15 December 2022
EMA/CHMP/2411/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dimethyl fumarate Accord

International non-proprietary name: dimethyl fumarate

Procedure No. EMEA/H/C/005950/0000

Note

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

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List of abbreviations

AE	Adverse Events
ANOVA	Analysis of Variance
ASMF	Active Substance Master File = Drug Master File
AUC_{0-t}	Area under the plasma concentration versus time curve from time zero to the last measurable concentration
$AUC_{0-\infty}$	Area under the plasma concentration versus time curve from time zero to infinity
AUC_%Extrap_obs	Residual area in percentage
BCS	Biopharmaceutics Classification System
BMI	Body mass index
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Intervals
C_{max}	Maximum measured plasma concentration
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures
CQA	Critical Quality Attribute
CV	Coefficient of Variation
DoE	Design of experiments
DSC	Differential Scanning Calorimetry
EC	European Commission
ECG	Electrocardiogram
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EU	European Union
GC	Gas Chromatography
GMR	Geometric least square mean ratio
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
KF	Karl Fischer titration

NLT	Not less than
NMR	Nuclear Magnetic Resonance
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PD	Pharmacodynamics
PSD	Particle size distribution
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
QbD	Quality by design
QTTP	Quality target product profile
SmPC	Summary of Product Characteristics
SWR	within subject standard deviation of reference product
RH	Relative Humidity
RMP	Risk Management Plan
RRMS	Relapsing Remitting Multiple Sclerosis
t_{max}	Time to reach the maximum concentration of drug in plasma
T_{lag}	Time prior to the first measurable (non-zero) concentration
λz	First order rate constant associated with the terminal (log-linear) portion of the curve
t½	elimination half-life
TSE	Transmissible Spongiform Encephalopathy
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 29 November 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Dimethyl fumarate Accord, 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 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

> *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 10 years in the EEA:

- Product name, strength, pharmaceutical form: Tecfidera, 120mg, 240mg gastro-resistant capsule, hard
- Marketing authorisation holder: Biogen Idec Ltd
- Date of authorisation: 30-01-2014
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/13/837/001; EU/1/13/837/002-003

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

- Product name, strength, pharmaceutical form: Tecfidera, 120mg, 240mg gastro-resistant capsule, hard
- Marketing authorisation holder: Biogen Idec Ltd
- Date of authorisation: 30-01-2014
- Marketing authorisation granted by:
  - Union

- Union Marketing authorisation number: EU/1/13/837/001; EU/1/13/837/002-003

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

- Product name, strength, pharmaceutical form: Tecfidera, 120 mg, 240 mg, gastro-resistant capsule, hard
- Marketing authorisation holder: Biogen Idec Ltd
- Date of authorisation: 30-01-2014
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number(s): EU/1/13/837/001; EU/1/13/837/002-003
- Bioavailability study number(s): 0856-16, 0857-16, 0002-21, 0003-21

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 and appointed by the CHMP were:

Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	29 November 2021
The procedure started on	24 December 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	11 March 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	14 March 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 April 2022
The applicant submitted the responses to the CHMP consolidated List of	12 August 2022

Questions on	
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	20 September 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 September 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	13 October 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	14 November 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	01 December 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 Accord on	15 December 2022

2. Scientific discussion

2.1. Introduction

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

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

The proposed indication for Dimethyl fumarate Accord is the same as for the reference product Tecfidera. During the assessment of this MAA, an extension of indication for paediatric patients aged 13 years and older was granted by the originator. Consequently, the proposed indication has been updated during this procedure. Therefore, the updated proposed indication for Dimethyl fumarate Accord is

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

To support the application the applicant submitted four pivotal bioequivalence studies comparing dimethyl fumarate gastro-resistant capsules 120 mg and 240 mg against Tecfidera (dimethyl fumarate) gastro-resistant capsules 120 mg 240 mg under fasting and fed conditions.

2.2. Quality aspects

2.2.1. Introduction

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

Other ingredients are:

Capsule content: silicified microcrystalline cellulose, talc, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, methacrylic acid-methyl methacrylate copolymer (1:1), triethyl citrate, methacrylic acid - ethyl acrylate copolymer (1:1) dispersion 30 per cent

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

Capsule ink: shellac (E904), iron oxide black (E172), potassium hydroxide (E525).

The product is available in PVC/PE/PVDC-Alu blisters 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 (*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:

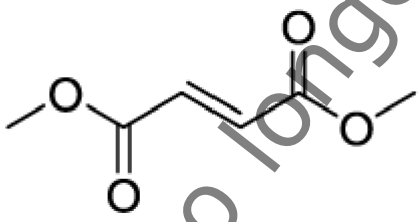


Figure 1: Active substance structure

The chemical structure of dimethyl fumarate was elucidated by a combination of the following techniques: IR, UV, ^{1}H-NMR and ^{13}C-NMR spectroscopy, mass spectrometry, and elemental analysis. The solid-state properties of the active substance were measured by XRD and DSC.

The active substance is a non-hygroscopic, white to off-white powder, practically insoluble in water at 15-25 ºC and highly soluble in aqueous media over the pH range of 1.2-6.8 at 37±1 ºC according to BCS system. The active substance has a non-chiral molecular structure. Polymorphism has not been observed for dimethyl fumarate. Dimethyl fumarate exists in one crystal form, which is consistently produced by the manufacturing process.

2.2.2.2. Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturing site. Dimethyl fumarate is synthesized in 4 main steps using well defined starting material with acceptable specifications.

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

The impurity profile of dimethyl fumarate has been evaluated with respect to the starting material, raw materials/reagents, intermediates and process. A discussion concerning possible organic and inorganic impurities, potential genotoxic impurities, elemental impurities and residual solvents has been presented and supported by analytical data. The initially provided information on genotoxic and nitrosamines impurities in the active substance was, however, considered inadequate, resulting in two major objections (MO). The applicant was asked to classify potential genotoxic impurities in line with

the ICH M7 guideline (as Class 1 to 5) and to propose a control strategy (options 1 to 4) for each specified impurity (MO 1). In addition, the applicant was asked to present a discussion on nitrosamine impurities in the active substance in-line with considerations given in the EMA and CMDh guidelines, EMA/369136/2020, EMA/409815/2020 Rev.8 and CMDh/412/2019, Rev.15 (MO 2).

In response to MO 1, the applicant has provided additional discussion and information concerning genotoxic impurities control strategy and demonstrated that the manufacturing process of the active substance is capable of effective purge out the impurities of concern. The additionally provided justification and data were considered sufficient, resulting in resolution of the MO 1. Potential and actual impurities were well discussed with regards to their origin and characterised. The genotoxic impurities are classified and controlled in line with the ICH M7.

In response to MO 2, the applicant has provided a risk assessment report concerning the possibility of formation of nitrosamine impurities in the active substance as per EMA guideline. The conclusion of the risk assessment is that the process of active substance synthesis is not likely to generate nitrosamine impurities, which was further supported by batch analysis data on three commercial scale batches of the active substance. Based on the obtained data, it was concluded that nitrosamines are not detected in dimethyl fumarate. The provided data were considered sufficient, MO 2 was resolved.

The active substance is packaged in a transparent polyethylene bag, which is tied with a strip seal and placed in another polyethylene bag. An activated silica bag is included between both materials. The finally packed material is placed in a HDPE container. The packaging material complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

2.2.2.3. Specification

The active substance specification includes tests for description (visual), solubility (Ph. Eur.), identification (IR, HPLC), water content (KF, Ph. Eur.), sulfated ash (Ph. Eur.), related substances (HPLC, GC), assay (HPLC), residual solvents (GC), particle size (Malvern analyzer), and microbial examination (Ph. Eur.).

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

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

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

2.2.2.4. Stability

The active substance is intended to be stored below room temperature (2 to 8ºC). Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 6 months under accelerated conditions (2 ºC / 60% RH) and for up to 60 months under long-term conditions (2 to 8ºC) according to the ICH guidelines were provided. Additional supportive stability data on three commercial size batches were provided for up to 6 months under accelerated conditions (25ºC / 60% RH) and for up to 12 months under long-term conditions (2 to 8ºC).

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

The physical and chemical parameters were well within the proposed limits during the accelerated and long-term storage conditions without showing any sign of degradation. All tested parameters were within the specifications, no trends were observed.

Results under stressed conditions (acid, alkali, oxidation, hydrolysis, thermal, UV, fluorescent light, and humidity degradation) were also provided on one batch. Significant degradation of the active substance and increase of impurities is observed under acid, alkali, oxidation, hydrolysis, UV and fluorescent stressed conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable when stored under the proposed storage conditions: "preserve in air tight container and store at 2 to 8°C, protect from light". The manufacturer proposed retest period of 36 months is considered acceptable.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

The finished product is a gastro-resistant hard capsule, available in two strengths: 120 mg and 240 mg.

The 120 mg capsules are size "0" hard gelatin capsules with a green cap and white body, printed with "HR1" in black ink on the capsule body, containing white to off-white, round, biconvex enterically coated mini-tablets which are plain on both the sides.

The 240 mg capsules are size "0" hard gelatin capsules with a green cap and body, printed with "HR2" in black ink on the capsule body, containing white to off-white, round, biconvex enterically coated mini-tablets which are plain on both the sides.

The aim of the development was to develop a robust, stable, and bioequivalent generic of the reference product Tecfidera. Pharmaceutical development of the finished product contains QbD elements. The quality target product profile (QTPP) was defined as an oral modified release dosage form that meets compendial and other relevant quality standards and was based on the properties of the active substance, characterization of the reference product and consideration of the reference product label and intended population.

The formulation and manufacturing development have been evaluated through the use of risk assessment and design of experiments (DoE) to identify the product critical quality attributes (CQAs) and critical process parameters. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The critical quality attributes identified were assay, content uniformity, related substances and dissolution, as these attributes can be altered by process parameters or formulation variables. The risk assessment of the active substance attributes was performed to evaluate the impact that each attribute could have on the finished product CQAs. Particle size of the active substance and impurities were identified as the active substance attributes, requiring further investigation. As the active substance is highly soluble, the impact of particle size on the drug release was considered low, which was confirmed by trials with active substance batches with various particle size distributions (PSD). Based on the provided data and taking into consideration the high solubility of the active substance, the 1-point specification for particle size is considered adequate to control the drug release during dissolution. The identified risk related to impurities was further ruled out by performing compatibility studies between the active substance and excipients.

Formulation development studies started with an extensive characterisation of reference products, including physical, chemical characterisation and evaluation of dissolution profiles. The formulation was designed considering pharmaceutical equivalence requirements and excipients used in the reference product. The main factors contributing to the choice of the dosage form design (mini-tablets in capsule) and the manufacturing process were QTTP target, accommodation of total fill content in comparable size of capsules and allowing dose proportionally to match the reference product. Furthermore, the capsule shell composition, mini-tablets, fill weight and manufacturing process was selected in a way that comparable release profiles to that of the reference product could be achieved. The formulation is based on a common mini-tablets concept for both 120 mg and 240 mg strength. Eleven different compositions were manufactured at the development stage to identify the final composition. Formulation development focused on evaluation of the high-risk formulation and composition variables as identified in the initial risk assessment. Further formulation optimisation was studied using DoE. Formulation optimisation was performed to understand if there is any significant interaction between these variables and any impact on dissolution of capsules. The studied response variables were compression parameters and dissolution. A total of nine trials were conducted with the optimised process parameters. None of the tested formulation variables were found to affect dissolution with any statistical significance in the studied range. No overages are used. The presented formulation development has been described and is considered satisfactory.

After the formulation was optimized, additional studies have been conducted to optimize the manufacturing process. A risk assessment was performed to identify critical process parameters and the impact of the manufacturing process variables on finished product CQAs. The process optimization study was performed by conducting trials and use of DoE. The studied manufacturing process parameters were pre-lubrication and blending time, lubrication time, and percentage range of enteric coating. To optimise the manufacturing process parameters at a larger scale, a scale-up batch has been manufactured using the equipment proposed to be used in validation batches. At this scale, seal coating process parameters were further optimised. Based on these studies, the process parameters for validation batches were established.

The selection of the dissolution media is based on the dosage form design, solubility characteristics and pharmacokinetic profile of the active substance and uses the compendial medium for gastro-resistant dosage forms (Ph. Eur. 2.9.3). The initially presented information and data related to the dissolution method development and choice of the dissolution limit was however considered inadequate, resulting in a major objection (MO). The applicant was asked to further justify the choice of the used stirring speed and to tighten the dissolution specification limit in line with the biobatch behaviour. Additionally, the applicant was asked to further demonstrate discriminatory power of the dissolution method, by providing comparative dissolution tests on batches with minor changes in the quantitative formulation or minor differences in the manufacturing process. As a response to the MO, the applicant provided additional justification and tightened the dissolution limit and provided experimental data by applying minor changes to the manufacturing process, to further investigate the discriminatory power of the dissolution method. The provided additional data and justification were considered satisfactory. The discriminatory power of the dissolution method has been adequately demonstrated.

In vitro dissolution profiles comparison of the test and reference product were presented for both strengths, 120 and 240 mg, at the acid stage (0.1N HCl) followed by buffer stage (pH 6.8 phosphate buffer) and at the acid stage (pH 4.5 acetate buffer) followed by buffer stage (pH 6.8 phosphate buffer). *In vitro* dissolution profiles of the test and reference product were considered comparable for both strengths. Four bioequivalence studies were conducted under fasting and fed conditions to compare the pharmacokinetic profiles and to demonstrate bioequivalence of the test and reference products. The formulations of the test product and reference products are considered comparable.

Minor differences in the used excipients have been shown to be non-significant and do not impact dissolution or bioequivalence of the product.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with exception of the silicified microcrystalline cellulose which complies with USP/NF. Empty hard gelatin capsule shells are tested according to the established in-house specification, the colorants used in capsule shells and printing ink comply with the directive (EU) No. 231/2012. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Compatibility studies between the active substance and excipients have been performed at accelerated temperature and humidity conditions (40 °C / 75% RH) at defined ratios for 1 month. No significant changes were observed physically and chemically, concluding that dimethyl fumarate is compatible with the studied excipients.

The primary packaging is PVC/PE/PVDC-Alu blisters. The materials comply 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 finished product is manufactured by one manufacturing site. A major objection (MO) has been raised in relation to the proposed secondary packaging site due to lack of a valid GMP certificate. The MO has been resolved, as the site will not be used and is removed from the dossier.

The manufacturing process consists of 7 main steps: sifting, blending and lubrication, compression, seal coating, enteric coating, encapsulation and packaging. The process is considered to be a non-standard manufacturing process due to the pharmaceutical dosage form. Blending, compression, seal coating, enteric coating and encapsulation are identified as the critical steps in the manufacturing process.

Major steps of the manufacturing process have been validated on three consecutive production scale batches per strength (120 mg and 240 mg). It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.2.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form including description (visual), average net content (in-house), identification (HPLC, UV), water content (KF), dissolution (HPLC), uniformity of dosage units (Ph. Eur.), related substances (HPLC, GC), assay (HPLC), microbial examination (Ph. Eur.) and residual solvents (GC).

The finished product specifications are in line with ICH Q6A. The limits for impurities are acceptable according to ICH Q3B. 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. 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.

Following the first round of assessment, a major objection (MO) was raised in relation to the potential risk of presence of nitrosamines in the finished product. The initially provided nitrosamines risk

evaluation was considered brief and inadequate to support the claim of absence of nitrosamines impurities. As a response to the MO, the applicant provided additional data and justification, demonstrating that a risk of presence of nitrosamines was sufficiently ruled out. The risk evaluation considered 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 three production scale batches of 120 mg and four production scale batches of 240 mg capsules confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the release specifications, through traditional final product release testing.

2.2.3.4. Stability of the product

Stability data from 6 production scale batches of finished product (3 batches of 120 mg and 3 batches of 240 mg) stored for up to 36 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. Additional data from 1 production scale batch of finished product (240 mg) stored for up to 12 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines was provided.

The batches of the finished product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for water content, dissolution, related substances, assay and microbiological quality. The analytical methods used were the same as for release and are stability indicating.

No significant changes have been observed in the tested parameters under long term and accelerated conditions. A minor increase in the level amount of specified impurity was observed, along with an associated increase in total impurities. However the values are well within the set specifications and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

In addition, 1 batch of the 240 mg capsules, was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes were observed. The finished product is not considered photosensitive.

Based on available stability data, the proposed shelf-life of 36 months with no special storage conditions as stated in the SmPC (section 6.3) is acceptable.

2.2.3.5. Post approval change management protocol

Not applicable.

2.2.3.6. Adventitious agents

Gelatine obtained from bovine sources is used in the product. A 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. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

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

All major objections raised during the evaluation (information provided on genotoxic impurities in the active substance, potential risk of presence of nitrosamines in the active substance and finished product, inadequate GMP certificate for the secondary packaging site, dissolution method development and related dissolution limit and discriminatory power of the dissolution method testing) have been satisfactorily resolved by provision of the relevant additional information and data or by amending the control strategy.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics (PK) 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, PK and toxicology data. The non-clinical aspects of the SmPC are in line with the Summary of Product Characteristics (SmPC) of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the Committee for Medicinal Products for Human Use (CHMP) agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

The applicant did not initially submit an environmental risk assessment (ERA) and was requested to submit one or justify that an increase in environmental exposure of the active substance is not to be expected.

During the procedure, an ERA was submitted consisting of two phases. In phase I assessment, the $PEC_{surfacewater}$ of dimethyl fumarate was calculated to be 0.036 mcg/L. The recommended Phase II assessment was conducted by evaluating the $PEC_{surfacewater}$ / $PNEC_{surfacewater}$ ratio which was estimated as below 1 for dimethyl fumarate. Further, logKow of dimethyl fumarate does not exceed 4.5. Based on these numbers, the CHMP agreed with the applicant's position that Dimethyl fumarate Accord is unlikely to represent a risk for the environment following its prescribed usage in patients.

2.3.3. Discussion on non-clinical aspects

Pharmacodynamic (PD), PK and toxicological properties of Dimethyl fumarate are well known. No new non-clinical studies were submitted by the applicant and they were not needed.

The applicant did not initially submit an ERA. However, in line with Guideline on the environmental risk assessment of medicinal products for human use EMEA/CHMP/SWP/4447/00 Rev. 1: *"An ERA is required for all new marketing authorisation applications for a medicinal product through a centralised, mutual recognition, decentralised or national procedure. According to Directive 2001/83/EC, applicants are required to submit an ERA irrespective of the legal basis. Generic medicinal products are therefore not exempted from providing an ERA*". Therefore, the applicant was requested to provide an ERA or present data to substantiate the claim that an increase in environmental exposure of the active substance is not to be expected e.g. consumption data or PEC determination.

Upon request, the applicant provided an ERA. Based on the phase I results of a $PEC_{surfacewater}$ of dimethyl fumarate being higher than 0.01- the threshold for which it is assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients if no other environmental concerns are apparent- a phase II assessment was conducted by the applicant. In this phase II assessment, the $PEC_{surfacewater}$ / $PNEC_{surfacewater}$ ratio for dimethyl fumarate was below 1. It is agreed that as per EMA guideline (EMEA/CHMP/SWP/4447/00 corr2) if the ratio $PEC_{surfacewater}$ / $PNEC_{surfacewater}$ for the drug substance is below 1, further testing in the aquatic compartment is not considered necessary and it can be concluded that the drug substance and/or its metabolites are unlikely to represent a risk to the aquatic environment. Further, logKow of dimethyl fumarate does not exceed 4.5 and then, it can also be agreed that dimethyl fumarate is not a Persistent, Bioaccumulative and Toxic substance. Based on these results, the applicant justified that the Dimethyl fumarate Accord is unlikely to represent a risk for the environment following its prescribed usage in patients. This position was agreed by the CHMP.

Non-Clinical sections of the SmPC are in line with the reference product SmPC.

2.3.4. Conclusion on the non-clinical aspects

Dimethyl fumarate Accord is considered approvable from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This application concerns a generic application according to article 10(1) of Directive 2001/83/EC for Dimethyl fumarate Accord 120 and 240 mg hard capsules. To support the marketing authorisation application the applicant conducted 4 bioequivalence study with design under fasting / fed conditions.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

GCP aspect

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

Exemption

Biowaiver Request for different strengths

The applicant intends to register two strengths of Dimethyl fumarate: 120 mg and 240 mg.

As the bioequivalence has been demonstrated for 240 mg strength, the "*Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms*" requires that other strength's composition is proportional, the formulations contain identical beads or pellets (and these are produced by the same manufacturing process) and the dissolution profiles are similar in order to exempt the other strengths from bioequivalence study.

In vitro dissolution profiles comparison of the test and reference product were presented for both strengths, 120 and 240 mg, at the acid stage (0.1N HCl) followed by buffer stage (pH 6.8 phosphate buffer) and at the acid stage (pH 4.5 acetate buffer) followed by buffer stage (pH 6.8 phosphate buffer).

During the assessment, the CHMP noted that 100 rpm was used but 50 rpm should have been used when performing dissolution studies with a paddle apparatus (100 rpm can be used using a basket apparatus). Therefore, the applicant was requested to repeat dissolution testing under acceptable apparatus/rpm conditions.

As part of the responses, the applicant explained that the impact of 50 and 100 rpm on test and reference product in the selected dissolution media (0.1N HCl followed by pH 6.8 phosphate buffer) was studied during development. As incomplete release was observed at 50 rpm; 100 rpm speed was considered

Further, the applicant also carried out dissolution study at 75 rpm

The data suggests that both test and reference product shows more than 85% drug release within 15 minutes at buffer stage for QC dissolution media (acid stage: 0.1N HCl + buffer stage: pH 6.8 phosphate buffer). Therefore, the dissolution profiles are considered similar without any mathematical calculation for similarity.

For 120 mg: Acid stage-pH 4.5 acetate buffer + Buffer stage-pH 6.8 phosphate buffer

Both test and reference product shows more than 70% release within 5 minutes. The test product shows very rapid release of 88% within 10 minutes. Therefore the calculation of *f*2 is not possible. However, in view of satisfactory bioequivalence studies and according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**), if results of comparative *in- vitro* dissolution of the bio-batches do not reflect bioequivalence as demonstrated *in-vivo* the latter prevails.

For 240 mg: Acid stage-pH 4.5 acetate buffer + Buffer stage-pH 6.8 phosphate buffer

Both test and reference product shows more than 80% release within 10 minutes. Therefore the calculation of *f*2 is not possible. However, in view of satisfactory bioequivalence studies and according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**), if results of comparative *in- vitro* dissolution of the bio-batches do not reflect bioequivalence as demonstrated *in-vivo* the latter prevails.

Considering above, the applicant's position was that it can be inferred that the test and reference product depicts comparable and complete release at 75 rpm and the proposed dissolution specification is achievable. Hence, the applicant proposes the selection of 75 rpm as appropriate.

As per Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1), *for multiple unit formulations of a medicinal product with several strengths, it is sufficient to conduct the studies listed in section 6.1.1 only at the highest/most sensitive strength if the compositions of the strengths are proportional, the formulations contain identical beads or pellets (and these are produced by the same manufacturing process) and the dissolution profiles are similar.* The applicant performed dissolution profile comparison between Test product bio-batch of Dimethyl fumarate 120mg and 240 mg gastro-resistant capsules (manufactured by: Intas Pharmaceuticals Limited India) with Reference product Dimethyl fumarate 120 and 240mg gastro-resistant capsules.

However, the waiver of the additional strength is based on dissolution >85% before 15 minutes, but this rule is applicable for immediate release products where the 15 minutes represent the gastric emptying time. In such cases, the drug is considered as almost a solution when reaching the intestine. That rule, however, is not applicable for gastro-resistant products where the dosage form is tested for 2 h at pH 1.2 or 4.5 and later dissolution occurs in the intestine at pH 6.8, which is 120+15 minutes, not 15 minutes.

This is also described in the Clinical Pharmacology Q&A document 3.8: "*Concluding similarity if dissolution of more than 85% is obtained within 15 minutes is not applicable for gastro-resistant formulations. In case of gastro-resistant formulations the release occurs after gastric emptying (median approx. 13-15 min). Therefore, the comparison of dissolution profiles should be performed even if dissolution is more than 85% before 15 min in either products or strengths. Hence, a tight sampling schedule is recommended after the product has been investigated for 2 hours in media mimicking the gastric environment (pH 1.2 or 4.5) since profile comparison (e.g. using the f2 calculation) is required*". Nevertheless, although sampling times were not frequent enough as to have 3 valid sampling times with only one above 85% or before the asymptote, it can be accepted that those profiles are similar as an exceptional case based on the difference lower than 10% in the valid sampling time at 5 and 10 minutes.

Tabular overview of clinical studies

To support the application, the applicant has submitted 4 four-period bioequivalence studies.

Table 1: Tabular overview of clinical studies

Study Identifier	Objective(s) of the study	Study design and Type of Control	Test Product(s); Dosage Regimen; Route of administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
0856-16	An open label, balanced, randomized, two-treatment, two-sequence, single oral dose, full replicate, bioequivalence study of two products of Dimethyl Fumarate 120	Four period, single oral dose, full replicate, bioequivalence Study, Fasting condition	Dimethyl Fumarate 120 mg gastro-resistance hard capsules, single dose, Oral	46	Healthy, adult, Human subjects	Single dose	Complete ; Full

Study Identifier	Objective(s) of the study	Study design and Type of Control	Test Product(s); Dosage Regimen; Route of administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
	mg gastro-resistance hard capsules in normal, healthy, adult, human subjects under fasting condition.						
0857-16	An open label, balanced, randomized, two-treatment, two-sequence, single oral dose, full replicate, bioequivalence study of two products of Dimethyl Fumarate 120 mg gastro-resistance hard capsules in normal, healthy, adult, human subjects under fed condition.	Four period, single oral dose, full replicate, bioequivalence Study, Fed condition	Dimethyl Fumarate 120 mg gastro-resistance hard capsules, single dose, Oral	47	Healthy, adult, Human subjects	Single dose	Complete ; Full
0002-21	An open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, crossover, fully replicate, bioequivalence study of Dimethyl Fumarate Gastro-Resistant Capsules 240 mg of Intas Pharmaceuticals Ltd., India with TECFIDERA® (Dimethyl fumarate) Gastro-Resistant Capsules 240 mg of Biogen Idec Ltd., Innovation House, 70 Norden Road, Maidenhead, Berkshire, SL6 4AY, United Kingdom in normal, healthy, adult human subjects under fasting condition	Four period, single oral dose, full replicate, bioequivalence study, fasting condition	Dimethyl Fumarate Gastro-Resistant Capsules 240 mg, single dose, Oral	46	Healthy, adult, human subjects	Single dose	Complete full
0003-21	An open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, crossover, fully replicate, bioequivalence study of Dimethyl Fumarate Gastro-Resistant Capsules 240 mg of Intas Pharmaceuticals Ltd., India with TECFIDERA® (Dimethyl fumarate) Gastro-Resistant Capsules 240 mg of Biogen Idec Ltd., Innovation House, 70 Norden Road, Maidenhead, Berkshire, SL6 4AY, United Kingdom in normal, healthy, adult human subjects under fed condition	Four period, single oral dose, full replicate, bioequivalence study, fed condition	Dimethyl Fumarate Gastro-Resistant Capsules 240 mg, single dose, Oral	42	Healthy, adult, human subjects	Single dose	Complete full

No pharmacodynamic and therapeutic equivalence studies were submitted.

According to the Dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg product-specific

bioequivalence guidance (EMA/CHMP/421315/2017) bioequivalence study for 120 mg strength is not required.

However, the applicant performed studies 0856-16 and 0857-16 evaluating the 120 mg dose under fast and fed conditions.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study 0856-16: An open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, full replicate, bioequivalence study of two products of Dimethyl Fumarate 120 mg gastro-resistant hard capsules in normal, healthy, adult, human subjects under fasting condition.

Methods

- **Study design**

The study was an open label, randomized, two-sequence, two-treatment, four-period, single oral dose, full replicate, bioequivalence study in healthy adult human subjects under fasting condition, with a screening period of 28 days prior to the dosing in Period-I. In each study period, 26 blood samples, including one pre- dose blood sample, were collected from each subject except for the discontinued/ withdrawn subjects to analyze the PK profile of the test product as well as the reference product.

After an overnight fast of at least 10 hours, a single oral dose (120 mg) of either the test product or the reference product was administered with 240 ± 02 mL of drinking water at ambient temperature with the subjects in sitting posture.

All the subjects were administered the study drug in each period except the discontinued/ withdrawn subjects (three subjects). The sequence of administration was determined by the randomization schedule. A washout period of 4 days was maintained between the successive dosing days. The duration of the clinical part of the study was about 14 days (11 hours prior to the dose administration in Period-I until the last PK sample in Period-IV). Dosing dates period I (23 January 2018), period II (27 January 2018), period III (31 January 2018) and period IV (04 February 2018).

For PK evaluation, a total of 26 blood samples were collected in each period at the time points specified in the protocol.

The venous blood samples were to be withdrawn at pre-dose (0.000 hour) and at 0.333, 0.667, 1.000, 1.250, 1.500, 1.750, 2.000, 2.250, 2.500, 2.750, 3.000, 3.333, 3.667, 4.000, 4.333, 4.667, 5.000, 5.500, 6.000, 6.500, 7.000, 8.000, 9.000, 10.000 and 12.000 hours following drug administration in each period.

As per protocol, the pre-dose blood samples were collected within a period of 60 minutes before dosing. Post-dose in-house blood samples were collected within ± 02 minutes from scheduled time. The actual time of collection of each blood sample was recorded immediately after blood collection. Post-dose blood samples not collected within this time frame from scheduled time were documented as sampling deviations.

- **Test and reference products**

Dimethyl fumarate 120 mg gastro-resistant hard capsules manufactured by Intas Pharmaceuticals Limited, India has been compared to Tecfidera 120 mg gastro-resistant hard capsules manufactured by Biogen (Denmark).

- **Population(s) studied**

Non-smoker, normal, healthy, adult, human volunteers between 18 to 45 years of age (both inclusive), having a Body Mass Index (BMI) between 18.5 to 30.0 kg/m2 (both inclusive), having clinically acceptable lymphocytes count, were able to understand and comply with the study procedures and having given their written informed consent were checked in for the study. They did not have any significant diseases or clinically significant abnormal findings during screening, medical history, clinical examination, vital signs assessment, laboratory evaluations (e.g. hematology, biochemistry, urine analysis and immunological tests), 12-lead Electrocardiogram (ECG) and chest X-ray (posterior anterior view) recordings.

- **Analytical methods**

Full validation of method for the determination of monomethyl fumarate in human plasma using LC-MS/MS (WATERS QUATTRO PREMIER XE). 182-16.

A validation process was performed to assess monomethyl fumarate in human plasma using LC-MS/MS to support clinical studies: 0002-21, 0003-21, 0856-16 and 0857-17. The detection method was found to be linear at ranges from 10.006 to 6005.758 ng/mL, using 8 point calibration curve (acceptable precision and accuracy). Following parameters were addressed during validation and met the acceptance criteria: selectivity (tested for normal, lipemic and hemolyzed plasma), precision and accuracy (within and between run), recovery, storage (at room temperature for 9.0 hours), extract stability (7°C ± 4°C for 82.0 hours), long-term storage (96 days at -65 ± 10°C & 98 days at -22 ± 5°C), whole blood stability. Sensitivity was set to 10.006 ng / mL. No interference of metabolites, matrix effect and carryover effect were found. Quantification of DMF was found to be precise and accurate in the presence of cetirizine, ibuprofen, aspirin, ranitidine, paracetamol, domperidone, diclofenac, nicotine and caffeine. Long term storage for 726 days at -22 ± 5°C and 728 days at -65 ± 10°C was not confirmed. Partial validation was performed to transfer bioanalytical method from different locations (addendum I, III, IV and VI), to approve long-term stability of analyte in human plasma: 96 days at -65 ± 10°C & 98 days at -22 ± 5°C (addendum I), to change extraction and mobile phase buffers, to change instrument (to API 6500) (addendum III and IV).

All parameters recommended for analytical method validation were addressed (EMEA/CHMP/EWP/192217/2009) and met the acceptance criteria. Validation seems to be acceptable.

Partial validation of method for the determination of monomethyl fumarate in human plasma using LC MS/MS. MV(C)-086-18.

A partial validation process for bioanalytical method transfer was performed to assess monomethyl fumarate in human plasma using LC-MS/MS to support clinical studies: 0856-16 and 0857-17. The detection method was found to be linear at ranges from 10.013 ng/mL to 6004.873 ng / mL, using 8 point calibration curve (acceptable precision and accuracy - 0.5 % to 5.7 % and from 98.1 % to 101.8 %, respectively). Following parameters were addressed during validation and met the acceptance criteria: selectivity (tested for normal, lipemic and haemolyzed plasma), precision and accuracy (within and between run), recovery, storage (stored in the refrigerator maintained at 4 ± 4°C for 13 days), extract stability (7°C ± 4°C for 74.0 hours), long-term storage (in human plasma: 96 days at -65 ± 10°C and 98 days at -22 ± 5°C). Sensitivity was set to 10.013 ng/mL. No interference of metabolites, matrix effect and carryover effect were found. Stability of analyte and IS in the working and stock solution was confirmed (stock solution stability of drug in methanol, methanol:water (50:50) solution, stored for 13 days at 4oC, methanol:water (50:50) solution stored for 14 days at 4oC).

Partial validation for bioanalytical method transfer seems to be acceptable.

Bioanalytical report LAMBDA'S project no. 0856-16. assay of monomethyl fumarate in human plasma (K2EDTA) BY LC-MS/MS (AB SCIEX API 6500).

Human plasma samples (4992 samples) were analysed for dimethyl fumarate in clinical study number 0856-16. Samples were stored for a maximum time of 102 days. Total 58 runs were analysed for DMF in human plasma, and 57 met the acceptance criteria. Incurred sample reproducibility was performed for 300 samples; 296 samples (98.7%) were acceptable as repeated samples had a relative difference not exceeding 20% compared to the first evaluation.

The accuracy and precision of QC samples has been approved – HQC, MQC, LMQC, LQC, (3.9, 2.6, 3.0, 4.5, precision respectively; and 97.9%, 99.2%, 98.7%, 97.5%, accuracy respectively). Total, 231 samples were reanalysed due to: variation in response of IS (126), poor chromatography (1) and failed to meet acceptance criteria (104). Total 4.8% samples were reanalysed in respect to total sample number. 20% of serially selected subject's chromatograms were submitted (16.5.7.2). Obtained results were within the range of the calibration curve.

- **Pharmacokinetic variables**

Primary PK parameters: C_{max} (Maximum measured plasma concentration), AUC_{0-t} (Area under the plasma concentration versus time curve from time zero to the last measurable concentration) and $AUC_{0-\infty}$ (Area under the plasma concentration versus time curve from time zero to infinity)

Secondary PK parameters: t_{max} (time to reach the maximum concentration of drug in plasma), λz (first order rate constant associated with the terminal (log-linear) portion of the curve), t½ (elimination half-life), AUC_%Extrap_obs (residual area in percentage) and Tlag (the time prior to the first measurable (non-zero) concentration)

These PK parameters were calculated for Monomethyl fumarate by using non-compartmental model of Phoenix® WinNonlin® Version 6.4 (Certara L.P.).

- **Statistical methods**

Descriptive statistics were calculated and reported for the PK parameters of Monomethyl fumarate.

ANOVA, power and ratio analysis for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are calculated and reported for Monomethyl fumarate.

Using two-one sided tests for bioequivalence, 90% confidence intervals (CI) for the geometric least square mean ratio (GMR) between drug formulations are calculated and reported for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate.

Criteria for conclusion of bioequivalence are as follows:

Based on the statistical results of 90% CI for the ratio of the geometric least squares means for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ conclusion was drawn for Test Product-T vs. Reference Product-R for Monomethyl fumarate with following considerations:

For AUC_{0-t} and $AUC_{0-\infty}$: If the 90% CI of GMR of Test to Reference falls within the acceptance range of 80.00–125.00% for ln-transformed PK parameter AUC_{0-t} and $AUC_{0-\infty}$.

For C_{max}:

1) If within-reference intra-subject coefficient of variation (CV) of ln-transformed $C_{max} \leq 30\%$ then bioequivalence of the test product with that of the reference product is concluded, if the 90% CI falls within the acceptance range of 80.00–125.00% for ln-transformed PK parameter C_{max}.

2) If within-reference intra-subject CV of ln-transformed C_{max} > 30% then BE limit is widen using scaled-average-bioequivalence. Under scaled-average bioequivalence, [U, L] = exp [±k·SWR], where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range k is the regulatory constant set to 0.760 and SWR is the within-subject standard deviation of the ln transformed values of C_{max} of the reference product.

3) If within-reference intra-subject CV of ln-transformed C_{max} ≥ 50% then C_{max} limit is widen maximum up to 69.84 to 143.19%.

Bioequivalence of the test product with that of the reference product was to be concluded for C_{max} of Monomethyl fumarate, if both of the following conditions are satisfied.

i) The 90% CI for ln-transformed data of C_{max} fell within the newly widened acceptance range [U, L] = exp [±k·SWR], which was to be based upon the within-subject variability of reference product observed for C_{max}.

ii) The GMR of test to reference for C_{max} fell within the acceptance range of 80.00-125.00%.

All statistical analyses for Monomethyl fumarate were to be performed using PROC GLM of SAS® Version 9.3 (SAS Institute Inc, USA).

Determination of Sample Size

Based on the in-house study data, the maximum intra-subject variability observed for primary PK parameter was found to be ~ 30%; the sample size computation was determined using SAS by considering the following assumptions:

- T/R ratio = 90.0 – 110.0%
- Intra-subject CV (%) ~ 30%
- Significance Level = 5%
- Power ≥ 80%
- Bioequivalence Limits=80.00-125.00%

A sample size of 32 subjects were required to establish bioequivalence between formulations with adequate power. Considering approximately 25% dropouts and/or withdrawals, a sample size of 48 subjects were to be sufficient to establish bioequivalence between formulations with adequate power for the pivotal fully replicated study.

Results

- **Disposition of subjects**

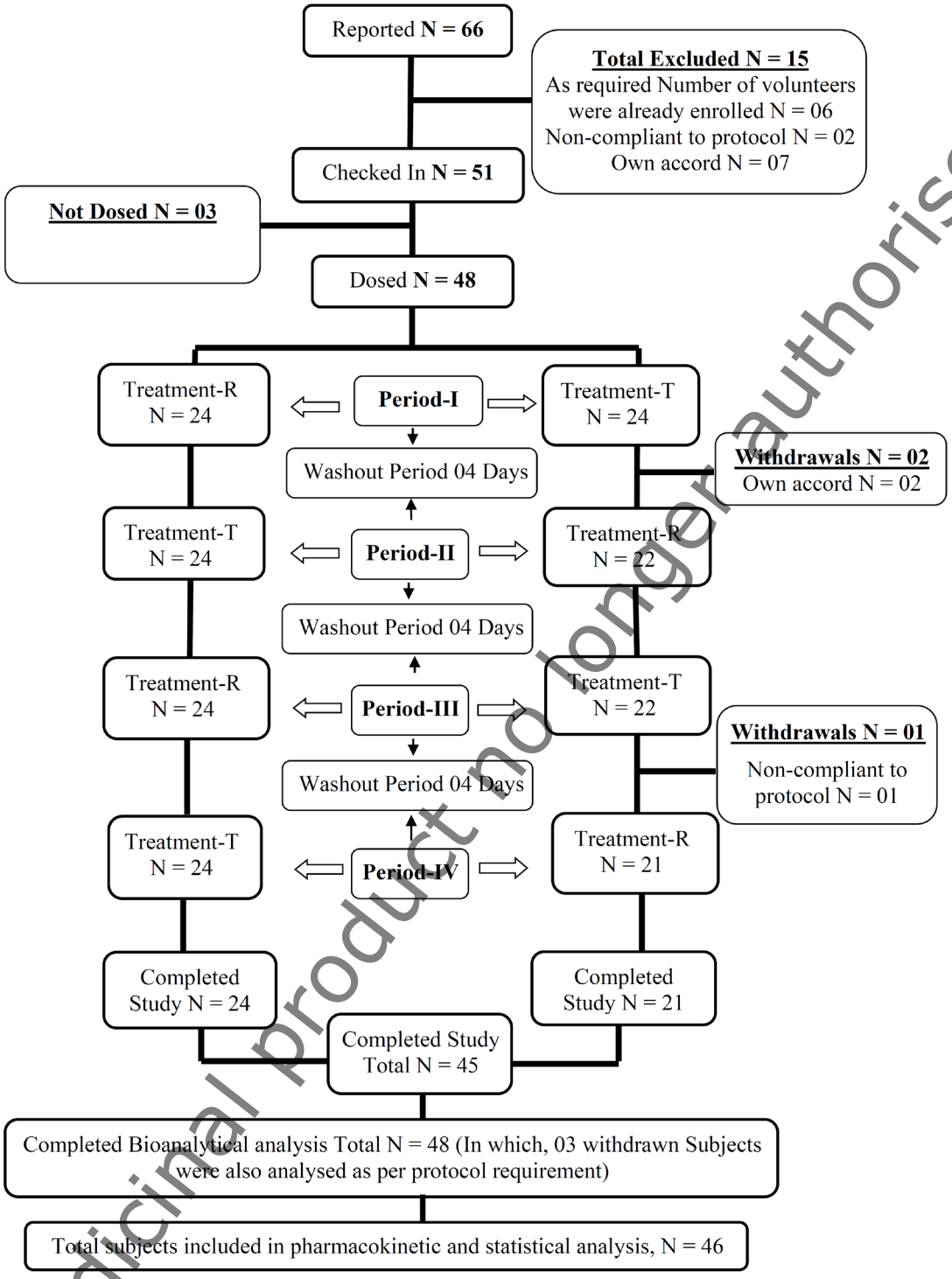
A total of 51 subjects were checked in for Period-I of the study. Three subjects were checked in for the study, in order to compensate for any dropouts prior to dosing in Period-I.

All the extra subjects were checked out of the facility as none of the subjects discontinued / were withdrawn from the study prior to dosing in Period-I.

Two subjects discontinued from the study on their own accord in Period-II. Another subject was withdrawn from the study in Period-IV on the grounds of protocol non-compliance.

In all, 45 subjects completed clinical phase of the study successfully.

Figure 1: Participants flow - Study 0856-16



Five protocol deviations were reported, two subjects were checked in later than the scheduled time and post-study safety assessment was not performed for three subjects because these three subjects were discontinued/withdrawn.

- **Data sets analyzed**

Plasma samples of 48 subjects were analysed. Three withdrawn subjects were also analysed as per protocol requirement. Total 46 subjects were included in the PK and statistical analysis. There were no missing samples during the conduct of the study.

- **Pharmacokinetic results**

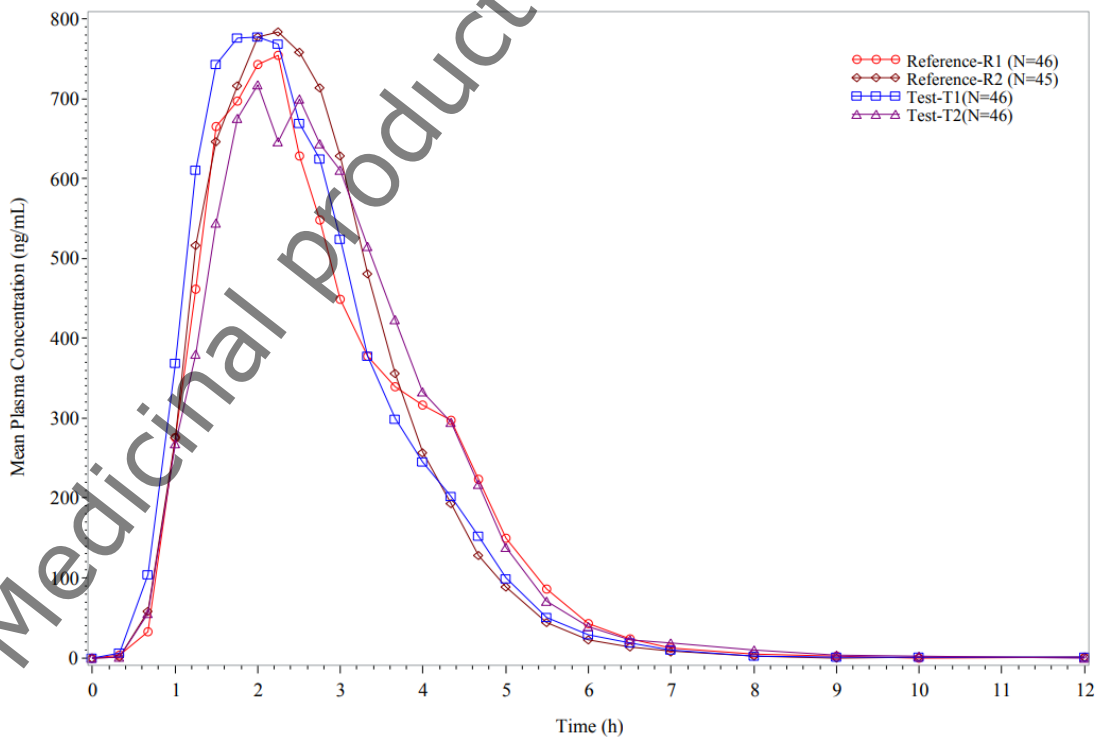
The GMR of the test to reference product and associated 90% CI of the AUC_{0-t} was contained within 80.00% - 125.00%. The GMR of the test to reference product of the C_{max} was contained within 80.00% - 125.00%. The 90% CI associated with the GMR of the test to reference product C_{max} was contained within the limits of 80.00% - 125.00% as the within-subject standard deviation (SWR) of the reference product for C_{max} was 0.2588.

Table 2: Descriptive Statistics of Formulation Means for Monomethyl fumarate (N = 46) - Study 0856-16

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T (N = 92 Observations)	Reference Product-R (N = 91 Observations)
T_{max} (h)#	2.000 (1.000 - 4.667)	2.000 (1.000 - 4.667)
C_{max} (ng/mL)	1315.362 ± 439.7573	1348.153 ± 419.6954
AUC_{0-t} (ng.h/mL)	2075.521 ± 432.6370	2039.740 ± 457.0103
$AUC_{0-\infty}$ (ng.h/mL)	2092.389 ± 431.5257	2059.038 ± 453.6241
λ_z (1/h)	1.118 ± 0.3351	1.239 ± 0.2884
$t_{½}$ (h)	0.710 ± 0.3400	0.678 ± 0.8488
AUC_%Extrap_obs (%)	0.842 ± 1.2944	0.968 ± 2.7714
T_{lag} (h)#	0.667 (0.000 - 2.750)	0.667 (0.000 - 2.750)

T_{max} and T_{lag} is represented in median (min-max) value

Figure 2 The mean plasma concentration vs. time curve for Monomethyl fumarate (Upper Panel: Linear Plot; Lower Panel: Semilog Plot) - Study 0856-16



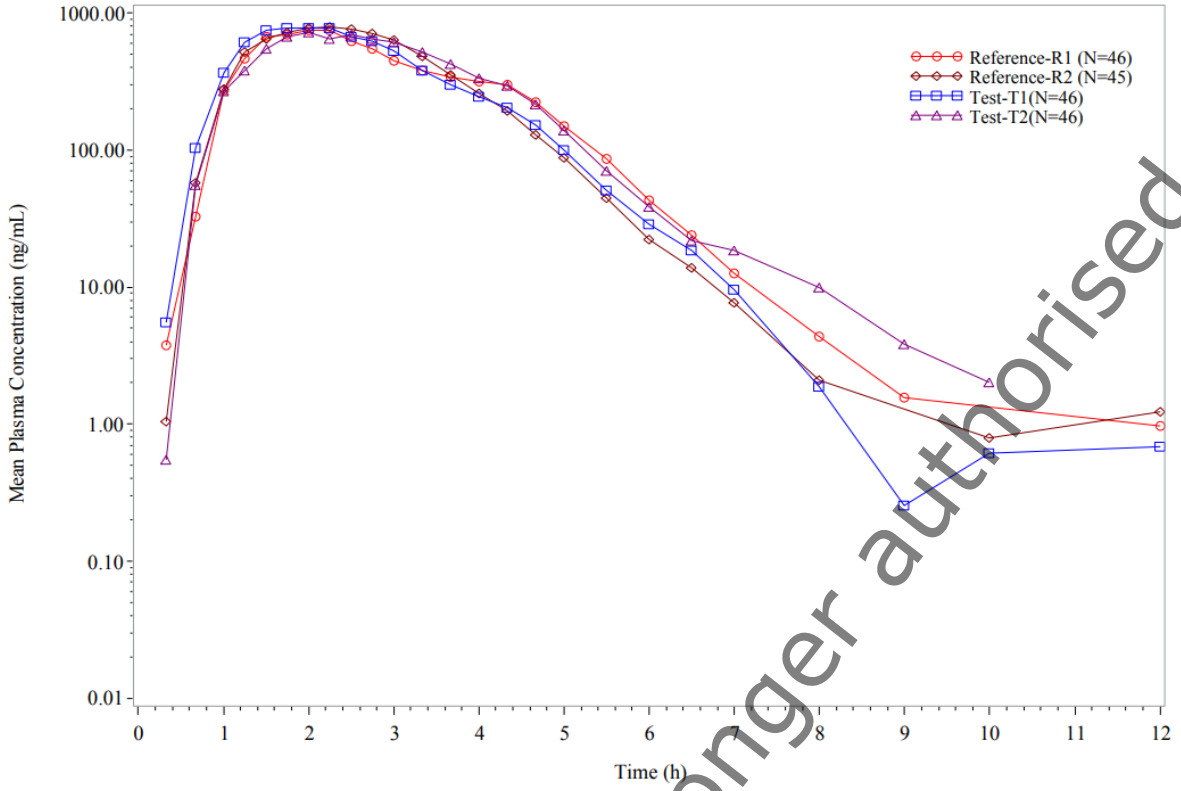
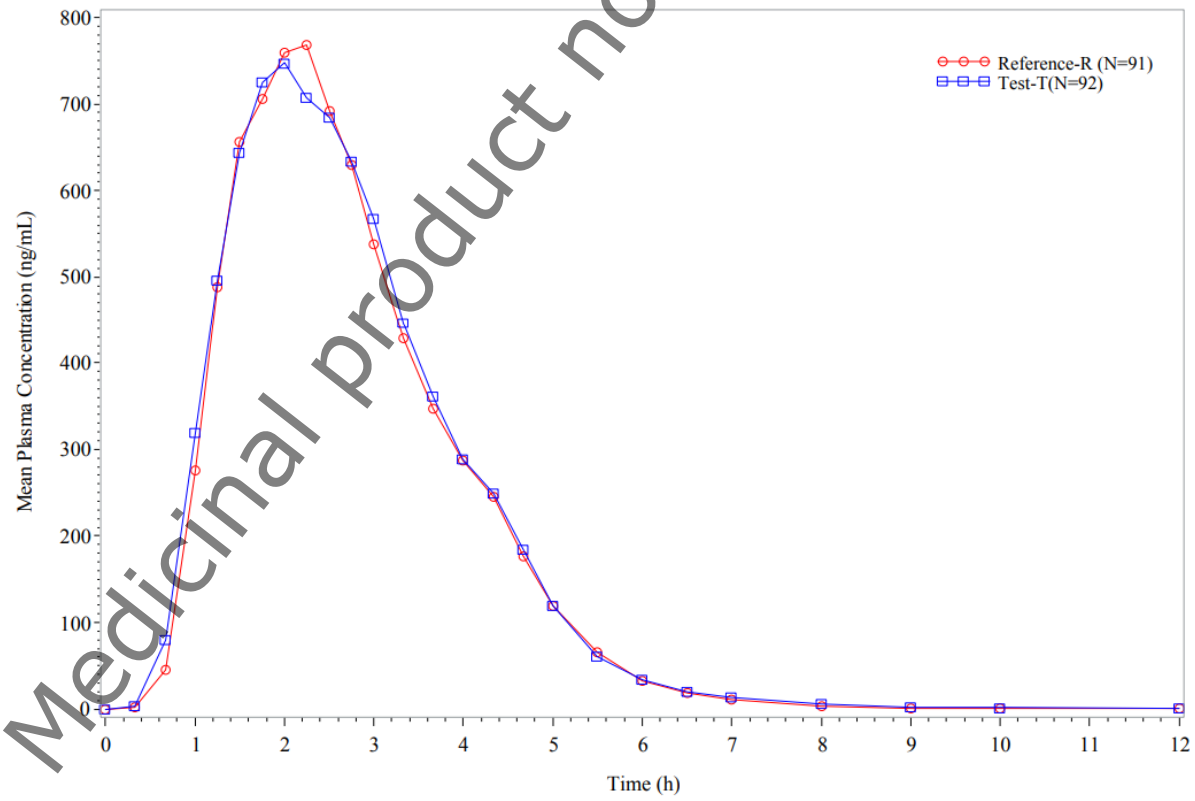
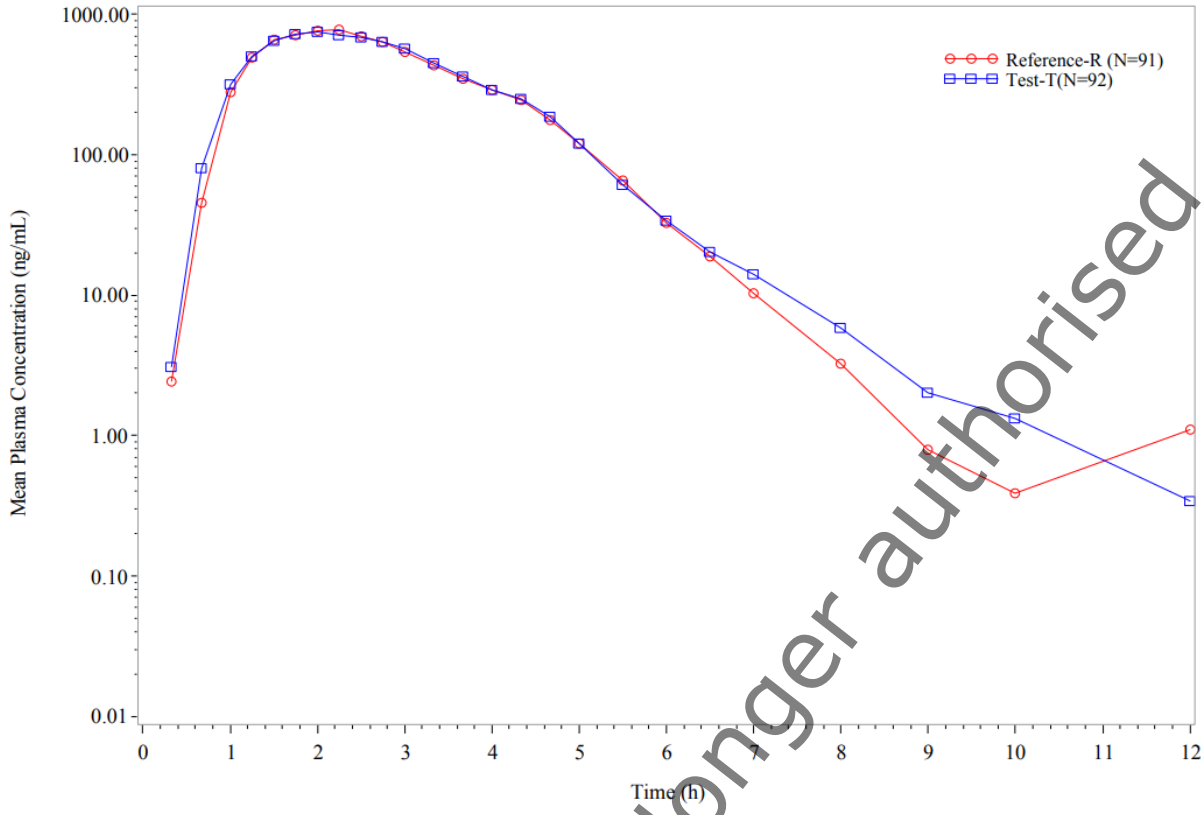


Figure 3: Combined mean plasma concentration vs. time curve for Monomethyl fumarate (Upper Panel: Linear Plot; Lower Panel: Semilog Plot) - Study 0856-16





- **Statistical Analysis**

Statistical analysis on ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Monomethyl fumarate are performed using PROC GLM of SAS® Version 9.3 (SAS Institute Inc, USA).

One subject has completed three treatment periods with one reference and two test formulations. Hence, this subject is included in PK and statistical analysis. However, the same subject is not considered in the calculation of SWR.

The intra-subject CV of reference product and SWR of C_{max} for Monomethyl fumarate are estimated using PROC GLM of SAS® Version 9.3 (SAS Institute Inc., USA).

Table 3: Intra-subject CV and Within-Subject Standard Deviation of Reference Product for Monomethyl fumarate (N = 90 Observations) - Study 0856-16

Dependent	lnC_{max}
Intra-Subject CV of Reference Product-R (%)	26.3
Within-Subject Standard Deviation of Reference Product-R (S_{WR})	0.2588

Intra-subject CV of reference product for ln-transformed PK parameter C_{max} is found to be ≤ 30%. Hence, for bioequivalence the acceptance limit for C_{max} is considered 80.00 - 125.00% as per criteria set in the protocol.

Table 4: Relative Bioavailability Results for Monomethyl fumarate (N = 46) - Study 0856-16

Parameters	Geometric Least Squares Means			90% Confidence Interval	Acceptance Criteria (%)	Intra-subject CV of Reference Product-R (%)	Power (%)
	Test Product-T (N = 92 Observations)	Reference Product-R (N = 91 Observations)	Ratio (T/R) %				
lnC_{max}	1245.966	1279.386	97.4	91.75 - 103.37	80.00 - 125.00	26.3	100.0
$lnAUC_{0-t}$	2031.605	1990.814	102.0	100.10 - 104.03	80.00 - 125.00	9.1	100.0
$lnAUC_{0-\infty}$	2049.235	2010.739	101.9	99.92 - 103.95	80.00 - 125.00	9.7	100.0

The point estimates and 90% CI for the ln-transformed PK variables C_{max} and AUC were within the predefined bioequivalence range of 80.00% - 125.00% and therefore the results could indicate bioequivalence between the test and reference products.

It can be concluded that bioequivalence between Dimethyl fumarate 120 mg gastro-resistant hard capsules and Tecfidera® 120 mg gastro-resistant hard capsules in healthy, male volunteers under fasting conditions was demonstrated.

Table 5: ANOVA p-values for Monomethyl fumarate - Study 0856-16

ANOVA p-values for Monomethyl fumarate

Parameters	ANOVA (p-values)			
	Formulation	Sequence	Period	Subject (Sequence)
lnC_{max}	0.4637	0.5032	0.1046	<0.0001
$lnAUC_{0-t}$	0.0832	0.0564	0.1647	<0.0001
$lnAUC_{0-\infty}$	0.1141	0.0867	0.1704	<0.0001

Note: Significant value if p-value < 0.05.

Formulation, Sequence and Period effect were found to be statistically insignificant for ln-transformed PK parameter C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate.

Subject (Sequence) effects were found to be statistically significant for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate. Since each subject was assigned only one sequence, subjects were said to be nested within sequence. This Subject (Sequence) effect is tested by the Residual and should be highly significant. This significance was an indication that the purpose of using the crossover design has been realized in that the between-subject variance is significantly larger than the residual.

- **Safety data**

A total of 51 subjects were checked in the study. Out of these 51 subjects, 48 subjects were dosed in Period-I. The safety assessment includes information for all 48 subjects who were dosed at least once during this study.

There were no adverse events (AEs) during the conduct of the study.

Study 0857-16: An open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, full replicate, bioequivalence study of two products of Dimethyl Fumarate 120 mg gastro-resistant hard capsules in normal, healthy, adult, human subjects under fed condition.

Methods

- **Study design**

The study was an open label, balanced, randomized, two-treatment, two sequence, four-period, single oral dose, crossover, fully replicate, bioequivalence study in healthy, adult, human subjects under fed conditions, with a screening period of 28 days prior to the dosing in Period-I. In each study period, 29 blood samples, including one pre-dose blood sample, were collected from each subject except for the withdrawn / discontinued subjects to analyze the PK profile of the test as well as the reference product.

After an overnight fast of at least 10 hours, the subjects were served standardised high fat high calorie vegetarian breakfast, which they consumed within 30 minutes. A single oral dose (120 mg) of either the test product or the reference product was administered to the subjects at 30 minutes after serving the breakfast. The investigational medical product was administered in sitting position with 240 ± 02 mL of drinking water at ambient temperature. The capsule was swallowed whole without chewing or crushing.

All the subjects were administered the study drug in each period except for the three discontinued / withdrawn subjects. The sequence of administration was determined by the randomization schedule. A washout period of 04 days was considered sufficient between the successive dosing days. The duration of the clinical part of the study was about 14 days (11 hours prior to the dose administration in Period-I until the last PK sample in Period-IV). Dosing dates period I (24 January 2018), period II (28 January 2018), period III (1 February 2018) and period IV (05 February 2018).

As per protocol, a total of twenty-nine (29) blood samples, each of 03 mL were to be collected from each subject in each period at pre-dose (0.000 hour) and at 0.333, 0.667, 1.000, 1.333, 1.667, 2.000, 2.333, 2.667, 3.000, 3.333, 3.667, 4.000, 4.333, 4.667, 5.000, 5.333, 5.667, 6.000, 6.333, 6.667, 7.000, 7.500, 8.000, 8.500, 9.000, 10.000, 11.000 and 12.000 hours following drug administration in each period.

As per protocol, the pre-dose blood samples were collected within a period of 60 minutes before scheduled time for all the subjects. The actual time of collection of each blood sample was recorded immediately after blood collection ended. Post-dose sample not collected within this time frame from the scheduled time were documented as sampling deviation.

- **Test and reference products**

Dimethyl fumarate 120 mg gastro-resistant hard capsules manufactured by Intas Pharmaceuticals Limited, India has been compared to Tecfidera 120 mg gastro-resistant hard capsules manufactured by Biogen (Denmark).

- **Population(s) studied**

Same eligibility criteria as Study 0856-16.

- **Analytical methods**

A validation process was performed to assess monomethyl fumarate in human plasma using LC-MS/MS to support clinical studies: 0002-21, 0003-21, 0856-16 and 0857-17. In addition the partial validation process for bioanalytical method transfer was performed to assess monomethyl fumarate in human plasma using LC-MS/MS to support clinical studies: 0856-16 and 0857-17, for details please see the description in the study 0856-16 section.

Bioanalytical report LAMBDA'S project no. 0857-16, assay of monomethyl fumarate in human plasma (K2EDTA) BY LC-MS/MS (AB SCIEX API 6500).

Human plasma samples (5568 samples) were analyzed for DMF in clinical study number 0857-16. Samples were stored for a maximum time of 112 days. Total 53 runs were analyzed for dimethyl fumarate in human plasma, and 52 met the acceptance criteria. Incurred sample reproducibility was

performed for 329 samples; 325 samples (98.8%) of them were acceptable as repeated samples had relative differences not exceeding 20% compared to the first evaluation.

The accuracy and precision of QC samples has been approved – HQC, MQC, LMQC, LQC, (2.6, 2.7, 2.3, 5.5, precision respectively; and 98.7% 100.0% 99.1% 98.4%, accuracy respectively). Total, 205 samples were reanalysed due to: variation in response of IS (89), and failed to meet acceptance criteria (116). Total 3.8% samples were reanalysed in respect to total sample number. 20% of serially selected subject's chromatograms were submitted (16.5.7.2). Obtained results were within the range of the calibration curve.

The applicant provided results the long term stability of analyte, monomethyl fumarate, in human plasma for 229 days at -70 ± 10°C during method validation MV (C)-086-18. The generated stability results cover the duration of study (that is 102 days and 122 days for 0856-16 and 0857-16 respectively). The experiment performed during this partial validation is acceptable. The experiment proves that the analyte is stable for 229 days in human plasma at -70 ± 10°C.

- **Pharmacokinetic variables**

Same as Study 0856-16.

- **Statistical methods**

Descriptive statistics are calculated and reported for the PK parameters of Monomethyl fumarate. ANOVA, power and ratio analysis for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are calculated and reported for Monomethyl fumarate.

Using two-one sided tests for bioequivalence, 90% CI for the GMR between drug formulations are calculated and reported for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate.

An F-test was to be performed to determine the statistical significance of the effects involved in the model at a significance level of 5% (alpha=0.05).

The power of the study was to be calculated and reported for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate.

The GMR of test and reference formulations was to be calculated and reported for the ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate.

The SWR of reference product and intra-subject variability of reference product was to be calculated and reported for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate.

Any missing samples (M) or non-reportable (NR) concentration values were to be disregarded in PK and statistical analysis.

Using two one-sided tests for bioequivalence, 90% CI for the GMR between drug formulations were to be calculated for ln-transformed data of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ Monomethyl fumarate.

Criteria for conclusion of bioequivalence were the same as the ones reported for Study 0856-16.

Determination of Sample Size

Based on the in-house study data, the maximum intra-subject variability observed for primary PK parameter was found to be ~ 30%; the sample size computation was determined using SAS by considering the same assumptions reported for Study 0856-16

A sample size of 36 subjects were required to establish bioequivalence between formulations with adequate power. Considering approximately 25% dropouts and/or withdrawals, a sample size of 48

subjects were to be sufficient to establish bioequivalence between formulations with adequate power for the pivotal fully replicated study.

Results

- **Disposition of subjects**

As per protocol, a total of 48 subjects were checked in for Period-I of the study.

On the day of dosing for Period-I, prior to dosing, one subject was withdrawn from the study on the grounds of the protocol non-compliance (he could not completely consume the high fat high calorie breakfast). He was replaced with extra available subject.

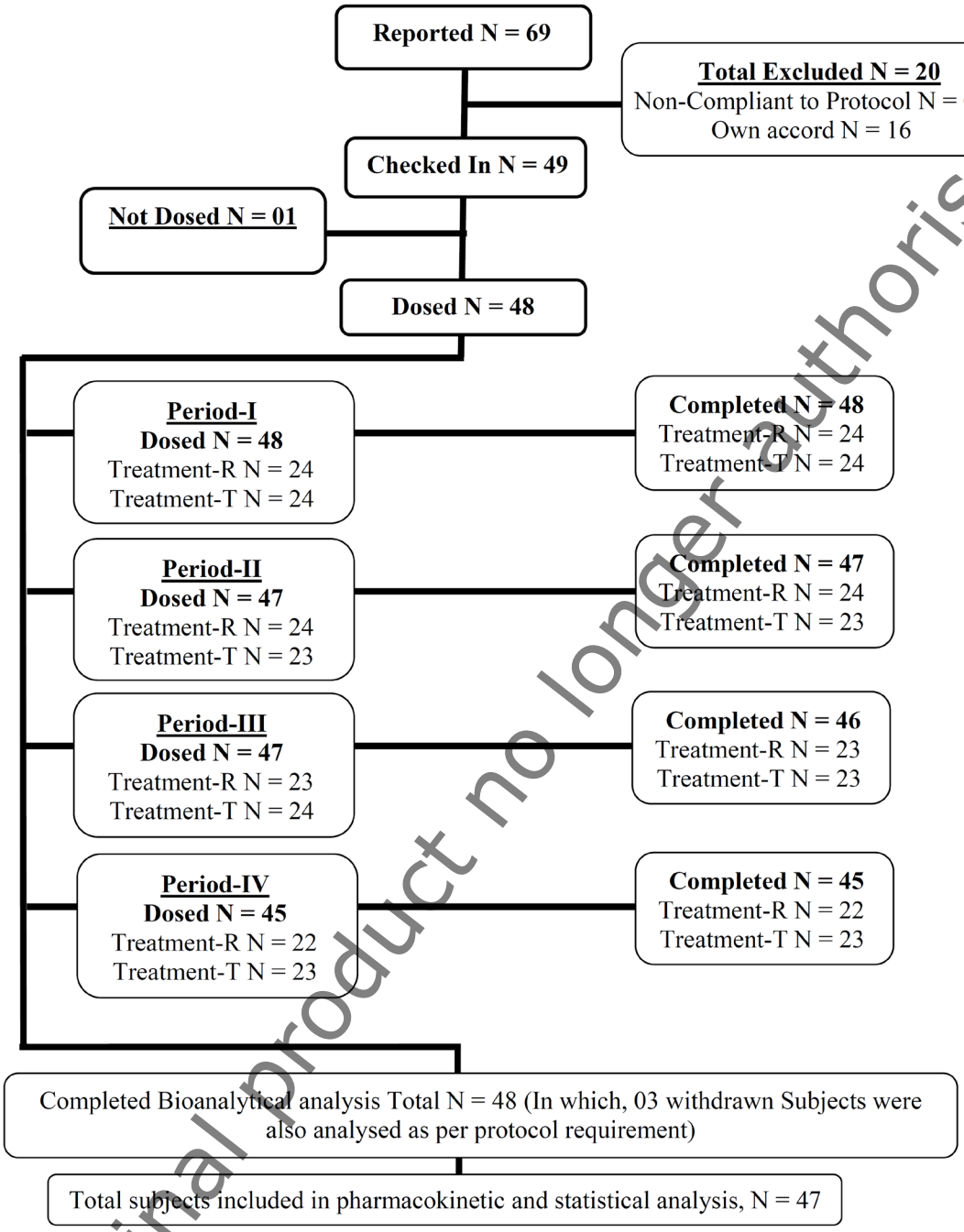
No female volunteers were checked in for the study.

As per protocol, a total of 48 subjects were dosed in Period-I.

One subject discontinued from Period-II, III and IV of the study on their own accord. Other subject was withdrawn from the study on medical grounds in Period-III and IV. Another subject was withdrawn from the study on the grounds of the protocol non-compliance in Period-IV.

In all, 45 subjects completed all the periods of the study successfully.

Figure 4: Participants flow - Study 0857-16



Twelve protocol deviations were reported, one subject was delayed from scheduled time. Six subjects were checked in later than the scheduled time, four postural restrictions were reported and post-study safety assessment was not performed for one subject.

- **Data sets analyzed**

The study was planned so as to obtain the data from 48 evaluable subjects. Out of these 48 dosed subjects, 45 subjects completed all the periods of the study successfully.

Plasma samples of 48 subjects were analysed. In which, withdrawn three subjects were also analysed as per protocol requirement.

Total 47 subjects were included in the PK and statistical analysis.

There were no missing samples during the conduct of study.

- **Pharmacokinetic results**

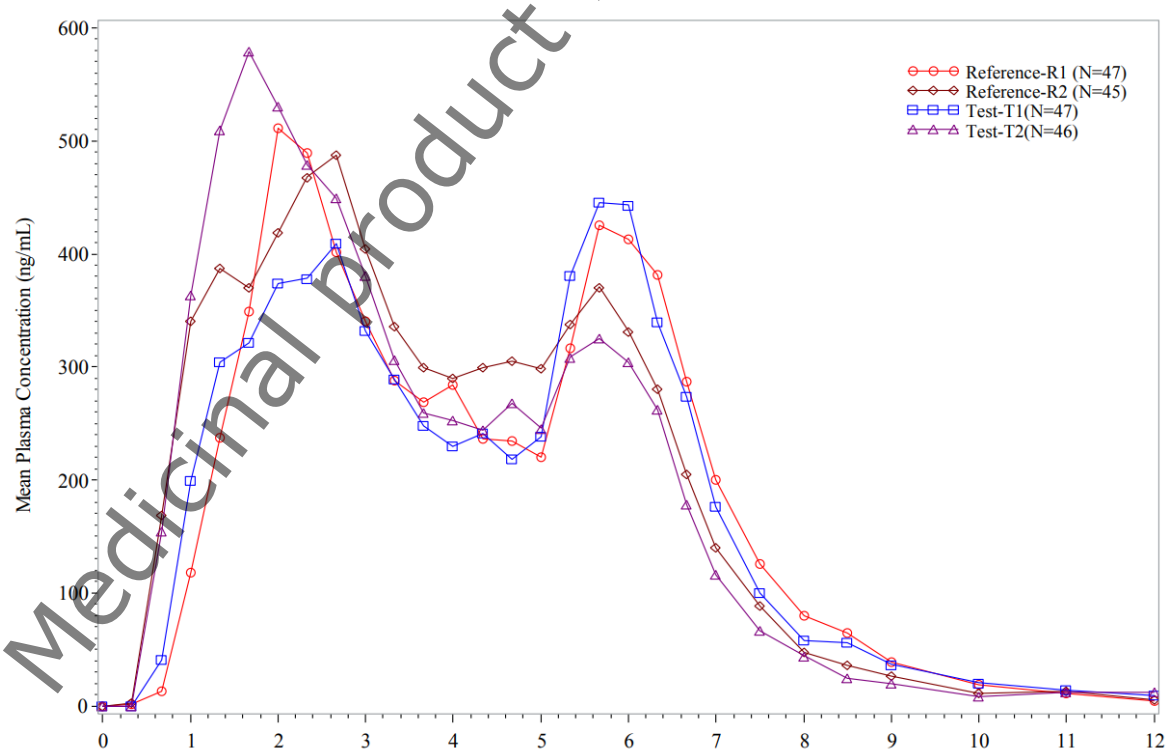
The GMR of the test to reference product and associated 90% CI of the AUC_{0-t} and $AUC_{0-\infty}$ were contained within 80.00% - 125.00%. However, as the intra subject CV of Reference Product -R (%) was >30% (37.2%) and within-subject standard deviation (SWR) of the reference product for C_{max} was 0.3601, the bioequivalence acceptance limit for C_{max} was widened up to 76.06 – 131.48%.

Table 6: Descriptive Statistics of Formulation Means for Monomethyl fumarate (N = 47) - Study 0857-16

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T (N = 93 Observations)	Reference Product-R (N = 92 Observations)
T_{max} (h)#	3.333 (0.667 - 6.667)	3.500 (1.000 - 8.500)
C_{max} (ng/mL)	1381.176 ± 621.0258	1446.627 ± 616.3116
AUC_{0-t} (ng.h/mL)	2211.552 ± 604.2813	2263.497 ± 665.2546
$AUC_{0-\infty}$ (ng.h/mL)	2256.797 ± 598.7727*	2286.282 ± 663.6227
λ_z (1/h)	1.216 ± 0.4293*	1.213 ± 0.3979
$t_{½}$ (h)	0.711 ± 0.4667*	0.668 ± 0.3252
AUC_%Extrap_obs (%)	1.556 ± 3.2194*	1.066 ± 1.6334
T_{lag} (h)#	1.000 (0.333 - 5.667)	1.333 (0.000 - 5.000)

Tmax and Tlag is represented in median (min-max) value. * N=92 observations; Note: Terminal rate constant (lambda_z) cannot be estimated based on obtained concentration data for one subject (Period-III, T). Hence, $AUC_{0-\infty}$ and other elimination phase dependent parameters cannot be calculated.

Figure 5: Mean plasma concentration vs. time curve for Monomethyl fumarate (Upper Panel: Linear Plot; Lower Panel: Semilog Plot) - Study 0857-16



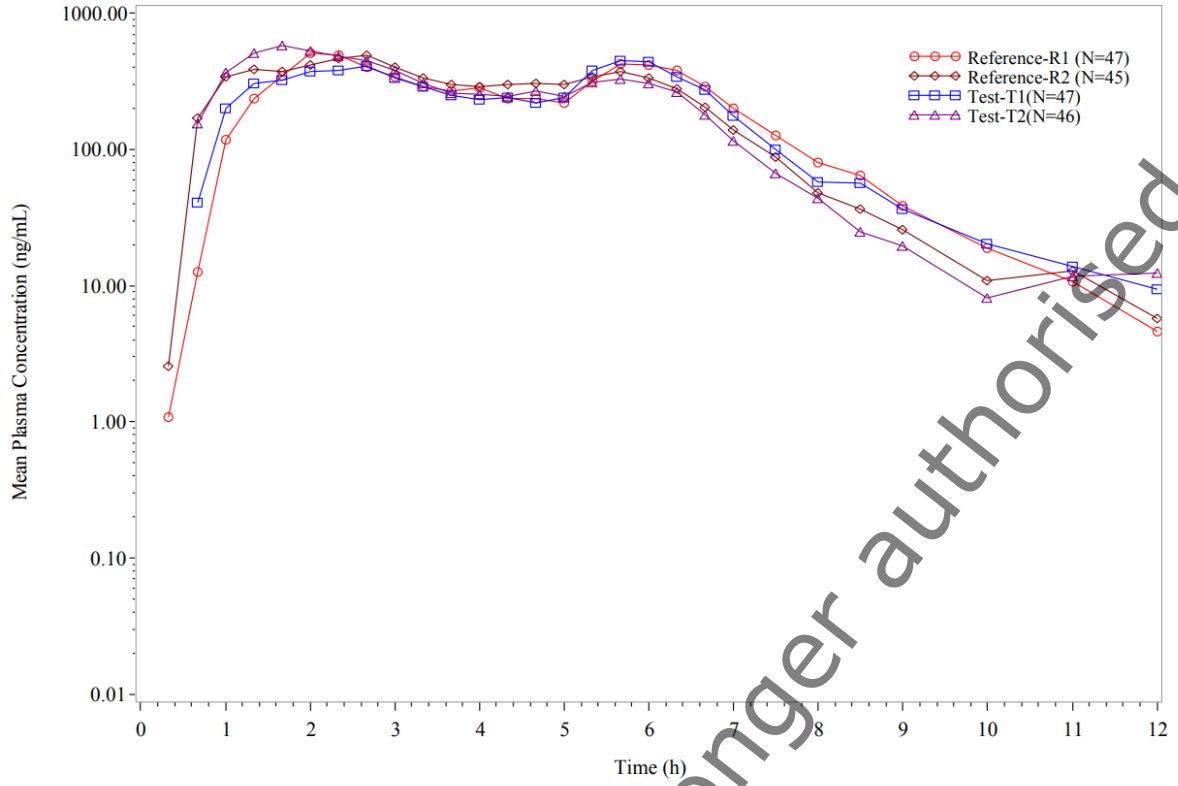
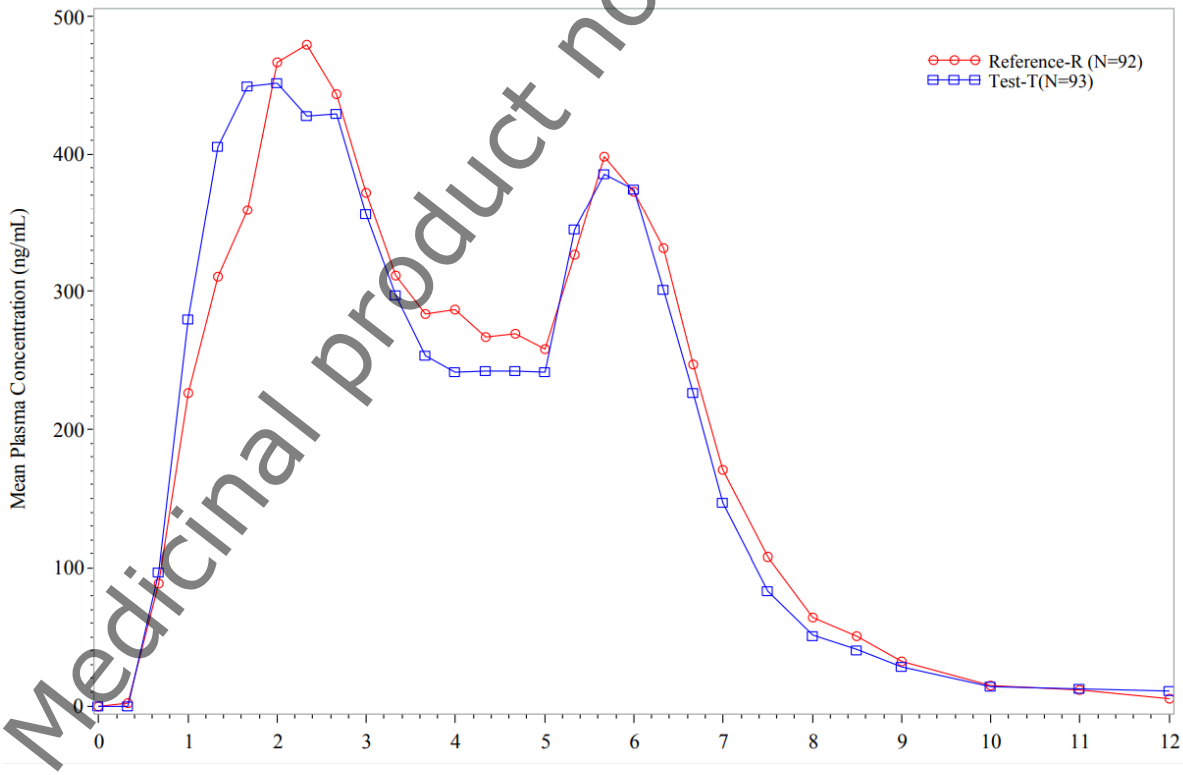
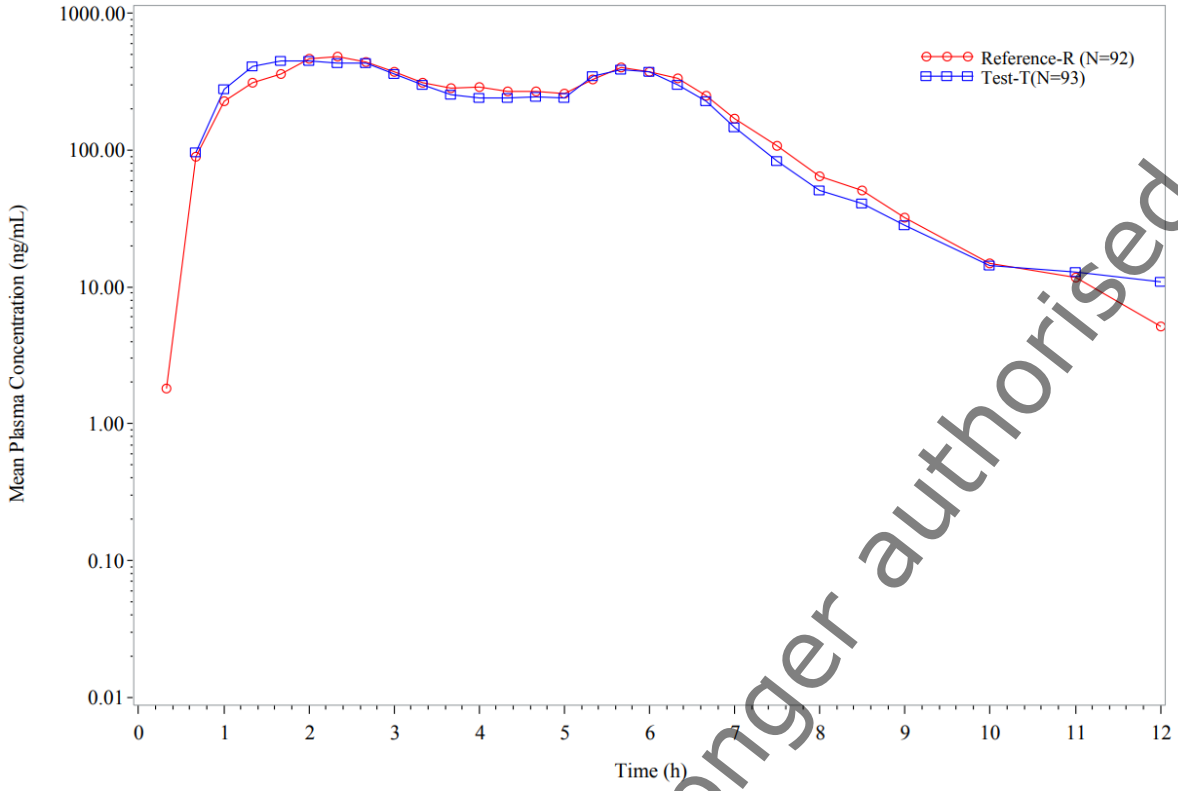


Figure 6: Combined mean plasma concentration vs. time curve for Monomethyl fumarate (Upper Panel: Linear Plot; Lower Panel: Semilog Plot) - Study 0857-16





The intra-subject CV of reference product and SWR of C_{max} for Monomethyl fumarate are estimated using PROC GLM of SAS® Version 9.3 (SAS Institute Inc., USA).

Table 7: Intra-subject CV and Within-Subject Standard Deviation of Reference Product for Monomethyl fumarate (N = 90 Observations) - Study 0857-16

Dependent	lnC_{max}
Intra-subject CV of Reference Product-R (%)	37.2
Within-subject Standard Deviation of Reference Product-R (S_{WR})	0.3601

Table 8: Relative Bioavailability Results for Monomethyl fumarate (N = 47) - Study 0857-16

Parameters	Geometric Least Squares Means			90% Confidence Interval	Acceptance Criteria (%)	Intra-subject CV of Reference Product-R (%)	Power (%)
	Test Product-T (N = 93 Observations)	Reference Product-R (N = 92 Observations)	Ratio (T/R) %				
lnC_{max}	1253.135	1319.178	95.0	86.49 - 104.33	76.06 - 131.48	37.2	99.9
$lnAUC_{0-t}$	2124.456	2160.548	98.3	96.29 - 100.41	80.00 - 125.00	9.4	100.0
$lnAUC_{0-\infty}$	2165.228*	2183.525	99.2	97.17 - 101.19	80.00 - 125.00	9.2	100.0

* N=92 observations

Table 9: ANOVA p-values for Monomethyl fumarate - Study 0857-16

Parameters	ANOVA (p-values)			
	Formulation	Sequence	Period	Subject (Sequence)
lnC_{max}	0.3659	0.6404	0.1992	0.0002
$lnAUC_{0-t}$	0.1845	<0.0001	0.0076	<0.0001
$lnAUC_{0-\infty}$	0.4926	<0.0001	0.0073	<0.0001

Note: Significant value if p-value < 0.05.

Based on the above table, Formulation effect is found to be statistically insignificant for ln-transformed PK parameter C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate.

Sequence and Period effects are found to be statistically insignificant for lntransformed PK parameter C_{max}; however, it is found to be statistically significant for ln-transformed PK parameters AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate.

The cause for significant sequence effect may not be found with certainty. Therefore under special circumstances the significant sequence effect can be ignored. The study [1] was a single dose study [2] was in healthy volunteers, [3] was not comparing an endogenous substance, [4] had an adequate washout and [5] used appropriate design and analysis. Hence, this sequence effect is just statistically significant for ln-transformed PK parameters AUC_{0-t} and $AUC_{0-\infty}$ and can be ignored.

In the study, clinical conditions were kept identical in both the period of the study, and there were no pre-dose concentrations observed. The decision of bioequivalence is based on the 90% CI by Schuirmann two one sided't-test' which is within the acceptance criteria 80.00-125.00%. This significant period effect for ln-transformed PK parameters AUC_{0-t} and $AUC_{0-\infty}$ is just statistically significant and can be ignored.

Subject (Sequence) effect is found to be statistically significant for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate.

Since each subject is assigned only to one sequence, subjects are said to be nested within sequence. This Subject (Sequence) effect is tested by the Residual and should be highly significant. This significance is an indication that the purpose of using the crossover design has been realized in that the between-subject variance is significantly larger than the residual.

- **Safety data**

A total of 49 subjects were checked in for the study. Out of these 49 subjects, 48 subjects were dosed in Period-I. The safety assessment includes information for all 48 subjects who were dosed at least once during this study.

Five AE were reported by two subjects during the conduct of the study. Three AEs were reported in Period-III and two AEs in Period- IV of the study. Three AEs were reported in subjects after administration of Test Product-T and two AEs were reported in subjects after administration of Reference Product-R. AEs reported after administration of the reference product were abdominal pain and diarrhoea, AEs reported after administration of the test product were upper respiratory tract infection, pyrexia and muscoskeletal pain. These three AEs reported after administration of the test product were considered significant.

All the AEs were mild in nature and the subjects were followed up until resolution of their AEs.

The causality assessment was judged as unlikely related for three AEs (upper respiratory tract infection, pyrexia and muscoskeletal pain) and as possibly related for two AEs (abdominal pain and diarrhoea). There were no deaths or serious AEs during the conduct of the study.

Study 0002-21: An open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, crossover, fully replicate, bioequivalence study of Dimethyl Fumarate Gastro-Resistant Capsules 240 mg of Intas Pharmaceuticals Ltd., India with TECFIDERA® (Dimethyl fumarate) Gastro-Resistant Capsules 240 mg of Biogen Idec Ltd., Innovation House, 70 Norden Road, Maidenhead, Berkshire, SL6 4AY, United Kingdom in normal, healthy, adult human subjects under fasting condition.

Methods

- **Study design**

The study was an open label, balanced, randomized, two-treatment, four-period, two sequence, single oral dose, crossover, fully replicate bioequivalence study in normal, healthy, adult human subjects under fasting condition, with a screening period of 28 days prior to investigational medical product administration in Period-I. In each study period, 26 blood samples, including one pre-dose blood sample, were collected from each subject except for the withdrawn/discontinued subjects to analyze the PK profile of the test product as well as the reference product. The duration of the clinical part of the study was about 15 days (11 hours prior to the IMP administration in Period-I until the time of check-out at 24 hours post-dose in Period-IV).

After an overnight fast of at least 10 hours, a single oral dose (240 mg) of either the test product or the reference product was administered with 240 ± 02 mL of drinking water at ambient temperature to the subjects in sitting posture. The investigational medical product administration was as per the randomization schedule and under open label conditions.

The capsule was swallowed whole without chewing or crushing.

A washout period of 04 days was maintained between the dosing days of two consecutive periods.

For PK evaluation, a total of 26 blood samples were collected from each subject in each period at the time points specified in the protocol.

The venous blood samples were withdrawn at pre-dose (0.000 hour) and at 0.333, 0.667, 1.000, 1.250, 1.500, 1.750, 2.000, 2.250, 2.500, 2.750, 3.000, 3.333, 3.667, 4.000, 4.333, 4.667, 5.000, 5.500, 6.000, 6.500, 7.000, 8.000, 9.000, 10.000 and 12.000 hours following IMP administration in each period.

The PK parameters were calculated from the plasma concentration vs. time profile by non-compartmental model using Phoenix® WinNonlin® Version 8.1 (Certara L.P.) for Monomethyl fumarate. Statistical comparison of the PK parameters of the two formulations was carried out using PROC GLM of SAS® Version 9.4 (SAS Institute Inc., USA) to assess the bioequivalence between test and reference formulations.

- **Test and reference products**

Dimethyl fumarate 240 mg gastro-resistant hard capsules manufactured by Intas Pharmaceuticals Limited, India has been compared to Tecfidera 240 mg gastro-resistant hard capsules manufactured by Biogen (Denmark).

- **Population(s) studied**

Same eligibility criteria as Studies 0856-16 and 0857-16.

- **Analytical methods**

A validation process was performed to assess monomethyl fumarate in human plasma using LC-MS/MS to support clinical studies: 0002-21, 0003-21, 0856-16 and 0857-17 (Full validation of method for the determination of monomethyl fumarate in human plasma using LC-MS/MS (WATERS QUATTRO PREMIER XE). 182-16), for details please see the description in the study 0856-16 section.

Bioanalytical report LAMBDA's PROJECT No. 0002-21.

Determination of monomethyl fumarate concentrations in study samples collected during clinical study NO. 0002-21. Human plasma samples (4992 samples) were analyzed for dimethyl fumarate in clinical study number 0002-21. Samples were stored for a maximum time of 31 days. That storage condition cover validated conditions. Total 55 runs were analyzed for DMF in human plasma, and 54 met the acceptance criteria. Incurred sample reproducibility was performed for 300 samples; 272 samples (90,7%) of them were acceptable as repeated samples had relative differences not exceeding 20% compared to the first evaluation. For each calibration curve, 16 non-zero QC and 4 blank samples were included for each run. The same number of QC samples was used for ISR.

The accuracy and precision of QC samples has been approved – HQC, MQC, LMQC, LQC, (3.0, 3.1, 5.2, 6.1, precision respectively; and 98.8% 101.8% 103.5% 102.0%, accuracy respectively). Total, 238 samples were reanalysed due to: variation in response of IS (1), poor chromatography (55), significant analyte concentration in pre dose sample of subject (2) and concentration above highest standard (2). Total 5.0% samples were reanalysed in respect to total sample number. 20% of serially selected subject's chromatograms were submitted. Obtained results were within the range of the calibration curve. Bioanalysis seems acceptable.

- **Pharmacokinetic variables**

Same PK variables as for studies 0856-16 and 0857-16.

The PK parameters were calculated for Monomethyl fumarate by using non-compartmental model of Phoenix® WinNonlin® Version 8.1 (Certara L.P.).

- **Statistical methods**

Descriptive statistics are calculated and reported for the PK parameters of Monomethyl fumarate.

ANOVA, power and ratio analysis for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are calculated and reported for Monomethyl fumarate.

Intra subject variability of Reference Product-R for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ is calculated and reported for Monomethyl fumarate.

The ANOVA model was to be included Sequence, Subject (Sequence), Formulation and Period as fixed effects.

Each analysis of variance was to be included calculation of least-squares means, the difference between adjusted formulation means and the standard error associated with this difference.

An F-test was to be performed to determine the statistical significance of the effects involved in the model at a significance level of 5% (alpha = 0.05).

The power of the study was to be calculated and reported for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate.

GMRs of test and reference formulations was to be calculated and reported for the ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate.

The SWR of reference product and intra-subject variability of reference product was to be calculated and reported for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate.

Any missing samples (M) or non-reportable (NR) concentration values were to be disregarded in PK and statistical analysis.

90% CI for the GMRs between drug formulations are calculated and reported for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate.

Criteria for conclusion of bioequivalence were same as for studies 0856-16 and 0857-16 but analysis are performed with using PROC GLM of SAS® Version 9.4 (SAS Institute Inc., USA) instead of Version 9.3.

Determination of Sample Size

Based on the past in-house study data, the maximum intra-subject variability observed for primary PK parameter was found to be ~ 32.1%, the sample size computation was determined by R Software with considering the following assumptions:

- T/R ratio = 90.0 – 111.1%
- Intra-subject C.V (%) ~ 32.1%
- Significance Level = 5%
- Power ≥ 80%

Based on the above estimates 34 completers subjects were required to establish bioequivalence between formulations with adequate power. Considering approximately 30% dropouts and/or withdrawals, a sample size of 48 subjects were sufficient to establish bioequivalence between formulations with adequate power for this study.

Results

- **Disposition of subjects**

A total of 50 subjects were checked in for Period-I of the study. Two subjects were checked in for the study, in order to compensate for any dropouts prior to dosing in Period-I.

No female volunteers were checked in for the study.

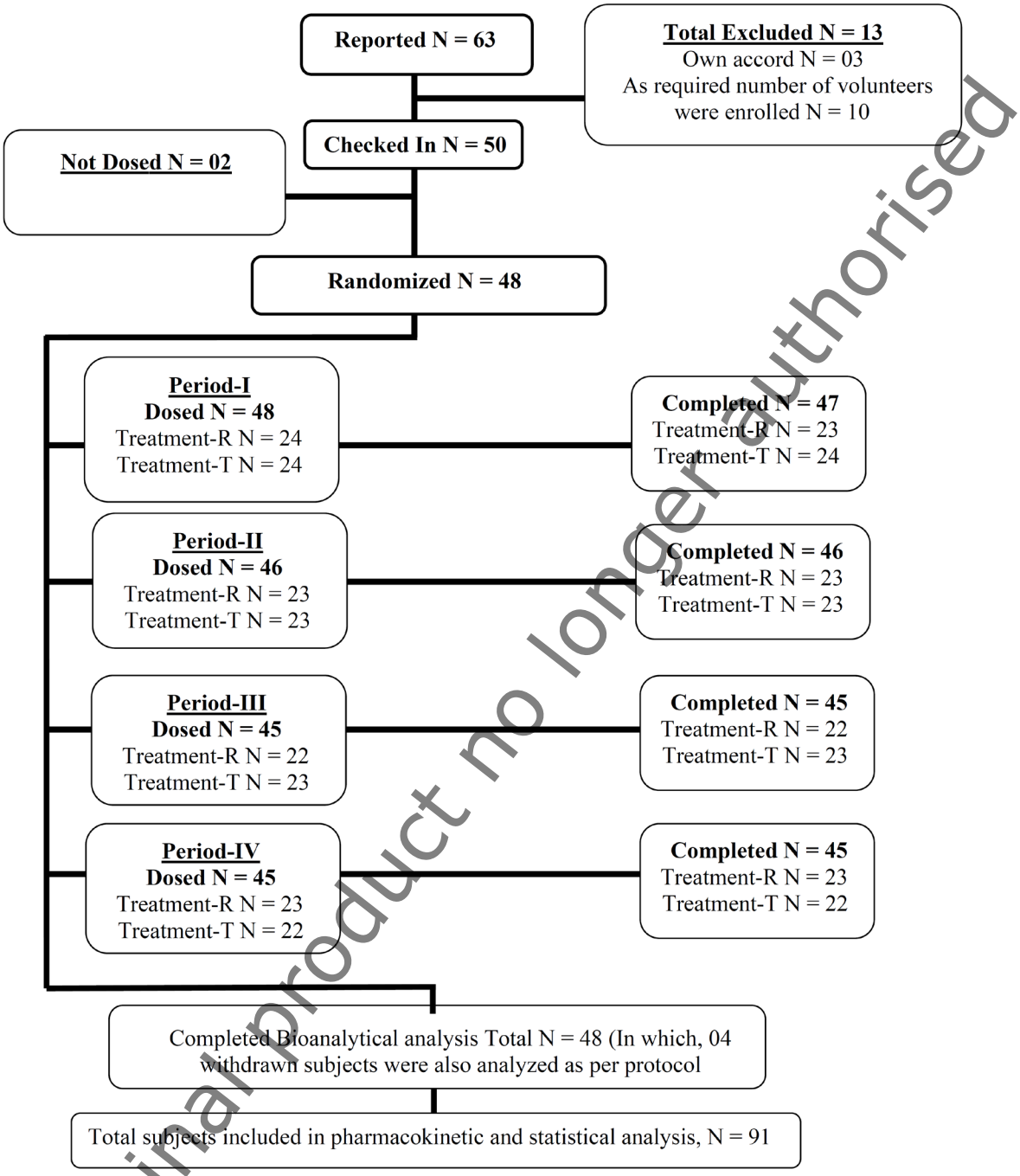
Both the extra subjects were checked out of the facility as none of the subjects discontinued / were withdrawn from the study prior to dosing in Period-I

Hence, as per protocol, 48 subjects were dosed in Period-I of the study.

Two subjects N were withdrawn from the study on medical grounds one in Period-I and another one in Period IV. One subjects discontinued from Period-I, II, III and IV on his own accord and another one from Period III.

In all, 44 subjects) completed all the periods of the clinical phase of the study successfully.

Figure 7: Participants flow - Study 0002-21



There were no protocol deviations during the conduct of the study.

- **Data sets analyzed**

The study was planned to obtain the data from 48 evaluable subjects. Out of the dosed 48 subjects, 44 subjects completed the clinical phase of all the periods of the study successfully.

Plasma samples of all 48 subjects were analyzed, in which, four withdrawn subjects were also analyzed as per protocol requirement.

Total 46 subjects were included in the PK and statistical analysis.

- **Pharmacokinetic results**

The GMR of the test to reference product and associated 90% CI of the AUC_{0-t} were contained within 80.00% - 125.00%. The GMR of the test to reference product of the C_{max} was contained within 80.00% - 125.00%. The 90% CI associated with the GMR of the test to reference product C_{max} was contained within the limits of 80.00% - 125.00% as the SWR of the reference product for C_{max} was 0.2578.

Table 10: Descriptive Statistics of Formulation Means for Monomethyl Fumarate (N = 46) - Study 0002-21

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T (N = 91 Observations)	Reference Product-R (N = 91 Observations)
T_{max} (h)#	2.267 (1.000 - 4.350)	2.500 (1.250 - 5.500)
C_{max} (ng/mL)	3075.126 ± 983.1448	2949.480 ± 973.2936
AUC_{0-t} (ng.h/mL)	4926.478 ± 1175.1555	4796.962 ± 1204.3278
$AUC_{0-\infty}$ (ng.h/mL)	4945.265 ± 1173.5030	4814.052 ± 1205.2226
λ_z (1/h)	1.044 ± 0.2744	1.008 ± 0.2833
$t_{½}$ (h)	0.726 ± 0.2608	0.779 ± 0.4021
AUC_%Extrap_obs (%)	0.407 ± 0.5585	0.377 ± 0.2730
T_{lag} (h)#	0.667 (0.000 - 2.750)	0.684 (0.000 - 3.750)

Tmax and Tlag are represented as median (min-max) value.

The subjects completing at-least two treatment periods with reference product are included for calculation of within-subject standard deviation of reference product.

The intra-subject CV of reference product and within subject standard deviation of reference product (SWR) of C_{max} for Monomethyl fumarate are estimated using PROC GLM of SAS® Version 9.4 (SAS Institute Inc., USA)

Table 11: Intra-subject CV and Within-Subject Standard Deviation of Reference Product for Monomethyl Fumarate (N = 90 Observations) - Study 0002-21

Dependent	lnC_{max}
Intra-Subject CV of Reference Product-R (%)	26.2
Within-Subject Standard Deviation of Reference Product-R (S_{WR})	0.2578

Intra-subject CV of reference product for ln-transformed PK parameter C_{max} was found to be < 30%. Hence, the statistical analysis for bioequivalence assessment was carried out using average bioequivalence approach for lntransformed PK parameter C_{max} for Monomethyl fumarate.

Table 12: Relative Bioavailability Results for Monomethyl Fumarate (N = 46) - Study 0002-21

Parameters	Geometric Least Squares Means			90% Confidence Interval	Acceptance Criteria (%)	Intra-subject CV of Reference Product-R (%)	Power (%)
	Test Product-T (N = 91 Observations)	Reference Product-R (N = 91 Observations)	Ratio (T/R) %				
lnC_{max}	2929.454	2804.216	104.5	98.13 - 111.21	80.00 - 125.00	26.2	100.0
$lnAUC_{0-t}$	4807.064	4668.242	103.0	100.33 - 105.68	80.00 - 125.00	12.9	100.0
$lnAUC_{0-\infty}$	4826.657	4685.769	103.0	100.37 - 105.71	80.00 - 125.00	12.8	100.0

Table 13: ANOVA p-values for Monomethyl Fumarate - Study 0002-21

Parameters	ANOVA (p-values)			
	Formulation	Sequence	Period	Subject (Sequence)
lnC_{max}	0.2494	0.8244	0.1765	<0.0001
$lnAUC_{0-t}$	0.0639	0.3809	0.4279	<0.0001
$lnAUC_{0-\infty}$	0.0608	0.3688	0.4631	<0.0001

p-value is statistically significant if it is < 0.05

Formulation, Sequence and period effects were found to be statistically insignificant for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate, Subject(Seq) effect was found to be statistically significant for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate.

Since each subject is assigned only one sequence, subjects are said to be nested within sequence. This Subject (Sequence) effect is tested by the Residual and should be highly significant. This significance is an indication that the purpose of using the crossover design has been realized in that the between-subject variance is significantly larger than the residual.

The point estimates and 90% CI for the ln-transformed PK variables C_{max} and AUC were within the predefined bioequivalence range of 80.00% - 125.00% and therefore the results showed bioequivalence between the test and reference products.

- **Safety data**

A total of 50 subjects were checked in for the study. Out of these 50 subjects, 48 subjects were dosed in Period-I of the study. The safety assessment includes information for all 48 subjects who were dosed at least once during this study.

Five adverse events were reported by five subjects during the conduct of the study. Two AEs were reported in Period-I, one AE was reported in Period-II, one AE was reported in Period-IV and one AE was reported during post-study safety assessment.

Two AEs were reported in the subjects after administration of Test Product-T (injury and eosinophile count increase) and three AEs were reported in the subjects after administration of Reference Product-R (2 cases of dizziness and one case of pain).

Four AEs were mild in nature and one AE was moderate in nature (injury). The subjects were followed up until resolution of their AEs.

The causality assessment was judged as unrelated for three AEs and as possible for two AEs (two cease of dizziness).

Out of the total reported five AEs, two AEs were significant (pain and injury). The subjects were withdrawn on medical grounds. The causality assessment was judged as unrelated for both significant AEs.

There were no deaths or serious AEs reported during the conduct of the study.

Study 0003-21: An open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, crossover, fully replicate, bioequivalence study of Dimethyl Fumarate Gastro-Resistant Capsules 240 mg of Intas Pharmaceuticals Ltd., India with TECFIDERA® (Dimethyl fumarate) Gastro-Resistant Capsules 240 mg of Biogen Idec Ltd., Innovation House, 70 Norden Road, Maidenhead, Berkshire, SL6 4AY, United Kingdom in normal, healthy, adult human subjects under fed condition.

Methods

- **Study design**

The study was an open label, balanced, randomized, two-treatment, four-period, two sequence, single oral dose, crossover, fully replicate bioequivalence study in healthy, adult human subjects under fed condition, with a screening period of 28 days prior to IMP administration in Period-I.

After an overnight fast of at least 10 hours, the subjects were served high fat and high calorie vegetarian breakfast, which they consumed completely within 30 minutes.

A single oral dose (240 mg) of either the test product or the reference product was administered with 240 ± 02 mL of drinking water at ambient temperature to the subjects in sitting posture. The IMP administration was as per randomization schedule and under open label conditions.

Capsule was swallowed whole without chewing or crushing.

The screening phase was carried out within 28 days prior to the scheduled dosing day of Period-I. The subjects were administered the study drug in each period except for the withdrawn/discontinued subjects. The sequence of administration was determined by the randomization schedule. A washout period of 04 days was considered sufficient between the dosing days of any two consecutive periods. The duration of the clinical part of the study was about 15 days (11 hours prior to the IMP administration in Period-I until the time of check-out at 24 hours post-dose in Period- IV).

In each study period, 28 blood samples, including one pre-dose blood sample, were collected from each subject except for the withdrawn/discontinued subjects to analyze the PK profile of the test product as well as the reference product.

The venous blood samples were withdrawn at pre-dose (0.000 hour) and at 0.333, 0.667, 1.000, 1.333, 1.667, 2.000, 2.333, 2.667, 3.000, 3.333, 3.667, 4.000, 4.333, 4.667, 5.000, 5.333, 5.667, 6.000, 6.333, 6.667, 7.000, 7.500, 8.000, 9.000, 10.000, 11.000 and 12.000 hours following IMP administration in each period.

The PK parameters were calculated from the plasma concentration vs. time profile by non-compartmental model using Phoenix® WinNonlin® Version 8.1 (Certara L.P.) for Monomethyl fumarate. Statistical comparison of the PK parameters of the two formulations was carried out using PROC GLM of SAS® Version 9.4 (SAS Institute Inc., USA) to assess the bioequivalence between test and reference formulations.

- **Test and reference products**

Dimethyl fumarate 240 mg gastro-resistant hard capsules manufactured by Intas Pharmaceuticals Limited, India has been compared to Tecfidera 240 mg gastro-resistant hard capsules manufactured by Biogen (Denmark).

- **Population(s) studied**

Same eligibility criteria as for studies 0856-16, 0857-16 and 0002-21.

- **Analytical methods**

A validation process was performed to assess monomethyl fumarate in human plasma using LC-MS/MS to support clinical studies: 0002-21, 0003-21, 0856-16 and 0857-17 (Full validation of method for the determination of monomethyl fumarate in human plasma using LC-MS/MS (WATERS QUATTRO PREMIER XE). 182-16), for details please see the description in the study 0856-16 section.

Bioanalytical report LAMBDA's PROJECT No. 0003-21.

Determination of monomethyl fumarate concentrations in study samples collected during clinical study NO. 0003-21. Human plasma samples (4704 samples) were analyzed for DMF in clinical study number 0003-21. Samples were stored for a maximum of 40 days, and that storage condition covers validated.

A total of 50 runs were analyzed for DMF in human plasma, and 49 of them met the acceptance criteria. Incurred sample reproducibility was performed for 286 samples; 286 samples (100%) were acceptable as repeated samples had relative differences not exceeding 20% compared to the first evaluation. For each calibration curve, 16 non-zero QC and 4 blank samples were included for each run. The same number of QC samples was used for ISR.

The accuracy and precision of QC samples has been approved – HQC, MQC, LMQC, LQC, (3.3, 3.4, 6.3, 6.0, precision respectively; and 99.2% 101.5% 103.2% 98.9% accuracy respectively). Total, 113 samples were reanalysed due to: not meeting acceptance criteria (112) and significant analyte concentration in pre dose sample of subject (1). Total 2.5% samples were reanalysed in respect to total sample number. 20% of serially selected subject's chromatograms were submitted. Obtained results were within the range of the calibration curve. Bioanalysis seems acceptable.

- **Pharmacokinetic variables**

Same as for study 0002-21

- **Statistical methods**

Descriptive statistics were calculated and reported for the PK parameters of Monomethyl fumarate.

ANOVA, power and ratio analysis for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were calculated and reported for Monomethyl fumarate.

Intra subject variability of Reference Product-R for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ is calculated and reported for Monomethyl fumarate.

90% CI for GMR between drug formulations are calculated and reported for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate.

Criteria for conclusion of bioequivalence were same as for studies 0856-16 and 0857-16 but analysis are performed with using PROC GLM of SAS® Version 9.4 (SAS Institute Inc., USA) instead of Version 9.3.

Determination of Sample Size

Based on the past in-house study data, the maximum intra-subject variability observed for primary PK parameter was found to be ~ 35%, the sample size computation was determined by R Software with considering the following assumptions:

- T/R ratio = 90.9 – 110.0%
- Intra-subject C.V (%) ~ 35%
- Significance Level = 5%
- Power ≥ 80%

Based on the above estimates 30 completers subjects were required to establish bioequivalence between formulations with adequate power. Considering approximately 30% dropouts and/or withdrawals, a sample size of 42 subjects were sufficient to establish bioequivalence between formulations with adequate power for this study.

Results

- **Disposition of subjects**

A total of 46 subjects were checked in for Period-I of the study. Four subjects were checked in for the study, in order to compensate for any dropouts prior to dosing in Period-I but were checked out of the facility as none of the subjects discontinued / were withdrawn from the study prior to dosing in Period-I.

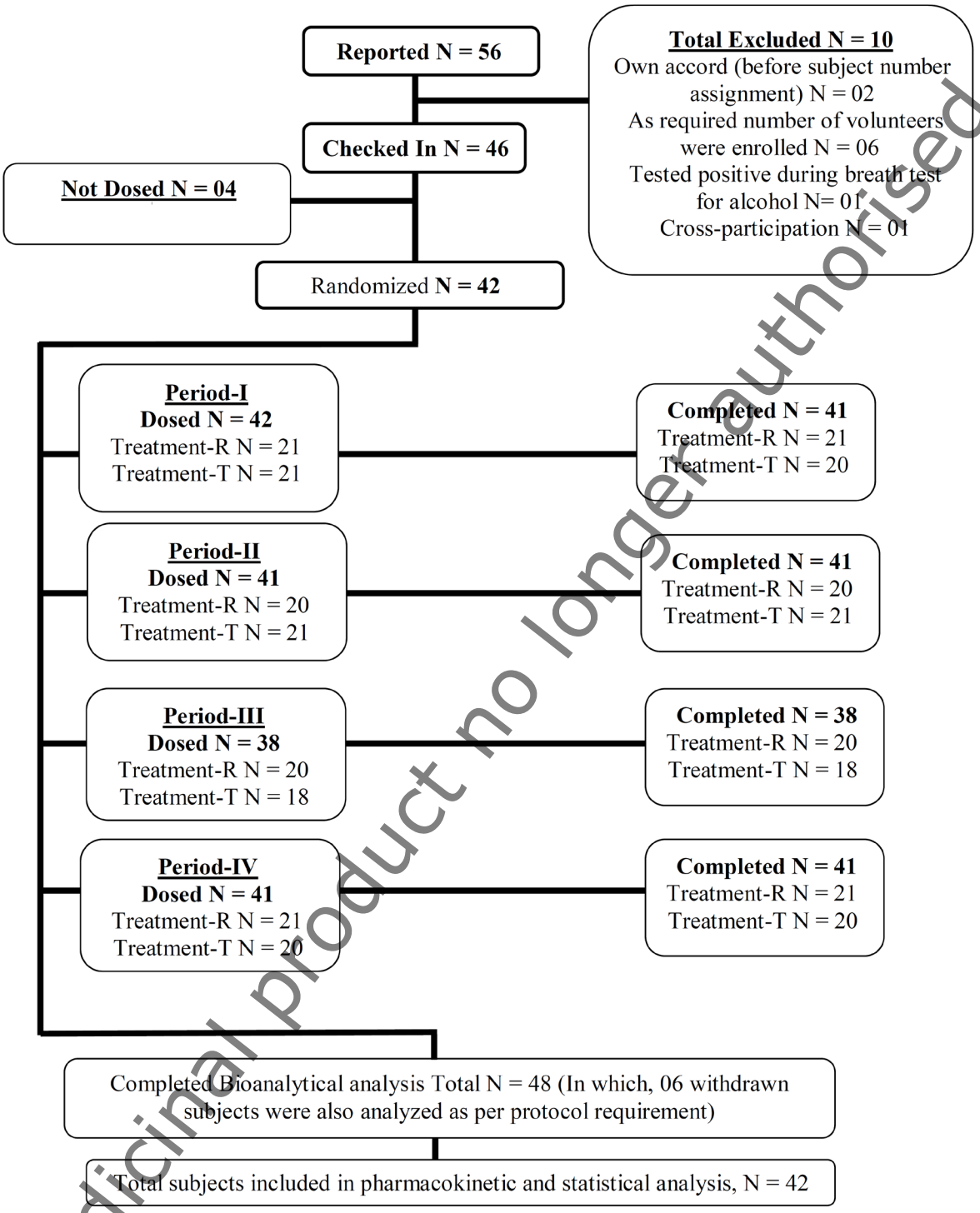
No female volunteers were checked in for the study.

Hence, as per protocol, 42 subjects were dosed in Period-I of the study.

Three subjects were withdrawn on medical grounds, one from Period I, one from Period-III and another one from Period IV One subject discontinued from Period-II and III on his own accord and another two subjects discontinued from Period-III on their own accord.

In all, 36 subjects completed all the periods of the clinical phase of the study successfully.

Figure 8: Participants flow - Study 0003-21



Three protocol deviations were reported, two subjects did not complete the high fat high calorie vegetarian breakfast and check-in clinical examination was performed before body and baggage check-in for one subject.

- **Data set analyzed**

The study was planned to obtain the data from 42 evaluable subjects. Out of the dosed 42 subjects, 36 subjects completed the clinical phase of all the periods of the study successfully.

Plasma samples of all 48 subjects were analysed. In which, six withdrawn subjects were also analysed as per protocol requirement.

Total 42 subjects were included in the PK and statistical analysis.

Descriptive statistics and statistical analysis are performed on subjects having PK parameters available for at-least two treatment periods; one with test product and other with reference product.

Amongst the withdrawn subjects, the six subjects completed at-least two treatment periods with one reference and one test formulation.

Hence, all completer subjects along with these six subjects (are included in the calculation of PK and statistical analysis for Monomethyl fumarate.

- **Pharmacokinetic results**

The GMR of the test to reference product and associated 90% CI of the AUC_{0-t} and $AUC_{0-\infty}$ were contained within 80.00% - 125.00%. However, as the intra subject CV of Reference Product -R (%) was >30% (36 %) and SWR of the reference product for C_{max} was 0.3489, the bioequivalence acceptance limit for C_{max} was widened up to 76.71 – 130.36%.

Table 14: Descriptive Statistics of Formulation Means for Monomethyl Fumarate (N = 42) - Study 0003-21

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T (N = 79 Observations)	Reference Product-R (N = 82 Observations)
T_{max} (h)#	5.667 (3.667 - 8.000)	5.667 (3.667 - 8.000)
C_{max} (ng/mL)	2964.674 ± 998.8345	2813.147 ± 1185.4572
AUC_{0-t} (ng.h/mL)	4527.453 ± 876.2673	4398.682 ± 1042.6584
$AUC_{0-\infty}$ (ng.h/mL)	4708.258 ± 936.4307^	4582.576 ± 951.9984*
λ_z (1/h)	0.960 ± 0.3516^	0.911 ± 0.3686*
$t_{½}$ (h)	0.918 ± 0.7080^	0.984 ± 0.6592*
AUC_%Extrap_obs (%)	2.324 ± 6.3847^	2.965 ± 6.6916*
T_{lag} (h)#	3.333 (0.000 - 5.333)	3.676 (0.000 - 5.333)

Tmax and Tlag are represented as median (min-max) value. ^N=78, *N = 81

The subjects completing at-least two treatment periods with reference product are included for calculation of within-subject standard deviation of reference product.

The intra-subject CV of reference product and SWR of C_{max} for Monomethyl fumarate are estimated using PROC GLM of SAS® Version 9.4 (SAS Institute Inc., USA).

Table 15: Intra-subject CV and Within-Subject Standard Deviation of Reference Product for Monomethyl Fumarate (N = 80 Observations) - Study 0003-21

Dependent	lnC_{max}
Intra-Subject CV of Reference Product-R (%)	36.0
Within-Subject Standard Deviation of Reference Product-R (S_{WR})	0.3489

Intra-subject CV of reference product for ln-transformed PK parameter C_{max} was found to be > 30%. Hence, the statistical analysis for bioequivalence assessment was carried out using average bioequivalence approach for lntransformed PK parameter C_{max} for Monomethyl fumarate.

Table 16: Relative Bioavailability Results for Monomethyl Fumarate (N = 42) - Study 0003-21

Parameters	Geometric Least Squares Means			90% Confidence Interval	Acceptance Criteria (%)	Intra-subject CV of Reference Product-R (%)	Power (%)
	Test Product-T (N = 79 Observations)	Reference Product-R (N = 82 Observations)	Ratio (T/R) %				
lnC_{max}	2792.490	2523.721	110.6	101.31 - 120.85	76.71 - 130.36	36.0	99.9
$lnAUC_{0-t}$	4423.849	4218.261	104.9	101.08 - 108.81	80.00 - 125.00	12.9	100.0
$lnAUC_{0-\infty}$	4533.442^	4378.541*	103.5	99.87 - 107.34	80.00 - 125.00	10.3	100.0

^N=78, *N = 81

Table 17: ANOVA p-values for Monomethyl Fumarate - Study 0003-21

Parameters	ANOVA (p-values)			
	Formulation	Sequence	Period	Subject (Sequence)
lnC_{max}	0.0596	0.7283	0.5459	<0.0001
$lnAUC_{0-t}$	0.0343	0.1403	0.3480	<0.0001
$lnAUC_{0-\infty}$	0.1126	0.0305	0.1736	<0.0001

Note: p-value is statistically significant if it is < 0.05

Based on the above table, period effect was found to be statistically insignificant for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate,

Formulation effect was found to be statistically insignificant for ln-transformed PK parameters C_{max} and $AUC_{0-\infty}$ but it was found to be statistically significant for ln-transformed PK parameter AUC_{0-t} for Monomethyl fumarate.

The significant formulation effect might be contributed to low T/R ratio observed in the study for ln-transformed PK parameter AUC_{0-t}. As the decision of bioequivalence is based on the 90% CI and T/R ratio for ln transformed PK parameter AUC_{0-t} the study met both the bioequivalence criteria with respect to AUC_{0-t}. Hence, this formulation effect is just statistically significant and can be ignored.

Sequence effect was found to be statistically insignificant for ln-transformed PK parameters C_{max} and AUC_{0-t} but it was found to be statistically significant for ln-transformed PK parameter $AUC_{0-\infty}$ for Monomethyl fumarate.

The cause for significant sequence effect may not be found with certainty. Therefore under special circumstances the significant sequence effect can be ignored. The study [1] was a single dose study [2] was in healthy volunteers, [3] was not comparing an endogenous substance, [4] had an adequate washout and [5] used appropriate design and analysis. Hence, this sequence effect is just statistically significant and can be ignored.

Subject(Seq) effect was found to be statistically significant for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Monomethyl fumarate.

Since each subject is assigned only to one sequence, subjects are said to be nested within sequence. This Subject (Sequence) effect is tested by the Residual and should be highly significant. This significance is an indication that the purpose of using the crossover design has been realized in that the between-subject variance is significantly larger than the residual.

- **Safety data**

A total of 46 subjects were checked in for the study. Out of these 46 subjects, 42 subjects were dosed in Period-I of the study. The safety assessment includes information for all 42 subjects who were dosed at least once during this study.

Four AEs were reported by three subjects during the conduct of the study. One AE was reported in Period-I, two AEs were reported in Period-III and one AE was reported in Period-IV of the study.

One AE was reported in the subject after administration of Test Product-T (vomiting) and three AEs were reported in the subjects after administration of Reference Product-R (white blood cell count increased and neutrophil count increased and pain).

All the AEs were mild in nature. The causality assessment was judged as unrelated for three AEs and as possible for one AE (vomiting).

However, out of the total reported four AEs, three AEs were significant. Three significant adverse events were reported by two subjects during the study (white blood cell count increased and neutrophil count increased and pain). All the significant AEs were reported in the subjects after administration of Reference Product-R. All the AEs were mild in nature. The causality assessment was judged as unrelated for all the significant AEs.

There were no deaths or serious AEs reported during the conduct of the study.

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 applicant conducted 4 separate bioequivalence studies under fasting and fed conditions to demonstrate that the Test Product – Dimethyl fumarate gastro – resistant hard capsules, 120 and 240 mg is bioequivalent to the Reference Product – Tecfidera.

Generally, the design of the performed bioequivalence studies can be considered acceptable.

The choice of analyte (monomethyl fumarate) is in line with EMA/CHMP/421315/2017 recommendations and is endorsed.

The chosen study population of healthy volunteers is appropriate. The validation method was performed according to the procedure recommended with the guidelines.

The point estimates and 90% CI for the ln-transformed PK variables $C_{max,}$ AUC_{0-t}, $AUC_{0-\infty}$, were within the predefined bioequivalence range of 80.00% - 125.00% in four performed studies for 120 mg and 240 mg strengths under fasting and fed conditions.

The applicant performed dissolution profile comparison between Test product bio-batch of Dimethyl fumarate 120mg and 240 mg gastro-resistant capsules (manufactured by: Intas Pharmaceuticals Limited India) with Reference product Dimethyl fumarate 120 and 240mg gastro-resistant capsules. It was demonstrated that more than 85% of the drug is dissolved within 15 minutes at buffer stage.

No dedicated studies evaluating efficacy or safety of the Test product was conducted. However, this is not required for a generic application. The safety of the Test Product was evaluated in the conducted bioequivalence studies. No new emerging safety issues were reported during the studies. No serious adverse events were reported.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence studies 0856-16 and 0857-16 Dimethyl fumarate gastro – resistant hard capsules, 120 mg can be considered bioequivalent with Tecfidera gastro – resistant hard capsules, 120 mg.

Based on the presented bioequivalence studies 0002-21 and 0003-21 Dimethyl fumarate gastro – resistant hard capsules, 240 mg can be considered bioequivalent with Tecfidera gastro – resistant hard capsules, 240 mg.

2.5. Risk Management Plan

2.5.1. 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
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 gastrointestinal (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

None

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 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.

2.7. Product information

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable because the content of the package leaflet of Dimethyl fumarate Accord is in line with the content of the package leaflet of the innovator Tecfidera (EMEA/H/C/002601). There are identical sections on indication, posology and method of administration, contraindications, warnings and precautions and interactions with other medicinal products or other forms of interactions and adverse drug reactions. Further and for the design and layout, a bridging report making reference to Solifenacin succinate 5/10mg film-coated tablets (DK/H/2339/001-002/DC) has been submitted and it has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg. The reference product Tecfidera is indicated for the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS). No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a 4 separate bioequivalence studies under fasting and fed conditions to demonstrate that the Test Product – Dimethyl fumarate gastro – resistant hard capsules, 120 and 240 mg is bioequivalent to the Reference Product – Tecfidera. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. The choice of analyte (MMF) is in line with EMA/CHMP/421315/2017 recommendations and is endorsed. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of dimethyl fumarate Accord met the protocol-defined criteria for bioequivalence when compared with the Tecfidera. The point estimates and their 90% CI for the ln-transformed PK

parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range [e.g. 80.00 to 125.00%] in both performed studies for 120 mg and 240 mg strengths under fasting and fed conditions. Bioequivalence of the two formulations was demonstrated.

The applicant performed dissolution profile comparison between Test product bio-batch of Dimethyl fumarate 120mg and 240 mg gastro-resistant capsules (manufactured by: Intas Pharmaceuticals Limited India) with Reference product Dimethyl fumarate 120 and 240mg gastro-resistant capsules. It was demonstrated that more than 85% of the drug is dissolved within 15 minutes at buffer stage.

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

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Outcome

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

> *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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

5. Appendix

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CHMP Assessment Report

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

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

1. Background information

On 9 August 1994, the German National Competent Authority (the *Bundesinstitut für Arzneimittel und Medizinprodukte;* "BfArM") granted two marketing authorisations for two strengths of a combination medicinal product known as Fumaderm (comprised of the active substances monoethyl fumarate salts ("MEF") and dimethyl fumarate ("DMF")), for the treatment of psoriasis. On 13 June 2013, the marketing authorisations for Fumaderm were renewed. The marketing authorisations ("MA") are held by the Biogen group of companies.[1]

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).[2] 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.[3]

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.[4]

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.[5]

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

[2] 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".

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

[4] In this respect, see: Case T-703/20, *Mylan Ireland v EMA*. [5] In this respect, see: paragraph 282 of the Judgment in Case T-611/18.

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

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

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

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

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

2. Assessment

2.1. Introduction

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

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

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

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

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

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

Two types of Fumaderm have been licensed in Germany, which serve for titration during the initial three weeks of treatment (*"Fumaderm initial magensaftresistente Tabletten für Erwachsene"*, German MA number 27561.00.00) and in the subsequent weeks including maintenance of therapy (*"Fumaderm magensaftresistente Tabletten für Erwachsene"*, German MA number 27561.01.00; hereafter referred to as Fumaderm).

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

Table 1: Composition of DMF and MEF in the two German Fumaderm medicinal products

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

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

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

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

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

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

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

2.2. Assessment of the therapeutic contribution of MEF within Fumaderm

2.2.1. Non-clinical aspects

Pharmacodynamic activities of fumaric acid esters in relation to psoriasis

At the time of assessment of the MAA of Fumaderm in Germany, the mechanism of action of its DMF and MEF active substances was largely unknown considering also that relevant animal models reflecting human psoriasis were not available. For this reason, presumptive pharmacodynamic effects of these FAE were solely based on clinical experience in psoriasis patients and experimental findings gained in pertinent cell culture systems *in vitro*, which were subsequently complemented by published scientific reports as further delineated below.

Early publications had described the concentration-dependent inhibition of nucleic acid synthesis at ≥10 µg/ml MEF in cultures of activated lymphocytes from healthy human subjects (Petres *et al*., 1975; Hagedorn *et al*., 1975). Based on these findings, another *in vitro* screen submitted during MAA of Fumaderm compared the activities of DMF and the calcium, magnesium and zinc salts of MEF on

fibroblasts prepared from healthy as well as from uninvolved and involved psoriatic human skin (Sarheim *et al*., 1990). As fumarate is endogenously synthesized from succinate by succinate dehydrogenase (SUDH) in the citric acid cycle, the impact of the various FAEs was determined by means of succinate dehydrogenase activity in the different fibroblast preparations.

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

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 (). 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 (19). 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 (). 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 19). 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 19). 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 C_{max} 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*.

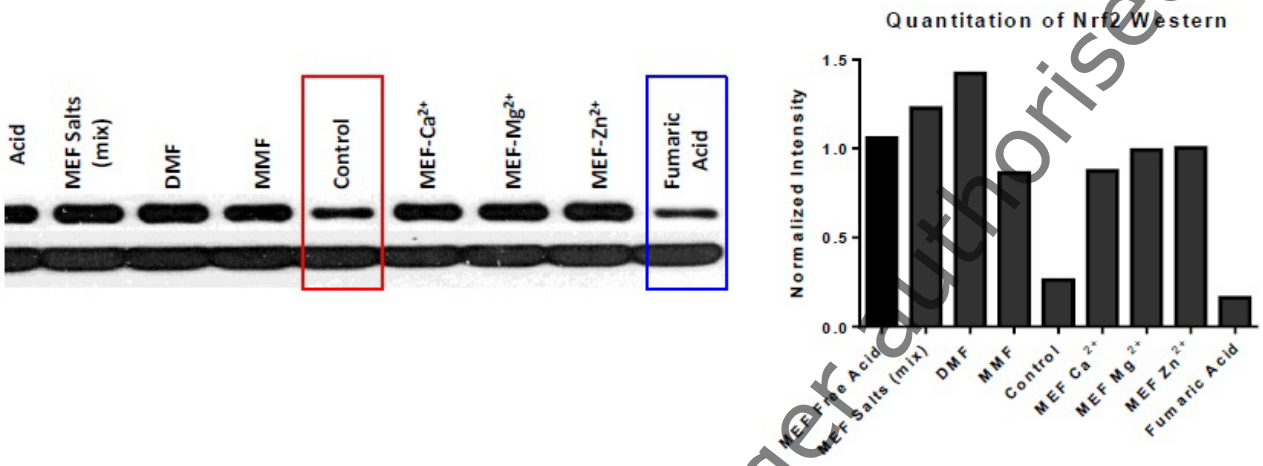
In all non-clinical investigations, the ratio of the calcium, magnesium, and zinc salts of MEF was 87:5:3 Ca-MEF, Mg-MEF, Zn-MEF, respectively, based on molecular weight. This reflects the ratio of these MEF salts in Fumaderm.

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 9: MEF salts increase Nrf2 protein in Cos-1 cells



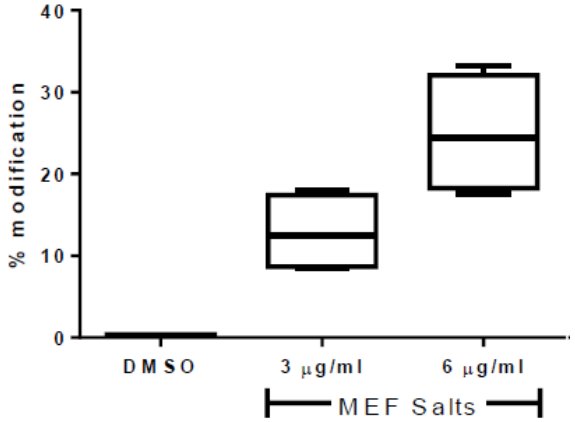
COS-1 cells were treated with 9 µg/ml of individual calcium, magnesium or zinc salts of MEF, with a mixture of MEF salts, the free acid form of MEF, DMF, MMF, FA or the vehicle control DMSO (boxed in red) to illustrate the basal Nrf2 level. Cells were harvested after 24 h and extracts analysed by Western 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 10: The mixture of MEF salts modifies Keap 1 at Cys151



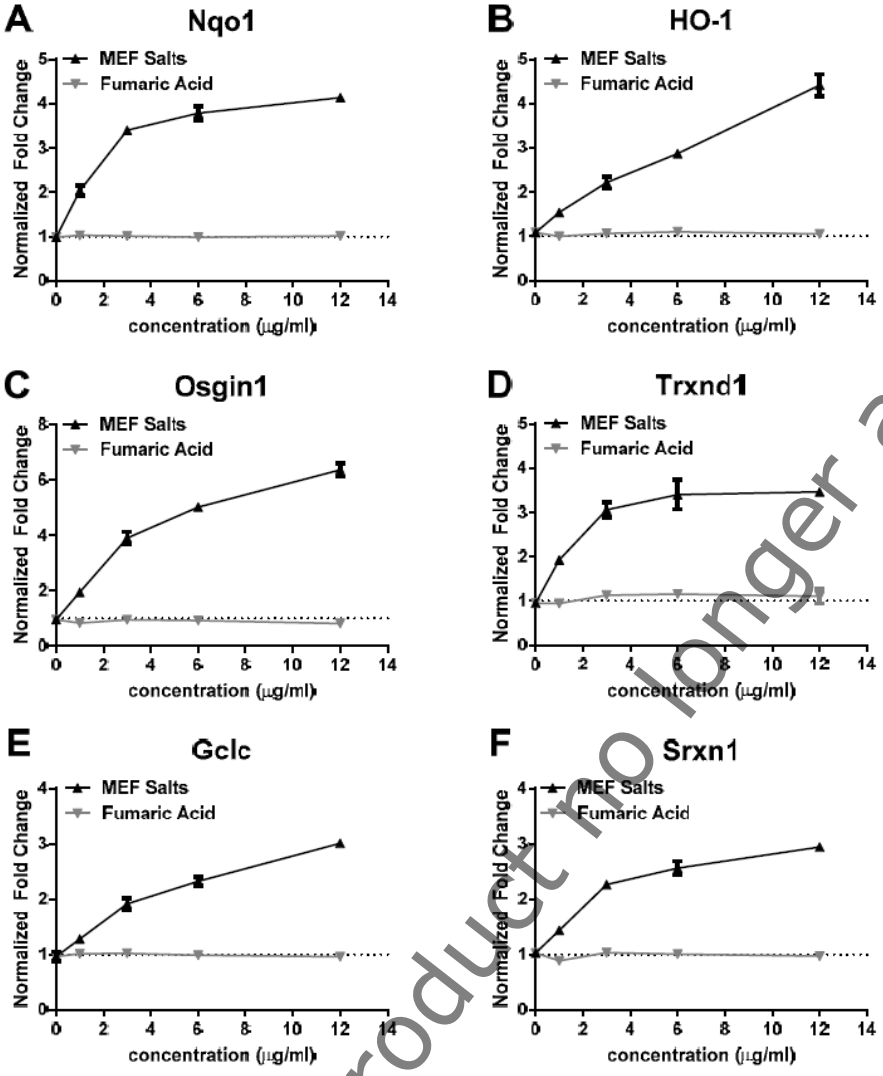
HEK293 cells were transfected with Keap1 and subsequently treated with either DMSO (control) or 3 or 6 µg/ml of calcium, magnesium and zinc salts of MEF. Keap1was immunopurified, fractioned by gel electrophoresis and then excised from the gel. The gel slice was reduced by DTT, alkylated by iodoacetamide, 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 11: The mixture of MEF salts induces Nrf2-dependent gene expression

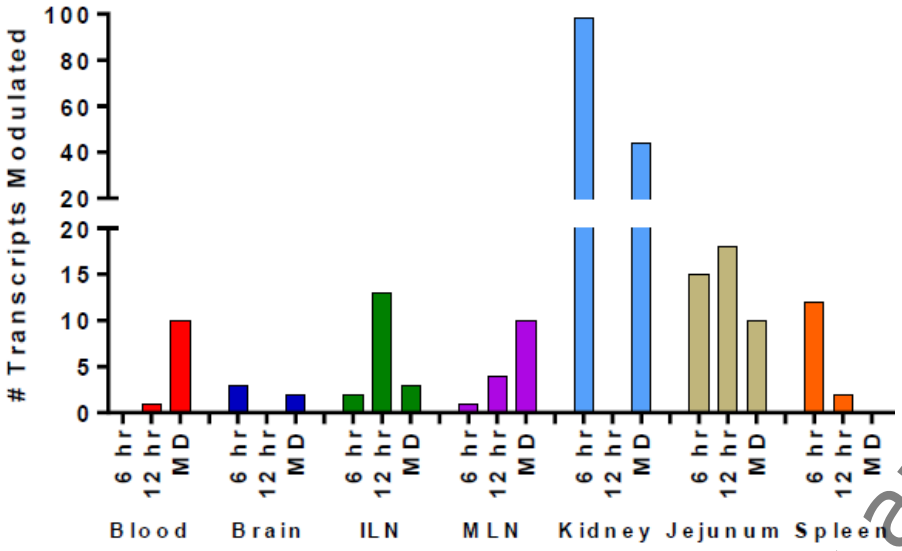


Human astrocytes were treated with a mixture of calcium, magnesium and zinc salts of MEF or fumaric acid. Transcriptional changes were evaluated by RT-PCR 24 h after treatment. (A) Nqo1, (B) HO-1, (C) Osgin 1, (D) Trxnd1, (E) (Gclc), (F) sulfiredoxin 1 (Srxn1). Responses have been normalised as a fold 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 12: The mixture of MEF salts significantly modulates tissue-specific transcription

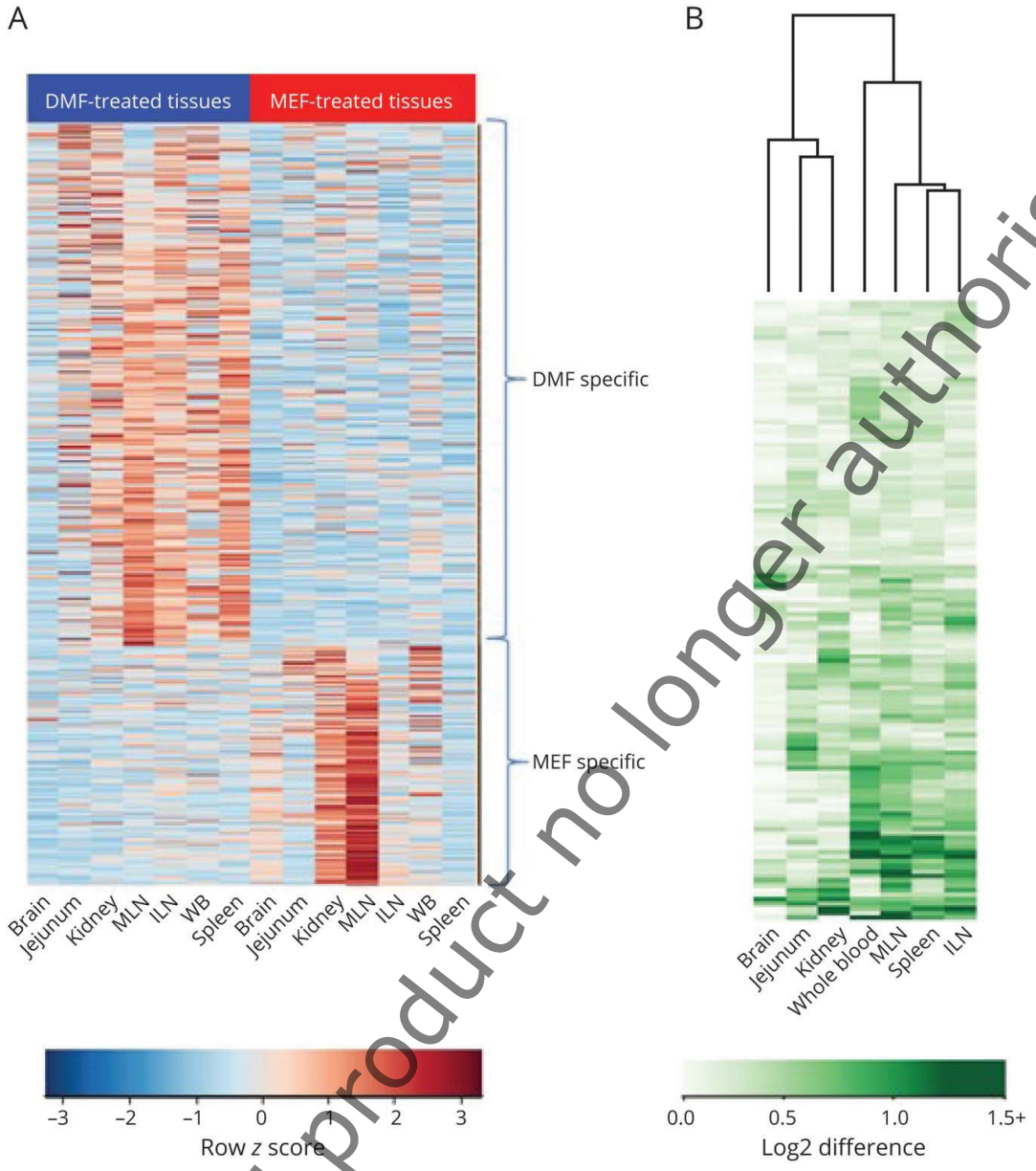


C57Bl/6 mice received single or repeated oral doses of 79.2 mg/kg MEF salts for 10 days (equivalent to 100 mg/kg DMF). Fumaric acid was not tested due to its lack of activity in previous investigations in vitro (see above). Transcriptional responses were evaluated by Affymetrix microarrays at 6 and 12 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 13: Differential and overlapping gene expression profiles after administration of DMF, MEF salts or the DMF/MEF combination in mice



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

Evaluation comment

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

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

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

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

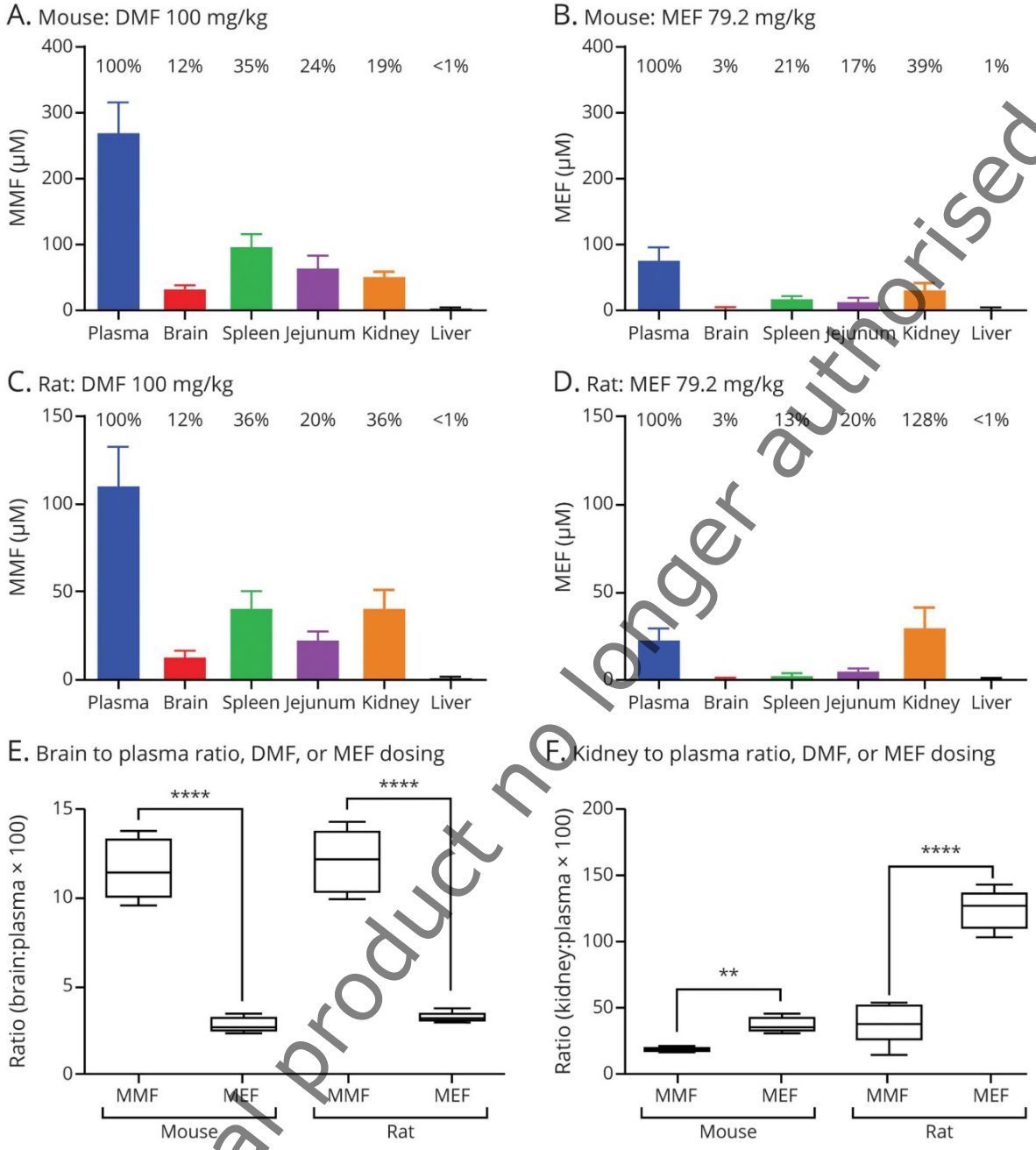
Pharmacokinetic properties of DMF and MEF

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

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

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

Figure 14: Distribution of MMF compared to MEF in mice and rats



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

Evaluation comment

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

Discussion on non-clinical aspects

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

2.2.2. Clinical aspects

- **Clinical pharmacology**

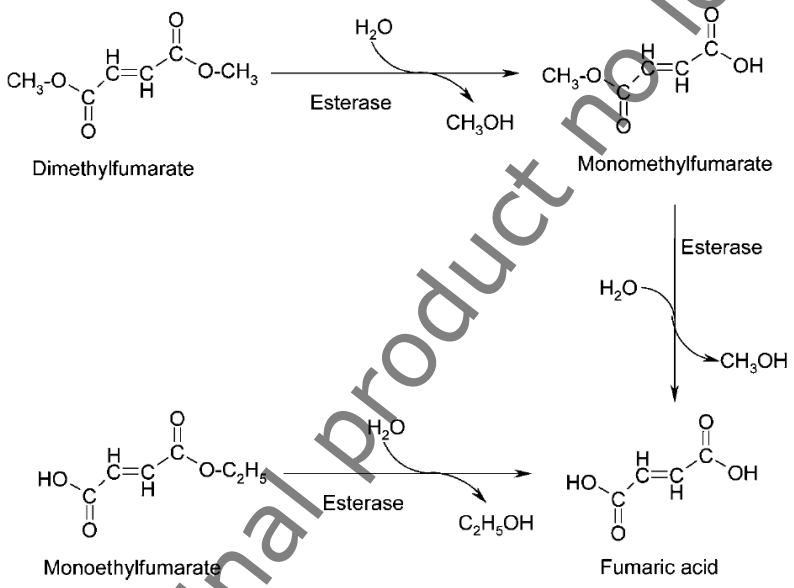
Pharmacological properties of DMF and the MEF salts

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

Pharmacokinetic properties

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

Figure 15: Presumptive metabolic pathway of DMF and MEF (Rostami-Yazdi et al., 2010)



MEF does not convert to either DMF or MMF, and DMF or MMF are not transformed into MEF. Thus, DMF and MEF are not metabolites of each other in vivo.

Pharmacodynamic properties

DMF, MMF and MEF are pharmacologically active

The main activity of DMF and MMF is considered to be immunomodulatory, resulting in a shift in T helper cells (Th) from the Th1 and Th17 profile to a Th2 phenotype and thus reducing inflammatory cytokine production with the induction of pro-apoptotic events, inhibition of keratinocyte proliferation, reduced expression of adhesion molecules, and diminished inflammatory infiltrate within psoriatic plaques.

In in vitro and in vivo studies MEF salts have been shown to: reduce IL-6 and TGF-alpha secretion in the psoriatic cocultures of KCs and T cells, suppress lymphocyte proliferation, induce early apoptotic effects on lympho-histiocytic cells and induce a rapid, transient Ca2+ increase in KCs and inhibit KC proliferation.

The mechanism by which dimethyl fumarate exerts therapeutic effects in multiple sclerosis is not fully understood. Preclinical studies indicate that dimethyl fumarate pharmacodynamic (PD) responses appear to be primarily mediated through activation of the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway. Dimethyl fumarate has been shown to up regulate Nrf2-dependent antioxidant genes in patients (e.g. NAD(P)H dehydrogenase, quinone 1; [NQO1]).

Effects on the immune system

In preclinical and clinical studies, dimethyl fumarate demonstrated anti-inflammatory and immunomodulatory properties. Dimethyl fumarate and monomethyl fumarate, the primary metabolite of dimethyl fumarate, significantly reduced immune cell activation and subsequent release of proinflammatory cytokines in response to inflammatory stimuli in preclinical models. In clinical studies with psoriasis patients, dimethyl fumarate affected lymphocyte phenotypes through a down-regulation of pro-inflammatory cytokine profiles (TH1, TH17), and biased towards anti-inflammatory production (TH2). Dimethyl fumarate demonstrated therapeutic activity in multiple models of inflammatory and neuroinflammatory injury. In Phase 3 studies in MS patients, upon treatment with Tecfidera mean lymphocyte counts decreased on average by approximately 30% of their baseline value over the first year with a subsequent plateau (Tecfidera, SmPC).

- **Clinical Efficacy**

Most of the published clinical efficacy and safety studies in the indication psoriasis refer to Fumaderm (DMF/MEF) or other DMF/MEF combinations. In these studies, a therapeutic effect of Fumaderm (DMF/MEF) in psoriasis has consistently been described (e.g. Altmeyer, 1994, and Gollnick, 2002). Also, the therapeutic effect of DMF monotherapy in psoriasis has been described in clinical studies (e.g. Langner 2004, Mrowietz 2006).

For the purpose of assessing whether MEF has a clinically relevant therapeutic contribution within Fumaderm from an efficacy standpoint, the following publications have been reviewed:

Altmeyer PJ, Matthes U, Pawlak F, Hoffmann K, Frosch PJ, Ruppert P, Wassilew SW, Horn T, Kreysel HW, Lutz G, Barth J, Rietzschel I, Joshi RK. Antipsoriatic effect of fumaric acid derivatives. J Am Acad Dermatol. 1994; 30: 977-81.

Atwan A, Ingram JR, Abbott R, Kelson MJ, Pickles T, Bauer A, Piguet V. Oral fumaric acid esters for psoriasis. Cochrane Database of Syst Rev. 2015.

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

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

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

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

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

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

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

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

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

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

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

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

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

These are the following:

- Kolbach DN, Nieboer C. Fumaric acid therapy in psoriasis: results and side effects of 2 years of treatment. J Am Acad Dermatol. 1992; 27: 769-71.
- Nieboer C, Langendijk PN, van Loenen AC, Gubbels J. Fumaric acid therapy in psoriasis: a double-blind comparison between fumaric acid compound therapy and monotherapy with dimethylfumaric acid ester. Dermatologica, 1990; 181:33-7.
- Mrowietz U, Szepietowski JC, Loewe R, et al. Efficacy and Safety of LAS41008 (Dimethyl Fumarate) in Adults with Moderate-to-Severe Chronic Plaque Psoriasis: a Randomized, Double-Blind, Fumaderm®- and Placebo-Controlled Trial (BRIDGE). Brit J Dermatol. 2017;176:615–623.
- Falkvoll S, Gerdes S, Mrowietz U. Switch of psoriasis therapy from a fumaric acid ester mixture to dimethyl fumarate monotherapy: results of a prospective study. J Dtsch Dermatol Ges 2019; 17: 906-912.

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

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

Kolbach and Nieboer, 1992

Efficacy and side effects of treatment with either DMF monotherapy or DMF/MEF salt combination in psoriatic patients were investigated over two years.

Group 1 (n=129) was treated with DMF, capsules filled with 60 mg of semi-enteric-coated. The dosage was increased weekly by 60 mg to a maximum of 240 mg DMF/day.

Group 2 (n=67) was treated with DMF/MEF (enteric-coated (Fumaderm) tablets): (1) *"Mite"*, containing 30 mg of DMF, 5 mg Mg^{2+}-, 3 mg Zn^{2+}-, and 56 mg Ca^{2+}-salts of MEF; or (2) *"Forte"*, containing 120 mg of DMF, 5 mg Mg^{2+}-, 3 mg Zn^{2+}-, and 87 mg Ca^{2+}-salts of MEF. Medication started with one *"Mite"* tablet per day to be increased weekly to three tablets per day. In the fourth week, medication was switched to

one *"Forte"* tablet per day and this was increased weekly to a maximum of four tablets per day amounting to a maximum of 480 mg DMF + 380 mg MEF salts (i.e. 860 mg fumarate esters/day).

Results: The percentage of patients that continued the therapy was significantly higher in the DMF/MEF combination group than in the DMF group after 6 months. After 24 months, 55 % continued the DMF/MEF medication versus 16 % of the DMF users. Sufficient therapeutic results were obtained in approximately 50 % of the DMF/MEF-treated patients during the entire study. In the DMF group, the percentage of sufficient responders declined from 32 to 18 during the 24 months. These differences were statistically significant. The most important reason to discontinue the therapy was insufficient efficacy in the DMF group (36 %).

The study authors concluded that DMF/MEF combinatorial treatment was significantly superior to DMF monotherapy.

Evaluation comment

The efficacy and safety of DMF monotherapy in comparison to DMF/MEF salt combination was evaluated in 196 patients with nummular or plaque-type psoriasis. Numerical superiority of DMF/MEF salt combination over DMF was shown (after 24 months, 55% of patients continued on DMF/MEF salt combination therapy, compared to 16% of patients on DMF). Moreover, in the DMF group the percentage of sufficient responders declined from 32% to 18% during the 24-month study, while in the DMF/MEF salt combination group the percentage remained unchanged. However, there were significant shortcomings in this study, including the fact that the amount of DMF in the DMF/MEF combination was twice of the amount of DMF in the monotherapy arm. Therefore, patients in the DMF monotherapy group may have been treated with doses which were not sufficient for all patients and it is therefore difficult to assess any additive effects of the MEF esters.

There is no information on demographics and patients' disease features (e.g. severity of psoriasis, disease duration, previous treatment) across the groups. In the absence of randomization or any other method to control for baseline unbalance (the article established that the choice of the therapy was determined by a patient´s insurance), this is a critical shortcoming that prevents the interpretation on causal effects.

Moreover, mild topical corticosteroid was allowed during the study. However, no further information about the topical treatment was provided. No information about statistical analysis was found. Taking into consideration the evaluation of psoriasis, usage of topical corticosteroid might have distorted the results of the study. There are critical flaws in the study methods and statistical analysis, therefore no conclusion can be drawn from this study.

Furthermore, longer dose titration scheme was used in the DMF/MEF combination group compared to DMF group. Finally, differences in formulations (galenical formulation of the DMF/MEF combination and semienteric-coated DMF capsules) preclude the comparison of efficacy and safety of both products.

Overall, it is concluded that this study does not allow a comparison of DMF vs. MEF/DMF.

Nieboer et al., 1989

This study contains 6 studies, however, only 2, considering MEF could be considered relevant for this AR.

Study II: controlled study with MEFAE sodium (Na). In a double-blind study 240 mg MEFAE-Na was compared with placebo in 38 patients (22 women and 16 men). The treatment started with one capsule of 60 mg MEFAE-Na or placebo a day for a week. The dosage was increased in 3 weeks to a maximum of 240 mg. The observation time was 4 months.

Study IV: comparative study of 720 mg MEFAE-Na compared with 240 mg MEFAE-Na. This dose- finding study was performed because the daily 240 mg dosage of MEFAE was ineffective. It was performed in

20 patients, 12 women and 8 men: 10 had been treated with 240 mg MEFAE and 10 with placebo in the previous 4 months. The first group was given 720 mg daily, the latter 240 mg. The observation time was 3 months.

Table 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:j:	Discontinued	
I: Open FACT studyt	36	4(11%)	6(17%)	23(64%)	0(0%)	3(8%)	
II: Double-blind study							
MEFAE-Na (240 mg)	19	9	6	1	3	1	
Placebo	19	8	5	2	4	1	
III: Double-blind study							
DMFAE (240 mg)	22	4	6	6	0	6	
Placebo	20	12	1	0	5	2	
IV: Comparative study							
MEFAE-Na (720 mg)	10	3	4	3	0	0	
MEFAE Na (240 mg)	10	6	1	3	0	0	
V: Open long-term study							
DMFAE (240 mg)	56	14(25%)	12(22%)	19(33%)	0(0%)	Early§ 11(20%)	Latell 4(7%)

Study II: double-blind study with 240 mg MEFAE-Na versus placebo

There was no difference between the numbers of improved, unimproved, or deteriorated cases in both groups. The average final score was the same in both groups, and so were the average final scores of each factor. Only the itching score showed a greater drop in the MEFAE-Na group than in the placebo group.

Study IV: comparative study 720 mg versus 240 mg MEFAE-Na

No difference was seen between the 720 mg versus the 240 mg regimen with regard to the number of improved patients. The average final scores of the total groups and the extent of the eruption, the redness and the thickness were the same, but significant differences ($p < 0.05$) were noted between the final scores of scaling and itching of both groups.

Evaluation comment

No difference between MEF-Na at the dose of 240 mg daily and placebo was observed in Study II.

Treatment with MEF-Na at the dose of 720mg or 240 mg daily resulted in comparable considerable improvements (>50% n=3 in both groups). Indeed, the same number of patients showed an improvement > 50% of the global score in both groups.

While the subscores for extent of the eruption, the redness and the thickness were not different between 720 mg – and 240 mg – treated patients, differences in favour of MEF-NA at the dose of 720mg – treated patients were observed in the final scores of scaling and itching in the study. The authors claimed these differences were statistically significant ($p<0.05$) and thus could be interpreted as supporting clinically relevant effects of MEF-Na. However, it should be noted that the average psoriasis severity score, established as efficacy endpoint in the section of methods in the article, was not different between both groups. Subscores were not presented as endpoints in this study and there was no evidence of adjustment for multiplicity. Therefore, the claim on statistical significance on scaling and itching scores could not be agreed. The small sample size is an additional limitation of the study.

Therefore, no conclusions on MEF-Na efficacy in psoriasis can be made based on this study. Moreover, no direct comparison to DMF was performed in these studies.

An *ad hoc* statistical analysis of Nieboer 1989 comparing the 240 mg Na-MEF data of Study IV, the 720mg MEF data of Study IV and a group including 240mg – and 720mg MEF data to the combined placebo data of Studies II and III was also taken into account. The patients in these groups were categorized as follows: "responders" who achieve at least 25% improvement, and "non-responders" who achieve less improvement or deterioration. The rate of response between the groups was compared using Fisher's Exact test (FET) or a chi-squared. Additionally, ordered logistic regression was applied considering 4 categories ("deteriorated," to < 25% improvement, to 25 to 50% improvement, and to > 50% improvement). In the context of that *ad hoc* statistical analysis, it was submitted that individually underpowered studies (Nieboer 1989) of the effect of MEF in the absence of DMF demonstrates statistically significant efficacy on the improvement of a psoriasis severity score compared to placebo when results are pooled to increase statistical power in an *ad hoc* statistical analysis.

While Nieboer 1989 used a global psoriasis score different than the one that is currently considered as a standard (PASI), it should be noted that in both cases the response is scored as a percentage of improvement with respect to the baseline value. In this regard, a 75% reduction in the PASI score with respect to baseline is the current standard of response assessment used for primary endpoints in most clinical trials of psoriasis. Lower level of responses (e.g. 50% reduction) have also been used as endpoints. However, responses below 50% are not considered as an acceptable demonstration of treatment response. This is in line with the CHMP guideline on clinical investigation of medical products indicated for the treatment of Psoriasis (CHMP/EWP/2454/02 corr).

Nieboer et al., 1990

The aim of this double-blind, 16 week trial was to assess the therapeutic effect of DMF monotherapy compared to DMF/MEF using the same DMF dosage and, thus, to assess the possible additional effect of MEF.

Treatment

Group 1 (n=22) received max. 480 mg DMF/day (max. 4 tablets/day of 120 mg each).

Group 2 (n=23) received max. 480 mg DMF/day + 380 mg MEF salts (max. 4 tablets/day of 120 mg DMF + 87 mg Ca^{2+}-MEF + 5 mg Mg^{2+}-MEF + 3 mg Zn^{2+}-MEF per tablet) for 4 months.

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

The individual results are shown in 22. 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 16: 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

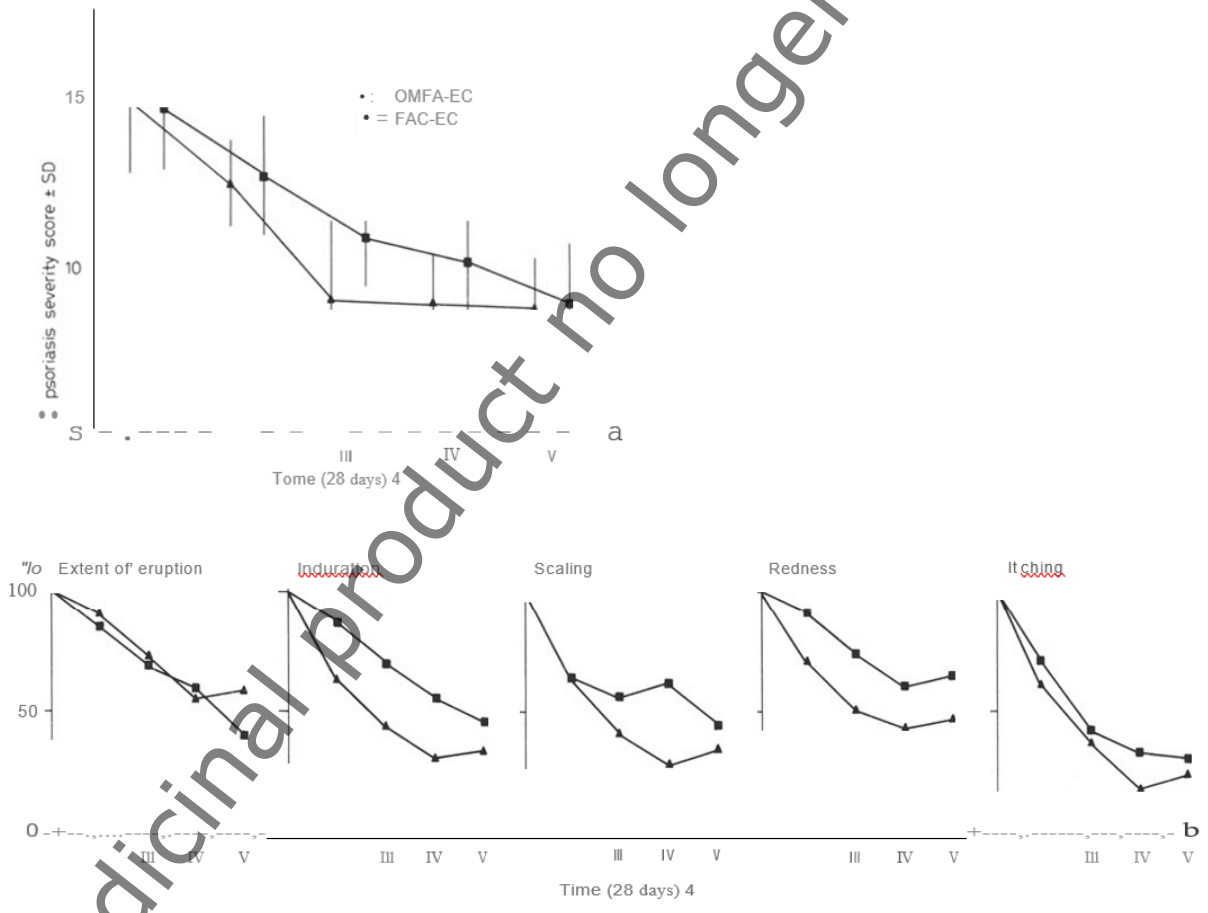


Table 5: Comparative study on the effects of DMFAE-EC (n = 22) and FAC-EC (n = 23) on 45 psoriasis patients

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)		22%	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 23, the anti-psoriatic effect, i.e. improvement of PASI with 240 mg DMF monotherapy was less pronounced than with 480 mg DMF resp. 480 mg DMF/MEF, which was administered in the Nieboer study (1990). This means, the DMF dose applied in the Nieboer 1989 studies (III and IV) was quite low (probably too low to achieve convincing results).

Evaluation comment

The aim of this double-blind study was to assess the therapeutic effect of DMF monotherapy compared to DMF/MEF using the same DMF dosage. There was a numerical difference in favour of DMF/MEF compared to DMF monotherapy in regard to the improvement of the psoriasis severity score. However, as acknowledged by the authors of the study, the difference is not statistically significant. Higher rate of discontinuations were observed in DMF/MEF group compared to DMF group. Overall, the evidence of this study is limited due to its small sample size, the short duration of treatment, and the absence of control for missing data (table 5 and figure 8 were based on a complete case analysis including 81% of patients in the DMFAE-EC [DMF] group and 65% of those in the FAC-EC [DMF/MEF] group). Subscores were not presented as endpoints in this study so the course of these scores over time should be regarded as exploratory. In this study, the greatest differences were observed for redness and induration scores while a lower difference and no numerical difference were found for scaling and itching, respectively, as opposed to Study II and Study IV previously conducted by these authors (Nieboer et al., 1989).

Mrowietz et al., 2017

The objective of the BRIDGE study was to assess the efficacy and safety of a new formulation of DMF (LAS41008), compared with placebo and Fumaderm, in adults with moderate-to-severe chronic plaque psoriasis.

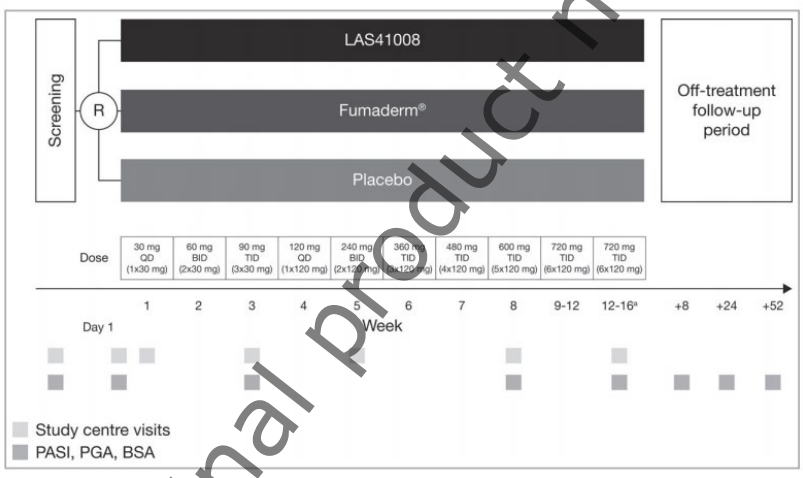
In this Phase III, double-blind, placebo-controlled, noninferiority trial, patients were randomized to receive LAS41008, Fumaderm, or placebo (2:2:1) for 16 weeks, up titrating to a maximum daily DMF dose of 720 mg, depending upon individual response.

The co-primary endpoints were the percentage of patients achieving ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75) and the percentage achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment (PGA) at Week 16. Secondary endpoints included PASI 75 at Weeks 3 and 8, PASI 50 and PASI 90 at Week 16, and scores of 0 to 1 in the PGA at Weeks 3 and 8 and BSA at weeks 3, 8, and 16.

Statistical analysis
The sample-size calculations were based on PASI 75 response rates of 50% and 10% for LAS41008 and placebo, respectively, and 'clear'/'almost clear' PGA response rates of 40% for LAS41008 and 10% for placebo. For the non-inferiority test of LAS41008 vs. Fumaderm® regarding PASI 75 at week 16, a zero difference was assumed and a noninferiority margin of 15% was set. An alpha level of 0.05 was defined and a dropout rate of 15% was factored into the calculations. A total of 690 patients (276 per active group and 138 in the placebo group) provided a power of > 99% for the two superiorities tests of LAS41008 vs. placebo, and 90% for the non-inferiority test of LAS41008 vs. Fumaderm.

In total, 671 patients were randomized and included in the full analysis set (n = 267, LAS41008; n = 273, Fumaderm; n = 131, placebo).

Figure 17: 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 18: Participants flow

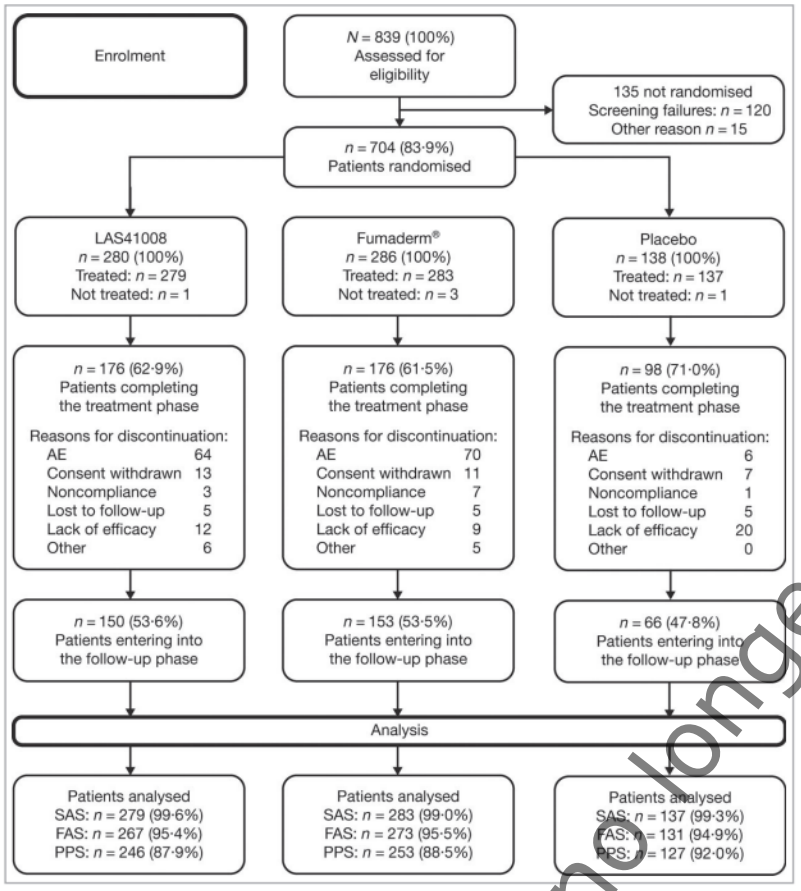


Table 7: Demographic and baseline patient characteristics (treated population)

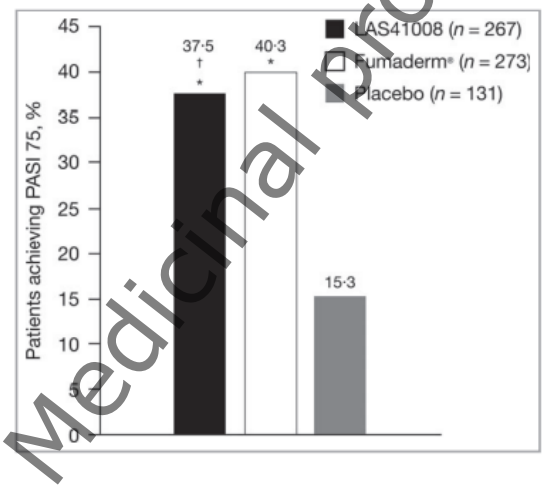
	LAS41008 (n = 279)	Fumaderm® (n = 283)	Placebo (n = 137)
Male, n (%)	174 (62·4)	185 (65·4)	93 (67·9)
Age (years)			
Mean ± SD	44·0 ± 15·2	45·0 ± 13·8	44·0 ± 14·3
Range	18–80	18–87	18–78
Race, n (%)			
White	275 (98·6)	280 (98·9)	137 (100·0)
Black/African American	1 (0·4)	0	0
Asian	1 (0·4)	3 (1·1)	0
Other	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	21·5 ± 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

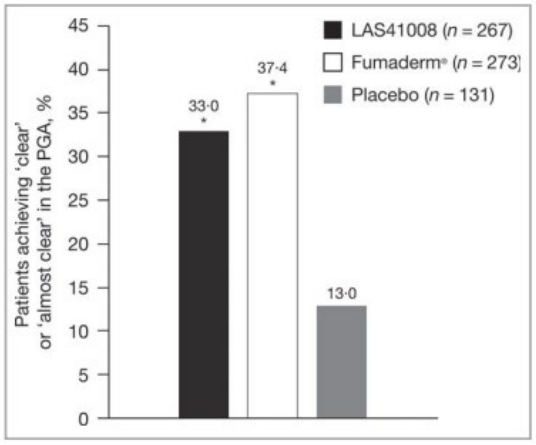
Co-primary endpoints: Significantly more patients achieved PASI 75 at week 16 following treatment with LAS41008 than with placebo [37.5% vs. 15.3%, P < 0.001; 99.24% confidence interval (CI) 10.7–33.7%]. Furthermore, LAS41008 was noninferior to Fumaderm at week 16 (37.5% vs. 40.3%, P < 0.001; 99.24% CI -14-0 to 8-4%) (Figure 11).

Figure 19: 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 20: Percentage of patients achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment (PGA) at week 16 (full analysis set). *P < 0.001 vs. placebo



Based on the above results, the Authors concluded that the study has demonstrated the efficacy and safety of LAS41008 (DMF) for adults with moderate-to-severe chronic plaque psoriasis, showing it to be significantly superior to placebo and noninferior to the approved combination of FAEs (Fumaderm).

Evaluation comment

The objective of this double-blind placebo-controlled study was to assess the efficacy and safety of DMF compared with placebo and Fumaderm (DMF/MEF) in adult patients with moderate-to-severe chronic plaque psoriasis. Patients were randomized to receive DMF, Fumaderm, or placebo (2:2:1) for 16 weeks, up titrating to a maximum daily DMF dose of 720 mg, depending upon individual response.

The coprimary endpoints were the percentage of patients achieving ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75) and the percentage achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment (PGA) at Week 16. Secondary endpoints included PASI 75 at Weeks 3 and 8, PASI 50 and PASI 90 at Week 16, and scores of 0 to 1 in the PGA at Weeks 3 and 8 and BSA at weeks 3, 8, and 16. In total, 671 patients were randomized and included in the full analysis set.

Significantly more patients achieved PASI 75 at week 16 with either DMF or Fumaderm compared to placebo (37.5%, 40.3% and 15.3%, respectively). 33% of patients treated with DMF achieved 'clear' or 'almost clear' based on PGA at Week 16, compared with 13.0% receiving placebo and 37.4% receiving Fumaderm.

There was a small numerical difference in favor of Fumaderm in regard to the co-primary endpoints and most of the secondary endpoints. As stated in the EPAR "*The effects in regard to the co-primary endpoints were numerically slightly lower in the Skilarence group compared to Fumaderm although this could be due to variability, a limited PD and the efficacy effect of MEFs in Fumaderm may also be contributing to an anti-psoriatic effect*". Therefore, these differences although suggesting an additional therapeutic effect of MEF in Fumaderm may also appear due to variability or a limited PD. More importantly, it should be noted that this study was aimed to demonstrate superiority of DMF versus placebo and non-inferiority versus DMF/MEF. Consequently, the design of this study does not allow to demonstrate superiority of DMF/MEF versus DMF.

Falkvoll S et al., 2019

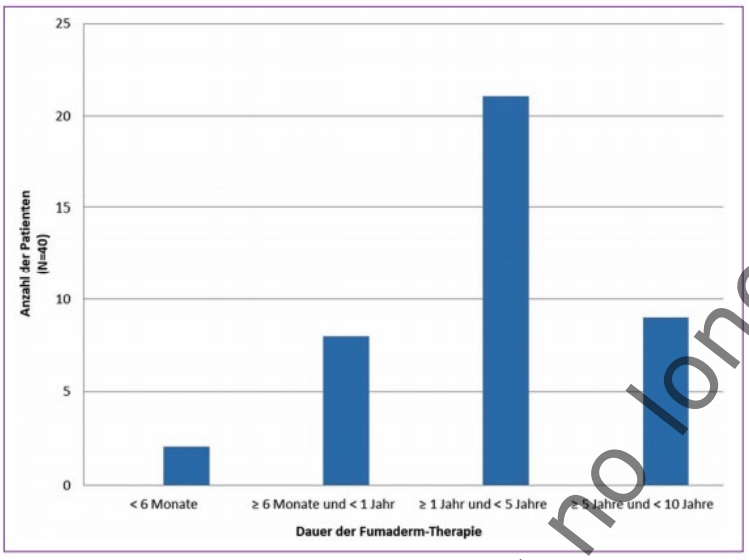
This was a prospective observational trial in patients who were treated with the FAE mixture. Patients whose psoriasis had improved and who could tolerate treatment with the FAE mixture were recruited. Treatment with the FAE mixture was switched to the DMF product without any interruption on the basis of the current DMF dose in the FAE mixture. Patients were then scheduled for the next regular check-up

three months later. To assess psoriasis severity, the PASI index (psoriasis area and severity index) was used. When presenting for their first check-up after switching, patients were handed a questionnaire to investigate their views about tolerability and efficacy and to provide a global judgment of the switch.

Results

A total of 40 patients (24 male, 16 female) were prospectively and consecutively recruited to the study and underwent a check-up after switching treatments. The age of adult patients ranged from 18 to 74 years with a mean age of 46 years. One patient was 13 years old and received treatment off-label.

Figure 21: 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)

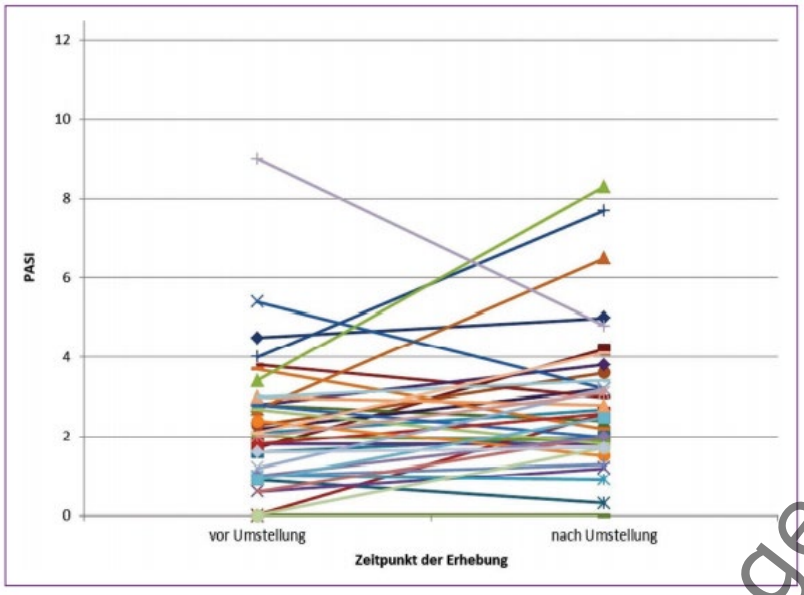


Most patients were treated with a daily DMF dose between 120 mg and 480 mg and had previously been treated with the FAE mixture for one to five years.

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 22: Clinical course of PASI in patients treated with the FAE mixture before (t1) and after (t2) switching to the DMF product. The mean time between the two visits was 91.8 days (minimum 42 days, maximum 133 days; n = 37)



The Authors concluded that the results of this study showed that psoriasis patients can switch from the traditional FAE mixture to the same dose of DMF with similar clinical relief but without any washout period.

Evaluation comment

This prospective study was aimed to investigate the switch from the currently used DMF/MEF to DMF monotherapy. The study was not designed to evaluate the treatment difference between DMF/MEF and DMF in the treatment of psoriasis. The objective of the study was to evaluate the clinical course of PASI in patients after switching to the DMF product.

Treatment with the DMF/MEF was switched to the DMF product without any interruption. Patients clinical state was evaluated after three months. To assess psoriasis severity, the PASI (psoriasis area and severity index) was used.

The patients regarded the outcome of the switch to the DMF product as neutral or positive (18 positive, 18 neutral, 4 negative). Efficacy as assessed with the PASI was equal or better in 34/37 patients, while 3/37 had a higher PASI severity after switching.

However, based on the presented data it is not possible to evaluate in how many patients PASI improved. Therefore, it is not possible to conclude on differences in efficacy between the two treatments.

Discussion on Efficacy

There are in a total 4 published studies which can be considered the most relevant for the evaluation of the clinical relevance of MEF in Fumaderm. However, the results of Kolbach & Nieboer (1992) were not included in the analysis due to severe limitations, described above.

Therefore, the assessment of the clinical relevance of MEF can be based on the results of 3 published studies:

In the Nieboer et al., study (1990), a numerical, but not statistically significant, difference in favour of DMF/MEF compared to DMF monotherapy (52% vs. 45%) was demonstrated in what regards the improvement of the psoriasis severity score.

When only patients who could be evaluated after 16 weeks were included in the analysis, the improvement percentage (i.e. a psoriasis severity score more than halved) was 55 % in the DMF group and 80 % in the DMF/MEF group. However, this complete case analysis may be biased. Except for the single patient for whom the tables were stolen, all other patients discontinued due to adverse events, an intercurrent event, likely informative that was completely disregarded by the investigators. Therefore, the comparison of 55% - 80% should not be considered a reliable estimate of the difference. Additionally, the evidence of this study is limited due to the small sample size and short duration of treatment.

In Falkvoll et al. (2019) study, efficacy as assessed with the PASI was equal or better in 34/37 patients, while 3/37 had a higher PASI severity after switching from DMF/MEF combination to DMF. However, it was not stated clearly in how many patients PASI improved. Therefore, it is not possible to conclude on differences in efficacy between the two treatments.

The most relevant study for this assessment appears to be study by Mrowietz et al. (2017), which was a pivotal study for the Skilarence MAA. The study was aimed to demonstrate superiority of DMF to placebo and non-inferiority to Fumaderm. Although both co-primary endpoints were met, the robustness of the demonstration of non-inferiority to Fumaderm was found questionable. As it was discussed in the EPAR for Skilarence, although the difference in proportion of patients achieving PASI 75 was -2.8 (99.24 CI =14.0 8.4; p-0.0003), and the lower limit of the confidence interval was within the prespecified non-inferiority limit of 15, given the absolute difference in proportion of responders by PASI 75 between DMF and placebo was 22%, the non-inferiority margin of 15% could not be appropriate.

The comparison between DMF and Fumaderm showed that Fumaderm consistently had a numerically higher response rate. In FAS population, 37.5% of the patients in the DMF group compared to 40.3% of the patients in the Fumaderm group achieved PASI 75 at Week 16. Moreover, the proportion of patients achieving PGA clear/almost clear was 33% and 37.4% in DMF and Fumaderm groups, respectively.

These data suggest that MEF may contribute to the efficacy in psoriasis to some extent. This assumption is supported by pharmacodynamic studies demonstrating MEF salts biological activities, including reducing IL-6 and TGF-alpha secretion in psoriatic cocultures of KCs and T cells, suppressing lymphocyte proliferation and inducing a rapid, transient [Ca2+] increase in KCs and inhibiting KC proliferation. However, and as stated in the EPAR for Skilarance, "*The effects in regard to the co-primary endpoints were numerically slightly lower in the Skilarence group compared to Fumaderm although this could be due to variability, a limited PD and the efficacy effect of MEFs in Fumaderm may also be contributing to an anti-psoriatic effect*". Therefore, reasons other than an additional therapeutic effect of MEF in Fumaderm could not be excluded. More importantly, the design of this study does not allow to demonstrate superiority of DMF/MEF versus DMF.

Overall, based on the available data, pharmacodynamic effects of MEF in psoriasis appear to be demonstrated. A numerical difference in favour of DMF/MEF combination reported in two independent randomized, double blind studies suggests that MEF could contribute to the efficacy of Fumaderm in the treatment of psoriasis. However, given the methodological limitations of the available clinical studies comparing directly DMF/MEF with DMF monotherapy in patients with psoriasis (small sample size, short duration of treatment, absence of methods to account for missing data, intercurrent events and multiple comparisons, absence of properly design studies to demonstrate superiority of DMF/MEF over DMF), a clinically relevant effect of MEF in Fumaderm has not been demonstrated.

- **Clinical Safety**

For the purpose of assessing whether MEF has a clinically relevant therapeutic contribution within Fumaderm from a safety standpoint, the following four publications have been reviewed.

Kolbach and Nieboer, 1992

In terms of tolerability, side effects were the most frequent reason to stop therapy in the DMF/MEF group (18%). For the DMF group, this percentage was 26%. In the first 6 months gastrointestinal complaints were the most frequent in both groups. However, the aforementioned difference was not significant and although the amounts of DMF in the DMF/MEF combination group were twice that of the DMF monotherapy, this is no sound proof that the MEF increased the tolerability.

Comparable to the studies from Nieboer *et al*. 1989, DMF in the DMF-monotherapy group was formulated as capsules filled with semi-enteric-coated granulate, whereas Fumaderm was formulated as enteric-coated tablets, which could have resulted in different drug release and hence affected the safety profile.

Evaluation comment

Although the amounts of DMF in the DMF/MEF combination were twice that of the DMF monotherapy, slightly higher discontinuation rate was reported in patients from DMF group compared to DMF/MEF group (16% vs 18%). However, it should be noted that differences in both formulations (semi-enteric coated vs enteric coated) could contribute to the overall tolerability.

Furthermore, taking into consideration different dose of DMF and different pharmaceutical formulation, no definite conclusion cannot be drawn from this study.

Nieboer et al., 1990

The subjective and objective side effects are shown in 25. The flushings started 3-4 h after the tablets were taken. They involved a feeling of tingling heat, accompanied by diffuse redness, which continued for about half an hour mainly localized in the face, arms and the upper part of the body. This symptom was not constantly present and in the course of the treatment its frequency decreased. More than half the patients were troubled by serious stomach complaints, involving gastralgia, but also nausea, vomiting and diarrhea. For 14% (n = 3) of the patients in the DMFAE-EC group and 30% (n = 7) in the FAC-EC group these complaints were a reason to discontinue the therapy. The abnormalities which were registered in the blood most generally were: leukopenia (< 3.0 x 10^9/1), lymphopenia (< 15%) and eosinophilia (> 5%). The former two developed in the course of the 3rd and 4th months. The eosinophilia usually began in the first 2 months and disappeared spontaneously in most of the cases.

Table 8: Side effects during treatment of psoriasis with DMFAE (n=22) or FAC-EC (n=23) over w period of 4 months

	DMFAE-EC (n = 22)		FAC-EC (n= 23)	
	11	0/0	n	0/0
Sy m pto m s				
Fl ushi n g	19	86	20	87
Dia rrh ea	12[2]	55	14[3]	61
Nausea/stomache	11[1]	50	14[3]	61
General malaise	2	9	1	4
Di zziness		5	0	0
Headac he		5		4
Laboratory				
Urine				
Albuminuria	0	0	2	9
Blood				
Leukopenia	3	14	3	13
Lympho pen ia	3	12	2	8
Eosinophilia	8	35	3	13
Increase of				
Creatinine/urea	0	0	0	0
Alkaline phosphatase	1	5	0	0
ASAT/A LAT	0	0		4

1 Patient discontinued the treatment as a result of this symptom.
2 3 Patients discontinued the treatment as a result of these symptoms.
3 7 Patients discontinued the treatment as a result of these symptoms.

Evaluation comment

In this study, higher discontinuation rate due to AEs (nausea, vomiting, diarrhoea) was reported in DMF/MEF group compared to DMF group (30% vs 14%). However due to small study size, no clear conclusion cannot be made.

Mrowietz et al., 2017

Treatment-emergent AEs (TEAEs) were reported in 83.9% and 84.1% of patients in the LAS41008 and Fumaderm® groups, respectively, and in 59.9% of patients in the placebo group. The majority were considered 'mild' in intensity (66.7%, 67.1% and 52.6% in the LAS41008, Fumaderm® and placebo groups, respectively). The most frequently reported TEAEs in both the LAS41008 (DMF) and Fumaderm® groups were gastrointestinal disorders (62.7% and 63.3%, respectively), including diarrhoea, abdominal pain, nausea and flatulence. Flushing was also commonly reported (18.3% and 16.3%, respectively) (26).

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 109 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 (26).

Twenty-three serious TEAEs were reported in 22 patients (3.2%, 2.8% and 3.6% of patients in the LAS41008, Fumaderm and placebo groups, respectively). Only four of these serious TEAEs, occurring in three patients randomized to Fumaderm, were assessed by the investigator as related to treatment (erosive gastritis, gastritis, gastric ulcer and gastroduodenitis).

One death considered unrelated to the medication was reported in a patient receiving Fumaderm (subendocardial ischaemia). No relationship between blood abnormalities and the onset of infections was detected.

Laboratory investigations

At week 16 or upon early treatment discontinuation, the mean total lymphocyte counts had decreased from baseline by 0.52 x109 cells L_1 in both the LAS41008 and Fumaderm groups, and by 0.08 x 109 cells L_1 in the placebo group.

Similarly, the mean leucocyte counts had decreased from baseline by 0.73 x109 and 0.69 x 109 cells L_1 in the LAS41008 and Fumaderm groups, respectively, compared with 0.04 x 109 cells L_1 in the placebo group. Lymphocyte counts below 0.7 x 109 cells L_1 were observed during the trial in 22 patients in the LAS41008 group (7.9%), 21 patients in the Fumaderm group (7.4%) and one patient in the placebo group (0.7%). Based on the available follow-up data, white blood cell counts progressively recovered after treatment with either LAS41008 or Fumaderm was stopped.

Evaluation comment

The safety profile was evaluated based on data of 699 patients. Comparable frequency of adverse events was observed in DMF and Fumaderm groups. Most of adverse events were considered mild in severity. Lymphopenia was reported in 10% of patients treated with DMF and 10.6% of patients from Fumaderm group.

Falkvoll S et al. 2019

The majority of patients (27/40) did not experience any difference in GI complaints after switching from the FAE mixture to the DMF product. Gastrointestinal tolerability was judged as better for the DMF product by 7/40 patients and worse by 2/40 patients. No GI complaints were reported with either drug product by 4/40 patients. Flushing was unchanged in 24/40 patients, 8/40 reported less flushing and 6/40 reported more flushing. Flushing did not occur with either drug product in 2/40 patients. Regarding the question of overall tolerability, 28/40 patients reported similar tolerability, 8/40 reported better tolerability with the DMF product and 4/40 said that tolerability was worse after switching. In answer to the question about skin status in general, 27/40 patients reported that it was unchanged after switching from the FAE mixture to the DMF product, patients, 7/40 reported that it was better and 6/40 said it was worse.

Evaluation comment

Overall, no significant differences in AEs and overall tolerability were observed after switching from DMF/MEF to DMF. 31/40 and 26/40 patients did not notice differences between DMF and DMF/MEF with respect to gastrointestinal symptoms and flushing, respectively.

Discussion on Safety

The safety of DMF/MEF combination in comparison to DMF was evaluated in four studies (Kolbach and Niebor (1992); Niebor et al., (1990); Mrowietz et al., (2017) and Falkvoll et al., (2019)).

Although in Kolbach and Niebor (1992) study higher percentage of patients from DMF group discontinued the therapy compared to DMF/MEF group (16% vs 18%), differences in both formulations (semi-enteric coated vs enteric coated) could contribute to the overall tolerability. Nevertheless, it should be noted that the amounts of DMF in the DMF/MEF combination were twice that of the DMF monotherapy.

Contrary, in Niebor et al., (1990) study, 30% from DMF/MEF group and 14% from DMF group discontinued the study due to AEs (nausea, vomiting, diarrhoea).

In Mrowietz et al., (2017) study, frequency of adverse events reported in DMF and Fumaderm groups was comparable.

Similarly, no significant differences in AEs and overall tolerability were observed after switching from DMF/MEF to DMF in Falkvoll et al., (2019) study.

In summary, no significant differences in the safety profiles of DMF compared to DMF/MEF combination were observed in the available studies.

Unsolicited submission received during the evaluation

During the assessment of the therapeutic contribution of MEF in Fumaderm, on 8 September 2021, the CHMP received an unsolicited submission from a company.

The unsolicited submission has been considered by the CHMP and supports its recommendation as outlined below (3. Recommendations and next steps).

3. Submission of additional scientific observations by an interested entity

On 1 October 2021, an interested entity submitted additional observations to the CHMP in response to the Rapporteurs' preliminary assessment report ("PAR").

The additional observations included, in particular, previously unsubmitted information relating to a pre-clinical study. In support of that information, it has been claimed that the associated study demonstrates that MEF is capable of producing an additive, synergistic benefit to DMF in a non-clinical disease model.

The Rapporteurs reviewed those additional observations including the pre-clinical study. Further to that assessment, it was found that these observations were not capable of altering their conclusion that the totality of the available data has not established that MEF has a clinically relevant therapeutic contribution within Fumaderm. The reasons for this are as follows:

First, the Rapporteurs reviewed the different elements of evidence, which was listed in support of the finding that MEF has a clinically relevant therapeutic contribution within Fumaderm. It was noted that the different elements of evidence put forward mainly reproduced the findings (and claims) that had been previously submitted to the CHMP. The only new element of evidence pertained to the non-clinical study mEAE-012 (which will be discussed below).

Second, the results from the non-clinical study mEAE-012 were taken into account. These results stemmed from an experiment conducted in an experimental autoimmune encephalomyelitis (EAE) model, which was designed to compare the impact of treatment with DMF or MEF monotherapy with a combination of DMF+MEF on clinical and histopathological characteristics. Of note, neither the literature reference nor the study report was provided and as such details of the study are not available.

However, a number of shortcomings were identified in relation to the usefulness of this pre-clinical study.

The interested entity has neither provided a study protocol nor a statistical analysis plan. In the absence of this information, it is unclear whether this is a therapeutic non-clinical exploratory study or a therapeutic non-clinical confirmatory study.

However, the definitions of the primary and secondary endpoints for this study have not been provided.

Additionally, no information has been provided about how the entity addressed the inflation of the type I error rate as a result of multiple testing (multiplicity). In absence of a pre-specification of a primary endpoint and information on control of multiplicity, a conclusion on statistically significant effect cannot be reached and the statistically significant claims submitted for the aforementioned differences cannot be accepted.

Altogether considered, these results are considered exploratory and difficult to interpret. Consequently, clear conclusions could not be made based on the presented histopathological examination results.

Moreover, it is not clear how the doses used in mice correspond to the doses used in humans.

In conclusion, although the available non-clinical data could suggest a different impact of DMF+MEF combination on progression of EAE in mice, compared to DMF monotherapy, taking into account the presented results and the above-described limitations, this data cannot be relied upon to establish the non-clinical efficacy of MEF within Fumaderm.

Without prejudice to the above, it also bears noting that, while it is true that (an) active substance(s) within a fixed combination medicinal product may have additive or synergistic effects, it is expected that clinical data is presented for the purpose of establishing its contribution to the overall effect in terms of efficacy. In particular, compelling mechanistic (in vitro data), preclinical and pharmacodynamic data could be adduced to support a claim of improved efficacy within the fixed combination medicinal product. That being so, improved efficacy over (an) individual active substance(s) that have established efficacy in the targeted indication (namely, DMF) needs to be shown. The design of the pivotal clinical studies should be according to specific clinical guidance, where placebo or standard of care – instead of those individual active substances - may be acceptable as comparators. A direct comparison against individual active substances with established efficacy in the targeted indication would however still be expected. More specifically, for the treatment of psoriasis, a three-armed, parallel-group studies with the active agent, placebo and comparative active treatment would be expected. Although the BRIDGE Study did take into account DMF, DMF+MEF and placebo, improved efficacy over DMF was not demonstrated.

The relevance of these non-clinical findings (either alone or in combination with the other elements of evidence presented) is limited in the context of the overall assessment, as these findings (account being taken of their above-outlined shortcomings) cannot suffice to establish the clinically relevant therapeutic contribution of MEF in the combination treatment. In that regard, the claim that MEF has an additive, synergistic effect within Fumaderm has not been demonstrated.

In light of all of the above and having taken into account all the available evidence (including the above-described non-clinical study), the additional observations submitted have not demonstrated that MEF has a clinically relevant therapeutic contribution within Fumaderm and the Rapporteurs' conclusion remains unchanged.

4. Recommendations and next steps

The CHMP reviewed all above-mentioned studies and data. The CHMP also considered all data submitted by the interested entities, including the data submitted by a company on 8 September 2021.

The available non-clinical data even if not extensive is not scarce and it suggests a potential PD effect and PK differences.

The available clinical data is not conclusive for the purpose of establishing that MEF has a clinically relevant therapeutic contribution within Fumaderm. Whilst said clinical data, including two clinical trials (Nieboer et al., 1990 and Mrowietz et al, 2017) showing numerical differences in favour of the DMF/MEF combination vs. DMF alone in psoriasis, may be indicative that MEF contributes to the efficacy of Fumaderm in the treatment of psoriasis to a small extent, this would need to be confirmed by appropriate data that demonstrate a clinically relevant therapeutic effect. In that respect, the evaluated data suffer, in part, from severe methodological limitations, including:

- Differences in DMF doses administered and differences in formulations (Kolbach and Nieboer, 1992);
- Small sample size and short duration (Nieboer, 1989; Nieboer, 1990);
- Lack of appropriate methods to account for missing data, intercurrent events and control for multiplicity (Nieboer, 1989 and Nieboer, 1990); and
- Lack of properly designed studies to demonstrate superiority of DMF/MEF over DMF (Kolbach and Nieboer, 1992; Mrowietz et al., 2017; Falkvoll S et al., 2019).

Taking into account the described results, including the severe methodological limitations of the clinical studies, it cannot be concluded based on these data that a clinically relevant therapeutic effect of MEF in Fumaderm has been demonstrated.

Therefore, the CHMP concludes that the totality of the available data cannot establish that MEF exerts a clinically relevant therapeutic contribution within Fumaderm.

Further to the above, the Rapporteurs recommend adoption of the opinion.

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