22 February 2024
EMA/CHMP/108990/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Teriflunomide Accord

International non-proprietary name: Teriflunomide

Procedure No. EMEA/H/C/005960/X/0002

Note

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

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Table of contents

List of abbreviations

AE	Adverse event
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
AUC	Area under the curve
BE	Bioequivalence
CC	Calibration curve
CEP	Certificate of Suitability of the European Pharmacopoeia
CHMP	Committee for medicinal products for human use
CI	Confidence interval
C_{max}	Maximal plasma concentration
CQA	Critical Quality Attributes
CV	Coefficient of variation
DQC	Dilution quality control
EDQM	European directorate for quality of medicines
EMA	European medicines agency
EU	European Union
FDA	Food and drug administration
Fpen	Penetration factor
GC	Gas Chromatography
GCP	Good clinical practice
GLM	General linear model
GLP	Good laboratory practise
GMP	Good Manufacturing Practice
HPLC	High performance liquid chromatography
HQC	High quality control
HSL	Heat Seal Lacquer
ICF	Informed consent form
ICH	International council for harmonization
IEC	Independent ethics committee
IMP	Investigational medicinal product
IR	Infrared
ISR	Incurred sample reanalysis
K_2EDTA	Dipotassium ethylene diamine tetra acetate
KF	Karl Fisher
LC-MS/MS	Liquid chromatography – tandem mass spectrometry
LDPE	Low-density polyethylene
LLOQ	Lower limit of quantification
LMQC	Low medium quality control
LOQQC	Limit of quantification quality control
LQC	Low quality control
MQC	Medium quality control
MS	Multiple sclerosis/Mass Spectrometry
MV	Method validation
NMR	Nuclear Magnetic Resonance
OC	Other concern
OECD	Organization for economic cooperation and development
OPA	Oriented Polyamide
PBT	Persistent, bioaccumulative and toxic

PEC	Predicted environmental concentration
PET	Polyethylene terephthalate
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PRAC	Pharmacovigilance Risk Assessment Committee
PROC	Procedure
PVC	Polyvinyl chloride
RMP	Risk management plan
QC	Quality control
RH	Relative Humidity
SAS	Statistical analysis system
SD	Standard deviation
SOP	Standard operating procedure
T_{max}	Time to maximum plasma concentration
UV	Ultraviolet
XRD	X-Ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

Accord Healthcare S.L.U. submitted on 3 March 2023 an extension of the marketing authorisation.

The MAH applied for an addition of a new strength of Teriflunomide Accord 7 mg film-coated tablets. The bioequivalence study data were submitted.

The MAH applied for the following indication for Teriflunomide Accord 7 mg film-coated tablets:

Teriflunomide Accord is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS) (please refer to section 5.1 for important information on the population for which efficacy has been established).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(s) (c) - Extensions of marketing authorisations

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 MAH 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 MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Nadrah Co-Rapporteur: N/A

The application was received by the EMA on	3 March 2023
The procedure started on	23 March 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 June 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	19 June 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	20 July 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	11 October 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	20 November 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 November 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	14 December 2023
The MAH submitted the responses to the CHMP List of Outstanding Issues on	22 January 2024
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	7 February 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 Teriflunomide Accord on	22 February 2024

2. Scientific discussion

2.1. About the product

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), which functionally connects with the respiratory chain. As a consequence of the inhibition, teriflunomide generally reduces the proliferation of rapidly dividing cells that depend on de novo synthesis of pyrimidine to expand. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but this is mediated by a reduced number of T-lymphocytes.

Pharmacotherapeutic group:

Immunosuppressants, Selective immunosuppressants, ATC Code L04AA31

Proposed indication:

Teriflunomide Accord is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS). (please refer to section 5.1 for important information on the population for which efficacy has been established).

2.2. Type of Application and aspects on development

Teriflunomide Accord 7 mg film-coated tablets is a line extension to Teriflunomide Accord 14 mg film-coated tablets. This application is submitted in accordance with Legal basis 10(1) of Directive 2001/83/EC as amended, so called "generic application".

The originator medicinal product with recognised efficacy and an acceptable level of safety is Aubagio, which contains teriflunomide as film-coated tablets of Sanofi Winthrop Industrie, France, and authorised in the community since 26th August 2013 via the centralised procedure.

The applicant is claiming essential similarity to Aubagio 7 mg film-coated tablets, marketed in Germany by Sanofi Winthrop Industrie, France (EU/1/13/838/006).

To support this application, the applicant submitted one bioequivalence study in accordance with the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) and the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

The applicant did not receive CHMP Scientific Advice pertinent to the clinical investigation.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as film-coated tablets containing 7 mg of teriflunomide. This line extension concerns the addition of this new strength to the previously approved strength of 14 mg film-coated tablets.

Other ingredients are: Tablet core - lactose monohydrate, maize starch, microcrystalline cellulose, sodium starch glycolate, colloidal anhydrous silica, hydroxypropylcellulose, magnesium stearate.

Tablet coating - hypromellose (E464), titanium dioxide (E171), talc (E553b), macrogol (E1521), indigo carmine aluminium lake (E132), yellow iron oxide (E172).

The product is available in aluminium-aluminium blisters as described in section 6.5 of the SmPC.

2.3.2. Active Substance

2.3.2.1. General information

The chemical name of teriflunomide is (2*Z*)-2-cyano-3-hydroxy-*N*-[4-(trifluoromethyl)phenyl]but-2-enamide corresponding to the molecular formula $C_{12}H_9F_3N_2O_2$. It has a relative molecular mass of 270.21 g/mol and the following structure:

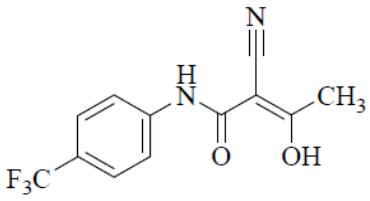

Figure 1: Active substance structure

As there is a monograph of teriflunomide in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for teriflunomide which has been provided within the current extension application.

The active substance documentation is identical to that registered for the previously authorised strengths and is acceptable. No new information has been provided.

2.3.2.2. Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the CEP.

2.3.2.3. Specification

The active substance specification includes tests for: description, solubility (Ph. Eur.), identity (IR), assay (HPLC), related substances (HPLC), residual solvents (GC), water content (KF), sulfated ash (Ph. Eur.), solid state form (XRD), particle size (laser light diffraction), microbiological quality (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for the solid state form, particle size and microbiological quality attributes. All additional methods have been adequately validated and described according to ICH Q2.

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

2.3.2.4. Stability

No retest period is included on the CEP for the active substance. The applicant's proposal for a retest period is the same as for the approved 14 mg strength which uses the same active substance source. The same retest period of 36 months in the proposed container with the storage condition 'Preserve in airtight container and store at 25 °C with excursions permitted to 15 °C - 30 °C' is acceptable.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

Teriflunomide 7 mg film-coated tablets are light greenish-bluish grey to pale greenish-blue, hexagonal shaped approximately 7.3 x 6.9 mm film coated tablet, debossed with "T1" on one side and plain on other side. They differ from 14 mg film-coated tablets in terms of colour, shape, size and debossing.

The development of the 7 mg strength was based on the work conducted for the approved 14 mg strength. The aim was to develop a formulation which was bioequivalent to the Aubagio originator

7 mg tablet formulation. The proposed 7 mg formulation is compositionally similar to the approved 14 mg strength, the formulations are qualitatively the same. The difference in quantitative amounts of active substance between the two formulations is compensated by a proportional increase in the amount of diluent present in the 7 mg strength so that the same overall tablet mass is maintained. The proposed formulation would not meet the criteria for a biowaiver of strengths based on the approved 14 mg strength.

The active substance is poorly soluble and considered BCS class II, a micronised form of the active substance has been chosen and the active substance factors which could potentially impact finished product performance are controlled in the specification. A control for particle size distribution is present for the micronised form. The data provided outlines there is only one known polymorphic form of the active substance, and the specification includes a control for this parameter. In addition to this the manufacturing process of the finished product does not impact the polymorphic form.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards or EU No. 231/2012. Functionality related characteristics were defined for relevant excipients and are reflected in the excipient specifications. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The manufacturing process development was based on the work conducted for the authorised 14 mg strength. The same type of process, wet granulation followed by compression and film-coating, was chosen. The process was used to manufacture batches at various scale, including the biobatch and the data provided indicates the process is sufficiently robust.

A bioequivalence study was performed comparing the 7 mg proposed strength to the 7 mg strength of the reference product, please refer to the clinical sections of this report for further information. The batches were found to be bioequivalent. Comparative dissolution testing of the test product and reference product batches used in the bioequivalence study also showed similar dissolution profiles.

The discriminatory power of the QC dissolution method has been demonstrated, the applicant demonstrated the method to be discriminatory with respect to qualitative changes in the product composition by decreasing the amounts of disintegrant present and increasing the amount of binder used. The applicant’s selected method is considered appropriate.

The primary packaging is aluminium-aluminium blisters. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.3.3.2. Manufacture of the product and process controls

The manufacturing process consists of eight main steps: raw material sifting, binder solution preparation, dry mixing, granulation, drying, sizing, blending and lubrication, compression and film-coating. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by the production of three commercial scale batches. 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.

2.3.3.3. Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form, description, average weight, identification of active substance (HPLC, UV), identification of

colourants (in-house), water content (Ph. Eur.), dissolution (in-house), content uniformity (Ph. Eur.), related substances (HPLC), assay (HPLC), microbiological quality (Ph. Eur.).

The specification limit for dissolution was initially not set in line with the performance of the biobatch in line with the requirements of the reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action (EMA/CHMP/CVMP/QWP/336031/2017). As this could lead to release of products with different in-vivo performance, a major objection (MO) was raised. The applicant was requested in this MO to tighten the specification in line with the biobatch performance. The applicant tightened and justified the specification in line with the biobatch performance and the MO was considered resolved.

Concerning related substances, the limits for impurities are set in line with ICH Q3B and the relevant qualification threshold is not exceeded. For a potential genotoxic impurity the limit for this impurity is set in line with ICH M7 and the relevant Ph. Eur. finished dosage monograph.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls 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 4 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.3.3.4. Stability of the product

Stability data from four commercial scale batches of finished product 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. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested in accordance with the shelf-life specification. The analytical procedures used are stability indicating. At long term and accelerated conditions the results remain within specification and no significant trend is observed, there is a slight increase in specified and total impurities however the results remain well within the specifications.

In addition, one commercial batch of the 14 mg strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No sensitivity to light was observed. Considering the compositional similarity the results are considered sufficiently representative for the 7 mg strength.

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

2.3.3.5. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.3.4. Discussion on chemical, pharmaceutical and biological 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.

In the course of the procedure one MO on quality aspects was raised, requesting the applicant to tighten the QC dissolution limit in line with the biobatch performance. The applicant resolved this MO by tightening of the limit and presenting relevant justification for the tightened limit.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.3.6. Recommendation(s) for future quality development

N/A

2.4. Non-clinical aspects

2.4.1. Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of teriflunomide are well known. As teriflunomide 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 overview on the pharmacology, pharmacokinetics and toxicology is based on up-to-date and adequate scientific literature. Provided updated non-clinical overview is adequate. Information on juvenile toxicity has been included in Non-Clinical overview. Information is supported with the SmPC of the reference product Aubagio.

The impurity profile of proposed teriflunomide 7 mg film-coated tablets is found to be similar with reference product impurity profile. Impurities were within specification limits.

The excipients presented in teriflunomide 7 mg film-coated tablets are qualitatively the same to that of the reference product, except for colloidal anhydrous silica, which is not present in the reference product. There is no safety or clinical concerns regarding the presence of any of these excipients in proposed formulation.

The non-clinical aspects of the proposed SmPC (section 4.6 and 5.3) are in line with the SmPC of the reference product Aubagio.

2.4.2. Ecotoxicity/environmental risk assessment

Proposed product will be available as generic product and marketing authorization of the proposed product will not lead to any increased environmental risk. Therapeutic indications and intended patient population groups for the proposed medicinal product are the same as for the reference medicinal product Aubagio. The proposed marketing authorization will not increase the use of this product; this would rather replace some of the product already available in the market.

Furthermore, the applicant has provided an environmental risk assessment.

Summary of main study results

Substance (INN/Invented Name): Teriflunomide/Teriflunomide Accord			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 U.S. FDA protocol 3.02	2.66 (pH 3) (Assessment report, Aubagio, 2021)	Potential PBT: No
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined based on the actual API consumption data	0.0016	µg/L	> 0.01 threshold: No
Other concerns (e.g. chemical class)	/	/	/

The calculated Predicted Environmental Concentration (using refined Fpen value) for teriflunomide was below 0.01 µg/L, therefore, it is assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients. Teriflunomide is not a persistent, bioaccumulative and toxic substance as log Kow does not exceed 4.5. Phase II environmental fate and effect analysis is not required.

It is concluded that the proposed teriflunomide medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients.

2.4.3. Discussion on non-clinical aspects

The submitted updated non-clinical overview on the pharmacology, pharmacokinetics and toxicology is based on up-to-date and adequate scientific literature.

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

The proposed teriflunomide medicinal product is already used in existing marketed products and no significant increase in environmental exposure is anticipated. Therefore teriflunomide is not expected to pose a risk for the environment following its prescribed usage in patients.

2.4.4. Conclusion on the non-clinical aspects

There are no objections to approval of Teriflunomide Accord 7 mg film-coated tablets from a non-clinical point of view.

2.5. Clinical aspects

2.5.1. Introduction

This application concerns a generic version of teriflunomide 7 mg film-coated tablets under trade name Teriflunomide Accord 7 mg film-coated tablets. Teriflunomide Accord 7 mg film-coated tablets is a line extension to Teriflunomide Accord 14 mg film-coated tablets.

The originator medicinal product with recognised efficacy and an acceptable level of safety is Aubagio, which contains teriflunomide as film-coated tablets of Sanofi Winthrop Industrie, France, and authorised in the community since 26th August 2013 via the centralised procedure.

The applicant is claiming essential similarity to Aubagio 7 mg film-coated tablets, marketed in Germany by Sanofi Winthrop Industrie, France (EU/1/13/838/006).

Both the test and reference product contain the same active substance - teriflunomide.

As this is an abridged application, the applicant has not conducted any efficacy or safety clinical studies with their formulation of teriflunomide film-coated tablets in support of this application. Teriflunomide is a well-known active substance with established efficacy and safety.

The present application is based on a literature overview with regard to the established efficacy and safety of teriflunomide and the bioequivalence study with Teriflunomide Accord 7 mg film-coated tablets compared to the originator product Aubagio on 7 mg strength film-coated tablets with parallel design under fasting conditions.

The updated clinical overview refers to 34 publications up to year 2023. Information on contraindications, special warnings and precaution for use, effects on ability to drive and use machines and accelerated elimination procedure with cholestyramine and activated charcoal have been addressed in Clinical overview as requested and appropriate references have been provided. Updated Clinical overview adequately addresses potential to prolong the QT interval and effect on renal tubular function, references have been cited and provided. Updated clinical overview address indication of teriflunomide also in paediatric patients aged 10 years and older. Updated Clinical overview and proposed SmPC are now aligned in adverse events and in frequencies of adverse events. Reference is SmPC of reference product Aubagio. Additionally, in Clinical overview safety outcomes from individually clinical trials are presented. The clinical overview on the clinical pharmacology, efficacy and safety of teriflunomide is now adequate.

The claimed indication and method of administration of the proposed SmPC are in accordance with the SmPC of reference product, Aubagio. Furthermore, all clinical sections of the proposed SmPC are in line with the SmPC of reference product, Aubagio.

Relevant for the assessment are the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev.1).

GCP aspects

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

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

- **Tabular overview of clinical studies**

To support the application, the applicant has submitted one bioequivalence study (study No. 0051-22).

Tabular overview of bioequivalence study comparing Teriflunomide Accord 7 mg film-coated tablets of Accord Healthcare S.L.U., to the already marketed product Aubagio 7 mg film-coated tablets of Sanofi Winthrop Industrie, France:

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	0051-22	• m5-3-1-2-vol 1 of 4 • m5-3-1-2-vol 2 of 4 • m5-3-1-2-vol 3 of 4 • m5-3-1-2-vol 4 of 4	An open label, balanced, randomized, two-treatment, single period, parallel, single oral dose, bioequivalence study of Teriflunomide Tablets 7 mg of Intas Pharmaceuticals Ltd, India with Aubagio® (Teriflunomide) 7 mg tablets of Sanofi-Aventis Groupe 54, Rue La Boetie F-75008 Paris France in normal healthy, adult, human male subjects under fasting conditions	Single-period, single oral dose, randomized, two-treatment, bioequivalence study, fasting condition.	Teriflunomide film-coated tablets 7mg, Single dose, Oral	84	Healthy, Adult, Human subjects	Single dose	Complete; Full

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Study No. 0051-22: An open label, balanced, randomized, two-treatment, single period, parallel, single oral dose, bioequivalence study of Teriflunomide Tablets 7 mg of with Aubagio (Teriflunomide) 7 mg tablets of Sanofi-Aventis Groupe 54, Rue La Boetie F-75008 Paris France in normal healthy, adult, human male subjects under fasting conditions

Protocol No. 0051-22, version 1.0 (dated 11th April 2022)

Summary of study information:

Clinical Facility, Bio-analytical, Pharmacokinetic, Bio-statistics and Programming, Quality Assurance and Clinical Laboratory Services	Lambda Therapeutic Research Ltd., Lambda House, Plot No. 38, Survey No. 388, Near Silver Oak Club, S.G. Highway, Gota, Ahmedabad-382481, Gujarat, India
Principal investigator:	Lambda Therapeutic Research Ltd. Lambda House, Plot No. 38, Survey No. 388, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-382481, Gujarat, India
Study Period:	Study initiation date: 6th August 2022 Study completion date: 17th September 2022
Bioanalytical Phase Dates:	Experimental start date: 19th August 2022 Experimental completion date: 20th September 2022

Date of the Clinical Study Report:	14th October 2022 (version 00)

The Anveshhan Independent Ethics Committee reviewed the study Protocol (Version 1.0, dated 11 April 2022), Informed Consent Form (ICF-English) (Version 1.0, dated 14 April 2022), Subject Diary (English, Version 1.0, Dated 21 April 2022), Informed Consent Form (ICF-Gujarati) (Version 1.0, dated 6 June 2022), Subject Diary (Gujarati, Version 1.0, Dated 6 June 2022), Undertaking by the Investigator (dated 13 April 2022), Risk Evaluation and Mitigation strategy (Protocol, Version 1.0, dated 11 April 2022) (signed on 18 April 2022), Product Information and gave approval for the study on 15 June 2022.

Errata No. 01 (ICF-Gujarati) (Dated 5 August 2022) was notified to IEC on 5 August 2022.

Addendum to ICF-English and Gujarati (Addendum No. 01, dated 4 August 2022), Risk Evaluation and Mitigation strategy (Protocol, Version 1.0, dated 11 April 2022) (Signed on 4 August 2022) were submitted separately to the IEC, which were approved on 5 August 2022.

1. Methods

- **Study design**

This study was an open-label, balanced, randomized, two-treatment, single period, single oral dose, parallel design in normal, healthy, adult, human male subjects under fasting conditions. The average terminal elimination half-life of teriflunomide ($t_{1/2z}$) is approximately 19 days after repeated doses of 14 mg, as stated in SmPC of reference product Aubagio. According to the Guideline on the Investigation of Bioequivalence, parallel design can be considered for substances with a very long half-life. The study was carried out in fasting conditions, which is acceptable as the drug product can be taken with or without food and it is known that food does not have a clinically relevant effect on teriflunomide pharmacokinetics (according to SmPC of reference product Aubagio). The bioequivalence study under fasting conditions is in accordance with the Guideline on the Investigation of Bioequivalence. Fasting conditions are considered to be the most sensitive conditions to detect a potential difference between formulations.

After an overnight fast of at least 10 hours, a single oral dose (7 mg) of either the test product or the reference product was administered to the subjects in sitting posture with 240 ± 2 mL of drinking water at ambient temperature. The IMP administration was as per the randomization schedule and under open label conditions.

To ensure rapid elimination of teriflunomide from the study subjects, a cholestyramine administration schedule was included from day 4 to day 14, after the sampling process was concluded. Subjects who showed teriflunomide plasma concentrations greater than 0.02 mg/L on day 15 were administered additional cholestyramine from day 16 to day 20. Accelerated elimination procedure with cholestyramine is described in SmPC of reference product Aubagio.

The study was conducted in two groups. 60 subjects were dosed in group I (7th August 2022) and 24 subjects were dosed in group II (13th August 2022).

Subjects were checked-in clinical site 11 hours prior to the IMP administration and were checked-out on day 4 morning.

Parent compound (teriflunomide) was analysed in plasma samples.

The venous blood samples were withdrawn pre-dose (0.000 hour) and at 0.083, 0.167, 0.500, 0.750, 1.000, 1.333, 1.667, 2.000, 2.500, 3.000, 3.500, 4.000, 4.500, 5.000, 5.500, 6.000, 7.000, 8.000, 10.000, 12.000, 16.000, 24.000, 36.000, 48.000 and 72.000 hours following IMP administration. The

sampling scheme to estimate pharmacokinetic parameters for conclusion regarding bioequivalence is adequate (frequent sampling around predicted T_{max} (according to reference SmPC T_{max} of teriflunomide occurs between 1 - 4 hours post-dose following repeat oral administration of teriflunomide)). As per the Guideline on the investigation of bioequivalence, the sampling time period 72 hours post-dose is sufficient to determine and provide a reliable estimate of the extent of exposure for immediate-release products.

The maximum time between the collection of samples and centrifugation was 45 minutes and the maximum time between centrifugation and storage in the freezer was 32 minutes. Stability has been validated for long enough period: stability in blood for 2 hours in ice cold bath during method validation and benchtop stability in human plasma for 11 hours at room temperature.

Apart from the above samples, sample was collected at 336.00 hour (Day 15) and/or 480.00 hours (Day 21) to measure Teriflunomide concentration. Fluid intake was standardized. Posture and physical activities after dosing were standardized. There were some restrictions (regarding taking some food and drinks, alcohol, tobacco, grapefruit, recreational drugs, unusual diet, concomitant medication) that subjects were to comply with prior to and during the course of this study.

During entire housing phase of study, standardised meals were provided to subjects as per meal menu designed by dietician and approved by Investigator. The date/time of meals were standardized. A composition of meals was the same for all subjects.

- **Test and reference products**

Detailed information on the proposed and reference product used in bioequivalence study 0051-22 are provided.

The originator medicinal product Aubagio is authorised in the community since 26th August 2013 via the centralised procedure.

According to information in Module 3 proposed commercial batch size of test product is 190000 tablets.

The certificates of analysis for the test and reference product bio-batch are provided. The assayed content of the batch used as test product does not differ more than 5% from that of the batch used as reference product.

The reference product marketed in Germany is a suitable comparator of the generic product.

The batch size of the test bio-batch (190.000 tablets) is equivalent to the commercial batch size and thus appropriate.

The full-scale production batch is 190.000 tablets. It is the same as bio-batch size. All supporting data has been submitted in registration dossier. Batch analysis confirm that dissolution results for three other full-scale production batches (stability/validation batches) have been within specification limits. If any additional batch size will be incorporated the applicant commit to proceed based on post-approval guidance for submission to agency. The applicant has provided statement confirming that Test product which is used as biobatch of Teriflunomide Accord 7 mg film-coated tablets has same qualitative and quantitative composition & manufacturing process with one which is submitted for marketing authorization application.

- **Population(s) studied**

The population chosen is according to the Guideline on the investigation of bioequivalence. Only male subjects participated in the study, they met all the inclusion criteria and none of the exclusion criteria described in the study protocol.

The study was conducted in two groups. 60 subjects were dosed in group I and 24 subjects were

dosed in group II. In combining both the groups, 84 subjects (Test Product: N = 42 and Reference Product: N = 42) completed the clinical phase of the study successfully were included in pharmacokinetic and statistical analysis. Plasma samples of all 84 subjects were analysed.

Information on discontinued subjects and reasons for discontinuations are provided. There were only pre-dose discontinued subjects (4 subjects discontinued from the study on their own accord). All the dosed subjects completed the clinical phase of the study successfully and were included in pharmacokinetic and statistical analysis.

The demographic data are presented and are appropriate.

Sample size calculation is presented and is appropriate. Sample size is adequate.

Reported protocol deviations (clinical safety measures, review of subject diary, temperature excursion) are considered not having impact on study outcome or safety of the subjects.

Sampling time deviations were reported. Since the actual time is used for computation in pharmacokinetic and statistical analysis, the sampling time deviations are not expected to have any impact on the overall assessment of the study. List of sampling time point deviations used for pharmacokinetic evaluation has been presented.

- **Analytical methods**

Analysis of study samples and within-study validation

Bioanalytical report Determination of teriflunomide concentrations in study samples collected during clinical study No. 0051-22, dated 14th October 2022 has been enclosed.

The purpose of the study was to measure teriflunomide in the subject samples. The concentrations of teriflunomide in human plasma (containing K_2EDTA as an anticoagulant) were determined using a selective, validated, reproducible, precise and accurate LC-MS/MS method using teriflunomide-d4 as an internal standard. Moreover, teriflunomide was also measured in all the collected safety samples, which were collected on day 15 and on day 21 after administration of cholestyramine to ensure complete elimination of teriflunomide from the body.

The sample analysis was performed at the bioanalytical facility. Bioanalytical phase has been performed from 19th August 2022 to 20th September 2022.

Subject samples details:

No. of subjects (as per protocol)	84
No. of sampling time-points (as per protocol)	26
Details of sampling time-points (as per protocol)	0.000 (pre-dose), and at 0.083, 0.167, 0.500, 0.750, 1.000, 1.333, 1.667, 2.000, 2.500, 3.000, 3.500, 4.000, 4.500, 5.000, 5.500, 6.000, 7.000, 8.000, 10.000, 12.000, 16.000, 24.000, 36.000, 48.000 and 72.000 hours post-dose
No. of periods (as per protocol)	1
Total No. of samples (as per protocol)	2184 (84 subjects X 26 time-points X 1 period)
Samples not received/lost	0
Total No. of study samples collected	2184
Total No. of safety samples collected	152

Samples analysed	2336 (2184 study samples + 152 safety samples)

The analyte and internal standard were extracted from plasma by protein precipitation method.

Instruments LC-MS/MS-19 and LC-MS/MS-45 were used for subject sample analysis. LC-MS/MS-17 was used for initial experiments only and not used for subject sample analysis. Precision and accuracy experiment was performed on each instrument before initiation of subject sample analysis.

Automatic liquid handling system was used for sample processing along with manual processing.

The plasma concentrations of teriflunomide in the study samples and safety samples has been determined using precise and accurate LC-MS/MS method according to method. Bioanalytical study plan Determination of teriflunomide concentrations in study samples collected during clinical study No. 0051-22 has been enclosed. Other relevant bioanalytical SOPs have been provided.

The calibration curve standards and quality control samples were prepared as per procedure is given in section 5.4 of method.

Date of preparation of CC and QC samples	22nd August 2022
Calibration curve standard range	10.009 to 4001.201 ng/mL
Quality control samples LOQ QC (LLOQ), LQC, LMQC, MQC, HQC and DQC	10.176 ng/mL, 29.929 ng/mL, 400.126 ng/mL, 1202.482 ng/mL, 3189.607 ng/mL and 11511.364 ng/mL

Statement on GLP, Protocol, Bioanalytical study plan and SOPs are compliant and Quality assurance statement have been enclosed.

Handling of samples was adequate. Maximal storage period of study samples (45 days at -65±10°C, however, freezer temperature excursions were observed for a cumulative duration of total 6 hrs and with the highest temperature observed -42.4°C) was within validated long-term stability of teriflunomide in K_2EDTA plasma (145 days at -65±10°C and at -22±5°C).Certificates of analysis of reference standard teriflunomide and internal standard teriflunomide-d4 used in study sample analysis have been enclosed.

Analytical method has been suitably within-study validated. Structure of analytical run (8 calibration standards, quality control samples in duplicate, study samples/safety samples/incurred samples, zero samples, blank samples) was acceptable. All analytical runs were acceptable, all analytical runs met analytical run acceptance criteria according to SOP Preparation of calibration curve and quality control samples and defining analytical run organization and its acceptance criteria (AHM/BA/0057-1).

Reasons for repeat samples (significant variations in response of internal standard and processing error) are according to SOP Repeat analysis and acceptance of results (AHM/BA/0059-2) and are considered justified. Original and repeated concentrations are presented in the documentation. Repeated values have been reported for pharmacokinetic in statistical analysis.

160 study samples out of 2184 study samples were considered for ISR evaluation. It represents 10 % of the first 1000 samples and 5 % of the number of samples exceeding 1000 samples (1184). Results of incurred sample reanalysis confirms the reproducibility of the analytical method.

All subject's chromatograms have been enclosed. SOP Chromatography acceptance criteria, re-

injection, integration and reintegration on HPLC and LC-MS/MS data systems (AHM/BA/0033-2) has been enclosed. None of analytical runs were reintegrated.

LLOQ (10.009 ng/mL) is less than 5% of min C_{max} (949.627 ng/mL for test product and 786.304 ng/mL for reference product) and therefore acceptable.

Pre-study method validation

The bioanalytical LC-MS/MS method for the quantification of teriflunomide in human plasma (containing K_2EDTA as an anticoagulant) was validated according to in-house SOP Nos. AHM/BA/0030-1, LTR.BA-05-04, LTR.BA-05-03 and LTR.BA-05-00 and Validation Plan No. MV-001 (version 02).

Bioanalytical method validation was performed at the bioanalytical facility Lambda Therapeutic Research Limited, Plot No. 38, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad, Gujarat, India.

Overview of validation:

MV/ Addendum No.	SOP	Reasons	Experiments performed
MV(I)-096-14	LTR.BA-05-00 MS-830-D-01	Full MV (CC Range: 9.998 to 4002.912 ng/mL)	• Requisite experiments as per SOP No. LTR.BA-05-00. • Mobile Phase Stability • Freeze thaw stability, Bench Top stability, Wet extract bench top stability and Auto sampler stability using freshly spiked and prepared QC samples
MV(I)-096-14 (Addendum-II)	LTR.BA-05-03 MS-830-00	Partial MV	• Blood stability • Matrix effect experiment • Robustness and ruggedness
MV(I)-096-14 (Addendum-III)	LTR.BA-05-03 MS-830-01	Partial MV	• Requisite experiments as per SOP No. LTR.BA-05-03 to update the method and to incorporate provision of liquid handling system.
MV(I)-096-14 (Addendum-V)	LTR.BA-05-04 MS-830-01	Partial MV	• Stability evaluation
MV(I)-096-14 (Addendum-VI)	LTR.BA-05-04 MS-1344-D-00 Method Validation Plan No. MV-001 (Version 02)	Partial MV	• Requisite experiments as per LTR.BA-05-04 and Method Validation Plan for change in mobile phase composition, extraction solvent, buffer & back extraction and column • Long-term stability of analyte in human plasma: 145 days (at -22 ± 5°C & -65 ± 10°C)
MV(I)-096-14 (Addendum-VII)	AHM/BA/0030-1 MS-1344-00	Partial MV	• To update the method as per SOP No. AHM/BA/0030-1 • Selectivity in presence of coadministered drugs (Linezolid, Pantoprazole, Nadifloxacin, Amoxicillin, Clavulanic Acid, Aceclofenac and Serratiopeptidase)
MV(I)-096-14 (Addendum-VIII)	AHM/BA/0030-1 MS-1344-00	Partial MV	• To update the method as per SOP No. AHM/BA/0030-1 • Short term solution stability • After taking prior authorization, below mentioned experiment was performed additionally: - One Precision and accuracy batch for bulk spiked samples. - Spiking check experiments for bulk spiked INTQC (final concentration ~1250.000 ng/mL).
MV(I)-096-14 (Addendum-IX)	AHM/BA/0030-1 MS-1344-00	Partial MV	• To update the method as per SOP No. AHM/BA/0030-1 • After taking prior authorization, below mentioned

			experiment was performed additionally: - Verification of analyte stability in human whole blood in ice cold water bath.

Note: Total Nine addendums were performed for the Method validation. However, addendums applicable to study are mentioned here.

Bioanalytical method validation reports have been enclosed for main validation and for all relevant partial validations (addendums II, III, V, VI, VII, VIII, IX).

Statement on GLP compliance and Quality assurance statement have been enclosed for main validation and all partial validations.

Certificates of analysis of reference standard teriflunomide and internal standard teriflunomide-d4 used in main validation and in partial validations have been enclosed.

Bioanalytical method validation has been evaluated according to Guideline on bioanalytical method validation since analysis of study samples was performed before ICH M10 Guideline has been effective (January 2023).

In partial validation Addendum VI most parameters have been revalidated to update the method and to perform requisite experiments for change in mobile phase composition, column and extraction solvent, buffer and back extraction. Sample preparation and analysis have been done as per draft method. The same mobile phase composition, column and extraction solvent, buffer and back extraction has been used for concerned study samples analysis, therefore this partial validation (and the following) is the most relevant. Validation concerns the following parameters: selectivity (including haemolysed and lipemic plasma, selectivity in presence of co-administered and pro-drug, verification of interfering potential by co-administered and pro-drug), calibration curve (linearity and coefficient of determination), lower limit of quantification (accuracy, precision), lower limit of detection, accuracy and precision (within-batch and between-batch), dilution integrity (dilution factor 5), batch size evaluation, recovery, matrix effect and matrix factor, reinjection reproducibility and stability (auto sampler/wet extract stability, wet extract bench top stability, long-term stability of analyte in human plasma, reagent stability, mobile phase stability) and carry over. Long-term stability in solution, freeze and thaw stability and bench top stability in human plasma have been validated in Addendum III.

In partial validation Addendum VII selectivity in presence of co-administered drugs has been validated.

In partial validation Addendum VIII short-term stability of solutions, precision and accuracy and precision of intermediate QC samples have been validated.

In partial validation Addendum IX stability in human whole blood has been validated.

SOP deviation regarding freeze and thaw stability in main validation does not have impact on validation results since freeze and thaw stability experiment was repeated later in the partial validation. There were no further SOP deviations in any of the partial validations.

Validation of long-term stability in solution, freeze and thaw stability and bench top stability in human plasma, performed with different mobile phase composition, different column and different extraction solvent, buffer and back extraction (in Addendum III) is relevant for analytical method used for study samples analysis. Those stabilities (long-term stability in solution, freeze and thaw stability and bench top stability in human plasma) are not affected by change in mobile phase composition, change in extraction solvent, buffer & back extraction and change in column.

- **Pharmacokinetic Variables**

Pharmacokinetic was primarily assessed by the pharmacokinetic properties of the test and the

reference formulations by measurement of Teriflunomide concentrations in plasma. The following pharmacokinetic parameters were calculated:

Primary pharmacokinetic parameters: C_{max} and AUC_{0-72}

Secondary pharmacokinetic parameter: T_{max}

These parameters are derived individually for each analyzed subject from the concentration vs. time profiles of Teriflunomide in Plasma using noncompartmental model of Phoenix WinNonlin Version 8.3 (Certara L.P.).

The maximum measured Plasma concentration (C_{max}) and the time of observing the peak concentration (T_{max}) was calculated from the Plasma concentration vs. time profile of the individual subjects. The units of C_{max} and T_{max} are ng/mL and hour (h) respectively.

Area under the Plasma concentration versus time curve (AUC_{0-72}) in ng.h/mL from time zero to the truncated time at 72-hour concentration was calculated by linear trapezoidal method.

Actual time-points of the sample collection are used for the calculation of pharmacokinetic parameters.

All concentration values below the lower limit of quantification are set to zero for the pharmacokinetic and statistical calculations.

- **Statistical methods**

Descriptive statistics were to be calculated and reported for all pharmacokinetic parameters for teriflunomide.

The ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72} (from all the groups) were subjected to analysis of variance (ANOVA) for teriflunomide.

ANOVA model was to be included group and formulation as fixed effects. If number of subjects for BE evaluation < 5 subjects in any group, then group was to be combined to subsequent group. The applicant has provided output of effect for group*formulation interaction. Since group*formulation effect has been found statistical insignificant for ln-transformed pharmacokinetic parameters C_{max} (p-value = 0.5621) and AUC_{0-72} (p-value = 0.1852), the current ANOVA model with the terms formulation and group as fixed effects for the assessment of bioequivalence is appropriate. Descriptive statistics of the main PK parameters by formulation by group have been presented.

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 for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72} was to be calculated and reported for teriflunomide.

Ratio of geometric least squares means of test and reference formulations was to be calculated and reported for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72} for teriflunomide.

Inter-subject variability was to be calculated and reported for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72} for teriflunomide.

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

90% confidence intervals for the ratio of geometric least squares means between drug formulations were to be calculated for ln-transformed data of C_{max} and AUC_{0-72} for teriflunomide.

All statistical analyses for teriflunomide were to be performed using PROC GLM of SAS Version 9.4 (SAS Institute Inc, USA).

Applicant has provided information about treatments group's characteristics regarding race, smoking status, gender, age, height, weight and BMI. No statistically significance difference has been observed between group which received test product and reference product for age and height (p-value > 0.05), while statistically significant difference has been observed between test and reference for BMI and weight (p-value < 0.05). Therefore, Applicant performed extra statistical analysis and together with literature findings provide a reasoning that the variation of body weight in treatment groups in bioequivalence study 0051-22 did not affect assessment of bioequivalence.

Criteria for conclusion of bioequivalence were as follows:

Bioequivalence of test product-T vs. reference product-R was to be concluded, if the 90% confidence interval fell within the acceptance range (80.00% - 125.00%) for ln-transformed pharmacokinetic parameters (C_{max} and AUC_{0-72}) for teriflunomide.

Results

The pharmacokinetic variables of teriflunomide of the Test and the Reference product and statistical evaluation of teriflunomide pharmacokinetic variables are shown in the following tables:

Table 1: Pharmacokinetic parameters for teriflunomide (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	Arithmetic mean	SD	Arithmetic mean	SD
AUC_{0-72} (ng*h/mL)	58934.011	6895.2627	57445.584	9278.2318
C_{max} (ng/mL)	1252.256	179.2541	1243.871	239.5325
T_{max}* (h)	1.667 (0.500 - 4.500)		1.333 (0.500 - 5.000)	
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours				
C_{max} maximum plasma concentration				
T_{max} time for maximum concentration (* median, range)				

Table 2: Statistical analysis for teriflunomide (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
AUC_{0-72h}	103.2	98.23 - 108.36	13.6
C_{max}	101.5	95.53 - 107.86	16.8
* estimated from the Residual Mean Squares			

Bioequivalence has been shown appropriately.

The test to reference ratio of geometric least squares means with corresponding 90% CI for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72} was within the acceptance range of 80.00-125.00% for teriflunomide. Therefore, the test product-T is considered to be bioequivalent to the reference product-R under fasting condition.

T_{max} values have been determined, which were comparable between test and reference products.

C_{max} of teriflunomide was not the first point of a concentration time curve in any subject.

Pre-dose plasma concentration of teriflunomide was below the limit of quantitation (10.009 ng/mL) for all subjects.

Following ANOVA evaluation of pharmacokinetic parameters statistically significant group effect was observed for AUC_{0-72}. The applicant has provided clarification that this significant effect is just statistically significant and can be ignored.

- **Safety data**

Clinical study was completed with one adverse event (observed with reference product). There were no deaths, serious or significant adverse events during the conduct of the study. The investigational products were well tolerated by healthy subjects, as a single dose administration.

There were no clinically significant findings in the vital sign assessments or the laboratory tests in any of the subjects in the study.

Subject 1040 received concomitant medication due to adverse event. However, all pharmacokinetic samples were collected before concomitant medication was administered. Therefore, concomitant medications do not have any impact on study results. Volunteer who experienced adverse event was treated and followed up until resolution of his adverse event.

- **Pharmacokinetic conclusion**

Based on the presented bioequivalence study No. 0051-22 Teriflunomide Accord 7 mg film-coated tablets is considered bioequivalent with Aubagio 7 mg film-coated tablets.

Comparative dissolution profiles between biobatches of test and reference product are considered similar in all tested dissolution media.

In pH 4.5 acetate buffer and purified water more than 85 % of teriflunomide from reference and test product is dissolved within 15 minutes. Dissolution profiles are considered similar without further mathematical evaluation.

In pH 6.8 phosphate buffer dissolution profiles are considered similar based on f2 calculation (f2 > 50).

In 0.1 N HCl dissolution profiles are considered similar based on f2 calculation (f2 = 98 according to Module 3.2.P.2 Pharmaceutical development). However, not all conditions for f2 calculation according to Guideline on the investigation of bioequivalence, Appendix I are fulfilled (the relative standard deviation or coefficient of variation of any product should be less than 20% for the first point and less than 10% from second to last time point). As the released teriflunomide is less than 3 % for the reference product and less than 4 % for the test product after 45 minutes no additional data on dissolution comparison is requested.

2.5.2.2. Experimental conditions for in vitro dissolution experiment are in accordance with Guideline on the investigation of bioequivalence, Appendix III, except volume of dissolution media (1000 mL is used, according to Guideline on the investigation of bioequivalence it should be 900 mL or less). Since in vitro dissolution profiles of test and reference product are only additional data and in vivo data demonstrating bioequivalence of test and reference product prevails over the in vitro dissolution testing no issue is raised.Pharmacodynamics

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

2.5.3. Clinical efficacy

No new studies were submitted, and none are required for applications of this type. Efficacy of the present formulation is based on the efficacy of the previously approved reference product.

2.5.4. Clinical safety

No new studies were submitted, and none are required for applications of this type. Safety of the present formulation is based on the safety of the previously approved reference product.

2.5.5. Discussion on clinical aspects

To support the application, the applicant has submitted a review of clinical data as well as an open-label, balanced, randomized, two-treatment, single period, single oral dose, parallel bioequivalence study under fasting conditions to demonstrate essential similarity with the reference product Aubagio 7 mg film-coated tablets.

According to the SmPC of the reference product, teriflunomide can be taken with or without food. Therefore, the conduct of the single dose study under fasting condition to detect a potential difference between formulations is justified and in accordance with bioequivalence guidelines. Parallel study design is considered appropriate considering the very slow elimination of teriflunomide. The bioequivalence study was conducted under standardised conditions. During entire housing phase of study, standardised meals (in regard to composition and time of administration) were provided to subjects. Sampling period was sufficient, sampling time schedule was adequate.

The maximum time between the collection of samples and centrifugation was 45 minutes and the maximum time between centrifugation and storage in the freezer was 32 minutes. Appropriate stabilities have been validated for long enough periods.

Data regarding the test and reference product are provided. Statement confirming that, the test product has the same quantitative composition and is manufactured by the same process as the one submitted for marketing authorization has been provided. Batch analysis confirm that dissolution results for three other full-scale production batches (stability/validation batches) have been within specification limits.

The study was conducted in two groups. All the checked in subjects satisfied all the inclusion and exclusion criteria. 60 subjects were dosed in group I and 24 subjects were dosed in group II. In combining both the groups, 84 subjects (Test Product: N = 42 and Reference Product: N = 42) completed the clinical phase of the study successfully were included in pharmacokinetic and statistical analysis. Plasma samples of all 84 subjects were analysed. There were only pre-dose discontinued subjects (4 subjects discontinued from the study on their own accord). All the dosed subjects completed the clinical phase of the study successfully. Reported protocol deviations (clinical safety measures, review of subject diary, temperature excursion) are considered not having impact on study outcome or safety of the subjects. Sampling time deviations were reported. Since the actual time is used for computation in pharmacokinetic and statistical analysis, the sampling time deviations are not expected to have any impact on the overall assessment of the study.

The bioanalytical method (LC-MS/MS) for quantification of teriflunomide (parent drug) in human K_2EDTA plasma samples was pre-study and in-study validated according to Guideline on bioanalytical method validation. Bioanalytical report and validation reports have been enclosed. Bioanalytical method is considered acceptable for study samples analysis. Handling of samples was adequate.

According to the Guideline on the investigation of bioequivalence in studies to determine bioequivalence after a single dose, AUC_{0-t}, $AUC_{0-\infty}$, residual area, C_{max} and T_{max} should be determined. In the study with a sampling period of 72 h, and where the concentration at 72 h is quantifiable, $AUC_{0-\infty}$ and residual area do not need to be reported, it is sufficient to report AUC truncated at 72h, AUC_{0-72}. The choice of pharmacokinetic variables (C_{max}, AUC_{0-72}, T_{max}) is in accordance with Guideline, and is thus acceptable. Pharmacokinetic parameters for teriflunomide were calculated using non-compartmental methods. The software used for determination of pharmacokinetic parameters was Phoenix WinNonlin Version 8.3 (Certara L.P.). Actual time points of the sample collection were used for the calculation of pharmacokinetic parameters.

The statistical method used for the pharmacokinetic analyses: Data transformations are acceptable. The ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72} (from all the groups) were subjected to analysis of variance (ANOVA) for teriflunomide. ANOVA model was to be included group and formulation as fixed effects. Additionally, the applicant has provided output of effect for group*formulation interaction. Since group*formulation effect has been found statistical insignificant for ln-transformed pharmacokinetic parameters C_{max} (p-value = 0.5621) and AUC_{0-72} (p-value = 0.1852), the current ANOVA model with the terms formulation and group as fixed effects for the assessment of bioequivalence is appropriate. Descriptive statistics of the main PK parameters by formulation by group have been presented.

All statistical analyses for teriflunomide were performed using the PROC GLM of SAS Version 9.4 (SAS Institute Inc, USA).

No statistically significant difference has been observed between group which received test product and reference product for age and height (p-value > 0.05), while statistically significant difference has been observed between test and reference for BMI and weight (p-value < 0.05). Therefore, the applicant has provided additional reasoning that the difference of body weight in treatment groups in bioequivalence study 0051-22 did not affect assessment of bioequivalence.

The criteria for bioequivalence were predefined and are acceptable. The test to reference ratio of geometric least squares means with corresponding 90% CI for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72} was within the acceptance range of 80.00-125.00% for teriflunomide. Therefore, the test product-T is considered to be bioequivalent to the reference product-R under fasting condition.

There were no deaths, serious or significant adverse events during the conduct of the study. The investigational products (test and reference) were well tolerated by healthy subjects, as a single dose administration.

Appropriate statements on GCP have been provided. The applicant has provided a list of inspections of clinical site and bioanalytical site where bioequivalence study was conducted. The outcomes of the most recent inspections performed by competent authorities/EU inspectors for clinical study site and bioanalytical study site have been provided. The relevance of major and critical findings for concerned study 0051-22 has been addressed by the applicant and it could be concluded that critical and major findings do not have any impact on concerned study 0051-22. Monitoring reports for study 0051-22 have been provided. According to monitoring reports there were no observations, that would have impact on the integrity of study data. There are no other observations, which could have raised concerns about the quality or validity of the sampling process or study sample analyses, the analytical method validation or the statistical analysis. There is no concern with regard to the GCP compliance of the study.

The comparative dissolution profiles between biobatch of reference product Aubagio 7 mg film-coated tablets and biobatch of test product Teriflunomide 7 mg film-coated tablets are considered as similar.

In pH 4.5 acetate buffer and purified water more than 85 % of teriflunomide from reference and test product is dissolved within 15 minutes. In pH 6.8 phosphate buffer dissolution profiles are considered similar based on f2 calculation (f2 > 50). In 0.1 N HCl less than 3 % of teriflunomide was released from the reference product and less than 4 % was released from the test product after 45 minutes. However, one of the experimental conditions (volume of dissolution media) was not fulfilled. Since in vitro dissolution profiles of test and reference product are only additional data and in vivo data demonstrating bioequivalence of test and reference product prevails over the in vitro dissolution testing no issue is raised.The clinical overview on the clinical pharmacology, efficacy and safety of teriflunomide is now adequate. The clinical sections of the SmPC of the proposed product are in accordance with the reference product, Aubagio 7 mg film-coated tablets.

2.5.6. Conclusions on the clinical aspects

The application contains an adequate review of published literature data on clinical pharmacology, efficacy and safety of teriflunomide.

Based on the presented bioequivalence study No. 0051-22 Teriflunomide Accord 7 mg film-coated tablets is considered bioequivalent with Aubagio 7 mg film-coated tablets.

Efficacy and safety of the proposed product is based on the efficacy and safety of the previously approved reference product Aubagio.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Hepatic effects • Hypertension • Hematologic effects • Infections • Acute Pancreatitis
Important potential risks	• Teratogenicity • Serious opportunistic infections, including PML
Missing information	• None

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

Table: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Hepatic Effects	Routine risk minimisation measures: - SmPC sections 4.4, 4.3 and 4.8 - PL section 2 and 4 - Information to perform/monitor liver test during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4. - The prescription only status Additional risk minimisation measures: Educational Materials (HCP guide and Patient card)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire for 'Hepatic effects. Additional pharmacovigilance activities: None

Hypertension	Routine risk minimisation measures: - SmPC sections 4.4 and 4.8 - PIL section 2 and 4 - Information to monitor blood pressure before and during the treatment with teriflunomide is included in SmPC section 4.4 and PIL section 2. - The prescription only status Additional risk minimisation measures: Educational Materials (HCP guide and Patient card)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: No Specific adverse reaction follow-up questionnaire for 'Hypertension'. Additional pharmacovigilance activities: None
Haematologic effects	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

	- SmPC sections 4.4, 4.3 and 4.8 - PIL section 4 - Instruction to perform complete blood cell count before and during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4. - The prescription only status Additional risk minimisation measures: Educational Materials (HCP guide and Patient card)	No Specific adverse reaction follow-up questionnaire for 'Haematologic effects'. Additional pharmacovigilance activities: None
Infections	Routine risk minimisation measures: - SmPC sections 4.4, 4.3 and 4.8 - PIL section 2 and 4 - Information to monitor symptoms of infections during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: No Specific adverse reaction follow-up questionnaire for 'Infection'. Additional pharmacovigilance activities: None

	- The prescription only status Additional risk minimisation measures: Educational Materials (HCP guide and Patient card)	

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	- The prescription only status Additional risk minimisation measures: Educational Materials (HCP guide and Patient card)	
Acute Pancreatitis	Routine risk minimisation measures: - SmPC section 4.4 and 4.8 - PIL section 2 and 4 - Information to monitor symptoms of symptoms of pancreatitis during the treatment with teriflunomide and treatment discontinuation information If pancreatitis is confirmed, is included in SmPC section 4.4. - The prescription only status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire for 'Acute Pancreatitis'. . Additional pharmacovigilance activities: None
Important Potential Risks		
Teratogenicity	Routine risk minimisation measures: - SmPC section 4.3 and 4.6	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	- PIL section 2 - Information on contraception recommendations and treatment discontinuation is included in SmPC section 4.6 - The prescription only status Additional risk minimisation measures: Educational Materials (HCP guide and Patients card)	Specific adverse reaction follow-up questionnaire for 'Teratogenicity'. Structured analyses of cases reporting pregnancy exposure will be submitted regularly, at harmonised submission dates (3-year cycle) synchronised with Teriflunomide PSUR submission requirements. Additional pharmacovigilance activities: None
Serious opportunistic infections, including PML	Routine risk minimisation measures: - SmPC section 4.3, 4.4 and 4.8 - PIL section 2 and 4 - Information to monitor symptoms of infections during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4. - The prescription only status Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire for 'Serious opportunistic infections, including PML'. Additional pharmacovigilance activities: None
	Educational Materials (HCP guide and Patients card)	

2.6.4. Conclusion

The CHMP considered that the risk management plan version 3.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

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

2.7.2. 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.

2.8. Product information

2.8.1. 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 Aubagio. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

This application concerns a generic version of teriflunomide film-coated tablets. The reference product Aubagio is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis.

The application contains adequate quality data. No nonclinical studies have been provided for this application but a summary of the available non-clinical information for the active substance has been adequately updated. 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 is considered sufficient.

The bioequivalence study forms the pivotal basis with an open-label, balanced, randomized, two-treatment, single period, single oral dose, parallel design in normal, healthy, adult, human male subjects under fasting conditions. The study design is considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. According to the Guideline on the Investigation of bioequivalence, parallel design can be considered for substances with a very long half-life. Fasting conditions are appropriate since SmPC of reference product Aubagio recommends dosing 'with or without food' and fasting conditions are considered the most sensitive condition to detect potential differences between formulations. Concentration of parent drug teriflunomide were measured in plasma samples. Choice of dose, sampling points and overall sampling time were adequate. The analytical method was validated. Pharmacokinetic and statistical

methods applied are adequate. Since group*formulation effect has been found statistical insignificant for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72}, the ANOVA model with the terms formulation and group as fixed effects for the assessment of bioequivalence is appropriate.

The test formulation of Teriflunomide Accord 7 mg film-coated tablets met the protocol-defined criteria for bioequivalence when compared with the reference product Aubagio 7 mg film-coated tablets. The point estimates and their 90% confidence intervals for the parameters AUC_{0-72} and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations is considered to be shown.

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

3.1. Conclusions

The overall benefit/risk balance of Teriflunomide Accord 7 mg film-coated tablets is positive, subject to the conditions stated in section 'Recommendations'.

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 Teriflunomide Accord 7 mg film-coated tablets is favourable in the following indication(s):

> Teriflunomide Accord is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS) (please refer to section 5.1 for important information on the population for which efficacy has been established).

The CHMP therefore recommends the extension(s) of the marketing authorisation for Teriflunomide Accord 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).

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.
- **Additional risk minimisation measures**

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree an educational programme with the National Competent Authority.

The MAH shall ensure that, following discussion and agreement with the National Competent Authorities in each Member State where Teriflunomide Accord is marketed, at launch and after launch, all healthcare professionals who are expected to use Teriflunomide Accord are provided with the following items:

- Summary of Product Characteristics (SmPC)
- Educational material for Healthcare professionals
- Patient Education Card

The educational material for HealthCare Professionals (HCP) will include the following key elements:

1. HCPs should discuss with their patients the specific safety concerns of Teriflunomide Accord detailed below including the tests and precautions needed for safe use at first prescription, and regularly during treatment as follows:
    - Risk of hepatic effects
        - Liver function tests are needed prior to the start of treatment and periodically during treatment
        - To educate the patient about the signs and symptoms of liver disease and the need to report to their HCP if they experience any of them
    - Potential risk of teratogenicity
        - To remind women of child-bearing potential (WOCP) including adolescents/their parents caregivers that Teriflunomide Accord is contraindicated in pregnant women and in WOCP not using an effective contraception during and after treatment.
        - To assess regularly the potential for pregnancy in female patients including patients below 18 years old.
        - To tell female children and/or parents/caregivers of female children about the need to contact the prescribing physician once the female child under Teriflunomide Accord treatment experiences menses. Counselling should be provided to the new patients of child-bearing potential about contraception and the potential risk to the fetus.
        - To check pregnancy status before starting treatment
        - To educate female patients of child-bearing potential on the need for effective contraception during and after treatment with teriflunomide
        - To remind patients to inform their doctor immediately if they stop contraception, or prior to changing contraceptive measures
        - If female patients become pregnant despite using contraceptive measures, they should

stop Teriflunomide Accord and contact their doctor immediately who should:

- Consider and discuss with the patient the accelerated elimination procedure,
- Report any pregnancy case to Accord Healthcare by calling or contacting [to be filled in at national level with the relevant contact details] irrespective of adverse outcomes observed.

- Risk of hypertension
  - To check for a history of hypertension and that blood pressure should be appropriately managed during treatment
  - The need for blood pressure checks before treatment and periodically during treatment,
- Risk of haematologic effects
  - To discuss the risk of decreased blood cell counts (affecting mainly white blood cells) and the need for complete blood cell counts before treatment and periodically during treatment based on signs and symptoms.
- Risk of infections/serious infections
  - To discuss the need to contact the doctor in the event of signs/symptoms of infection, or if the patient takes other medicines that affect the immune system. If serious infection occurs, consider the accelerated elimination procedure.

2. A reminder to provide patients/legal representative with a Patient Education Card, including filling-in their contact details, and to provide replacement Patient Education Cards as necessary;
3. A reminder to discuss the Patient Education Card content with the patient/legal representative regularly at each consultation at least annually during treatment;
4. To encourage patients to contact their MS physician and/or General Practitioner if they experience any of the signs and symptoms discussed in the Patient Education Card;
5. At prescription renewal, adverse events are checked, ongoing risks and their prevention are discussed, and checks are made to ensure adequate monitoring is taking place.

The educational card for the patients is aligned with labelling information and includes the following key elements:

1. A reminder for both patients and all HCPs involved in their treatment that the patient is being treated with teriflunomide, a medicine which:
   - Should not be used in pregnant women
   - Requires concomitant use of effective contraception in women of child-bearing potential
   - Requires a pregnancy status check before treatment
   - Affects liver function
   - Affects blood cell counts and the immune system

2. Information to educate the patient about important side effects:
   - To pay attention to certain signs and symptoms which might indicate liver disease, or infection, and if any of these occur, to contact their doctor/HCP promptly
   - To remind female patients to tell their doctor if breast-feeding

- A reminder for women of child-bearing potential including girls and their parents/ caregivers
    - to use effective contraception during and after treatment with teriflunomide
    - that your doctor will provide counselling on the potential risks to the fetus and on the need for effective contraception.
    - to stop treatment with teriflunomide immediately if they suspect they might be pregnant and also to contact their doctor immediately.
- A reminder for parents / caregivers or girls
    - to contact your doctor when the girl experiences menses for the first time in order to get counselling about the potential risk to the fetus and the need for contraception
- If women of child-bearing potential become pregnant:
    - To remind both patients and HCPs about the accelerated elimination procedure
- To remind patients to show the Patient Education Card to Doctors/HCPs involved with their medical care (especially in the event of medical emergencies and/or if new Doctors/HCPs are involved.)
- To record the first date of prescription and the contact details of their prescriber

3. To encourage the patients to read the PIL thoroughly

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

Not applicable.