20 September 2018
EMA/779102/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Gilenya

International non-proprietary name: fingolimod

Procedure No. EMEA/H/C/002202/X/0044/G

Note

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

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List of abbreviations

AS	Active substance
API	Active Pharmaceutical Ingredient
AR	Assessment Report
BCS	Biopharmaceutics Classification System
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
CMA	Critical Material Attributes
CoA	Certificate of Analysis
CPP	Critical process parameter
CQA	Critical Quality Attribute
CRS	Chemical Reference Substance (official standard)
DoE	Design of experiments
DPM	Drug Product Manufacturer
EDQM	European Directorate for the Quality of Medicines
EC	European Commission
EP	European Pharmacopoeia
EU	European Union
FMEA	Failure mode effects analysis
FPM	Finished Product Manufacturer
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IR	Infrared
IU	International Units
IUPAC	International Union of Pure and Applied Chemistry
KF	Karl Fischer titration
LDPE	Low density polyethylene
LOD	Loss on drying
LoD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MS	Mass Spectrometry
ND	Not detected
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOR	Normal Operating Range

OOS	Out of Specifications
PAR	Proven Acceptable Range
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PIL	Patient information leaflet
PIP	Paediatric Investigation Plan
PSD	Particle Size Distribution
PVC	Poly vinyl chloride
PVDC	Polyvinylidene chloride
QbD	Quality by design
QC	Quality Control
QOS	Quality Overall Summary
QP	Qualified person
QTPP	Quality target product profile
QWP	Quality Working Party
RH	Relative Humidity
rpm	Revolutions per minute
RRT	Relative retention time
RSD	Relative standard deviation
SmPC	Summary of Product Characteristics
TLC	Thin layer chromatography
TSE	Transmissible Spongiform Encephalopathy
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

Novartis Europharm Limited submitted on 2 November 2017 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an extension application to introduce a new strength of hard capsules (0.25 mg) to the currently approved presentations of Gilenya, grouped with a type II variation (extension of indication) to add a new indication for the treatment of paediatric patients of 10 years of age and above with relapsing multiple sclerosis (RMS). As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3, 6 and 8 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. In addition, Annex II is updated to be brought in line with the latest QRD template version 10.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0050/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0050/2017 was completed.

The PDCO issued an opinion on compliance for the PIP P/0050/2017.

Information relating to orphan market exclusivity

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.

Additional marketing protection

The MAH requested consideration of one year marketing protection in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) 726/2004. The CHMP reviewed the data submitted by the marketing authorisation holder, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical

benefit in comparison with existing therapies on grounds of improved efficacy and major contribution to patient care.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau

The application was received by the EMA on	2 November 2017
The procedure started on	23 November 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	13 February 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	20 February 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 March 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 March 2018
The MAH submitted the responses to the CHMP consolidated List of Questions on	25 May 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	27 June 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	20 February 2018
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	26 July 2018
The MAH submitted the responses to the CHMP List of Outstanding Issues on	21 August 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	6 September 2018
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 Gilenya on	20 September 2018
The CHMP adopted a report on the significant clinical benefit for Gilenya in comparison with existing therapies. (see Appendix 1)	20 September 2018

2. Scientific discussion

2.1.1. Disease or condition

Multiple sclerosis (MS) is a chronic, immune-mediated neurodegenerative disorder of the central nervous system (CNS), characterized by inflammation, demyelination, and axonal/neuronal destruction ultimately leading to severe disability. Although MS generally affects young adults (average age of onset is 29 years), it can present in childhood and adolescence.

2.1.2. Epidemiology

In childhood and adolescence, the disease will manifest in around 5% (from 2 to 10%) of MS cases, with less than 1-2% occurring in children before the age of 10-12 years (Waldman et al 2016). Hence, the overall prevalence estimates for paediatric MS are low, ranging from 0.07 to 2.9 per 100,000 (Gadoth 2003, Pohl et al 2007, Renoux et al 2007, Chitnis et al 2009, Waldman et al 2016).

2.1.3. Clinical presentation, diagnosis and stage / prognosis

As in adults, a diagnosis of MS in paediatric patients is made based on clinical and magnetic resonance imaging (MRI) features. According to the consensus definition proposed by the International Paediatric MS Study Group, a diagnosis of MS in paediatric patients requires multiple episodes of CNS demyelination separated in time and space (Krupp et al 2013), but these events must not meet acute disseminated encephalomyelitis (ADEM) criteria. Symptomatic overlap with ADEM and the increased chance of leukodystrophies and metabolic disorders, complicates the differential diagnosis of paediatric-onset MS relative to adult onset MS (Venkateswaran and Banwell 2010, Krupp et al 2013).

The initial course of MS is more often relapsing (-remitting) in paediatric onset MS (>98%) than in adult onset (approximately 85%) (Waldman et al 2016). The relapse rate in paediatric MS is reported to be 2-3 times higher than in adult onset MS (Weinshenker et al 1989a, Weinshenker et al 1989b, Trojano et al 2002, Yeh et al 2009, Benson et al 2014, Waldman et al 2016). Although MRI features in paediatric MS are less well described, available data show that the underlying pathology is similar to adult relapsing MS. Children, however, tend to have a higher number of T2 lesions at the time of first event than adults (Waubant et al 2009) and a lower propensity for lesions to enhance with gadolinium (Gd) (Banwell et al 2007). A consistent finding in most of the paediatric cohort studies is lower disability scores in paediatric MS compared to adult MS, even when disease duration is taken into account. In the paediatric cohort described by (Renoux et al 2007), the estimated median times from onset to the assignment of Disability Status Scale (DSS) scores of 4, 6 and 7 were 20 years, 29 years and 37 years, respectively. Compared to the adult-onset population, the time to DSS scores of 4, 6 and 7 were approximately 10 years longer for patients with childhood onset MS. Similarly, and in line with this slower progression of disability, the conversion to secondary progressive MS (SPMS) took approximately 10 years longer in paediatric MS than in adult patients, occurring at a median of 28.1 years after the first attack of paediatric MS compared to 18.8 years for adult-onset patients. The median age of the person at SPMS onset was 41 years in paediatric patients with MS vs 52 years in adult MS (~10 years earlier in paediatric patients vs adult MS).

2.1.4. Management

Similarly to adults, treatment strategies in paediatric MS are focused on treatment of acute relapse, MS symptoms, and disease-modification. Despite limited published data suggesting that the efficacy and safety profile in adolescents (≥12 years of age) is similar to that seen in adults, 3 IFN β agents (2 IFN β-1a and 1 IFN β-1b) and glatiramer acetate are allowed to be used in paediatric patients with MS according to the dosage and administration sections of the EU summary of product characteristics (SmPC).

About the product

Fingolimod was first registered in Russia on 17-Aug-2010 under the brand name Gilenya. Since then, Gilenya was registered on 21-Sep-2010 in the US, on 17-Mar-2011 in the EU and now in more than 85 countries worldwide for adult patients with relapsing MS.

Type of Application and aspects on development

The aim of this type II variation is to extend the indication to the paediatric population (10 to 18 years).

The Paediatric Investigation Plan (PIP) for fingolimod (Gilenya®) was first approved by the EMA on 05-Dec-2008 (EMEA-000087-PIP01-07; EMA decision P/125/2008) for the Condition: "Multiple Sclerosis"; pharmaceutical form: hard capsule. The PIP has been modified in agreement with the Paediatric Committee (PDCO):

- on 27 September 2011, decision # P/223/2011,
- on 21 November 2012, decision # P/0272/2012,
- on 26 April 2013, decision # P/0117/2013,
- on 9 September 2016, decision # P/0230/2016,
- on 3 April 2017, final agreed on PIP version (EMEA-000087-PIP01-07-M05), decision # P/0050/2017.

In the original PIP, an open label, randomized, active controlled (IFN β-1a) study (Study D2311) in paediatric MS patients at the age of 10 to <18 years was planned. Modifications to the study design to incorporate a double dummy, double blind scheme were implemented to meet the Food and Drug Administration's (FDA) Written Request (EMA decision P/272/2012). Other modifications were also implemented during this PIP decision in order to:

- Replace an initially planned lead-in PK study by a run-in PK study: Considering the limited number of paediatric MS patients available to enroll in the clinical trial, Novartis proposed not to conduct a PK lead-in study but to enroll all patients in the core efficacy and safety study which will include on-line PK assessment of adequacy of exposure at the starting dose in the patients with a body weight of 40 kg or less.
- Implement a clinical primary endpoint (annualized relapse rate, ARR) instead of one based on MRI. This change was made to take into account the specific requests from FDA.
- Enlarge the number of study participants by paediatric subset: 95 patients by treatment arm, instead of the initially planned 45 patients by treatment arm.
- Consider dose adjustment for children weighting less than 40 kg. In these children, initial dose was halved (0.25 mg/d) and adjusted following the collection of blood samples at month 1 (predose and at approx. 6 hours post-dose, close to fingolimod-P peak concentration time), the on-line analysis of concentrations allowing to increase the dose if patients are below the target exposure.

In 2016, the Novartis proposed the following changes to the study:

- Switching from a fixed duration study design (2 years treatment) to a flexible duration design (up to 2 years), leading to a reduction of the time of participation for some patients in the trial, but maintaining the required power of 80% to detect a 50% relative treatment effect on the annualized relapse rate. Indeed, Novartis proposed to add a blinded sample size re-estimation (BSSR) in the first half of 2017. If the results of this repeated BSSR would indicate that the amount of information maintained the same 80% power needed for the primary analysis (based on the relapse activity of the recruited patient population and the observed dispersion parameter), then the study could be stopped earlier.
- Pre-pubertal population requirement changed from 20% to approximately 10% of patients ~12 years old, due to advanced puberty status in patients with MS and thus a low availability of pre-pubertal patients.
- A modeling approach using a negative binomial model adjusted by treatment, age, pubertal status, treatment-age interaction, and treatment-pubertal status interaction, to evaluate the effect of pubertal status on efficacy and to extrapolate efficacy for the very young patients (≤12 years of age).

An Opinion was adopted by the PDCO on 27 January 2017. On 8 March 2017 Novartis submitted to the EMA a written request including detailed grounds for a re-examination of the Opinion. After re-examination of the additional analysis provided by the MAH, and after an extensive discussion the PDCO agreed on the proposed changes to the study design (on 3 April 2017).

On 10 November 2017, the PDCO adopted an opinion confirming the compliance of all studies in the agreed PIP as set out in the latest Agency's Decision (P/0050/2017) of 3 April 2017.

To be noted, the MAH requested also a scientific advice (SA) from the SWAP on 24 August 2016 regarding issues also discussed during the last request form PIP amendment. This SA was given on 13 October 2016. Its discussion and conclusions have been taken into account through the last validated PIP.

2.2. Quality aspects

2.2.1. Introduction

The new strength of finished product is presented as hard capsules containing fingolimod hydrochloride, equivalent to 0.25 mg fingolimod, as active substance.

Other ingredients are:

Capsule fill: mannitol, hydroxypropylcellulose, hydroxypropylbetadex and magnesium stearate

Capsule shell: gelatin, titanium dioxide (E171) and yellow iron oxide (E172)

Printing ink: Shellac glaze, iron oxide black (E172), propylene glycol and ammonium hydroxide

The product is available in PVC/PVDC/aluminium blister packs and unit dose blister packs as described in section 6.5 of the SmPC.

2.2.2. Active Substance

Gilenya 0.25 mg hard capsules contain the same active substance, fingolimod hydrochloride, as that used to manufacture the already authorised 0.5 mg hard capsules. The active substance is sourced from the same manufacturer, manufactured with the same process and released in accordance with the same active

substance specifications. Therefore, the applicant presented no new information in the dossier to support this line extension application.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is an immediate release hard capsule for oral administration. The capsule is an ivory, opaque, size 3 (16 mm) capsule, with “FTY 0.25mg” radially imprinted in black ink on the cap and a black radial band on the body. The capsule contains a white to almost white powder.

The aim was to develop a lower dose (0.25 mg) fingolimod capsule as compared to the marketed 0.5 mg capsule, suitable for paediatric patients. The quality target product profile (QTPP) is defined as an immediate release orally available dosage form containing 0.25 mg of fingolimod, suitable for paediatric patients from 10 years old upwards and weighing less than 40 kg, packed in a container closure system offering the required protective properties supporting the proposed shelf-life, and labelled according to local requirements.

The active substance is soluble at pH 1, very slightly soluble at pH 4, and practically insoluble from pH 5-8 and is considered to be BCS class II. Therefore, the same grade of active substance is used as in the 0.5 mg capsules. The grades and quantities of the different excipients were optimised during further development studies. The final formulation was shown to be bioequivalent to the 0.5 mg capsules, despite the different formulation and excipients, in a bioavailability study. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Optimisation of the manufacturing process had to take into account the reactivity of the active substance, as well as its low content in the final formulation.

It is recommended that capsules are taken intact since the active substance is considered as pharmacologically highly active, exposure to caregivers should be avoided and dose accuracy cannot be assured if the capsules are opened. Therefore the statement “The capsules should always be swallowed intact, without opening them” is added in section 4.2 of the SmPC.

The dissolution method is the same as used for the marketed 0.5 mg capsules. Due to the properties of the active substance, it wasn’t possible to demonstrate the discriminatory power vis-à-vis meaningful changes in active substance attributes and process parameters. However, since the rate-limiting factor in terms of drug release was shown to be capsule rupture rather than granulate dissolution, and capsule rupture is monitored during manufacture with an in-process control (IPC) for disintegration, the dissolution method is considered to be adequate.

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

Manufacture of the product and process controls

The manufacturing process consists of 13 main steps The major steps are preparation of the active substance and excipients solution, spray granulation, blending with extra-granular excipients, and capsule filling. The process is considered to be a non-standard manufacturing process.

Critical steps were defined. For each of these steps, critical process parameters were identified and suitable set-points or ranges have been defined. The in-process controls re considered adequate for this type of manufacturing process and pharmaceutical form.

The process has been validated on 3 production scale batches of capsules. Process parameters were varied within the proposed ranges for the critical steps and no impact on finished product quality was observed. All 3 batches complied with the release specifications. The applicant will manufacture a further 3 production scale batches at the target set-points. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The process is considered validated.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance of contents and shell (visual examination), mean mass of contents, identity (UV, HPLC), water content (Karl Fischer – coulometric or titrimetric), degradation products (HPLC), assay (HPLC), dissolution (HPLC), uniformity of dosage units (Ph. Eur.) and microbial enumeration (Ph. Eur.).

The impurities have been qualified at levels much higher than those specified. A risk assessment for elemental impurities was carried out in line with ICH Q3D, considering all potential sources including raw materials, equipment, and packaging. No elemental impurities were detected above 30% of the respective PDEs in batches tested and so no control of elemental impurities is 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 3 production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

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

Stability of the product

Stability data from 3 production batches of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH), 12 months under intermediate conditions (30 ºC / 75% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The capsules were packed in the primary packaging proposed for marketing.

Samples were tested for appearance of capsule shell and contents, assay, degradation products, dissolution, water content and microbial enumeration. The analytical procedures used are stability indicating. Results at later time-points were generally within specification for all tested parameters. Analogous results were

observed under intermediate conditions. Under accelerated conditions, assay had decreased by 5% compared to the initial time-point.

Samples were also analyzed after storage at 5 ^{o}C, -20 ^{o}C, in an open dish under long term and intermediate conditions, and after multiple freeze/thaw cycles. The results indicate that there should be no restrictions as regards freezing or refrigerating, and that capsules may be used for up to 3 months following removal from the original PVC/PVDC blisters.

In addition, 1 batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results show that the finished product is not photosensitive.

Based on available stability data, the proposed shelf-life of 18 months stored not above 25 ^{o}C as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

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

2.2.4. 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. Although a different formulation from the marketed 0.5 mg capsules is used, the two formulations were shown to be bioequivalent. Compliance with the paediatric investigation plan (PIP) was demonstrated and the formulation is deemed to be suitable for the target age range. The capsules are to be taken whole, in line with the instructions in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

The purpose of this application is to add a new indication for the treatment of paediatric patients of 10 years of age and above with relapsing multiple sclerosis (RMS) and also a line extension (new dose strength of 0.25mg). No new study was submitted for the extension of indication; however two juvenile toxicity studies

in rats were previously submitted. The targeted population, children from 10 years to less than 18 years of age, is covered by these studies.

In both juvenile toxicity studies, fingolimod induce expected pharmacological effect on hematological cells and lymphoid organs at all tested doses. It also affected body weight and food intake. No significant adverse effect on behavioural tests or sexual development parameters were reported, however a clear impact on growth as evidenced by reduced bone (femur) length was reported in the second juvenile toxicity. Given the targeted population of adolescent having a rapid growth and where maturation of skeletal system will continue into adulthood, the impact of fingolimod on growth, bone architecture, and bone strength should be addressed. The proposed post-authorization study collecting long term safety data, in addition to the proposed long term extension of D2311 study, especially in the subpopulation (patients aged ≤ 12 years, ≤ 40 kg or Tanner Stage <2 (pre-pubertal) group, would provide crucial data in this aspect.

The applicant provided some additional in vitro and in vivo studies on S1P4 receptor to explore his role on the effect of FTY720 on the immune system. It was concluded that S1P4 could partially contribute to the effect but was not the main receptor responsible of the lymphoid depletion. Mechanism of action of bradycardia and vasoconstriction were also studied in vitro in guinea pigs and isolated rabbit aorta and coronary artery. It was concluded that bradycardia could be mediated primarily by IK(ACh)/GIRK activation and that vasoconstriction seems to be mediated by a Rho kinase and calcium dependant mechanism.

Fingolimod is not expected to pose a risk to the environment.

2.4. Clinical aspects

GCP

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

2.4.1. Pharmacokinetics

Fingolimod (FTY720) is already commercialized and currently available as a 0.5 mg hard capsule. The pharmacokinetics of FTY720 has been well characterized in MS adult patients. It was described in detail in the previously submitted global dossiers and included in the approved labels.

The current Type II variation of extension of the indication of FTY720 in the paediatric population (10 to < 18 years) have been addressed according to the paediatric investigation part of FTY720 clinical development. Novartis conducted a Study D2311 (Pivotal Study) in paediatric patients aged 10 to < 18 years old with multiple sclerosis (MS). According to the proposed doses selected, a lower dose formulation (0.25 mg hard gelatin capsule) was developed specifically for the paediatric patients enrolled with a body weight of 40 kg or less.

To note, a preliminary PK assessment in 7 stable paediatric renal patients on Neoral® (cyclosporine) based immunosuppression aged 11 to 16 years, dosed at 0.07 mg/kg, have been conducted (Study A0115) and was join to the dossier.

Study D2311 was a two year, double-blind, randomized, multicenter, active controlled Core Phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a i.m. once weekly in paediatric patients with multiple sclerosis with five-year fingolimod extension phase. 215 patients were enrolled, 107 were treated with fingolimod.

Only one relevant biopharmaceutic study (Study D2117) for the current submission have been conducted to compare the new fingolimod formulation (0.25 mg) to the FMI of 0.5 mg, since the paediatric study have been conducted with both strength. Study Results were conclusive, the two formulations are bioequivalent.

Two bionanalytical methods for the simultaneous quantification of FTY720 and its active metabolite fingolimod-P (FTY720-P) have been developed at two different sites for Study D2311 earlier samples (Novartis Contract Research Organization) Wuxi Apptec (China), and later samples at SGS Cephac Europe (France), a second bioanalytical laboratory (Novartis Contract Research Organization).

Generally, based on the validation report, the used bioanalytical methods developed at the two different sites appear adequate and comply with acceptance criteria regarding selectivity, sensitivity accuracy and precision. Analytical validation reports were provided with satisfactory results. Short and long-term stability of the analytes in biological matrix were tested and shown to be satisfactory. ISR were performed with satisfactory results.

As no cross-validation studies have been performed to confirm that these two methods produce equivalent quantification of FTY720-P in whole blood in the same sample, the applicant proposed an ISR on n=38 samples to provide evidence that the two developed methods (at two different sites) for the quantification of fingolimod-P were similar. The CHMP concluded that the cross check between the two analytical sites met the predefined acceptance criteria.

For the extension of the indication of FTY720 in the paediatric population, four PK and PKPD analysis were provided, a population PK analysis to describe FTY720-P steady-state concentration in paediatric, and three population PK/PD analysis with pooled PD data from adults and paediatrics to link steady-state concentrations of FTY720-P effects on Lymphocyte count, annualized remitting relapse (ARR) and new and newly enlarging T2 lesions (T2), decrease. Nonmem® and SAS® software were used for PK and PD parameters estimation.

- Population PK analysis of FTY720-P in paediatrics

The main applicant assumption was that the current approved strength of 0.5 mg in adults would produce similar exposure at the same dosage in paediatrics weighting more than 40 kg, and also the new strength of 0.25 mg for paediatric patients weighting less than 40 kg.

According to applicant the objectives of this analysis were:

- to assess by graphical exploration if the steady-state FTY720-P concentrations in MS paediatric patients aged 10 years old to <18 years old achieve the desired adult target FTY720-P stead:-state concentration level (1.353 ng/mL, (90% CI: 0.62-3.1 ng/mL) defined with pooled PK data from Studies D2301 and D2302 (Pivotal Phase III studies from the initial MAA)
- To develop a linear mixed effects PK model to describe the FTY720-P concentrations at steady-state in the MS paediatric population using data from Study D2311

A sparse PK sampling protocol have been performed in paediatrics, from which only samples which have reach steady-state were included in the Population PK analysis, this is supported since in adults it have been demonstrated that exposure levels were the best predictor of efficacy (ARR). Therefore only 544 steady-state concentrations of FTY720-P from n=103 patients were available.

Dosing regimen consisted of 0.25 mg OD for patients with weighting less than 40 kg and 0.5 mg OD above 40 kg. The dosing regimen rationale with a 40 kg cut-off have been identified by simulation using two independent datasets, PK data from Study A0115 (preliminary PK assessment in paediatrics and PK data from two Phase II and III in adult MS patient). According to the applicant, this analysis indicated that an allometric scaling method based on normalized body weight with an exponent of 0.53 was adequate to describe the relationship between body weight and elimination clearance.

Overall, 9 Patients with weight < 40 kg have received 0.25 mg OD and were monitoring at Visit 5 (Month 1). From the observed concentrations at predose and 6h post dose, Cav,ss of FTY720-P have been estimated and compared to the 65% lower bound (0.9 ng/mL) of the adult target concentration (1.353 ng/mL). 6 of 9

patients had their Cav,ss above 0.9 ng/mL. For those who have not reach the targeted concentration it was proposed to increase the dose at 0.5 mg OD.

An exploratory graphical analysis was performed to assess the overlap between FTY720-P steady-state concentrations observed in paediatrics and the targeted steady state concentration levels of FTY720-P in adults. This analysis show that FTY720-P steady-state concentration in paediatrics are 23% lower (median 1.1 ng/mL in paediatrics vs 1.35 ng/mL in adults) than in adults.

A Population PK analysis have been performed to characterize steady-state concentrations of FTY720-P in paediatrics. This PK model is of particular of interest, since the predicted steady-state concentration of FTY720-P would be used as an input in three developed PK/PD model. A linear mixed effect model have been developed on log transformed steady-state concentrations of FTY720-P. The developed structural model is supported given the sparse sampling protocol which does not allow to estimate with a good precision FTY720-P PK parameters (such as Clearance, distribution volume…) from a two compartment model (Previous studies). Covariates search is well documented, dose and baseline body weight (centered to 70 kg) effects on intercept have been maintained in the final model. To note baseline body weight effect was not statistically significant according to the covariates screening procedure but was maintained in the final model.

Fixed effects parameter estimates were estimated with a poor precision and particularly the intercept parameter (with a RSE of 235%) which is the most important parameter (Log-transformed PK data, exp(intercept)=steady-state concentration in the original scale) of the linear model. Diagnostic plots have not shown any misspecification, except the NPD QQ plot from which distribution is not clearly around the identity line. Therefore the NPDE computation and the dedicated statistical work to test the validity of the normality assumption is needed (See PK OC3b). Predictive performance of the Final PK model was evaluated using a pcVPC. This graph shows a tendency to over predict the higher range of observed concentrations in paediatrics. Indeed, the 95th percentile of observed data is on the extreme lower limit of the 90%CI of the 95th percentile. Finally a simulation analysis based on the developed PK model was provided to explore the impact of baseline body weight (20 to 80 kg) and dose (0.25 or 0.5 mg OD) on the predicted steady-state concentration of FTY720-P. This analysis confirm the expected nonlinear relationship (see dosing rationale) between weight and steady-state concentration with nonlinear decreased of steady-state concentration with increasing weight.

Population PKPD analyses

Three PK/PD analyses were performed by the applicant and presented below. Main applicant assumption was that the current approved strength of 0.5 mg in adults would produce similar exposure-response (PK/PD) relationship at the same dosage in paediatrics weighting more than 40 kg, and also for the new strength of 0.25 mg in MS children < 40 kg.

The applicant modelling strategy for all these analyses was to use the previous developed PKPD model in adults and check its predictive performance on paediatric PD data. If the results were not conclusive, this implies that the response was different between adult and paediatrics. Then the PKPD model was updated using pooled PD data from adults and paediatrics, and to account for difference between the two populations, binary paediatric covariates effects were introduced in the PD parameters of interest.

The three chosen PD/clinical efficacy endpoints (lymphocyte counts, ARR and T2) have been already used and validated in the initial dossier. PK and PD data from adults MS came from Studies D2301 and D2302 (Pivotal studies from the MAA).

This strategy could not be considered as optimal because a formal PKPD model with only PK and PD data in the paediatric population would have been more relevant. However, taken into account, the scarcity of the available paediatric PD data, the applicant strategy could be supported; at the risk to have a POP-PKPD estimation parameters driven by adults data.

- Population PKPD analysis-Lymphocyte

A Population PKPD model have been developed to describe the effect of steady-state concentration of FTY720-P on decreased Lymphocyte count. A nonlinear mixed effect model have been developed on log transformed Lymphocyte count, with FTY720-P steady state concentration as an input. The link function

between PK and PD is an Imax model. Predictive performance of the adult PK/PD model have been evaluated using a pcVPC. This is supported.

From the pooled data between adults (Study D2301 and D2302) and paediatrics, a total of 11742 lymphocyte count records from 1269 adults in Study 2301, 845 adults from Study D2302 and 107 paediatric patients were available and included in the final POPPKPD analysis. Out of 2114 patients from adult data, 851 (40%) were on 0.5 mg treatment, 846 (40%) were on 1.25 mg treatment and 417 (20%) were on placebo. Out of 107 paediatric patients, 98 (92%) were on 0.5 mg treatment and only 9 (8%) were on 0.25 mg treatment.

From the data included in the analysis, the median (range) baseline lymphocyte counts from the Studies D2301, D2302 and D2311 were 1.77 (0.620-6.23), 1.70 (0.740-4.06) and 2.00 (0.9004.90) 10^9/L. It is therefore expected that lymphocyte count in paediatrics is greater than observed in adults. From the Study D2311 data included in the analysis, the overall median (range) baseline lymphocyte counts were 2.00 (0.900–4.90) 10^9/L. The median (range) baseline lymphocyte counts corresponding to 0.25 mg and 0.5 mg FTY720 treatments were 2.50 (1.504.90) and 2.00 (0.900–4.00) 10^9/L, respectively.

Lymphocyte counts for only paediatrics have not been provided. However based on the protocol a maximum of 1391 (107 x 13 = 1391) lymphocyte counts are expected. Then, the paediatric lymphocyte data will count in the best case for 11.8% (1391/11742*100) of the total pooled dataset. It is therefore expected that the results from the Final POPPKPD analysis will be driven by adults (as discussed above).

The first step on the analysis shows that the previous developed PKPD model in adults provide under prediction of the lymphocyte count than the observed lymphocyte count in paediatrics. Therefore to account for paediatric effect, three covariates were introduced on Imax, IC50 and baseline. The second step was conclusive, this therefore could be expected.

Parameters of the final PKPD model have been well estimated except for the paediatric covariates effect on Imax and IC50, respectively with RSE of 115 and 226% and were considered not statistically different from adults by the applicant, as they were respectively associated with 6 and 12% decrease in paediatrics. The maximum reduction in lymphocytes from baseline was estimated 81% in adult patients and 79% in paediatric patients, the IC50 was estimated at 0.327 ng/mL. Paediatric covariate effect on baseline lymphocyte count has been well estimated and to note is expected to be maintained in the final POPPKPD model since at baseline lymphocyte count was different between the two populations.

- Population PKPD analysis-Relapse

An exposure-response analysis have been developed to describe the effect of steady-state concentration of FTY720-P on decreased of annualized relapse rate (ARR). Remitting-relapse have been modeled using a 2-state continuous Markov model whereas, decreasing relapse by an Imax function. Predictive performance of the adult PK/PD model have been evaluated using a PPC. This is supported.

The paediatric patients receiving FTY720 0.5 mg have similar relapse values at 1 or 2 year compared to the Interferon (INF) treatment group. To note the paediatric patients receiving FTY720 0.25 mg OD have lower number of relapse in the previous 1 or 2 years prior to treatment than that of treated with FTY720 0.5 mg QD or INF. The total number of relapse with FTY720 is around 80% lower than that observed with INF (25 vs 118) with an ARR of 0.141 vs 0.762 respectively. Moreover it seems that as FTY720-P increased (low tertile: 0.243-0.885, mid: 0.885-1.292, high: 1.292-1.963 ng/mL) the AAR decreased (respectively, 0.215, 0.131, 0.082).

The first step on the analysis shows that the previous developed PKPD model in adults provide over prediction of the AAR than the observed paediatric data. Therefore to account for paediatric effect, five covariates were introduced and maintained in the final PKPD analysis. From these covariates only one covariate (paediatric effect on the intercept log transition rates from the relapse to the remitting state) was found to be statistically significant.

- Population PKPD analysis-T2

An exposure-response analysis have been developed to describe the effect of steady-state concentration of FTY720-P on decreased of new and newly enlarged T2 lesions. New and newly enlarging T2 lesions have been

modeled using a negative binomial distribution whereas, decreasing T2 lesion by an Imax function. Predictive performance of the adult PK/PD model have been evaluated using a PPC. This is supported.

The paediatric patient receiving FTY720 0.5 mg have similar baseline values, except for the volume of T2 lesions at baseline which have a higher mean in the INF group. To note the paediatric patient receiving FTY720 0.25 mg OD have lower number galodinium enhanced T1 lesions, lower EDSS score and higher volume of T2 lesions than that of treated with FTY720 0.5 mg OD or INF. the observed new and newly enlarging T2 lesions at 12 months with regards to the binning (3 groups: low, mid, high, see PK/PD model evaluation) of the steady-state predicted FTY720-P concentrations. It could be observed that as FTY720-P increased (low tertile: 0.243-0.885, mid: 0.885-1.292, high: 1.292-1.963 ng/mL) the new and newly enlarging T2 lesions at 12 months decreased (respectively, 4, 3, 2 in median).

The first step on the analysis shows that the previous developed PKPD model in adults provide under prediction of the T2 than the observed paediatric data. Therefore four paediatric effect covariates were introduced in the PKPD model and two (covariate effects on baseline and interferon effect on baseline) was include in the final model with regards to a covariate screening procedure (backward deletion). The second step was fully conclusive. To note the full covariates paediatric effects screening was provided by the applicant. The developed PKPD model could be considered endorsed.

Overall, FTY720-P PK have been well described in the paediatric population. Applicant proposal dose 0.25 mg for patients with weight ≤40 kg and 0.5 mg above 40 kg is supported.

From the four population PK and PKPD analysis, only the results of the exposure-response analysis (new and newly enlarged T2 lesions) could be supported.

2.5. Clinical efficacy

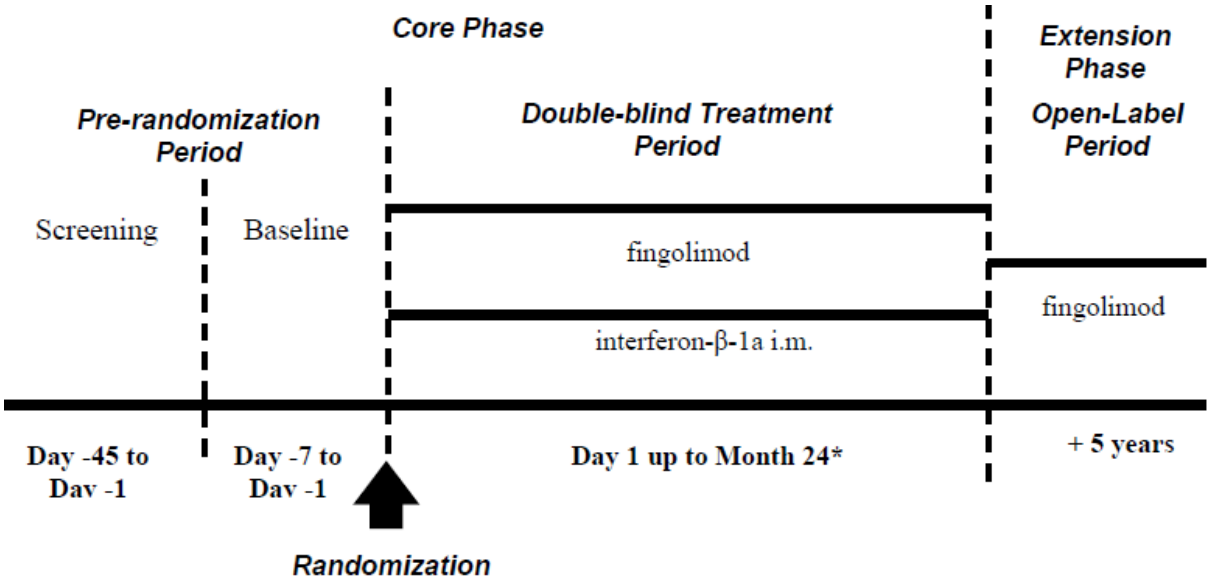
2.5.1. Dose-response study

No dedicated dose response study in this population was conducted by the MAH. However, during the main study submitted to support the indication extension, the dose of fingolimod was adjusted with regards to the baseline patient weight:

- In patients ≤40 kg, the initial dose was 0.25 mg/d, then after one month of treatment, and based on on-line PK assessment, this dose could be increased to 0.5 mg/d.
- In patients >40 kg, the chosen dose was the same as for MS adults patients (0.5 mg/d).

2.5.2. Main clinical study (D2311)

In order to support the extension of indication in paediatric population, the MAH conducted a phase 3, flexible duration (up to 2 years), double-blind, double dummy, randomized, multi-center, active controlled study evaluating the efficacy/safety of fingolimod once daily (weight-based dosing; 0.25 mg ≤40 kg or 0.5 mg >40 kg) vs IFN β-1a 30 µg im once/week. This double-blind phase was followed by an open-label extension phase of 5 years duration in order to evaluate long-term safety and tolerability of fingolimod in this population. The Core phase study was stopped by 14-Jul-2017 (last patient received last treatment), the extension phase is still on-going at the time of this assessment Report (AR). This study was performed in 87 centres Worldwide (from Europe, North and South America, and Russia).



* The 3 months follow-up visit was required for those patients who did not continue into the Extension Phase.

The primary efficacy endpoint chosen was the reducing the frequency of annualized relapse rate (ARR – confirmed relapses) after a treatment for up to 24 months.

The key secondary endpoint used was to compare fingolimod and IFN β-1a groups in reducing the number of new/newly enlarging T2 (n/neT2) lesions after a treatment for up to 24 months.

Other main secondary efficacy endpoints used during this clinical study were:

- Other relapse-related parameters:
  - Time to first relapse
  - Proportion of patients relapse-free
- T1 Gd-enhancing lesions on brain MRI.

Also, there were exploratory endpoints during Core Phase, including:

- Other MRI measures including change in total T2 hyperintense and T1 hypointense lesion volumes, new T1 hypointense lesion count….
- Efficacy parameters in the subset of pre-pubertal children with MS.
- Effects on physical and sexual development.
- Effects on measures of cognition and health related quality of life.

In addition to the above pre-planned analyses, the MAH provided other post-hoc efficacy subgroup analyses on primary (confirmed ARR) and key secondary (number of new/newly enlarged T2 lesions) variables up to Month 24. The main analyses included:

- Pre-pubertal vs. pubertal subgroups baseline on Tanner staging score
- Age ≤12 yrs vs. >12 yrs subgroups
- Body weight at randomization visit ≤40 kg vs. >40 kg

The first patient was enrolled on 26-Jul-2013, and the last patient completed the Core Phase on 14-Jul-2017 (last treatment). In total, 214 (107 in each treatment group) of 215 randomized patients were treated by study drug; 1 patient in the IFN β-1a group was randomized but not treated due to inability to swallow study medication.

The percent of screening failure showed high values (38.2%). On the other hand, 43 patients were randomized after rescreening (i.e. failed first screening). The majority (105/133 patients who failed at screening) of screening failure was due to strict exclusion criteria such as vaccination requirements and the need for positive antibody testing as proof for vaccination status. Amendments were implemented to change exclusion criteria and rescreening was authorised according to the initial protocol. Rescreening did not have any impact into the global MS paediatric population.

At baseline, the groups were balanced for main demographic features, but not for pre-pubertal status and body weight ≤40 kg (significantly more pre-pubertal patients were included in fingolimod group vs IFN [7 vs 3 patients] and also for those weighting ≤40 kg [9 vs 1 patients]). These two points are of interest regarding the subgroup analyses on main efficacy endpoints (primary and key secondary endpoints), because they can weaken the results and the conclusions from these comparisons.

Regarding MS baseline characteristics, overall, they were well balanced between the two treatment groups showing similar level of disease activity prior to the study start. The study population consisted of relatively newly diagnosed MS patients, with a low mean baseline EDSS score of 1.54, and treatment naïve (~64% of patients).

Since D2311 was a flexible duration the study (up to 24 months), patients exposure was variable. Thus:

- 102 (95.3%) and 88 (82.2%) patients in the fingolimod and IFN β-1a groups respectively were exposed to ≥ 360 days (12 months) of study treatment
- 74 (69.2%) and 55 (51.4%) patients in the fingolimod and IFN β-1a groups respectively were exposed to ≥ 540 days (18 months) of study treatment
- 30 (28.0%) and 19 (17.8%) patients in the fingolimod and IFN β-1a groups respectively were exposed to ≥ 720 days (24 months) of study treatment.

Since MS is a chronic disease and the treatment is intended to be used on a long-term period, there is a lack of comparative blinded data regarding:

a. The long-term efficacy data to support the maintenance effect of fingolimod;
b. The long-term safety data in this special population.

These two points were discussed by the MAH. The Rapporteur acknowledges the efficacy of fingolimod demonstrated. The superiority of fingolimod to interferon beta is recognized. However, long term efficacy and safety data remains at the time being speculative and not clearly demonstrated in the results of this study.

For the MAH, there is no evidence from the safety analysis of paediatric patients in Study D2311 to substantiate a 'potentially worse' safety profile to that of adults as was mentioned in the CHMP assessment report. This is endorsed at this stage with the available study data however the use in paediatric patients in PM is not expected to be different as compared to adults. There are very limited safety data available in paediatric patients.

Regarding study discontinuation, the number of patients who discontinued from the Core phase and those from study drug prematurely for reasons other from lack of efficacy and adverse events (i.e. Physician's decision, Patient/guardian decision, Administrative problems, Protocol deviation, and Patient withdrew consent) were imbalanced between fingolimod and IFN beta-1a groups (more in IFN group). Indeed, in the Core phase, 13 patients in IFN beta-1a group versus 4 patients in fingolimod group discontinued their treatment for these other reasons. Also, those who discontinued the treatment prematurely were 11 in IFN group versus 5 patients in fingolimod group. Further explanation was given by the MAH as requested. The MAH did not identify noteworthy reason. This point is solved.

Similarly, the number of protocol deviations was high in this study (n=~360), taking into account that a subject with multiple occurrences of a protocol deviation is counted only once. A high number of protocol deviations was related to safety follow-up measures not fully respected by study investigators. This issue was discussed by the MAH: All protocol deviations led to corrective actions which included onsite retraining of the site and subsequent monitoring to ensure future compliance. None of these were considered to have affected patient safety or overall study results. This point is solved.

Regarding the primary efficacy endpoint (ARR) up to 24 months (analyzed using negative binomial [NB] regression), the results showed statistically superiority of fingolimod vs IFN β-1a in paediatric patients (10 to 18 years) with MS (Table 1) with adjusted ARR estimate of 0.122 vs 0.675. This corresponded to a significant reduction (p<0.001) of 81.9% in ARR for fingolimod-treated patients compared with IFN β-1a-treated patients.

Table 1. Annualized relapse rate (ARR) up to Month 24 (confirmed relapses) (FAS)

	FTY720 N=107	IFN β-1a N=107
Number (%) of patients with relapse	15 (14.0%)	58 (54.2%)
Number of relapses	25	120
Time in study (days)	65575	59678
Raw ARR (time-based)[1]	0.139	0.734
Adjusted ARR (95% CI)[2]	0.122 (0.078,0.192)	0.675 (0.515,0.885)
Treatment comparison of FTY720 vs IFN β1-a		
ARR ratio (95% CI)[2]	0.181 (0.108,0.303)	
Percent rate reduction[2]	81.9%	
p-value[2]	<0.001	

N: Total number of patients included in the analysis.

ARR=annualized relapse rate

[1] Raw ARR (time-based) is calculated by taking the total number of relapses observed for all patients within a treatment group, divided by the total number of days in study of all patients within the treatment group and multiplied by 365.25 days.

[2] Adjusted ARR, ARR ratio, Percent rate reduction, p-value are obtained from fitting a negative binomial regression model adjusted for treatment, region, pubertal status (the stratification factor in IVRS), and the number of relapse in the last 2 years (offset: time in study).

The primary analysis was adjusted, among other covariates, on the pubertal status according to the IVRS and geographical regions (Eastern and Western Europe and rest of the world). A complementary sensitivity analysis of the primary criteria, adjusting on the pubertal status according to Tanner's score and on geographical regions where the Western Europe region is restricted to EU countries, and a By-country ARR ratios have been provided. A negative binomial regression model adjusted for treatment, region, pubertal status (the stratification factor in IVRS), subgroup, subgroup-by-treatment interaction, and baseline T2 lesion number was also provided. All these analysis were statistically significant in favour of fingolimod.

Regarding the key secondary efficacy endpoint (new or newly enlarged T2 lesions up to Month 24), the data showed statistically significantly lower rate in fingolimod group compared with IFN β-1a group. Treatment with fingolimod resulted in a 52.6% reduction in the number of new or newly enlarged T2 lesions compared with IFN β-1a (p<0.001), see Table 2.

The effect on MRI lesions in study 2311 is less than expected in adult population when indirect comparison on the effect on relapses is concerned.

Table 2. Annualized rate of the number of new or newly-enlarged T2 lesions compared to baseline up to Month 24 (Full analysis set) (table 11-7 of CSR)

		Between-treatment comparison[1]		
Treatment	Adjusted mean (95% CI)[1]	Percent rate reduction	Rate ratio (95% CI)	P-value
FTY720 N=106	4.393 (3.617,5.336)	52.6%	0.474 (0.361,0.622)	<0.001
IFN β-1a N=102	9.269 (7.661,11.214)			

N: Total number of patients with available results and included in the analysis.
Adjusted mean refers to the adjusted number of new/newly enlarged T2 lesions per patient per year.
[1] Obtained from fitting a negative binomial regression model adjusted for treatment, region, pubertal status (the stratification factor in IVRS), and baseline T2 lesion number (offset: time in study).

The MAH also conducted sub-group analyses, including:

- Excluding patients positive for neutralizing antibodies (NAbs) in the IFN β-1a treatment group (81.5% ARR reduction in favour fof fingolimod); ARR ratio=0.185 (95% IC=0.109-0.314); p<0.001;
- Only DMT naive patients: 85.8% reduction in ARR (p<0.001), and a 53.4% reduction in the annualized rate of the number of new or newly enlarged T2 lesions (p<0.001) up to 24 months in fingolimod-treated patients compared with IFN β-1a-treated patients
- Age ≤12, and also in Age 10, 11 and 12: the limited number of patients and the imbalanced repartition in subgroup of age (e.g. For 10 yrs, there were only 5 patients all in fingolimod group, for 11 yrs, there were 4 patients, 3 in fingolimod and 1 in IFN group) weaken the drawn conclusions.
- Baseline body weight ≤40 kg (and >40 kg): the limited number of patients (10 patients in all groups) and its imbalanced repartition between groups (9 in fingolimod and 1 patient in IFN groups) preclude drawing firm conclusions.
- Pubertal status - Tanner stage <2 (and >=2): as for weight sub-groups, the limited number of patients (10 in all groups) and its imbalanced repartition between groups (7 and 3 patients in fingolimod and IFN groups) would lead to doubtful conclusions.

Other secondary endpoints of interest were analysed in this study, including:

- Time to first relapse and proportion of relapse-free patients: results were in line with previous efficacy results in favour of fingolimod (see Figure 1 and Table 1).
- The EDSS score change from baseline: no significant difference was observed between treatment groups, even if the mean change in the EDSS score at EOS compared to baseline was numerically improvement in the fingolimod group (−0.23) as compared to IFN β-1a group (0.22).
- Cognitive testing: the results did not show a difference between treatment arms after 12 and 24 months of treatment for all five cognitive tests.

Figure 1. Kaplan-Meier curves: percentage of patients relapse-free (confirmed relapses) across study week by treatment (Full analysis set)

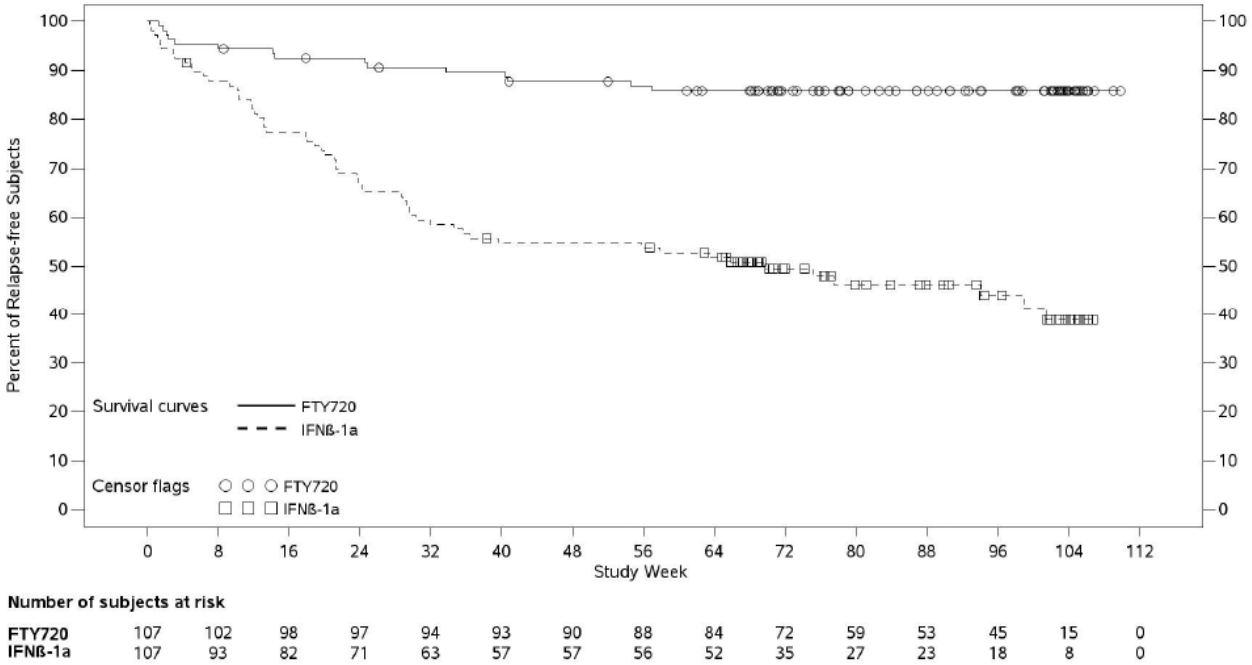


Table 3. Risk of confirmed relapse (Full analysis set)

		Between-treatment comparison[2]		
Treatment	% Relapse free (95% CI)[1]	Risk reduction	Hazard ratio (95% CI)	P-value
FTY720 N=107	85.7 (79.04,92.43)	82.2%	0.18 (0.10,0.32)	<0.001
IFN β-1a N=107	38.8 (27.40,50.26)			

[1] Estimated at M24 from Kaplan Meier analysis.
[2] Performed on time to event using a Cox regression model adjusted for treatment, region, pubertal status (the stratification factor in IVRS), and number of relapse within the previous two years before randomization.
N: Total number of patients included in the analysis.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 4. Summary of efficacy for trial D2311

Title: A two-year, double-blind, randomized, multicenter, active controlled Core Phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a im once weekly in paediatric patients with multiple sclerosis with five-year fingolimod Extension Phase			
Study identifier	CFTY720D2311		
Design	Double-blind, randomized, active controlled, parallel-group, double-dummy, multicenter study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Flexible - Up to 24 months + 5 years Up to 24 months 5 years
Hypothesis	Superiority of fingolimod compared to IFN beta-1a on ARR		
Treatments groups	Fingolimod group		0.5 mg capsule, administered orally once daily in patients weighing >40 kg or 0.25 mg in patients weighing ≤40 kg. 107 patients randomized.
	Interferon β-1a group		30 µg administered on intramuscular (im) injection once weekly. 108 patients randomized.
Endpoints and definitions	Primary endpoint	ARR	Reduction of the annualized relapse rate (confirmed relapses only) (time-based)
	Key secondary endpoint	n/neT2	Reduction of the annualized rate of the number of new/newly enlarging T2 (n/neT2) lesions
	Other secondary endpoint	Time to first relapse & Proportion of patients relapse-free	Comparison using Kaplan–Meier (KM) estimates of the survival function of the time to first relapse at Month 24
		T1 Gd-enhancing lesions	Comparison of the number of T1 Gd-enhancing lesions per scan up to Month 24
Database lock	11-Aug-2017		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set: all randomized patients with assigned treatments who received at least one dose of study medication following the intention-to-treat principle, even if they actually received a different treatment. Time point: Up to Month 24.		
Descriptive statistics and estimate variability	Treatment group	Fingolimod (FNG)	Interferon β-1a (IFN)
	Number of subject	107	107
	confirmed ARR up to M24 (%)	0.122	0.675
	95% CI	(0.078, 0.192)	(0.515, 0.885)
	n/neT2 (Adjusted mean)	4.393	9.269

	95% CI	(3.617, 5.336)	(7.661, 11.214)
	Rate of patients free of confirmed relapse at M24	85.7%	38.8%
	95% CI	(81.4, 94.0)	(45.3, 64.2)
	T1 Gd-enhancing up to Month 24 (Adjusted mean)	0.436	1.282
	95% CI	(0.313, 0.608)	(0.934, 1.758)
Effect estimate per comparison	Primary endpoint	Reduction of ARR up to 24 months (FNG vs IFN)	0.181 81.9% reduction
		95% IC	(0.108, 0.303)
		P-value	<0.001
	Key Secondary endpoint	n/neT2 up to Month 24 (FNG vs IFN)	0.474 52.6% reduction
		95% IC	(0.361, 0.622)
		P-value	<0.001
	Other Secondary endpoint	Proportion of patients free of relapse Month 24 (FNG vs IFN)	0.18 82.2% reduction
		95% IC	(0.10,0.32)
		P-value	<0.001
	Other Secondary endpoint	T1 Gd-enhancing up to Month 24 (FNG vs IFN)	0.340 66.0% reduction
		95% IC	(0.215, 0.540)
		P-value	<0.001
Notes			

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In order to demonstrate fingolimod efficacy in relapsing remitting MS in children (10 to 18 years), the MAH conducted a clinical study (CFTY720 or D2311) with respect to the PIP approved by the EMA on 05-Dec-2008 (EMEA-000087-PIP01-07; EMA decision P/125/2008).

D2311 was a randomized, double-blind, double-dummy study, active-controlled, parallel group, multicenter study in paediatric patients (10 to <18 years old) with a confirmed diagnosis of MS with relapsing remitting course. Initially planned to be a fixed 24-month treatment duration study, assessing the efficacy and safety of fingolimod compared to IFN β-1a, it was amended to a flexible up to 24-month treatment duration study in November 2016. The study comprised of an open-label extension period of 5 years duration, in order to assess long term safety profile of fingolimod in this specific population.

The population enrolled in this study (n=215; in a 1:1 ratio between fingolimod and IFN beta-1a) was composed of males (37.7%) and females (62.3%) (i.e. similar to sex-ratio repartition in general population), aged from 10 to 18 years. The number of children aged under 12 years was small (~10% of overall enrolled population, n=22) and limited for those who were pre-pubertal (Tanner staging score<2), n=10 (4.7% of overall study population). Regarding the disease progression stage and previous MS treatment, the mean

EDSS score of included patients was 1.54 (median 1.5), the mean of MS duration since first symptom was 2.1 years (median 1.5), and percent of treatment naïve patients was of 63.3% (while 32.1% had already been treated by an Interferon Beta treatment). Thus, the included population was manly composed of early stage and treatment naïve MS patients.

The dose of IFN beta-1a used in this study was fixed, 30 µg once by week i.m, when the dose of fingolimod was adaptable according to:

a. Patient weight: 0.5 mg/d in patients > 40 kg and 0.25 mg/d in those ≤ 40 kg
b. On online PK assessment for those under 0.25 mg/d: the PK analyses where done at Month 1 and at Month 2 if the dose was increased to 0.5 mg/d after the first PK analysis.

According to a population PK analysis, the MAH considered that the dose of 0.5 mg/d was suitable for children > 40 kg and 0.25 mg/d for those ≤ 40 kg. This is acceptable.

The primary efficacy endpoint chosen for this study was the comparison of the Annual Relapse Rate between treatment groups, based on a negative binomial regression model with log link, using treatment, pubertal status, and region as factors and number of relapses within the previous two years before randomization as covariate. The choice of this endpoint is supported in this population, especially in this population. Indeed, MS in children presents a slower progression, relapses more often, and recovers better from relapses than MS in adults.

The choices of the key secondary endpoint (new/newly enlarging T2 lesions) and the other secondary endpoints (including "Time to first relapse"/"Proportion of patients relapse-free") are also supported, these are reflecting (and related to) MS inflammatory activity (i.e. relapses), the most important component of this disease at this age/stage.

Efficacy data and additional analyses

Regarding the primary efficacy endpoint, the results showed that fingolimod significantly reduced the Annual Relapses Rate (ARR) (confirmed relapses) up to Month-24 by almost 82% compared to IFN beta-1a (ratio 0.181; IC95% 0.108-0.303; p<0.001).

Similar results were observed with regards to the secondary endpoints (key and other secondary endpoints) in favour of fingolimod:

- Mean adjusted new/newly enlarging T2 lesions up to Month-24: 4.393 and 9.269 in fingolimod and IFN beta-1a groups, respectively (52.6% of reduction; rate ratio=0.474 - IC95%=0.361-0.622; p<0.001);
- Time to first confirmed relapse and proportion of patients free of relapse at Month-24: 85.7% and 38.8% in fingolimod and IFN beta-1a groups, respectively (reduction in the risk of 82.2% of reduction; hazard ratio=0.18 - IC95%=0.10-0.32; p<0.001);
- Mean adjusted Gd-enhancing T1 lesions up to Month 24: number of lesions of 0.436 and 1.282 in fingolimod and IFN beta-1a groups, respectively (66% of reduction, rate ratio: 0.340 - IC95%: 0.215, 0.540; p<0.001).

2.5.4. Conclusions on clinical efficacy

The efficacy results from the current paediatric study (D2311) are in-line with those obtained from one of the pivotal studies (D2302) in RRMS adult patients, a 12-Month treatment trial (~44% were treatment-naïve patients), where fingolimod showed superiority over IFN beta-1a on most efficacy endpoints.

In D2302 adult study, the superiority of fingolimod was observed on the primary endpoint (ARR), one of the two key secondary endpoints[1] (number of new/newly enlarged T2 lesions), and other secondary endpoints (mainly the proportion of patients free of Gd-enhanced T1 lesions, the proportion of relapse-free patients, the proportion of patients free of new or newly enlarged T2 lesions at 12 month, the number of Gd-enhanced T1 lesions, etc.).

A number of important safety concerns have previously been identified for Gilenya in the adult population. This resulted in the granting of a marketing authorization for restricted use (patients with highly active disease despite a full and adequate course of treatment with at least one DMT or patients with rapidly evolving severe relapsing remitting MS, as described in 4.1). In addition, a number of measures to ensure safe and effective use of the product were implemented. The initial approval has been followed by several variations to update sections 4.4 and 4.8 of the SmPC with new safety concerns.

Thus, fingolimod efficacy data are in line with those seen in adult patients suffering from highly active relapsing disease MS, where its indication was restricted due to the safety profile "after at least one disease modifying therapy […]" or "in rapidly evolving severe relapsing remitting multiple sclerosis (2 or more disabling relapses in one year […])". According to the MAH, fingolimod seems to have the same safety profile in paediatric population as in adult population. Moreover, there is a lack of safety data in this population including on the long term, and also regarding the neuro- and sexual-development. Therefore in children, an indication reflecting the above points was proposed.

Fingolimod seems to be an efficacious treatment and potentially a valuable alternative after the first line existing disease-modifying treatments (interferon and glatiramer acetate) have failed in paediatric MS patients.

D2311 study enrolled patients from 10 to 18 years old. However, the number of patients aged 10-12 years and pre-pubertal patients (Tanner stage≤ 2) enrolled in this study, even though consistent with PDCO recommendations, creates uncertainties for the assessment of the B/R ratio in these subgroups.

Therefore, as patients who were aged 10 to 12 years, had a weight <40kg, - were pre-pubertal (<2 Tanner stage scoring) were underrepresented and taking into that SAEs were found in a higher number in children and adolescents on fingolimod vs. IFN β-1a and differences seem to be even more pronounced in children ≤ 12 years, which is of concern, further long term safety data are needed.

The MAH was requested to propose a post authorization study to collect long term safety data, in addition of the proposed long term extension of D2311 study especially in the subpopulation (patients age ≤ 12 years, ≤ 40 kg or Tanner Stage <2 (pre-pubertal) group).The MAH proposed to open the recruitment of additional patients in this sub-population in the current 5 year extension of D2311 study (through an amendment) instead of putting in place a new safety study. This was considered acceptable.

Information that very limited data are available and proposal for additional data in this subpopulation is added in section 4.2, 4.4, 4.8 and 5.1 to inform prescribers as requested.

[1] But not on the second key secondary endpoint (3-month confirmed disability progression as measured by EDSS, no statistically significant difference was found between treatment arms).

2.5.5. Clinical safety

Patient exposure

The safety profile of fingolimod has been characterized with data on AE and SAE issued from D2311 which included paediatric patients between 10 and < 18 year-old. In addition, as the sample size of paediatric patients in Study D2311 is limited (214 patients, 107 in fingolimod arm and 107 in interferon arm), and given that MS is an indication that fingolimod is already approved for adult patients, 3 MS studies in adults (Studies D2301, D2302, D2309) were pooled and presented side by side with Study D2311 Core Phase data as supportive safety data.

214 patients were followed in the safety set of D2311 (107 in fingolimod arm and 107 in interferon arm). Among these 314 patients:

- 10 patients were pre-pubertal subjects (Tanner staging score<2 e.g. Tanner staging = 1) (7 in fingolimod arm and 3 in interferon arm) therefore it is difficult to conclude anything in this category of age.

- 9 patients were in the subgroup < 12 years and ≤ 40 kg (8 in fingolimod arm and 1 in interferon β1a arm) therefore it is difficult to conclude anything in this category of age.

- 21 patients were in the subgroup ≤ 12 years (whatever the weight) (13 in fingolimod arm and 9 in interferon armβ1a) therefore it is difficult to conclude anything in this category of age.

- 16 patients between 12 and 14 y-o in fingolimod arm and 19 in interferon arm (whatever the weight), the number of patients were also limited in this category of age.

Regarding duration of the treatment, the large majority of patients were treated during 1 year (102 (95.3%) in fingolimod arm versus 88 (82.2%) in interferon arm) but only 28% of patients on fingolimod treatment arm (30/107) and 17.8% (19/107) on interferon arm were treated during 2 years (any age). It is therefore difficult to assess long-term safety in paediatric patient.

No data is provided for long term exposure in paediatric population (e.g. ≥ 2 years of exposure). As this is a chronic pathology with theoretically no limit for treatment time duration this is also difficult to estimate the long term safety profile in this specific population.

Adverse events

The overall number of adverse events was similar in fingolimod group versus interferon group (95 versus 102).

Regarding the SOC Blood and lymphatic system disorders:

Leukopenia, Lymphopenia and anaemia are the 3 most frequent AE in fingolimod arm. Of note, Lymphopenia and leukopenia (NMQ, Novartis MedDRA query) were reported in more paediatric patients in the fingolimod treatment group (n=25, IR=15.7) compared to the IFN β-1a treatment group (n=3, IR=1.8). That is expected taking into account the mechanism of action of fingolimod.

Furthermore, white blood cell decreased is the most AEs reported in the SOC investigations (n=6 (IR =3.3 in fingolimod arm versus n=0 (IR=0) in interferon arm). There is indeed an effect of fingolimod that seems

particularly noticeable regarding hematological disorders in paediatric population. This has to be considered in the perspective of long term use in children. This also should be closely monitored in paediatric population.

Regarding the SOC infections and infestations:

There is an imbalance between the fingolimod arm (64 (IR=67.6) and interferon arm 60 (IR=61.8). According to the MAH, no opportunistic infection were reported in the CT2311. However, it is to be noted that one case of Mycoplasma pneumonia was reported.

Regarding the SOC nervous system disorders:
The number of AEs in this SOC in the paediatric population was similar for the fingolimod group compared to the IFN β-1a group (n=46 (IR=37.8) versus n= 45 (IR = 43.2)).

In adults, convulsions are an important potential risk in the RMP. Regarding CT in adult, the IR in FTY 0.5 mg arm is twice compared to IR in arm placebo (0.4 vs 0.2 for SMQ convulsion) but the difference was not statistically significant (IR ratio 1.77 (04.-10.52). Of note, according to the EuPSUR9 (EMEA/H/C/PSUSA/00001393/201702 - PRAC recommendation 28 September 2017), 56 cases of status epilepticus at least were reported in adult (DLP 28 Feb 2017). From the PRAC opinion, even if the frequency is stable during the time, there are still very severe cases taking into account that the number of cases is underestimated. Therefore, the question to add a warning in the SmPC to alert physician of the possible occurrence of convulsion, especially status epilepticus, and to be particularly vigilant in patients with underlying conditions is a safety concern discussed in PSUSA in adult.

Furthermore, regarding fingolimod arm in D2311, 16 SAE were reported in patients ≤ 12 year-old including 5 SAE in the SOC Nervous system disorders in 3 patients. Of note 4/5 were related to convulsion such as: generalized convulsions at Day 202, generalized tonico-clonic seizure at Day 320, Migraine without aura at Day 67, Convulsion at Day 251 and convulsion at D99. Regarding serious epileptic seizure (including at least 2 generalized convulsions), the role of Fingolimod cannot be excluded, especially since there is no other explanation in those cases except MS reactivation. The second option could be that fingolimod might not be the appropriate treatment for those patients.

Of note 22 patients were randomized in this CT in the subgroup ≤ 12 years including 13 in fingolimod arm and 9 in interferon arm. That means 9/13 patients experienced a SAE (69 %) in the fingolimod Arm. 5/9 SAEs were in the SOC Neurology and 4/9 SAEs were related to convulsions. 2/13 patients included in fingolimod arm and reported a SAE with convulsions were ≤ 12 year-old.

Assessment of causality is complicated by the fact that the incidence of epileptic seizures in MS patients is higher than in the general population. Also, the relatively long timeline of treatment with fingolimod prior to convulsive symptoms and the absence of action taken with study medication should be considered. In the view of the assessor, a causal relationship to fingolimod cannot be excluded, however.

'Seizures' (uncommon) has already been added by the Applicant to the tabulated list of ADRs (uncommon) of the SmPC, together with the statement in section 4.8. A warning is also added in section 4.4 as requested.

Regarding the SOC Cardiac disorders, the incidence rate is higher in fingolimod arm than in interferon arm (n=6 (IR 3.3) in fingolimod arm vs n=3 (IR 1.8) in interferon arm). Tachycardia (n=3 on fingolimod versus n=0 on interferon) is the most reported and all the other PT were reported once. Of note, 2 AEs of Electrocardiogram QT prolonged were reported in fingolimod arm (versus none in interferon arm).

It is obvious that more patients required extending monitoring in the fingolimod arm, more patient required hospitalization also. There is a patient in the fingolimod treatment group t had an AVB I at 0.25 mg (FDO)

and then an AVB type II when the dose was increased at 0.5 mg. No information is provided on the reason of the increase dose.

Cardiac disorders should be closely monitored taking into account the known safety profile of fingolimod in adult. Of note, the MAH did not discuss cardiac disorders as this is an important and very serious (potentially fatal) risk in adult.

Of note, the size of the study is small and patients in this study were excluded for select medical history, including severe cardiac, pulmonary, hepatic and other conditions, as well as for taking excluded medications that can explain the low number of cases (even if there are cases).

Anyway, cases reported in this study strongly justify that the minimisation risk measures put in place in adult for cardiac risks are also necessary to be applied in children at least. It would be interesting to have the analysis of cardiac risk, hospitalisation, required prolonged monitoring by age and by weight (e.g. dose). Of note, 9 patients were treated at 0.25 mg and 5 were increased to 0.5 mg depending on their weight or pharmacokinetic parameters (it is not known). No analysis was done regarding the AE / SAE by dose (0.25 mg and 0.5 mg) / weight (≤ and > 40 kg).

Cardiac SAE occurred in a patient. The lack of knowledge on the AEs at 0.25 mg is a concern.

Regarding the SOC Psychiatric disorders

In the study D2311, the incidence rate is higher in fingolimod arm than in interferon arm (n=20 (IR 11.9) in fingolimod arm vs n=11 (IR 7.1) in interferon arm). It is important to consider that the brain of children and adolescent is not completely mature on a point of view of neurobiology and therefore cognitive and psychiatric behaviour are not comparable with adult.

Psychiatric adverse effects are expected in adult population and SmPC already mentions “depression, depressed mood”.

There is an evident risk factor for depression and anxiety by the underlying MS disease. But there are also still uncertainties regarding potential increased risk in paediatric patients. Indeed, in study D2311, there was a higher incidence in fingolimod treated paediatric patients compared to IFN β-1a paediatric treated patients. Depression, suicidal ideation and anxiety are listed and expected as class effect for interferon treatments such as IFN β-1a. Consequently, despite the small number of paediatric patients exposed, the imbalance observed for fingolimod versus IFN β-1a has to be considered as a signal in paediatric patients.

To conclude, there is a rationale to further closely follow psychiatric disorders in children in future safety data but at this time it is not strong enough to propose inclusion in the RMP. Information in SmPC in sections 4.4 and 4.8 appears sufficient, waiting for complementary data form the extensive PASS.

Regarding the SOC General Disorders and administration site conditions, the incidence rate is higher in the interferon arm than in the fingolimod arm ((n=29 (IR 19.7) in fingolimod arm vs n=73 (IR 123.8) in interferon arm. Pyrexia (n=8 (IR=4.4) on fingolimod versus n=22 (IR=16.1 on interferon), Influence like illness (n=5 (IR=2.8) on fingolimod versus n=40 (IR=36.8) on interferon) and Chills ((n=1 (IR=0.5) on fingolimod versus n=11 (IR=7.4 on interferon) which are known and very common ADR on interferon treatment, are the most reported. It can be noticed that these high number of these common AE on interferon arm are mostly the reason that induces an imbalance of AEs in the interferon arm versus fingolimod.

Regarding the SOC investigation:

More Blood cholesterol increased were reported in fingolimod arm than in interferon arm. LDL increased is more reported also in fingolimod arm. This is not expected in paediatric patients neither an ADR of fingolimod.

The percentage of patients with notable elevations in total bilirubin (>20.52 µmol/L: 15.0% vs. 3.7%) and ALP (>116 U/L: 15.9% vs. 8.4%) were higher for the fingolimod group, elevations in transaminase levels were also reported (ALT ≥3xULN: 7.5% vs 5.6% patients; AST ≥3xULN: 0 vs 2.8% patients). Of note, one SAEs including ALT increase (severe, > 5 × ULN), and GGT increase (severe, GGT > 8 × ULN) was reported in an 11-year-old child. Regarding liver transamination elevation, the same precaution should be applied in children as in adult at least.

Regarding the SOC metabolism and nutrition:

More AEs are reported in fingolimod arm than in interferon arm in paediatric patients (9 versus 1). Decreased appetite (4 versus 0) and hypovitaminosis (3 versus 0) are the most reported AEs in fingolimod arm. Other AEs are reported once. Hypovitaminosis is not expected in paediatric patients. Decreased appetite is also surprising if we consider that patients improve on fingolimod treatment, this AE might not be reported. This might be a sign of impaired tolerance of fingolimod.

Serious adverse events and deaths

No fatal cases were reported in any treatment arm. More SAEs were reported in fingolimod arm versus interferon. Indeed, 33 SAE occurred in 19 patients in fingolimod arm and 13 SAE occurred in 9 patients in interferon arm. In patient ⩽ 12 year-old, 16 SAE were reported in fingolimod arm in 8 patients versus one SAE in interferon arm (the only SAE in patient ≤ 12 y-o in interferon arm was reported 38 days after the stop of interferon). Regarding pre-pubertal patient (Tanner staging score<2) 5 patients experienced a SAEs among the 7 patients included in fingolimod arm.

The most frequently SAEs with fingolimod belong to the SOC neurology (4 events of Epileptic seizure including 2 events of generalized tonic clonic seizures in 2 patients). (Please refer above in the SOC neurology / AEs, where a synthesis is already proposed including SAE and AE).

Discontinuation due to AES

5 patients permanently discontinued the treatment permanently in each arm. The reasons to permanently discontinue in fingolimod arm were: MS relapse, Hypersensitivity, vasculitis, radiological worsening of multiple sclerosis lesions, leukopenia, Macular oedema.

Regarding the patients who temporally discontinued the treatment, 12 AEs were reported in the fingolimod arm versus 3 in interferon arm. The principal reasons in fingolimod arm were convulsion and immunosuppression (leukopenia, lymphopenia, lymphocyte decreased, agranulocytosis, WBC decreased).

2.5.6. Discussion on clinical safety

Around 100 patients were exposed for 1 year with fingolimod and only 28 % of patients on fingolimod treatment arm (30/107) and 17.8 % (19/107) on interferon arm were treated during 2 years (any age). Only

10 patients were pre-pubertal subjects (Tanner staging score<2) (7 in fingolimod arm and 3 in interferon arm) therefore it is difficult to conclude anything in this category of age. 22 patients were in the subgroup ≤ 12 years (13 in Fingolimod arm and 9 in interferon β 1a arm) therefore it is difficult to conclude anything in this category of age. Of note, the number of patients between 12 and 14 y-o is also very small (16 in fingolimod arm and 19 in interferon arm).The overall number of adverse events were similar in fingolimod group versus interferon group (95 versus 102).Specific events of fingolimod involved mainly hematologic (Lymphopenia and total WBC), infectious (Upper respiratory tract infection), cardiovascular (tachycardia, QT prolongation), hepatic (mainly increases in ALT and GGT), and pulmonary (dyspnea) events. These AEs are expected taking into account the safety profile of fingolimod in adult. Of note, 2 SOC neurology (convulsion) and psychiatric disorders (anxiety, depressed mood and depression) reported a higher incidence of events in fingolimod treated patients compared to IFN β-1a treated patients, which is not known at the time being in adult.

Regarding specific subpopulation in this study:

Regarding patients ≤ 12 years: 21 patients were in the subgroup ≤ 12 years (13 in fingolimod arm and 9 in interferon armβ1a) in D2311. In this subgroup, 16 SAE were reported in fingolimod arm in 8 patients versus one SAE in interferon arm. The only SAE reported in interferon arm, is a patient who reported paronychia 38 days after the last dose of interferon. This is worrying.

Regarding Pre-pubertal subjects (Tanner staging score < 2): 10 pre-pubertal subjects were randomized in this CT, 7 on fingolimod and 3 on interferon: 5 patients had Tanner staging of 1 at visit 1 and experienced a SAE on fingolimod, none on interferon e.g. 5/10, 50 % of patients reported a SAE among all the patients including in this study at this age, 5/7 in the fingolimod arm had a SAE and all SAE were reported in fingolimod arm. Furthermore, all pre-pubertal patients in both the treatment groups reported at least an AE. Leucopenia (2 in fingolimod arm vs 0 in interferon arm), infection (Viral upper respiratory tract infection 6 vs. 1 patient) and Gamma-glutamyltransferase increased (2 versus 0) and eczema (2 vs 0) were the most reported in fingolimod arm.

Regarding long term data

11 SAEs were reported > 360 days and < 720 days: Acute symptomatic seizures (655 days), Muscular weakness (618 days), Migraine (658 days), Appendicitis (390 days), Small bowel obstruction Gastrointestinal necrosis (Necrotic bowel) (481 days), Epilepsy (generalized tonic clonic seizures) (498 days), Epilepsy (Epileptic seizure) (604 days), Multiple sclerosis relapse (399 days), Multiple sclerosis plaque Radiological worsening of MS disease (378 days), Generalised tonic-clonic seizure (378 days), Autoimmune uveitis (401 days).

These 11 SAEs were reported by 9 patients. The age was between 11 and 17 year-old.

Of note, 5 patients pre-pubertal subjects (Tanner staging score<2) had ≥ 360 days in this CT in the fingolimod arm. 1/5 experienced a SAE.

9/19 (47 %) patients experienced SAE after at least one year of treatment on fingolimod.

Among the 30 patients treated with fingolimod≥ 720 days, no SAE were reported. None pre-pubertal patients were exposed ≥ 720 days (24 months). Therefore, it is difficult to conclude anything taking into account the very low number of patients exposed and especially in pre pubertal stage.

Of note, long term data (> 1 year) are limited in paediatric patients treated for more than one year, therefore the long term risk in patients >10 y-o is difficult to be assessed.

Regarding the study D2311 results related to those specific subpopulation, only 9 patients below ≤ 40 kg were treated with fingolimod, started at the dose level of 0.25 mg, therefore it is difficult to draw definitive conclusion in this category of weight. 8/9 reported an AE (88.9%), 4/9 patients reported SAE (44.4%).

Regarding postmarketing data, 7 years after the MA, it is no more possible to only consider the 3 pivotal studies to determine the safety profile in adult. At the time being, data from post marketing including safety studies (D2403, D2406 and D2409) and the 7 years of post-marketing data that is yearly assessed in the PSUSA (EuPSUR9 (EMEA/H/C/PSUSA/00001393/201702 - PRAC recommendation 28 September 2017), can allow to consider that fingolimod is known to induce the following 3 major risks in adult:

- Bradycardia and polymorphic ventricular arrhythmia (due to the mechanism of action of fingolimod, e.g. a sphingosine-1-phosphate receptor modulator) that requires a cardiologist examination before to start the treatment and a at least 6 hour ECH monitoring at initiation

- Macular oedema that requires at least an ophthalmological evaluation at 3 to 4 months after treatment initiation

- Immunosuppressive effect that predisposes patients to an infection risk, including opportunistic infections that can be fatal (such as PML and cryptococcal meningitis), and increases the risk of developing lymphomas and other malignancies, particularly those of the skin. Therefore, Physicians have to carefully monitor patients, especially those with concurrent conditions or known factors (such as previous immunosuppressive therapy). It is important to consider that if this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis. Due to the risk of cutaneous neoplasms, an evaluation of the skin is recommended at initiation and then every 6 to 12 months taking into consideration clinical judgement.

Other potential and identified important risks are also carefully monitored in adults (please see RMP section).

Furthermore, as mentioned in the Guideline on conduct of pharmacovigilance for medicines used by the paediatric population (Ref. EMEA/CHMP/PhVWP/235910/2005- rev.) “Safety data cannot necessarily be extrapolated from data in adults because certain ADRs may only be seen in the paediatric population depending on the maturation of organ systems (e.g. skin, airways, kidney, liver, blood-brain-barrier), metabolism, growth and development in the case of life-long treatments for chronic diseases, the total duration of treatment is longer if started in childhood. This may expose the patient to increased risks of developing an ADR”.

The MAH reviewed post marketing paediatric patients as requested. A total of 916 events were reported in 385 paediatric patients in PM data. Of note, there were cumulatively 40 cases with children between 1 and 12Y old (30 between 3 and 12Y), including 11 serious HCP cases. The analysis of paediatric post marketing data are not convincing to conclude that the safety profile of fingolimod is more favourable in children than in adults.

2.5.7. Conclusions on clinical safety

Fingolimod has many known very serious, potentially fatal risks, in particular due to the mechanism of action (immunosuppressive effect) and long term treatment is a safety concern in particular in paediatric patients. Limited safety data are available on the long term (> 1 year and especially > 2 years). Because of the uncertainties related to the small number of paediatric patients included in this clinical trial, and especially

the very few data for children < 12 years old and < 40 kg, further long term safety data in paediatric population are needed.

Overall, the safety profile in adult is already known and is expected to be similar in the paediatric population. Furthermore, there seems to be additional safety concerns regarding neurological AEs and psychiatric disorders. The SmPC was updated accordingly.

Of note, very long term data missing in paediatric patients and the number of patient exposed is small, therefore the long term risk in paediatric patients at this time should be further studied. Further long term data are awaited both from long term extension study and from long term data in a larger number of patients that could document the safety profile of fingolimod in paediatric population.

2.6. Risk Management Plan

Safety concerns

Summary of the Safety Concerns

Important identified risks	Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose 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 Interaction with Beta blockers Interaction with Class Ia or Class III antiarrhythmic medicinal products
Missing information	Long term use in paediatric patients, including impact on growth and development (including cognitive development) Elderly patients 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 Unexplained death Switch from other disease modifying therapy

In the next Gilenya PSUR, the MAH should provide a cumulative review of all safety concerns specifically related to the paediatric population.

Pharmacovigilance plan

Table of Ongoing and planned additional pharmacovigilance activities

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
CFTY720D2409 The primary objective is to estimate the long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event after the first dose. Status: Ongoing	To estimate the long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event after the first dose	Bradyarrhythmia Hypertension Thrombo-embolic events QT interval prolongation Patients with cardiovascular conditions Long-term risk of cardiovascular morbidity/mortality Unexplained death	Protocol submission	15 Dec 2020
			Final report submission	4Q 2020
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
CFTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Status: Ongoing	To further explore the overall safety profile and incidence of selected safety-related outcomes of fingolimod under conditions of routine medical practice. To observe long-term effectiveness outcomes. To evaluate safety and effectiveness of switch from other disease modifying therapies.	Bradyarrhythmia Hypertension Liver transaminase elevation PRES Macular edema Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection) Bronchoconstriction Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma) ADEM like events Lymphoma	Annual update	Progress reports on enrolment and intermediate analysis results will be provided yearly in Q3.
			Final report submission	Final report: 2Q 2023

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
		Other malignant neoplasms Thrombo embolic events QT interval prolongation Convulsions Patients with diabetes mellitus Patient with cardiovascular conditions* Long-term risk of cardiovascular morbidity/mortality Long term risk of malignant neoplasms Unexplained death Switch from other disease modifying therapy		
CFTY720D2404: Prospective, observational study in pregnant MS patients with confirmed or suspected maternal exposure to fingolimod any time during pregnancy or shortly before pregnancy (up to 8 weeks before last menstrual period). Status: Ongoing	To collect data regarding fingolimod exposure during pregnancy and maternal, fetal and infant outcomes	Reproductive toxicity	Annual update	Progress reports on enrollment and intermediate analysis results will be provided yearly in Q3.
			Final report submission	2Q 2031
PRIM: Gilenya Pregnancy outcomes Intensive Monitoring (enhanced pharmacovigilance data collection). Status: Ongoing	To collect data regarding fingolimod exposure during pregnancy and maternal, fetal and infant outcomes	Reproductive toxicity	Annual update	Progress reports on enrollment and intermediate analysis results will be provided yearly in Q3.
			Final report submission	1Q 2020

Study / Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
CFTY720D2406: Long-term prospective non interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Status: Ongoing	To further explore the overall safety profile and incidence of selected safety-related outcomes of fingolimod under conditions of routine medical practice. To observe long-term effectiveness outcomes. To evaluate safety and effectiveness of switch from other disease modifying therapies.	Bradyarrhythmia Hypertension Liver transaminase elevation PRES Bronchoconstriction Macular edema Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection) Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma) ADEM like events Lymphoma Other malignant neoplasms Thrombo-embolic events QT interval prolongation Convulsions Patients with diabetes mellitus Patients with cardiovascular conditions* Long-term risk of cardiovascular morbidity/mortality Long-term risk of malignant neoplasms Unexplained death Switch from other disease modifying therapy	Annual update	Progress reports on enrollment and intermediate analysis results will be provided yearly in Q3.
			Final report submission	4Q 2020
Study CFTY720D2311: A 2-year, double blind, randomised, multicenter, active-controlled Core Phase study to evaluate the safety and efficacy of fingolimod administered oraly once daily versus interferon beta 1a (IFN beta-1a) IM once weekly in paediatric patients with multiple sclerosis, with a 5-year fingolimod Extension Phase Status: planned	Core Phase: the primary objective of the study was to evaluate the efficacy of fingolimod relative to intramuscular IFN-beta 1a in reducing the frequency of relapses as assessed by the annualized relapse rate (ARR) in children / adolescent MS patients aged 10 to < 18 years when treated for up to 24 months.	Long-term use in paediatric patients including impact on growth and development (including cognitive development)	Revised protocol Interim reports Extension Phase final report	Within 2 months from the EC decision for procedure EMEA/H/C/002202/X/0044/G Annually (1st report by 31 December 2020) 3Q 2027

Study / Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	The key secondary objective was to evaluate the efficacy of fingolimod relative to IFN beta 1-a in reducing the number of new /newly enlarging T2 (n/ne T2) lesions in children / adolescent MS patients aged 10 to < 18 years treated for up to 24 months Extension phase: To examine long-term safety, tolerability and efficacy parameters in patients treated with fingolimod			

The MAH proposal to open the recruitment of additional patients in the *subpopulation of patients aged ⩽12 years, ⩽40 kg or Tanner Stage <2 (pre-pubertal) group.*sub-population in the current 5-year extension of D2311 study (through an amendment), instead of put in place a new safety study, is acceptable provided the following conditions are met:

- The safety assessments should be added and closely followed by the MAH;

-The MAH should modify selection criteria of the study to include patients with highly active relapsing remitting multiple sclerosis aged ⩽12 years, ⩽40 kg or Tanner Stage <2 (pre-pubertal) group:

- 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.

A one year interim data of safety data for this specific subpopulation is expected. Pooled analysis with data of patients already included can be done if possible considering characteristics of the patients.

In order to update the inclusion criteria, a revised protocol for study D2311 should be submitted for review and approval within 2 months from the EU commission decision. The MAH also agreed to submit the first interim report during the latter half of 2020. Thereafter, annual reports will be submitted annually.

Risk minimisation measures

Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important Identified Risks		
Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	Routine risk minimization measures: SmPC section 4.4, 4.5 and 4.8 Additional risk minimization measures: Educational materials for physicians and patients: -Physician's checklist for adult and paediatric population - Patient/Parent/Caregiver reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection : Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another disease-modifying therapy. Study FTY720D2406: Long-term prospective non interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2409: The primary objective is to estimate the long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose
Hypertension	Routine risk minimization measures: SmPC section 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2409: The primary objective is to estimate the long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.
Liver transaminase elevation	Routine risk minimization measures: SmPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2 Additional risk minimization measures: Educational materials for physicians and patients: --Physician's checklist for adult and paediatric population - Patient/Parent/Caregiver reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study

Safety concern	Risk minimization measures	Pharmacovigilance activities
		monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
Posterior Reversible Encephalopathy Syndrome (PRES)	Routine risk minimization measures: SmPC section 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel cohort study monitoring safety in patients with MS newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease-modifying therapy Study FTY720D2406: Long-term prospective non interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy
Macular edema	Routine risk minimization measures: SmPC section 4.4 and 4.8 Additional risk minimization measures: Educational materials for physicians and patients: --Physician's checklist for adult and paediatric population - Patient/Parent/Caregiver reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection)	Routine risk minimization measures: SmPC sections 4.3, 4.4 and 4.8 Additional risk minimization measures: Educational materials for physicians and patients: --Physician's checklist for adult and paediatric population - Patient/Parent/Caregiver reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
Leukopenia and lymphopenia	Routine risk minimization measures: SmPC section 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Reproductive toxicity	Routine risk minimization measures:	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimization measures	Pharmacovigilance activities
	SmPC section 4.6 Additional risk minimization measures: Educational materials for physicians and patients: --Physician's checklist for adult and paediatric population - Patient/Parent/Caregiver reminder card	reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Enhanced Pharmacovigilance Program: PRIM (Gilenya Pregnancy outcomes Intensive Monitoring) Study FTY720D2404: The Multinational Pregnancy Gilenya Exposure Registry in Multiple Sclerosis to prospectively collect outcome data on the babies born to women treated with fingolimod.
Bronchoconstriction	Routine risk minimization measures: SmPC section 4.4, 4.8 and 5.1 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel cohort study monitoring safety in patients with MS newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term prospective non interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
Hypersensitivity	Routine risk minimization measures: SmPC section 4.3, 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None
Basal Cell Carcinoma	Routine risk minimization measures: SmPC section 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
Convulsions	Routine risk minimization measures: SmPC sections 4.4, 4.8 Additional risk minimization measures: Educational materials for physicians and patients: --Physician's checklist for adult and	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-

Safety concern	Risk minimization measures	Pharmacovigilance activities
	paediatric population - Patient/Parent/Caregiver reminder card	modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
Important Potential Risks		
Skin cancer other than BCC	Routine risk minimization measures: SmPC section 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
Acute disseminated encephalomyelitis-like (ADEM-like) events	Routine risk minimization measures: SmPC section 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel cohort study monitoring safety in patients with MS newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term prospective non interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
Lymphoma	Routine risk minimization measures: SmPC section 4.8 and 5.3 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2399: A single arm, open-label, multicenter study evaluating the long-term safety, tolerability and efficacy of 0.5 mg fingolimod (FTY720) administered orally once daily in patients

Safety concern	Risk minimization measures	Pharmacovigilance activities
		with MS.
Other malignant neoplasms	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2399: A single arm, open-label, multicenter study evaluating the long-term safety, tolerability and efficacy of 0.5 mg fingolimod (FTY720) administered orally once daily in patients with MS.
Thrombo-embolic events	Routine risk minimization measures: SmPC section 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.
QT interval prolongation	Routine risk minimization measures: SmPC section 4.4 and 4.9 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to

Safety concern	Risk minimization measures	Pharmacovigilance activities
		estimate the long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.
Off-label use	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Atypical MS relapse	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None
Hemophagocytic syndrome	Routine risk minimization measures: SmPC section 4.8 Additional risk minimization measures: Healthcare Professional Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None
Interaction with Ketoconazole	Routine risk minimization measures: SmPC section 4.5 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Interaction with Carbamazepine	Routine risk minimization measures: SmPC section 4.5 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Interaction with Beta blockers	Routine risk minimization measures: SmPC section 4.4 and 4.5 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Interaction with Class Ia or Class III antiarrhythmic medicinal products	Routine risk minimization measures: SmPC section 4.4 and 4.5 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing information		
Long-term use in paediatric patients, including impact on growth and	Routine risk minimization measures: SmPC sections 4.2 and 5.2	Study FTY720D2311: A two-year, double-blind, randomized, multicenter, active-controlled Core Phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a

Safety concern	Risk minimization measures	Pharmacovigilance activities
development (including cognitive development)	Additional risk minimization measures: Educational materials for physicians and patients: -Physician's checklist for adult and paediatric patients -Patient / Parent / Caregiver reminder card	(IFN β-1a) IM once weekly in paediatric patients with multiple sclerosis, with a five-year fingolimod Extension Phase.
Elderly patients	Routine risk minimization measures: SmPC section 4.2 and 5.2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Lactating women	Routine risk minimization measures: SmPC section 4.6 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None
Patients with diabetes mellitus	Routine risk minimization measures: SmPC section 4.2, 4.4, and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, parallel-cohort study monitoring safety in patients with MS, either recently initiated on fingolimod or receiving another DMT according to local label and exclude patients previously treated with Natalizumab. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
Patients with cardiovascular conditions*	Routine risk minimization measures: SmPC section 4.4 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate the long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.
Long-term risk of	No risk minimization measures	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimization measures	Pharmacovigilance activities
cardiovascular morbidity/mortality		reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate the long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.
Long-term risk of malignant neoplasms	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2399: A single arm, open-label, multicenter study evaluating the long-term safety, tolerability and efficacy of 0.5 mg fingolimod (FTY720) administered orally once daily in patients with MS.
Unexplained death	Routine risk minimization measures: SmPC section 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate the long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular

Safety concern	Risk minimization measures	Pharmacovigilance activities
		event during the first dose.
Switch from other disease modifying therapy	Routine risk minimization measures: SmPC section 4.4, 4.5 and 5.1 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy

The Physician check list, included in annex 6 of the RMP, has been updated to include a recommendation to consider re-assessing the benefit versus risk in each patient receiving Gilenya on an annual basis, particularly for paediatric patients.

Conclusion

The CHMP and PRAC considered that the RMP version 15.0 (dated 19 September 2018), also including the changes requested in the PSUSA (EMEA/H/C/PSUSA/00001393/201802), is acceptable.

2.7. Pharmacovigilance

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.

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

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1.1. Disease or condition

Multiple sclerosis (MS) is a chronic, immune-mediated neurodegenerative disorder of the central nervous system (CNS), characterized by inflammation, demyelination, and axonal/neuronal destruction ultimately leading to severe disability. The course of symptoms occurs in two main patterns initially: either as episodes of sudden worsening that last a few days to months (called relapses, exacerbations, attacks) followed by improvement (85% of cases) or as a gradual worsening over time without periods of recovery (10–15% of cases). A combination of these two patterns may also occur or people may start in a relapsing and remitting course that then becomes progressive later on.

The initial course of MS is more often relapsing (-remitting) in paediatric onset MS (>98%) than in adult onset (approximately 85%). The relapse rate in paediatric MS is reported to be 2-3 times higher than in adult onset.

Available data showed that MRI features in paediatric MS are similar to adult relapsing MS. Children, however, tend to have a higher number of T2 lesions at the time of first event than adults and a lower propensity for lesions to enhance with gadolinium (Gd).

Treatment strategies in paediatric MS, as for adults, are focused on treatment of acute relapses, MS symptoms, and disease-modification.

Disease-modification treatments aim to reduce relapses in MS relapsing-remitting forms, which eventually should lead to delay disease progression occurrence. Thus, the main endpoints of interest in this disease form, especially in children, are the reduction of annual relapse rate (ARR) and MRI findings (most sensitive tool currently available to monitor inflammatory disease activity).

3.1.2. Available therapies and unmet medical need

Despite limited published data suggesting that the efficacy and safety profile in adolescents (≥12 years of age) is similar to that seen in adults, 3 IFN β agents (2 IFN β-1a and 1 IFN β-1b) and glatiramer acetate are allowed to be used in paediatric patients with MS according to the dosage and administration sections of the EU summary of product characteristics (SmPC).

3.1.3. Main clinical study

D2311 a phase 3, flexible duration (up to 2 years), double-blind, double dummy, randomized, multi-center, active controlled study evaluating the efficacy/safety of fingolimod once daily (weight-based dosing; 0.25 mg ≤40 kg or 0.5 mg >40 kg) vs IFN β-1a 30 µg im once/week.

The study included children aged 10 to 18 years old, suffering from RRMS, in majority composed of:

- Newly diagnosed MS patients,
- With a low mean baseline EDSS score (disability score) of 1.54,
- Treatment naïve patients (~64%),
- Aged > 12 years (~90%)
- Pubertal at baseline according to Tanner staging score >= 2 (94.4%)

- Weighting > 40 kg (95.3%)

3.2. Favourable effects

The primary endpoint was ARR, defined as the average number of confirmed relapses per year. Regarding this endpoint, fingolimod showed statistically superiority vs IFN β-1a with adjusted ARR estimate of 0.122 vs 0.675. This corresponded to a significant reduction (p<0.001) of 81.9% in ARR for fingolimod-treated patients compared with IFN β-1a-treated patients.

The key secondary variable was the annualized rate of the number of new/newly enlarged T2 lesions (n/neT2) from baseline to up to Month-24, which showed statistically significantly lower rate in fingolimod group compared with IFN β-1a group, with a 52.6% reduction in the number of new or newly enlarged T2 lesions (p<0.001).

Fingolimod showed also superiority over IFN beta-1a regarding other secondary endpoints:

- The time to first confirmed relapse was significantly delayed in fingolimod-treated patients compared to IFN β-1a-treated patients (log-rank test p<0.001).
- The risk of confirmed relapse up to 2 years was significantly reduced (82.2%) with fingolimod compared with IFN β-1a (hazard ratio of 0.18; p<0.001).

Also, supportive, sensitivity analyses, and subgroup (pre-planned or post-hoc) analyses on primary and key secondary endpoints confirmed those observed with primary and key secondary endpoints.

Similar results were observed in RRMS adult patients study (D2302), a 12-Month treatment trial (~44% were treatment-naïve patients), where fingolimod showed superiority over IFN beta-1a in one of the pivotal studies (D2302) on most efficacy endpoints.

3.3. Uncertainties and limitations about favourable effects

According to the claimed indication in paediatric patients:

"Gilenya is indicated as a single disease modifying therapy for the treatment of paediatric patients of 10 years of age and above with relapsing multiple sclerosis."

Dose adjustment recommendation in children is set-up according to children weight:

- Paediatric patients with body weight ≤40 kg: one 0.25 mg capsule taken orally once daily.
- Paediatric patients with body weight >40 kg: one 0.5 mg capsule taken orally once daily.

The rational of cut-off weight of 40 kg was endorsed.

As mentioned earlier regarding age, puberty status, and weight subgroups in the population included in the main study, the repartition is unbalanced between treatment groups and the overall number of patients in the lower subgroup ranges is limited (see the table below). It is understood that this follows the recommendations issued by the PDCO, but still creates uncertainties for the assessment of the B/R ratio in these subgroups.

	FTY720 N=107	**IFN β-1a N=108**	**Total N=215**
Age group (years), n (%)			
<=12	13 (12.1)	9 (8.3)	22 (10.2)
>12	94 (87.9)	99 (92.7)	193 (89.8)

Age group repartition in patients <=12 years			
10 years	5	0	5
11 years	3	1	4
12 years	5	8	13
Pubertal status (Tanner staging scores), n (%)			
Pre-pubertal (<2)	7 (6.5)	3 (2.8)	10 (4.7)
Pubertal (>=2)	98 (91.6)	105 (97.2)	203 (94.4)
Weight group (kg), n (%)			
<=40	9 (8.4)	1 (0.9)	10 (4.7)
>40	98 (91.6)	107 (99.1)	205 (95.3)

These uncertainties should be taken into account with regards to the known fingolimod safety profile.

Since the study design was updated from fixed to flexible study duration (up to 24 months), there are limited efficacy and safety data comparing fingolimod to IFN β-1a. Indeed, only 30 (28.0%) patients in fingolimod group and 19 (17.8%) patients in the IFN β-1a group completed 24 months of treatment (see also below the durations of exposure in fingolimod group):

- 102 (95.3%) patients in the fingolimod group were exposed to ≥360 days (12 months) of treatment
- 74 (69.2%) patients in the fingolimod group were exposed to ≥540 days (18 months) of treatment
- 30 (28.0%) patients in the fingolimod group were exposed to ≥720 days (24 months) of treatment.

3.4. Unfavourable effects

The current fingolimod indication in adults RRMS patients is as follows:

"*Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:*

- 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."

This restricted indication was given with regards to fingolimod safety profile, which is in adult population well characterised at present, taking into account post marketing safety data available from PSURs.

Since the safety profile of fingolimod in paediatric population is considered the same as in adult population, the 3 major risks should also be considered in children:

- Bradycardia and polymorphic ventricular arrhythmia;
- Macular oedema;
- Immunosuppressive effect that predisposes patients to the risk of infections, including opportunistic infections that can be fatal (such as cryptococcal meningitis, herpetic encephalitis, ….) and increases the risk of developing lymphomas and other malignancies, particularly those of the skin.

All these risks, as for other potential and identified risks, have to be carefully monitored in adult (please refer to fingolimod RMP) and in paediatric patients.

Overall, there are safety concerns especially regarding immunity (as in adult population), but also neurological (convulsion and generalized tonico-clonic seizure) and psychiatric disorders (depression and anxiety) according to safety data from Study D2311, which are of special concern in this particular population.

Moreover, the overall incidence of SAEs was higher in patients treated with fingolimod (33 SAE in 19 patients, 17.8%) compared with IFN β-1a (13 in 10 patients, 9.3%). AEs requiring temporally interruption of study drug were more frequent in the fingolimod group than in the IFN β-1a treatment group (11.2% vs 2.8%, respectively) and this difference was due to primary SOCs of investigations (4 patients with ALT/AST abnormal, blood pressure increased, lymphocyte or white blood cell count decreased), nervous system disorders (2 patients with seizure and 1 patient with tonic-clonic seizure), and blood and lymphatic disorders (2 patients with leukopenia, 1 patient with agranulocytosis and 1 patient with lymphopenia).

Among the 19 patients from fingolimod group who experienced SAEs, 8 were ≤ 12 years (13 patients ≤ 12 years were included in this study) how reported 16 SAEs. In interferon subgroup of patients aged ≤ 12 years, one SAE (paronychia) was reported 38 days after stopping the treatment (relationship with interferon treatment is therefore unlikely). Also, 10 pre-pubertal subjects (Tanner staging score<2) were randomized in the study, 7 in fingolimod group. All pre-pubertal patients (100%) reported at least an AE. Among these patients 5 experienced a SAE on fingolimod, and none in interferon group. Thus, the safety profile of fingolimod in this special subgroup of patients (Tanner 1 or 12 years and below) appears to be more severe/serious than in older children and adult population.

3.5. Uncertainties and limitations about unfavourable effects

Overall, the safety profile of fingolimod is limited due to the limited number of patients exposed to fingolimod in D2311 study.

Moreover, there is a lack or at least very limited safety data regarding:

- Long-term exposure to fingolimod, which is an immunosuppressive molecule;
- Patients aged 12 years and less;
- Patients 40 kg and less;
- Pre-pubertal population, and thus lack of data regarding sexual development;
- Behaviour, cognitive and physical development in this special (paediatric) population.

For note, a rebound effect must be considered when stopping treatment with fingolimod. This should be taken into account when considering that MS concerns mainly young female patients that could have a desire of pregnancy and need to stop fingolimod treatment. Females adolescent, who wish to procreate in the future, could face this issue if they are on fingolimod treatment.

3.6. Effects Table

Table 5. Effects Table for fingolimod in paediatric (10 to 18 years, data cut-off: 11-Aug-2017)

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence
Annualized relapse rate (ARR)	Primary endpoint – rates of ARR up to Month-24	Adjusted rates and percent of reduction	0.122 [0.078-0.192]	0.675 [0.515-0.885]	ARR ration=0.181 [0.11-0.3]; Reduction ~82% ; p<0.001
Annualized rate of new or newly-enlarged T2 lesions	Key secondary endpoint – rates up to Month-24	Adjusted rates and percent of reduction	~4.4 [3.6-5.34]	~9.3 [7.67-11.2]	Rate ratio=0.474 [0.36-0.62]; Reduction=52.6%; p<0.001
Proportion of patients free of relapse	Other secondary endpoint – rates up to Month-24	Percent of patients free of relapse	85.7% [79.0-92.4]	38.8% [27.4-50.3]	Rate ratio=0.18 [0.10-0.32] Reduction=82.2%; p<0.001
Mean Change of EDSS from baseline	Exploratory endpoint – scores the disability progression – up to Month-24	Score from 0 to 10 (0=normal – 10=death)	−0.23	+0.22	Numeric superiority of fingolimod versus IFN beta-1a (not statistically significant)
Annualized relapse rate (ARR) on subgroups - Age <= 12 years - Weight <=40 kg - Tanner <2	Supportive and sensitivity analyses of the primary endpoint	See above	0.095 0.145 0.195	0.721 0.735 1.494	Limited number of patients for each subgroup pattern. It is difficult to conclude anything in this category of age.
PK and PKPD analysis	The rational of dose adjustment (0.25 mg/d versus 0.5 mg/d) according to patient weight (⩽40 kg and > 40 kg)	-	Fingolimod	-	The rationale of dose adjustment is acceptable.
Immunosuppressive effect	Risk of infections, including fatal opportunistic infections (PML, cryptococcal meningitis, …) Increased risk of lymphomas and other malignancies, particularly those of the skin		Fingolimod	-	Know safety issue in adult
Rebound effect	New or re-emerging neurological symptoms after stopping treatment (development of multiple new or enhancing lesions exceeding baseline disease activity), beyond what is expected in the patient		Fingolimod	-	Know safety issue in adult
Overall incidence of SAEs	Compare SAEs between treatment groups		33 in 19 pts, 17.8%	13 in 10 pts, 9.3%	The number of SAE in fingolimod group is almost twice the number of SAEs in IFN group

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence
AEs leading to temporally study drug interruption	Compare important AEs (leading to temp. drug interruption) between treatment groups		11.2%	2.8%	The number of AEs leading to temp. drug interruption is almost three time higher in fingolimod group vs IFN
SAEs after long-term exposure (>360 d and<720 d)	Compare SAEs occurrences after long-term exposure between treatment groups		11 SAEs in 9 pts	3 SAEs in 1 pts	The number of SAEs occurring after one year of treatment is almost three time higher in fingolimod group vs IFN group
SAEs in sub-groups - <=12 years (22 pts) - pre-pubertal (10 pts)	Compare AEs in sub-groups of interest		- 13 pts: 16 SAEs - 7 pts: 5 SAEs	- 9 pts: 1 SAE* - 3 pts: 0 SAE	The number of SAEs in two sub-groups (<=12 yrs and pre-pubertal) if far higher in fingolimod sub-groups compared with interferon group
Risk of convulsions (SMQ) - All AEs - SAEs	Compare this increased risk in children versus adults in both treatment groups		- 6 (3.2%) - 7 SAEs (in 3 pts)	- 1 (0.6%) - 0 SAE	The risk of convulsions (epilepsy, generalized tonic-clonic seizure, etc.) is increased in fingolimod group vs interferon, and the freq. is above what is known in adult population
Effect on sexual maturation and physical development	Effect of fingolimod on these points is not fully specified due to the limited number of per-pubertal patients and limited exposure duration		Fingolimod	-	Lacking data - Effect to be specified

3.7. Benefit-risk assessment

3.7.1. Importance of favourable and unfavourable effects

The efficacy of fingolimod in the treatment of RRMS adult patients is already known and demonstrated in relation to authorised medicinal products. The efficacy data from Study D2311 in children with RRMS aged 10 to 18 years are consistent with those from adult patients, including one of the pivotal adult study comparing fingolimod to IFN beata-1a (D2302).

In paediatric study (D2311), as in adult study (D2302), fingolimod showed significant superiority over IFN beta-1a regarding the primary endpoint (ARR), the key secondary endpoint (new/newly enlarging T2 lesions), other secondary endpoints (Time to first confirmed relapse and proportion of patients free of relapse at Month-24; Gd-enhancing T1 lesions, etc.) and some pre- or post-planned sub-groups analyses of interest (ex. excluding Nabs-positive patients from IFN beta-1a group and DMT naive patients only).

However, these efficacy data are still lacking in some aspects regarding:

- The limited number of patients having sufficient duration of exposure: only 30 (28.0%) patients in the fingolimod group and 19 (17.8%) patients in the IFN β-1a group were exposed to ≥ 720 days (24 months) of study treatment;
- Body weight ≤40 kg: the number of patients this subgroup is limited (10 patients, 9 in fingolimod group) and rational of the chosen cut-off of 40 kg allowing dose adjustment (0.25 mg/d or 0.5 mg/d) is not fully provided;
- Age ≤ 12 years: the number of patients this subgroup is also limited (22 patients) and their repartition between treatment groups by age range (10, 11 and 12 years) is very unbalanced (10 years: 5 patients all in fingolimod group, 11 years: 3/4 patients were in fingolimod group);
- Pre-pubertal status (Tanner <2): the number of patients in this subgroup is also limited (10 patients) and their repartition between treatment groups is unbalanced (7 in fingolimod and 3 in interferon group, respectively).

Regarding safety profile of fingolimod in paediatric population, and as claimed by the MAH, this profile seems to be similar to what is known in adult population (this assumption should be considered as the better case at present time). Therefore, the 3 major risks (cardiac, ocular, and immunosuppressive effects) and all other known risks related to fingolimod should be taken into account in the benefit/risk assessment of fingolimod treatment in RRMS in children.

Furthermore, since MS concerns mainly young female that could have a desire of pregnancy, a rebound effect must be considered after stopping treatment with fingolimod in adolescent females on fingolimod treatment. Females adolescent, who wish to procreate in the future, could face this issue if they are on fingolimod treatment.

It is also important to notice the increased risk of AEs/SAEs/AEs leading to study drug interruption in some subgroup of patients (≤ 12 years and pre-pubertal patients).

Finally, there is a lack of long term safety data in all paediatric population, and mostly in those aged 12 years and less, pre-pubertal patients, and weighing ≤40 kg, and limited data for patients aged more than 12 years.

3.7.2. Balance of benefits and risks and conclusion

Based on the review of data on quality, safety and efficacy, the overall benefit- risk balance of fingolimod is considered positive in the following indication:

“Gilenya 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.”

This is due to the fact that the efficacy of fingolimod in this population has been sufficiently demonstrated, but the risks that the treatment presents with are the same for both the adult and paediatric population, so a similar indication as in adults was agreed on.

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, Gilenya 0.25 mg, hard capsules is favourable in the following indication:

"Gilenya 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."

The CHMP therefore recommends the extension(s) of the marketing authorisation for Gilenya subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to 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 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 of GILENYA in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The MAH shall ensure that in each Member State (MS) where GILENYA is marketed, all physicians who intend to prescribe GILENYA are provided with an updated Physician Information Pack, including:

1. Summary of Product Characteristics (SmPC);
2. Physician's checklist for adult and paediatric patients, to consider prior to prescribing GILENYA, including information about the fingolimod Pregnancy Outcomes Intensive Monitoring Program and the Pregnancy Exposure Registry;
3. The reminder card, to be provided to all patients, their parents (or legal representatives), and caregivers

Physician's checklist

The physician's checklist shall contain the following key messages:

- Monitoring requirements at treatment initiation:

  Before first dose
  - o Perform baseline ECG prior to the first dose of GILENYA;
  - o Perform blood pressure measurement prior to the first dose of GILENYA;
  - o Perform a liver function test prior to (within 6 months) treatment initiation;
  - o Arrange ophthalmological assessment before starting GILENYA treatment in patients with diabetes mellitus or with a history of uveitis;

  Until 6 hours after first dose
  - o Monitor the patient for 6 hours after the first dose of GILENYA has been administered for signs and symptoms of bradycardia, including hourly pulse and blood pressure checks. Continuous (real time) ECG monitoring is recommended;
  - o Perform an ECG at the end of the 6-hour monitoring period.

  >6 to 8 hours after first dose
  - o If, at the 6-hour time point, the heart rate is at the lowest value following the first dose, extend heart rate monitoring for at least 2 more hours and until the heart rate increases again.

- Recommendation for re-initiating GILENYA therapy after treatment interruption:
  The same first dose monitoring as for treatment initiation is recommended when treatment is interrupted for:
  - o One day or more during the first 2 weeks of treatment;
  - o More than 7 days during weeks 3 and 4 of treatment;
  - o More than 2 weeks after at least 1 month of treatment.

- Recommendation for overnight monitoring after the first dose (or if the first dose monitoring applies during treatment re-initiation):
  - o Extend heart rate monitoring for at least overnight in a medical facility and until resolution of findings in patients requiring pharmacological intervention during monitoring at treatment initiation/re-initiation. Repeat the first dose monitoring after the second dose of GILENYA;

- Extend heart rate monitoring for at least overnight in a medical facility and until resolution of findings in patients:
    - With third degree AV block occurring at any time;
    - Where at the 6-hour time point:
        a. Heart rate <45 bpm, <55 bpm in paediatric patients aged 12 years old and above, or <60 bpm in paediatric patients 10 to below 12 years of age;
        b. New onset second degree or higher AV block;
        c. QTc interval ≥500 msec.

- GILENYA is contraindicated in patients with:
    - Known immunodeficiency syndrome;
    - Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies);
    - Severe active infections, active chronic infections (hepatitis, tuberculosis);
    - Known active malignancies;
    - Severe liver impairment (Child-Pugh class C);
    - In the previous 6 months, myocardial infarction (MI), unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure;
    - Severe cardiac arrhythmias requiring anti-arrhythmic treatment with class Ia or class III anti-arrhythmic drugs;
    - Second-degree Mobitz type II atrioventricular (AV) block or third-degree AV block, or sick-sinus syndrome, if they do not wear a pacemaker;
    - Patients with a baseline QTc interval ≥500 msec;
    - Hypersensitivity to the active substance or to any of the excipients.

- GILENYA is not recommended in patients with:
    - Sino-atrial heart block;
    - QTc prolongation >470 msec (adult females), QTc >460 msec (paediatric females) or >450 msec (adult and paediatric males);
    - History of cardiac arrest;
    - Severe sleep apnea;
    - History of symptomatic bradycardia;
    - History of recurrent syncope;
    - Uncontrolled hypertension;

    If GILENYA treatment is considered in these patients anticipated benefits must outweigh potential risks and a cardiologist must be consulted to determine appropriate monitoring, at least overnight extended monitoring is recommended.

- GILENYA is not recommended in patients concomitantly taking medicines known to decrease the heart rate. If GILENYA treatment is considered in these patients anticipated benefits must outweigh potential risks and a cardiologist must be consulted to switch to non-heart-rate-lowering therapy or, if not possible, to determine appropriate monitoring. At least overnight extended monitoring is recommended;

- GILENYA reduces peripheral blood lymphocyte counts. Peripheral lymphocyte count (CBC) should be checked in all patients prior to initiation (within 6 months or after discontinuation of prior therapy) and monitored during treatment with GILENYA. Treatment should be interrupted if lymphocyte count is confirmed as <0.2x109/L. The approved dosing of 0.5 mg once daily (or 0.25 mg once daily in paediatric patients 10 years of age and above with a body weight of ≤40 kg) when restarting Gilenya should be administered. Other dosing regimens have not been approved.

- GILENYA has an immunosuppressive effect that predisposes patients to an infection risk, including opportunistic infections that can be fatal, and increases the risk of developing lymphomas (including mycosis fungoides) and other malignancies, particularly those of the skin. Surveillance should include vigilance for both skin malignancies and mycosis fungoides. Physicians should carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive

therapy. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis.

  - Treatment initiation in patients with severe active infection should be delayed until the infection is resolved. Suspension of treatment during serious infections should be considered. Anti-neoplastic, immunomodulatory or immunosuppressive therapies should not be co-administered due to the risk of additive immune system effects. For the same reason, a decision to use prolonged concomitant treatment with corticosteroids should be taken after careful consideration.
  - Vigilance for basal cell carcinoma and other cutaneous neoplasms including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merckel cell carcinoma is recommended, with skin examination prior to treatment initiation and then every 6 to 12 months taking into consideration clinical judgement. Patients should be referred to a dermatologist if suspicious lesions are detected. Caution patients against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

- Patients should be instructed to report signs and symptoms of infections immediately to their prescriber during and for up to two months after treatment with GILENYA;
  - Prompt diagnostic evaluation should be performed in patient with symptoms and signs consistent with cryptococcal meningitis; appropriate treatment, if diagnosed, should be initiated.

    Reports of cryptococcal meningitis (sometimes fatal) have been received after approximately 2-3 years of treatment, although an exact relationship with the duration of treatment is unknown.
  - Physicians should be vigilant for clinical symptoms or MRI findings suggestive of PML. If PML is suspected, treatment with GILENYA should be suspended until PML has been excluded.

    Cases of PML have occurred after approximately 2-3 years of monotherapy treatment although an exact relationship with the duration of treatment is unknown.
  - Specific recommendations regarding vaccination for patients initiating or currently on GILENYA treatment. Check varicella zoster virus (VZV) antibody status in patients without a healthcare professional confirmed history of chickenpox or documentation of a full course of varicella vaccination. If negative, a full course of vaccination with varicella vaccine is recommended and treatment initiation should be delayed for 1 month to allow full effect of vaccination to occur.
  - Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported in the post-marketing setting. Cancer screening, including Pap test, and vaccination for HPV-related cancer is recommended for patients, as per standard of care.

- A full ophthalmological assessment should be considered:
  - 3-4 months after starting GILENYA therapy for the early detection of visual impairment due to drug-induced macular edema;
  - During treatment with GILENYA in patients with diabetes mellitus or with a history of uveitis.

- GILENYA is teratogenic. Therefore, women of childbearing potential, including female adolescents should avoid pregnancy during GILENYA treatment; a negative pregnancy test result should be confirmed prior to starting treatment, and it should be repeated at suitable intervals;

  Women of child-bearing potential, including adolescent females, their parents (or legal representatives), and caregivers, should be informed about the serious risks of GILENYA to the fetus. Effective contraception during treatment and for at least two months following treatment discontinuation should be recommended.

  While on treatment, women should not become pregnant. Treatment discontinuation is recommended if a patient becomes pregnant.

- Liver function should be monitored at months 1, 3, 6, 9 and 12 during GILENYA therapy and periodically thereafter; the approved dosing of 0.5 mg daily (or 0.25 mg once daily in paediatric patients 10 years of age and above with a body weight of ≤40 kg) should be administered. Other dosing regimens have not been approved.

- In the post-marketing setting, severe exacerbation of disease has been observed rarely in some patients stopping fingolimod. The possibility of recurrence of exceptionally high disease activity should be considered.
- Cases of seizure, including status epilepticus, have been reported. Physicians should be vigilant for seizures and especially in those patients with underlying conditions or with a pre-existing history or family history of epilepsy.
- Physicians should provide patients with the patient reminder card.
- Physicians should reassess on an annual basis the benefit of GILENYA treatment versus risk in each patient, especially paediatric patients.

The safety profile in paediatric patients is similar to adults and therefore the warnings and precautions in adults also apply for paediatric patients.

Specifically with paediatric patients, physicians should also:

- Assess Tanner staging and measure height and weight as per standard of care;
- Perform cardiovascular monitoring;
- Take precautions when the first dose is administered / patients are switched from 0.25 to 0.5 mg daily, due to the potential for bradyarrhythmia;
- Monitor the patient for sign and symptoms of depression and anxiety;
- Emphasize treatment compliance and misuse to patients, especially about treatment interruption and the importance of repeating cardiovascular monitoring;
- Emphasize GILENYA immunosuppressive effects;
- Consider a complete vaccination schedule before starting GILENYA;
- Provide guidance on seizure monitoring.

Patient/ Parent / Caregiver Reminder Card

The reminder card shall contain the following key messages:

- Patients should have a baseline ECG and blood pressure measurement prior to receiving the first dose of GILENYA;
- Heart rate should be monitored for 6 or more hours after the first dose of GILENYA, including hourly pulse and blood pressure checks. Patients may be monitored with continuous ECG during the first 6 hours. An ECG at 6 hours should also be performed and, in some circumstances, monitoring may involve an overnight stay;
- Patients should call their doctor in case of treatment interruption as the first dose monitoring may need to be repeated, depending on duration of interruption and time since starting of GILENYA treatment;
- Patients should report immediately symptoms indicating low heart rate (such as dizziness, vertigo, nausea or palpitations) after the first dose of GILENYA;
- GILENYA is not recommended in patients with cardiac disease or those taking medicines concomitantly known to decrease heart rate, and they should tell any doctor they see that they are being treated with GILENYA.
- Signs and symptoms of infection, which should be immediately reported to the prescriber physician during and up to two months after GILENYA treatment.
- The need to undergo cancer screening, including Pap test, and vaccination for HPV-related cancer, as per standard of care, will be assessed by the prescriber physician;
- Any symptoms of visual impairment should be reported immediately to the prescriber during and for up to two months after the end of treatment with GILENYA.
- GILENYA is teratogenic. Women of child-bearing potential, including adolescent females, should be informed about GILENYA's serious risks to the fetus and must:
  - Have a negative pregnancy test before starting GILENYA;

- Be using effective contraception during and for at least two months following discontinuation of GILENYA treatment;
- Report immediately to the prescribing physician any (intended or unintended) pregnancy during and up to two months following discontinuation of GILENYA treatment;

- A liver function test should be performed prior to treatment initiation; liver function monitoring should be performed at months 1, 3, 6, 9 and 12 during GILENYA therapy, and periodically thereafter;
- Skin cancers have been reported in MS patients treated with GILENYA. Patients should inform their doctor immediately if any skin nodules (e.g., shiny, pearly nodules), patches or open sores that do not heal within weeks are noted. Symptoms of skin cancer may include abnormal growth or changes of skin tissue (e.g., unusual moles) with a change in color, shape or size over time;
- Seizure may occur. The doctor should be informed about a pre-existing history or family history of epilepsy;
- Stopping GILENYA therapy may result in return of disease activity. The prescribing physician should decide whether and how the patient should be monitored after stopping GILENYA.

Specifically for Paediatric patients:

The following should be considered:

- Physicians should assess Tanner staging and measure height and weight as per standard of care;
- Precautions should be taken during the first dose of GILENYA and when patients are switched from 0.25 to 0.5 mg daily;
- Depression and anxiety are known to occur with increased frequency in the MS population and have been reported also in paediatric patients treated with GILENYA;
- Cardiac monitoring guidance;
- Patients should ensure medication compliance and avoid misuse, especially treatment interruption, and repeat cardiac monitoring;
- Signs and symptoms of infection;
- Seizure monitoring guidance.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Conduct of a prospective cohort study assessing the incidence of cardiovascular adverse events in patients starting GILENYA treatment for relapsing remitting multiple sclerosis based on a CHMP approved protocol.	Final Study report by 15 December 2020

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

Not applicable.

Additional Data exclusivity / Marketing protection

Furthermore, the CHMP reviewed the data submitted by Novartis Europharm Limited, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers, that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0050/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIB

Extension of indication to add a new indication for the treatment of paediatric patients of 10 years of age and above with relapsing multiple sclerosis (RMS); as a consequence, sections 1, 2, 3, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3, 6 and 8 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Annex II is updated to reflect an amendment in the Physician check list including that re-assessing the benefit versus risk in each patient receiving Gilenya should be considered on an annual basis, particularly for paediatric patients. In addition, the product information is updated to be brought in line with the latest QRD template version 10.