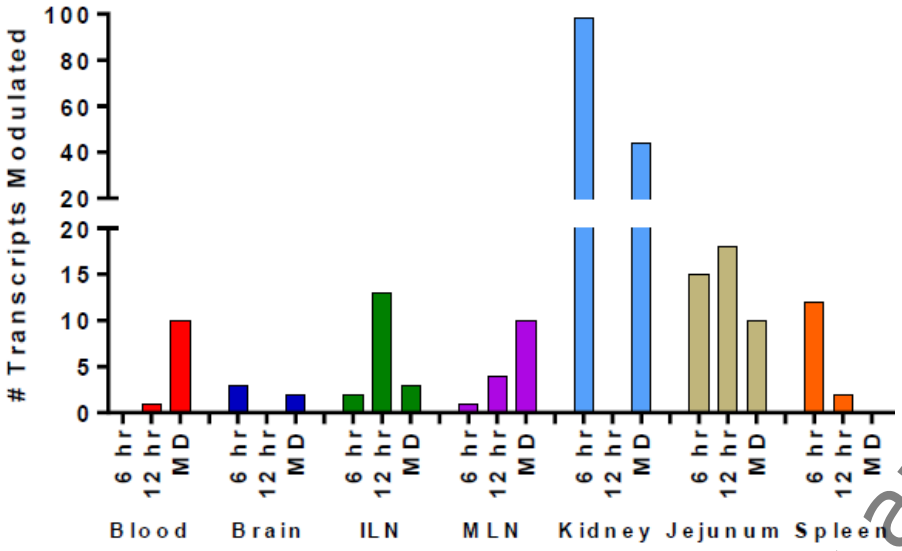


Human astrocytes were treated with a mixture of calcium, magnesium and zinc salts of MEF or fumaric acid. Transcriptional changes were evaluated by RT-PCR 24 h after treatment. (A) Nqo1, (B) HO-1, (C) Osgin 1, (D) Trxnd1, (E) (Gclc), (F) sulfiredoxin 1 (Srxn1). Responses have been normalised as a fold 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 4). 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

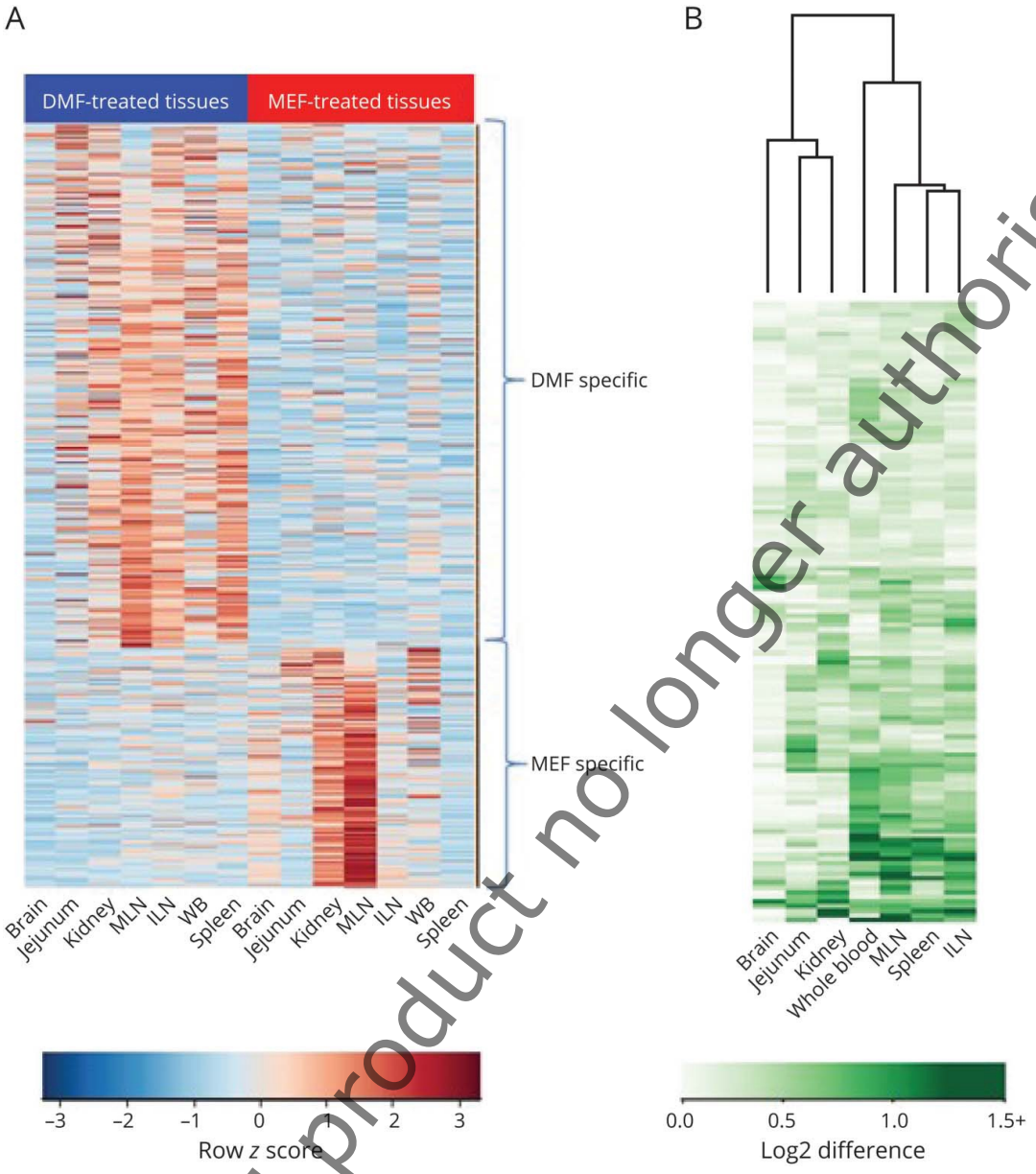


C57Bl/6 mice received single or repeated oral doses of 79.2 mg/kg MEF salts for 10 days (equivalent to 100 mg/kg DMF). Fumaric acid was not tested due to its lack of activity in previous investigations *in vitro* (see above). Transcriptional responses were evaluated by Affymetrix microarrays at 6 and 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 6). The expression of 487 genes was specifically altered in response to DMF treatment, which comprise the known Nrf2-mediated oxidative stress response, glutathione (GSH)-mediated detoxification and others (Figure 5A). These DMF-induced changes were particularly evident in mesenteric and inguinal lymph nodes, spleen and whole blood. For MEF, 224 gene expression changes were specifically noted that predominated in kidney and mesenteric lymph node. The MMF altered transcripts corresponded to apoptosis, death receptor and autophagy-related pathways.

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

Figure 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 normalisation(n = 7 biological sample sets each). DMF specificity is most pronounced in MLN, ILN, spleen, and whole blood, whereas MEF specificity is most evident in the kidney and MLN. (B) Hierarchical clustering shows 132 interaction probe sets, which is most pronounced in immunologic tissues: whole blood, MLN, ILN, and spleen. ILN = inguinal lymph node; MLN = mesenteric lymph node; WBC = white blood cell; (from Wipke *et al.*, 2021).

Evaluation comment

A sparse set of non-clinical data is provided for a comparison of the pharmacological effect of MEF in contrast to either DMF or fixed combination of MEF/DMF. Some of the comparative studies shows that *in vitro* the individual MEF salts, the free acid of MEF, DMF and MMF similarly increase Nrf2 concentrations as analysed by Western blotting, whereas FA was ineffective. Perhaps, the most relevant study for purpose of the comparison between DMF, MEF and their combination was recently published (Wipke et al., 2021). Gene expression profiles were reported following repeated oral administration of 100 mg/kg DMF, a total dose of 79 mg/kg of the calcium, magnesium and zinc salt mixture of MEF or the DMF/MEF combination for 10 days in mice. The expression of 487 genes was specifically altered in response to

DMF treatment, which comprise the known Nrf2-mediated oxidative stress response, glutathione (GSH)-mediated detoxification and others. These DMF-induced changes were particularly evident in mesenteric and inguinal lymph nodes, spleen and whole blood. For MEF, 224 gene expression changes were specifically noted that predominated in kidney and mesenteric lymph node. The MMF altered transcripts corresponded to apoptosis, death receptor and autophagy-related pathways. Following dosing of the DMF/MEF combination, 132 genes demonstrated a significant interaction effect between DMF and MEF, which was most pronounced in immunological tissues, like whole blood, spleen, mesenteric and inguinal lymph node

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

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

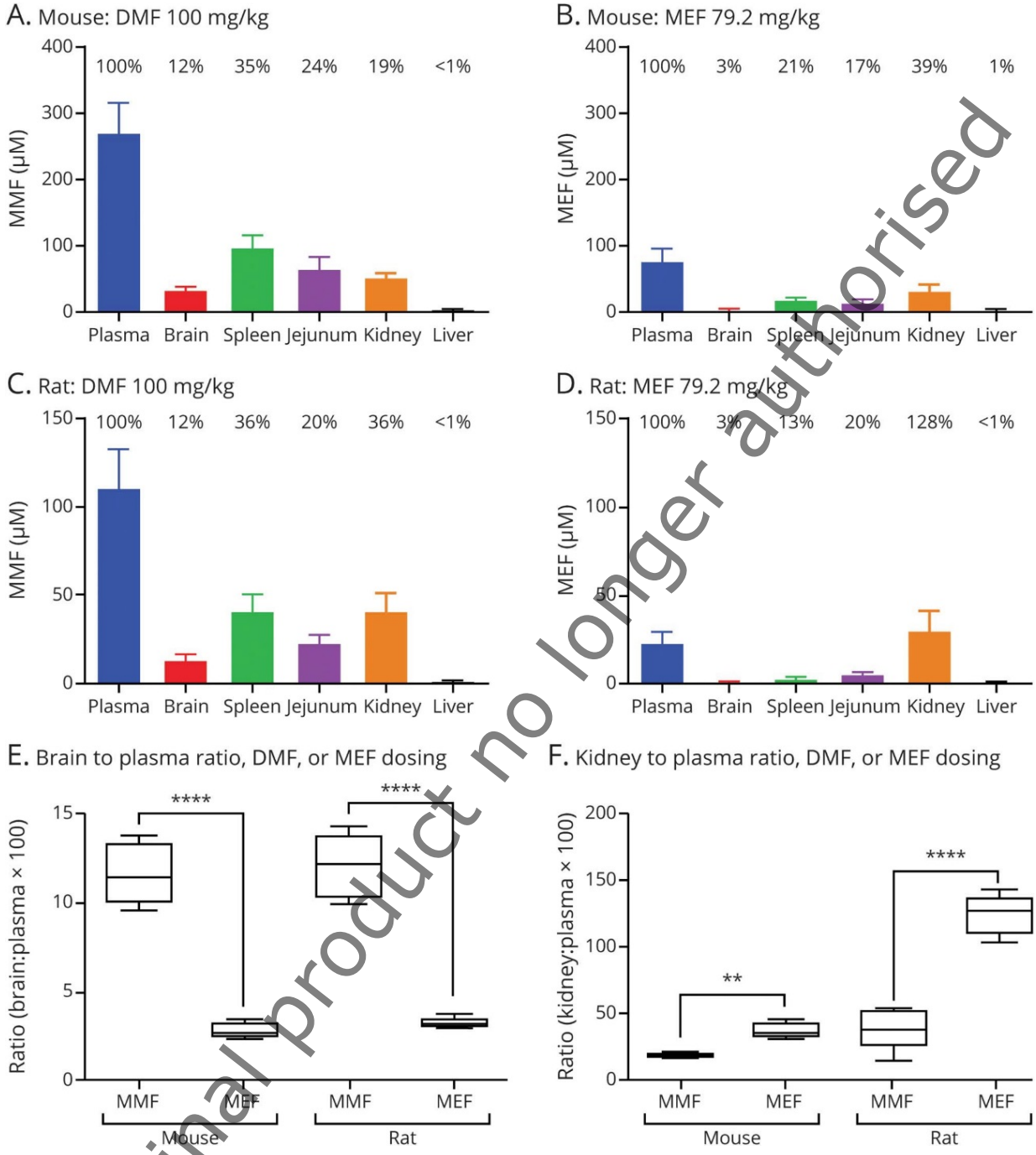
Pharmacokinetic properties of DMF and MEF

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

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

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

Figure 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**

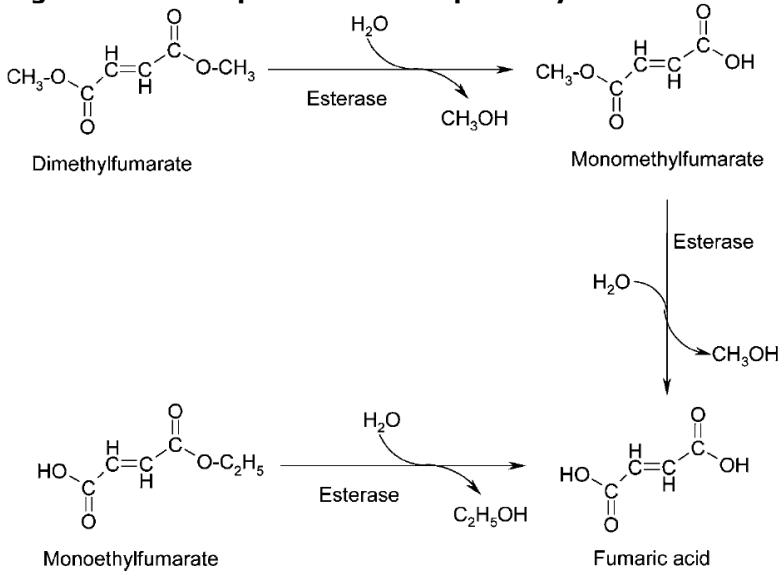
Pharmacological properties of DMF and the MEF salts

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 metabolised 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.

Gollnick H, Altmeyer P, Kaufmann R, Ring J, Christophers E, Pavel S, Ziegler J. Topical calcipotriol plus oral fumaric acid is more effective and faster acting than oral fumaric acid monotherapy in the treatment of severe chronic plaque psoriasis vulgaris. Dermatology. 2002; 205: 46-53.

Kolbach DN, Nieboer C. Fumaric acid therapy in psoriasis: results and side effects of 2 years of treatment. J Am Acad Dermatol. 1992;27: 769-71.

Landeck L, Asadullah K, Amasuno A, et al. Dimethyl Fumarate (DMF) vs. Monoethyl Fumarate (MEF) Salts for the Treatment of Plaque Psoriasis: a Review of Clinical Data. Arch Dermatol Res. 2018;310:475–483.

Langner A et al. Results of a phase II study of a novel oral fumarate, BG-12, in the treatment of severe psoriasis. J Europ Academ Dermatol Venereol. 2004; 18:798.

Lijnen R, Otters E, Balak D, Thio B. Long-term safety and effectiveness of high-dose dimethylfumarate in the treatment of moderate to severe psoriasis: a prospective single-blinded follow-up study. J Dermatolog Treat. 2016; 27: 31-6.

Mrowietz U, Reich K, Spellman MC. Efficacy, safety and quality of life effects of a novel oral formulation of dimethyl fumarate in patients with moderate to severe plaque psoriasis. Results of a phase 3 study. J Am Academ Dermatol. 2006: 54: AB202.

Nieboer C, de Hoop D, van Loenen AC, Langendijk PN, van Dijk E. Systemic therapy with fumaric acid derivates: new possibilities in the treatment of psoriasis. J Am Acad Dermatol. 1989; 20: 601-608.

Nieboer C, Langendijk PN, van Loenen AC, Gubbels J. Fumaric acid therapy in psoriasis: a double-blind comparison between fumaric acid compound therapy and monotherapy with dimethylfumaric acid ester. Dermatologica, 1990; 181:33-7.

Nugteren-Huying WM, van der Schroeff JG, Hermans J, Suurmond D. Fumaric acid therapy for psoriasis: a randomized, double-blind, placebo-controlled study. J Am Acad Dermatol. 1990; 22: 311-2.

Peeters AJ, Dijkmans BA, van der Schroeff JG. Fumaric acid therapy for psoriatic arthritis. A randomized, double-blind, placebo-controlled study. Br J Rheumatol 1992; 31: 502-4.

Walker F, Adamczyk A, Kellerer C, et al. Fumaderm® in Daily Practice for Psoriasis: Dosing, Efficacy and Quality of Life. Br J Dermatol. 2014;171:1197–1205.

Four publications, which compared the efficacy of DMF to DMF/MEF directly are considered the most relevant and are further described below.

These are the following:

- Kolbach DN, Nieboer C. Fumaric acid therapy in psoriasis: results and side effects of 2 years of treatment. J Am Acad Dermatol. 1992; 27: 769-71.

- Nieboer C, Langendijk PN, van Loenen AC, Gubbels J. Fumaric acid therapy in psoriasis: a double-blind comparison between fumaric acid compound therapy and monotherapy with dimethylfumaric acid ester. Dermatologica, 1990; 181:33-7.

- Mrowietz U, Szepietowski JC, Loewe R, et al. Efficacy and Safety of LAS41008 (Dimethyl Fumarate) in Adults with Moderate-to-Severe Chronic Plaque Psoriasis: a Randomized, Double-Blind, Fumaderm®- and Placebo-Controlled Trial (BRIDGE). Brit J Dermatol. 2017;176:615–623.

- Falkvoll S, Gerdes S, Mrowietz U. Switch of psoriasis therapy from a fumaric acid ester mixture to dimethyl fumarate monotherapy: results of a prospective study. J Dtsch Dermatol Ges 2019; 17: 906-912.

Moreover, study by Nieboer et al. (1989), which evaluated the efficacy and safety of MEF-Na is discussed below.

However, the non-randomised study of Kolbach and Nieboer (1992) is not suitable for a comparison, as the DMF-treatment group received only half of the DMF-dose in the Fumaderm-group. Moreover, this study was not randomised. 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 randomisation 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 categorised 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

Randomisation into two groups was made between 45 patients. 25 female, 20 male. Aged between 18 and 70 years. 22 were treated with DMFAE-E C. 23 with FAC-EC. At the end of the study 33 patients could be evaluated. 18 had been treated with DMFAE-EC and 15 with FAC-EC. At least 10% of the body surface was affected. At the beginning of the study 22 of these 33 patients showed the plaque type; 10 the macular type; and 1 the guttate type of psoriasis. 11 patients had joint complaints, 6 in the DM FAE-EC group and 5 in the FAC-EC group.

Results

The individual results are shown in Table 5. Compared to the initial population score, a considerable improvement (i.e. score more than halved) was observed in 45% of the patients treated with DMFAE-EC and in 52% of the treated with FAC-EC. This improvement was statistically significant.

In both groups 4 patients (18 and 15%) showed a full clearance. Considerable improvement occurred in 15 out of 22 (68%) patients with the plaque type and in 4 out of 10 (40%) of those with the macular type. The patient with the guttate type showed a full clearance after a treatment of 2 months with FAC-EC, but had an extensive relapse 1 month later even though the therapy had been continued. For 5 patients (22%) in the DMF AE-EC group and 1 patient (4%) in the FAC-EC group the psoriasis did not show any reaction to the therapy. The observed differences between the two groups appeared to be not

significant. Deterioration, that is an increase of the score up to more than 125%, was not observed in either of the groups.

The course of the score in both groups with regard to the total average score and the separate parameters is shown in Figure 8 a, b. It covers the observations of those patients who could be evaluated after 4 months: 18 in the DMFA E- EC group and 15 in the FAC-EC group. The total average score in the DMFAE-EC group dropped from 9.7 to 4.1 and in the FAC-EC group from 10.5 to 4.1. The course of this score in both treatment groups was not significantly different at any time point (1- V). Subsequently, the separate parameters, too, did not show a significant difference in time course. The results after 4 months were not statistically different.

The joint complaints of the 6 patients in the DMFAE-EC group showed considerable improvement for 2 patients, and some improvement for 1, and deteriorated or remained unchanged for the other 3. In the 5 patients in the FAC-EC group a considerable improvement occurred in 2 cases and a slight improvement in 3 cases.

The general evaluation of the therapy by the patients usually corresponded with that of the investigators.

Figure 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

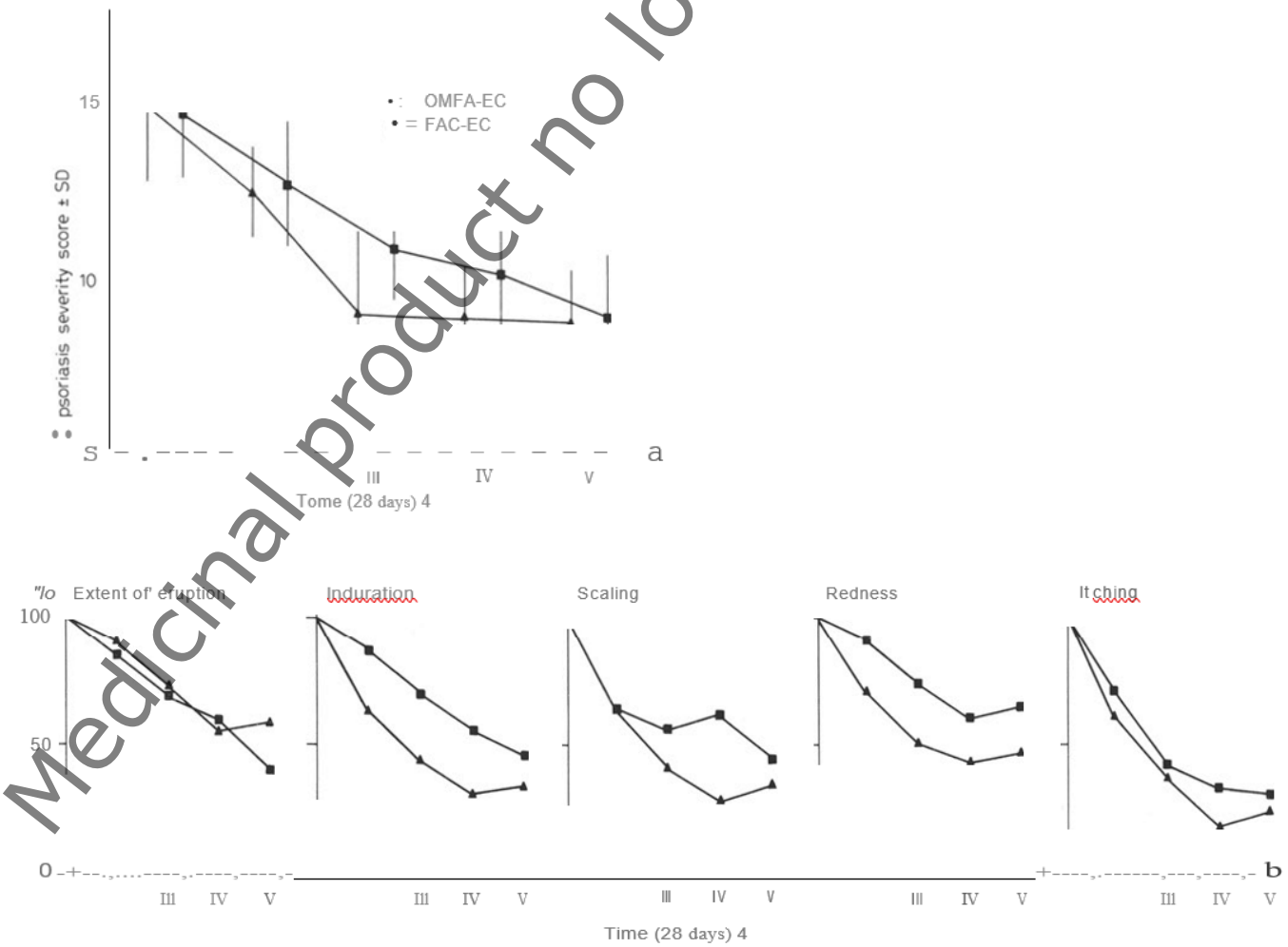


Table 5: Comparative study on the effects of DMFAE-EC (n = 22) and FAC-EC (n = 23) on 45 psoriasis patients

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 randomised 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.

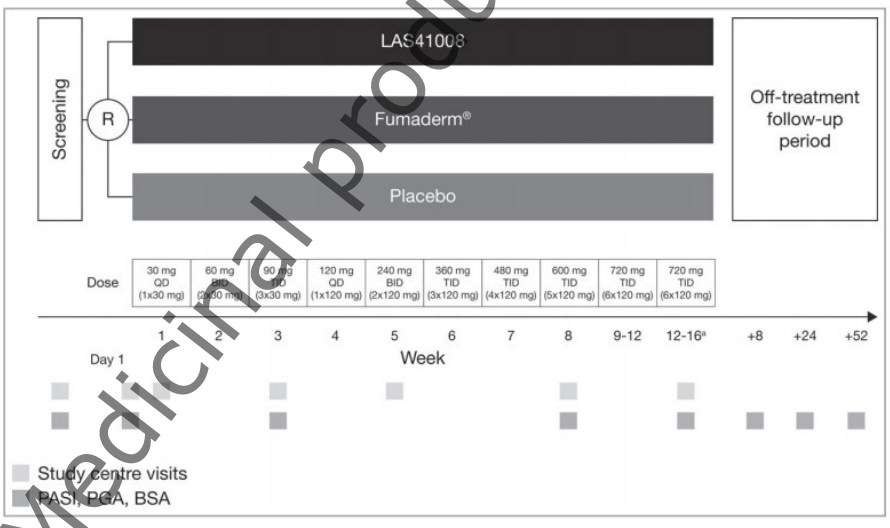
The co-primary endpoints were the percentage of patients achieving ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75) and the percentage achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment (PGA) at Week 16. Secondary endpoints included PASI 75 at Weeks 3 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 randomised 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

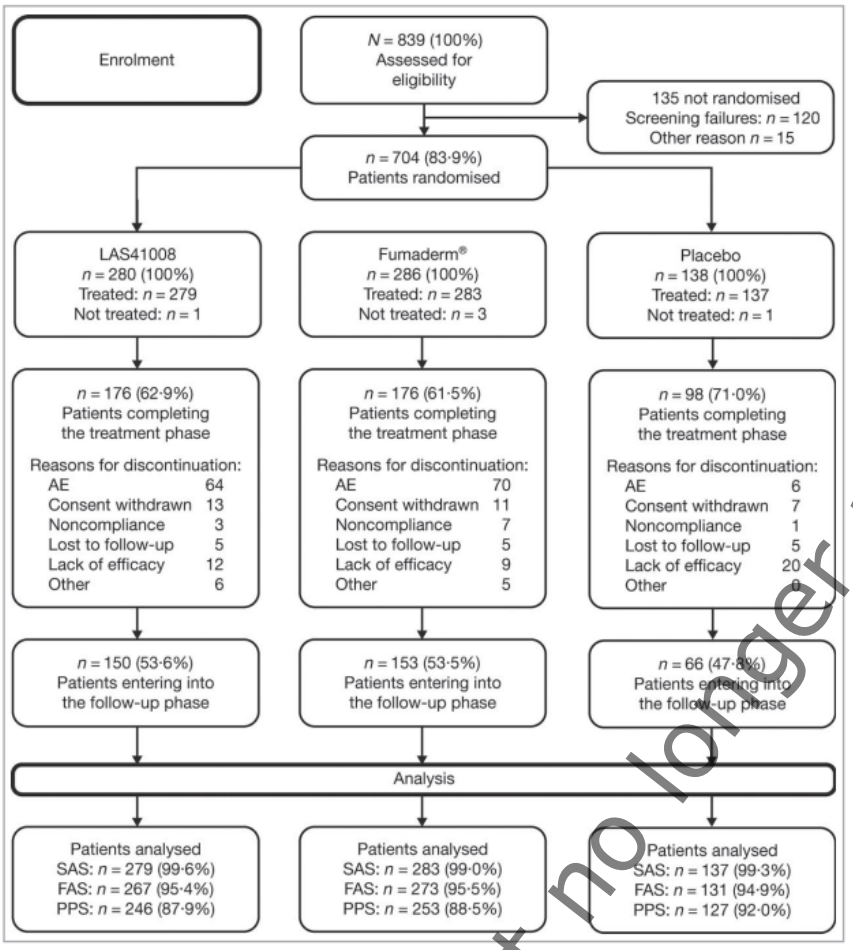


Table 7: Demographic and baseline patient characteristics (treated population)

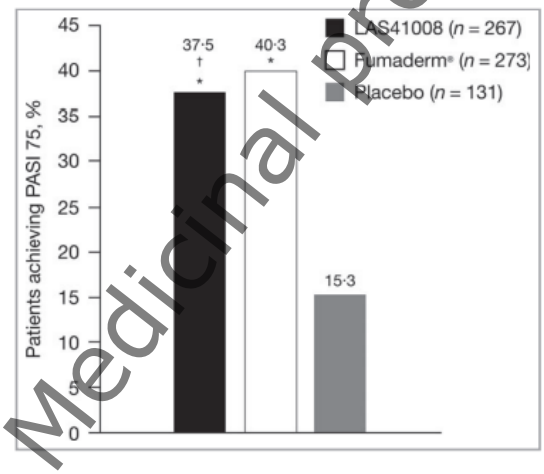
	LAS41008 (n = 279)	Fumaderm® (n = 283)	Placebo (n = 137)
Male, n (%)	174 (62·4)	185 (65·4)	93 (67·9)
Age (years)			
Mean ± SD	44·0 ± 15·2	45·0 ± 13·8	44·0 ± 14·3
Range	18–80	18–87	18–78
Race, n (%)			
White	275 (98·6)	280 (98·9)	137 (100·0)
Black/African American	1 (0·4)	0	0
Asian	1 (0·4)	3 (1·1)	0
Other	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 11).

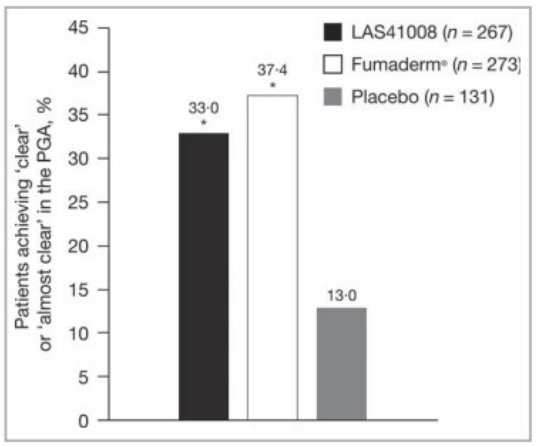
Figure 12: Percentage of patients achieving ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75) at week 16 (full analysis set). *P < 0001 vs. placebo; † P < 0001 noninferiority vs. Fumaderm



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 randomised 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 randomised 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

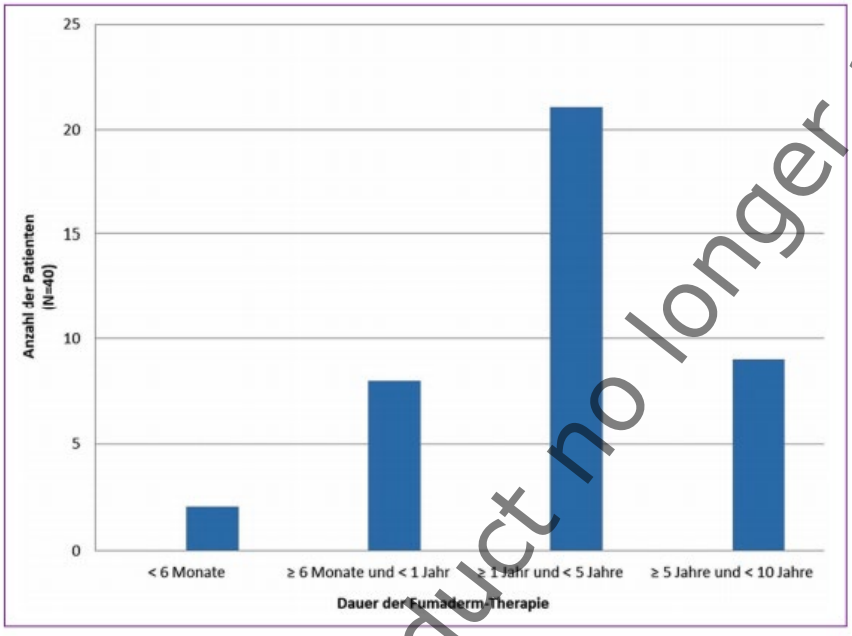
This was a prospective observational trial in patients who were treated with the FAE mixture. Patients whose psoriasis had improved and who could tolerate treatment with the FAE mixture were recruited.

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)

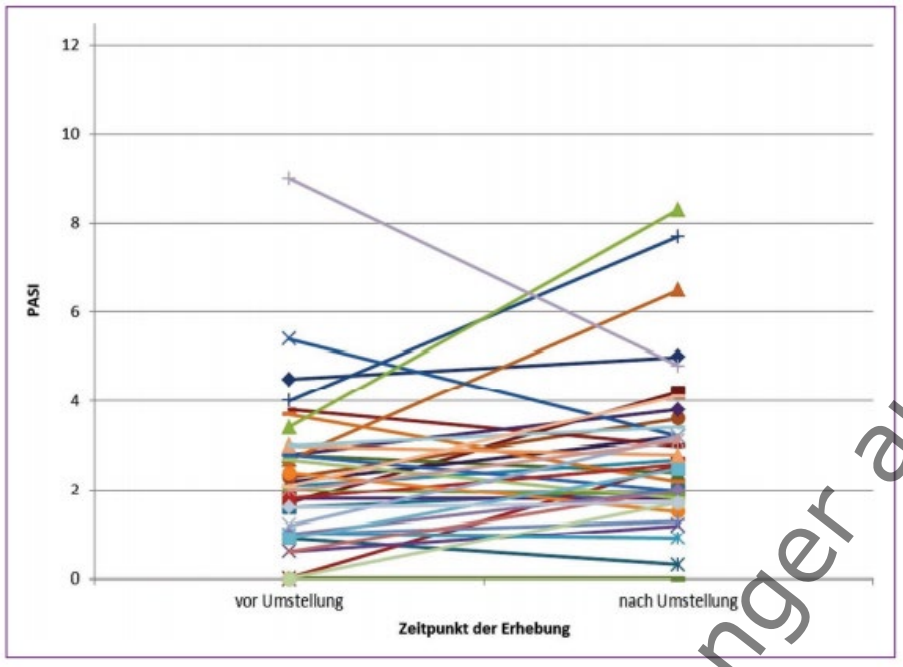


Most patients were treated with a daily DMF dose between 120 mg and 480 mg and had previously been treated with the FAE mixture for one to five years.

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 14). 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 randomised, 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 localised 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 diarrhoea. 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 randomised 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 CHMP 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 CHMP's 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 CHMP recommend adoption of the opinion.

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