21 March 2024
EMA/146707/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dimethyl fumarate Accord

International non-proprietary name: dimethyl fumarate

Procedure No. EMEA/H/C/006471/0000

Note

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

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

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List of abbreviations

AE	Adverse Events
ANOVA	Analysis of Variance
ASMF	Active Substance Master File = Drug Master File
AUC_{0-t}	Area under the plasma concentration versus time curve from time zero to the last measurable concentration
$AUC_{0-\infty}$	Area under the plasma concentration versus time curve from time zero to infinity
AUC_%Extrap_obs	Residual area in percentage
BCS	Biopharmaceutics Classification System
BMI	Body mass index
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Intervals
C_{max}	Maximum measured plasma concentration
CQA	Critical Quality Attribute
CV	Coefficient of Variation
DoE	Design of experiments
DSC	Differential Scanning Calorimetry
EC	European Commission
ECG	Electrocardiogram
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EU	European Union
GC	Gas Chromatography
GMR	Geometric least square mean ratio
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
KF	Karl Fischer titration
NLT	Not less than
NMR	Nuclear Magnetic Resonance
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PD	Pharmacodynamic
PSD	Particle size distribution
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride

QbD	Quality by design
QTTP	Quality target product profile
SmPC	Summary of Product Characteristics
SWR	within subject standard deviation of reference product
RH	Relative Humidity
RMP	Risk Management Plan
RRMS	Relapsing Remitting Multiple Sclerosis
t_{max}	Time to reach the maximum concentration of drug in plasma
T_{lag}	Time prior to the first measurable (non-zero) concentration
λz	First order rate constant associated with the terminal (log-linear) portion of the curve
t½	elimination half-life
TSE	Transmissible Spongiform Encephalopathy
UV	Ultraviolet
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The Applicant Accord Healthcare submitted on 2 January 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Dimethyl fumarate Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004 – 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 June 2021.

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

The Applicant applied for the following indication:

> Dimethyl fumarate Accord 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:

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

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

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Tecfidera, 120 mg and 240 mg gastro-resistant hard capsules
- 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/1/13/837/002-003

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

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

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

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

- Product name, strength, pharmaceutical form: Tecfidera, 120 mg and 240 mg gastro-resistant hard capsules
- 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/1/13/837/002-003
- Bioavailability study number(s): 0856-16, 0857-16, 0002-21, 0003-21

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	2 January 2024
The procedure started on	22 January 2024
The Rapporteurs first CHMP and PRAC Joint Assessment Report was circulated to all CHMP and PRAC members on	23 February 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	7 March 2024
The CHMP members comments on	11 March 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint updated Assessment Report to all CHMP members on	13 March 2024

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Dimethyl fumarate Accord on	21 March 2024

2. Scientific discussion

2.1. Introduction

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

The reference product is Tecfidera 120 mg and 240 mg gastro-resistant hard capsules. Tecfidera was approved in Europe on 30 January 2014 (EU/1/13/837/001-003, Biogen Netherlands B.V.).

The proposed indication for Dimethyl fumarate Accord is the same as for the reference product Tecfidera:

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

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

2.2. Quality aspects

2.2.1. Introduction

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

Other ingredients are:

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

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

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

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

2.2.2. Active substance

2.2.2.1. General Information

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

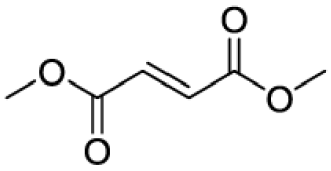

Figure 1: Active substance structure

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

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

2.2.2.2. Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturing site. Dimethyl fumarate is synthesized in 4 main steps using well defined starting material with acceptable specifications. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

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

The impurity profile of dimethyl fumarate has been evaluated with respect to the starting material, raw materials/reagents, intermediates and process. A discussion concerning possible organic and inorganic impurities, potential genotoxic impurities (including nitrosamines), elemental impurities and residual solvents has been presented and supported by analytical data. The information provided is considered adequate.

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

2.2.2.3. Specification

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

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

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

Batch analysis data on 6 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

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

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

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

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

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

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

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

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

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

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

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

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

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

The selection of the dissolution media is based on the dosage form design, solubility characteristics and PK profile of the active substance and uses the compendial medium for gastro-resistant dosage forms (Ph. Eur. 2.9.3). The discriminatory power of the dissolution method has been adequately demonstrated by comparing dissolution profiles of batches made with minor changes to the manufacturing process, or with minor changes to the formulation.

In vitro dissolution profiles comparison of the test and reference product were presented for both strengths, 120 and 240 mg, at the acid stage (0.1N HCl) followed by buffer stage (pH 6.8 phosphate buffer) and at the acid stage (pH 4.5 acetate buffer) followed by buffer stage (pH 6.8 phosphate buffer). *In vitro* dissolution profiles of the test and reference product were considered comparable for both strengths. Four bioequivalence studies were conducted under fasting and fed conditions to compare the PK profiles and to demonstrate bioequivalence of the test and reference products. The formulations of the test product and reference products are considered comparable. Minor differences in the used excipients have been shown to be non-significant and do not impact dissolution or bioequivalence of the product.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with exception of the silicified microcrystalline cellulose which complies with USP/NF. Empty hard gelatin capsule shells are tested according to the established in-house specification, the colorants used in capsule shells and printing ink comply with the directive (EU) No. 231/2012. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

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

The primary packaging is PVC/PE/PVDC-Alu blisters. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.

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

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

2.2.3.3. Product specification

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

The finished product specifications are in line with ICH Q6A. The limits for impurities are acceptable according to ICH Q3B. The limits for residual solvents are in accordance with ICH Q3C.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Additionally, batch

analysis data on three finished product batches per strength using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

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

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

Batch analysis results are provided for three production scale batches of 120 mg and four production scale batches of 240 mg capsules confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

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

2.2.3.4. Stability of the product

Stability data from 6 production scale batches of finished product (3 batches of 120 mg and 3 batches of 240 mg) stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Additional data from 1 production scale batch of finished product (240 mg) stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines was provided.

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

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

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

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

2.2.3.5. Adventitious agents

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

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

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

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

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics (PK) and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, PK and toxicology data. Pharmacodynamic, pharmacokinetic and toxicological properties of dimethyl fumarate are well known. As dimethyl fumarate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate. The non-clinical aspects of the Summary of Product Characteristics (SmPC) are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

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

2.3.2. Ecotoxicity/environmental risk assessment

The Applicant submitted Environmental Risk Assessment.

Dimethyl fumarate active-product-ingredient (API) consumption data covering the years 2018- 2021 (IMS data base) does not show a significant increase of API consumption during last four-year period for the combined sales volume. Considering this fact, the applicant did not submit a complete ERA.

Thus, the dimethyl fumarate gastro-resistant capsules are unlikely to represent a risk for the environment following its prescribed usage in patients.

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

Table 1: Summary of main study results

Substance (INN/Invented Name): dimethyl fumarate					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	0.77			Potential PBT (N)
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)	0.036	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} =			List all values
Ready Biodegradability Test	OECD 301				
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	2000	µg/L	

2.3.3. Discussion on non-clinical aspects

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

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

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

2.3.4. Conclusion on the non-clinical aspects

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

2.4. Clinical aspects

2.4.1. Introduction

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

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

GCP aspect

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

Exemption

Biowaiver Request for different strengths

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

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

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

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

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

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

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

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

Considering above, it can be inferred that the test and reference product depicts comparable and complete release at 75 rpm and the proposed dissolution specification is achievable.

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

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

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

- **Tabular overview of clinical studies**

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

Table 12: Tabular overview of clinical studies

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
BE	0856-16	• m5-3-1-2-vol 1 of 3 • m5-3-1-2-vol 2 of 3 • m5-3-1-2-vol 3 of 3	An open label, balanced, randomized, two-treatment, two-sequence, single oral dose, full replicate, bioequivalence study of two products of Dimethyl Fumarate 120 mg gastro-resistance hard capsules in normal, healthy, adult, human subjects under fasting condition.	Four period, single oral dose, full replicate, bioequivalence Study, Fasting condition	Dimethyl Fumarate 120 mg gastro-resistance hard capsules, single dose, Oral	46	Healthy, adult, Human subjects	Single dose	Complete; Full
BE	0857-16	• m5-3-1-2-vol 1 of 3 • m5-3-1-2-vol 2 of 3 • m5-3-1-2-vol 3 of 3	An open label, balanced, randomized, two-treatment, two-sequence, single oral dose, full replicate, bioequivalence study of two products of Dimethyl Fumarate 120 mg gastro-resistance hard capsules in normal, healthy, adult, human subjects under fed condition.	Four period, single oral dose, full replicate, bioequivalence Study, Fed condition	Dimethyl Fumarate 120 mg gastro-resistance hard capsules, single dose, Oral	47	Healthy, adult, Human subjects	Single dose	Complete; Full
BE	0002-21	• m5-3-1-2-vol 1 of 3 • m5-3-1-2-vol 2 of 3 • m5-3-1-2-vol 3 of 3	An open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, crossover, fully replicate, bioequivalence study of Dimethyl Fumarate Gastro-Resistant Capsules 240 mg of Intas Pharmaceuticals Ltd., India with TECFIDERA® (Dimethyl fumarate) Gastro-Resistant Capsules 240 mg of Biogen Idec Ltd., Innovation House, 70 Norden Road, Maidenhead, Berkshire, SL6 4AY, United Kingdom in normal, healthy, adult human subjects under fasting condition	Four period, single oral dose, full replicate, bioequivalence study, fasting condition	Dimethyl Fumarate Gastro-Resistant Capsules 240 mg, single dose, Oral	46	Healthy, adult, human subjects	Single dose	Complete full
BE	0003-21	• m5-3-1-2-vol 1 of 3 • m5-3-1-2-vol 2 of 3 • m5-3-1-2-vol 3 of 3	An open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, crossover, fully replicate, bioequivalence study of Dimethyl Fumarate Gastro-Resistant Capsules 240 mg of Intas Pharmaceuticals Ltd., India with TECFIDERA® (Dimethyl fumarate) Gastro-Resistant Capsules 240 mg of Biogen Idec Ltd., Innovation House, 70 Norden Road, Maidenhead, Berkshire, SL6 4AY, United Kingdom in normal, healthy, adult human subjects under fed condition	Four period, single oral dose, full replicate, bioequivalence study, fed condition	Dimethyl Fumarate Gastro-Resistant Capsules 240 mg, single dose, Oral	42	Healthy, adult, human subjects	Single dose	Complete full

No pharmacodynamic and therapeutic equivalence studies were submitted.

According to the Dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg product-specific bioequivalence guidance (EMA/CHMP/421315/2017) bioequivalence study for 120 mg strength is not

required.

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

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

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

Methods

- **Study design**

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

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

All the subjects were administered the study drug in each period except the discontinued/ withdrawn subjects (3 subjects). The sequence of administration was determined by the randomization schedule. A washout period of 4 days was maintained between the successive dosing days. The duration of the clinical part of the study was about 14 days (11 hours prior to the dose administration in Period-I until the last PK sample in Period-IV). Dosing dates period I (23 January 2018), period II (27 January 2018), period III (31 January 2018) and period IV (04 February 2018).

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

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

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

- **Test and reference products**

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

- **Population(s) studied**

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

- **Analytical methods**

Validation of method for the determination of monomethyl fumarate in human plasma using LCMS/ MS (AB SCIEX API 6500). MV(C)-086-18.

The objective was to validate a reliable LC-MS/MS method for the determination of the monomethyl fumarate in human plasma. A validation was performed to approve reliable detection of analyte during clinical studies – 0856-16, 0857-16. The method was found to be reliable for monomethyl fumarate in the range of 10.013 ng/mL to 6004.873 ng/mL. The LLOQ was set to 10.013 ng/mL. During validation following parameters were addressed and met the acceptance criteria for monomethyl fumarate: within-run precision (intra-day precision, ranged from 0.8 % to 4.3 %); between-run precision (inter-day precision, ranged from 1.4 % to 4.0 %); within-run accuracy (intra-day accuracy, ranged from 88.9 % to 101.6 %), between-run accuracy (inter-day accuracy, ranged from 88.4 % to 100.3 %); selectivity (six normal, two hemolyzed and two lipemic, in the presence of metabolites); and recovery. Stability was approved for stock solution of the drug at 4°C for 13 days, spiking solution at lower and higher level, auto sampler / wet extract stability after storage at 7°C ± 4°C for 74.0 hours; analyte stability for 229 days in human plasma at -70 ± 10°C. Lipemia and hemolysis did not affected monomethyl fumarate analysis. No matrix and carryover effects were found.
All parameters recommended for analytical method validation using chromatographic tandem mass spectrometric method were addressed (EMEA/CHMP/EWP/192217/2009) and met the acceptance criteria.

Validation of method for the determination of Monomethyl fumarate in human plasma using LCMS/ MS (waters quattro premier XE). MV(I)-182-16

The objective was to validate a reliable LC-MS/MS method for the determination of the monomethyl fumarate in human plasma. A validation was performed to approve reliable detection of analyte during clinical studies – 0856-16, 0857-16, 0002-21 and 0003-21. The method was found to be reliable for monomethyl fumarate in the range of 10.006 to 6005.758 ng/mL. The LLOQ was set to 10.006 ng/mL. During validation following parameters were addressed and met the acceptance criteria for monomethyl fumarate: within-run precision (intra-day precision, ranged from 1.2 % to 8.9 %); between-run precision (inter-day precision, ranged from 3.0 % to 7.9 %); within-run accuracy (intra-day accuracy, ranged from 91.5 % to 98.7 %); between-run accuracy (inter-day accuracy, ranged from 95.9 % to 101.5 %); robustness and ruggedness; recovery; selectivity (six normal, two hemolyzed and two lipemic, in the presence of metabolites and in the presence of co-administered drugs); recovery; and re-injection reproducibility.
Stability was approved for stock solution of drug at RT for 9.0 hours and at 2 to 8 °C for 7 days, spiking solution at lower and higher level at 2 to 8°C for 6 days and RT for 9.0 hours, stability in whole human blood; auto sampler / wet extract stability after storage at 2 to 8°C for 82.0 hours; four freeze thaw stability; for analyte for 96 days at -65 ± 10°C and 98 days at -22 ± 5°C in human plasma containing K_2EDTA as an anticoagulant. The methods was found valid when using monomethyl fumarate-d5 as an internal standard. Lipemia and hemolysis did not affected monomethyl fumarate analysis. No matrix effect was found.
The Applicant provided results the long term stability of analyte, monomethyl fumarate, in human plasma for 229 days at -70 ± 10°C during method validation MV (C)-086-18. The generated stability results

cover the duration of study (that is 102 days and 122 days for 0856-16 and 0857-16 respectively). The experiment performed during this partial validation is acceptable. The experiment proves that the analyte is stable for 229 days in human plasma at -70 ± 10°C.

Bioanalytical report was provided by the Applicant as support clinical study 0856-16 for monomethyl fumarate detection in human plasma. The analysis was performed according to the validation MV(I)-182-16 and MV(C)-086-18.

Human plasma samples (n= 4810) were analyzed for monomethyl fumarate. The samples were stored for 102 days at -70°C. The calibration curve exhibited acceptable precision (1.2% to 2.4%) and accuracy (98.3% to 101.5%), and QC samples met the criteria for acceptability. A total of 58 runs were analyzed, with one unacceptable. ISR was performed for 300 samples. The ISR is considered acceptable, as 98.7% of the repeated results fell within the acceptance criteria of 20%. The results were BLQ at pre dose and were within range of the detection after dosing. The LLOQ was less than 5% of Cmax for all subjects.

- **Pharmacokinetic variables**

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

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

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

- **Statistical methods**

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

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

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

Criteria for conclusion of bioequivalence are as follows:

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

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

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

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

the regulatory constant set to 0.760 and SWR is the within-subject standard deviation of the ln transformed values of C_{max} of the reference product.

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

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

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

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

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

Determination of Sample Size

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

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

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

Results

- **Disposition of subjects**

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

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

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

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

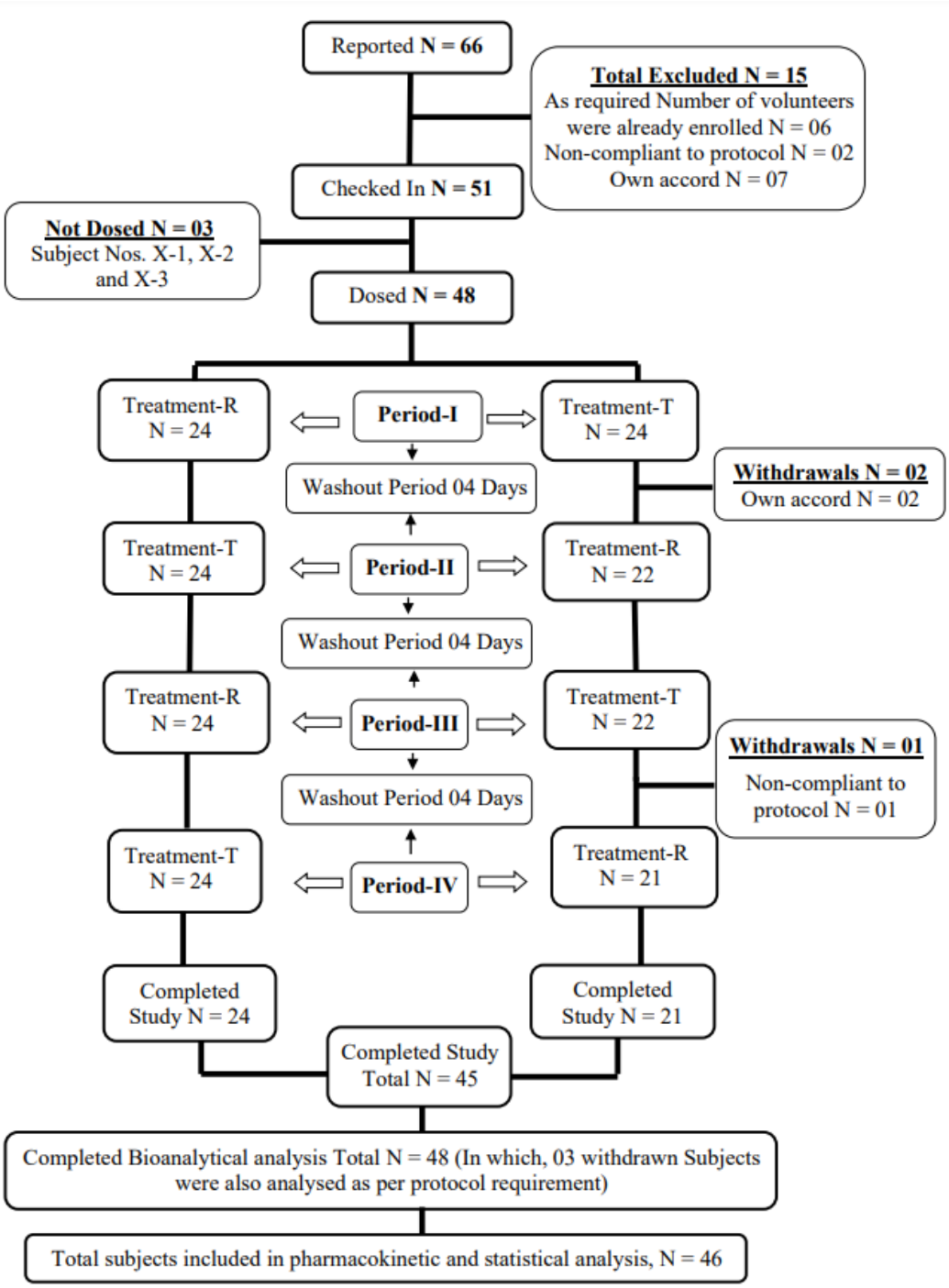

Figure 2: Participants flow - Study 0856-16

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

- **Data sets analyzed**

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

- **Pharmacokinetic results**

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

Table 23: Descriptive Statistics of Formulation Means for Monomethyl fumarate (N = 46) - Study 0856-16

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

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

- **Statistical Analysis**

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

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

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

Table 34: Intra-subject CV and Within-Subject Standard Deviation of Reference Product for Monomethyl fumarate (N = 90 Observations) - Study 0856-16

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

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

Table 45: Relative Bioavailability Results for Monomethyl fumarate (N = 46) - Study 0856-16

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

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

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

Table 6: ANOVA p-values for Monomethyl fumarate - Study 0856-16

ANOVA p-values for Monomethyl fumarate

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

Note: Significant value if p-value < 0.05.

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

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

- **Safety data**

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

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

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

Methods

- **Study design**

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

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

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

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

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

- **Test and reference products**

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

- **Population(s) studied**

Same eligibility criteria as Study 0856-16.

- **Analytical methods**

Bioanalytical report was provided by the Applicant as support clinical study 0857-16 for monomethyl fumarate detection in human plasma. The analysis was performed according to the validation MV(I)-182-16 and MV(C)-086-18 (for method validation details please see study 0856-16).
Human plasma samples (n= 5409) were analyzed for monomethyl fumarate. The samples were stored for 112 days at -70°C. The calibration curve exhibited acceptable precision (1.1% to 2.2%) and accuracy (98.9% to 100.7%), and QC samples met the criteria for acceptability. A total of 53 runs were analyzed, with one unacceptable. ISR was performed for 329 samples. The ISR is considered acceptable, as 98.8% of the repeated results fell within the acceptance criteria of 20%. The results were BLQ at pre dose and were within range of the detection after dosing. The LLOQ was less than 5% of Cmax.

- **Pharmacokinetic variables**

Same as Study 0856-16.

- **Statistical methods**

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

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

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

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

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

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

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

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

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

Determination of Sample Size

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

A sample size of 36 subjects were required to establish bioequivalence between formulations with adequate power. Considering approximately 25% dropouts and/or withdrawals, a sample size of 48 subjects were to be sufficient to establish bioequivalence between formulations with adequate power for the pivotal fully replicated study.

Results

- **Disposition of subjects**

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

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

No female volunteers were checked in for the study.

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

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

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

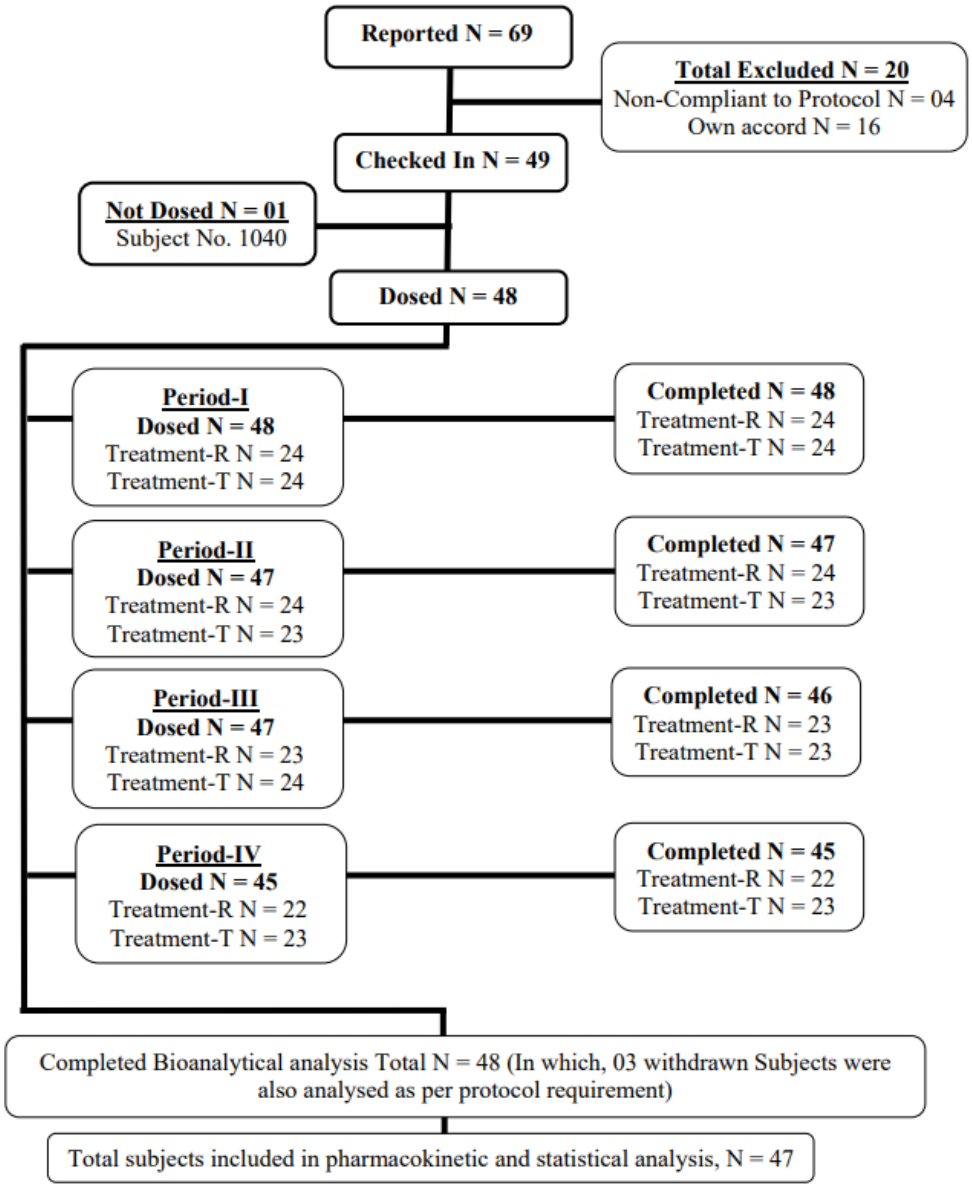

Figure 3: Participants flow - Study 0857-16

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

- **Data sets analyzed**

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

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

In total 47 subjects were included in the PK and statistical analysis.

There were no missing samples during the conduct of study.

- **Pharmacokinetic results**

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

Table 7: Descriptive Statistics of Formulation Means for Monomethyl fumarate (N = 47) - Study 0857-16

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

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

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

Table 8: Intra-subject CV and Within-Subject Standard Deviation of Reference Product for Monomethyl fumarate (N = 90 Observations) - Study 0857-16

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

Table 9: Relative Bioavailability Results for Monomethyl fumarate (N = 47) - Study 0857-16

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

* N=92 observations

Table 10: ANOVA p-values for Monomethyl fumarate - Study 0857-16

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

Note: Significant value if p-value < 0.05.

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

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

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

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

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

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

- **Safety data**

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

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

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

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

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

Methods

- **Study design**

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

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

The capsule was swallowed whole without chewing or crushing.

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

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

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

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

- **Test and reference products**

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

- **Population(s) studied**

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

- **Analytical methods**

Bioanalytical report was provided by the Applicant as support clinical study 0002-21 for monomethyl fumarate detection in human plasma. The analysis was performed according to the validation MV(I)-182-16 and MV(C)-086-18 (for method validation details please see study 0856-16).

Human plasma samples (n= 4774) were analyzed for monomethyl fumarate. The samples were stored for 96 days at -70°C. The calibration curve exhibited acceptable precision (1.8% to 3.7%) and accuracy (93.7% to 104.2%), and QC samples met the criteria for acceptability. A total of 55 runs were analyzed, with three unacceptable. ISR was performed for 300 samples. The ISR is considered acceptable, as 90.7% of the repeated results fell within the acceptance criteria of 20%. The results were BLQ at pre dose and were within range of the detection after dosing. The LLOQ was less than 5% of Cmax. The bioanalysis appears to be acceptable.

- **Pharmacokinetic variables**

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

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

- **Statistical methods**

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

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

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

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

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

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

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

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

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

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

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

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

Determination of Sample Size

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

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

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

Results

- **Disposition of subjects**

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

No female volunteers were checked in for the study.

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

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

One subject was withdrawn from the study on medical grounds in Period-I.

One subject discontinued from Period-I, II, III and IV on his own accord.

One subject discontinued from Period-III on his own accord. One subject was withdrawn from Period-IV on medical grounds.

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

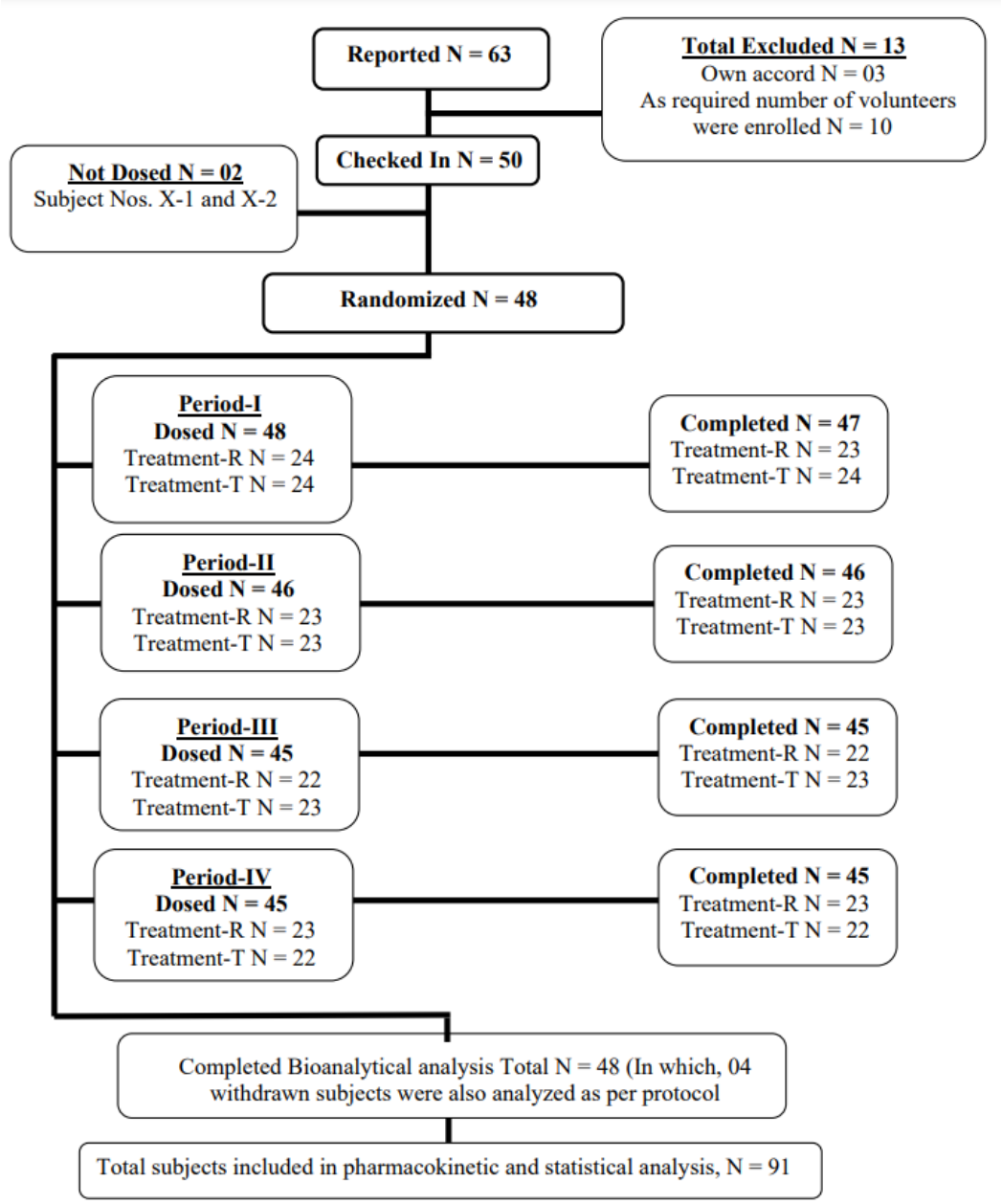

Figure 4: Participants flow - Study 0002-21

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

- **Data sets analyzed**

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

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

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

- **Pharmacokinetic results**

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

Table 511: Descriptive Statistics of Formulation Means for Monomethyl Fumarate (N = 46) - Study 0002-21

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

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

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

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

Table 612: Intra-subject CV and Within-Subject Standard Deviation of Reference Product for Monomethyl Fumarate (N = 90 Observations) - Study 0002-21

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

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

Table 713: Relative Bioavailability Results for Monomethyl Fumarate (N = 46) - Study 0002-21

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

Table 14: ANOVA p-values for Monomethyl Fumarate - Study 0002-21

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

p-value is statistically significant if it is < 0.05

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

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

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

- **Safety data**

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

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

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

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

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

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

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

Study 0003-21: An open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, crossover, fully replicate, bioequivalence study of Dimethyl Fumarate Gastro-Resistant Capsules 240 mg of Intas Pharmaceuticals Ltd., India with TECFIDERA (Dimethyl fumarate) Gastro-Resistant Capsules 240 mg of Biogen Idec Ltd., Innovation House, 70 Norden Road, Maidenhead,

Berkshire, SL6 4AY, United Kingdom in normal, healthy, adult human subjects under fed condition.

Methods

- **Study design**

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

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

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

Capsule was swallowed whole without chewing or crushing.

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

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

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

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

- **Test and reference products**

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

- **Population(s) studied**

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

- **Analytical methods**

Bioanalytical report was provided by the Applicant as support clinical study 0003-21 for monomethyl fumarate detection in human plasma. The analysis was performed according to the validation MV(I)-182-16 and MV(C)-086-18 (for method validation details please see study 0856-16).

Human plasma samples (n= 4525) were analyzed for monomethyl fumarate. The samples were stored for 40 days at -70ºC. The calibration curve exhibited acceptable precision (1.6% to 4.4%) and accuracy (93.5% to 104.1%), and QC samples met the criteria for acceptability. A total of 51 runs were analyzed, with one unacceptable. ISR was performed for 286 samples. The ISR is considered acceptable, as 100% of the repeated results fell within the acceptance criteria of 20%. The results were BLQ at pre dose and were within range of the detection after dosing. The LLOQ was less than 5% of Cmax for all subjects. The bioanalysis appears to be acceptable.

- **Pharmacokinetic variables**

Same as for study 0002-21

- **Statistical methods**

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

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

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

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

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

Determination of Sample Size

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

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

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

Results

- **Disposition of subjects**

A total of 46 subjects were checked in for Period-I of the study. Four subjects were checked in for the study, in order to compensate for any dropouts prior to dosing in Period-I.

No female volunteers were checked in for the study.

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

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

One subject was withdrawn from Period-I on the grounds of emesis. One subject discontinued from Period-II and III on his own accord. Two subjects discontinued from Period-III on their own accord. One

subject was withdrawn from Period-III on medical grounds. One subject was withdrawn from Period-IV on medical grounds.

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

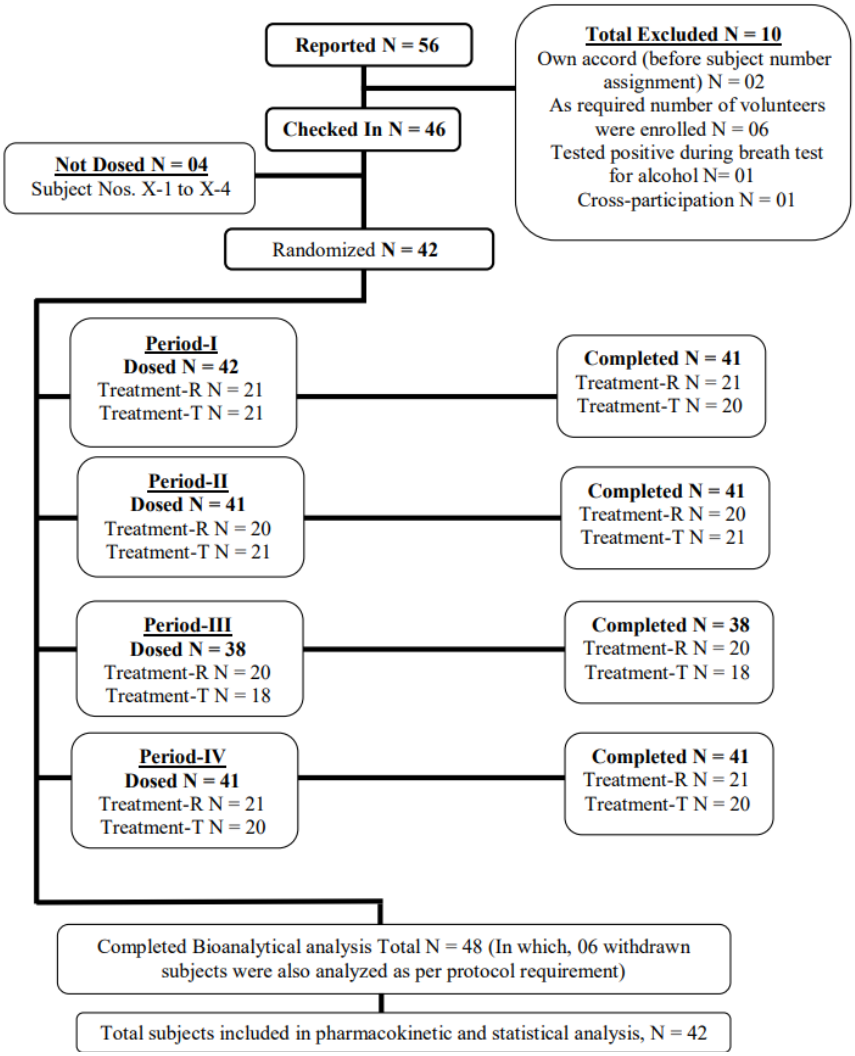

Figure 5: Participants flow - Study 0003-21

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

- **Data set analyzed**

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

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

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

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

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

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

- **Pharmacokinetic results**

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

Table 815: Descriptive Statistics of Formulation Means for Monomethyl Fumarate (N = 42) - Study 0003-21

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

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

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

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

Table 916: Intra-subject CV and Within-Subject Standard Deviation of Reference Product for Monomethyl Fumarate (N = 80 Observations) - Study 0003-21

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

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

Table 1017: Relative Bioavailability Results for Monomethyl Fumarate (N = 42) - Study 0003-21

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

^N=78, *N = 81

Table 18: ANOVA p-values for Monomethyl Fumarate - Study 0003-21

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

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

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

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

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

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

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

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

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

- **Safety data**

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

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

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

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

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

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

2.4.2.2. Pharmacodynamics

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

2.4.3. Discussion on clinical aspects

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

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

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

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

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

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

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

2.4.4. Conclusions on clinical aspects

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

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

2.5. Risk Management Plan

2.5.1. Safety concerns

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

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

None.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

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

2.6.2. Periodic Safety Update Reports submission requirements

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

2.7. Product information

2.7.1. User consultation

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 Tecfidera 120 mg and 240 mg gastro-resistant hard capsules and Solifenacin succinate 5 mg and 10 mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

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

The Applicant conducted 4 separate bioequivalence studies under fasting and fed conditions to demonstrate that the test product – Dimethyl fumarate Accord 120 mg and 240 mg gastro-resistant hard capsules is bioequivalent to the reference product – Tecfidera.
Generally, the design of the performed BE studies could be considered acceptable. The choice of analyte (MMF) is in line with EMA/CHMP/421315/2017 recommendations and is endorsed.
Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied are adequate.

The point estimates and 90% confidence intervals for the ln-transformed pharmacokinetic variables AUC0-t, AUCinf and Cmax were within the predefined bioequivalence range of 80.00% - 125.00% in both performed studies for 120 mg and 240 mg strengths under fed conditions.

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

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

4. Recommendations

Outcome

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

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

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

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

Not applicable.