30 April 2020
EMA/CHMP/267761/2020
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Fingolimod Mylan

International non-proprietary name: fingolimod

Procedure No. EMEA/H/C/005282/0000

Note

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

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List of abbreviations

AE	Adverse event
ANOVA	Analysis of variance
AP	Applicant's Part (or Open Part) of ASMF
API	Active Pharmaceutical Ingredient
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AUC	Area under the curve
BMI	Body-mass index
CI	Confidence interval
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CoA	Certificate of Analysis
CRFs	Case Report Forms
CRO	Clinical Research Organization
CRS	Chemical Reference Substance (official standard)
CV	Coefficient of Variation
EMA	European Medical Agency
EPCRS	European Pharmacopoeia Chemical Reference Substance
FING	Fingolimod
GCP	Good clinical practice
GPL	Good laboratory practice
HDPE	High-density polyethylene
HPLC	High Performance Liquid Chromatography
HSGC	Headspace Gas Chromatography
IEC	Independent Ethics Committee
IPC	In-process control
IR	Infrared
K_2EDTA	Potassium (K_2) Ethylene Diamine Tetraacetic Acid
KF	Karl Fisher
LC-ESI-MSMS	Liquid chromatography/electrospray ionization tandem mass spectroscopy
LDPE	Low-density polyethylene
LLOQ	Lower limit of quantitation
MAH	Marketing Authorisation holder
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MS	Mass Spectrometry
NLT	Not less than
NMT	Not more than
Ph. Eur.	European Pharmacopoeia
QA	Quality assurance
QC	Quality Control
RH	Relative Humidity
RP	Restricted Part (or Closed Part) of ASMF
RSD	Relative standard deviation
S1P	sphingosine 1-phosphate receptor
SLS	Sodium lauryl sulfate
SOP	Standard Operating Procedure

$t_{1/2}$	Half-life
T_{max}	Time to maximum plasma concentration
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
WIRB	Western Institutional Review Board
XRPD	X-Ray Powder Diffraction

1. Recommendation

Based on the CHMP review of the data and the Applicant's responses to the CHMP questions on quality, safety and clinical development, the generic application for Fingolimod Mylan 0.5 mg hard capsules **is not approvable** in the claimed indication:

"Treatment as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and paediatric patients aged 10 years and older:

• Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (for exceptions and information about wash-out periods see sections 4.4 and 5.1).

or

• Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.",

since quality and clinical major objections remain, which preclude a recommendation for marketing authorisation at the present time. More details on these are available in the report below.

Questions to be posed to additional experts

N/A

Inspection issues

GMP inspection(s)

No pre-approval inspections are requested.

GCP inspection(s)

No trigger for inspection was identified from the data provided for the BE-study.

2. Executive summary

2.1. Problem statement

N/A

2.2. About the product

The product Fingolimod Mylan 0.5 mg hard capsules has been developed by Mylan, as a generic to the innovator's product Gilenya 0.5 mg hard capsules, Novartis Europharm Limited.

Both the test and the reference product contain the same active ingredient i.e. fingolimod hydrochloride.

One bioequivalence (BE) study has been performed with the originator. The test product (Fingolimod Mylan, 0.5 mg hard capsules, Batch number: 1001046) and the reference product (Gilenya, 0.5 mg

hard capsules, Batch number: S0105) were compared in the fasting conditions (Study No. FING-15026).

Proposed indications

Fingolimod Mylan is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and paediatric patients aged 10 years and older:

• Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (for exceptions and information about washout periods see sections 4.4 and 5.1).

or

• Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

2.3. The development programme/Compliance with CHMP Guidance/Scientific Advice

The CHMP Guidelines were followed.

The applicant has conducted one fasting bioequivalence study on 0.5 mg strength in accordance with the Guideline on the Investigation of bioequivalence and Fingolimod product-specific bioequivalence guidance (EMA/CHMP/154812/2016).

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

2.4. General comments on compliance with GMP, GLP, GCP

GMP

The QP declaration for fingolimod hydrochloride is based on on-site audit at the active substance manufacturing site. The declaration is made on behalf of the QPs from batch release sites and bulk product manufacturer. Acceptable standards of GMP are in place for this product at all sites responsible for the manufacture, primary packaging, secondary packaging, quality control testing and batch release. For manufacturing site outside the Community (bulk manufacture site) a copy of GMP certificate issued by the competent authority in the Community is enclosed.

GLP

As applicant did not submit new non-clinical studies, this paragraph is considered non-applicable.

GCP

The applicant confirmed that the bioequivalence study FING-15026 was performed in accordance with the protocol, relevant SOPs, pertinent requirements of EMA, the ethical requirement of Directive 2001/20/EC, the ICMR Ethical guideline, International Conference on Harmonization (ICH), Guidance on Good Clinical Practice and Declaration of Helsinki.

Moreover, the applicant has also confirmed that the bioequivalence study FING-15026, carried out outside the European Union, meets the ethical requirements of Directive 2001/20/EC.

For the analytical, PK and statistical site, the applicant has provided a list of GCP and GLP inspections. The most recent inspection by an EU MS Inspectorate was undertaken by the MHRA in 2014. No significant issues of non-compliance were identified.

For the clinical site, the applicant clarified in response to the CHMP request, that this site no longer initiates new studies in support of clinical Bioavailability and Bioequivalence programs due to a change in business scope and provided a list of GCP inspections conducted prior to 2018. Inspections were undertaken by the FDA in 2014, 2015 and 2017, where no significant issues of non-compliance were identified. Competent European authorities have not inspected the clinical site. However, the clinical site was monitored for Quality Assurance and no specific concerns were identified during the assessment of the dossier that would trigger the request for inspection.

In response to the CHMP request, the applicant submitted the Monitoring Report of the bioequivalence study FING-15026. The data confirmed that the study was closely monitored by the sponsor for compliance with the procedures described in the protocol (FING-15026).

2.5. Type of application and other comments on the submitted dossier

Legal basis

- Article 10(1) of Directive 2001/83/EC.

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: Gilenya 0.5 mg capsules, hard
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: (17-03-2011)
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/11/677/001-006

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

- Product name, strength, pharmaceutical form: Gilenya 0.5 mg capsules, hard
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: (17-03-2011)
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/11/677/001-006

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: Gilenya 0.5 mg capsules, hard (EU/1/11/677/001-006) as reference product sourced from United Kingdom (BE study FING-15026)
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: (17-03-2011)
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number(s): EU/1/11/677/001-006
- Bioavailability study number(s): BE study FING-15026

Orphan designation

Not Applicable.

Similarity with orphan medicinal products

The application did not contain a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

Derogation(s) from orphan market exclusivity

Not Applicable.

Information on paediatric requirements

Not applicable.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as immediate release, hard gelatin capsules containing 0.5 mg of fingolimod hydrochloride as active substance.

Other ingredients are:

- **Capsule content**: calcium hydrogen phosphate dihydrate**,** glycine**,** silica, colloidal anhydrous**,** magnesium stearate.
- **Capsule shell**: gelatin**,** titanium dioxide (E171)**,** yellow iron oxide (E172)**,** red iron oxide (E172).
- **Printing ink**: shellac (E904)**,** dehydrated alcohol**,** isopropyl alcohol**,** butyl alcohol**,** propylene glycol (E1520)**,** ammonia solution**,** black iron oxide (E172)**,** potassium hydroxide**,** purified water.

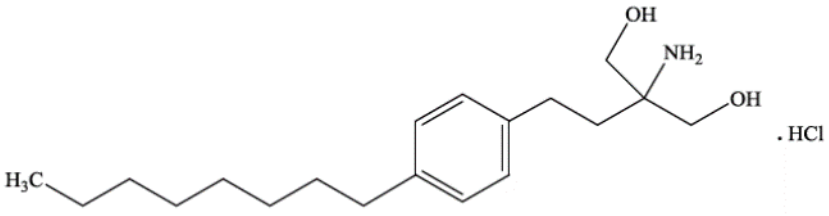
The product is available in PVC/Aclar-Alu blisters, PVC/PE/PVdC-Alu blisters and HDPE bottles.

3.1.2. Active Substance

General Information

Fingolimod hydrochloride is an immunomodulating active substance used in treatment of multiple sclerosis. It is described in the Ph. Eur. (monograph 04/2019:2988). An ASMF procedure is followed.

Figure 1 Structural formula:



Molecular formula: $C_{19}H_{34}ClNO_2$

Molecular weight: 343.9

Fingolimod hydrochloride is non-hygroscopic, freely soluble in water and methanol, soluble in ethanol and freely soluble in the range from pH 1.2 – 4.5.

It does not contain any chiral or asymmetric carbon atoms; hence, it does not exhibit stereoisomerism.

Fingolimod hydrochloride exhibits polymorphism. The test for identification of polymorph by XRPD is part of drug substance release and stability specifications. According to XRPD data of three consecutive production scale batches Mylan Laboratories Limited consistently produces one crystalline form. Stability of polymorphic form when stored at 5 ± 3°C is confirmed by results of stability studies.

Manufacture, process controls and characterisation

The synthesis route for fingolimod hydrochloride consists of five chemical transformations. The short description of the synthesis in the Applicant`s part of the ASMF is followed by the detailed description of every step from starting material in Restricted Part. Question regarding reagents listed in Applicant`s part was appropriately resolved in the Response to CHMP Day 120 Questions, all the reagents used in manufacturing process have been included in the flow diagram and route of synthesis.

According to the information in the Restricted Part reprocessing and blending procedures are used. The Applicant's Part was properly updated with this information in the Response to CHMP Day 120 Questions. The information about reprocessing procedure has been deleted from ASMF in the Response to CHMP Day 180 Questions as no reprocessing has been used so far and the ASMF holder has no experiences with the reprocessing.

The proposed starting materials are acceptable as both show compliance to ICH Q11 and the EMA Guideline on the Chemistry of active substances as starting material (sufficient number of chemical steps, well established specification to ensure the quality of starting material, sufficiently characterised starting material by IR, UV, NMR and mass spectroscopy, suitable control of potential genotoxic impurities). Supplier`s name, address and synthesis are provided. Specification for starting materials with impurity control, analytical procedures for the control of starting material and certificate of analysis are presented.

For in-process controls and intermediate testing specifications and details of analytical procedures are provided. The discussion on carry-over of impurities from the starting material is provided.

With the results of analyses provided in the Response to CHMP Day 180 Questions, it was demonstrated that the nitrosamine impurities were not present in the intermediate diester and in final API, however the validations of the methods are deficient. At least summary of the method validation should be provided. The limit of detection is far below the acceptable intake of impurities. On the other hand, the carry-over of nitrites is not completely excluded and there is no control of nitrosamine impurities in any stage of the API manufacturing process, although the risk of formation of N-nitrosodimethylamine (NDMA) cannot be excluded. Hence, it is found necessary to include the control for presence of nitrosamines. It is recommended to include the appropriate limit for NDMA in the specification for intermediate or in the specification of API. The complete validation for this analytical procedure should be also provided. As not adequate response for this issue was provided in the Response to CHMP Day 180 Questions, the major objection has not been resolved and remains.

Structure elucidation and chemical properties of active substance are documented via different analytical techniques (IR spectroscopy, UV spectroscopy, NMR spectroscopy (^{1}H-NMR and ^{13}C-NMR), mass spectrometry, elemental analysis and XRPD analysis).

Potential impurities have been identified and the origin of each impurity is stated. The exclusion of three Ph.Eur. impurities in the specification of final active substance is adequately elaborated. The carryover of impurities from starting material onwards is discussed and an appropriate control strategy is defined.

The contents of all solvents used in the manufacturing process of API are controlled in the specification of the active substance. In addition, benzene was found to be not detected in drug substance batches. Palladium (Class-2B) is used in the manufacturing process of drug substance. The results obtained for palladium with validated ICP-MS method in three production scale batches of drug substance are below detection limit and under 30% of ICH Q3D limit. No other metal catalyst or reagents which could contribute to the elemental impurities are used in the manufacturing process of drug substance. Hence, the results for ICH Q3D Class-1 and Class-2A elements are sufficient. A minor question about Zn control has been resolved in the Response to CHMP Day 180 Questions.

Discussion on the carry-over of (potential genotoxic) impurities and residual solvents from both starting materials into the final drug substance is provided and all relevant parts of ASMF (AP and RP) updated accordingly. An appropriate control strategy has been defined. Nevertheless, the ASMF holder should resolve the issue regarding the potential presence of NDMA.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Proposed specifications for fingolimod hydrochloride from drug product manufacturer include tests for appearance, solubility (Ph. Eur.), identification (IR, chloride, PXRD), water content (Ph. Eur.), sulfated ash (Ph. Eur.), related substances (HPLC), assay (HPLC), residual solvents (HSGC) and particle size (in house).Specification limits are set according to the Ph. Eur. monograph for fingolimod hydrochloride and general requirements of Ph.Eur. Additional test parameters are residual solvents, identification of polymorph and particle size. The limits for residual solvents are in line with the ICH Q3C limits. Stability indicating parameters are included in stability testing. The test parameters included in the specification are adequate, and the corresponding acceptance limits are considered justified. The drug product manufacturer control fingolimod hydrochloride in line with the specification of drug substance manufacturer in ASMF and with additional test for particle size. Regarding the particle size question

raised in CHMP Day 120 Questions, the applicant has made a review on particle size batch data. The data on more recent batches confirm the specification.

Description of analytical procedures is provided for all specified tests. The in-house HPLC analytical procedure is used for assay of active substance and for related substances instead of Ph.Eur. method. In order to prove that the in-house methods are equivalent to the Ph.Eur. monograph methods, an equivalency study has been carried out for related substances and assay. The results obtained from both in-house method and Ph.Eur. monograph method are comparable and meet the acceptance criteria. Therefore, the in-house method for determination of related substances for fingolimod hydrochloride is comparable to that of Ph.Eur. monograph method. The analytical results for demonstrating the stability indicating nature of HPLC method for assay and related substances (in-house method) are provided.

In addition, analytical procedures for residual solvents and methods used in the carry-over studies of potential impurities are sufficiently validated.

The analytical results for three production scale batches are provided and are in compliance with the proposed specification. The provided batch analysis data confirm consistency of the manufacturing process and the quality of the drug substance. The data on more recent batches are provided in the Response to CHMP Day 120 Questions.

For evaluation of active substance fingolimod hydrochloride Ph.Eur. and working standard, USP Fingolimod System Suitability reference standard and impurities (A, B, C, D, G, I, alcohol analogue) standards are used.

The active substance is stored in LDPE bag inserted in black polyethylene bag and outer triple laminated aluminium bag, placed in HDPE drum. The provided information on description and control of the container closure system for the drug substance is considered satisfactory.

Stability

Stability studies (long term and accelerated) were carried out for three production scale batches under ICH conditions and the tested parameters are stability indicating. Storage under long-term (60 months at 5 ± 3°C) and accelerated conditions (6 months at 25°C ± 2°C, RH 60 ± 5%) showed no upward or downward trends, all results remain within specification up to 60 months.

The stability batches are tested as per old in-house specifications and test procedure. Nevertheless, the same batches are tested at 60-month time-point per specification and analytical procedures, given in currently submitted ASMF in sections S.4.1 and S.4.2, to justify the claimed re-test period. The results comply with specification. The ASMF holder confirms that for the future stability studies, specification and analytical procedures in sections S.4.1 and S.4.2 will be used. Moreover, the API is stored at restricted conditions, at 5°C ± 3°C, for which the provided results at 60-months time point are sufficient. Post-approval stability commitment is provided in Module 3 that every year one production batch will be added to the stability study program if manufactured and assessed as per long-term annual stability conditions as per specification and analytical procedures in sections S.4.1 and S.4.2.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description and composition

The finished product is formulated as immediate release hard gelatin capsules in 0.5 mg strength. According to the SmPC the recommended dose is one capsule taken orally once daily. The capsule is a No. 3 with brown-orange opaque cap and white opaque body. It is filled with white to off white powder. The capsule is axially printed with "**MYLAN**" over "**FD 0.5**" in black ink on both the cap and body.

The qualitative composition of components of final drug product are presented in section 3.1.1 above.

The capsules are purchased as pre-printed empty capsule shells, therefore, the finished product manufacturer does not test and release the individual ingredients of capsule shells. The capsule shells and printing ink are listed with supplier code(s), which are liable to administrative change. Any updates will be automatically incorporated provided the composition and material specifications for these empty hard gelatin capsule shells and printing ink remain unchanged.

The product is presented in the following pack types; PVC/PE/PVdC - Alu blister pack, PVC/Aclar - Alu blister pack and high-density polyethylene (HDPE) bottle pack. Bulk packs are proposed for holding the finished product before packaging or for transportation to any other approved re-packaging site in European Economic Area.

Pharmaceutical development

The purpose of the pharmaceutical development studies was to develop a generic version of the reference formulation Gilenya® (Fingolimod) 0.5 mg hard capsules of "Novartis Europharm Limited, UK".

The reference product is an immediate release product with low dose of active substance therefore content uniformity and maintenance of assay were considered critical criteria for selecting an appropriate manufacturing process. Wet granulation was evaluated but a dry granulation process was found more acceptable to maintain potency during processing. Manufacturing process was further optimized including roller compaction, milling and second blending.

The qualitative composition of the excipients is different between proposed and reference product. Optimization studies were performed on the selection of fill weight, fillers and disintegrants. The excipients compatibility studies with drug substance have been performed. Test product and EU reference product exhibit similar impurity profile.

The quality target product profile (QTPP) was defined and critical quality attributes (CQAs) were identified. These CQAs include assay, content uniformity, dissolution and related compounds. A risk assessment of the drug substance attributes, formulation variables and manufacturing process variables was performed to evaluate their impact on the drug product CQAs.

The dissolution method was described in sufficient detail and choice of dissolution media is considered justified. As requested at d120 LoQ discriminatory power of proposed dissolution method has been proven for the proposed dissolution limit. A bioequivalence study between proposed Fingolimod 0.5 mg capsules and the reference product Gilenya® (fingolimod) 0.5 mg capsules (Novartis Europharm Ltd., UK) was performed. According to the applicant there is no difference in the unit composition and the manufacturing process principle of the biobatch and the proposed commercial batch. However, the proposed commercial manufacturing process uses a different compactor fitted with different mill equipment. Effect of the change in mill equipment was evaluated and demonstrated similarity of the produced capsules. In day 120 responses a discussion on the effect of different compactor fitted with different mill on similarity between biobatch and the proposed commercial batch has been provided. Similarity between the products made using the two compactor types has been proven.

Comparative dissolution profiles, complementary to the in vivo bioequivalence study, between test product and European reference product were generated. In the Response to CHMP Day 120 Questions

additional dissolution data of the reference product and submission batches manufactured at the proposed manufacturing site have been provided.

The drug product is proposed for use in adult patients and paediatric patients of 10 years and older. As requested, some aspects of the specific needs of the paediatric population have been sufficiently discussed. As requested at day 180 additional discussion on the specific needs for paediatric population was provided.

Standard container closure system is used (blister pack and HDPE bottle). Provided stability data confirm suitability and compatibility of container closure system with the drug product.

Manufacture of the product and process controls

Manufacturing process

The manufacturing process is a standard dry granulation process. It is combined of several blending steps, dry granulation and final encapsulation. Comprehensive narrative description of the manufacturing process is provided. The level of detail in the description is found sufficient.

In the Response to CHMP Day 120 Questions additional clarifications regarding the batch formula, potency calculation, overages of excipients and holding time of process intermediates have been provided.

Filled capsules may be stored and transported as bulk product packaged in LDPE bag. Bulk packaging is appropriately described. In day 120 responses updated bulk stability data have been provided.

The control strategy for these critical steps is based on the process development studies performed. As requested, the test frequency of specific in-process tests has been updated.

The amount of dug substance in medicinal product is low (0,75 %) therefore the submission of process validation data is mandatory. The validation reports for three validation batches (proposed as a production-scale batch) are provided together with process validation protocol. In day 120 responses the production batch size has been redefined to submission batch size for which the process validation study has already been completed.

Product specification, analytical procedures, batch analysis

The proposed release and shelf-life specifications for Fingolimod Mylan tablets include tests for description, identification (HPLC), dissolution (HPLC), uniformity of dosage units (content uniformity), related compounds (HPLC), assay (HPLC), microbiological test (Ph. Eur.), colour identification (iron oxide, titanium dioxide), water (KF).

The test parameters included in specifications are adequate, some limits have been tightened as requested.

Specification limits for specified and any other unidentified impurity are in accordance with ICH Q3B. Nevertheless, in day 120 responses limits for specified and total impurities have been tightened in accordance with batch results.

As requested, the specification limit for dissolution, shelf-life limit for assay and water content have been tightened.

Analytical procedures and reference standards

The analytical procedures used in the control of drug product are satisfactory described. Validation data of in-house analytical methods are in accordance with the requirements of the relevant ICH guidelines and acceptable. As requested, the applicant has demonstrated the discriminatory power of dissolution method in development section of documentation.

In responses further information on reference standards has been provided.

Batch analysis

Batch analysis data for three submission batches and the biobatch are provided. The manufacturing site, date of manufacture, use and batch size of each batch are stated. The batch size corresponds to the production-scale batch. The analytical results for all batches are in compliance with the proposed specification. The provided batch results confirm consistency of the manufacturing process and uniformity of drug product.

Container closure

The specification, IR spectra and compliance certificates are provided for all the packaging materials of the container closure system (PVC/PE/PVdC - Alu blister, PVC/Aclar - Alu blister, HDPE bottle pack and LDPE bulk pack). As requested, a compliance statement to EU regulation 10/2011 for the sealant layer of the wad with induction seal has been provided.

Stability of the product

In day 120 responses the proposed shelf-life is 17 months with storage conditions: "Do not store above 25°C. Store in the original package in order to protect from moisture".

According to provided in-use stability data in-use shelf-life up to 180 days for HDPE bottle containing 500 capsules is confirmed. This in-use period covers pack sizes stated in the Application Form (90 or 100 capsules in bottle). In the response to CHMP Day 120 Questions in line with EMA Q&A (Part 2) no in-use shelf life was proposed.

Three submission batches are included in stability testing program. The submission batches are proposed production scale batches and are representative for the commercial production.

During stability studies following parameters are controlled: description, assay, dissolution, water, microbiological test and related substances.

The stability of Fingolimod 0.5 mg capsules is being assessed at ICH accelerated i.e. 40 ± 2°C / 75 ± 5% RH, intermediate i.e. 30 ± 2°C / 65 ± 5% RH and long-term stability conditions i.e. 25 ± 2°C / 60 ± 5% RH. The finished product batches have completed the stability study up to 6 months at accelerated and up to 12 months at intermediate and long-term stability conditions. The batches were stored in blister packs PVC/PE/PvdC, blister packs PVC/Aclar and HDPE bottles.

All tested parameters remained within the applied acceptance criteria specification during storage under intermediate and long-term stability conditions. There is a trend of slightly increase of impurities but well within acceptable limits.

In response to CHMP d120 Questions the applicant performed statistical evaluation on updated long-term stability data according to the ICH Q1E guidance. Based on evaluation the shelf-life of the product was proposed. Major objection was resolved.

Forced degradation studies were performed during validation of the assay and related test methods. Drug substance, drug product and analytical placebo were exposed to harsh environmental conditions. The observed degradation was low in acidic, basic, humid, hot and light conditions. The maximum

degradation was observed at oxidative conditions. There are no significant interferences as the observed impurities are well resolved from the active and placebo peaks. Fingolimod is spectrally pure in all intentional stress conditions. As requested, the applicant has provided additional discussion in a view of stability indicating nature of HPLC related substances method.

Photostability study was conducted as per ICH Q1B guideline and there were no out of specification results. Capsules are not photosensitive.

Open pot stability study was performed by loading the sample into open containers exposed at 25 ± 2°C / 60 ± 5% RH. The product was found to be stable at the studied open pot stability conditions.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Drug substance

Fingolimod hydrochloride is a well-known active substance with the Ph.Eur. monograph, which has been recently released (since April 2019). One source of active substance is proposed and ASMF procedure is used. The section Control of active substance by the drug product manufacturer is provided with information on specifications, analytical procedures and their validation. The reference standards from drug product manufacturer are provided. Most of the issues on active substances are satisfactorily addressed in the Response to CHMP Day 120 Questions and CHMP Day 180 Questions, however the major objection regarding nitrosamine issue remains unresolved.

Drug product

Major objection had been raised in relation to limited stability data. In response to CHMP d120 Questions updated long term and intermediate stability data were provided. Statistical evaluation on updated stability data was performed and shelf life of 17 months proposed. Major objection was resolved.

The drug product is proposed for use in adult patients and paediatric patients of 10 years and older. As requested, some aspects of the specific needs of the paediatric population were sufficiently discussed in the responses to CHMP Day 120 and Day 180 Questions.

In the Response to CHMP Day 120 Questions for the reference product and the test product additional comparative dissolution data generated at three dissolution media were provided. The discriminatory power of the dissolution method has been demonstrated for revised dissolution limit. Additional data to demonstrate similarity of the produced capsules has been included at day 120 response. The description of manufacturing process is sufficient. Additional clarification has been provided regarding the batch formula and overages of excipients. The specification parameters set for the drug product are adequate, some limits have been tightened. Standard container closure system is used.

The chemical-pharmaceutical documentation (Module 3) and Quality Overall Summary in relation to Fingolimod Mylan 0.5 mg hard capsules are currently of sufficient quality in view of the present European regulatory requirements.

3.2. Non clinical aspects

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

The impurity profiles of Fingolimod Mylan 0.5 mg hard capsules were compared with European reference product Gilenya 0.5 mg hard capsules, marketed by Novartis Europharm Limited. Both test product and EU reference product exhibit similar impurity profile.

In response to the CHMP request, the non-clinical overview dated October 25, 2019 was updated with adequate and comprehensive assessment of the impurities and degradants present in the drug substance and product along with what is known of their potential pharmacological and toxicological effects as requested. All impurities (organic, elemental and mutagenic) and residual solvents in drug substance and drug product are controlled within the ICH specifications, which is acceptable.

3.2.1. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment (ERA) was submitted. This was justified by the applicant, as the introduction of Fingolimod Mylan is considered unlikely to result in any significant increase in the combined sales volumes for all Fingolimod containing products and the exposure of the environment to the active substance. Thus, a risk for the environment is therefore not anticipated for Fingolimod. Discussion on non-clinical aspects

Pharmacodynamics, pharmacokinetic and toxicological properties of fingolimod is widely used, well-known active substances. It is agreed that no further non-clinical studies are required. Overview based on literature review is appropriate.

The impurity profiles of Fingolimod Mylan 0.5 mg hard capsules were compared with European reference product Gilenya 0.5 mg hard capsules, marketed by Novartis Europharm Limited. Both test product and EU reference product exhibit similar impurity profiles. The impurity profiles have been discussed and was considered acceptable.

The applicant's justification for non-submission of an Environmental Risk Assessment is considered acceptable.

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

3.2.2. Conclusion on non-clinical aspects

There are no objections to approval of Fingolimod Mylan 0.5 mg hard capsules from a non-clinical point of view.

3.3. Clinical aspects

Relevant guidance documents for this assessment are the Fingolimod product-specific bioequivalence guidance (EMA/CHMP/154812/2016) and Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

This centralised application concerns a generic application according to article 10(1) of Directive 2001/83/EC for Fingolimod Mylan 0.5 mg hard capsules. The originator product is Gilenya, which contains fingolimod hydrochloride as capsule, hard of Novartis, Europharm Limited authorised in the community on 17 March 2011 via the centralised procedure.

One bioequivalence (BE) study has been performed using the originator, using the test product (Fingolimod Mylan 0.5 mg hard capsules) and the reference product (Gilenya 0.5 mg hard capsules).

The applicant has provided a clinical overview, Mylan Pharmaceuticals, Inc. Morgantown, US. Report refers to 38 publications up to year 2018. Information stated in the clinical overview is up-to-date, adequately supported with the scientific literature.

Pharmacodynamic, pharmacokinetic, efficacy and safety profiles of fingolimod are well known. As fingolimod is a widely used, well-known active substance. An overview based on literature review is, thus, appropriate. The clinical overview adequately justifies the proposed indication.

The claimed indication and method of administration of the proposed SmPC are in line with the SmPC of the reference product, Gilenya. The posology information of the SmPC is requested to be in line with that of the reference product, please refer to separate comments on PI.

3.3.1. Exemption

Not applicable.

- **Tabular overview of clinical studies**

Table 1

CTD SECTION	STUDY NUMBER AND TITLE	STUDY TYPE	STUDY SUB TYPE	DOSAGE
CTD section 5.3.1.2	Single-Dose Fasting Bioequivalence Study of Fingolimod Capsules (0.5 mg; Mylan), GILENYA® Capsules (0.5 mg; Novartis-Canada) and GILENYA® Capsules (0.5 mg; Novartis-UK) in Healthy Adult Male Volunteers FING-15026	Pharmacokinetics	Fasting	1 x 0.5 mg

3.3.2. Pharmacokinetics

To support the application, the applicant has submitted a review of clinical data as well as one bioequivalence study`s report was presented for this application:

Bioequivalence study No.: FING-15026 under **fasting conditions**

Methods

Study design

This was a blinded, single-dose, randomized, **three-period**, **three-treatment**, **crossover study** to investigate the bioequivalence of **Mylan's Fingolimod** capsules, 0.5 mg to **Novartis Canada's GILENYA®** Capsules, 0.5 mg and to **Novartis UK's GILENYA®** Capsules, 0.5 mg following a single, oral 0.5 mg (1 x 0.5 mg) dose administration in healthy male volunteers under fasting conditions.

The study design employed (as a randomized fasting single dose cross-over design) is appropriate for the bioequivalence study according to the requirements of the Fingolimod product-specific bioequivalence guidance (EMA/CHMP/154812/2016). The study was conducted in two groups (Group-I and Group-II). The option of possible multi-cohort was mentioned in the protocol (The protocol cites "In the event that separate enrolment are necessary to complete the intended number of subjects, appropriate adjustment may be made to the statistical model to reflect the multi-cohort nature of the study"). In response to the CHMP request, the applicant clarified that two-stage design was not used for this study.

The study was conducted under fasting conditions, which is acceptable as the drug product can be taken with or without food and the fasting condition is the most sensitive to identify differences

between the formulations. As fingolimod is highly distributed in red blood cells, blood was used as matrix for the evaluation of fingolimod concentrations, which is acceptable. The measurement of the parent compound (fingolimod) in blood is in line with the requirements of the Fingolimod product-specific bioequivalence guidance (EMA/CHMP/154812/2016).

The study was conducted with 24 healthy, adult, male subjects in accordance with the protocol. 16 subjects completed at least two periods of the study with test and EU reference product.

In each group, the subjects received one tablet of either test (A) or reference products (B or C) randomly with 240 mL of ambient temperature on the day of dosing as per the randomization schedule under fasting conditions in each period of the study. Drug product was administered after at least 10.00 hours overnight fasting. The total duration of the study was 3 months and 14 days from period-1 check-in until the last blood sample collection of period-3 including a wash-out period of 28 days between each dosing.

In response to the CHMP request to adequately justified a short wash-out period of 28 days or conduct an additional bioequivalence cross-over study with sufficient wash-out periods between treatments, the applicant performed a second analysis using bioanalytical extrapolation to recalculate pre-dose concentration values for Periods 2 and 3 previously considered below the limit of quantitation (BLQ) and performed pharmacokinetic based extrapolations to strip away carryover to Periods 2 and 3. This new analysis was not considered acceptable as extrapolation based on a lower LLOQ was not possible considering the elimination half-life of the active substance in the concerned subjects in a period. Since the sampling period was only until 72h post-dose, there was no elimination half-life (washout should had been 6-9 days according to the innovator's SPC and this cannot be determined based on a 3-day curve).

Due to the fact that fingolimod has a very long half-life of 6-9 days, adequate wash-out periods between treatments in the cross-over study should be ensured. In this cross-over study, the washout period of 28 days is less than 5 half-lifes of the active substance, and thus not enough to avoid potential carry-over effects. Outstanding issue related to the inadequate study design **still remains unresolved**.

Blood samples were collected in K_2EDTA tubes at pre-dose (0.00 hours) and at intervals over 72.00 hours after administration of dose, which is acceptable for a substance with a long half-life to characterize the plasma concentration-time profile. The issue regarding the frequency of blood sampling around the peak concentration of fingolimod to determine the T_{max} accurately was resolved within the Applicant`s responses. It this it was explained that the expected Tmax is generally around 12-16 hours as per Gilenya® label, therefore the applicant is of the opinion that sampling every 2 hours from 2 to 20 hours is adequate: 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 36, 48 and 72 hours. Due to the slow clearance, along with the large volume of distribution, blood concentration time curve is relatively flat. David (2012) provides a summary of single-dose fingolimod data with profiles similar to the bioequivalence study FING-15026. Additional timepoints after 24 hours would not have provided any more meaningful PK information.

No other protocol deviations have been registered other than minor deviations from the blood sampling time points and two subjects did not complete study exit evaluation. The deviations in scheduled sampling time had no impact on study results as actual sampling times were used for PK calculations.

In response to the CHMP request, the applicant submitted the table of schedule of events.

Test and reference products

The identity of all three tested products **A**, **B** (Canadian submission) and **C** (EU submission) are provided in the submission from the Applicant. However, **only information of the test formulation A and the reference formulation C for EU submission are presented in this assessment report**.

The reference and test products are acceptable.

In the response to Day 120 LoQ, a signed statement confirming that the test product has the same quantitative composition and is manufactured by the same process as the one submitted for authorisation is provided.

Population(s) studied

24 subjects (male) participated in this study. Subjects were dosed in two groups.

In Group-I, a total of **20 healthy subjects** (subject numbers 1-6, 8-16, 18, 19, 22-24) who met the inclusion and exclusion criteria as mentioned in the study protocol were enrolled into the study. From Group I, **Subject number 01, 19 and 22** did not meet the pre-dose vital sign criteria prior to Period 2 dosing. **Subject 8** withdrew consent due to personal reasons prior to Period 2 dosing. **Subject 16** did not report to the clinic for Period 2 dosing. **Subjects 18 and 23** withdrew consent due to personal reasons prior to Period 3 dosing. **Subject 2** was discontinued due to a positive breathalyzer test at Period 3 check-in. **Subject 11** withdrew consent due to personal reasons prior to Period 3 dosing. Two subjects (**Subjects 5 and 15**) had pre-dose concentrations greater than 5% C_{max}, and were excluded from the statistical analysis for Canadian submission.

In Group-II, a total of **4 healthy subjects** (subject numbers 7, 17, 20-21) who met the inclusion and exclusion criteria as mentioned in the study protocol were enrolled into the study to ensure the dosing of 24 subjects.

Fifteen (15) subjects completed the clinical phase of the study successfully.

A total of sixteen subjects (16) completed at least two periods of the study with test and **EU reference product (C)** and **were included in the pharmacokinetic and statistical analysis for EU submission.**

The population chosen is according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1). Inclusion and exclusion criteria are acceptable and performed according to the protocol requirements. All the subjects were dosed as per the randomization. The reason of the withdrawal is acceptable. As response to the CHMP queries regarding withdrawn subjects from the study, the applicant adequately justified withdrawal of subjects 01, 02, 08, 11, 16, 18, 19, 22, and 23 from the Study FING-15026 by presenting the Case Report Forms (CRFs) of those volunteers.

Sample size determination

According to applicant, the sample size estimation was based on assumption of ratio between 90%-111% and an intra-subjects' variability of 10%. A minimum of 12 subjects was calculated to be required to conclude bioequivalence with approximately 80% power. To account for withdrawal and dropouts, 24 subjects were randomized and dosed.

Analytical methods

A validated high-performance liquid chromatography electrospray ionization tandem mass spectrometric method (LC-ESI-MS/MS) for the determination of fingolimod (FING) in K_2EDTA human whole blood was used to assay all biostudy samples. Sample processing involved liquid-liquid extraction followed by LC-MS/MS analysis, using Analyst 1.5.1 software as the chromatography data system.

The analysis of the blood samples for fingolimod were carried out by the Bioanalytical Department of Mylan Pharmaceuticals Inc., Morgantown.

A total number of 928 collected samples were received frozen from WVU Clinical and Pharmacologic Research, (Morgantown, WV) to the bioanalytical facility. However, only the primary set of samples (784 subject samples) was analysed for the biostudy. Samples were stored at -70°C from the date of initial sample collection on 01 Aug 2015, until the final day of sample processing on 18 Dec 2015, resulting in the maximum sample storage period of 139 days at -70°C. Stability of fingolimod in blood has been demonstrated for 488 days of storage at -70°C.

The calibration curve for fingolimod ranged from about 50.00 – 600.00 pg/mL with a LLOQ of 50.00 pg/mL used in subject sample analysis of Fingolimod. A weighted (1/C2) linear regression was performed to determine the concentration of the analyte. The quality control sample data for fingolimod were assessed with between-run precision of 3.79 – 5.63 % and accuracy of 95.38 – 97.33%.

The analytical method was validated, either pre-study and within study according to Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009.

Long-term stability data of fingolimod in blood at -70°C for 488 days showed stability of the subject samples stored under these conditions for 139 days.

The reasons for reanalysis of samples in each of the sample analysis are considered justified.

The incurred sample reanalysis confirmed the reproducibility of the method.

Certificates of analysis for reference and internal standard were included in the dossier.

Analytical chromatograms of calibrant, QC and study samples (and corresponding sample sequences) from at least 20% of the subjects were included in the dossier.

Neither carry–over, nor matrix effect was observed.

Selectivity of the fingolimod in the presence of the fingolimod phosphate metabolite has been demonstrated. As well as selectivity of the fingolimod in presence of the metabolites (butanoic acid metabolite and ceramide metabolite M29 and ceramide metabolite M30) has been demonstrated in response to the CHMP request. Although no concomitant medication was given to subjects, the analytical method has been validated for selectivity for 20 over-the-counter medicinal products.

In the Day 120 Assessment Report, some other concerns identified in the bioanalytical and validation reports were resolved within the Applicant`s Responses to the LoQ Based on the comment regarding the sensitivity of the lower limit of quantitation (LLOQ), the applicant re-estimated the FING-15026 study concentration data based on extrapolation of the bioanalytical standard curve for all below the limit of quantitation (BLQ) values previously reported, down to a cut-off of 5 pg/mL. This response is not acceptable, partially based on that extrapolation based on a lower LLOQ is not possible considering the elimination half-life of the active substance in the concerned subjects in a period. Since the sampling period was only until 72h post-dose, there was no elimination half-life (washout should had been 6-9 days according to the innovator’s SPC and this cannot be determined based on a 3-day curve).

In addition, in cases where there is extension of the bioanalytical range, the method should be re-validated according to the Guideline on Bioanalytical method validation.

Therefore, the applicant is asked to re-validate the method with an extended range and submit new analytical method validation report.

As a conclusion, this **major objection** combined with insufficient wash-out has **not been resolved** and **remains**.

Pharmacokinetic Variables

Single-dose pharmacokinetic parameters for fingolimod were calculated using non-compartment techniques.

The following pharmacokinetic parameters were determined from the time and concentration data:

The parameters calculated were AUC_{0-72}, C_{max} and T_{max}

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

Secondary pharmacokinetic parameters: T_{max}

The choice of pharmacokinetic variables is in line with the Fingolimod product-specific bioequivalence guidance (EMA/CHMP/154812/2016).

Non-compartmental analysis approach has been used for estimation of pharmacokinetic parameters in bioequivalence study.

In response to the CHMP request, the applicant informed that the T_{max} Nonparametric Analysis was performed using the Wilcoxon's Signed Rank Test.

Statistical methods

Statistical analysis were performed on the pharmacokinetic parameters using the General Linear Models Procedures (PROC GLM) of SAS Software (SAS Institute, Cary, NC). The model tested for treatment effects in the parameters means at an alpha level of 0.05.

Analysis of variance (ANOVA) taking into account sequence, formulation, period and subject within sequence fixed effects was performed on the ln transformed C_{max} and AUC_{0-72} parameters.

Bioequivalence between the Test (Treatment A) and Reference (Treatment C) was tested by the 90% confidence intervals for the ratio of the population geometric means (T/R) for the parameters.

Confidence intervals (CI) were determined for the ln- transformed AUC_{72}, and C_{max} for fingolimod using the treatments least squares means (LS-Means) obtained from ANOVA.

Bioequivalence was concluded when the 90% confidence intervals of geometric least square mean ratio of the test and reference product falls within the acceptance range of 80.00 % -125.00% for ln-transformed C_{max} and AUC_{0-72}.

Pharmacokinetic and statistical analyses were performed on the 16 subjects who completed at least two study periods with test and EU reference product.

In response to the CHMP request, the applicant clarified that two-stage design was not used for this study.

Results

The pharmacokinetic data were analysed as per the statistical method defined in the protocol. The pharmacokinetic and statistical analyses were performed on all three tested products (A, B and C). However, **only data of the test formulation A and the reference formulation C are presented in this assessment report**. This is in line with the Guideline on the Investigation of Bioequivalence which states "In studies with more than two treatment arms (*e.g. a three period study including two references, one from EU and another from USA, or a four period study including test and reference in fed and fasted states), the analysis for each comparison should be conducted excluding the data from the treatments that are not relevant for the comparison in question*".

The pharmacokinetic variables of fingolimod of the Test and the Reference product (C) and statistical evaluation of fingolimod pharmacokinetic variables are shown in Table 2 and Table 3.

Table 2 Pharmacokinetic parameters of Fingolimod of Test and Reference (EU submission); N=16

Pharmacokinetic Parameter	Arithmetic Means (± SD)	
	Test Product	Reference Product
$AUC_{(0-72h)}$ (pg•hr/mL)	20453 ± 4296	20576 ± 3335
Cmax (pg/mL)	339.9 ± 67.10	347.0 ± 62.49
Tmax (hr) †	36.00 (6.000 – 48.00)	36.00 (12.00 – 48.00)

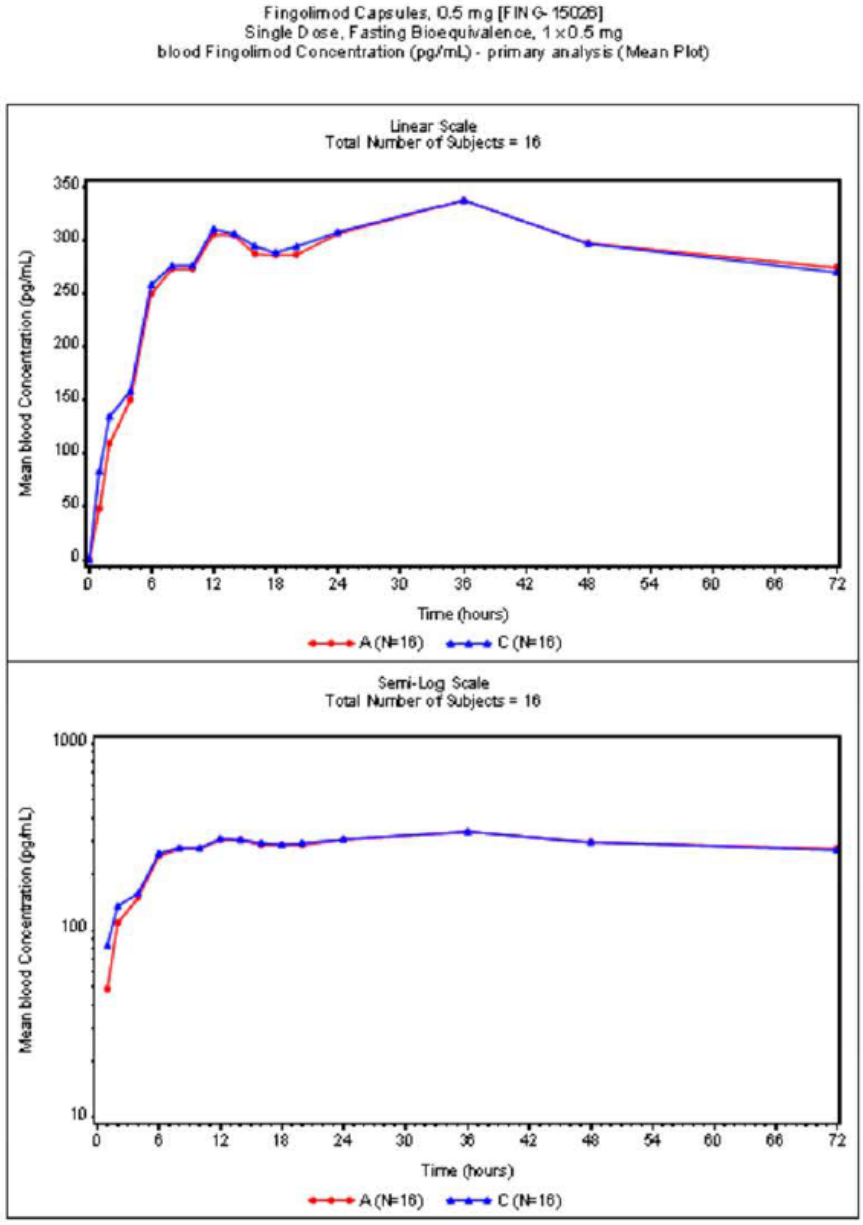
†median (minimum-maximum)

Table 3 Statistical evaluation of Fingolimod pharmacokinetic parameters (EU submission); N=16

Pharmacokinetic Parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%
$AUC_{(0-72h)}$ (pg•hr/mL)	0.98	93.06% – 103.43%	8.42
Cmax (pg/mL)	0.97	91.51% – 102.75%	9.24

Mean concentration-time profiles (semi-log and linear) of **Fingolimod** are depicted in Figure 2.

Figure 2 Linear and Semi Log Plot:



Treatment A: Fingolimod Capsules, Lot#: 1001046, Dose: 0.5 mg (1 X 0.5 mg), Mylan
Treatment B: GILENYA Capsules, 0.5 mg, Lot#: S0097A, Dose: 0.5 mg (1 x 0.5 mg), Novartis-Canada
Treatment C: GILENYA Capsules, 0.5 mg, Lot#: S0105, Dose: 0.5 mg (1 x 0.5 mg), Novartis-UK

Selection of PK parameters, statistical evaluation of the PK parameters and the acceptance ranges for bioequivalence are in accordance with the bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev.1 Cor**).

No subject reached C_{max} at the first sample time.

Based on the reference data, fingolimod reaches maximal blood concentrations ($C_{max)}$ in 12-16 hours. However, in this study delayed T_{max} was observed for the test product ranged from 6 to 48 hours post dose with a median of 36.00 hours. The same tendency of delayed T_{max} was also observed for the reference product (C) ranged from 12 to 48 hours post dose with a median of 36.00 hours. This long absorption time is likely because fingolimod is absorbed along the length of the gastrointestinal tract. No concern is raised.

No statistically significant treatment, or period or formulation effects have been identified for C_{max} and AUC_{0-72} parameters.

In the Day 120 Assessment Report, pre-dose levels of fingolimod observed for two subjects before period 2 or period 3 indicating an inadequate wash-out period, was regarded as a major objection. As described in the Analytical methods section above, this **major objection** combined with a too high LLOQ has not been resolved and **remains**.

Safety data

All 24 subjects were included in the safety and tolerability evaluation.

There were no deaths and other serious adverse events and withdrawals due to AE over the course of the study. Both the formulations (Test A and Reference C) were very well tolerated during the conduct of the study. The reported adverse events were mild in severity and only one AE (headache) possibly related to the study drug (Reference C). Adverse events observed in this study were in line with the known safety profile of the reference product.

Missing case report forms were provided in Day 120 response to the CHMP request.

3.3.3. Pharmacokinetic conclusion

Based on the presented bioequivalence study No: FING-15026 Fingolimod capsule, 0.5 mg is **not** considered bioequivalent with GILENYA capsule, 0.5 mg, as stated above, the presented pharmacokinetic documentation is not fully acceptable and major concerns have been identified.

3.3.4. Pharmacodynamics

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

3.3.5. Additional data

N/A

3.3.6. Post marketing experience

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

3.3.7. Discussion on clinical aspects

To support the application, the company submitted one bioequivalence study and literature data on clinical pharmacology, efficacy and safety, which was considered appropriate and relevant for a generic product application.

The bioequivalence study was designed, as a blinded, single-dose, randomized, three-period, three-treatment, single-dose, crossover bioequivalence study to compare the bioavailability of 2 formulations of fingolimod under fasting conditions.

The reference and test products are acceptable.

Twenty-four healthy, adult, male subjects were enrolled in accordance with protocol. The study was conducted in two groups and in each group, the subjects received one capsule of either test or reference products (B or C) randomly as per the randomization schedule under fasting conditions. A 28

days washout separated each period in group-I and group-II. Given a long terminal elimination half-life ($t_{1/2}$) of fingolimod of 6-9 days, the washout period of 28 days between treatments in the cross-over study was not long enough to prevent any carry-over effect. The washout period should last at least 5 times of the half-live of fingolimod (i.e. 30-45 days). In response to the CHMP request to adequately justify a short wash-out period of 28 days or conduct an additional bioequivalence cross-over study with sufficient wash-out periods between treatments, the applicant performed a second analysis using bioanalytical extrapolation to recalculate pre-dose concentration values for Periods 2 and 3 previously considered below the limit of quantitation (BLQ) and performed pharmacokinetic based extrapolations to strip away carryover to Periods 2 and 3. This new analysis was not considered acceptable, as extrapolation based on a lower LLOQ was not possible considering the elimination half-life of the active substance in the concerned subjects in a period. Since the sampling period was only until 72h post-dose, there was no elimination half-life (washout should had been 6-9 days according to the innovator's SPC and this cannot be determined based on a 3-day curve). Since fingolimod has a very long half-life of 6-9 days, adequate wash-out periods between treatments in the cross-over study should be ensured. The applicant was further asked to provide an analysis of only period 1 data (will resemble a parallel design study) for test and reference in order to avoid influence of carry-over effects. Furthermore, the applicant was asked to submit descriptive PK data for the primary PK parameters Cmax and AUC0-72 presented per period (1, 2 and 3) in order to understand the magnitude of the carry over.

In the Day 180 response, the applicant submitted multiple analyses on the BE study data. Among them was a parallel analysis based on Period 1 data only (analysis 3), for comparison of Test to EU Reference. This analysis was limited in size, there were only 5 subject profiles for Mylan Test product in Period 1 and 6 subject profiles for the EU Reference product in Period 1 as this was a 3-period, 3-treatment BE study and there was a number of dropouts and subjects excluded from bioanalysis. The data from those subjects did not meet the BE criteria for $AUC_{0\text{-}72hr}$ and C_{max}. No conclusion could be drawn from this analysis due to limited in size (11 subjects).

The applicant submitted an additional Analysis (4) in order to understand the magnitude of the carry over. The results of this analysis met BE criteria. However, since extrapolated data shows that carryover from period 1 to period 2 to period 3 occurred in 10 subjects (period 2) and in 11 subjects (period 3), such data should be excluded from bioequivalence calculation according to the current Guideline on the Investigation of Bioequivalence. Therefore, this analysis is not considered acceptable.

The applicant also submitted additional analyses based on the PK stripping method, such that the pre-dose concentrations for Test or EU reference products were set at the extreme limits that would impact Kel estimation: 1) at high pre-dose extreme 50pg/mL, equal to the lower limit of validated assay, or 2) at low pre-dose extreme 12pg/mL, equal to the level required for assay validation to detect 5% corresponding Cmax. The results of these analyses met BE criteria. However, the Analyses 5 and 6 could not be accepted for the BE study, because this approach is not in accordance with the current Guideline on the Investigation of Bioequivalence, also it is against the validated method criteria. Thus, an outstanding issue related to the inadequate study design **still remains unresolved.**

Sixteen subjects completed at least two periods of the study with test and EU reference product and were included in the pharmacokinetic and statistical analysis for EU submission. From Group I, 3 subjects (subject number 01, 19 and 22) did not meet the pre-dose vital sign criteria prior to Period 2 dosing, 1 subject (subject number 08) withdrew consent due to personal reasons prior to Period 2 dosing. One subject (subject number16) did not report to the clinic for Period 2 dosing. Two subjects (subject number 18 and 23) withdrew consent due to personal reasons prior to Period 3 dosing. One subject (subject 02) was discontinued due to a positive breathalyzer test at Period 3 check-in. One subject (subject 11) withdrew consent due to personal reasons prior to Period 3 dosing. The reason of

the withdrawal is acceptable. Withdrawal of subjects has been documented. As well as the Case Report Form for subjects No.: 01, 02, 08, 11, 16, 18, 19, 22 and 23) ware submitted.

The analytical method was validated, either pre-study and within study, however not entirely conducted according to Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009. All other concerns identified in the bioanalytical and validation reports were resolved.

Based on the comment regarding the sensitivity of the lower limit of quantitation (LLOQ), the applicant re-estimated the FING-15026 study concentration data based on extrapolation of the bioanalytical standard curve for all below the limit of quantitation (BLQ) values previously reported, down to a cut-off of 5 pg/mL. This **major objection** combined with insufficient wash-out periods has **not been resolved** and **remains**.

The statistical method used for the pharmacokinetic analyses is considered acceptable. The ANOVA model used is adequate for a bioequivalence study. The study was conducted in two groups (Group-I and Group-II). The applicant clarified that two-stage design was not used for this study.

The pharmacokinetics parameters measured/calculated are standard for a single-dose study. They are acceptable and according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

Although the 90% confidence intervals for the ln-transformed AUC_{0-72h} and C_{max} are within the 80-125% acceptance range, the CHMP considers that the generic application for Fingolimod Mylan capsule is currently not approvable, due to major objections that have been raised regarding the inadequate study design with insufficient wash-out combined with the lower LLOQ.

Both the formulations (Test and Reference C) were very well tolerated during the conduct of the study. The adverse events mentioned above were in line with the known safety profile of the reference product and there are no new concerns arising from this study.

The Clinical sections of the SmPC of Fingolimod Mylan are in accordance with the reference product Gilenya, Novartis Europharm Limited, UK (EU/1/11/677/001-00).

3.3.8. Conclusions on clinical aspects

Based on review of the clinical data, the CHMP considers that the generic application for Fingolimod Mylan capsule is currently not approvable, due to unresolved major objections that have been raised regarding inadequate study design with a short washout period, combined with a too high LLOQ, leading to difficulties to accurately determine if subjects were having pre-dose concentrations above 5% of C_{max}.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of the safety concerns

The applicant identified the following safety concerns in the RMP.

Table 4 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose

Summary of safety concerns	
	Hypertension Liver transaminase elevation Posterior Reversible Encephalopathy Syndrome (PRES) Macular edema Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection) Reproductive toxicity Bronchoconstriction Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma) Convulsions
Important potential risks	Acute disseminated encephalomyelitis-like (ADEM- like) events Lymphoma Other malignant neoplasms Thrombo-embolic events QT interval prolongation
Missing information	Long-term use in pediatric patients, including impact on growth and development (including cognitive development) Elderly patients (≥65 years) Lactating women Patients with diabetes mellitus Patients with cardiovascular conditions including myocardial infarction, angina pectoris, Raynaud's phenomenon, cardiac failure or severe cardiac disease, increased QTc interval, uncontrolled hypertension, patients at risk for bradyarrhythmia and who may not tolerate bradycardia, patients with second degree Mobitz type 2 or higher AV block, sick-sinus syndrome, sino-atrial heart block, history of cardiac arrest, cerebrovascular disease and severe sleep apnea Long-term risk of cardiovascular morbidity/mortality Long-term risk of malignant neoplasms

Summary of safety concerns	
	Unexplained death Switch from other disease modifying therapy

The Applicant has submitted an updated risk management plan, version 1.2, dated 24-Mar-2020.

No updates to the safety specification from the previous version 1.1 were made. The list of safety concerns is in line with the reference medicinal product.

Having considered the data in the safety specification, the CHMP agrees that the safety concerns listed by the Applicant are appropriate.

3.4.2. Pharmacovigilance plan

The Applicant states in this section that routine pharmacovigilance activities are considered adequate. No additional PhV activity is proposed by the Applicant.

Overall conclusions on the PhV Plan

The Committees, having considered the data submitted, are of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product. No additional pharmacovigilance studies should be required.

The Committees considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures. The generic Marketing authorisation holders should be required to submit PSURs and should review all the received pregnancy cases in yearly PSUR submissions.

3.4.3. Risk minimisation measures

Table V.I has been updated with the update of safety concerns.

3.4.3.1. Routine risk minimisation measures

Routine risk minimisation measures of the generic have been updated with the updated safety concerns of the originator.

However, the Applicant is recommended to include the specific clinical measures/monitoring information for healthcare professionals in SmPC/PL when describing *Routine risk minimisation activities recommending specific clinical measures to address the risk* as requested in line with the originator.

- For the safety concerns Bradyarrhythmia and Unexplained death, the PL sections have been included.

3.4.3.2. Additional risk minimisation measures

The additional risk minimisation measures have been updated.

The planned distribution path is mentioned.

The applicant has updated section V.2 with the Additional Risk Minimisation Measures:

- Physician checklist for adult and paediatric population

- Patient/Parent/Caregiver's guide
- Pregnancy specific patient reminder card

With reference to section *V.3. Summary table of pharmacovigilance and risk minimisation activities by safety concern*, the following sections have been added:

- Reproductive toxicity: section 5.3
- Lymphoma: section 4.4
- Lactating women: section 5.3
- Long-term use in paediatric patients, including impact on growth and development (including cognitive development): Section 4.4 and corresponding PIL

It has to be noted that the Patient/Parent/Caregiver's guide is not named as a reminder guide in the originator. Part V.3 has been amended accordingly.

Overall conclusions on risk minimisation measures

The PRAC having considered the data submitted was of the opinion that in line with the reference product the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

3.4.4. Summary of the risk management plan

The Applicant has updated the Part VI "Summary of the risk management plan", in line with the issues raised in other parts of the RMP.

The following sentence has been corrected by the applicant: This is a summary of the risk management plan (RMP) for Fingolimod Mylan. The RMP details important risks of Fingolimod Mylan, how these risks can be minimised, and how more information will be obtained about Fingolimod Mylan's risks and uncertainties (missing information).

- Annex 4: The specific adverse drug reaction follow-up questionnaires of the annex 4 should be in line with those of the originator. As mentioned in the GVP module V rev2, the MA holders are strongly encouraged to share the content of their questionnaire upon request from other MA holders.

  A confirmation that the follow-up questionnaires will be aligned with those of the originator is added in Annex 4. It is noted that, the Risk Management Plan of the innovator Gilenya requested via the Agency has not been received by the Applicant.

- Annex 6: Details of proposed additional risk minimisation measures: the following sentence has been deleted as required *(or 0.25 mg once daily in paediatric patients 10 years of age and above with a body weight of ≤40 kg)* from the paragraph starting with: - Fingolimod Mylan reduces peripheral blood lymphocyte counts, since it is not an approved dosing for Fingolimod Mylan.

3.4.5. Overall Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 1.2 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed assessment report and in the list of outstanding issues in section 6.4.

3.5. Pharmacovigilance system

The Applicant has provided the Summary of the Pharmacovigilance System version 16.0 dated May 16, 2018. A statement is signed by the EEA QPPV and Head of Regulatory Affairs Europe, Mylan, ensuring that the Applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC and has at its disposal a qualified person responsible for pharmacovigilance.

The EU QPPV resides in the United Kingdom. PSMF is located at the same address where QPPV resides and carries out his tasks.

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

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.

4. Benefit/risk assessment

Based on the review of the clinical data, the CHMP considers that the generic application for Fingolimod Mylan capsule, 0.5 mg is not approvable, due to a major objection that has been raised regarding inadequate clinical data. In addition, a new major objection that has been raised on quality on Day 180 remains unresolved.

4.1. Conclusions

The overall B/R of Fingolimod Mylan is negative at present due to major objections regarding Quality and Clinical issues.

4.2. Pharmacovigilance system

None.