22 May 2025
EMA/221770/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Riulvy

International non-proprietary name: tegomil fumarate

Procedure No. EMEA/H/C/006427/0000

Note

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

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List of abbreviations

ANOVA	Analysis of variance
ASMF	Active Substance Master File = Drug Master File
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time 0 to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t hours
$AUC_{\%extra}$	Extrapolated area under the plasma concentration-time curve
BMI	Body mass index
Cis	Confidence intervals
C_{max}	Maximum concentration
CV	Coefficient of variation
DMF	Dimethyl fumarate
DOSEai	Maximum daily dose consumed per inhabitant
DSC	Differential Scanning Calorimetry
ERA	Environmental risk assessment
FA	Fumaric acid
FA-TTEG-MMF	Demethylated metabolite
FATTEG- FA	double demethylated metabolite
FaSSIF	Fasted-state simulated intestinal fluid
FeSSIF	Fed-state simulated intestinal fluid
Fpen	Fraction of market penetration
FT-IR	Fourrier Transform Infrared Spectroscopy
GC	Gas Chromatography
GMP	Good Manufacturing Practice
Kel	Elimination rate constant
HDPE	High Density Polyethylene
HPLC-(MS/MS)	High-performance liquid chromatography (with tandem mass spectrometry)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
ISR	Incurred sample retest
KF	Karl Fischer titration
LLOQ	Lower limit of quantification
MMF	Monomethyl fumarate
MMF-TTEG-MMF	Dimethyl fumarate tetraethylene glycolate = bis(methylfumaryl) tetraethylene glycol = tegomil fumarate
MMF-TTEG	Monomethyl fumarate tetraethylene glycolate
MRT	Mean residence time
NMR	Nuclear Magnetic Resonance
NOAEL	No observed effect level
oPA	Oriented Polyamide
PECsurfacewater	Predicted environmental concentration in local surface water concentration
PD	Pharmacodynamics
PDA	Photodiode array
PK	Pharmacokinetics
Ph. Eur.	European Pharmacopeia
QC	Quality Control
QTPP	Quality target product profile

RH	Relative Humidity
(R)(RR)MS	(Relapsing) (Relapsing Remitting) Multiple Sclerosis
(S)AE	(Serious) Adverse Event
SD	Standard Deviation
SEM	Standard error of the man
SmPC	Summary of Product's Caractheristics
$t_{1/2}$	half-lives plasma half-life
TK	Toxicokinetics
TGA	Thermo-Gravimetric Analysis
t_{max}	Time of C_{max}
TSE	Transmissible Spongiform Encephalopathy
TTEG	Tetraethylene glycol
UV	Ultraviolet
WASTEWinhab	Amount of wastewater per inhabitant per day
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Neuraxpharm Pharmaceuticals S.L. submitted on 8 March 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Riulvy, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 September 2023.

The application concerns a hybrid medicinal product as defined in Article 10(3) 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:

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

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

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

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6 / 8 / 10 years in the EEA:

- Product name, strength, pharmaceutical form: Tecfidera, 240 mg, gastro-resistant capsule, hard
- Marketing authorisation holder: Biogen Netherlands B.V.
- 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, EU/1/13/837/003

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

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

- 240 mg: EU/1/13/837/001, EU/1/13/837/002, EU/1/13/837/003
- 120 mg: EU/1/13/837/001, EU/1/13/837/002, EU/1/13/837/003

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

- Product name, strength, pharmaceutical form: Tecfidera, 240 mg, gastro-resistant capsule, hard
- Marketing authorisation holder: Biogen Netherlands B.V.
- Date of authorisation: 30-01-2014
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number(s): EU/1/13/837/001, EU/1/13/837/002, EU/1/13/837/003
- Bioavailability study number(s): MMF-BESD-05-TFB/22, MMF-BEFI-06-TFB/22, MMF-BEFI-07-TFB/24

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 received the following scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
14 October 2021	EMA/SA/0000062072	*Ewa Balkowiec Iskra* *Audrey Sultana* *Karl-Heinz Huemer*
21 July 2022	EMA/SA/0000086723	*Ewa Balkowiec Iskra* *Audrey Sultana*

The scientific advice (EMA/SA/0000062072) pertained to the following quality, non-clinical and clinical aspects:

- Quality: prodrug of the same active moiety; limits above ICH qualification threshold for degradation products.
- Non-clinical: adequacy of non-clinical package.
- Clinical: bridging to reference product according to product specific bioequivalence guidance.

The scientific advice (EMA/SA/0000086723) pertained to the following quality, non-clinical and clinical aspects:

- Quality: shelf-life limits for drug product degradation products.
- Non-clinical: need for further nonclinical pharmacology, pharmacokinetic and toxicology studies.
- Clinical: bioequivalence study design.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Grzegorz Cessak

The application was received by the EMA on	8 March 2024
The procedure started on	28 March 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 June 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	1 July 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 July 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	27 January 2025
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at clinical investigator site in Moldova and the bioanalytical site in Romania between 18 June 2024 and 5 July 2024. The outcome of the inspection carried out was issued on	5 September 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	28 February 2025

The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 March 2025
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	27 March 2025
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	22 April 2025
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	5 & 25 May 2025
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 Riulvy on	22 May 2025

2. Scientific discussion

2.1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative disease of the central nervous system characterised by inflammation, demyelination, neuronal and oligodendrocyte loss, and disruption of the blood-brain barrier, leading to irreversible deficits in physical function and cognition and an impaired quality of life. Typically, MS starts in the second or third decade of life.

Relapsing Remitting MS (RRMS) is the most common form of MS, representing approximately 85% of patients at diagnosis, and it is characterised by alternating exacerbations of neurological dysfunction followed by periods of remission with partial or total recovery and clinical stability, which can last for months or years.

Worldwide, the number of people with MS is estimated at 2.8 million. In 2020, the global incidence was estimated at 2.1 individuals per 100 000 and the global prevalence was estimated at 36 individuals per 100 000, with women being at a 2-times (in some countries at a 4-times) higher likelihood to develop MS than men. Regionally, the median prevalence of MS in 2020 was greatest in Europe (143 per 100 000), followed by the Americas (117 per 100 000), and the Eastern Mediterranean (33 per 100 000). Prevalence of MS in Africa, South East Asia and Western Pacific was less than 10 per 100 000. Overall, the incidence of MS appears to increase.

Symptoms of RRMS can include numbness and weakness in the legs leading to difficulty in walking, vision loss, incoordination, cognitive dysfunction, fatigue, and pain. These lesion-driven symptoms are also associated with considerable anxiety and distress for patients. Relapses may result in incomplete recovery of function and leave permanent disability and impairment that accumulates over time.

The diagnosis of RRMS can be based on clinical considerations alone, but magnetic resonance imaging (MRI), cerebrospinal fluid, and/or electrophysiological findings can support, supplement, or even replace some of the clinical diagnostic criteria for MS. Given the complexities of diagnosing MS, the McDonald diagnostic criteria have been developed and continue to be revised to facilitate earlier diagnosis and initiation of treatment. The McDonald diagnostic criteria comprise clinical observation, neurologic examination, brain and spinal cord MRI scans, visual/auditory evoked potentials, and cerebrospinal fluid examination.

In addition to medicines approved for the symptomatic treatment of MS (e.g., aminopyridine for improvement of walking ability) and for the treatment of relapses (such as corticosteroids), there are several disease modifying treatments approved for use in patients with RRMS and/or other forms of relapsing MS (RMS) in the EU including dimethyl fumarate.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a gastro-resistant hard capsule containing 174 mg or 348 mg of tegomil fumarate, 174.2 mg of tegomil fumarate corresponds to 120 mg of dimethyl fumarate, and 348.4 mg of tegomil fumarate corresponds to 240 mg of dimethyl fumarate.

The other ingredients are:

Capsule contents (enteric-coated minitablets): Microcrystalline cellulose (E460i), croscarmellose sodium (E466), talc, colloidal anhydrous silica, magnesium stearate (E470b), hypromellose (E464), hydroxypropylcellulose (E463), titanium dioxide (E171), triethyl citrate (E1505), methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30%, poly(vinyl alcohol) (E1203), macrogol, iron oxide, yellow (E172).

Capsule shell: Gelatin (E428), titanium dioxide (E171), brilliant Blue FCF (E133).

Capsule printing ink: Shellac, potassium hydroxide, titanium dioxide (E171), propylene glycol (E1520).

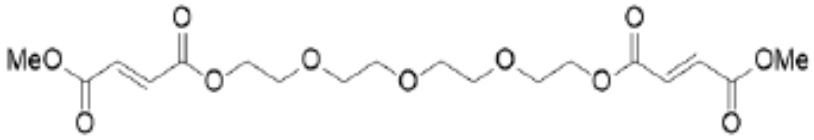
The product is available in HDPE bottles and oPA/Aluminium/PVC-Aluminium blisters as described in section 6.5 of the Summary of product information (SmPC).

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of tegomil fumarate is dimethyl-O,O'-(((oxybis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))difumarate corresponding to the molecular formula $C_{18}H_{26}O_{11}$. It has a molecular mass of 418.40 g/mol and the following structure:

Figure 1: active substance structure



The chemical structure of tegomil fumarate was elucidated by a combination of UV, FT-IR, NMR and MS. The solid state properties of the active substance were measured by TGA, DSC, and XRPD.

The active substance is a white to light brown coloured powder, it is very slightly soluble in water across the physiological pH range and it is not hygroscopic.

Tegomil fumarate exhibits stereoisomerism due to the presence of diastereomeric double bonds, the trans-trans isomer is consistently manufactured by the proposed synthetic route, as demonstrated by data. The relevant double bond configuration is formed during the manufacture of the active substance and suitably controlled, potential isomeric impurities are detectable through the method used to detect related substances in the active substance. Diastereomeric impurities of the active substance have not been detected above the applicable unspecified impurities level and therefore these are controlled as potential unspecified impurities of the active substance.

Polymorphism has not been observed for tegomil fumarate, only one crystal form has been observed. The results of analysis by XRPD confirm this form is consistently produced and is stable.

2.2.2.2. Manufacture, characterisation and process controls

The active substance is manufactured at one manufacturing site; the ASMF procedure is used and satisfactory information concerning GMP standards has been provided.

Tegomil fumarate is synthesised in three main steps using well defined starting materials with acceptable specifications, some of which are commercially available. One of the materials which contributes to the structure of the active substance had not originally been designated as a starting material by the applicant. As this could impact the appropriate control and synthesis of the active substance a Major Objection (MO) was raised on this point, and the applicant was requested to appropriately define the compound as a starting material in line with the requirements of ICH Q11. To address this MO the applicant defined this as a starting material, the material is commercially available and suitable information was provided

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

The assessment of all potential mutagenic impurities in the synthesis of the active substance was initially insufficient and not in accordance with ICH M7. An MO was raised requesting the applicant to provide information concerning mutagenicity on all potential impurities and the approach used to support this evaluation. The applicant resolved this MO by providing the assessment of potential mutagenicity which was conducted in line with ICH M7 requirements, these impurities are appropriately controlled in line with ICH M7 and do not impact the quality of the active substance. Following the resolution of this MO, potential and actual impurities were well discussed with regards to their origin and characterised. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

The active substance is packaged in a transparent polyethylene bag, this is placed into a black polyethylene bag with silica gel sachets present between the bags. These are then placed into a triple aluminium bag, all bags used are blanketed and purged with nitrogen, the bags are finally placed into HDPE drums. The relevant materials comply with Commission Regulation (EU) 10/2011, as appropriate.

2.2.2.3. Specification(s)

The active substance specification includes tests for: description (visual), identification (IR, HPLC), water content (KF, Ph. Eur.), residue on ignition (Ph. Eur.), assay (HPLC), related substances (HPLC, GC), residual solvents (GC-MS), and particle size (laser light diffraction).

The active substance specification parameters and limits are in line with relevant guidelines and are acceptable. No related substances are present at levels higher than the qualification threshold according to ICH Q3A.

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

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

2.2.2.1. Stability

Stability data from three production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions (25 ºC / 60% RH), 12 months at intermediate conditions (30 ºC / 65% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

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

At accelerated conditions the testing for related substances was out of specification at the 6 month time-point for all batches. Therefore, testing at the intermediate condition was necessary. The long term and intermediate results all remain within specification showing little to no variability and no significant changes.

Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions of exposure to heat, acidic conditions, oxidative conditions, and hydrolytic conditions were also provide on one batch.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 27 months with an instruction to store below 30°C in the proposed container in order to protect from moisture.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and pharmaceutical development

The finished product is formulated into two strengths, a 174 mg and a 348 mg gastro-resistant hard capsule. The visual descriptions are outlined as follows:

174 mg: Light blue and white gastro-resistant hard gelatin capsules, size 0 with the dimension of approximately 21 mm, printed with '174' in white ink on body, containing pale yellow mini tablets.

348 mg: Light blue gastro-resistant hard gelatin capsules, size 00 with the dimension of approximately 24 mm, printed with '348' in white ink on body, containing pale yellow mini tablets.

All excipients are well known pharmaceutical ingredients and where applicable their quality is compliant with Ph. Eur. standards, all excipients used are pharmacopoeial with the exception of the in-house colouring agents. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The aim of the pharmaceutical development was to develop a hybrid version of the reference product Tecfidera 120 mg and 240 mg gastro-resistant hard capsules, which contains dimethyl fumarate as active substance, rather than tegomil fumarate, as proposed in this application.

The pharmaceutical development of the finished product contains QbD elements. The Quality Target Product Profile (QTPP) was defined during development. A gastro-resistant formulation, consisting of gastro-resistant hard capsules containing enteric-coated minitablets, was chosen in line with the formulation of the reference product. Tegomil fumarate is a prodrug that converts to monomethyl fumarate which is the active moiety, this is the same moiety as is contained in dimethyl fumarate. The physical characteristics of the active substance which could impact the performance of the finished product are appropriately controlled; polymorphism of tegomil fumarate has not been observed, and a suitable test parameter for the particle size of the active substance is outlined in the active substance specification.

The critical quality attributes that may impact quality, safety, or efficacy were identified.

In order to achieve equivalence with respect to the active moiety monomethyl fumarate, the required dose of the proposed active substance (tegomil fumarate) is higher than the dose of the reference active substance (dimethyl fumarate). Two different manufacturing processes for the minitablets were evaluated during the manufacturing development, wet granulation and direct compression. Based on the preliminary evaluations conducted and nature of the active substance, wet granulation was considered not suitable for the routine manufacturing process. The proposed finished product formulation includes a high percentage of the active substance and a direct compression was found to be suitable. The development performed was used to inform the proposed control strategy and process parameters for the commercial scale manufacturing process.

The formulation was developed with the aim of using a common minitablet for both capsule strengths, by using a different amount of minitablets to achieve the desired dose. Formulation development proceeded with the chosen direct compression method of manufacture. Different formulation variables were trialled and refined during development. The proposed composition is the same as the one used in the bioequivalence study, which was performed using the highest strength of the proposed and reference product, the proposed product was shown to be equivalent. For details of the bioequivalence testing performed please refer to the clinical sections of the report. Comparative dissolution studies were performed in support of the bioequivalence testing, the *in-vitro* dissolution profiles were not

similar between the proposed test and reference product. The *in-vivo* results however take precedence over *in-vitro* dissolution dissimilarity.

The proposed product is formulated in two strengths and a biowaiver was requested for the lower strength, based on the acceptable bioequivalence results for the higher strength, and as the relevant requirements of the guideline on the investigation of bioequivalence are fulfilled. As discussed in the clinical section of the report, the applicant showed similar dissolution profiles between the higher and lower proposed product strengths, and the biowaiver for the lower strength was accepted. *In-vitro* dissolution testing was also performed to investigate the potential impact of dose dumping in the presence of alcohol given the gastro-resistant nature of the formulation. The dissolution profiles demonstrated that potential dose dumping was not a concern for the proposed product.

The dissolution method proposed for QC release of the product was developed in line with the gastro-resistant nature of the product. In line with Ph. Eur. requirements this involves exposure to a low pH condition to mirror the gastric environment followed by dissolution at a high pH value. The applicant's method involves dissolution testing of exposure to 0.1 HCl, followed by dissolution testing at pH of 6.8 in phosphate buffer using the paddle apparatus. The selected method was justified. The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is HDPE bottles or oPA/Aluminium/PVC-Aluminium blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The finished product is manufactured at one manufacturing site and satisfactory information regarding GMP has been provided.

During the manufacturing process, the excipients and active substance are blended together and compressed into minitablets. The minitablets are then coated and finally encapsulated into hard gelatine capsules. The process is considered to be a non-standard manufacturing process, due to the modified release dosage form.

The initially proposed commercial batch sizes were larger than what the applicant had manufactured during validation studies. As the process is considered to be non-standard, validation data related to batches manufactured at production scale were considered necessary. As it was not yet assured that the applicant could manufacture the product with sufficient quality at the intended scale an MO was raised on this aspect. To resolve this MO the applicant defined the proposed commercial batch sizes in line with the process validation data, and also outlined that the common minitablet approach means the manufacturing of both strengths is similar in nature. Following resolution of the MO, 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(s)

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: description (visual), identification (HPLC, PDA), water content (KF, Ph. Eur.), assay (HPLC), dissolution (HPLC, Ph. Eur.), uniformity of dosage units (Ph. Eur.), related substances (HPLC), microbiological quality (Ph. Eur.).

The specification for the control of the finished product contains the typical tests for this type of pharmaceutical form and the limits have been adequately justified.

The limits for related substances are set in line with ICH Q3B requirements, impurities present at greater than the qualification threshold of 0.2% are appropriately qualified based on toxicological considerations.

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 it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/Applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The limit proposed for the dissolution quality control test did not initially reflect the performance of the proposed product that was used in the bioequivalence study, as the limit was set too wide. As this aspect could impact the performance of the product an MO was raised. To resolve this MO the applicant tightened the dissolution limit as requested in line with the product used in the bioequivalence study.

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 commercial scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.2.3.1. Stability of the product

Stability data from production scale batches of each strength of the finished product stored for up to 18 months under long term conditions (25 ºC / 60% RH), 12 months under intermediate conditions (30 ºC / 60% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The analytical methods used were the same as for release and were stability indicating. For the HDPE bottle presentation, at long term and accelerated conditions all results were within specification. For the blister presentation, out of specification results were observed under accelerated conditions. As a result of this, this presentation was subject to stability testing at the intermediate condition (30ºC / 65% RH). The stability results at the intermediate condition were acceptable and remained within specification.

With respect to ongoing stability studies, in accordance with EU GMP guidelines any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is not sensitive to light.

Based on available stability data, the proposed shelf-lives are acceptable:

HDPE bottles – 30 months without special storage conditions

oPA/Aluminium/PVC-Aluminium blisters – 24 months and do not store above 30°C.

2.2.3.2. Adventitious agents

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

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

During the procedure four MOs concerning quality aspects were raised. Two of these related to the active substance and these concerned the designation of a starting material, and the completeness of the assessment for potential mutagenic impurities. To resolve these aspects the applicant defined the requested material used in the synthesis of the active substance as a starting material and provided the full assessment of potential mutagenic impurities in line with ICH M7 requirements. With respect to the finished product the initially proposed batch sizes, and the proposed limit for QC dissolution were raised as major objections during the procedure. The applicant resolved these objections by adjusting the proposed commercial batch sizes of the finished product in line with the manufacturing experience gained to date and revised the limit for QC dissolution in line with the request

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

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

N/A

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 primary and secondary pharmacodynamics (PD) data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

PD, PK and toxicological properties of monomethyl fumarate (MMF) are well known. The non-clinical PK program performed for tegomil fumarate aims to bridge the existing data from Tecfidera®, while providing detailed information on the metabolic breakdown.

The nonclinical evaluation of the toxicity of tegomil fumarate aimed at bridging to MMF, the active metabolite of Tecfidera®.

2.3.2. Pharmacology

No primary and secondary PD, safety and PD drug interactions studies have been conducted to support this marketing authorisation application.

2.3.3. Pharmacokinetics

The PK program performed for tegomil fumarate aims to bridge the existing data from Tecfidera®, while providing detailed information on the metabolic breakdown.

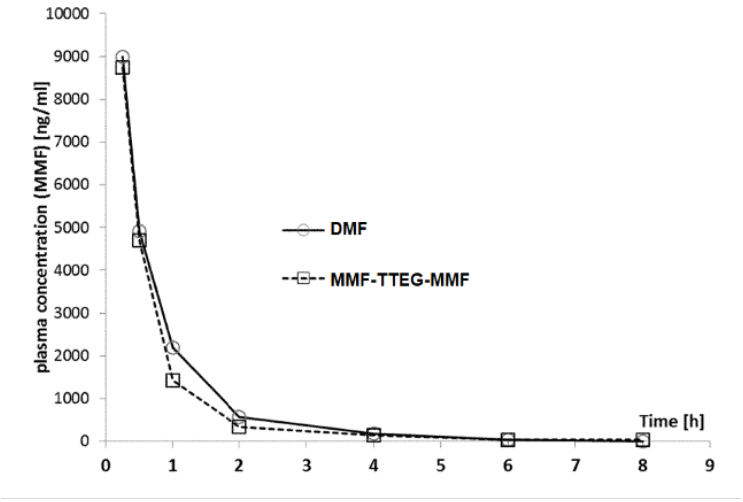
Study 14-076-DMF-12 - Membrane Permeability using Caco-2 Cells

In an *in vitro* experiment using Caco-2 cells, Tegomil fumarate showed lower mean apparent permeability compared to dimethyl fumarate (DMF). Based on the results, DMF and tegomil fumarate can be categorized as moderate and low permeable drugs, respectively. Both DMF and tegomil fumarate have similar susceptibility to hydrolysis.

Study No 504.220.4951 - Pharmacokinetic Study of Active Metabolite Monomethylfumarate after Single p.o. Administration of Dimethyl fumarate and the Different Pro-drugs RN6081, RN6045, RN5830 and RN6087 in Female NMRI Mice.

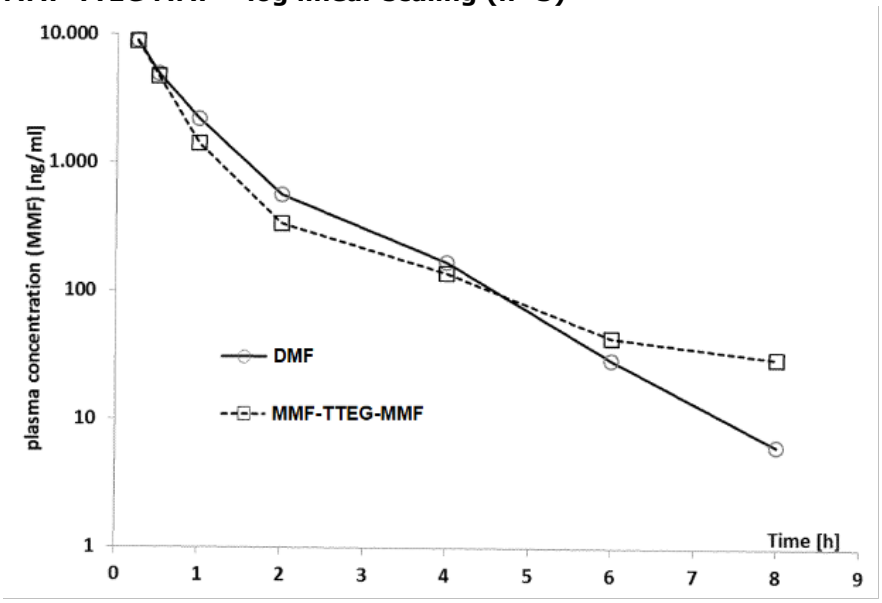
In a non-GLP PK study administration of tegomil fumarate at the dose of 65.3 mg/kg and DMF at the dose of 45.0 mg/kg comparable rate and extent of systemic exposure to MMF was shown. Compared to DMF, the relative bioavailability of MMF after administration of tegomil fumarate was ~94% for maximum concentration (C_{max}), and ~89% for area under the curve from time 0 to infinity ($AUC_{0-\infty}$). For both substances, the time of C_{max} (t_{max}) values are uniformly 0.25 hours (Figure 2 and Figure 3).

Figure 2: Mean concentration vs. time profiles of MMF after oral administration of Tegomil fumarate (65.3 mg/kg) and DMF (45.0 mg/kg) to female NMRI mice – linear scaling (n=3)



MMF-TTEG-MMF = Tegomil fumarate

Figure 3: Mean concentration vs. time profiles of MMF after oral administration of doses of MMF-TTEG MMF – log linear scaling (n=3)



MMF-TTEG-MMF = Tegomil fumarate

Distribution

No distribution studies have been performed with tegomil fumarate.

Metabolism

In the completed *in vitro* dissolution and metabolism Studies Nos. 14-076-DMF-12 and 13-004-DMF-02 and Study Nos. 2020AET002 a fast and linear MMF-release was observed for DMF and after 90 min, a quantitative hydrolysis was observed.

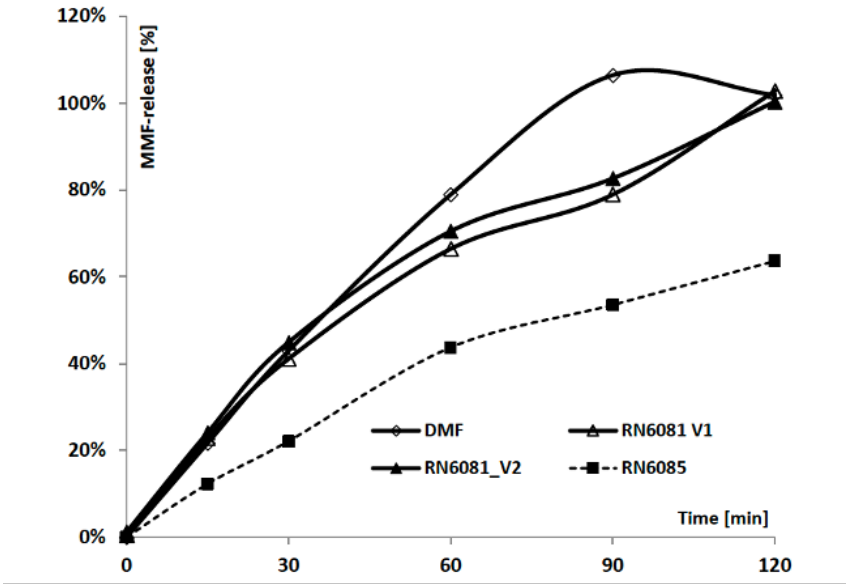
Of note, the kinetics of MMF-release from tegomil fumarate was very similar to that observed for DMF, but after release of approx. 50%, an intermittent decreased rate of hydrolysis was observed. The rate of hydrolysis of MMF-TTEG was substantially lower compared to Tegomil fumarate.

In the study aimed to evaluate the metabolic stability of tegomil fumarate and DMF (Study No. 2020AET002), tegomil fumarate rapidly degraded in fasted-state simulated intestinal fluid (FaSSIF)

and fed-state simulated intestinal fluid (FeSSIF) as indicated by 4.7% and 6.9% remaining compound after 1 h with half-lives ($t_{1/2}$) of 0.2 and 0.3 h, respectively. MMF, MMF-TTEG and tetraethylene glycol (TTEG) were extensively released during incubation. In phosphate buffer at pH 6.8, no degradation was observed for the test item within 4 hours; only low formation rates in the low nM-range of MMF, MMF-TTEG and TTEG occurred. In FaSSIF and FeSSIF, DMF was degraded displaying $t_{1/2}$ of 1.3 h and 0.5 h. Extensive formation of MMF occurred in both matrices. In phosphate buffer at pH 6.8, DMF was stable over the tested incubation period. In Study 2021AET001 for Tegomil fumarate the main metabolites were MMF and TTEG, and to a lesser extent the intermediate MMF-TTEG and MMF-TTEG-FA (fumaric acid).

When liver S9 fractions was used, tegomil fumarate, MMF-TTEG-FA and MMF-TTEG were metabolized fast (tegomil fumarate and MMF-TTEG) to moderate (MMF-TTEG-FA). Tegomil fumarate, MMF-TTEG-FA and MMF-TTEG were nearly completely converted to MMF, TTEG and FA.

Figure 4: Release of MMF during incubation of DMF, Tegomil fumarate (RN6081) and MMF-TTEG (RN6085) with 20x diluted minipig intestinal fluid (Study No. 14-076-DMF-12 and 13-004-DMF-01).



When liver S9 fractions was used, tegomil fumarate, MMF-TTEG-FA and MMF-TTEG were metabolized fast (tegomil fumarate and MMF-TTEG) to moderate (MMF-TTEG-FA). Tegomil fumarate, MMF-TTEG-FA and MMF-TTEG were nearly completely converted to MMF, TTEG and fumaric acid.

Figure 5: Metabolization of MMF-TTEG-MMF (Tegomil fumarate) with human liver S9 (Study No.2021AT001)

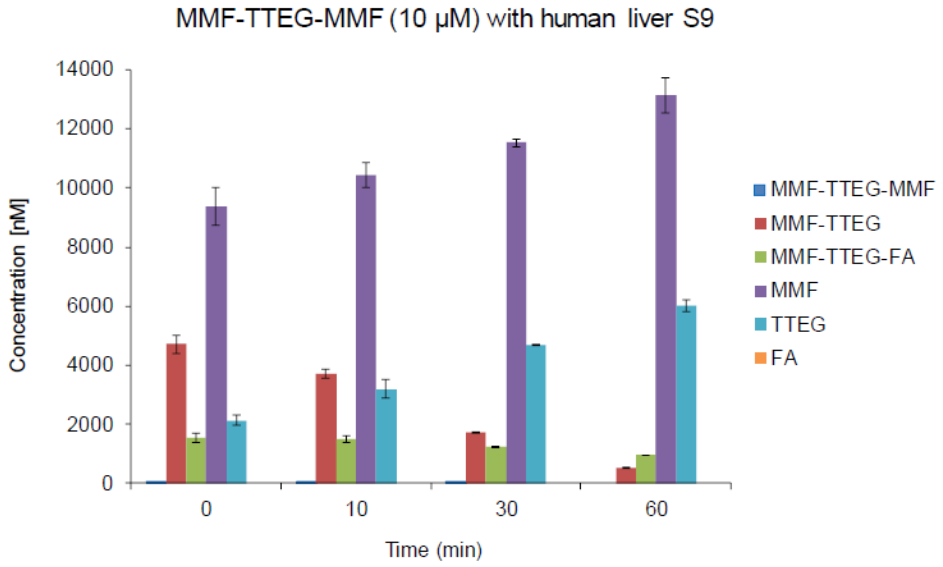


Figure 6: Metabolization of MMF-TTEG-FA with human liver S9 (Study No.2021AT001).

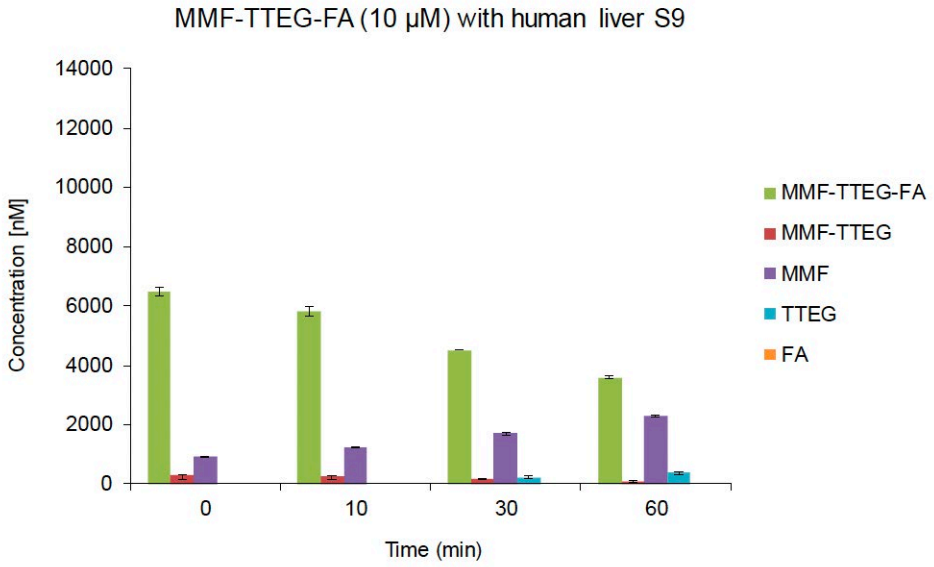


Figure 7: Metabolization of MMF-TTEG with human liver S9 (Study No.2021AT001).

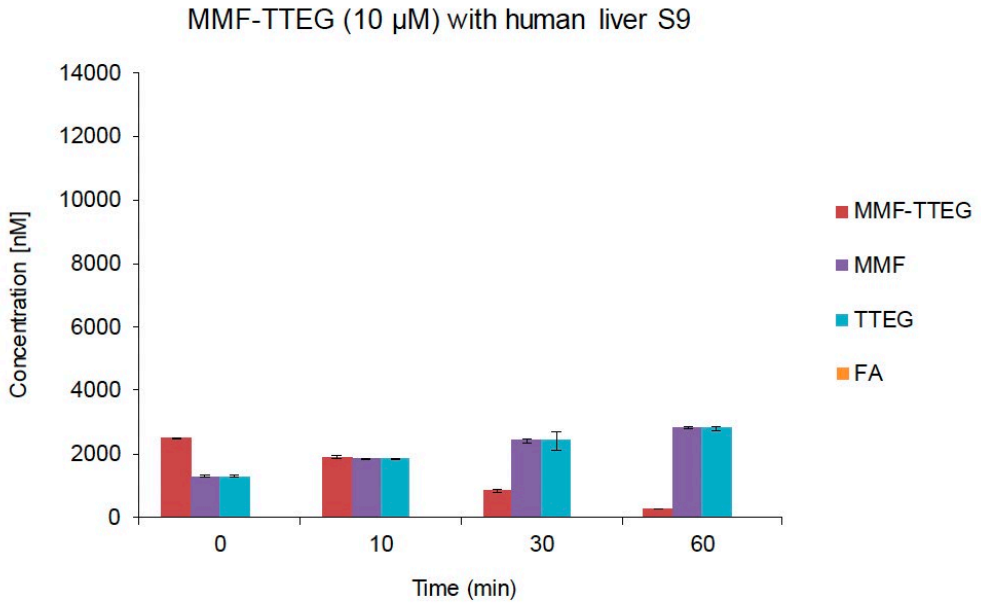


Figure 8: Pre-systemic metabolization of MMF-TTEG-MMF (Tegomil fumarate) with human intestinal S9 (Study No.2021AT001).

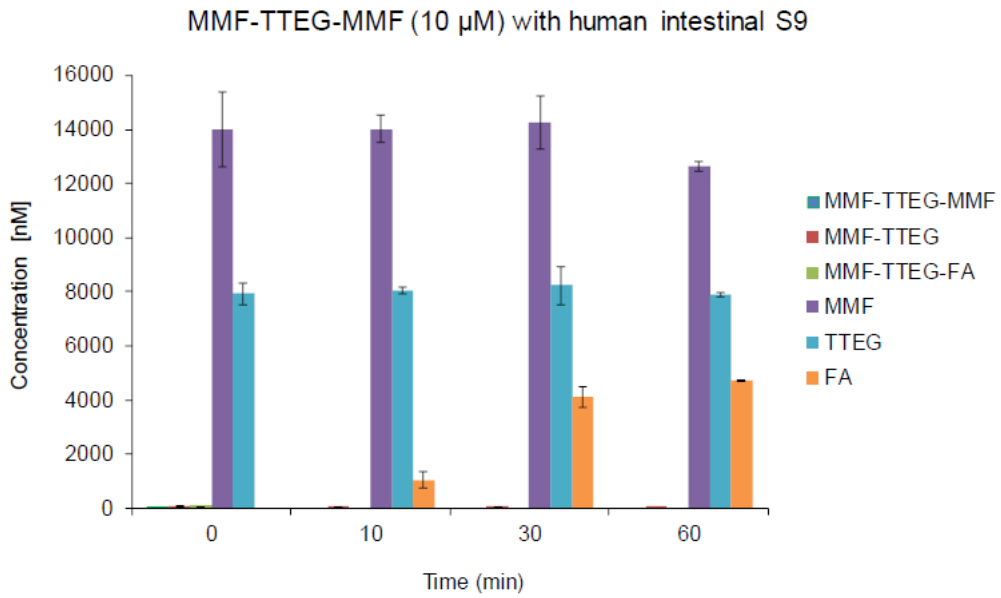


Figure 9: Pre-systemic metabolization of MMF-TTEG-FA with human intestinal S9 (Study No.2021AT001).

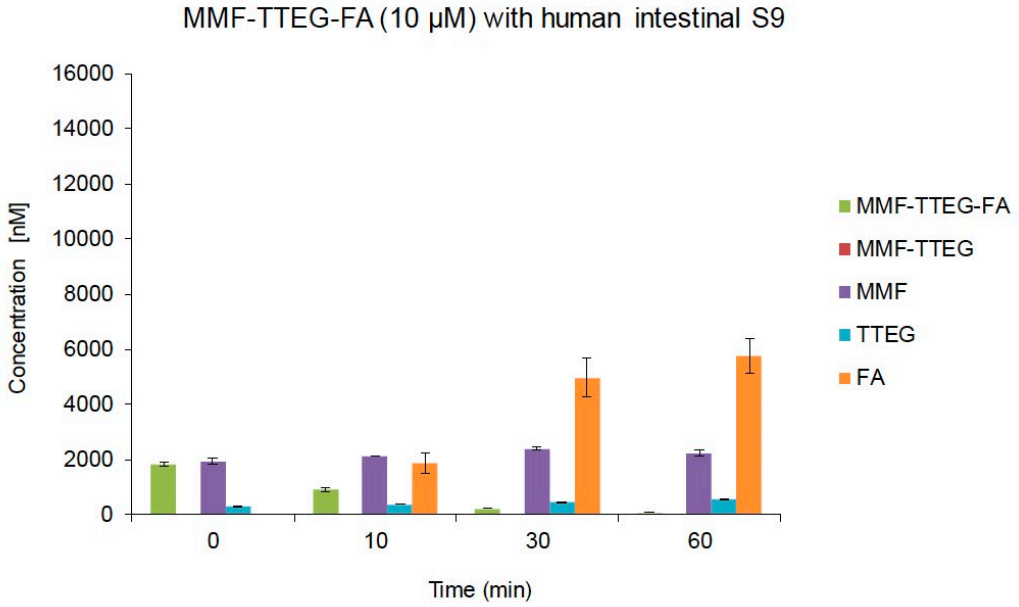
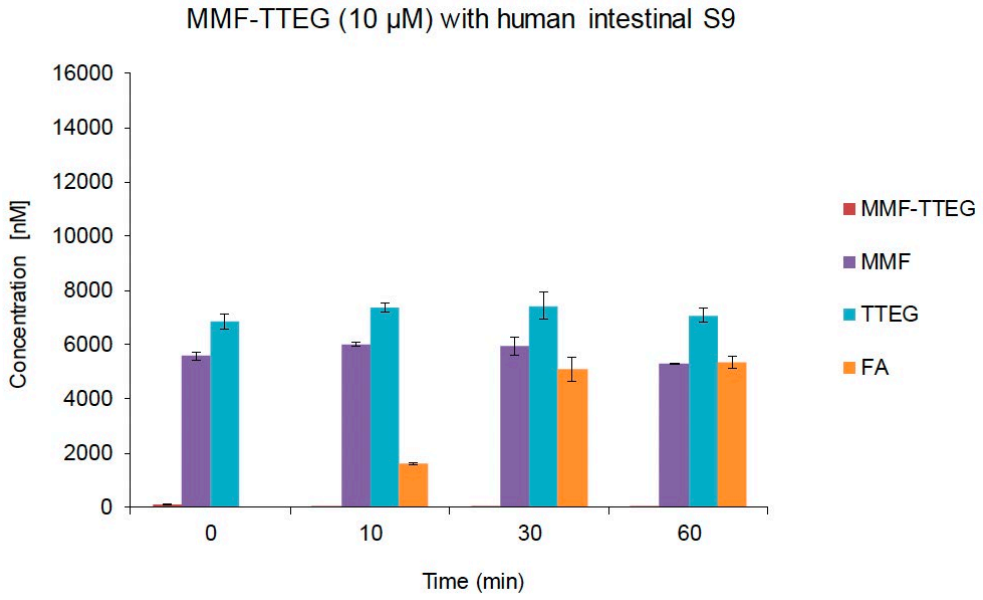


Figure 10: Pre-systemic metabolization of MMF-TTEG with human intestinal S9 (Study No.2021AT001).



Excretion

No excretion studies have been performed with tegomil fumarate. MMF is excreted primarily via exhalation of carbon dioxide. Based on TK results of the rat GLP toxicology study with tegomil fumarate, TTEG is efficiently removed from plasma with $t_{1/2}$ ranging between 1.05 – 4.16 hours.

2.3.4. Toxicology

2.3.4.1. Single dose toxicity

No single dose or acute toxicity studies have been performed with tegomil fumarate.

2.3.4.2. Repeat dose toxicity

The applicant conducted a 90-day comparative repeat-dose toxicity study (G19873/ G19873_Amd1) with a 4-week recovery period in SD rats.

Tegomil fumarate and DMF were administered at three (equimolar) doses of 36.3 mg/kg, 145.1 mg/kg, 290.2 mg/kg (tegomil fumarate) and 25 mg/kg, 100 mg/kg and 200 mg/kg (DMF). Throughout the study, animals were evaluated for clinical signs, mortality, ophthalmological examination, body weights, food consumption, clinical pathology investigations (haematology, coagulation, clinical chemistry and urinalysis) gross pathology, organ weights and histopathology.

At steady state (Day 90) the 8-fold higher dose (from the low to the high dose) resulted in a 4.4-fold and 5.3-fold increase of AUC_T. For tegomil fumarate, this was due to a less than proportional increases of AUC_T at both dose escalation steps. A comparable pattern emerged for the dose dependency of C_{max}.

No accumulation of MMF was observed for mid and high-dose and test-item groups. Negligible accumulation of MMF (ratios >3) was only observed for the low dose of tegomil fumarate and DMF, respectively, which indicates similar drug disposition *in vivo*.

For both compounds, the no observed effect level (NOAEL) has been determined to be the highest

dose evaluated (290.2 mg/kg/day for the tegomil fumarate and 200 mg/kg/day for the DMF, respectively). No clinical signs, mortality, changes in body weights, body weight gains and food consumption, clinical pathology parameters (ocular abnormalities, hematology, coagulation, clinical chemistry and urinalysis) and terminal fasting body weights were reported. The microscopic changes in stomach, kidneys and pancreas were observed in both test and reference items. However, the changes observed in kidneys were similar in both test and reference items. At necropsy, kidney weights were higher at 145.1 and 290.2 mg/kg/day tegomil fumarate treated groups (increase of 15 - 35%) and at 100 and 200 mg/kg/day DMF groups (increase of 10 - 28%) in both sexes. Microscopically, tubular basophilia (males) and tubular vacuolation and few incidences of degeneration (females) were noted in the outer medullary tubules of kidneys. The applicant claims these changes occurred at a comparable incidence in tegomil fumarate and DMF treated animals and reversed at the end of recovery period and were thus considered non-adverse. In female rats, tubular vacuolation was observed more frequently in tegomil fumarate (in 8 vs. 5 animals) compared to DMF.

Of note, all the tegomil fumarate and DMF related findings were reversible at the end of 28 days recovery period except for the minimal severity acinar cell apoptosis in pancreas of females.

2.3.4.3. Genotoxicity and carcinogenicity

No genotoxicity and carcinogenicity studies as per ICH S2(R1) and ICH S1A have been performed with tegomil fumarate. For genotoxicity and carcinogenicity evaluation of tegomil fumarate it is considered justified to make reference to the lack of a genotoxic and carcinogenic response for the observed and/or expected ultimate metabolites MMF, TTEG and FA, which are generated in the gastro-intestinal tract and to a limited extent systemically following absorption. MMF and FA can be considered well-characterized, and the risk related to these compounds is adequately covered by the nonclinical program performed for the originator DMF, which is metabolized to MMF, FA and methanol.

DMF and MMF were negative in a battery of *in vitro* assays (Ames, chromosomal aberration in mammalian cells). DMF was negative in the *in vivo* micronucleus assay in rats. Carcinogenicity studies of DMF were conducted for up to 2 years in mice and rats.

No genotoxic or carcinogenic risk has been identified for TTEG. Nevertheless, the applicant further substantiates the lack of expected genotoxic and carcinogenic risks for TTEG (see impurities).

2.3.4.4. Reproduction toxicity and developmental toxicity

No reproductive- and developmental toxicity studies have been performed with tegomil fumarate, since the applicant states that ultimate metabolites MMF and TTEG can be considered well-characterized. However, the applicant in the non-clinical documentation refers to the SmPC of Tecfidera as the supportive data for this reproductive and developmental toxicity claim. Nevertheless, the applicant further substantiates the lack of expected reproduction toxicity for TTEG (see impurities).

Since in a 90-Day toxicology study in rats animals 6 – 7 weeks old were included, which is equivalent to an adolescent child of 12 years (ICH S11, 2020), it is agreed that this study data can be considered sufficient to support safety of tegomil fumarate, as well as its main metabolites TTEG and MMF in subjects from 12-year of age. No new relevant safety issues were observed in this study.

2.3.4.5. Toxicokinetic data

Toxicokinetics (TK) by means of determination of tegomil fumarate, as well as metabolites (MMF, TTEG, TTEG-MMF, FA-TTEG-MMF, and FA-TTEG) have been evaluated as part of the 90-day repeated

dose toxicity study with tegomil fumarate or the 28-day repeated dose toxicity study with FA-TTEG-MMF and FA-TTEG, respectively. Summary of toxicokinetic parameters for MMF-TTEG-MMF, DMF, MMF, MMFTTEG, TTEG and DMF following once daily oral gavage administration of Dimethyl Fumarate Tetraethylene Glycolate (Test Item) and Dimethyl Fumarate IH (Reference Item) in 90-day repeated dose toxicity study is presented below.

Table 1: Summary of toxicokinetic parameters

Treatment	Analyte	Day	Gender	Dose (mg/kg/day)	T_{max} (h)	C_{max} (µg/mL)	AUC_{last} (h*µg/mL)	AUC_{INF} (h*µg/mL)	Clast (µg/mL)	Tlast (h)	$T_{1/2}$ (h)
MMF-TTEG-MMF	MMF-TTEG-MMF	1	Male	36.3	No quantifiable concentration and not calculated						
				145.1							
				290.2							
			Female	36.3							
				145.1							
				290.2							
		90	Male	36.3							
				145.1							
				290.2							
			Female	36.3							
				145.1							
				290.2							
DMF	DMF	1	Male	25	NA	NA	NC	NC	NA	NA	NC
				100	0.5	0.00853	0.00107	NC	0.00853	0.5	NC
				200	0.25	0.0132	0.00644	NC	0.00777	0.75	NC
			Female	25	NA	NA	NC	NC	NA	NA	NC
				100	NA	NA	NC	NC	NA	NA	NC
				200	0.75	0.0204	0.00848	NC	0.00673	1	NC
		90	Male	25	0.083	0.0183	0.000761	NC	0.0183	0.083	NC
				100	0.083	0.0308	0.015	NC	0.0232	1	NC
				200	0.083	0.0612	0.0245	NC	0.0551	0.75	NC
			Female	25	NA	NA	NC	NC	NA	NA	NC
				100	0.75	0.0492	0.0309	NC	0.0136	1	NC
				200	0.083	0.119	0.0454	NC	0.0545	0.75	NC

Treatment	Analyte	Day	Gender	Dose (mg/kg/day)	T_{max} (h)	C_{max} (µg/mL)	AUC_{last} (h*µg/mL)	AUC_{INF} (h*µg/mL)	C_{last} (µg/mL)	T_{last} (h)	$T_{1/2}$ (h)
MMF-TTEG-MMF	MMF	1	Male	36.3	0.083	4.34	4.12	4.4	0.199	4	1.03
				145.1	0.25	16.7	16.1	16.9	0.614	4	1
				290.2	0.5	23.5	38.5	NC	0.946	8	NC
			Female	36.3	0.083	5.03	2.94	2.98	0.0497	4	0.733
				145.1	0.083	21.5	24.5	24.8	0.123	8	1.41
				290.2	0.25	32.1	46.2	NC	0.513	8	NC
		90	Male	36.3	0.083	15.8	5.56	NC	0.27	2	NC
				145.1	0.25	13.2	10.4	NC	0.0733	8	NC
				290.2	0.25	22.6	27	27.3	0.198	8	1.17
			Female	36.3	0.25	16.5	6.72	NC	0.0321	4	NC
				145.1	0.083	26.1	21.2	NC	0.165	8	NC
				290.2	0.25	27.8	27.2	28.3	0.354	8	2.08
DMF	MMF	1	Male	25	0.25	1.95	1.77	NC	0.25	2	NC
				100	0.5	9.63	9.24	9.36	0.104	4	0.655
				200	0.25	18.1	20.6	NC	2.19	4	NC
			Female	25	0.25	1.46	1.51	1.84	0.28	2	0.833
				100	0.25	8.74	9.32	9.53	0.209	4	0.713
				200	0.25	20.8	23	25	1.26	4	1.23
		90	Male	25	0.083	12.5	5.03	5.09	0.147	2	0.274
				100	0.083	17.9	18.2	18.5	0.101	8	1.72
				200	0.083	23.3	23.6	25.6	0.513	8	2.72
			Female	25	0.083	7.31	5.13	5.31	0.319	2	0.391
				100	0.75	18.9	23.1	NC	0.148	8	NC
				200	0.083	34.2	29.8	32	0.582	8	2.8
MMF-TTEG-MMF	MMF-TTEG	1	Male	36.3	0.25	0.000383	0.000032	NC	0.000383	0.25	NC
				145.1	0.75	0.00155	0.00105	NC	0.00073	1	NC
				290.2	0.25	0.00253	0.00239	0.00266	0.000343	2	0.549
			Female	36.3	0.25	0.000503	0.000042	NC	0.000503	0.25	NC
				145.1	0.25	0.00195	0.00102	NC	0.00135	0.75	NC
				290.2	0.25	0.00241	0.00312	NC	0.00123	2	NC
		90	Male	36.3	NA	NA	NC	NC	NA	NA	NC
				145.1	0.5	0.000427	0.0000533	NC	0.000427	0.5	NC
				290.2	0.75	0.00124	0.000593	NC	0.00124	0.75	NC
			Female	36.3	0.75	0.000827	0.000373	NC	0.000827	0.75	NC
				145.1	0.25	0.00229	0.00147	0.00212	0.000827	1	0.512
				290.2	0.5	0.00254	0.00242	NC	0.000447	2	NC

Treatment	Analyte	Day	Gender	Dose (mg/kg/day)	T_{max} (h)	C_{max} (µg/mL)	AUC_{last} (h*µg/mL)	AUC_{INF} (h*µg/mL)	C_{last} (µg/mL)	T_{last} (h)	$T_{1/2}$ (h)
MMF-TTEG-MMF	TTEG	1	Male	36.3	0.5	11.8	31.3	34.5	0.989	8	2.28
				145.1	0.5	32.8	105	119	3.83	8	2.51
				290.2	0.5	48.5	202	235	9.28	8	2.64
			Female	36.3	0.25	9.1	20.6	23.7	0.686	8	3.05
				145.1	0.5	36	102	109	2.37	8	1.97
				290.2	0.75	61.9	166	173	3.19	8	1.67
		90	Male	36.3	0.5	6.01	13.1	14.3	0.753	4	1.05
				145.1	0.5	13.5	48.5	53.4	1.5	8	2.25
				290.2	2	17.2	88.2	123	6.04	8	4.16
			Female	36.3	0.25	8.08	12.9	14.2	0.802	4	1.15
				145.1	0.5	21.1	42	48	1.51	8	2.98
				290.2	0.5	22.7	71.4	NC	5.36	8	NC
MMF-TTEG-MMF	DM	1	Male	36.3	No quantifiable concentration and not calculated						
				145.1							
				290.2							
			Female	36.3							
				145.1							
				290.2							
		90	Male	36.3							
				145.1							
				290.2							
			Female	36.3							
				145.1							
				290.2							

NA: Not Applicable; NC – Not Calculated due to non-linear elimination phase and $r^2<0.8$

Dimethyl Fumarate Tetraethylene Glycolate (MMF-TTEG-MMF) concentrations were not quantifiable (was BLQ) after oral gavage administration of test drug MMF-TTEG-MMF. Suggesting test item is completely converted to metabolites after oral gavage administration on both day 1 and day 90, hence no TK parameters were calculated.

Following oral gavage administration of test drug MMF-TTEG-MMF, the t_{max} of MMF was ranged from 0.083 to 0.5 h. Plasma concentrations were quantifiable till 2 to 8 h (t_{last}) in both genders at all the tested dose levels on study Days 1 and 90.

In general, as the dose increased, the plasma exposure of MMF also increased, the change in plasma exposure (AUC_{last}), was dose-proportional in both genders on day 1, and less than dose-proportional on day 90 in both genders across tested dose level.

Following oral gavage administration of test drug Dimethyl Fumarate reference item suspension, the time to reach MMF peak plasma concentration was ranged from 0.083 to 0.75 h. Plasma concentrations of MMF were quantifiable till 2 to 8 h in both genders at all the tested dose levels.

In general, as the dose increased, the exposure to MMF also increased. On day 1, AUC_{last} increased in a more than proportional manner, essentially with the escalation from low to medium dose. On day 90, AUC_{last} increased in a dose proportional manner with the escalation from low to medium dose but did not increase almost at all with escalation to the high dose.

Following oral gavage administration of test drug MMF-TTEG-MMF, on Day-90, about just a quarter of the plasma samples analysed contained MMF-TTEG at concentrations marginally above the lower limit

of quantification; most of these values were observed within 45 minutes after administration of the test item. No concentration occurred later than after two hours, indicating rapid metabolic degradation and/or elimination of MMF-TTEG.

In principle, the frequency of quantifiable concentrations increased with increasing dose: n = 5, 13, and 20 samples, respectively. However, the mean concentrations (and their ranges) were not related to dose: 1.18, 1.78, and 1.26 ng/mL.

Due to the fragmentary concentration-time profiles, a further TK analysis for MMF-TTEG is not considered reasonable.

Following oral gavage administration of test drug Dimethyl Fumarate Tetraethylene Glycolate, the time to reach TTEG peak plasma concentration (t_{max}) was ranged from 0.250 to 2 h. Plasma concentrations were quantifiable till 4 to 8 h (t_{last}) in both genders at all the tested dose levels on study Days 1 and 90.

In general, as the dose increased, the plasma exposures of TTEG also increased, the change in plasma exposure (AUC_{last}), was less than dose-proportional in both genders at the tested dose range of 36.3 to 290.2 mg/kg/day except the females dosed from 36.3 to 145.1 mg/kg/day dose level on day 1.

Comparison of MMF exposure following treatment with Dimethyl Fumarate Tetraethylene Glycolate and Dimethyl Fumarate

Day-1

The ratio of the MMF AUC_{last} after administration of Dimethyl Fumarate Tetraethylene Glycolate vs. the administration of Dimethyl Fumarate ranges from 1.74 to 2.63 across the 3 doses investigated and both genders; the mean calculated for all the resulting 6 groups is 2.09 (median 1.98).

The ratio of the MMF C_{max} after administration of Dimethyl Fumarate Tetraethylene Glycolate vs. the administration of Dimethyl Fumarate ranges from 1.30 to 3.45 across the 3 doses investigated and both genders; the mean calculated for all the resulting 6 groups is 2.12 (median 1.98).

Day-90

The ratio of the MMF AUC_{last} after administration of Dimethyl Fumarate Tetraethylene Glycolate vs. the administration of Dimethyl Fumarate ranges from 0.57 to 1.31 across the 3 doses investigated and both genders; the mean calculated for all the resulting 6 groups is 0.99 (median 1.02).

The ratio of the MMF C_{max} after administration of Dimethyl Fumarate Tetraethylene Glycolate vs. the administration of Dimethyl Fumarate ranges from 0.74 to 2.26 across the 3 doses investigated and both genders; the mean calculated for all the resulting 6 groups is 1.24 (median 1.12).

Overall, the exposure to MMF after administration of Dimethyl Fumarate Tetraethylene Glycolate and Dimethyl Fumarate, is about twice by equivalent dose of DMF on day 1 and very similar on day 90 across the dose range investigated.

2.3.4.6. Local tolerance

No local tolerance studies have been performed with tegomil fumarate.

Local tolerability of tegomil fumarate following oral use has been evaluated as part of the 90-day repeated dose toxicity study in rats. Results of this study do not point to any detrimental local toxicity of tegomil fumarate compared to DMF over a 90-day treatment period. In fact, DMF-related local findings in stomach were not or at a significant lower incidence observed in tegomil fumarate treated groups at equimolar doses.

2.3.4.7. Other toxicity studies

The purpose of a GLP bacterial genotoxicity study AD-G0946 was to assess the potential of FA-TTEG-MMF to induce point mutations, viz., substitution, addition or deletion of one or a few DNA base pairs in the *Salmonella typhimurium* and *Escherichia coli* reverse mutation assay. The study was conducted in-line with OECD Guideline No. 471 for testing of chemicals, "*Bacterial Reverse Mutation Test*".

The results of the study from both the initial and confirmatory mutation assay showed that the test item did not show any positive mutagenic increase at any of the tested doses either in the presence or in the absence of metabolic activation. Under identical test conditions, more than 3-fold increase in the mean numbers of revertant colonies in the positive controls was observed, demonstrating the sensitivity of the assay procedure used.

The study A4920 was aimed to assay the test item FA-TTEG-MMF for the ability to induce DNA strand breaks in cell suspensions isolated from liver and cytogenetic damage in bone marrow after *in vivo* treatment of Sprague Dawley rats. For this purpose, the *in vivo* alkaline comet assay and the erythrocyte micronucleus test were combined. The study was performed in line with OECD Guidelines for the testing of chemicals No. 474 Mammalian Erythrocyte Micronucleus Test as well as No. 489 *In Vivo* Mammalian Alkaline Comet Assay, respectively.

Following treatments with the test item, no clinical signs nor body weight loss were seen.

MMF-TTEG-FA did not cause excessive DNA damage (necrotic and apoptotic cells) which could have interfered with Comet analysis.

No bone marrow toxicity was observed at any dose level as indicated by the mean group percentage of PCEs over the total number of erythrocytes. No statistically significant increase in the incidence of micronucleated PCEs was observed in any treatment group or dose effect relationship was seen.

Both for the Comet Assay and micronucleus test, negative vehicle control data were considered acceptable when compared with our historical control data. Statistically significant increases in Comet parameters and micronuclei incidence were observed following treatment with the positive control items, indicating the correct functioning of the test system.

The objective of study AD-N0287 was to determine the MTD of test item, FA-TTEG-MMF and FA-TTEG following single intravenous route administration to Sprague-Dawley rats during Phase I and to determine the toxicity potential and TKs when administered repeatedly through intravenous route for 7 consecutive days in Phase II.

In Phase I (MTD) the single dose intravenous administration of FA-TTEG-MMF and FA-TTEG at the dose levels of 3, 15, 30 and 60 mg/kg did not result in any mortalities, clinical signs, body weight changes or gross pathological changes. No injection site reactions were observed in all rats treated with FA-TTEG-MMF and FA-TTEG. Body weight and food consumption values were unaffected at all the tested dose levels. Under the conditions of this study, MTD of FA-TTEG-MMF and FA-TTEG could not be achieved in this study due to limitations in solubility of test item and expected to be more than 60 mg/kg.

In Phase II (DRF) repeated intravenous administration of FA-TTEG-MMF and FA-TTEG at the dose levels of 3, 15, and 60 mg/kg did not result in any mortalities, clinical signs, body weight changes, food consumption, clinical pathology or organ weights. No injection site reactions were observed after the 7-day treatment period for either compound.

Grossly observed red discoloration of thymus in few males and/or females treated with both test items (FA-TTEG-MMF and FA-TTEG) at all the dose levels. Microscopically, minimal to mild severity of congestion / hemorrhages were noted in ≥ 15 mg/kg/day in males and at ≥ 3 mg/kg/day in females

treated with FA-TTEG-MMF and at ≥ 3 mg/kg/day in females treated with test item- FA-TTEG. This finding is of no toxicological significance in the absence of any changes in the circulating cell counts.

This study also evaluated TKs.

Following FA-TTEG injection the time for peak blood concentration (t_{max}) of FA-TTEG was 0.25 h post dose in both genders, on Days 1 and 7. C_{max} values in males are 95.2, 855 and 6040 ng/mL and in females are 118, 833 and 7390 ng/mL at 3, 15 and 60 mg/kg/day dose levels, respectively.

On repeat administration, no tendency of accumulation was observed in both genders. Overall, as the dose of FA-TTEG increased, the change in both peak blood concentration (C_{max}) and blood exposure (AUC_{last}) of FA-TTEG were linear and more than dose proportional in both sexes at the tested dose levels.

Study AD-G0948 was aimed to evaluate the toxicological and toxicokinetic profile of FA-TTEG-MMF and FA-TTEG, when administered by intravenous route to Sprague-Dawley rats for a period of 28 days and to assess the potential reversibility of any findings.

No clinical signs or mortalities were observed in all groups and dose levels throughout the treatment and recovery periods. No ocular abnormalities were observed in all groups and dose levels. There were no relevant changes in the hematology parameters observed for FA-TTEG-MMF and FA-TTEG at all dose levels tested. The clinical chemistry parameters were not affected by FA-TTEG-MMF and FA-TTEG

No concerning findings were reported after 28-day intravenous administration of FA-TTEG-MMF and FA-TTEG.

The NOAEL of 60 mg/kg body weight/day for both FA-TTEG-MMF and FA-TTEG was established.

Studies with impurities

Specified shelf-life impurity limits for tegomil fumarate drug product have been defined for MMF (1.0%), MMF-TTEG (1.0%) FA-TTEG-MMF (1.0%) and DMF (0.5%).

The risk for genotoxicity of DMF and MMF can be excluded based on the existing safety and toxicity data generated for the reference drug Tecfidera®.

For FA-TTEG-MMF the risk for genotoxicity has been excluded in an ICH S2(R1) compliant set of *in vitro* an *in vivo* genotoxicity studies. In addition, the risk for systemic toxicity over 28-days repeated intravenous administration to rats has been evaluated. The study did not point to any toxicity over and above what has also been observed for tegomil fumarate. A NOAEL of 60 mg/kg has been defined for FA-TTEG-MMF when administered for 28 days intravenously to the rat. This dose provides a 1034-fold safety margin (based on mg/kg) to exposure of the impurity at maximum clinical dose levels (0.058 mg/kg for a 60 kg adult assuming a maximum clinical dose of 348 mg tegomil fumarate) of tegomil fumarate.

TTEG represents a major non-active metabolite of tegomil fumarate and therefore, the toxicity of TTEG was subjected to special consideration.

In the non-clinical overview, the applicant states that the systemic toxicity of TTEG has been evaluated as part of the comparative 90-day repeated dose toxicity study performed with tegomil fumarate and DMF. TTEG is a major, non-active metabolite of Tegomil fumarate. TK results for TTEG showed steady state exposure ($AUC_{0\text{-}last}$) of 88.2 and 71.4 µg.h/mL at the NOAEL of 290.2 mg/kg tegomil fumarate. Maximum blood concentrations (C_{max}) were 17.2 and 22.7 µg/mL for males and females, respectively, at Day 90.

With respect to genotoxicity and carcinogenicity, the applicant clarified that PEGs are not genotoxic; none of them caused gene mutations in bacterial or mammalian cells, either in the absence or

presence of S9 metabolic activation fraction. In particular, PEG 200 was not mutagenic *in vitro* (AMES test) and was negative (non-clastogenic) in the *in vivo* micronucleus test. No risk for carcinogenicity has been observed in a 2-year study in rats with TTEG administration via diet (up to 4%, equal to 2,000 mg/kg) [Fowles *et al*, 2017]

With respect to reproductive and developmental toxicity, although reproductive toxicity data are not available for TTEG, the lack of reproductive findings from the three lower oligomers (EG, DEG, and Triethylene Glycol) strongly supports the consideration of low potential for reproductive toxicity of TTEG. This aspect includes the proven safety of ethylene glycols in terms of fertility. There is no evidence of developmental toxicity with TTEG.

Upon request, the applicant provided data from the 90-Day oral toxicology study of tegomil fumarate in rats where kinetic profile of TTEG was evaluated following single administration and at steady state at Day 90. Based on that data indicating that the accumulation ratios (Day 90 vs. Day 1) derived from AUCT were 0.62, 0.44, and 0.43 for the three doses, indicating that there is about half the exposure to TTEG at steady state compared to the first administration of the tegomil fumarate it is agreed that a risk for accumulation of TTEG in rats can be considered very low.

2.3.5. Ecotoxicity/environmental risk assessment

The applicant submitted Environmental Risk Assessment (ERA).

According to the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1), the following formula was used to estimate the $PEC_{surfacewater}$:

$$\mathrm{PEC}surfacewater = \frac{\mathrm{DOSE}ai \times \mathrm{F}pen}{\mathrm{WASTEW}inhab \times \mathrm{DILUTION}}$$

where:

PEC*s*$_{surfacewater}$ – local surface water concentration [mg x L-1]
DOSE*ai* – maximum daily dose consumed per inhabitant [mg x inh-1 x d-1]
F*pen* - fraction of market penetration
WASTEW*inhab* – amount of wastewater per inhabitant per day [L x inh-1 x d-1]
DILUTION – dilution factor

DOSEai (maximum daily dose of Tegomil fumarate as a component of Tegomil fumarate 174 mg and 348 mg gastro-resistant capsules) DOSEai = 696 mg/inhabitant/day

WASTEW inhab (amount of wastewater/inhabitant/day) 200 l/inhabitant/day (default value, according to the guideline)

DILUTION (dilution factor): 10 (default value, according to the guideline)

Calculation of PECSURFACEWATER for Tegomil fumarate according to Equation 1 using default Fpen value

$$PEC_{SURFACEWATER} = \frac{696\,mg * 0.01}{200\,L * 10} = 0.00348\frac{mg}{L} = 3.48\,\mu g/L$$

Based on the available data the worst-case prevalence for MS has been found in Germany with 303 cases per 100,000 inhabitants of which 85 % account for RRMS, resulting in a prevalence of 258 cases per 100,000 inhabitants.

According to the equation, the following Fpen is obtained:

$$\text{Fpen} = \frac{0.00258}{365 \text{ days per year}} \times \frac{1 \text{ day} \times 365 \text{ days}}{} = 0.00258$$

Using a Fpen of 0.00258, the following PEC value is obtained:

$$PEC_{SURFACEWATER} = \frac{696\,mg * 0.00256}{200\,L * 10} = 0.000891 \frac{mg}{L} = 0.89\,\mu g/L$$

The $PEC_{surfacewater}$ value is not within the limit established in the guideline (0.01 µg/L) and phase II environmental effect analysis should be performed.

However, for tegomil fumarate neither parent drug nor the active metabolite MMF is excreted after intake in the environment. Tegomil fumarate and the already marketed compound DMF are essential similar prodrugs for MMF with respect to the PD and PK profile and mode of action via an active metabolite.

For DMF environmental relevant study results are reported in a public assessment report for Tefidera® [EMA 2013] with the final conclusion that DMF is not expected to pose a risk for the environment.

For both, tegomil fumarate and DMF, the active component represents MMF, for which the primary PD can be considered well-established.

Tegomil fumarate (MMF-TTEG-MMF) rapidly degraded in FaSSIF and FeSSIF by 4.7% and 6.9% remaining compound after 1 h (last time point with quantifiable concentration) with $t_{1/2}$ of 0.2 and 0.3 h, respectively.

Based on the essential similarity between tegomil fumarate and DMF the obtained environmental data for DMF are applicable and representative for tegomil fumarate as well.

Table 2: Summary of main study results for Dimethyl fumarate

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	0.77	Potential PBT No
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	0.77	not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater , default or refined (e.g. prevalence, literature)	Default 3.6	µg/L	> 0.01 threshold Yes
Other concerns (e.g. chemical class)			No
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OOOTS 835.1110	K_{oc} = not detactable	Substance not soluble in water
Ready Biodegradability Test	OECD 109MS301	Readily biodegradeble	

Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole system}$ = % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	Not valid	µg/L	Species: blue algae – test not valid
Daphnia sp. Reproduction Test	OECD 211	NOEC	55.9	µg/L	Daphnia magna
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	45.7	µg/L	Species: Pimephales promelas
Activated Sludge, Respiration Inhibition Test	OECD 209	EC 10	2000	µg/L	

The cleavage of the prodrug Tegomil fumarate results in two MMF moieties and the formation of TTEG which is pharmacologically inactive.

The applicant updated the ERA in line with the new Guideline recommendations and included data of TTEG.

2.3.6. Discussion on non-clinical aspects

The non-clinical PK and toxicity programme performed for tegomil fumarate aims to bridge the existing data from Tecfidera®, while providing detailed information on the metabolic breakdown. PD, PK and toxicological properties of MMF are well known. No primary and secondary PD and safety pharmacology studies have been conducted to support the marketing authorisation application. This is considered acceptable as MMF is the only active compound of tegomil fumarate.

In an *in vitro* experiment using Caco-2 cells, tegomil fumarate showed lower mean apparent permeability compared to DMF. Based on the results, DMF and tegomil fumarate can be categorized as moderate and low permeable drugs, respectively. Both DMF and tegomil fumarate have similar susceptibility to hydrolysis.

In a non-GLP PK study administration of tegomil fumarate at the dose of 65.3 mg/kg and DMF at the dose of 45.0 mg/kg comparable rate and extent of systemic exposure to MMF was shown. Compared to DMF, the relative bioavailability of MMF after administration of Tegomil fumarate was ~94% for C_{max}, and ~89% for $AUC_{0-\infty}$. For both substances, the t_{max} values are uniformly 0.25 hours.

In the completed *in vitro* dissolution and metabolism Studies Nos. 14-076-DMF-12 and 13-004-DMF-02 and Study Nos. 2020AET002 a fast and linear MMF-release was observed for DMF and after 90 min, a quantitative hydrolysis was observed.

Of note, the kinetics of MMF-release from Tegomil fumarate was very similar to that observed for DMF, but after release of approx. 50%, an intermittent decreased rate of hydrolysis was observed. The rate of hydrolysis of MMF-TTEG was substantially lower compared to Tegomil fumarate.

In the study aimed to evaluate the metabolic stability of tegomil fumarate and DMF (Study No. 2020AET002), tegomil fumarate rapidly degraded in FaSSIF and FeSSIF as indicated by 4.7% and 6.9% remaining compound after 1 h) with $t_{1/2}$ of 0.2 and 0.3 h, respectively. MMF, MMF-TTEG and TTEG were extensively released during incubation. In phosphate buffer at pH 6.8, no degradation was observed for the test item within 4 hours; only low formation rates in the low nM-range of MMF, MMF-TTEG and TTEG occurred. In FaSSIF and FeSSIF, DMF was degraded displaying $t_{1/2}$ of 1.3 h and 0.5 h. Extensive formation of MMF occurred in both matrices. In phosphate buffer at pH 6.8, DMF was stable

over the tested incubation period. In Study 2021AET001 for tegomil fumarate the main metabolites were MMF and TTEG, and to a lesser extent the intermediate MMF-TTEG and MMF- TTEG-FA.

In a conducted 90-day comparative repeat-dose toxicity study with a 4-week recovery period in SD rats, the NOAEL has been determined to be the highest dose evaluated (290.2 mg/kg/day for the Tegomil fumarate and 200 mg/kg/day for the DMF, respectively). No clinical signs, mortality, changes in body weights, body weight gains and food consumption, clinical pathology parameters (hematology, coagulation, clinical chemistry and urinalysis) and terminal fasting body weights were reported. The microscopic changes in stomach, kidneys and pancreas were observed in both test and reference items. However, the changes observed in kidneys were similar in both test and reference items. Of note, all the tegomil fumarate and DMF related findings were reversible at the end of 28 days recovery period except for the minimal severity acinar cell apoptosis in pancreas of females.

Two human metabolites have been identified during clinical development, FA-TTEG-MMF and FA-TTEG. However, they were not observed or analyzed as part of the 90-day rat toxicity study FA-TTEG-MMF.

No genotoxicity and carcinogenicity studies have been conducted with tegomil fumarate and its metabolites. This is considered acceptable. The only major difference between tegomil fumarate and DMF breakdown is TTEG which is formed instead of methanol. Thus, the information available for the reference medicinal product provides reassurance on MMF and FA. As per TTEG, the applicant's claim that no genotoxicity and carcinogenicity toxicity is expected to TTEG based on available results from the literature can be accepted.

Similarly, no reproductive- and developmental toxicity studies have been performed with tegomil fumarate and its metabolites. This is considered acceptable. The information available for the reference medicinal product provides reassurance on MMF and FA. The applicant acknowledged that reproductive toxicity data are not available for TTEG but claimed that the lack of reproductive findings from the three lower oligomers (EG, DEG, and Triethylene Glycol) strongly supports the consideration of low potential for reproductive toxicity of TTEG. The applicant's justification can be followed.

Further, since in a 90-Day toxicology study in rats animals 6 – 7 weeks old were included, which is equivalent to an adolescent child of 12 years (ICH S11, 2020), it is agreed that this study data can be considered sufficient to support safety of tegomil fumarate, as well as its main metabolites TTEG and MMF in subjects from 12-year of age. No new relevant safety issues were observed in this study.

ERA is considered acceptable.

2.3.7. Conclusion on the non-clinical aspects

Riulvy is considered approvable from a non-clinical perspective. The applicant presented results from own non-clinical studies and a summary of the literature to justify that tegomil fumarate does not differ significantly in properties with regards to safety and efficacy from the active substance of the reference medicinal product (dimethyl fumarate). This was accepted by the CHMP. This is in accordance with the relevant guideline and additional non-clinical studies were not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for Riulvy containing [tegomil fumarate]. To support the marketing authorisation

application the applicant conducted 3 pivotal bioequivalence studies under fasting and fed conditions.

CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

Relevant for the assessment are the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev.1) Guideline on the pharmacokinetic and clinical evaluation of modified-release dosage forms (EMA/CHMP/EWP/280/96 Rev.1).

GCP aspect

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

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

Exemption

The gastro-resistant, multiparticulate formulation tegomil fumarate is developed in the strengths 174 mg, containing 174.2 mg tegomil fumarate (equimolar to 120 mg DMF in terms of MMF release) and 348 mg, containing 348.4 mg Tegomil fumarate (equimolar to 240 mg DMF in terms of MMF release).

The bioequivalence studies (Study No. MMF-BESD-05-TFB/22 MMF-BEFI-05-TFB/22, MMF-BEFI-07-TFB/24) to establish bioequivalence of MMF following administration of tegomil fumarate and DMF under (low-) fed and fasting conditions were performed with the highest strength as the most sensitive strength in accordance with the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/ EWP/280/96 Rev1).

The qualitative composition of tegomil fumarate gastro-resistant hard capsules is shown in Table 3.

Table 3: Qualitative and Composition of the Test Product

Name of Ingredients	**Function**	**Reference to Standard**
Active substance		
Tegomil fumarate	Active Substance	In-house
Excipients		
Silica, colloidal anhydrous	Glidant	Ph. Eur.
Cellulose, microcrystalline	Diluent	Ph. Eur.
Croscarmellose sodium	Disintegrant	Ph. Eur.
Talc	Glidant	Ph. Eur.
Magnesium stearate	Lubricant	Ph. Eur.
Barrier coating		
Barrier coating mixture *Consisting of:* *Hypromellose, 2910* *Hydroxypropylcellulose* *Titanium dioxide* Water, purified	Coating agent *Film former* *Film former* *Opacifier* Solvent	In-house Ph. Eur.
Enteric coating		
Methacrylic acid – Ethyl acrylate copolymer (1:1)	Gastro-resistant / delayed release polymer	Ph. Eur.
Triethyl citrate	Plasticizer	Ph. Eur.
Talc	Anti-tacking agent	Ph. Eur.

Name of Ingredients	Function	Reference to Standard
Water, purified	Solvent	Ph. Eur.
Top coating		
Top coating mixture	Coating agent	In-house
Consisting of:		
Poly(vinyl alcohol)	*Film former*	
Titanium dioxide (E 171)	*Opacifier*	
Macrogol	*Plasticizer*	
Talc	*Anti-tacking agent*	
Iron oxide yellow (E 172)	*Colorant*	
Water, purified	Solvent	Ph. Eur.
Capsule shells including white printing ink		In-house
White opaque capsule cap		
Titanium dioxide (E171)	Opacifier	
Gelatin	Structure	
Water, purified	Solvent	
Light blue capsule cap and/or body		
Titanium dioxide (E171)	Opacifier	
Gelatin	Structure	
FD & C Blue 1 (E133)	Colorant	
Water, purified	Solvent	

Comparative dissolution of the different strengths

Since the subject product is gastro-resistant dosage form, it does not show drug release at acidic conditions viz., pH 1.2 and pH 4.5. Therefore, comparative dissolution data of the biostrength 348 mg versus the additional dosage strength 174 mg was performed in the following media:

A. pH 1.2 for 2 hours, followed by pH 6.8 for 60 minutes

B. pH 4.5 for 2 hours, followed by pH 6.8 for 60 minutes

The dissolution profiles of all batches are generated on 12 units.

A. Dissolution in 0.1 N HCl followed by Tribasic sodium phosphate buffer pH 6.8

Comparison: EK148 (348 mg) Vs EK135, EK145 & EK146 (174 mg)

Table 4: Similarity factor (f2-value) between biobatch 348 mg Vs test batches 174 mg Multimedia (50 rpm)

Batch No.	Strength: 174 mg		
	EK135	EK145	EK146
Tegomil fumarate 348 mg capsules (B. No. EK148) Versus	68	85	61

Time points considered for f2 calculation are 10, 15, 20, 30, 45 and 60 minutes. Since f2-value of all test batches of 174 mg is more than 50, test batches of 174 mg batches are considered similar to Biobatch (EK148, 348 mg).

As per Guideline on investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1), the criteria to calculate similarity factor was not met for all batches due to high percentage RSD. Therefore, similarity was also evaluated using bootstrap statistical method. The results are presented in Table 5.

Table 5: Comparison of dissolution profiles using bootstrap statistical analysis (Comparison: EK148 Vs EK135, EK145, EK146)

Statistics	Bootstrap statistics		
	EK148 Vs EK135	EK148 Vs EK145	EK148 Vs EK146
5% percentile	56.722	65.786	51.071

Time points considered for bootstrap analysis were 10, 15, 20, 30, 45 and 60 minutes.
The dissolution profiles of the biobatch tegomil fumarate capsules 348 mg is similar to other dosage strength 174 mg in 0.1N HCl followed by phosphate buffer solution pH 6.8 at 50 rpm.

B. Dissolution in Acetate buffer pH 4.5 followed by Phosphate buffer pH 6.8, 50rpm

Table 6: Similarity factor (f2-value) between biobatch 348 mg Vs test batches 174 mg Multimedia (50 rpm).

Batch No.	Strength: 174 mg		
	EK135	EK145	EK146
Tegomil fumarate 348 mg capsules (B. No. EK148) Versus	62	50	73

Time points considered for f2 calculation are 10, 15, 20, 30, 45 and 60 minutes

The dissolution profiles of the biobatch Tegomil fumarate capsules 348 mg is similar to other dosage strength 174 mg in acetate buffer solution pH 4.5 followed by phosphate buffer solution pH 6.8 at 50 rpm.

In the comparative dissolution tests of the different strengths for the purpose of the biowaiver, one borderline value of 50 for the f_2 similarity factor has been reported (media pH 4.5 to pH 6.8, batch EK148 vs EK145).

The applicant provided comparison of dissolution data in media pH 4.5 to pH 6.8, of EK147 batch (348 mg) with the bio batch (EK148). Similarity between the batches is demonstrated by a similarity factor f2=54.

Moreover, in pH 1.2 followed by pH 6.8 the batch EK145 showed similarity with the biobatch EK148 (f2=84, bootstrap 5% percentile=65.8).

2.4.2. Clinical pharmacology

Tabular overview of clinical studies

To support the application, the applicant has submitted 3 pivotal bioequivalence studies (under fed and fasted conditions and under low-fat, low-calories fed conditions defined as light meal), and one pilot PK/safety study.

Moreover, one Phase 1 GI tolerability study in HV is ongoing.

Type of Study	Study Identifier	Location of Study Report	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
Phase 1, Pilot	MMF-SAD-BA-04-TFB/21	Module 5, Section 5.3.1.1	**Part 1:** To investigate the safety, tolerability, and pharmacokinetics of single ascending doses of MMF-TTEG-MMF (4 Cohorts) and also, in order to compare the systemic safety, tolerability and bioavailability of MMF-TTEG-MMF (Dimethylfumarate tetraethylene glycolate gastro resistant capsules) versus Tecfidera® 120 mg (REFERENCE 1) in a parallel group setting in Cohort 5. **Part 2:** To compare the MMF bioavailability of DMF (Tecfidera® 240 mg REFERENCE 2) vs. three different 261.3 mg MMF-TTEG-MMF formulations after single dose administration in healthy subjects.	Single center, open label study in healthy volunteers conducted in two parts, one single ascending dose part (Part 1) and one bioavailability part (Part 2).	Single dose, Oral administration Dimethylfumarate tetraethylene glycolate 174 mg gastro resistant capsules, Dimethylfumarate tetraethylene glycolate 218 mg gastro resistant capsules, Dimethylfumarate tetraethylene glycolate 261 mg gastro resistant capsules, Dimethylfumarate tetraethylene glycolate 348 mg gastro resistant capsules Tecfidera® 120 mg Tecfidera® 240 mg	56 subjects Part 1: 8 subjects in Cohort 1 to 5, Part 2: 16 Subjects	Healthy volunteers	Single dose	Complete; Full
Phase 1, Pivotal	MMF-BESD-05-TFB/22	Module 5, Section 5.3.1.2	To evaluate the bioequivalence of the TEST formulation relative to an equimolar dose (based on MMF release) of REFERENCE product, after single oral administration under fasting conditions, and to compare the safety/tolerability profiles of the two formulations	Single center, open label, four-period, two-sequence, fully replicated, randomized, controlled, single dose bioequivalence study in healthy volunteers under fasting conditions	Single dose, Oral administration Tegomil fumarate 348 mg gastro-resistant capsules Tecfidera® 240 mg	30 subjects	Healthy volunteers	Single dose	Complete; Full
Phase 1, Pivotal	MMF-BEFI-06-TFB/22	Module 5, Section 5.3.1.2	To evaluate the bioequivalence of the TEST formulation relative to an equimolar dose (based on MMF release) of REFERENCE product, after single oral administration under fed conditions, and to compare the safety/tolerability profiles of the two formulations	Single center, open label, four-period, two-sequence, fully replicated, randomized, controlled, single dose bioequivalence study in healthy volunteers under fed conditions	Single dose, Oral administration Tegomil fumarate 348 mg gastro-resistant capsules Tecfidera® 240 mg	30 subjects	Healthy volunteers	Single dose	Complete; Full
Phase 1	NXPTEGO/23/P1-4	-	To compare the GI tolerability of Tegomil fumarate and DMF in healthy volunteers when administered orally in equimolar dose regimens.	randomized, double-blind study designed to evaluate the gastrointestinal (GI) tolerability of tegomil fumarate 348 mg vs dimethyl fumarate 240 mg administered orally twice daily	Tegomil fumarate 348 mg gastro-resistant capsules Tecfidera® 240 mg	210 subjects	Healthy subjects	Multiple dose	ongoing
Pivotal	MMF-BEFI-07-TFB/24	Module 5, Section 5.3.1.2	To evaluate the bioequivalence of the TEST formulation relative to an	two-sequence, fully replicat-	Tegomil fumarate 348 mg gastro-resistant capsules	40 subjects	Healthy volunteers	Single dose	Complete; Full

Type of Study	Study Identifier	Location of Study Report	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
			equimolar dose (based on MMF release) of REFERENCE product, after single oral administration under low-fat, low-calories fed conditions, and to compare the safety/tolerability profiles of the two formulations	ed, randomized, controlled, single dose bioequivalence study of Tegomil fumarate 348 mg gastro-resistant capsules versus Tecfidera® 240 mg gastro-resistant hard capsules in healthy volunteers under low-fat, low-calories fed conditions					

2.4.2.1. Pharmacokinetics

Study MMF-SAD-BA-04-TFB/21: A single center, open label study in healthy volunteers, conducted in order to investigate the safety, tolerability, and pharmacokinetics of single ascending doses of 174 mg, 218 mg, 261 mg and 348 mg Dimethylfumarate tetraethylene glycolate gastro resistant capsules (TEST) and to compare the systemic safety, tolerability and bioavailability of MMFTTEG- MMF gastro resistant capsules versus Tecfidera® 120 mg gastro-resistant hard capsules (REFERENCE 1) in a parallel group setting, under fasting conditions.

Methods

- **Study design**

Study Center: Institutia Medico-Sanitara Publica, "*Clinical Hospital of the Ministry of Health, Labour and Social Protection*", Chisinau / The Republic of Moldavia.

A single center, open label study in healthy volunteers conducted in two parts, one single ascending dose part and one bioavailability part, as follows:

- Part 1: The first part of the study was conducted to investigate the safety, tolerability, and PK of single ascending doses of MMF-TTEG-MMF (4 Cohorts) and also, in order to compare the systemic safety, tolerability and bioavailability of MMF-TTEG-MMF versus Tecfidera® 120 mg (REFERENCE 1) in a parallel group setting in Cohort 5. The first four cohorts were treated sequentially and in ascending order of dose strength.
- Part 2: The second part of this study was conducted to compare the MMF bioavailability of DMF (Tecfidera® 240 mg – REFERENCE 2) vs. three different 261.3 mg MMF-TTEG-MMF formulations (TEST 1, TEST 2 and TEST 3 formulations) after single dose administration in healthy subjects in a randomized, cross-over setting, in four periods separated by a wash-out of 7 days between one treatment and the next one (cohort 6).

Hospitalization of subjects until 24 hours post dose.

Study medication administration in Part 1: one Dimethylfumarate tetraethylene glycolate 174 mg gastro resistant capsule in Cohort 1; one Dimethylfumarate tetraethylene glycolate 218 mg gastro resistant capsules in Cohort 2; one Dimethylfumarate tetraethylene glycolate 261 mg gastro resistant

capsules in Cohort 3; one Dimethylfumarate tetraethylene glycolate 348 mg gastro resistant capsules in Cohort 4, Test 1 formulations, and one Tecfidera® 120 mg gastro resistant hard capsules, REFERENCE 1, in Cohort 5 under fasting conditions.

Study medication administration in Part 2: one gastro resistant capsule of TEST 1 formulation (Dimethylfumarate tetraethylene glycolate 261 mg gastro resistant capsules) or TEST 2 formulation (Dimethylfumarate tetraethylene glycolate 261 mg gastro resistant capsules) or TEST 3 formulation (Dimethylfumarate tetraethylene glycolate 261 mg gastro resistant tablets) or one gastro resistant capsule of REFERENCE product (Tecfidera® 240 mg gastro resistant hard capsules), as per the randomization table, were administered.

Within each cohort (Cohort 1 to Cohort 6) and treatment period (as Cohort 6 had four treatment periods) blood samplings were collected: pre-dose and at 0.50 (30 min), 1.0, 1.5 (1 h 30 min), 2.0, 2.5 (2 h 30 min), 3.0, 3.5 (3 h 30 min), 4.0, 4.5 (4 h 30 min), 5.0, 5.5 (5 h 30 min), 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 14.0 and 16.0 hours after each administration (5 ml for each sample) for the quantification of MMF concentration in the plasma.

Within Cohort 4, another 5.0 mL blood samples were collected for the quantification of dimethyl fumarate tetraethylene glycolate (MMF-TTEG-MMF), monomethyl fumarate tetraethylene glycolate (MMF-TTEG) and tetraethylene glycolate (TTEG). Demethylated metabolite (FA-TTEG-MMF), double demethylated metabolite (FATTEG-FA) and FA-TTEG were also quantified in the plasma of Cohort 4.

Within Cohort 6, the quantification of MMF-TTEG-MMF, MMF-TTEG and TTEG was also determined in the plasma samples prior and after TEST 3 formulation administration (dimethylfumarate tetraethylene glycolate 261 mg gastro resistant tablets).

An additional reserve blank sample of 20 mL was drawn before first dosing in each Cohort (thus, only in Period I for Cohort 6).

Washout period: 7 days between periods for Cohort 6.

- **Test and reference products**

Test1 formulation, dose and mode of administration, batch number:

- Dimethylfumarate tetraethylene glycolate 174 mg gastro resistant capsules –strength 1Retest date: 12/2021. Administered orally, 1 tablet with 200 ml of room temperature water, under fasting conditions for subjects of Cohort 1
- Dimethylfumarate tetraethylene glycolate 218 mg gastro resistant capsules –strength 2 Retest date: 12/2021. Administered orally, 1 tablet with 200 ml of room temperature water, under fasting conditions for subjects of Cohort 2
- Dimethylfumarate tetraethylene glycolate 261 mg gastro resistant capsules – strength 3 Retest date: 12/2021. Administered orally, 1 tablet with 200 ml of room temperature water, under fasting conditions for subjects of Cohort 3 and Cohort 6
- Dimethylfumarate tetraethylene glycolate 348 mg gastro resistant capsules –strength 4Retest date: 12/2021. Administered orally, 1 tablet with 200 ml of room temperature water, under fasting conditions for subjects of Cohort 4.

Test2 formulation, dose and mode of administration, batch number: Dimethylfumarate tetraethylene glycolate 261 mg gastro resistant capsules. Administered orally, 1 tablet with 200 ml of room temperature water, under fasting conditions for subjects of Cohort 6.

Test3 formulation, dose and mode of administration, batch number: Dimethylfumarate tetraethylene glycolate 261 mg gastro resistant tablets. Administered orally, 1 tablet with 200 ml of room temperature water, under fasting conditions for subjects of Cohort 6.

Reference1 product, dose and mode of administration, batch number: Tecfidera® 120 mg gastro-resistant hard capsules, MAH: Biogen Netherlands B.V., The Netherlands., Expiry date: 01/2024. Country of origin: Germany. Administered orally, 1 capsule with 200 ml of room temperature water, under fasting conditions, for subjects of Cohort 5.

Reference2 product, dose and mode of administration, batch number: Tecfidera® 240 mg gastro-resistant hard capsules, MAH: Biogen Netherlands B.V., The Netherlands. Expiry date: 12.2023. Country of origin: Austria. Administered orally, 1 capsule with 200 ml of room temperature water, under fasting conditions, for subjects of Cohort 6.

- **Population(s) studied**

Diagnosis and main selection criteria: Healthy male and non-pregnant female volunteers, age between ≥18 years and ≤55 years, body mass index (BMI) ≥20 and ≤ 29 kg/m2.

Number of subjects planned to be enrolled: 56 subjects. Part 1: 8 subjects in Cohort 1, 8 subjects in Cohort 2, 8 subjects in Cohort 3, 8 subjects in Cohort 4, and 8 subjects in Cohort 5; Part 2: 16 Subjects in Cohort 6; completed: 56; analyzed: 56.

- **Analytical methods**

Bioanalysis of obtained samples in the study was performed according to validation method described in protocol FMD-BE-LCMSMS-01/16. For details of validation method please see description of the study MMF-BESD-05-TFB/22.

In bioanalytical part, a total of 2080 human plasma samples were analyzed for MMF. The coefficient of variation (%CV) for calibration standards and quality control samples was were acceptable. The lower limit of quantification (LLOQ) was well established, with values not exceeding 5% of C_{max} for all patients.

The applicant has provided long-term stability results that cover the storage conditions for samples collected during the clinical study MMF-SAD-BA-04-TFB/21. A justification for not performing the incurred sample reproducibility (ISR) test on samples collected during the clinical study MMF-SAD- BA-04-TFB/21 was provided, based on the consideration of MMF-SAD-BA-04-TFB/21 as a pilot study.

- **Pharmacokinetic variables**

PK of MMF: C_{max}, AUC_{0-t} and AUC_{0-inf} (as primary); t_{max} (as secondary); $AUC_{\%extra}$ (extrapolated area (AUC_{0-inf} - AUC_{0-t})/AUC_{0-inf} *100), $t_{1/2}$ (plasma half-life, calculated as 0.693/Kel), Kel (elimination rate constant), MRT (mean residence time) (as additional).

- **Statistical methods**

The following procedures were used:

PK data from Cohorts 1 to 5

MMF: for the primary PK parameters (C_{max}, AUC_{0-t} and AUC_{0-inf}): bioequivalence was assessed by means of an analysis of variance (ANOVA) (model: treatments, sequences, subject-within-sequence and periods of administration) and calculating the 90% confidence intervals (CIs) of the geometric mean ratio T1 (strength 174.2 mg)/R1, T1 (strength 217.7 mg)/R1, T1 (strength 261.3 mg)/R1 and T1 (strength 348.4 mg)/R1 (equivalent to two one-sided t-test procedure).

The doses linearity/proportionality between the different strengths was also be investigated. The PK parameters of the different strengths of T1 were compared: T1 (strength 174.2 mg)/ T1 (strength 217.7 mg), T1 (strength 217.7 mg)/ T1 (strength 261.3 mg) and T1 (strength 174.2 mg)/ T1 (strength 348.4 mg).

For t_{max}: Wilcoxon Signed-Rank Test.

For $AUC_{\% extra}$, $t_{1/2}$, Kel, MRT: standard descriptive statistics only.

MMF-TTEG-MMF, MMF-TTEG, TTEG, FA-TTEG-MMF, FA-TTEG-FA, FA-TTEG (Cohort 4): descriptive statistics was done as far as data are available: arithmetic mean, harmonic mean, geometric mean, standard error of the man (SEM), standard deviation (SD), median, range.

PK data from Cohort 6

For C_{max}, AUC_{0-t} and AUC_{0-inf}: ANOVA after logarithmic transformation (model: treatments, sequences, subject within sequence, periods of administration), classic (shortest) 90% CIs for the intra-individual ratios T1/R2, T2/R2 and T3/R2.

For t_{max}: Wilcoxon Signed-Rank Test.

For $AUC_{\% extra}$, $t_{1/2}$, Kel, MRT: standard descriptive statistics only.

MMF-TTEG-MMF, MMF-TTEG, TTEG (determined in plasma samples prior and after Test 3 formulation administration): descriptive statistics was done as far as data are available: arithmetic mean, harmonic mean, geometric mean, SEM, standard deviation, median, range.

Determination of Sample Size

A number of 56 subjects was enrolled in the study (8 subjects in each of Cohort 1 to Cohort 5, and 16 subjects in Cohort 6, as follows: Cohort 1 – subjects from 1 to 8, Cohort 2 – Subjects from 9 to 16, Cohort 3 – subjects from 17 to 24, Cohort 4 – subjects from 25 to 32, Cohort 5 – subjects from 33 to 40 and Cohort 6 – subjects from 41 to 56). This number of subjects was considered sufficient for a preliminary evaluation of safety, tolerability and bioavailability of the studied products, while still limiting the exposure of healthy volunteers to unneeded medication.

Results

- **Disposition of subjects**

In the present study, 93 adult male and female healthy volunteers were screened. The screening results for the enrolled volunteers (medical history, physical examination, vital signs, ECG, COVID-19, hepatitis B, hepatitis C, HIV and pregnancy test). Out of all screened volunteers, 56 healthy male and female volunteers were enrolled. All 56 enrolled volunteers completed the study and underwent the follow-up examination.

- **Protocol deviations**

Some protocol deviations occurred in the present study regarding the evaluation of the MMF (bioavailability for the adjusted of the detected concentrations as following:

Deviations regarding dose-adjustment:

For the Cohorts 2-4 where Test formulation 1 strengths T2-T4 were administered, all concentrations were adjusted to the 174.2 mg strength of T1 representing the equimolar equivalent to the 120 mg Reference 1, therefore by dividing the concentrations with: for Cohort 2: 217.7/174.2, for Cohort 3: 261.3/174.2 and for Cohort 4: 348.4/174.2. There was no dose adjustment for strength T1 as this was equimolar to 120 mg Reference 1, therefore no dose adjustment for Cohort 1 (T1) and Cohort 5 (R1).

Test formulation 1 strength T1-T4 from Cohorts 1-4 present Test formulation 1 Dimethylfumarate tetraethylene glycolate gastroresistant capsules in strengths 174.2, 217.7, 261.3 and 384.4 mg.

For Cohort 6, the 348.4 MMF-TTEG-MMF strength is equimolar to the 240 mg Reference 2, therefore, tables/assessment were modified by dividing all T1-T2-T3 concentrations with 261.3/348.4 to get the equivalent of 240 mg Reference 2. Test formulations coded as T1, T2, T3 in Cohort 6 represent different Dimethylfumarate 261 mg, gastroresistant formulations as denoted with T1 in the study protocol.

- **Pharmacokinetic parameters**

The PK key results of the different TEST1 dose strengths and REFERENCE1 formulations are presented in the below tables.

Part 1

Table 7: PK results - MMF – Test 1 formulation, strength 1, 174.2 mg MMF-TTEG-MMF (Cohort 1)

N = 8	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)	AUC_{0-inf} (ng/ml*h)	AUC%extra (%)	T_{half} (hours)	K_{el} (1/Hours)	MRT (hours)
Mean	1030.195	1519.460	1527.472	0.522	0.670	1.096	2.492
GeoMean	986.088	1490.319	1498.143	0.498	0.651	1.065	2.079
SD	323.823	331.318	333.245	0.174	0.178	0.273	1.799
CV	31.433	21.805	21.817	33.408	26.514	24.897	72.201

N = 8	T_{max} (hours)
Median	1.000
Min	1.000
Max	4.000

Table 8: PK results - MMF – Test 1 formulation, strength 2, 217.7 mg MMF-TTEG-MMF (Cohort 2)

N = 8	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)	AUC_{0-inf} (ng/ml*h)	AUC%extra (%)	T_{half} (hours)	K_{el} (1/Hours)	MRT (hours)
Mean	1210.554	2055.584	2071.026	0.739	1.063	0.940	3.090
GeoMean	1149.518	1981.160	1995.966	0.503	0.841	0.824	2.707
SD	369.736	600.546	604.858	0.831	1.010	0.393	1.771
CV	30.543	29.215	29.206	112.552	94.997	41.810	57.319

N = 8	T_{max} (hours)
Median	1.750
Min	1.000
Max	4.500

Table 9: PK results - MMF – Test 1 formulation, strength 3, 261.3 mg MMF-TTEG-MMF (cohort 3)

N = 8	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)	AUC_{0-inf} (ng/ml*h)	AUC%extra (%)	T_{half} (hours)	K_{el} (1/Hours)	MRT (hours)
Mean	1915.272	2767.706	2778.759	0.412	0.834	1.112	2.325
GeoMean	1697.808	2674.640	2685.710	0.371	0.709	0.978	2.195
SD	1166.796	820.529	821.568	0.199	0.593	0.564	0.788
CV	60.921	29.647	29.566	48.209	71.053	50.706	33.884

N = 8	T_{max} (hours)
Median	1.500
Min	0.500
Max	4.500

Table 10: PK results - MMF – Test 1 formulation, strength 4, 384.4 mg MMF-TTEG-MMF (cohort 4)

N = 8	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)	AUC_{0-inf} (ng/ml*h)	AUC%extra (%)	T_{half} (hours)	K_{el} (1/Hours)	MRT (hours)
Mean	2690.731	3433.545	3449.197	0.543	0.740	1.100	2.542
GeoMean	2420.509	3334.383	3352.726	0.267	0.680	1.019	2.266
SD	1500.188	937.791	928.693	0.977	0.337	0.436	1.337
CV	55.754	27.313	26.925	179.896	45.550	39.624	52.609

N = 8	T_{max} (hours)
Median	1.250
Min	1.000
Max	5.000

Table 11: PK results - TTEG – Test 1 formulation, strength 4, 384.4 mg MMF-TTEG-MMF (cohort 4)

N = 8	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)	AUC_{0-inf} (ng/ml*h)
Mean	1673.078	4208.218	4344.343
GeoMean	1604.009	4119.899	4261.518
SD	492.190	906.633	894.561
CV	29.418	21.544	20.591

Table 12: PK results - FA-TTEG – Test 1 formulation, strength 4, 384.4 mg MMF-TTEG-MMF (cohort 4)

N = 8	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)	AUC_{0-inf} (ng/ml*h)
Mean	4.471	4.891	5.690
GeoMean	3.358	4.204	4.969
SD	2.894	2.748	3.032
CV	64.734	56.177	53.281

Table 13: PK results - FA-TTEG-MMF – Test 1 formulation, strength 4, 384.4 mg MMF-TTEG-MMF (cohort 4)

N = 3	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)
Mean	0.256	0.064
GeoMean	0.255	0.064
SD	0.018	0.004
CV	6.912	6.912

Note: For Cohort 4 MMF-TTEG-MMF and MMF-TTEG couldn't be determined due an almost complete pre-systemic conversion of MMF-TTEG-MMF and MMF-TTEG to respective metabolites. In their response to a question during the procedure, the applicant has clarified that the demethylated metabolite FA-TTEG-FA has not been observed in plasma samples above the LLOQ of 0.2 ng/mL.

Table 14: PK results - MMF – Reference 1, 120 mg DMF (cohort 5)

N = 8	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)	AUC_{0-inf} (ng/ml*h)	AUC%extra (%)	T_{half} (hours)	K_{el} (1/Hours)	MRT (hours)
Mean	1257.469	1692.812	1702.386	0.572	0.592	1.188	2.305
GeoMean	1174.714	1640.221	1649.671	0.502	0.588	1.179	2.136
SD	473.217	424.596	425.678	0.363	0.077	0.162	1.043
CV	37.633	25.082	25.005	63.437	13.059	13.618	45.246

N = 8	T_{max} (hours)
Median	1.500
Min	1.000
Max	4.000

174.2 mg MMF-TTEG-MMF is equimolar to 120 mg DMF, based on MMF release. Dose adjustment is necessary to assess for bioequivalence and linearity/ proportionality.

- **Bioequivalence comparison, Primary parameters**

Unadjusted results

Table 15: The 90% CIs MMF mean treatment T1 formulation, strength1, 174.2 mg/Reference 1 ratios.

Test name	Parameter	Test value (T1 strength1 /R1)	Lower 90% CL	Upper 90% CL
90% CI	C_{max}	83.94	60.79	115.91
90% CI	AUC_{0-t}	90.86	73.06	113.00
90% CI	AUC_{0-inf}	90.81	73.03	112.93

The 90% CIs of C_{max}, AUC_{0-t} and AUC_{0-inf} ratio were not inside the accepted bioequivalence range, 80.00 – 125.00%, thus not permitting to conclude for bioequivalence for T formulation 1 strength 174.2 mg vs R1.

Table 16: The 90% CIs MMF mean treatment T1 formulation, strength2, 217.7 mg /Reference 1 ratios.

Test name	Parameter	Test value (T1 strength2 /R1)	Lower 90% CL	Upper 90% CL
90% CI	C_{max}	97.86	69.65	137.47
90% CI	AUC_{0-t}	120.79	93.98	155.23
90% CI	AUC_{0-inf}	120.99	94.14	155.50

The 90% CIs of C_{max}, AUC_{0-t} and AUC_{0-inf} ratio were not inside the accepted bioequivalence range, 80.00 – 125.00%, thus not permitting to conclude for bioequivalence for T formulation 1 strength 217.7 mg vs R1.

Table 17: The 90% CIs MMF mean treatment T1 formulation, strength 3, 261.3 mg /Reference1 ratios.

Test name	Parameter	Test value (T1 strength3 /R1)	Lower 90% CL	Upper 90% CL
90% CI	C_{max}	144.53	97.06	215.22
90% CI	AUC_{0-t}	163.07	127.78	208.09
90% CI	AUC_{0-inf}	162.80	127.62	207.68

The 90% CIs of C_{max}, AUC_{0-t} and AUC_{0-inf} ratio were not inside the accepted bioequivalence range, 80.00 – 125.00%, thus not permitting to conclude for bioequivalence for T formulation 1 strength 261.3 mg vs R1.

Table 18: The 90% CIs MMF mean treatment T1 formulation, strength 4, 348.4 mg /Reference1 ratios.

Test name	Parameter	Test value (T1 strength4 /R1)	Lower 90% CL	Upper 90% CL
90% CI	C_{max}	206.05	140.07	303.11
90% CI	AUC_{0-t}	203.29	160.75	257.09
90% CI	AUC_{0-inf}	203.24	161.01	256.54

The 90% CIs of C_{max}, AUC_{0-t} and AUC_{0-inf} ratio were not inside the accepted bioequivalence range, 80.00 – 125.00%, thus not permitting to conclude for bioequivalence for T formulation 1 strength 348.4 mg vs R1.

Dose-adjusted results

Table 19: The 90% CIs MMF mean treatment T1 formulation, strength2, 217.7 mg after dose-adjustment treatment/Reference1 ratios.

Test name	Parameter	Test value (T1 strength2 /R1)	Lower 90% CL	Upper 90% CL
90% CI	C_{max}	78.30	55.74	110.00
90% CI	AUC_{0-t}	96.65	75.20	124.22
90% CI	AUC_{0-inf}	96.82	75.33	124.43

The 90% CIs of C_{max}, AUC_{0-t} and AUC_{0-inf} ratio were not inside the accepted bioequivalence range, 80.00 – 125.00%, thus not permitting to conclude for bioequivalence for T formulation 1 strength 217.7 mg vs R1.

Table 20: The 90% CIs MMF mean treatment T1 formulation, strength 3, 261.3 mg after dose adjustment/ Reference1 ratios

Test name	Parameter	Test value (T1 strength3 /R1)	Lower 90% CL	Upper 90% CL
90% CI	C_{max}	96.35	64.71	143.48
90% CI	AUC_{0-t}	108.71	85.19	138.73
90% CI	AUC_{0-inf}	108.54	85.08	138.46

The 90% CIs of C_{max}, AUC_{0-t} and AUC_{0-inf} ratio were not inside the accepted bioequivalence range, 80.00 – 125.00%, thus not permitting to conclude for bioequivalence for T formulation 1 strength 261.3 mg vs R1.

Table 21: The 90% CIs MMF mean treatment T1 formulation, strength 4, 348.4 mg after dose adjustment/ Reference1 ratios

Test name	Parameter	Test value (T1 strength4 /R1)	Lower 90% CL	Upper 90% CL
90% CI	C_{max}	103.03	70.03	151.56
90% CI	AUC_{0-t}	101.64	80.37	128.54
90% CI	AUC_{0-inf}	101.62	80.50	128.27

The 90% CIs of C_{max}, AUC_{0-t} and AUC_{0-inf} ratio were not inside the accepted bioequivalence range, 80.00 – 125.00%, thus not permitting to conclude for bioequivalence for T formulation 1 strength 348.4 mg vs R1.

Table 22: tmax analysis (secondary parameter)

Parameter	Statistic Method	T1-strength1 vs R1	T1-strength2 vs R1	T1-strength3 vs R1	T1-strength4 vs R1
		Probability (p)	Probability (p)	Probability (p)	Probability (p)
T_{max}	Kruskal-Wallis Test	0.5362 Not Significant	0.4514 Not Significant	0.8719 Not Significant	0.8251 Not Significant

Table 23: Linearity results

Dose-adjusted	AUC_{0-t} T1 (ng/mL * Hours)	AUC_{0-t} T2 (ng/mL * Hours)	T1/T2 (%)	Dose Linearity?*
174.2 vs 217.7	1490.319	1585.292	94.009	Yes

Dose-adjusted	AUC_{0-t} T1 (ng/mL * Hours)	AUC_{0-t} T3 (ng/mL * Hours)	T1/T3 (%)	Dose Linearity?*
174.2 vs 261.3	1490.319	1783.093	83.581	Yes

Dose-adjusted	AUC_{0-t} T1 (ng/mL * Hours)	AUC_{0-t} T4 (ng/mL * Hours)	T1/T4 (%)	Dose Linearity?*
174.2 vs 348.4	1490.319	1667.191	89.391	Yes

Dose-adjusted	AUC_{0-t} T2 (ng/mL * Hours)	AUC_{0-t} T3 (ng/mL * Hours)	T2/T3 (%)	Dose Linearity?*
217.7 vs 261.3	1585.292	1783.093	88.907	Yes

Part 2

- **Pharmacokinetic parameters**

Table 24: PK results - MMF – Reference 2, 240 mg DMF (cohort 6)

N = 16	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)	AUC_{0-inf} (ng/ml*h)	AUC%extra (%)	T_{half} (hours)	K_{el} (1/Hours)	MRT (hours)
Mean	2303.630	3526.012	3536.471	0.300	0.761	0.962	2.921
GeoMean	2155.284	3407.100	3417.370	0.277	0.739	0.938	2.824
SD	829.288	951.302	953.241	0.120	0.206	0.208	0.816
CV	35.999	26.980	26.955	40.004	27.097	21.651	27.928

N = 16	T_{max} (hours)
Median	2.500
Min	1.500
Max	5.000

Table 25: PK results - MMF – Test 1 formulation, 261.3 mg, MMF-TTEG-MMF (cohort 6)

N = 16	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)	AUC_{0-inf} (ng/ml*h)	AUC%extra (%)	T_{half} (hours)	K_{el} (1/Hours)	MRT (hours)
Mean	1798.421	2701.566	2717.835	0.564	0.872	0.975	2.736
GeoMean	2248.651	3517.437	3537.466	0.405	0.772	0.898	2.507
SD	728.756	598.792	606.635	0.714	0.595	0.382	1.399
CV	40.522	22.165	22.321	126.585	68.282	39.200	51.122

N = 16	T_{max} (hours)
Median	2.000
Min	1.000
Max	5.000

Table 26: PK results - MMF – Test 2 formulation, 261.3 mg MMF-TTEG-MMF (cohort 6)

N = 16	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)	AUC_{0-inf} (ng/ml*h)	AUC%extra (%)	T_{half} (hours)	K_{el} (1/Hours)	MRT (hours)
Mean	1509.364	2471.435	2498.292	1.086	1.177	0.746	3.005
GeoMean	1834.981	3218.015	3254.146	0.578	1.016	0.682	2.853
SD	640.178	552.262	550.780	2.222	0.894	0.274	1.036
CV	42.414	22.346	22.046	204.657	75.899	36.780	34.482

N = 16	T_{max} (hours)
Median	2.500
Min	1.000
Max	4.500

Table 27: PK results - MMF – Test 3 formulation, 261.3 mg MMF-TTEG-MMF (cohort 6)

N = 16	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)	AUC_{0-inf} (ng/ml*h)	AUC%extra (%)	T_{half} (hours)	K_{el} (1/Hours)	MRT (hours)
Mean	1810.650	2517.715	2684.171	0.421	0.664	1.089	3.158
GeoMean	1794.635	2709.237	3235.556	0.545	0.651	1.065	3.069
SD	887.489	1129.902	970.427	0.370	0.135	0.246	0.840
CV	49.015	44.878	36.154	87.961	20.294	22.609	26.609

N = 16	T_{max} (hours)
Median	2.500
Min	1.500
Max	12.000

Table 28: PK results - TTEG - Test formulation 3, strength 261.3 mg MMF-TTEG-MMF (cohort 6)

N = 16	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)	AUC_{0-inf} (ng/ml*h)
Mean	1150.663	2899.641	3055.566
GeoMean	1008.648	2550.236	2762.486
SD	473.986	1221.688	1195.322
CV	41.192	42.132	39.119

Note: For cohort 6, the MMF-TTEG-MMF and MMF-TTEG couldn't be determined

The summary results obtained for the different statistical tests used to compare the log transformed data for AUC_{0-t}, AUC_{0-inf} and C_{max} obtained for TEST formulation 1 and REFERENCE 2 products are presented in Table 29, Table 30, and Table 31.

Table 29: PK results - 261.3 mg Test formulation 1 Multiparticulate vs. 240 mg Reference 2 (DMF)

Parameter	GeoMean Test	GeoMean Reference	Intra-subject CV (%)	Ratio T/R (%)	Lower 90% CL	Upper 90% CL	Dose-adjusted Ratio T/R
C_{max} (ng/ml)	1686.488	2155.284	35.735	78.249	62.89	97.35	104.332
AUC_{0-t} (ng/ml*h)	2638.078	3407.100	11.373	77.429	72.09	83.16	103.239
AUC_{0-inf} (ng/ml*h)	2653.099	3417.370	11.060	77.636	72.43	83.22	103.515

Table 30: PK results - 261.3 mg Test formulation 2 Multiparticulate vs. 240 mg Reference 2 (DMF)

Parameter	GeoMean Test	GeoMean Reference	Intra-subject CV (%)	Ratio T/R (%)	Lower 90% CL	Upper 90% CL	Dose-adjusted Ratio T/R
C_{max} (ng/ml)	1376.236	2155.284	40.987	63.854	49.89	81.72	85.139
AUC_{0-t} (ng/ml*h)	2413.511	3407.100	12.501	70.838	65.52	76.58	94.451
AUC_{0-inf} (ng/ml*h)	2440.609	3417.370	11.739	71.418	66.37	76.85	95.224

Table 31: PK results - 261.3 mg Test formulation 3 Monolithic vs. 240 mg Reference 2 (DMF)

Parameter	GeoMean Test	GeoMean Reference	Intra-subject CV (%)	Ratio T/R (%)	Lower 90% CL	Upper 90% CL	Dose-adjusted Ratio T/R
C_{max} (ng/ml)	1345.976	2155.284	83.121	62.45	39.55	98.60	83.267
AUC_{0-t} (ng/ml*h)	2031.928	3407.100	60.392	59.638	41.97	84.75	79.517
AUC_{0-inf} (ng/ml*h)	2414.272	3455.859	36.027	69.86	55.46	88.00	93.147

- **Bioequivalence comparison**

Table 32: PK results - The 90% CIs MMF mean treatment Test 1 formulation, 261.3 mg after dose-adjustment/Reference 2 ratios.

Test name	Parameter	Test value (T1 /R2)	Lower 90% CL	Upper 90% CL
90% CI	C_{max}	104.33	83.86	129.80
90% CI	AUC_{0-t}	103.24	96.12	110.88
90% CI	AUC_{0-inf}	103.51	96.57	110.96

The 90% CIs of C_{max} ratio were not inside the accepted bioequivalence range, 80.00 – 125.00%, but the 90% CIs of AUC_{0-t} and AUC_{0-inf} ratio were inside the accepted bioequivalence range, thus not permitting to conclude for bioequivalence with regard to the rate of absorption and permitting to conclude for bioequivalence with regard to the extent of absorption for T formulation 1 vs R 2.

Table 33: PK results - The 90% CIs MMF mean treatment Test 2 formulation, 261.3 mg after dose-adjustment / Reference 2 ratios.

Test name	Parameter	Test value (T2 /R2)	Lower 90% CL	Upper 90% CL
90% CI	C_{max}	85.14	66.52	108.96
90% CI	AUC_{0-t}	94.45	87.37	102.11
90% CI	AUC_{0-inf}	95.22	88.50	102.46

The 90% CIs of C_{max} ratio were not inside the accepted bioequivalence range, 80.00 – 125.00%, but the 90% CIs of AUC_{0-t} and AUC_{0-inf} ratio were inside the accepted bioequivalence range, thus not permitting to conclude for bioequivalence with regard to the rate of absorption and permitting to conclude for bioequivalence with regard to the extent of absorption for T formulation 2 vs R 2.

Table 34: PK results - The 90% CIs MMF mean treatment Test 3 formulation, 261.3 mg after dose-adjustment / Reference2 ratios.

Test name	Parameter	Test value (T3 /R2)	Lower 90% CL	Upper 90% CL
90% CI	C_{max}	83.27	52.74	131.47
90% CI	AUC_{0-t}	79.52	55.96	113.00
90% CI	AUC_{0-inf}	93.15	73.94	117.34

The 90% CIs of C_{max}, AUC_{0-t} and AUC_{0-inf} ratio were not inside the accepted bioequivalence range, 80.00 – 125.00%, thus not permitting to conclude for bioequivalence with regard both to the rate of absorption and to the extent of absorption for T formulation 3 vs R 2.

For t_{max} the statistical test used demonstrates that no significant difference exists between T formulation 1 vs. R2 formulations, no significant difference exists between T formulation 2 vs. R 2 formulations and no significant difference exists between T formulation 3 vs. R 2 formulations for Cohort 6.

- **Safety data (Part 1 and 2)**

47 adverse events (AEs) out of which 39 of mild intensity and 8 of moderate intensity occurred in the present study. AEs occurred in 29 out of 56 subjects who received the study medication in the present study. These were not serious AEs (SAEs). The volunteers that experienced the adverse events

completely recovered before the end of the study.

In part 1 of the study 20 AEs occurred after study drug administration, 6 AEs occurred after administration of 174.2 mg MMF-TTEG-MMF, 5 AEs occurred after administration of 217.7 mg MMF-TTEG-MMF, 4 AEs occurred after administration of 261.3 mg MMF-TTEG-MMF, 1 AE occurred after administration of 348.4 mg MMF-TTEG-MMF and 4 AEs occurred after administration of 120 mg Reference (DMF).

In Part 2 of the study 27 AEs occurred after study drug administration, 5 AEs occurred after administration of 261.3 mg TEST 1 formulation, 8 AEs occurred after administration of 261.3 mg TEST 2 formulation, 8 AEs occurred after administration of 261.3 mg TEST 3 formulation and 6 AEs occurred after administration of 240 mg Reference (DMF).

ANOVA test analysis of clinical laboratory parameters found three statistically significant differences regarding lower values of haematocrit, aspartate aminotransferase and lactate dehydrogenase and two statistical significant regarding higher values of white blood cells and lymphocytes at follow-up vs. screening. Results of the ANOVA comparison for vital signs found one statistically significant difference regarding lower value of diastolic arterial pressure, follow up vs. screening. These statistical differences are devoid of clinical significance.

Pivotal Bioequivalence Study in Fasted State, MMF-BESD-05-TFB/22: Single Center, Open Label, Four-Period, Two-Sequence, Fully Replicated, Randomized, Controlled, Single Dose Pivotal Bioequivalence Study of Tegomil Fumarate 348 mg Gastro-Resistant Capsules [TEST Formulation] Versus Equimolar Dose (Based on MMF Release) of Tecfidera® 240 mg Gastro-Resistant Hard Capsules [REFERENCE formulation] in Healthy Volunteers Under Fasting Conditions.

Methods

- **Study design**

Study Center: Institutia Medico-Sanitara Publica, "Clinical Hospital of the Ministry of Health", Chisinau / The Republic of Moldavia

The study was a single center, open label, four-period, two-sequence, fully replicated, randomized, controlled, single dose pivotal bioequivalence study of Tegomil fumarate 348 mg gastro-resistant capsules [Test formulation] versus equimolar dose (based on MMF release) of Tecfidera® 240 mg gastro-resistant hard capsules [Reference formulation] study in healthy volunteers.

Study objectives: to evaluate the bioequivalence of the Test formulation relative to an equimolar dose (based on MMF release) of Reference product, after single oral administration under fasting conditions, and to compare the safety/tolerability profiles of the two formulations.

A four-period fully replicate design was deemed most appropriate due to the high common intra-subject variability observed in the previous single crossover pilot bioavailability study [MMF-SAD-BA-04-TFB/21].

Treatments administered: each subject received a single oral dose consisting of one multiparticulate capsule of 348.4 mg Tegomil fumarate Test formulation, or a single oral dose consisting of one gastro-resistant hard capsule of 240 mg DMF, Reference formulation, per study period, under fasting conditions. Each treatment was administered at two separate occasions, according to a four period fully replicate design. Treatments were separated by wash-out periods of 7 days.

PK study procedures: In each study period serial blood samplings were collected for the quantification of MMF in plasma: pre-dose and at 0.25 (15 min), 0.50 (30 min), 0.75 (45 min), 1.0, 1.33 (1 h 20 min), 1.67 (1 h 40 min), 2.0, 2.33 (2 h 20 min), 2.67 (2 h 40 min), 3.0, 3.33 (3 h 20 min), 3.67 (3 h

40 min), 4.0, 4.5 (4 h 30 min), 5.0, 5.5 (5 h 30 min), 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, and 14.0 hours after each administration (5 ml blood for each sample; 24 samples in total).

Sample analysis: High-performance liquid chromatography (HPLC) validated method, with MS/MS detection technique for MMF.

- **Test and reference products**

Test formulation, dose and mode of administration, batch number: tegomil fumarate 348 mg gastro-resistant capsules. Re-test date: 12/2024. Administered orally, 1 capsule with 200 ml of room temperature water, under fasting conditions for all subjects.

Reference product, dose and mode of administration, batch number: Tecfidera® 240 mg gastro-resistant hard capsules, MAH: Biogen Netherlands B.V., The Netherlands. Country of origin: Germany. Administered orally, 1 capsule with 200 ml of room temperature water, under fasting conditions, for all subjects.

- **Population(s) studied**

Diagnosis and main selection criteria: Healthy male and non-pregnant female volunteers, age between ≥18 years and ≤55 years, BMI ≥18.5 and ≤ 30 kg/m2.

Number of subjects planned: to be enrolled: 30 subjects; enrolled: 30 subjects; completed: 28 subjects; analyzed: 30 subjects; included in the statistical evaluation of PK data: 29 subjects.

- **Analytical methods**

Validation of High-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) for determination of monoethyl fumarate and MMF in plasma samples - FMD-BE-LCMSMS-01/16.

The aim of the analysis submitted in protocol FMD-BE-LCMSMS-01/16 was to validate HPLC-MS/MS for determination of monoethyl fumarate and MMF in plasma samples to support pivotal clinical study – MMF-BEFI-06-TFB/22, MMF-BESD-05-TFB/22 and pilot study (MMF-SAD-BA-04-TFB/21). Calibration curve ranged from 3 to 1500 ng/ml for monoethyl fumarate and from 6 to 3000 ng/ ml for MMF. The accuracy of calibrators, the between-run accuracy; between-run precision, within-run accuracy and within-run precision were addressed and were acceptable. Following parameters were also addressed and were acceptable: reinjection reproducibility, extraction recovery, specificity, dilution integrity (approved for 1/4 dilution). No matrix and carryover effects were observed. Stability analyses have been performed and approved for following conditions for both analytes: up to 1 hour at room temperature, up to 6 hours on crunched ice, up to 1 week at – 5 ºC, up to 4 weeks below – 20 ºC, up to 1 week below – 70 ºC, after 5 freeze thaw cycles, and in spiked plasma samples extract kept in -5 and below -20ºC up to 48 hours. Hemolysis and lipemia of the plasma did not affect the quantification of both analytes. During validation interconversion tests were also performed.

During bioanalytical assessment a total of 2784 human plasma samples were analyzed for MMF. The %CVs for calibration standards and QC samples were acceptable. The LLOQ was well established, with values not exceeding 5% of C_{max} for all patients. ISR was assessed for 230 samples, and results were acceptable.

The applicant has provided long-term stability results that cover the storage conditions for samples collected during the clinical study MMF-BESD-05-TFB/22.

In analytical method partial validation (FMD-BELCMSMS-01/16 revision 6.0) the following parameters were addressed and were acceptable: within-run and between run precision and accuracy, stability of MMF up to 28 weeks below -20 ºC, stability of monomethyl fumarate in plasma extract up to 72 hours at -5 ºC (nominal) or dried below -20 °C. No back-conversion of MMF was detected.

- **Pharmacokinetic variables**

Primary parameters:

- C_{max}: peak drug concentration, obtained directly from the data – without interpolation
- AUC_{0-t}: area under the curve integrated, by the trapezoidal rule, from blood concentrations between time 0 to the last quantifiable sample
- AUC_{0-}inf: area under the curve integrated from the plasma concentrations extrapolating the terminal elimination phase. Elimination rate constant was evaluated from at least three concentrations above LLOQ in the terminal profile. In case that the last three concentrations contain C_{max} then the subject was excluded from the statistics on the AUC_{0-inf} parameter.

Secondary parameter: t_{max}: time of the peak drug concentration, obtained directly from the data, without interpolation.

Additional parameters: AUC% extra, $t_{1/2}$:, kel MRT

- **Statistical methods**

Standard descriptive statistics (arithmetic mean, harmonic mean, geometric mean, SEM, standard deviation, coefficient of variation, median, range) were performed for all PK metrics (C_{max}, AUC_{0-t}, AUC_{0-inf}, t_{max}, $AUC_{\% extra}$, $t_{1/2}$, Kel, MRT) calculated for the TEST and REFERENCE formulations from MMF plasma concentrations.

Each subject was reported with two observations per each type of treatment (corresponding to first/second administration of the respective treatment as per the replicate setting) provided that the subject completed the study as planned.

For the primary PK parameters (C_{max}, AUC_{0-t} and AUC_{0-inf}): bioequivalence was assessed by means of an analysis of variance (ANOVA) (model: treatments, sequences, subject-within-sequence and periods of administration) and calculating the 90% CIs of the geometric mean Test formulation /Reference formulation ratio.

The standard acceptance range for bioequivalence of 80.00-125.00% was used for AUC_{0-t} and AUC_{0-inf}, while for C_{max}, the acceptance range could be widened based upon the REFERENCE within-subject variability to a maximum of 69.84-143.19%. If the within-subject CV of the REFERENCE product (or CVWR) is ≤ 30%, then the 90% CIS of the geometric mean TEST/REFERENCE ratio obtained for C_{max} should lie within an acceptance interval of 80.00% - 125.00%. If the CVWR for the REFERENCE product was > 30%, the bioequivalence acceptance limits were scaled based on the within-subject variability of the REFERENCE product. The extent of the widening was defined based upon the within-subject variability seen in the bioequivalence study using scaled-average-bioequivalence.

T_{max} values have been compared between Test vs. Reference formulations using a nonparametric test (Wilcoxon Signed-Rank Test).

PK and statistic calculations were performed using SAS® statistical software (Version: 9.4 or higher; SAS Institute Inc., USA), using PROC GLM with fixed effects.

Determination of sample size

A number of 30 subjects was enrolled in the study. This number of subjects had been estimated taking in consideration: a) the significance level (alpha) of 0.05; b) an a priori test power of 80 %; c) an intra-subject coefficient of variation of up to 36% for the primary PK metric C_{max}; d) an expected geometric mean T/R ratio of the primary PK metric C_{max} of approximately 1.09 e) the fact that for the 90% CI of the geometric least square means ratio T/R for the primary PK metric C_{max}, the acceptance

range can be widened based upon the REFERENCE within-subject variability; f) a potential dropout/withdrawal rate of up to 20% due to the ongoing COVID19 pandemic.

Results

- **Disposition of subjects**

A total of 51 adult male and female healthy volunteers were screened. Thereof, 30 healthy adult male (16) and female (14) study participants were enrolled. Out of the 30 enrolled volunteers 28 subjects (14 m / 14 f) completed the study according to protocol, but all 30 subjects underwent the follow-up safety examination. The mean ± SD age of the study population was 33.33±9.88 years; the mean ± SD body weight was 72.57±9.57 kg; and the mean ± SD BMI was 24.97±3.68 kg/m2.

One subject was withdrawn from the study because of a decision of the clinical investigator, and another subject withdrew further participation for personal reasons (family related).

- **Protocol deviations**

There were no protocol deviations in this study.

- **Data sets analysed**

For the bioequivalence assessment, PK data coming from all 29 subjects were statistically analysed. One subject was excluded from the statistical analysis. This subject was administered only the Reference product in Period 1. Another subject was included in the statistical analysis. This subject missed Period 4.

The descriptive statistics of demographic characteristics of all 30 enrolled subjects has been performed. Safety data have been evaluated on 30 complete datasets.

- **Pharmacokinetic parameters**

Table 35: The mean values of MMF pharmacokinetic parameters for reference and test formulations

MMF – Reference

N = 58	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)	AUC_{0-inf} (ng/ml*h)	AUC%extra (%)	T_{half} (hours)	K_{el} (1/Hours)	MRT (hours)
Mean	2411.060	3391.981	3407.858	0.473	1.015	0.932	3.086
GeoMean	2279.329	3311.483	3327.347	0.338	0.822	0.843	2.921
SD	764.862	723.718	725.170	0.821	1.186	0.349	1.047
CV	31.723	21.336	21.279	173.351	116.782	37.416	33.922

N = 58	T_{max} (hours)
Median	2.330
Min	0.750
Max	5.000

MMF - Test formulation

N = 57	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)	AUC_{0-inf} (ng/ml*h)	AUC%extra (%)	T_{half} (hours)	K_{el} (1/Hours)	MRT (hours)
Mean	2846.121	3656.399	3693.052	1.031	2.706	0.833	2.914
GeoMean	2670.912	3584.907	3623.899	0.391	1.089	0.636	2.547
SD	965.825	715.071	709.414	2.875	7.375	0.430	1.941
CV	33.935	19.557	19.209	278.938	272.530	51.606	66.596

N = 57	T_{max} (hours)
Median	2.000
Min	0.750
Max	5.000

The intra-subject variability coefficients registered for MMF, were for AUC_{0-t} = 9.50%, AUC_{0-inf} = 9.84% and for C_{max} = 28.27%. The within-subject coefficient of variation of the REFERENCE product was for C_{max} = 26.54%.

Mean plasma concentrations following single administration of REFERENCE and TEST are presented in Figure 11 and Figure 12.

Figure 11: Mean MMF plasma concentrations following single administration of REFERENCE (Tecfidera® 240 mg gastro-resistant hard capsules) and TEST (tegomil fumarate 348 mg gastro-resistant hard-capsules) treatments to healthy adult subjects in fasted state (linear scale).

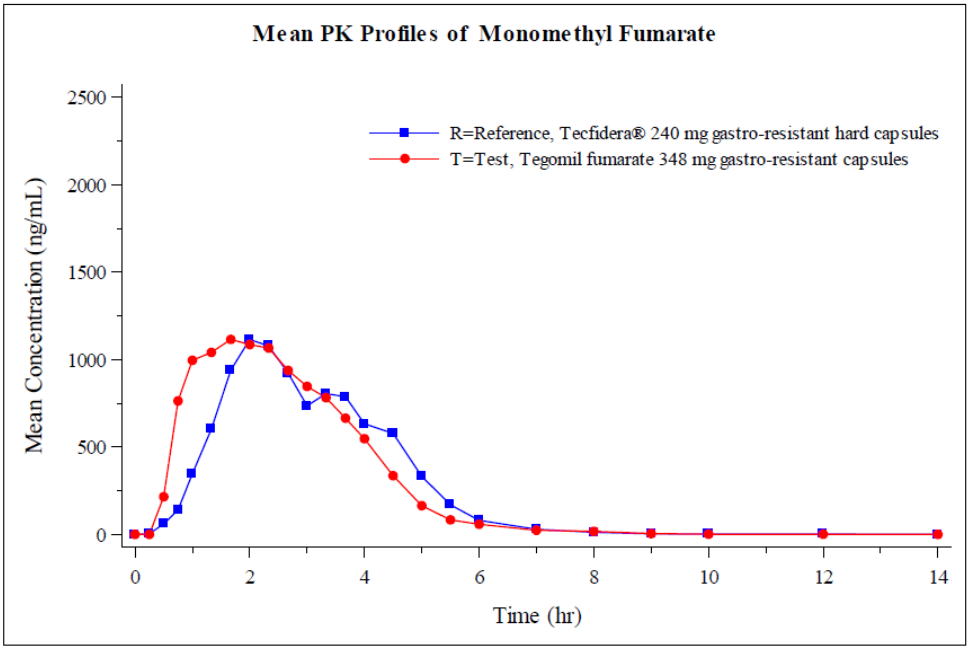
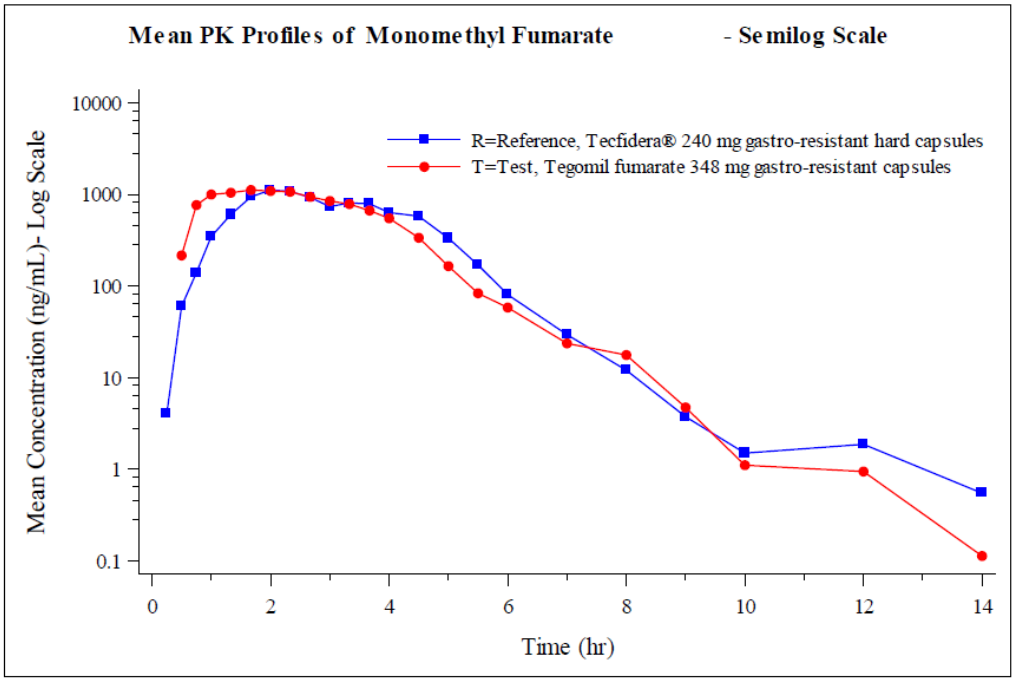


Figure 12: Mean MMF plasma concentrations following single administration of REFERENCE (Tecfidera® 240 mg gastro-resistant hard capsules) and TEST (Tegomil fumarate 348 mg gastro-resistant hard-capsules) treatments to healthy adult subjects in fasted state (semi-log scale)



- **Bioequivalence assessment**

Analysis of variance ANOVA showed no significant effect of sequence on all primary parameters. A subject within sequence effect and treatment effect was observed on all three primary parameters. A period effect was observed only for AUC_{0-t} (Table 36).

Table 36: Evaluation of the sequence, period, subject within sequence and treatment influence on primary pharmacokinetics parameters - MMF (T vs. R).

Source of error	Probability (p)		
	C_{max}	AUC_{0-t}	AUC_{0-inf}
SEQUENCE	0.44910	0.41738	0.41659
SUBJECT(SEQUENCE)	0.00000*	0.00000*	0.00000*
PERIOD	0.15783	0.02701*	0.06312
TREATMENT	0.00331*	0.00002*	0.00001*

* = p<0.05 = significant

Table 37: The 90% CIs MMF mean treatment Test formulation /Reference ratios.

Test name	Parameter	Test value (T /R)	Lower 90% CL	Upper 90% CL
90% CI	C_{max}	116.99	107.32	127.53
90% CI	AUC_{0-t}	108.46	105.31	111.71
90% CI	AUC_{0-inf}	109.10	105.82	112.49

The 90% CIs of C_{max} ratio were not inside the accepted bioequivalence range, 80.00 – 125.00%, but the 90% CIs of AUC_{0-t} and AUC_{0-inf} ratio were inside the accepted bioequivalence range, thus not permitting to conclude for bioequivalence with regard to the rate of absorption and permitting to conclude for bioequivalence with regard to the extent of absorption for T formulation vs R formulation.

As the within-subject coefficient of variation of C_{max} for the Reference product was 26.54%, a scaling of the C_{max} acceptance limits was not required.

The 90% CIs of the C_{max} ratio was not entirely inside the standard bioequivalence range, 80.00 – 125.00%. The upper 90% CI slightly exceeded the upper acceptance range by 2.53%, and the point estimate exceeded unity by about 17% (Table 38). However, the 90% CIs of AUC_{0-t} and AUC_{0-inf} ratio were inside the standard acceptance bioequivalence range, indicating bioequivalence with regard to the extent of absorption between TEST and REFERENCE formulations, while bioequivalence with regard to the rate of absorption in the fasted state could not be concluded.

Table 38: Point Estimates and 90% CI of MMF TEST / REFERENCE C_{max} and AUC Ratios

Test Name	Parameter	Point Estimates of T/R Treatment Ratios	Lower 90% CI	Upper 90% CI
90% CI	C_{max}	116.99	107.32	127.53
90% CI	AUC_{0-t}	108.46	105.31	111.71
90% CI	AUC_{0-inf}	109.10	105.82	112.49

No significant difference exists for t_{max} between TEST and REFERENCE formulations (p=0.0082).

- **Pharmacokinetic Conclusions**

For bioequivalence assessment, the statistical tests used to compare AUC_{0-t}, AUC_{0-inf} and C_{max} did show statistically significant differences depending on the MMF preparation which is, however, irrelevant for AUC_{0-t}, and AUC_{0-inf}.

The TEST formulation and REFERENCE formulations are not bioequivalent with regard to the rate of absorption and are bioequivalent with regard to the extent of absorption after single dose administration under fasting conditions.

- **Safety data**

Extent of Exposure: A total of 28 subjects received at two different occasions (i.e. replicate design) one dose of the Test formulation (Tegomil fumarate 348 mg gastro-resistant capsules), and 28 subjects received at two different occasions one dose of the Reference formulation (Tecfidera® 240 mg gastro-resistant hard capsules), according to a four-period replicate design.

Adverse Events: One hundred and eighteen AEs of mild (95) and moderate (23) intensity occurred in twenty-four subjects after treatment with Test and in twenty-four subjects after treatment with Reference during the present study. From the total of AEs that occurred in the present study, 50.43% of AEs occurred after the administration of Test (59 AEs) and 50.43% of AEs occurred after the administration of Reference (59 AEs). None of these AEs met the criteria for a SAE. All AEs completely resolved without sequelae before the end of the study.

- Reference Treatment: Following treatments with the Reference formulation 'skin hyperemia' was the most frequently reported AE, with 17 study participants (28.81%) experiencing this AE with mild intensity, and 7 study participants (11.86%) in which the AE was considered to be of moderate intensity. All events of 'skin hyperemia' were considered by the investigator as being related to treatment. Other AE reported for Reference treatment included 'feeling hot', reported by 9 study participants (15.25%) with mild intensity; 'pricking sensation', reported by 8 study participants (13.56%) with mild intensity. 'Itching'; 'headache'; 'dizziness'; and

'nausea' were each reported by 1 study participant (1.69%) with mild intensity. 'Retrosternal pain' was reported by 1 study participant (1.69%) with moderate intensity. All of these AEs were considered by the investigator as being related to treatment.

- Test Treatment: Following treatments with the TEST formulation 'skin hyperemia' was the most frequently reported AEs, with 16 study participants (28.07%) experiencing this AE with mild intensity, and 9 study participants (15.78%) in which the AE was considered to be of moderate intensity. All events of 'skin hyperemia' were considered by the investigator as being related to treatment. Other AE reported for Test treatment included 'feeling hot', reported by 10 study participants (17.54%) with mild intensity, and 1 study participant (1.75%) in which the AE was considered to be of moderate intensity. 'Pricking sensation' was reported by 11 study participants (19.30%) with mild intensity. 'Itching' and 'headache' were each reported by 1 study participant (1.69%) with mild intensity. All of these AEs were considered by the investigator as being related to treatment.

Analysis and Discussion of AEs: From the total number of study participants having experienced AEs, 24 subjects (85.71%) experienced AEs after treatment with Test, while 24 study participants (85.71%) experienced AEs after treatment with Reference, indicating that the number of subjects experiencing AEs was similar for Test and Reference treatments. From the total number of AEs reported in the present study (118 AEs), 59 AEs (50%) occurred after the administration of the Test treatments, and 59 AEs (50%) occurred after the administration of the Reference treatments, indicating that the total number of AEs reported for Test and Reference treatments was also similar. The distribution of the severity rating of AEs was also well comparable between Test and Reference treatments with most study participants reporting AEs of mild intensity (39 subjects and 38 subjects for Test and Reference treatments), and 10 and 8 subjects experiencing AEs of moderate intensity Test and Reference treatments. None of the study participants experienced any AE of severe intensity. There were also no SAE or deaths reported from the present study. The AEs noted in the present study were highly consistent with the AE pattern described for DMF in the current SPC of Tecfidera®. There were no new or hitherto unreported AEs for DMF-releasing products (e.g. Tecfidera®) observed in the present study. The similarity of the numbers of study participants experiencing AEs, the total number of AEs reported, and the similar nature and severity of AEs reported for Test and Reference treatments further indicates that the mean 18% higher C_{max} value observed for the Test treatment does not translate into any notable safety alterations.

Clinical Laboratory Evaluations: As safety clinical laboratory examinations were only conducted at screening and at the end-of-study visits, these data cannot be attributed to a particular treatment in view of the replicate crossover design. Overall, however, there were no safety laboratory deviations observed over the course of the study that were considered to be of clinical relevance.

Vital Signs: As vital signs (systolic and diastolic arterial pressures, heart rate, body temperature and respiratory rate) were assessed only at screening and at the end-of study visits, and pre-dose at the treatment days (i.e. after a wash-out period of the preceding treatment of 7 days), these data cannot be attributed to a particular treatment in view of the replicate crossover design. Overall, however, there were no vital sign deviations or trends observed over the course of the study that were considered to be of clinical relevance.

Pivotal Bioequivalence Study in Fed State, MMF-BEFI-06-TFB/22: Single Center, Open Label, Four-Period, Two-Sequence, Fully Replicated, Randomized, Controlled, Single Dose Pivotal Bioequivalence Study of Tegomil Fumarate 348 mg Gastro-Resistant Capsules [TEST Formulation] Versus Equimolar Dose (Based on MMF Release) of Tecfidera® 240 mg Gastro-Resistant Hard Capsules [REFERENCE formulation] in Healthy Volunteers under Fed

Conditions.

Methods

- **Study design**

Study Center(s): Institutia Medico-Sanitara Publica, "Clinical Hospital of the Ministry of Health", Chisinau / The Republic of Moldavia

The study was a single center, open label, four-period, two-sequence, fully replicated, randomized, controlled, single dose pivotal bioequivalence study of Tegomil fumarate 348 mg gastro-resistant capsules [Test formulation] versus equimolar dose (based on MMF release) of Tecfidera® 240 mg gastro-resistant hard capsules [Reference formulation] study in healthy volunteers under fed conditions.

Subjects received a standard light dinner (that ended no later than 10 hours prior to the study drug administration) in the evening before administration. On the treatment days all subjects received standard light meals: a standard high-fat, high-calories breakfast (1 slice of bread (25 grams bread + 10 grams of butter to be applied on the slice), 2 hard-boiled eggs, 1 slice of bacon (25 grams), 125 g French fries, 250 ml of whole milk) served 30 minutes prior to treatment intake and consumed within approximately 25 minutes, then standardized meals were also served at 4h, 6h, 8h and 12 hours post-dosing, respectively. No other food was consumed during confinement.

During study days of each study periods, the subjects had free access to water until 1.0 hour before the study drug administrations and there were not allowed to drink water (or any other liquids) until 2.0 hours after the study drug administrations. Thereafter water was provided in a standardized amount (200 mL) at 2.0, 4.0, 6.0, and 8.0 hours post dose. After 8 hours the volunteers were free to drink still bottled water, as desired.

Study Objectives: to evaluate the bioequivalence of the Test formulation relative to an equimolar dose (based on MMF release) of Reference product, after single oral administration under fed conditions, and to compare the safety/tolerability profiles of the two formulations.

A four-period fully replicate design was deemed most appropriate due to the high common intra-subject variability observed in the previous single crossover pilot bioavailability study [MMF-SAD-BA-04-TFB/21].

Treatments Administered: each subject received a single oral dose consisting of one multiparticulate capsule of 348.4 mg Tegomil fumarate Test formulation, or a single oral dose consisting of one gastro-resistant hard capsule of 240 mg DMF, Reference formulation, per study period, under fed conditions. Each treatment was administered at two separate occasions, according to a four period fully replicate design. Treatments were separated by wash-out periods of 7 days.

PK Study Procedures: In each study period serial blood samplings were collected for the quantification of MMF in plasma: pre-dose and at 0.33 (20 min), 0.67 (40 min) 1.0, 1.5 (1 h 30 min), 2.0, 2.5 (2 h 30 min), 3.0, 3.33 (3 h 20 min), 3.67 (3 h 40 min), 4.0, 4.33 (4 h 20 min), 4.67 (4 h 40 min), 5.0, 5.33 (5 h 20 min), 5.67 (5 h 40 min), 6.0, 6.50 (6 h 30 min), 7.0, 8.0, 9.0, 10.0, 12.0 and 14.0 hours after each administration (5 ml blood for each sample; 24 samples in total).

Sample Analysis: HPLC validated method, with tandem mass spectrometry (MS/MS) detection technique for MMF.

- **Test and reference products**

Test formulation, dose and mode of administration, batch number: tegomil fumarate 348 mg gastro-resistant capsulesRe-test date: 12/2024. Administered orally, 1 capsule with 200 ml of room temperature water, under fed conditions for all subjects.

Reference product, dose and mode of administration, batch number: Tecfidera® 240 mg gastro-resistant hard capsules, MAH: Biogen Netherlands B.V., The Netherlands. Country of origin: Germany. Administered orally, 1 capsule with 200 ml of room temperature water, under fed conditions, for all subjects.

- **Population(s) studied**

Diagnosis and main selection criteria: Healthy male and non-pregnant female volunteers, age between ≥18 years and ≤55 years, BMI ≥18.5 and ≤ 30 kg/m2.

Number of subjects planned: to be enrolled: 30 subjects; enrolled: 30 subjects; completed: 28 subjects; analyzed: 30 subjects; included in the statistical evaluation of PK data: 29 subjects.

- **Analytical methods**

Bioanalysis of obtained samples in the study was performed according to validation method described in protocol FMD-BE-LCMSMS-01/16. For details of validation method please see description of the study MMF-BESD-05-TFB/22.

During bioanalytical assessment a total of 2784 human plasma samples were analyzed for MMF. The %CVs for calibration standards and QC samples were acceptable. The LLOQ was well established, with values not exceeding 5% of C_{max} for all patients. ISR was assessed for 230 samples, and results were acceptable.

The applicant has provided long-term storage stability results for plasma samples stored for up to 28 weeks at -20°C. The validated conditions cover the storage conditions for samples collected during the clinical study MMF-BEFI-06-TFB/22.

- **Pharmacokinetic variables**

PK of MMF: C_{max}, AUC_{0-t} and AUC_{0-inf} (as primary); t_{max} (as secondary); $AUC_{\%extra}$, $t_{1/2}$, Kel, MRT (as additional).

- **Statistical methods**

Standard descriptive statistics (arithmetic mean, harmonic mean, geometric mean, SEM, standard deviation, coefficient of variation, median, range) were performed for all PK metrics (C_{max}, AUC_{0-t}, AUC_{0-inf}, t_{max}, $AUC_{\% extra}$, $t_{1/2}$, Kel, MRT) calculated for the TEST and REFERENCE formulations from MMF plasma concentrations.

For the primary PK parameters (C_{max}, AUC_{0-t} and AUC_{0-inf}): bioequivalence was assessed by means of GLM Procedure in SAS and calculating the 90% CIs of the least square geometric mean ratio T/R.

The standard acceptance range for bioequivalence of 80.00-125.00% was used for interpretation of AUC_{0-t} and AUC_{0-inf} results, while for C_{max} the acceptance range for bioequivalence was individually determined based on the REFERENCE within-subject variability to a maximum of 69.84-143.19% as next described.

If the within-subject coefficient of variation of the REFERENCE product (or CVWR) was ≤ 30%, then the 90% CIs of the geometric mean TEST/REFERENCE ratio obtained for C_{max} should lie within the standard acceptance interval of 80.00% - 125.00%.

If the CVWR for the REFERENCE product was > 30%, the bioequivalence acceptance limits were scaled based on the within-subject variability of the REFERENCE product. The extent of the widening was

defined based upon the within-subject variability seen in the bioequivalence study using scaled-average-bioequivalence.

Tmax values have been compared between Test vs. Reference formulations using a nonparametric test (Wilcoxon Signed-Rank Test).

Determination of Sample Size

A number of 30 subjects was enrolled in the study. This number of subjects had been estimated taking in consideration: a) the significance level (alpha) of 0.05; b) an a priori test power of 80 %; c) an intra-subject coefficient of variation of up to 36% for the primary PK metric C_{max}; d) an expected geometric mean T/R ratio of the primary PK metric C_{max} of approximately 1.09; e) the fact that for the 90% confidence interval of the geometric least square means ratio T/R for the primary PK metric C_{max}, the acceptance range can be widened based upon the REFERENCE within-subject variability; f) a potential dropout/withdrawal rate of up to 20% due to the ongoing COVID19 pandemic.

Results

- **Disposition of subjects**

A total of 48 adult male and female healthy volunteers were screened. Thereof, 30 healthy adult male (21) and female (9) study participants were enrolled. The mean ± SD age of the study population was 31.97±11.22 years, the mean ± SD body weight was 71.63±10.06 kg, and the mean ± SD BMI was 24.65±3.16 kg/m2.

Out of the 30 enrolled volunteers 28 subjects (19m / 9f) completed the study according to protocol, but all 30 subjects underwent the follow-up safety examination. Two subjects withdrew further participation for personal reasons (job related).

- **Protocol deviations**

No protocol deviations were reported.

- **Pharmacokinetic results**

Table 39: The mean values of MMF PK parameters for the test and reference formulations

MMF – Reference

N = 58	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)	AUC_{0-inf} (ng/ml*h)	AUC%extra (%)	T_{half} (hours)	K_{el} (1/Hours)	MRT (hours)
Mean	1588.027	2917.623	2981.320	2.032	1.384	0.857	5.621
GeoMean	1439.190	2843.663	2904.612	0.811	1.001	0.692	5.228
SD	750.458	662.920	679.418	3.504	1.413	0.466	1.988
CV	47.257	22.721	22.789	172.446	102.071	54.313	35.359

N = 58	T_{max} (hours)
Median	4.670
Min	0.670
Max	10.017

MMF - Test formulation

N = 57	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)	AUC_{0-inf} (ng/ml*h)	AUC%extra (%)	T_{half} (hours)	K_{el} (1/Hours)	MRT (hours)
Mean	1443.491	2967.625	3086.558	3.557	1.978	0.695	5.672
GeoMean	1295.571	2879.012	2994.046	1.173	1.330	0.521	5.139
SD	673.561	728.563	760.067	6.841	2.227	0.476	2.491
CV	46.662	24.550	24.625	192.298	112.580	68.506	43.921

N = 57	T_{max} (hours)
Median	4.670
Min	0.670
Max	9.000

The common intra-subject variability coefficients registered for MMF, were for AUC_{0-t} = 14.85%, AUC_{0-inf} = 14.61% and for C_{max} = 36.65%. The within-subject coefficient of variation of the REFERENCE product was for C_{max} = 33.96%.

Figure 13: Mean MMF plasma concentrations following single administration of Reference (Tecfidera® 240 mg gastro-resistant hard capsules) and Test (Tegomil fumarate 348 mg gastro-resistant hard-capsules) treatments to healthy adult subjects in fed state (linear scale)

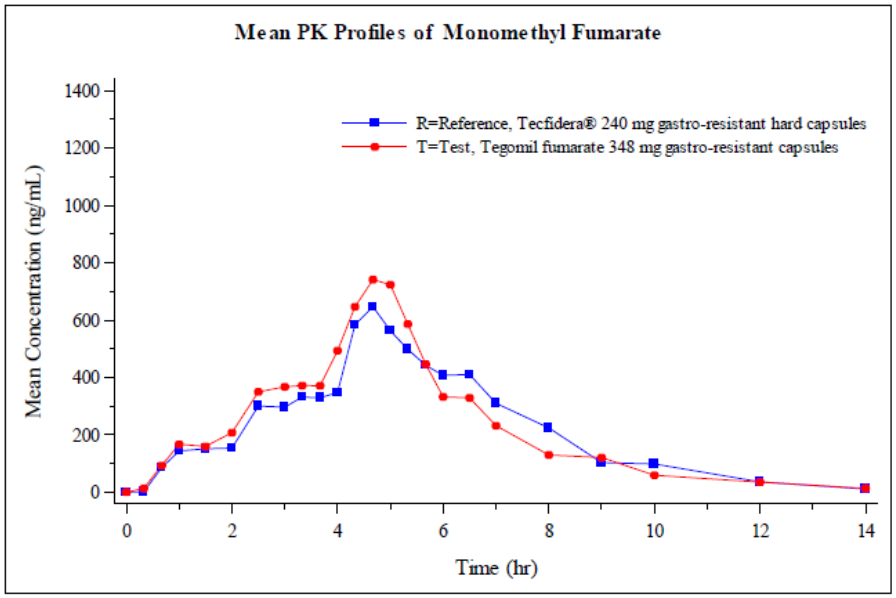
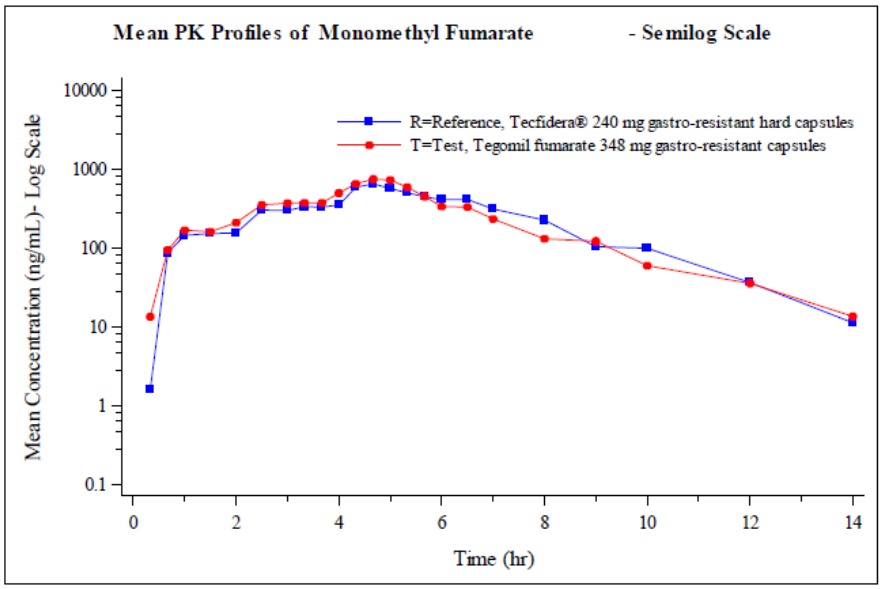


Figure 14: Mean MMF plasma concentrations following single administration of Reference (Tecfidera® 240 mg gastro-resistant hard capsules) and Test (Tegomil fumarate 348 mg gastro-resistant hard-capsules) treatments to healthy adult subjects in fed state (semi-log scale).



Analysis of variance ANOVA showed no significant effect of sequence, period or treatment on all primary parameters. A subject within sequence effect was observed on all three primary parameters. Subject effects are frequently observed due to inter-individual variations, without affecting the validity of the study (Table 40).

Table 40: Analysis of variance of the main MMF pharmacokinetic parameters for TEST formulation vs REFERENCE products.

Source of error	Probability (p)		
	C_{max}	AUC_{0-t}	AUC_{0-inf}
SEQUENCE	0.79343	0.69904	0.68575
SUBJECT(SEQUENCE)	0.00000*	0.00000*	0.00000*
PERIOD	0.12545	0.35208	0.32349
TREATMENT	0.09446	0.66253	0.27757

* = $p<0.05$ = significant

- **Bioequivalence assessment**

The CVWR for the REFERENCE product for Cmax was 33.96% in this study (> 30%). Therefore, the 90% CI of the geometric mean TEST/REFERENCE ratio obtained for C_{max} should be within the scaled acceptance interval of 77.80 – 128.54% to demonstrate bioequivalence for C_{max}. However, the 90% CI of the geometric mean TEST/REFERENCE ratio obtained for C_{max} lied also within the standard acceptance interval of 80.00% - 125.00%.

Table 41: The 90% CIs MMF mean treatment Test formulation /Reference ratios.

Test name	Parameter	Test value (T /R)	Lower 90% CL	Upper 90% CL
90% CI	C_{max}	89.38	80.03	99.81
90% CI	AUC_{0-t}	101.22	96.67	105.98
90% CI	AUC_{0-inf}	103.02	98.46	107.78

The 90% CIs of C_{max}, AUC_{0-t} and AUC_{0-inf} ratios were all inside the accepted bioequivalence range, 80.00 – 125.00%, thus permitting to conclude for bioequivalence with regard to the rate of absorption and with regard to the extent of absorption for T formulation vs. R formulation. No significant difference exists for t_{max} between Test and Reference formulations.

- **Safety data**

Extent of Exposure: A total of 28 subjects received at two different occasions (i.e. replicate design) one dose of the Test formulation (tegomil fumarate 348 mg gastro-resistant capsules), and 28 subjects received at two different occasions one dose of the Reference formulation (Tecfidera® 240 mg gastro-resistant hard capsules), according to a four-period replicate design. 83 AEs of mild (68) and moderate (15) intensity occurred in seventeen (17) subjects (68%) after treatment with Test and in twenty-three (23) subjects (92%) after treatment with Reference during the present study. None of these AEs represented a SAE. All adverse events completely resolved without sequelae before the end of the study.

- Reference formulation: Following treatments with the Reference formulation 'skin hyperemia' was the most frequently reported AE, with 15 study participants (25.42%) experiencing this AE with mild intensity, and 10 study participants (16.95%) in which the AE was considered to be of moderate intensity. All events of 'skin hyperemia' were considered by the investigator as being related to treatment. Other AE reported for Reference treatment included 'feeling hot', reported by 9 study participants (15.25%) with mild intensity; 'pricking skin sensation' reported by 4 study participants (6.79%) with mild intensity. 'Itching' was reported by 3 study participants (5.08%) with mild intensity; and 'nausea' was reported by 1 study participant (1.69%) with mild intensity. All of these AEs were considered by the investigator as being related to treatment.
- Test formulation: Following treatments with the Test formulation 'skin hyperemia' was the most frequently reported adverse event, with 10 study participants (17.54%) experiencing this AE with mild intensity, and 4 study participants (7.02%) in which the AE was considered to be of moderate intensity. All events of 'skin hyperemia' were considered by the investigator as being related to treatment. Other AE reported for TEST treatment included 'feeling hot' was reported by 7 study participants (12.28%) with mild intensity. 'Pricking skin sensation' was reported by 1 study participant (1.75%) with mild intensity. 'Itching' was reported by 5 study participants (8.77%) with mild intensity; and 'nausea' was reported by 1 study participant (1.69%) with mild intensity. All of these AEs were considered by the investigator as being related to treatment. From the total number of study participants having experienced AEs, 17 subjects (68%) experienced AEs after treatment with Test, while 23 study participants (92%) experienced AEs after treatment with Reference, indicating that the number of subjects experiencing AEs was lower for Test as compared to the Reference treatment.

From the total number of AEs reported in the present study (83 AEs), 32 AEs (39.75%) occurred after the administration of the Test treatments, and 51 AEs (60.97%) occurred after the administration of the Reference treatments, indicating that also the total number of AEs reported for Test was substantially lower as compared to the Reference treatment.

The distribution of the severity rating of AEs was also well comparable between Test and Reference treatments with most study participants reporting AEs of mild intensity (17 subjects and 21 subjects for Test and Reference treatments), and 4 and 10 subjects experiencing AEs of moderate intensity Test and Reference treatments. None of the study participants experienced any AE of severe intensity.

There were also no SAE or deaths reported from the present study. The AEs noted in the present study were highly consistent with the AE pattern described for DMF in the current SPC of Tecfidera®. There were no new or hitherto unreported AEs for DMF-releasing products (e.g. Tecfidera®) observed in the present study.

There were no safety laboratory deviations and vital sign deviations observed over the course of the study that were considered to be of clinical relevance.

Pivotal Bioequivalence Study under low-fat, low-calories fed conditions defined as light meal (study MMF-BEFI-07-TFB-24): Single center, open label, four-period, two-sequence, fully replicated, randomized, controlled, single dose pivotal bioequivalence study of tegomil fumarate 348 mg gastro-resistant capsules [TEST formulation] versus equimolar dose (based on MMF release) of Tecfidera® 240 mg gastro-resistant hard capsules [REFERENCE formulation] in healthy volunteers under low-fat, low-calories fed conditions.

Methods

- **Study design**

This study was a single center, open label, four-period, two-sequence, fully replicated, randomized, controlled, single dose pivotal bioequivalence study of tegomil fumarate 348 mg gastro-resistant capsules [TEST formulation] versus equimolar dose (based on MMF release) of Tecfidera® 240 mg gastro-resistant hard capsules [REFERENCE formulation] in healthy volunteers under low-fat, low-calories fed conditions. Hospitalization of subjects until 24 hours post dose.

The main objective of the study was to evaluate the bioequivalence of the TEST formulation [Tegomil fumarate 348 mg gastro-resistant capsules (containing 348.4 mg of Tegomil fumarate)] relative to an equimolar dose (based on MMF release) of REFERENCE product [Tecfidera® 240 mg gastro-resistant hard capsules], after single oral administration under low-fat, low-calories fed conditions, and to compare the safety/tolerability profiles of the two formulations. A four-period fully replicate design was deemed most appropriate due to the high REFERENCE within-subject variability observed for C_{max} in a previously conducted single dose replicate design pivotal bioequivalence study with administration under high-fat, high-calories fed conditions (MMFBEFI- 06-TFB/22).

Products administered: one gastro resistant capsule of TEST formulation [Tegomil fumarate 348 mg gastro-resistant capsules] or one gastro-resistant hard capsule of REFERENCE formulation [Tecfidera® 240 mg gastro-resistant hard capsules], as per the randomization table. The capsules were administered orally with 200 mL of still bottled water at room temperature.

Within each study period, 5.0 mL blood samples for the quantification of MMF were drawn pre-dose and at 0.25 (15 min), 0.50 (30 min), 0.75 (45 min), 1.0, 1.5 (1 h 30 min), 2.0, 2.33 (2 h 20 min), 2.67 (2 h 40 min), 3.0, 3.33 (3 h 20 min), 3.67 (3 h 40 min), 4.0, 4.33 (4 h 20 min), 4.67 (4 h 40 min), 5.0, 5.50 (5 h 30 min), 6.0, 6.50 (6 h 30 min), 7.0, 8.0, 9.0, 10.0, 12.0 and 14.0 hours after dose administration. Washout period: 7 days between periods.

Safety: laboratory data, vital signs, electrocardiogram, and AEs.

- **Test and reference products**

Test formulation, dose and mode of administration, batch number: Tegomil fumarate 348 mg gastro-resistant capsules, Re-test date: 12/2024. Administered orally, 1 capsule with 200 ml of room temperature water, under low-fat, low-calories conditions for all subjects.

Reference product, dose and mode of administration, batch number: Tecfidera® 240 mg gastro-resistant hard capsules, MAH: Biogen Netherlands B.V., Netherlands. Country of purchase: Germany. Administered orally, 1 capsule with 200 ml of room temperature water, under low-fat, low-calories conditions, for all subjects.

- **Population(s) studied**

Healthy male and non-pregnant female volunteers, age between ≥18 years and ≤55 years, BMI ≥18.5 and ≤ 30 kg/m2.

- **Analytical methods**

Determination of MMF (in all samples). All analyses were performed by HPLC/MS/MS methods. LLOQ = 6 ng/mL and calibration range: 6 - 3000 ng/mL. Using this analytical method (FMD-BE-LCMSMS-01/16 up to revision 6.0) 4000 plasma samples have been analysed. The analytical samples collection was performed in the interval: 23.10.2024 - 15.11.2024. The study samples analytical runs were performed in the interval: 22.11.2024 - 07.12.2024. All the analysed samples were completely inside the validated stability period (up to 28 weeks). One analytical sequence, representing 2.439% from the total analytical sequences (without incurred samples sequences) has been rejected and repeated. Twenty-six (26) analytical samples (representing 0.650% from the total study samples) have been re-assayed. Other 100 samples have been re-assayed due to analytical sequence rejection (sequence 39). LLOQ concentrations monoethyl fumarate and MMF were 3.000 and 6.000 ng/ml, respectively.

In order to test the accuracy of incurred samples, two samples for each subject and study period have been selected for systematic ISR: one representing the maximum concentration and one representing the elimination phase. The results are adequate: 309 out of 320 re-assayed incurred samples (96.562%) lie within 20% of differences from the mean] and provide sufficient confidence that the study samples concentrations obtained are accurate.

- **Pharmacokinetic variables**

Primary parameters: C_{max}, $AUC_{0-t,}$ AUC_{0-inf} estimated as explained in MMF-BESD-05-TFB/22.

Secondary Parameter: t_{max} estimated as explained in MMF-BESD-05-TFB/22.

Additional Parameters: $AUC_{\%extra}$, $t_{1/2}$, Kel, MRT as defined in MMF-BESD-05-TFB/22

- **Statistical methods**

Standard descriptive statistics (arithmetic mean, harmonic mean, geometric mean, SEM, standard deviation, coefficient of variation, median, range) were performed for all PK metrics (C_{max}, AUC_{0-t}, AUC_{0-inf}, t_{max}, $AUC_{\%extra}$, $t_{1/2}$, Kel, MRT) calculated for the TEST and REFERENCE formulations from MMF plasma concentrations. Each subject was reported with two observations per each type of treatment (corresponding to first/second administration of the respective treatment as per the replicate setting) provided that the subject completed the study as planned.

The following procedures were used:

- For C_{max}, AUC_{0-t} and AUC_{0-inf}: ANOVA after logarithmic transformation (model: treatments, sequences, subject within sequence, periods of administration), classic (shortest) 90% CIs for the intra-individual ratios T/R.

- For t_{max}: Wilcoxon Signed-Rank Test.
- For $AUC_{\%extra}$, $t_{1/2}$, Kel, MRT only descriptive statistics was performed.

The standard acceptance range for bioequivalence of 80.00-125.00% was used for AUC_{0-t} and AUC_{0-inf}, while for C_{max}, the acceptance range could be widened based upon the REFERENCE within-subject variability to a maximum of 69.84-143.19%. If the within-subject CV of the REFERENCE product (or CVWR) is ≤ 30%, then the 90% CIS of the geometric mean TEST/REFERENCE ratio obtained for C_{max} should lie within an acceptance interval of 80.00% - 125.00%. If the CVWR for the REFERENCE product was > 30%, the bioequivalence acceptance limits were scaled based on the within-subject variability of the REFERENCE product. The extent of the widening was defined based upon the within-subject variability seen in the bioequivalence study using scaled-average-bioequivalence.

Safety data

- For clinical laboratory parameters screening vs. follow-up: ANOVA test.
- For vital signs at screening vs. follow-up: ANOVA test.
- Vital signs measured before and after dosing: descriptive statistic (mean, standard deviation and range).

For AEs a single sample proportion test was applied by group of treatment for the incidence of subjects having encountered Adverse Events and for the incidence of AEs a table presenting all individual data related to AEs occurrence is presented.

This was an open label but, in order to reduce bias, laboratory data were analysed in a blinded manner.

PK and statistic calculations were performed using SAS® statistical software (Version: 9.4 or higher; SAS Institute Inc., USA), using PROC GLM with fixed effects.

Sample size calculation

A number of 40 subjects were enrolled in the study. This number of subjects had been estimated taking in consideration: a) the significance level (alpha) of 0.05; b) an a priori test power of 80 %; c) an intra-subject coefficient of variation of up to 35% for the primary PK metric C_{max}; d) an expected geometric mean T/R ratio of the primary PK metric Cmax of approximately 1.11; e) the fact that for the 90% confidence interval of the geometric least square means ratio T/R for the primary PK metric C_{max}, the acceptance range can be widened based upon the REFERENCE within-subject variability; f) a potential dropout/withdrawal rate of up to 15%.

Results

- **Disposition of Subjects**

In the present study, 65 adult male and female healthy volunteers were screened. Out of all screened volunteers, 40 healthy male and female volunteers were enrolled. All 40 enrolled volunteers completed the study and all subjects underwent the follow-up examination.

For the bioequivalence assessment, PK data coming from all 40 subjects were statistically analyzed. The descriptive statistics of demographic characteristics of all 40 enrolled subjects has been performed. Safety data have been evaluated on 40 complete datasets.

- **Protocol Deviations**

There were no protocol deviations in this study.

- **Pharmacokinetic Results**

Table 42: PK parameters of MMF for reference and test formulations

MMF – Reference

N = 80	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)	AUC_{0-inf} (ng/ml*h)	AUC%extra (%)	T_{half} (hours)	K_{el} (1/Hours)	MRT (hours)
Mean	1910.662	2765.232	2799.348	1.070	0.999	1.093	4.335
GeoMean	1785.122	2665.331	2695.272	0.416	0.727	0.953	4.096
SD	667.650	749.246	774.401	2.749	1.386	0.435	1.482
CV	34.943	27.095	27.664	257.036	138.727	39.783	34.178

N = 80	T_{max} (hours)
Median	3.670
Min	1.000
Max	7.000

MMF - Test formulation

N = 80	C_{max} (ng/ml)	AUC_{0-t} (ng/ml*h)	AUC_{0-inf} (ng/ml*h)	AUC%extra (%)	T_{half} (hours)	K_{el} (1/Hours)	MRT (hours)
Mean	2016.824	2863.449	2887.535	0.896	0.999	1.018	3.869
GeoMean	1891.533	2733.233	2758.354	0.456	0.778	0.891	3.668
SD	642.044	810.752	812.289	1.685	1.024	0.420	1.261
CV	31.834	28.314	28.131	188.082	102.483	41.276	32.594

N = 80	T_{max} (hours)
Median	3.330
Min	0.750
Max	8.000

The common intra-subject variability coefficients registered for MMF, were for AUC_{0-t} = 15.54%, AUC_{0-inf} = 15.42% and for C_{max} = 36.61%. The within-subject coefficient of variation of the REFERENCE product was for C_{max} = 41.45%.

Figure 15: Mean MMF plasma concentrations following single administration of Reference (Tecfidera® 240 mg gastro-resistant hard capsules) and Test (Tegomil fumarate 348 mg gastro-resistant hard-capsules) treatments to healthy adult subjects under low-fat, low-calories fed conditions state (linear scale)

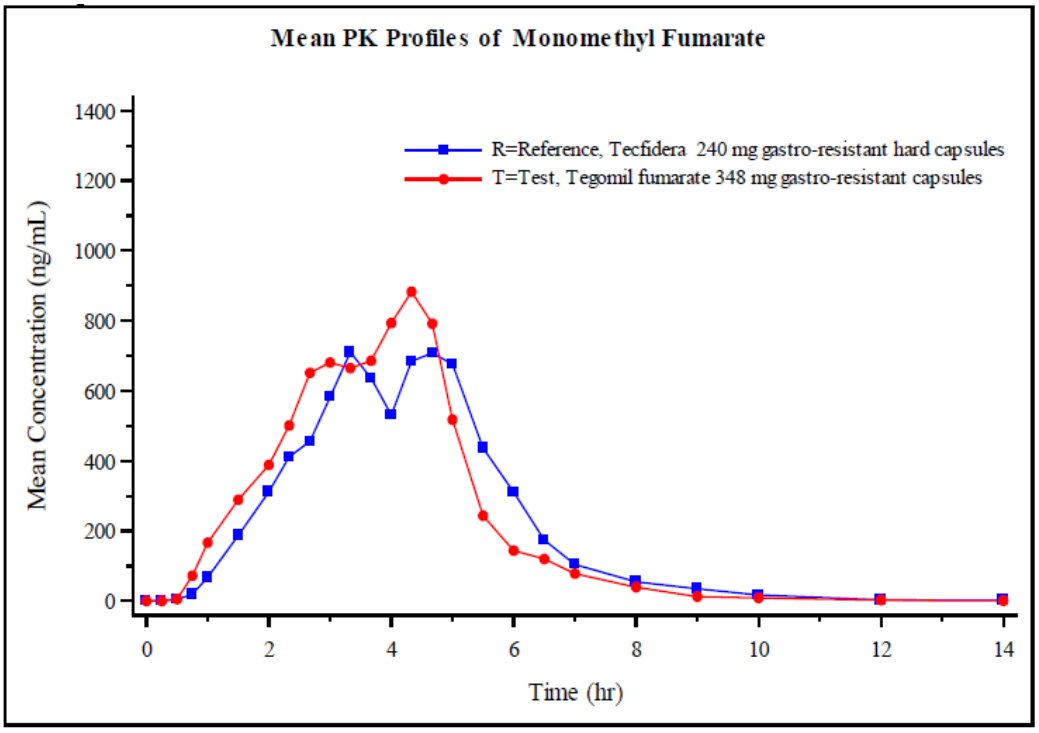
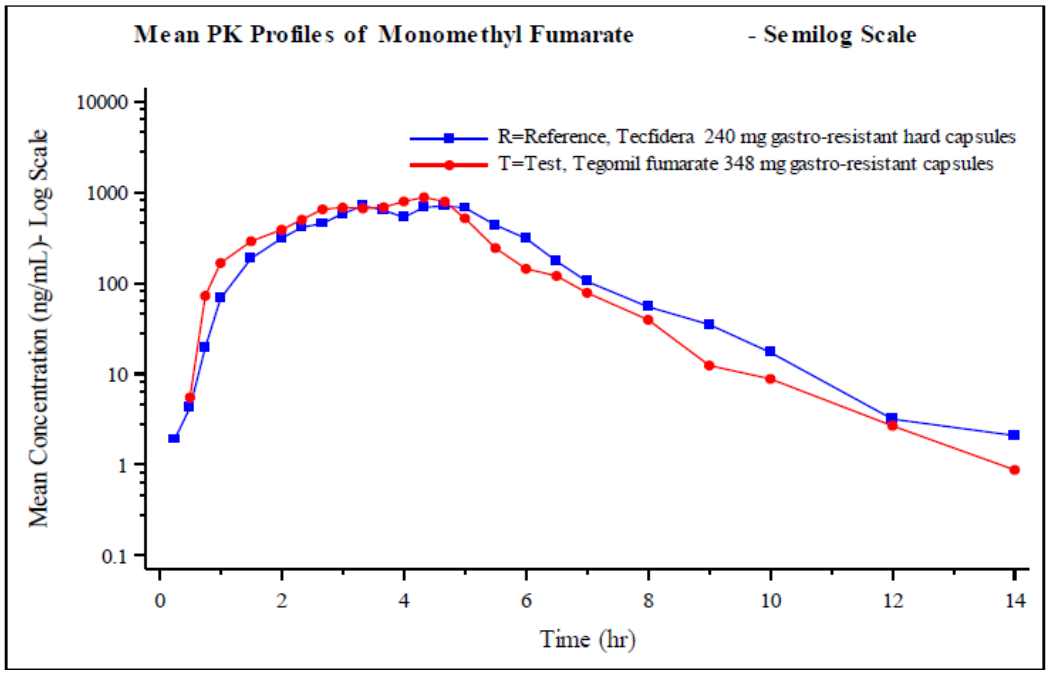


Figure 16: Mean MMF plasma concentrations following single administration of Reference (Tecfidera® 240 mg gastro-resistant hard capsules) and Test (Tegomil fumarate 348 mg gastro-resistant hard-capsules) treatments to healthy adult subjects under low-fat, low-calories fed conditions state (semi-log scale)



- **Bioequivalence assessment**

Table 43: Analysis of variance of the main MMF pharmacokinetic parameters for TEST formulation vs REFERENCE products.

Source of error	Significance level	Probability (p)		
		C_{max}	AUC_{0-t}	AUC_{0-inf}
SEQUENCE	0.10000	0.36717	0.52271	0.51900
SUBJECT(SEQUENCE)	0.05000	0.00401*	0.00000*	0.00000*
PERIOD	0.05000	0.11409	0.03365*	0.03473*
TREATMENT	0.05000	0.30395	0.30507	0.34177

* = $p<0.05$ = significant

Analysis of variance ANOVA showed no significant effect of sequence and treatment on all primary parameters. A period effect was observed on AUC0-t and AUC0-inf. A subject within sequence effect was observed on all three primary parameters. The subject-within-sequence is almost always significant, and it simply captures the difference between subjects (which are not identical) in respect to the analyzed PK parameters (Table 44).

A significant period effect may potentially arise from differences between the periods, in the physiological status of subjects and/or changes in the environmental conditions. During this study, the conditions were maintained similar for all periods, trying to minimize the occurrence of such influences. Moreover, the plasma samples of each subject of all periods were analyzed all together and in a sequence in which the plasma samples were collected excluding any chance of analytical error.

The CVWR for the REFERENCE product for C_{max} was 41.45% in this study (> 30%). Therefore, the 90% CI of the geometric mean TEST/REFERENCE ratio obtained for C_{max} should be within the scaled acceptance interval of 73.89 – 135.34% to demonstrate bioequivalence for C_{max}. However, the 90% CIS of the geometric mean TEST/REFERENCE ratio obtained for C_{max} lied also within the standard acceptance interval of 80.00% - 125.00%.

Table 44: The 90% CIs MMF mean treatment Test formulation /Reference ratios.

Test name	Parameter	Test value (T /R)	Lower 90% CL	Upper 90% CL
90% CI	C_{max}	105.96	96.55	116.29
90% CI	AUC_{0-t}	102.55	98.48	106.79
90% CI	AUC_{0-inf}	102.34	98.31	106.54

The 90% CIs of C_{max}, AUC_{0-t} and $AUC0_{-inf}$ ratios were all inside the accepted bioequivalence range, 80.00 – 125.00%, thus permitting to conclude for bioequivalence with regard to the rate of absorption and with regard to the extent of absorption for T formulation vs. R formulation.

A significant difference exists between T formulation vs. R formulation (p=0.059).

- **Pharmacokinetic conclusion**

Based on the presented bioequivalence studies Riulvy 174 mg, 348 mg gastro-resistant hard capsules can be considered bioequivalent with Tecfidera, Gastro-resistant capsule, hard 120 mg and 240 mg.

The results of study MMF-BEFI-06-TFB/22 with 348 mg formulation CAN be extrapolated to other strengths 174mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

- **Safety data**

*Extent of Exposure***:** 40 subjects received one dose of TEST formulation - Tegomil fumarate 348 mg gastro-resistant capsules and 40 subjects received one dose of REFERENCE formulation -Tecfidera® 240 mg gastro-resistant hard capsules, each formulation in two different occasions, according to a four periods replicate design. The administrations were separated by washout periods of 7 days between 2 consecutive periods.

Adverse Events: Fifty-eight (58) AEs out of which 40 of mild intensity and 18 of moderate intensity occurred in the present study. AEs occurred in twenty-five (25) out of forty (40) subjects who received the study medication in the present study, in twenty one (21) subjects after treatment with TEST (32 AEs) and eighteen (18) subjects after treatment with REFERENCE (26 AEs). These were not SAE. The volunteers that encountered the AE completely recovered before the end of the study. ANOVA test analysis of clinical laboratory parameters found four statistically significant differences regarding lower values of hemoglobin, red blood cells, hematocrit and aspartate aminotransferase and three statistically significant differences regarding higher values of platelets, creatinine and lactate dehydrogenase at follow-up vs. screening. These statistical differences are devoid of any clinical significance. Results of the ANOVA comparison for vital signs found no statistically significant difference at follow up vs. screening.

From the total of subjects having experienced AEs (25 subjects), 84% experienced AEs after treatment with TEST (21 subjects) and 72% experienced AEs after treatment with REFERENCE (18 subjects).

The total percentage of subjects encountering AEs is higher than 100% due to the fact that some subjects encountered AES after both TEST and REFERENCE treatments.

From the total of AEs that occurred in the present study (58 AEs), 55.17% of AEs occurred after the administration of TEST (32 AEs) and 44.83% of AEs occurred after the administration of REFERENCE (26 AEs).

2.4.2.2. Pharmacodynamics

No new PD studies were presented for this application.

2.4.2.3. Post marketing experience

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

2.4.3. Discussion on clinical aspects

To support the application, the applicant has submitted 3 pivotal bioequivalence studies (under fed and fasted conditions and under low-fat, low-calories fed conditions defined as light meal), and one pilot PK/safety study. Moreover, one Phase 1 GI tolerability study in HV is ongoing.

The applicant conducted a Phase 1 pilot study MMF-SAD-BA-04-TFB/21 to evaluate the safety, tolerability and PK of single ascending doses of MMF-TTEG-MMF compared to the reference product Tecfidera 120 mg (Part 1 of the Study). In the part 2 of the Study, bioavailability of three different MMF-TTEG-MMF formulations compared to the reference product Tecfidera 240mg, administered in a randomized, cross-over setting, in four periods separated by a wash-out of 7 days between one treatment and the next one was evaluated. The overall design of the Study is considered adequate. Choice of the dose, sampling time points, overall sampling time and a wash-out period of 7 days appear reasonable. The choice of the EU reference medicinal product, sourced from Germany and Austria is appropriate.

In total 56 subjects were included in the Study and dosed in Part 1 and Part 2. Samples from all included subjects were analyzed and included in the PK and statistical analysis. Inclusion and exclusion criteria are acceptable. PK variables (C_{max}, AUC_{0-t} and AUC_{0-inf} (as primary); t_{max} (as secondary); $AUC_{\%extra}$, $t_{1/2}$, Kel, MRT (as additional)) and methods are adequate. Statistical methods are acceptable. Sample size calculation can be followed.

The results of the statistical analysis of the PK data from Part 1 of the pilot study demonstrated the dose proportional increases in MMF exposure after administration of single doses of TEST formulation 1 in the 174.2 mg to 348.4 mg dose range.

However, the ANOVA analyses did not show bioequivalence between the Test 1 formulation at all evaluated strengths (174.2 mg, 217.7 mg, 261.3 mg and 348.4 mg) and the Reference product Tecfidera® 120 mg gastro-resistant hard capsules with regard both to the rate of absorption or to the extent of absorption after single dose administration under fasting conditions.

In addition to MMF, also TTEG, FA-TTEG-MMF and FA-TTEG have been identified as human metabolites. It should be noted that TTEG, FA-TTEG-MMF and FA-TTEG were assessed only in Cohort 4. However, the applicant clarified that it was decided to evaluate metabolites only in Cohort 4 since this cohort received the highest dose of tegomil fumarate and was therefore, most likely to detect any traces of these metabolites. The results demonstrating that in Cohort 4 TTEG was detected only up to 8 hours after administration and was not detected after 12 hours support this assumption.

In Part 2 of the Study an advantage of multiparticulate formulations over the monolithic formulation in terms of their lower intra-subject variability was shown. However, none of the tested formulation

showed bioequivalence with the reference product Tecfidera 240 mg. No serious or severe AE were reported during the Study. The overall safety profile of the Test product in Part 1 of the Study was generally consistent with the safety profile of the Reference product except for the highest strength of the Test product (only 1 AE was reported for this strength). Safety profile of the Test 1 formulation appears to be slightly more favourable comparted to both Test 2 and Test 3 formulations, evaluated in the Part 2. However, taking into account the limited data available, no clear conclusions can be made. Overall, no relevant differences in the safety profiles were reported between the Test and the Reference products in this Study. All evaluated formulations were well tolerated by the participating subjects.

The applicant performed a single-dose, randomised, open label, four way BE study MMF-BESD-05-TFB/22 under fasting conditions to evaluate bioequivalence of the test formulation - Tegomil fumarate 348 mg gastro-resistant capsules versus equimolar dose (based on MMF release) of Tecfidera® 240 mg gastro-resistant hard capsules [reference formulation] study in healthy volunteers. It is agreed that a four-period fully replicate design can be considered appropriate due to the high common intra-subject variability observed in a pilot single crossover pilot bioavailability study.

The washout period of 7 days is considered appropriate, taking into account that the terminal half-life of MMF is approximately 1 hour. In addition to MMF, also TTEG, FA-TTEG-MMF and FA-TTEG have been identified as human metabolites The chosen time points for blood samples collection are adequate.

The inclusion and exclusion criteria are acceptable. PK variables and methods are adequate. Statistical methods are acceptable. Sample size calculation can be followed.

In total 30 subjects were included in the study. One participant voluntarily withdrew due to personal reasons and one subject was withdrawn based on a decision of the clinical Investigator. One subject received REFERENCE formulation in Period I and III and TEST formulation in Period II. Another subject received only REFERENCE formulation in Period I.

In total samples from 29 subjects were included in the statistical analysis. Subject no 27 was excluded from the statistical analysis. Subjects no 27 was administered only the Reference product in Period 1. Exclusion of this subject is in line with the recommendations of the CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, which states that subjects in a crossover trial who do not provide evaluable data for both of the test and reference products should not be included.

A pre-dose plasma level of MMF was not detected in any sample, thus it can be concluded that the wash-out period of 7 days was long enough to avoid carry-over effect.

The point estimates and 90% CIs for the ln-transformed PK variables AUC_{0-t} and AUC_{0-inf} were within the predefined bioequivalence range of 80.00% - 125.00%. However, the point estimates and 90% CI for the ln-transformed PK variable C_{max} were not within the predefined bioequivalence range of 80.00% - 125.00%. Therefore, based on the results of the Study, the test formulation Tegomil fumarate 348 mg gastro-resistant capsules is not considered bioequivalent to the reference formulation - Tecfidera® 240 mg gastro-resistant hard capsules.

In total 118 AEs of mild (95 AE) and moderate (23 AE) intensity were reported in twenty-four subjects after treatment with Test and with Reference during the Study. The most frequently reported AEs after administration of the reference and the test formulation were skin hyperemia, feeling hot and pricking sensation. There were no SAEs or deaths reported in the study. Overall, there were no relevant differences in tolerability and safety between the test and the reference formulations reported in the Study.

The applicant conducted a single center, open label, four-period, two-sequence, fully replicated, randomized, controlled, single dose pivotal bioequivalence study of Tegomil fumarate 348 mg gastro-

resistant capsules versus equimolar dose (based on MMF release) of Tecfidera® 240 mg gastro-resistant hard capsules in healthy volunteers under low-fat, low-calories fed conditions to investigate the possible extreme conditions of administration with food according to the SmPC (administration with a light meal to administration with a high-fat meal). The overall design of the study is considered acceptable.

The 90% CIs of C_{max}, AUC_{0-t} and AUC_{0-inf} ratios were all inside the accepted bioequivalence range, 80.00 – 125.00%. Therefore, it can be concluded that bioequivalence with regard to the rate of absorption and with regard to the extent of absorption for T formulation vs. R formulation has been demonstrated under study conditions.

21 subjects and 18 subjects experienced AEs after treatment with TEST with REFERENCE products, respectively. From the total of AEs that occurred in the present study (58 AEs), 55.17% of AEs occurred after the administration of TEST (32 AEs) and 44.83% of AEs occurred after the administration of REFERENCE (26 AEs). There were 40 AE of mild intensity and 18 of moderate intensity. These were not SAEs.

The applicant performed a single-dose, randomised, open label, four way BE study MMF-BEFI-06-TFB/22 under fed conditions to evaluate bioequivalence of the test formulation - Tegomil fumarate 348 mg gastro-resistant capsules versus equimolar dose (based on MMF release) of Tecfidera® 240 mg gastro-resistant hard capsules [reference formulation] study in healthy volunteers. It is agreed that a four-period fully replicate design can be considered appropriate due to the high common intra-subject variability observed in a pilot single crossover pilot bioavailability study. The washout period of 7 days is considered appropriate, taking into account that the terminal half-life of MMF is approximately 1 hour. The chosen time points for blood samples collection are appropriate. The choice of the EU reference medicinal product, sourced from Germany is appropriate.

The inclusion and exclusion criteria are acceptable. PK variables ($C_{max,}$ AUC_{0-t} and AUC_{0-inf} (as primary); t_{max} (as secondary); $AUC_{\%extra}$, $t_{1/2}$, Kel, MRT (as additional)) and methods are adequate. Statistical methods are acceptable. Sample size calculation can be followed.

In total 30 subjects were included in the Study. Two participants voluntarily withdrew due to personal reasons. One of the subjects who withdrew received only REFERENCE formulation in Period I. The other subject received REFERENCE formulation in Period I and III and TEST formulation in Period II.

In total samples from 29 subjects were included in the statistical analysis. This is in line with the recommendations of the CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, which states that subjects in a crossover trial who do not provide evaluable data for both of the test and reference products should not be included. A pre-dose plasma level of MMF was not detected in any sample, thus it can be concluded that the wash-out period of 7 days was long enough to avoid carry-over effect.

The point estimates and 90% CIs for the ln-transformed PK variables AUC_{0-t}, AUC_{0-inf} and C_{max} were within the predefined bioequivalence range of 80.00% - 125.00%. Therefore, based on the results of the Study, the test formulation Tegomil fumarate 348 mg gastro-resistant capsules is considered bioequivalent to the reference formulation - Tecfidera® 240 mg gastro-resistant hard capsules.

In total 83 AEs of mild (68 AE) and moderate (15 AE) intensity were reported in twenty-four subjects after treatment with Test and with Reference during the Study. The most frequently reported AEs after administration of the reference and the test formulation were skin hyperemia, feeling hot and pricking sensation. There were no SAEs or deaths reported in the study. Overall, there were no relevant differences in tolerability and safety between the test and the reference formulations reported in the Study.

In dissolution studies the dissolution profiles of the biobatch Tegomil fumarate capsules 348 mg was

similar to other dosage strength 174 mg in 0.1N HCl followed by phosphate buffer solution pH 6.8 at 50 rpm. The dissolution profiles of the biobatch tegomil fumarate capsules 348 mg was similar to other dosage strength 174 mg in acetate buffer solution pH 4.5 followed by phosphate buffer solution pH 6.8 at 50 rpm.

In the context of a hybrid application, it should be demonstrated that there are no significant differences in safety and efficacy between the active substance in the hybrid medicinal product (tegomil fumarate) and that included in the reference medicinal product (dimethyl fumarate). As per Article 10(2)b of Directive 2001/83/EC, "(…) The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.

Tegomil fumarate is a double ester of MMF with TTEG. Tegomil fumarate undergoes rapid pre-systemic hydrolysis by non-specific esterases to MMF-TTEG-FA, FA-TTEG and MMF-TTEG as intermediate metabolites and to MMF and TTEG and FA as ultimate metabolites. FA is also a well-known demethylation product, that occurs during DMF metabolism. Even in the event intermediate metabolites become systemically available they will eventually undergo the same metabolic pathway with MMF, TTEG and FA as ultimate metabolites. In fact, TK analysis identified MMF and TTEG as major metabolites at steady state. Overall, the only major difference between tegomil fumarate and DMF breakdown is TTEG which is formed instead of methanol.

TTEG is a non-active compound. MMF is the only active moiety for DMF and TMF. Based on the presented bioequivalence studies Riulvy 174 mg, 348 mg gastro-resistant hard capsules can be considered bioequivalent with Tecfidera, Gastro-resistant capsule, hard 120 mg and 240 mg. Accordingly, it is considered that the two active substances do not substantially differ in efficacy.

TTEG is used as excipient in pharmaceutical products for oral or topical administration. It is listed in FDA's Inactive Ingredient Database for oral use in extended-release tablets, capsules or solutions (December 2023). According to the applicant's results TTEG was rapidly eliminated from blood with a half-life ranging between 1 – 2 hours across the dosing groups. Results from HV showed that exposure to TTEG was <LOQ at 10 hours post dose in 7 out of 8 subjects it can be agreed that TTEG is efficiently removed from systemic circulation in human. Accordingly, the risk for accumulation of TTEG following repeated administration of Tegomil fumarate can be expected to be very low. No risk for accumulation of TTEG following repeated administration has been expected. The systemic toxicity of TTEG has been evaluated as part of the comparative 90-day repeated dose toxicity study performed with Tegomil fumarate and DMF. As reported before, TK results for TTEG showed $AUC_{0\text{-last}}$ of 88.2 and 71.4 µg.h/mL at the NOAEL of 290.2 mg/kg tegomil fumarate. C_{max} were 17.2 and 22.7 µg/mL for males and females, respectively, at Day 90. In the FIH/pilot study with tegomil fumarate in healthy volunteers, mean C_{max} in plasma was 1.67 µg/mL and $AUC_{0\text{-}\infty}$ 4.34 µg/mL.h were observed following a single oral dose of 348.4 mg. Accordingly, plasma exposure during clinical use is adequately covered by the existing toxicology study with tegomil fumarate, where a comparable safety profile between tegomil fumarate and DMF has been observed in all bioequivalence studies. The applicant's justification can be followed. Accordingly, it is considered that the two active substances do not substantially differ in safety.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence studies Riulvy 174 mg, 348 mg gastro-resistant hard capsules can be considered bioequivalent with Tecfidera, Gastro-resistant capsule, hard 120 mg and 240 mg.

According to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms, for delayed release multiple unit formulation for which the SmPC recommends intake under fed conditions, bioequivalence should be shown under fasting and fed conditions.

Bioequivalence is not shown for C_{max} under fasting conditions. However, the applicant performed a single center, open label, four-period, two-sequence, fully replicated, randomized, controlled, single dose pivotal bioequivalence study of tegomil fumarate 348 mg gastro-resistant capsules versus equimolar dose (based on MMF release) of Tecfidera® 240 mg gastro-resistant hard capsules in healthy volunteers under low-fat, low-calories fed conditions to investigate the possible extreme conditions of administration with food according to the SmPC (administration with a light meal to administration with a high-fat meal).

The 90% CIs of C_{max}, AUC_{0-t} and AUC_{0-inf} ratios were all inside the accepted bioequivalence range, 80.00 – 125.00%. Therefore, it can be concluded that bioequivalence with regard to the rate of absorption and with regard to the extent of absorption for T formulation vs. R formulation has been demonstrated under study conditions.

The results of study MMF-BEFI-06-TFB/22 with 348mg formulation can be extrapolated to other strengths 174mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

Based on the presented bioequivalence study(ies) RYULVI is considered bioequivalent with Tecfidera.

In the context of a hybrid application, it should be demonstrated that there are no significant differences in safety and efficacy between the active substance in the hybrid medicinal product (tegomil fumarate) and that included in the reference medicinal product (dimethyl fumarate). The applicant has justified that tegomil fumarate does not differ significantly in properties with regards to safety and efficacy compared to the active substance of the reference medicinal product (dimethyl fumarate). This was accepted by the CHMP. This is in accordance with the relevant guideline and additional non-clinical studies were not considered necessary.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 45: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Progressive Multifocal Leukoencephalopathy (PML)
Important potential risks	Malignancies Effects on pregnancy outcome
Missing information	Long term efficacy and safety Safety profile in patients with moderate to severe renal impairment

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

The safety information in the proposed product information is aligned to the reference medicinal product.

No additional risk minimisation measures were proposed by the applicant, which is considered acceptable.

2.5.4. Conclusion

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

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

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

2.6.2. Periodic Safety Update Reports submission requirements

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

Since the major active metabolite MMF was established to be the same for tegomil fumarate as for dimethyl fumarate, tegomil fumarate should be added to the entry for dimethyl fumarate (multiple sclerosis) in the EURD list.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Capecitabin Tiefenbacher 500 mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a hybrid version of Tecfidera (dimethyl fumarate) 120 mg and 240 mg, gastro-resistant hard capsule. The reference medicinal product Tecfidera is indicated for the treatment of adult and paediatric patients aged 13 years and older with RRMS. Non-clinical studies have been provided for this application and considered sufficient. From a clinical perspective, this application does not contain new data on the 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.

To support the application, the applicant has submitted 3 pivotal bioequivalence studies (under fed and fasted conditions and under low-fat, low-calories fed conditions), and one pilot PK/safety study. Moreover, one Phase 1 GI tolerability study in HV is ongoing.

The applicant conducted a Phase 1 pilot study MMF-SAD-BA-04-TFB/21 to evaluate the safety, tolerability and PK of single ascending doses of MMF-TTEG-MMF compared to the reference product

Tecfidera 120 mg (Part 1 of the Study). In the part 2 of the Study, bioavailability of three different MMF-TTEG-MMF formulations compared to the reference product Tecfidera 240mg, administered in a randomized, cross-over setting, in four periods separated by a wash-out of 7 days between one treatment and the next one was evaluated. The overall design of the Study is considered adequate. Choice of the dose, sampling time points, overall sampling time and a wash-out period of 7 days appear reasonable. The results of the statistical analysis of the PK data from Part 1 of the pilot study demonstrated the dose proportional increases in MMF exposure after administration of single doses of TEST formulation 1 in the 174.2 mg to 348.4 mg dose range. However, the ANOVA analyses did not show bioequivalence between the Test 1 formulation at all evaluated strengths (174.2 mg, 217.7 mg, 261.3 mg and 348.4 mg) and the Reference product Tecfidera® 120 mg gastro-resistant hard capsules with regard both to the rate of absorption or to the extent of absorption after single dose administration under fasting conditions.

The applicant performed a pivotal single-dose, randomised, open label, four way bioequivalence study MMF-BESD-05-TFB/22 under fasting conditions to evaluate bioequivalence of the test formulation - Tegomil fumarate 348 mg gastro-resistant capsules versus equimolar dose (based on MMF release) of Tecfidera® 240 mg gastro-resistant hard capsules [reference formulation] study in 30 healthy male and non-pregnant female subjects, aged between ≥ 18 years and ≤ 55 years, BMI ≥ 18.5 and ≤ 30 kg/m2. In total samples from 29 subjects were included in the statistical analysis. A pre-dose plasma level of MMF was not detected in any sample, thus it can be concluded that the wash-out period of 7 days was long enough to avoid carry-over effect. The point estimates and 90% CIs for the ln-transformed PK variables AUC_{0-t}, AUC_{0-inf} were within the predefined bioequivalence range of 80.00% - 125.00%. However, the point estimates and 90% CIs for the ln-transformed PK variable C_{max} were not within the predefined bioequivalence range of 80.00% - 125.00%. Overall, there were no relevant differences in tolerability and safety between the test and the reference formulations reported in the Study.

The bioequivalence study MMF-BEFI-06-TFB/22 forms the pivotal basis with a single-dose, randomised, open label, four way BE study under fed conditions to evaluate bioequivalence of the test formulation - Tegomil fumarate 348 mg gastro-resistant capsules versus equimolar dose (based on MMF release) of Tecfidera® 240 mg gastro-resistant hard capsules [reference formulation] study in healthy male and non-pregnant female subjects, aged between ≥ 18 years and ≤ 55 years, BMI ≥ 18.5 and ≤ 30 kg/m2. The study design is considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. PK and statistical methods applied were adequate. The test formulation of tegomil fumarate met the protocol-defined criteria for bioequivalence when compared with the Tecfidera. The point estimates and their 90% CIs for the parameters C_{max}, AUC_{0-t} and AUC_{0-inf} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

The applicant conducted a single center, open label, four-period, two-sequence, fully replicated, randomized, controlled, single dose pivotal bioequivalence study of tegomil fumarate 348 mg gastro-resistant capsules versus equimolar dose (based on MMF release) of Tecfidera® 240 mg gastro-resistant hard capsules in healthy volunteers under low-fat, low-calories fed conditions to investigate the possible extreme conditions of administration with food according to the SmPC (administration with a light meal to administration with a high-fat meal). The overall design of the study is considered acceptable. The 90% CIs of C_{max}, AUC_{0-t} and AUC_{0-inf} ratios were all inside the accepted bioequivalence range, 80.00 – 125.00%. Therefore, it can be concluded that bioequivalence with regard to the rate of absorption and with regard to the extent of absorption for T formulation vs. R formulation has been demonstrated under study conditions.

In the context of a hybrid application, it should be demonstrated that there are no significant

differences in safety and efficacy between the active substance in the hybrid medicinal product (tegomil fumarate) and that included in the reference medicinal product (dimethyl fumarate). As per Article 10(2)b of Directive 2001/83/EC, "(…) The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.".

Tegomil fumarate is a double ester of MMF with TTEG. Tegomil fumarate undergoes rapid pre-systemic hydrolysis to MMF and TTEG and FA as ultimate metabolites. Overall, the only major difference between tegomil fumarate and DMF breakdown is TTEG which is formed instead of methanol.

TTEG is a non-active compound. MMF is the only active moiety for DMF and TMF and bioequivalence has been demonstrated. Accordingly, it is considered that the two active substances do not significantly differ in efficacy.

TTEG is used as excipient in pharmaceutical products for oral or topical administration. Based on study results from the applicant and available literature, no relevant toxicity has been observed linked to TTEG exposition. Further, safety data has been evaluated in bioequivalence studies supporting similar safety profile between tegomil fumarate and dimethyl fumarate. Accordingly, it is considered that the two active substances do not significantly differ in safety.

A benefit/risk ratio comparable to the reference product is considered positive.

Having considered the data submitted in the application and available on the chosen reference medicinal product, 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 Riulvy is favourable in the following indication:

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

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

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

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.