24 September 2015
EMA/CHMP/549382/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Gilenya

International non-proprietary name: FINGOLIMOD

Procedure No. EMEA/H/C/002202/II/0034

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

AE adverse event

ARR annualized relapse rate

AV atrio-ventricular

CEE Central and East European

CHMP Committee for Medicinal Products for Human Use

CI confidence interval

CNS central nervous system

CTD Common Technical Document/Dossier

DMT disease-modifying treatment

ECG electrocardiogram

EDSS expanded disability status scale

EMA European Medicines Agency

EU European Union

FAS Full analysis set

FTY720 fingolimod

GA glatiramer acetate

Gd gadolinium

HR hazard ratio

IFN (-β) (-β1a) interferon-β (-beta) (-beta 1a)

im intramuscular

ITT intent-to-treat

MAA Marketing Authorization Application

MRI magnetic resonance imaging

MS multiple sclerosis

NB negative binomial

NHS National Health Service

NICE National Institute for Health and Clinical Excellence

PSUR Periodic safety update report

RRMS relapsing-remitting multiple sclerosis

S1P sphingosine 1-phosphate

SAE serious adverse event

sc subcutaneous

SCE Summary of clinical efficacy

SCS Summary of clinical safety

SmPC Summary of Product Characteristics

SOC System organ class

SPMS secondary progressive multiple sclerosis

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 9 April 2015 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product(s): **For presentations: See Annex A**	**International non-proprietary name:**
Gilenya	Fingolimod

The following variation was requested:

Variation 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

Extension of Indication to update the Gilenya indication in second line use to 'patients with active disease defined by clinical or imaging features despite treatment with at least one disease modifying therapy' As a consequence, section 4.1 of the SmPC is updated.

In addition, the applicant took the opportunity to relocate documents from section 5.3.5.1 to 5.3.5.2.

The variation proposed amendments to the Summary of Product Characteristics.

Information on paediatric requirements

At the time of submission of the application, the PIP P/117/2013 was not yet completed as some measures were deferred.

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 applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the DHMA (July 2014), MHRA (August 2014) and Rapporteurs

(January 2015). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Pierre Demolis Co-Rapporteur: Filip Josephson

Timetable	Actual dates
Rapporteur's preliminary assessment report circulated on:	23 June 2015
Co-Rapporteur's preliminary assessment report circulated on:	26 June 2015
Joint Rapporteur's updated assessment report circulated on:	17 July 2015
Request for supplementary information and extension of timetable adopted by the CHMP on:	23 July 2015
MAH's responses submitted to the CHMP on:	25 August 2015
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	14 September 2015
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	16 September 2015
CHMP opinion:	24 September 2015

2. Scientific discussion

2.1. Introduction

Fingolimod (FTY720, Gilenya) is an oral, once daily, synthetic sphingosine 1-phosphate (S1P) receptor modulator that is marketed in the European Union (EU) under the name Gilenya for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS). By acting as a functional antagonist of S1P receptors on lymphocytes, fingolimod-phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution of lymphocytes.

This redistribution reduces the infiltration of pathogenic lymphocytes into the CNS, where they would be involved in nerve inflammation and nervous tissue damage. Fingolimod readily crosses the blood-brain barrier (BBB) to bind to S1P receptors located on neural cells in the CNS which may reduce proinflammatory activity and inhibit astrogliosis. Due to the presence of S1P receptors in multiple tissues, fingolimod manifests a number of other biological effects in addition to the reduction in circulating lymphocytes. These include a transient reduction in heart rate and atrioventricular conduction upon treatment initiation, a dose-dependent mild increase in airway resistance, macular edema, a mild increase in blood pressure, and asymptomatic elevations in serum levels of hepatic transaminases.

GILENYA (fingolimod) 0.5 mg has been approved on March 2011 and its current indication is the following:

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

Patients with high disease activity despite treatment with at least one disease modifying therapy (for exceptions and information about washout periods see sections 4.4 and 5.1)

These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of at least one disease modifying therapy. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

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".

Fingolimod at 0.5 mg daily demonstrated efficacy in reducing the frequency of relapses by greater than 50% as compared to both placebo (2-year Study FTY720D2301) and IFN-β1a (1–year Study FTY720D2302) in patients with RRMS as well as in reducing the risk of disability progression relative to placebo over 2 years. The clinical benefits of fingolimod were further supported by the robust efficacy seen on MRI measures, including a significant reduction in the number of new T2 lesions and gadolinium (Gd)- enhancing lesions, decreased total T2 and T1 lesion burden, and reduction in brain volume loss (BVL).

Based on the principles used in the revision to the McDonald criteria led to updated diagnostic criteria that accounted for subclinical disease activity as evidenced by MRI lesions, the MAH submit a type II variation to update section 4.1 of SmPC "Therapeutic indications". This submission seeks to modify the criteria for disease activity that need to be fulfilled in order to enable a switch from a first line disease modifying therapy (DMT) to Gilenya.

The wording for section 4.1 which was applied for was the following:

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

- *- Patients with ~~high~~ active disease ~~activity~~ defined by clinical or imaging features 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).*

- ~~These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of at least one disease modifying therapy. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2- hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion. A "nonresponder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year~~.

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."

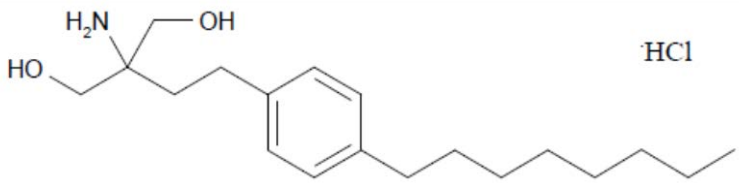
According to the proposal, the disease activity is to be defined by either **clinical or imaging** features, instead of the current label wording which refers to highly active disease criteria defined by imaging and clinical features. With the currently proposed modification in the indication Gilenya would remain as second line therapy except in patients with rapidly evolving severe RRMS (which remains unchanged).

2.2. Non-clinical aspects

2.2.1. Ecotoxicity / environmental risk assessment

In support of this extension of indication an updated environmental risk assessment was provided.

2.2.1.1. Physicochemical properties of the drug

Chemical structure	
Chemical name	Amino-2-(2-(4-octylphenyl)ethyl)propan-1,3-diol hydrochloride
Molecular formula	$C_{19}H_{33}NO_2$ HCl
Relative molecular mass	343.94 g/mol
Melting point	~260 °C
pK_a	8.0
Water solubility	> 200 g/L (at 25°C)
n-Octanol water partition coefficient	log P = 5.5 and log D = 4.5 at pH 7.4 (diffusion through octanol liquid membrane) (RD-2010-00593)

2.2.1.2. Phase I: Estimation of exposure

2.2.1.2.1. Assessment of persistence, bioaccumation and toxicity

Based on the fact that fingolimod is a surface active substance, diffusion of fingolimod through an octanol liquid membrane is considered as the most reliable parameter to assess the partition coefficients for this API. This experiment revealed **a log P value of 5.5 and extrapolated log D at pH 7.4 of 4.5**., therefore exceeding the trigger value for screening for bioaccumulation potential.
A screening for bioaccumulation potential has subsequently been conducted according to the criteria laid down in the current guidance on PBT assessment used for the implementation of REACH (ECHA, 2008) leading to the conclusion that fingolimod cannot be considered as PBT or vPvB substance for the following reasons:

- The criteria for persistence is not fulfilled as a study on transformation in aquatic sediment systems following OECD 308 showed half-lives of 0.23 - 0.25 days for the water phase and 0.35 – 0.39 days for the total systems (Harlan Laboratories Study B53998). These results suggest rapid degradation of fingolimod in surface waters and consequently no risk for the aquatic environment and no significant bioaccumulation potential.
- As the relevant pathway investigated by the current environmental risk assessment according to EMEA/CHMP/SWP/4447/00 is via patient use, it has to be taken into account that fingolimod will pass the human body and be significantly metabolised before excretion by patients and subsequently entry into the environment. In this regard, about 81% of a dose of fingolimod has been found to be excreted in the urine as pharmacologically inactive metabolites. Only 2.5% of the dose is excreted by patients as parent substance in faeces.
- Considering results from aquatic toxicity testing, the criteria for toxicity is not fulfilled as No Observed Effect Concentrations (NOECs) from chronic toxicity testing in fish, Daphnia and algae do not meet the trigger value of 0.01 mg/L with NOECs of 0.090 mg/L, 0.089 mg/L, 0.020 mg/L for zebra fish, Daphnia and algae growth rate reduction, respectively (RCC Study B54022), (RCC Study B54000), (NOTOX Study 305101).

CHMP conclusion

Fingolimod log D was 4.5. Fingolimod did not meet the criteria for persistence and toxicity

2.2.1.2.2. Calculation if the Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) is given by the formula proposed in guideline EMEA/CHMP/SWP/4447/00:
PECsurface water = (DOSEai * Fpen) / (WASTEWinhab * DILUTION)
= (0.5 mg * 0.01) / (200 L/inhabitant/day * 10)
= **0.0025 µg/L**
Where:

$DOSE_{ai}$ = 0.5 mg/inhabitant/day

Fpen = 1% (default)

$WASTEW_{inhab}$ = 200 L/inhabitant/day
DILUTION = 10

CHMP comment

PECsurfacewater is below the trigger value of 0.01 µg/L. Therefore, fingolimod is unlikely to represent a risk for the environment following its prescribed usage in patients. Nevertheless the applicant had submitted PhII ERA which was assessed.

2.2.1.3. Phase II: Environmental fate and effects analysis

2.2.1.3.1. Tier A

2.2.1.3.2. Physical-chemical, fate and effects studies

Table 1: Physical-chemical, fate and effects studies

Adsorption/Desorption using a batch equilibrium method (OECD 106)	K_{oc} (sludge) = 366-637 L/kg K_{oc} (soil) = 1025-7624 L/kg (Harlan Laboratories Study B53976)
Ready Biodegradability Test (OECD 301B)	No significant degradation. Not readily biodegradable. (NOTOX Project 305134)
Transformation in Aquatic Sediment Systems (OECD 308)	DT_{50} (total system) = 0.35-0.39 days DT_{90} (total system) = 1.17-1.30 days (Harlan Laboratories Study B53998)
Algae Growth Inhibition Test (OECD 201)	72h-NOEC = 0.0203 mg/L (NOTOX Project 305101)
Daphnia Reproduction test (OECD 211)	21d-NOEC = 0.089 mg/L (RCC Study B54000)
Fish Early Life Stage Toxicity Test (OECD 210)	34d-NOEC = 0.090 mg/L (RCC Study B54022)
Activated Sludge Respiration Inhibition Test (OECD 209)	3h-EC_{20} = 26.0 mg/L (NOTOX Project 305123)

2.2.1.3.3. Calculation of PNEC using assessment factors

The **PNECsurface water** derived from the NOEC for algae as the most sensitive species is 0.0203 mg/L /10 = **2.03 µg/L**.

For microorganisms, an assessment factor of 10 is generally used, hence the **PNECmicroorg**. derived from the activated sludge respiration inhibition study is 26.0 mg/L / 10 = **2.6 mg/L**.

The **PNECgroundwater** is based on the NOEC of the test with Daphnia sp. and applying an assessment factor of 10 thus calculates as 0.089 mg/L / 10 = **8.9 µg/L**.

2.2.1.3.4. PECs

$PEC_{surfacewater}$ is 0.0025 µg/L (see 1.2).

Based on the default dilution factor of 10 used between surface water and sewage treatment plants, the $PEC_{microorg}$ is ten times higher than the $PEC_{surface\ water}$.
$PEC_{microorg}$ = 0.025 µg/L

According to the guideline, the $PEC_{groundwater}$ can be assumed to be typically 0.25 times the $PEC_{surface\ water}$. This leads to a **$PEC_{groundwater}$ of 0.000625 µg/L** for fingolimod.

2.2.1.4. Outcome of Tier A fate and effects analysis

Surface water assessment
Refined $PEC_{surface\ water}$ = 0.0025 µg/L
$PNEC_{surface\ water}$ = 2.03 µg/L
$PEC/PNEC_{surface\ water}$ = 0.0025 µg/L / 2.03 µg/L**= 0.00123**

Microorganisms / sewage treatment plant assessment
$PEC_{microorg.}$ = 0.025 µg/L
$PNEC_{microorg}$ = 2.6 mg/L = 2600 µg/L
$PEC/PNEC_{microorg.}$ = 0.025 µg/L / 2600 µg/L **= 0.0000096**

Groundwater assessment
$PEC_{groundwater}$ = 0.000625 µg/L
$PNEC_{groundwater}$ = 8.9 µg/L
$PEC/PNEC_{groundwater}$ = 0.000625 µg/L / 8.9 µg/L **= 0.00007**

All the PEC/PNEC are below the trigger values. No further action is required.

Table 2: Hazard/risk assessment fingolimod hydrochloride

Hazard/risk criterion	Data requirement
Screening for persistence, bioaccumulation and toxicity (PBT)	No PBT or vPvB as not persistent and not fulfilling the toxicity criteria based on chronic data set.
Adsorption – Desorption: K_{oc} < 10'000	Negligible sorption to sludge and soil expected.
Partitioning to sediment compartments	No significant amounts of bioavailable parent in sediment at and after day 14. No risk assessment for sediment dwelling organisms required.
PECsurface water / PNECsurface water < 1	0.0025 µg/L / 2.03 µg/L= 0.00123
PECmicroorg / PNECmicroorg < 0.1	0.025 µg/L / 2600 µg/L = 0.0000096
PECgroundwater / PNECgroundwater < 1	0.000625 µg/L / 8.9 µg/L = 0.00007

2.2.1.5. Conclusion on ERA

Based on the high lipophilicity of fingolimod a screening for PBT potential has been conducted for this active pharmaceutical ingredient. Fingolimod is not readily biodegradable, but shows very short half-lives

in water-sediment systems and does therefore not fulfill the criteria for persistence. Moreover, the pathway considered for APIs in the current ERA, i.e. through use in patients, is expected to result in very low amounts of fingolimod entering the environment based on extensive metabolism during patient's passage. In spite of significant toxicity found in aquatic organisms, the criteria for toxicity is not met based on the chronic toxicity studies. In general, fingolimod cannot be considered a PBT or vPvB substance.

The low persistence of fingolimod in water-sediment systems and consequently low partitioning of fingolimod to sediments suggests no risk for sediment compartments. Moreover, the potential to adsorb to sludge has been found to be low resulting in no concern for terrestrial compartments.

In the current ERA, the highest risk ratio has been observed for surface waters with 0.00123, thus remaining significantly below any concern for the environment, including surface waters, groundwater, sewage treatment plants, sediments and terrestrial compartments.

In spite of the fact that no concern for the environment is anticipated from the use of fingolimod by patients, intake of active pharmaceutical ingredients into surface waters should be avoided as far as possible. Therefore, as with all non-readily biodegradable human medicines, patients should be advised not to dispose of unused drug product via sinks or toilets. The package leaflet accompanying FTY720 drug product should thus include the following statement: "*Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.*"

Based on the assessment, no concern has been raised regarding fingolimod impact on the aquatic environment, the microorganisms, the sediment or the terrestrial compartment. Fingolimod did not meet the criteria for persistence and toxicity. No further studies are necessary.

2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of fingolimod.

- Considering the above data, fingolimod is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

Updated diagnostic criteria for MS acknowledge the role of MRI as an important and sensitive measure of disease activity relevant to MS diagnosis: at the core of the 2010 revision to the McDonald criteria (after fingolimod approval) is the importance of considering subclinical disease activity as evidenced by MRI lesions (Polman et al 2011). Capturing dissemination of subclinical activity through MRI in time (rather than clinical dissemination in time alone) allows a more rapid diagnosis and earlier treatment of MS as per the revised diagnostic criteria. Appearance of new MRI activity, even if clinically silent, is considered sufficient to diagnose the patient with having the disease that can negatively impact long-term patient outcomes if not treated in a timely manner.

Acute MS disease activity is a consequence of focal disruption of the BBB with ensuing infiltration of auto-reactive immune cells into a region of the CNS parenchyma that ultimately results in edema, demyelination, and axonal injury. Such an event, if occurring in a clinically eloquent region, will result in

a clinical relapse, an acute deterioration of the patient's physical or cognitive functioning. It is a purely random occurrence if this focal pathology will induce a clinical relapse or remain silent. In the latter case, such MS activity would be evidenced by MRI.

While it has been shown that MS relapses are associated with the appearance of "active" Gd T1 lesions on MRI scans (Noseworthy et al 2000), the frequency of active MRI lesions outnumber relapses (Thorpe et al 1996). New Gd-enhancing lesions, even when completely asymptomatic, are associated with significant demyelination and axonal loss and up to 55% of them may become chronic T1 hypointense lesions (ie, "black holes") indicative of permanent tissue loss (Bagnato et al 2003). This accumulation of permanent tissue loss, as seen on MRI, ultimately has proven prognostic value for disability progression (Rieckmann 2005, Goodin and Bates 2009, Gold et al 2010).

The MAH position was that for patients who already receive a DMT, evidence of MRI activity could be an indicator of poor response with consecutive risk of treatment failure leading to relapses or permanent clinical progression. Thus, the occurrence of MRI activity in this setting would justify a treatment switch to prevent future disability. Rio et al (2008) showed that active and new MRI lesions can predict future MS disease course. Patients receiving IFN-β1a and with high numbers of new MRI lesions have significantly more disease progression i.e. were treatment non-responders (Rudick et al 2004). In patients treated with IFN-β, development of new T2-hyperintense lesions and Gd lesions predicted long-term response to therapy (Prosperini et al 2009, Bermel et al 2013). The ability of MRI changes (new T2 lesions and the presence of Gd enhancement) to predict long-term clinical outcomes was confirmed by Dobson et al (2014). Further evidence of the prognostic value of MRI in identifying poor responders can be obtained from meta-analyses of randomized, placebo-controlled studies (Sormani et al 2009) and a more recent meta-analysis that included fingolimod studies (Sormani and Bruzzi 2013).

Based on the above, the MAH claimed that the totality of data available in the published literature at this point supported the conclusion that the effectiveness of DMTs could be assessed by MRI active lesions and that MRI activity correlated with long-term clinical outcomes**.**

This was the reasoning to propose revision of the second-line part of the fingolimod indication to: *"patients with active disease defined by clinical or imaging features despite treatment with at least 1 DMT."* Based on this proposal fingolimod would still remain a second-line therapy, with the exception of patients with rapidly evolving severe RRMS as per current SmPC.

The post-hoc efficacy analyses provided by the MAH aimed to show that the overall treatment effect in the current SmPC population and, in conjunction with a comparable safety profile for these populations, the benefit-risk ratio remained favorable. To confirm that efficacy remained consistent under the conditions of the proposed updated indication, efficacy was compared in the full analysis set (FAS)-current SmPC and FAS-proposed SmPC subpopulations using data from pooled and individual controlled studies.

To further support the proposed change in the SmPC, additional study groupings were identified and subgroups defined to examine the treatment effect in the presence or absence of a priori defined clinical and/or imaging features.

Clinical activity was defined as 1 relapse in the previous 6 months, as this cut-off has been described as an appropriate time to evaluate the efficacy of a DMT and potentially trigger a decision for treatment switch (Teter et al 2014). Patients receiving DMT treatment for 6 months and experiencing relapses may be considered as having a suboptimal response to treatment. MRI activity was defined as Gd+ lesions at baseline MRI scan, as such lesions often result demyelination (later evidenced as T2 lesions).

These comparisons (in the supportive analysis based on subgroups defined by imaging and/or clinical features) were conducted in:

- Patients with prior DMT exposure in the pooled placebo-controlled, 2-year Studies D2301 + D2309
- Patients with prior DMT exposure in active-controlled, 1-year Study D2302
- Patients who received IFN-β1a during the core study of Study D2302 and switched to receiving fingolimod 0.5 mg during extension Study D2302E1 (using data from the 12-month dose-blind phase of the extension study)

Within these groups of patients, the following subgroups were evaluated:

- Patients with imaging AND clinical features
- Patients with imaging OR clinical features (but not both)
- Patients who comprised the proposed SmPC (i.e. “patients with imaging features only” and “patients with clinical features only”).

The first 2 of these subgroups were chosen to represent the patient populations covered by the current label as compared to the proposed label; the patients with imaging AND clinical features represent patients in the current SmPC and patients with imaging OR clinical features represent additional patients in the proposed SmPC but not in current SmPC. For completeness, treatment effects were also evaluated for the second 2 subgroups for patients who comprised the proposed SmPC (ie, “patients with imaging features only” and “patients with clinical features only”) and all analyses were presented for the endpoint of ARR.As RRMS patients experience relapses that lead to accumulation of disability over time a reduction in relapses is therefore an acceptable endpoint, also relevant for long-term outcomes.

The ARR (relapse rate) endpoint was assessed in all clinical studies conducted, and was the primary endpoint in the Phase 3 studies with fingolimod. Since ARR is widely used for the demonstration of efficacy in patients with RRMS, in the context of this submission, ARR provides a meaningful clinical endpoint to be analyzed in the selected subgroups. Disability progression (Expanded Disability Status Scale (EDSS)) was not analyzed in the subgroups; the low number of patients with disability progression during the relatively short duration of the studies would not provide reliable estimates.

GCP

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

2.3.2. Main study(ies)

2.3.2.1. Overview of efficacy studies relevant to the current procedure

The post-hoc efficacy analyses for this submission are based on data from all randomized, placebo- and active-controlled, double-blind studies which included the approved 0.5 mg dose: Studies D2301, D2309, D2302, and D1201 and Study D2302E1.

Study D2301 and Study D2302 formed the basis of the original MAA submission (2009).

Study D2309 and Study D2302E1 were ongoing at the time of the initial submission for fingolimod; these studies have since been completed. Full results from completed [Study D2309] were provided in the submission for the Follow-up Measure (FUM)-009 and full results from [Study D2302E1] were provided in FUM-008.

Study D2301 was a 24-month double-blind, randomized, multicenter, placebo-controlled, parallel group study comparing the efficacy and safety of fingolimod 1.25 mg and 0.5 mg administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis. The efficacy evaluations included relapses, EDSS, MSFC and MRI.

Study D2302 was a 12-month double-blind, randomized, multicenter, active-controlled, parallel group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720) administered orally once daily versus interferon β-1a (Avonex®) administered i.m. once weekly in patients with relapsing-remitting multiple sclerosis.

Study D2309 was 24-month double-blind, randomized, multicenter, placebo-controlled, parallel group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis.

Study D2302E1 was an extension of the 12-month double-blind, randomized, multicenter, active-controlled, parallel group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720) administered orally once daily versus interferon β-1a (Avonex®) administered i.m. once weekly in patients with relapsing-remitting multiple sclerosis.

Study D1201 was a 6-month, randomized, multicenter, double-blind, placebo-controlled, parallel-group trial that enrolled 171 patients with relapsing MS at 43 centers in Japan. Patients were randomized to receive oral fingolimod 1.25 mg/day, fingolimod 0.5 mg/day, or placebo. The primary objective was to evaluate the effect of 2 doses (0.5 mg and 1.25 mg) of fingolimod compared to placebo on the percentage of patients free of Gd-enhancing T1 weighted MRI lesions at both 3 months and 6 months of treatment. This study enrolled a patient population with substantially higher disease activity than that in the other studies; this study has not been submitted previously and the study report was included with this submission.

The doses of 0.5 mg, 1.25 mg, and 5 mg/day have been evaluated in the Phase 2 and 3 clinical studies in MS. In this submission, the emphasis is placed on the approved dose of fingolimod 0.5 mg as compared to placebo or IFN-β1a.

2.3.2.2. Summary of controlled efficacy studies

The randomized, controlled, double-blind studies of at least 6 months duration were conducted on a total of 3818 patients (Randomized population).

For the D2302/D2302E1 post-hoc analyses, data from the 12-month core study (Study D2302) and the 12-month dose-blind phase of the extension study (Study D2302E1) were used.

Prospectively collected data from the core phase of Study D2302 for patients receiving IFN- β1a were compared with data from the extension of Study D2302E1. Patients who received IFN-β1a during the core phase of Study D2302 were re-randomized to fingolimod (1.25 mg or 0.5 mg) for extension Study D2302E1.

Study groupings used for efficacy analyses

For the evaluation based on the current and proposed SmPC (see Table 1-3), the following data were used from the Phase 2 and 3 placebo- and active-controlled studies as listed below:

- Pooled data from Studies D1201, D2301, and D2309 (all placebo-controlled, double-blind with at least 6 months duration)

- Pooled data from Studies D2301 and D2309 (placebo-controlled, double-blind with 2 years of treatment duration and comparable design)
- Study D2301
- Study D2309
- Study D1201
- Study D2302 (active-controlled, double-blind with 1 year of treatment duration)

The above studies comprise data from all randomized, placebo- and active-controlled, double-blind studies of at least 6 months duration which included the approved 0.5 mg dose of fingolimod (Studies D1201, D2301, D2302, and D2309).

Study groupings for imaging and/or clinical features subgroups

For the evaluation based on imaging and/or clinical features, the following 3 study groupings were defined:

- Pooled data from Studies D2301 and D2309 (placebo-controlled, double-blind with 2 years of treatment duration and comparable design)
- Study D2302 (active-controlled, double-blind with 1 year of treatment duration)
- Study D2302/D2302E1

Study D1201, 6 months duration, was not included in the pooled study grouping due to the small number of patients in the study, resulting in low (single digit) patients in the according subgroups.

For the third study grouping (Study D2302/D2302E1), a within-subgroup comparison was conducted for patients who were re-randomized from IFN-β1a during Study D2302 to fingolimod 0.5 mg during the extension of Study D2302E1. These post-hoc analyses are considered supportive given the prospective collection of data during the core study phase.

The data provide a detailed understanding of MRI activity and DMT exposure prior to switching to fingolimod 0.5 mg. It is noted that patients who are included in the analyses from Study D2302/D2302E1 for this submission received IFN-β1a for the full 12 months during the core phase prior to switching to fingolimod.

Subpopulation and subgroup definitions

Definition of current and proposed SmPC subpopulations

The objective of this submission was to revise the Gilenya indication to: *"patients with active disease defined by clinical or imaging features despite treatment with at least 1 DMT."*

To support the proposed label change, 2 subpopulations were defined and analyzed based on the MS history data collected during the studies at Baseline: the FAS-current SmPC and the FAS-proposed SmPC.

Table 1-3 Subpopulation definitions for evaluation based on the current and proposed SmPC

Subpopulations	Study groupings evaluated	Definition
Evaluation based the current and proposed SmPC		
FAS	D1201 + D2301 + D2309 D2301 + D2309 D1201 D2301 D2309 D2302	All patients who were randomized and took at least 1 dose of study medication (corresponding to patients treated according to the intent-to-treat principle).

FAS-current SmPC	D1201 + D2301 + D2309
	D2301 + D2309
	D1201
	D2301
	D2309
	D2302
		All patients in the FAS who fulfilled at least 1 of the following 2 criteria in the current SmPC:
		• Patients who received at least 1 DMT during the year before treatment initiation but,
		  • Had as many or more relapses in the year immediately before the study than in the preceding year, or
		  • Had at least 1 relapse in the previous year plus at least either 1 Gd-enhancing T1 lesion or 9 T2 lesions at Baseline
		• Patients with rapidly evolving severe RRMS: ≥2 relapses within the year before Baseline and ≥1 Gd-enhancing T1 lesion at Baseline

FAS-proposed SmPC	D1201 + D2301 + D2309 D2301 + D2309 D1201 D2301 D2309 D2302	All patients in the FAS who fulfilled at least 1 of the following active MS criteria defined by clinical or imaging features: • Patients who received at least 1 DMT during the year before treatment initiation and had either at least 1 Gd-enhancing T1 lesion at Baseline and/or at least 1 relapse during the year prior to Screening. • Patients with rapidly evolving severe RRMS: ≥2 relapses within the year before Baseline and ≥1 Gd enhancing T1 lesion at Baseline.

The overall FAS population represents patients who were randomized and took at least 1 dose of study medication. This includes patients who were previously treated with DMTs and patients who were treatment naïve. The FAS-current SmPC and FAS-proposed SmPC, however, include only patients who were previously treated in the year prior to treatment initiation (with the exception of rapidly progressing patients), leading to a notable difference in the number of patients in the FAS compared to the FAS-current SmPC and FAS-proposed SmPC subpopulations (see Table 1-4).

For the FAS-current SmPC and FAS-proposed SmPC it is noted that the definition for patients with rapidly evolving severe RRMS remains the same for both subpopulations.

Prior DMTs are defined as any prior MS medication as reported by the investigator on the case report form at baseline. This definition includes the 5 treatments that were approved at the time of the conduct of the Phase 3 trials (IFN-β1a im, IFN-β1a sc, IFN-β1b sc, glatiramer acetate, and natalizumab) and also "other MS medications", e.g. investigational treatments.

MRI activity in the FAS-proposed SmPC subpopulation is defined as the presence of Gd enhancement at the baseline MRI scan. New or newly enlarging T2 lesions could not inherently be included in the subpopulation definition since determination of this variable would require comparison to a previous scan, which was not planned in the clinical studies.

It is noted that patients included in FAS-current SmPC account for more than 95% of patients included in FAS-proposed SmPC in the pooled studies of interest. The inclusion criteria of the studies required patients to have clinical disease activity during the year prior to randomization, with the majority of the patients having relapses in the year prior to randomization. Therefore, there is a notable overlap between

the patients included in each subpopulation due to the inclusion criteria, leading to a small difference between the FAS-proposed SmPC and FAS-current SmPC for pooled Studies D1201 + D2301 + D2309 and Study D2302 (Table 1-4). For that reason, the difference between the FAS-current SmPC and the FAS-proposed SmPC was not evaluated. The number of patients included in the overall FAS, FAS-current, and FAS-proposed are presented in Table 1-4.

Table 1-4 Number of patients in each study grouping, by subpopulation

	Pooled Studies D1201 + D2301 + D2309	Pooled Studies D2301 + D2309	Study D2302
Randomized population	1670	1556	866
Evaluation based on the current and proposed SmPC			
FAS	1670	1556	860
FAS-current	710	660	482
FAS-proposed	725	675	492

FAS = full analysis set; SmPC = Summary of Product Characteristics.

Note: the number of patients in this table includes fingolimod 0.5 mg and placebo for pooled Studies D1201 + D2301 +D2309 and pooled Studies D2301 + D2309, and includes fingolimod 0.5 mg and IFN-β1a for Study D2302.

Definition of imaging and/or clinical features subgroups

To further support the proposed label change which would allow second-line treatment in RRMS patients with disease activity defined by either imaging and/or clinical features, further subgroups were defined for the evaluation based on imaging and/or clinical features (Table1.5).

MRI activity in the imaging subgroups is defined as the presence of Gd enhancement at the baseline MRI scan. New or newly enlarging T2 lesions could not inherently be included in the imaging subgroup definition since determination of this variable would require comparison to a previous scan which was not planned in the clinical studies.

For the subgroups defined for pooled Studies D2301 + D2309 and Study D2302 the time period used to define clinical features (i.e. relapse) was 6 months prior to randomization. The 6 month time frame has been described as an appropriate time to evaluate the efficacy of a DMT and potentially trigger a decision for treatment switch (Teter et al 2014).

For the evaluation based on imaging and/or clinical features including pooled data from Studies D2301 + D2309 and Study D2302, patients were considered who were previously treated with DMTs 1 year prior to randomization and that had MRI at Baseline, and relapse 6 months prior to randomization. In these 3 Phase 3 studies where ARR was the primary endpoint, an “active” patient population was studied. For inclusion, the patients should have had 1 relapse in the past year (vast majority of patients, 97%) or 2 relapses in the past 2 years.

In this submission for the subgroup analysis, ‘clinical features’ was defined as 1 relapse or more in the past 6 months, as this would extract the most clinically “active” patients from the Phase 3 patient population.

Treatment effect for fingolimod vs control based on ARR was evaluated for each subgroup as reduction in relapse rate is considered relevant for long-term clinical outcomes. In addition, demonstration of the efficacy of fingolimod on ARR in the Phase 3 studies is consistent with other relapse-related variables (proportion of relapse-free patients; time to first relapse) and MRI endpoints that mark inflammatory disease activity (number of Gd lesions, new/ newly enlarging T2 lesions, brain volume).

MRI endpoints were not analyzed, as the focus of this submission is to demonstrate benefit on clinical endpoints in patients receiving DMT with MRI activity. Disability progression is not analyzed in the subgroups; the low number of patients with disability progression in relatively small subgroups of patients would not provide reliable estimates. In summary, ARR is included as a relevant and representative parameter for demonstration of the efficacy of fingolimod in the subpopulations and for the purpose of this submission.

The numbers of patients included in each of the study groupings by analysis population and by subgroup are presented in Table 1-6.

Table 1-5 Subpopulation and subgroup definitions for evaluation based on imaging and/or clinical features

Subpopulations Subgroups	Study groupings evaluated	Definition
Evaluation based on imaging and/or clinical features		
FAS		All patients who were randomized and took at least 1 dose of study medication (corresponding to patients treated according to the intent-to-treat principle).
Imaging AND clinical features	D2301 + D2309 D2302	Previously treated with DMT, had Gd-enhancing T1 lesion at Baseline **AND** had ≥1 relapse during the 6 months prior to randomization
Imaging OR clinical features	D2301 + D2309 D2302	Previously treated with DMT, had Gd-enhancing T1 lesion at Baseline **OR** had ≥1 relapse during the 6 months prior to randomization (**not both**)
Imaging AND NO clinical features	D2301 + D2309 D2302	Previously treated with DMT, had Gd-enhancing T1 lesion at Baseline **AND NO** relapse during the 6 months prior to randomization
NO imaging AND WITH clinical features	D2301 + D2309 D2302	Previously treated with DMT, had **NO** Gd-enhancing T1 lesion at Baseline **AND WITH** ≥1 relapse during the 6 months prior to randomization
IFN-β1a switch to fingolimod 0.5 mg		Patients in Study D2302E1 who switched from IFN-β1a im during the Core phase to fingolimod 0.5 mg in the extension phase and took at least 1 dose of study medication in the extension phase.
Imaging AND clinical features	D2302/D2302E1	Had an MRI lesion (Gd-enhancing T1 lesion or new/newly enlarging T2 lesion) at Month 12 in Core phase **AND** had ≥1 relapse during Core phase
Imaging OR clinical features	D2302/D2302E1	Had an MRI lesion (Gd-enhancing T1 lesion or new/newly enlarging T2 lesion) at Month 12 in Core phase **OR** had ≥1 relapse during Core phase (**not both**)
Imaging AND NO clinical features	D2302/D2302E1	Had an MRI lesion (Gd-enhancing T1 lesion or new/newly enlarging T2 lesion) at Month 12 in Core phase **AND NO** relapse during Core phase
NO imaging AND WITH clinical features	D2302/D2302E1	Had **NO** MRI lesion (Gd-enhancing T1 lesion or new/newly enlarging T2 lesion) at Month 12 in Core phase **AND WITH** ≥1 relapse during Core phase

DMT = disease-modifying therapy; FAS = full analysis set; Gd = gadolinium; IFN-β1a = interferon-β1a; MRI = magnetic resonance imaging.

Table 1-6 Numbers of patients in each study grouping, by subgroup

	Pooled Studies D2301 + D2309	Study D2302	Study D2302/D2302E1
Randomized population	1556	866	167 [1]
Evaluation based on imaging and/or clinical features [2]			
Imaging AND clinical features	107	84	28
Imaging OR clinical features	242	202	72
Imaging AND NO clinical features	86	59	53
NO imaging AND WITH clinical features	156	143	19

FAS = full analysis set; SmPC = Summary of Product Characteristics.

Note: the number of patients in this table includes fingolimod 0.5 mg and placebo for pooled Studies D2301 + D2309 and fingolimod 0.5 mg and IFN-β1a for Study D2302.

[1] This number represents the number of patients who received IFN-β1a during core Study D2302 and switched to fingolimod 0.5 mg during Study D2302E1.

[2] Definition for the subgroups for pooled Studies D2301 + D2309 and Study D2302 are provided in Table 1-5. The definition for the subgroups for Study D2302/D2302E1 are different and also provided in Table 1-6.

2.3.2.3. Results

Summary of results of individual studies not assessed in other procedures

All studies (Studies D2301, D2302, D2309 and SD1201) demonstrate a comparable, clinically meaningful effect on ARR (48% to 54% reduction for fingolimod 0.5 mg vs comparator placebo or IFN-β1a).

The main efficacy results on ARR for Gilenya have been demonstrated in studies D2301 and D2302 which had been submitted for initial marketing authorization application. A third study (D2309) was completed after registration and has shown comparable results. Study D2302E1 was a 12 month, optional extension phase of Study D2302 consisting of a double-blind/dose-blind period followed by an open-label period and was assessed in the context of a post –approval measure.

Study D1201 was a 6 month, double-blind, placebo -controlled randomized study in patients 18 to 60 years, with RRMS and an EDSS score of 0 to 6.0 who had had at least one relapse in the previous year or at least two relapses in the previous two years. Less than half of all patients were treatment naïve (approximatively 42-49% across the groups). Among those who had been previously treated, interferon beta had been used (95%). In this trial 2 doses of fingolimod were tested (0.5 mg and 1.25 mg, once a day). Only results with the 0.5 mh dose are of interest. The Primary efficacy endpoint was the proportion of patients free of Gd enhanced T1 weighted MRI lesions at both month 3 and month 6.

The population has included 69% of women. The mean age was 35.3. The mean duration of the disease was 7.9 years and the mean of relapses in the last year was 1.5 and in the last two years 2.4. The mean EDSS score was 2.10. The number of randomized patients in each group was 57.

The results on primary efficacy parameter (ITT population) showed statistically significantly higher percentage of patients free of Gd-enhanced T1 lesions at both Month 3 and Month 6 with 0.5 mg (70%) versus placebo (40.4) ; odds ratio (95%CI) for 0.5 mg 3.628 (1.504, 8.753), p:0.004.

Regarding the results on the secondary MS relapse-related endpoint, fingolimod 0.5 mg decreased the aggregate ARR estimates at Month 6 (0.50 for fingolimod 0.5 mg) with statistically significant reductions compared to placebo (49% (p=0.047)) compared to placebo.

Overall incidence of AEs by proportion of patients was higher in the 2 fingolimod treatment groups than in the placebo group. The most frequently reported AEs in the fingolimod treatment group were nasopharyngitis and liver function test abnormal.

Combined efficacy data analysis

Statistical analyses

Evaluation based on the current and proposed SmPC

The efficacy endpoint analyzed for this SCE is ARR based on confirmed relapses only. This endpoint was analyzed by study and in a meta-analysis for the pooled studies (ie, Studies D1201 + D2301 + D2309 and Studies D2301 + D2309) and was assessed for the overall FAS, FAS-current SmPC, FAS-proposed SmPC. The ARR of a treatment group was calculated as the sum of the number of confirmed relapses of all patients in the group divided by the sum of the number of days on study of all patients in the group and multiplied by 365.25. As previously noted, other clinical endpoints such as disability progression are not analyzed in this submission; the low number of patients with disability progression in relatively small subgroups of patients would not provide reliable estimates.

The treatment effect based on ARR was evaluated by between-group comparisons in ARR for fingolimod 1.25 mg vs placebo and fingolimod 0.5 mg vs placebo for pooled Studies D1201 D2301 + D2309, pooled Studies D2301 + D2309, and individual Study D1201, Study D2301, and Study D2309 (see Table 2-1). The treatment effect for fingolimod 1.25 mg vs IFN-β1 and fingolimod 0.5 mg vs IFN-β1a was evaluated by between-group comparisons in ARR based on Study D2302. Comparisons of fingolimod 0.5 mg are the main presentations and included in-text below; comparisons of fingolimod 1.25 mg are considered supportive and are included in post-text summaries.

Results from an alternate random effects model based on pooled studies D1201 + D2301 D2309 were also provided for evaluation of treatment effect assuming uncommon effect size between studies.

To determine if the treatment effect differed between different placebo-controlled studies, an exploratory p-value was obtained from the global type 3 test of the study-by-treatment interaction from the statistical model on the 3 subgroups (FAS, FAS-current SmPC, and FAS-proposed SmPC) for the pooled Studies D1201 + D2301 + D2309 and pool Studies D2301 + D2309.

No multiplicity adjustment was applied to these efficacy analyses. These post-hoc analyses as such have limitations; data for the evaluation of efficacy for subgroups are reviewed in their totality. Of note, only the efficacy of the fingolimod 0.5 mg (approved dose) is of interest for this submission and the fingolimod 1.25 mg comparisons to placebo or IFN-β1a are used as supportive evidence.

A summary of the analyses conducted for ARR is presented in Table 2-1.

Table 2-1 Analyses of ARR for evaluation based on the current and proposed SmPC

Endpoint	Study groupings	Fixed effect model	Random effects model
ARR	• Pooled Studies D1201 +D2301 + D2309 • Pooled Studies D2301 + D2309 • Study D1201 • Study D2301 • Study D2309 • Study D2302	• Negative binomial model (treatment as factor; number of relapses in previous 2 years, baseline EDSS score as covariates). Estimate the treatment effect with corresponding 95% CI and p-values. This model was conducted for individual and pooled studies. • Negative binomial model (treatment, number of relapses in previous 2 years, baseline EDSS score, study, treatment x study). Obtain the heterogeneity test as the type 3 test of the treatment*study interaction. This model was only conducted for pooled Studies D1201 + D2301 + D2309 and pooled Studies D2301 + D2309.	• Mixed effects meta-analysis: negative binomial model (fixed effects are treatment, number of relapses in previous 2 years, baseline EDSS score, treatment, and study. Random effects are treatment*study). Estimate the treatment effect with corresponding 95% CI and p-values. This model was only conducted for pooled Studies D1201 + D2301 + D2309.

ARR = annualized relapse rate; CI = confidence interval; EDSS = Expanded Disability Status Scale.

Evaluation based on imaging and/or clinical features

For analysis based on pooled Studies D2301 + D2309 and Study D2302, as previously noted, the efficacy endpoint analyzed for this SCE is ARR (confirmed relapses only). For analyses based on imaging and/or clinical features, the treatment effect of fingolimod 0.5 mg vs comparator treatment was estimated for ARR based on the same fixed effect model included in Table 2-1 and was analyzed by study (Study D2301, D2309, and D2302) and for pooled Studies D2301 + D2309 for each subgroup defined in Table 1-5. A summary of the analyses conducted for pooled Studies D2301 + D2309 and Study D2302 is presented in Table 2-2.

For analyses based on Study D2302/D2302E1, a within-subgroup comparison of ARR during the extension (Month 12 to Month 24) vs ARR during the core phase (Month 0 to Month 12) was conducted for each subgroup defined in Table 1-6. A summary of the analyses conducted for Study D2302/D2302E1 is presented in Table 2-2.

Depending on the size of the subgroup, the models may not have converged, in which case, a reduced model without baseline covariate(s) was applied to the corresponding subgroup(s) interest.

Table 2-2 Analyses of ARR for evaluation based on imaging and/or clinical features

Endpoint	Study groupings	Analyses conducted
ARR	• Pooled Studies D2301 + D2309 • Study D2302	**Fixed effect model** • Negative binomial model (treatment as factor; number of relapses in previous 2 years, baseline EDSS score as covariates). Estimate the treatment effect with corresponding 95% CI and p-values. • Negative binomial model (treatment, number of relapses in previous 2 years, baseline EDSS score, study, treatment x study). Obtain the

Endpoint	Study groupings	Analyses conducted
		heterogeneity test as the type 3 test of the treatment*study interaction. This model was only conducted for pooled Studies pooled Studies D2301 + D2309.
	• Study D2302/D2302E1	• Poisson model with repeated measures where treatment period (core, extension) is the main effect, adjusted for the number of relapses in the 2 years prior to enrollment and using the natural log of (days on study/365.25) as the offset variable. ARR estimate is the LS mean from Poisson model with repeated measures. Rate ratio (ratio of ARR estimate during the extension vs the ARR estimate during the core phase) is presented with corresponding 95% CI and p-values.

ARR = annualized relapse rate; CI = confidence interval; EDSS = Expanded Disability Status Scale; LS = least square.

Comparison and analyses of results across studies

Study populations

A summary of the number of patients included in the overall FAS, FAS-current, and FAS-proposed is presented in Table 3-1. In the overall FAS, there were 3803 patients, of which, 1786 patients and 1831 patients were included in the FAS-current SmPC and FAS proposed SmPC, respectively. There is a notable overlap between the patients included in the FAS-current SmPC and FAS-proposed SmPC subpopulations. As previously noted, the overall FAS population represents patients who were randomized and took at least 1 dose of study medication. This includes patients who were previously treated with DMTs and patients who were treatment naïve. The FAS-current SmPC and FAS-proposed SmPC, however, includes only patients who were previously treated in the year prior to treatment initiation (with the exception of rapidly progressing patients), leading to a notable difference in the number of patients in the FAS compared to the FAS-current SmPC and FAS-proposed SmPC subpopulations.

Table 3-1 Number of patients by subpopulation and study (randomized population)

Population Study	Fingolimod 0.5 mg N=1271 n (%)	Placebo N=830 n (%)	IFN-β1a N=435 n (%)	Total N=3818 [1] n (%)
FAS	1269 (99.8)	830 (100.0)	431 (99.1)	3803 (99.6)
D1201	57 (4.5)	57 (6.9)	--	168 (4.4)
D2301	425 (33.4)	418 (50.4)	--	1272 (33.3)
D2302	429 (33.8)	--	431 (99.1)	1280 (33.5)
D2309	358 (28.2)	355 (42.8)	--	1083 (28.4)
FAS-current SmPC	605 (47.6)	350 (42.2)	237 (54.5)	1786 (46.8)
D1201	23 (1.8)	27 (3.3)	--	71 (1.9)
D2301	158 (12.4)	140 (16.9)	--	432 (11.3)
D2302	245 (19.3)	--	237 (54.5)	724 (19.0)
D2309	179 (14.1)	183 (22.0)	--	559 (14.6)
FAS-proposed SmPC	615 (48.4)	358 (43.1)	244 (56.1)	1831 (48.0)
D1201	23 (1.8)	27 (3.3)	--	73 (1.9)
D2301	159 (12.5)	142 (17.1)	--	440 (11.5)
D2302	248 (19.5)	--	244 (56.1)	741 (19.4)
D2309	185 (14.6)	189 (22.8)	--	577 (15.1)

IFN-β1a = interferon-β1a; FAS = full analysis set; SmPC = Summary of Product Characteristics.

[1] The number of patients in the fingolimod 1.25 mg treatment group is included in the post-text table and contributes to the overall total number of patients presented in this column.

Comparison of efficacy results of all studies

ARR for evaluation based on the current and proposed SmPC Studies (Studies D2301 and D2309)

The primary data presented for ARR analysis for evaluation based on the current and proposed SmPC are the pooled placebo-controlled Studies.

The data presented below provide evidence that patients treated with fingolimod 0.5 mg in subpopulations defined to closely match the current SmPC and proposed SmPC demonstrate treatment benefits based on reductions in ARR.

Table 3-2 ARR, fingolimod 0.5 mg vs placebo (overall FAS, FAS-current SmPC, and FAS-proposed SmPC)

Study/pool Size	n, ARR LS mean		FTY720D 0.5 mg vs placebo Ratio (95% CI) % change (p-value*)
	FTY720 0.5 mg	Placebo	
Overall FAS			
Combined (fixed effects)			
D2301 + D2309	783	773	0.48 (0.41, 0.56)
N=2355, M=2355	0.20	0.42	-52.1 (<0.0001)
FAS-current SmPC			
Combined (fixed effects)			
D2301 + D2309	337	323	0.54 (0.43, 0.68)
N=2355, M=991	0.26	0.49	-45.7 (<0.0001)
FAS-proposed SmPC			
Combined (fixed effects)			
D2301 +D2309	344	331	0.55 (0.44, 0.69)
N=2355, M=1017	0.27	0.48	-44.8 (<0.0001)

ARR = annualized relapse rate; CI = confidence interval; FAS = full analysis set; LS = least squares; SmPC = Summary of Product Characteristics.

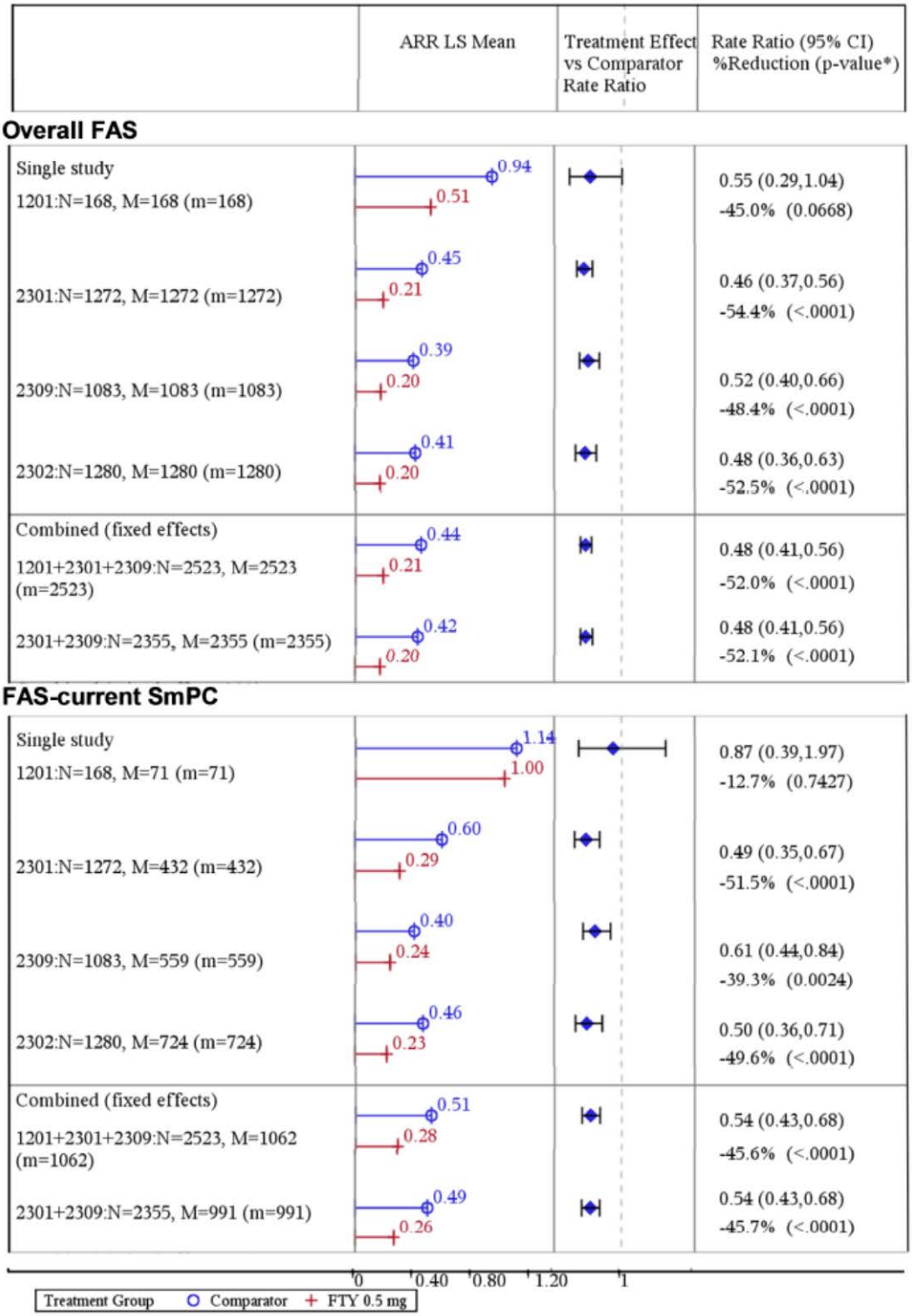
N(M)=number of FAS (subgroup) patients

Negative binomial regression of number of confirmed relapses with treatment as factor, covariates EDSS score at Baseline, and number of relapses in the last 2 years prior to study, adjusted by time on study (yielding ARR), with ln(time) used as offset.

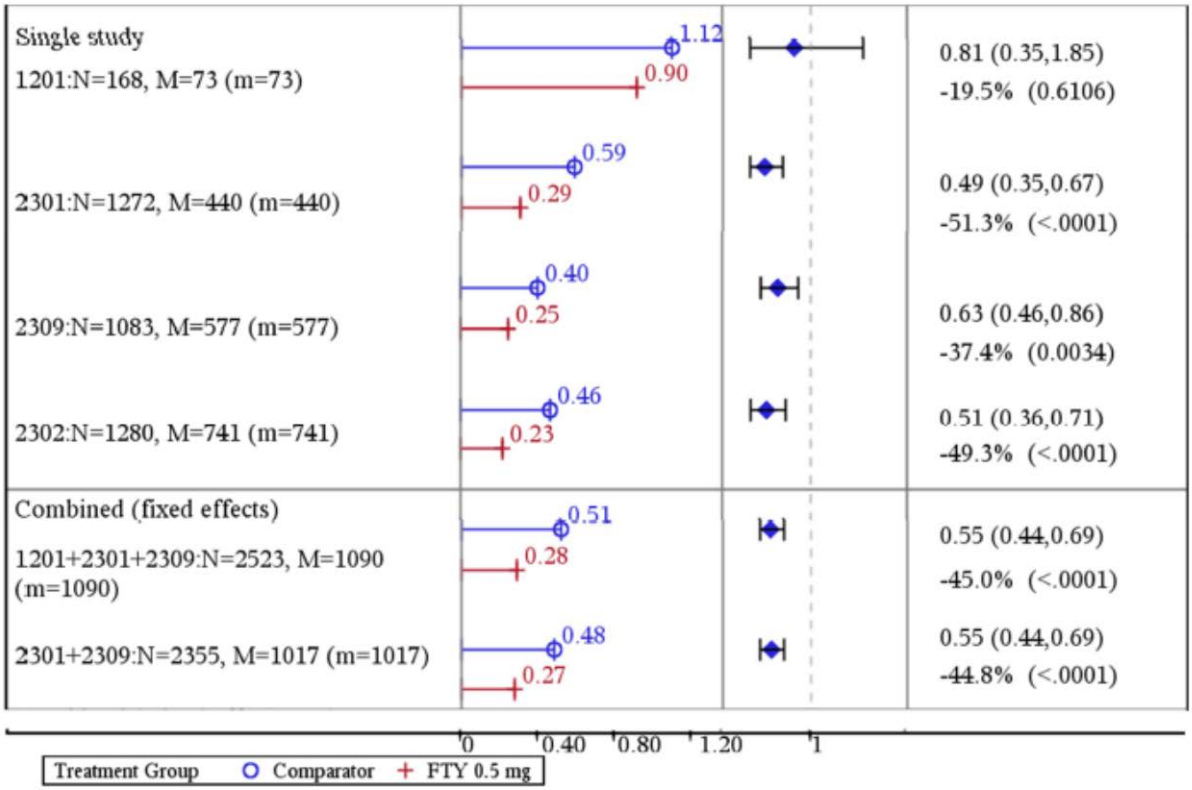
* P-value for treatment contrast.

In both subpopulations (current restricted indication and proposed broader indication populations) of the pooled studies (D2301 + D2309), there was a significant percent reduction in ARR (45.7% and 44.8% reduction, respectively) in the fingolimod groups compared to placebo ($p<0.0001$). Additionally, a significant percent reduction in ARR was observed for the overall initial population (52.1%) in the fingolimod group compared to placebo ($p<0.0001$), with a similar reduction as was observed for both subgroups. There was a consistent reduction in ARR for fingolimod compared to placebo for all populations, overall initial population (naïve and previously treated patients), as well for current restricted indication and proposed broader indication populations (subpopulations of patients who were all previously treated with DMT).

Figure 3-1 **ARR, fingolimod 0.5 mg vs placebo, pooled Studies D1201 + D2301 + D2309, pooled Studies D2301 + D2309, and individual studies (overall FAS, FAS-current SmPC, and FAS-proposed SmPC)**



FAS-proposed SmPC



ARR = annualized relapse rate; CI = confidence interval; FAS = full analysis set; LS = least square; SmPC = Summary of Product Characteristics.

N(M)=number of FAS (subgroup) patients, m=number of patients with non-missing values

For the pooled Studies D1201 + D2301 + D2309, there was an ARR reduction of 52% in the overall population, 45.6% in the current restricted population and 45% in the proposed broader population as compared to placebo.

Comparison of ARR results in subgroups

This section includes results for the evaluation based on imaging and/or clinical features which identifies subgroups based on the presence or absence of MRI lesions and/or relapses prior to receiving fingolimod.

The study groupings included for this analysis are:

1. Pooled Studies D2301 + D2309

2. Study D2302

3. Study D2302/D2302E1

For each of the 3 study groupings above, the following 4 subgroups were defined for this analysis :

- Patients with imaging AND clinical features
- Patients with imaging OR clinical features (but not both)
- Patients with imaging features only (“imaging AND NO clinical features”)
- Patients with clinical features only (“NO imaging AND WITH clinical features”)

-

For the above subgroups, it is noted that:

- The “imaging AND clinical features” subgroup represents patients covered by the current SmPC.
- The “imaging OR clinical features” subgroup represents the additional patients with active disease who would be included in the proposed SmPC but not in the current SmPC.
- The “imaging OR clinical features” subgroup is pooled from 2 other subgroups: “imaging AND NO clinical features” and “NO imaging AND WITH clinical features”.

Number of patients by subgroup

Table 3-3 Number of patients in pooled Studies D2301 + D2309 and Study D2302, by subgroup (FAS)

Study grouping Subgroup	Fingolimod 0.5 mg N=1214 n (%)	Placebo N=773 n (%)	IFN-β1a N=435 n (%)	Total N=2422 n (%)
Pooled studies D2301 + D2309				
Imaging AND clinical features[1]	54 (4.4)	53 (6.9)	--	107 (4.4)
Imaging OR clinical features[2]	122 (10.0)	120 (15.5)	--	242 (10.0)
Imaging AND NO clinical features[3]	44 (3.6)	42 (5.4)	--	86 (3.6)
NO imaging AND WITH clinical features[4]	78 (6.4)	78 (10.1)	--	156 (6.4)
Study D2302				
Imaging AND clinical features[1]	37 (3.0)	--	47 (10.8)	84 (3.5)
Imaging OR clinical features[2]	109 (9.0)	--	93 (21.4)	202 (8.3)
Imaging AND NO clinical features[3]	30 (2.5)	--	29 (6.7)	59 (2.4)
NO imaging AND WITH clinical features[4]	79 (6.5)	--	64 (14.7)	143 (5.9)

FAS = full analysis set; IFN-β1a = interferon-β1a.

[1] Patients previously treated with DMT, had Gd-enhancing T1 lesion at Baseline AND had ≥1 relapse during the 6 months prior to randomization.

[2] Patients previously treated with DMT, had Gd-enhancing T1 lesion at Baseline OR had ≥1 relapse during the 6 months prior to randomization.

[3] Patients previously treated with DMT, had Gd-enhancing T1 lesion at Baseline AND NO relapse during the 6 months prior to randomization.

[4] Patients previously treated with DMT, had NO Gd-enhancing T1 lesion at Baseline AND WITH ≥1 relapse during the 6 months prior to randomization.

Table 3-4 Number of patients in Study D2302/D2302E1, by subgroup (IFN-beta1a switch to fingolimod 0.5 mg)

Study grouping Subgroup	Total IFN-β1a/fingolimod 0.5 mg N=167 n (%)
Study D2302/D2302E1	
Imaging AND clinical features[1]	28 (16.8)
Imaging OR clinical features[2]	72 (43.1)
Imaging AND NO clinical features[3]	53 (31.7)
NO imaging AND WITH clinical features[4]	19 (11.4)

Patient disposition and study discontinuation by subgroup

Pooled Studies D2301 + D2309

Patient disposition and reasons for discontinuing the study were similar across the subgroups.

In pooled Studies D2301 + D2309, the proportion of patients who completed the study for all 4 subgroups was greater for patients in the fingolimod 0.5 mg group (range: 79.5% to 85.2%) compared with patients in the placebo group (range: 64.2% to 76.9%).

Study D2302

Patient disposition and reasons for discontinuing the study were similar across the subgroups.

The proportion of patients who completed the study was slightly greater for patients in the fingolimod 0.5 mg group (range: 91.9% to 94.9%) compared with patients in the IFN-β1a group (79.3% to 91.5%).

Study D2302/D2302E1

The proportion of patients who received IFN-β1a during Study D2302 and switched to fingolimod 0.5 mg during Study D2302E1 and discontinued the study prior to 24 months during the extension phase was similar across all 4 subgroups (range: 15.8% to 17.9%).

Demographics and MS disease baseline characteristics by subgroup

Demographics

Pooled Studies D2301 + D2309

Overall, demographics were similar across all 4 subgroups in pooled Studies D2301 + D2309.

The mean age ranged from 36.7 to 40.1 years, as expected there were notably more women (range: 73.3% to 76.9%), and the majority of patients were Caucasian (approximately 90%).

Study D2302

Overall, demographics were similar across all 4 subgroups in Study D2302. The mean age ranged from 34.3 to 38.0 years, as expected there were notably more women (range: 67.1% to 72.6%), and the majority of patients were Caucasian (>91%).

Study D2302/D2302E1

Demographics in each of the 4 subgroups are presented for patients who received IFN-β1a

during Study D2302 and switched to fingolimod 0.5 mg during Study D2302E1 in

[SCS-Appendix 1-Table S3.3-1.1a, Table S3.3-1.1b, Table S3.3-1.1c, and Table S3.3-1.1d].

Overall, demographics were similar across all 4 subgroups for patients included in the Study D2302/D2302E1 analysis. The mean age was ranged from 34.0 to 38.2 years, there were notably more women (range: 64.2% to 68.4%), and the majority of patients were Caucasian (range: 88.7% to 100%).

MS disease history

Pooled Studies D2301 + D2309

MS disease history in each of the 4 subgroups is presented for pooled Studies D2301 + D2309 in [SCS-Appendix 1-Table S2.4-1.1a, Table S2.4-1.1b, Table S2.4-1.1c, and Table S2.4-1.1d].

Overall, MS disease history was similar across all 4 subgroups in pooled Studies D2301 + D2309. The duration of MS since first symptom was approximately 9.5 years and the number of relapses in the previous year ranged from 1.2 to 1.7 relapses. For the subgroup of “imaging AND NO clinical features”, the mean time since onset of most recent relapse was notably longer (10.49 months prior to randomization) compared with the subgroups of “imaging AND clinical features” (3.67 months), “imaging OR clinical features” (6.16 months), and “NO imaging AND WITH clinical features” (3.78 months), as

expected based on the definition of this subgroup (patients who had a Gd-enhancing T1 lesion at Baseline and no relapse during the 6 months prior to randomization).

Study D2302

Overall, MS disease history was similar across all 4 subgroups in Study D2302. The duration of MS since first symptom ranged from 8.13 to 9.47 years and the number of relapses in the previous year ranged from 1.2 to 1.9 relapses. For the subgroup of "imaging AND NO clinical features", the mean time since onset of most recent relapse was notably longer (10.52 months since randomization) compared with the subgroups of "imaging AND clinical features" (3.62 months), "imaging OR clinical features" (5.67 months), and "NO imaging AND WITH clinical features" (3.68 months), as expected based on the definition of this subgroup (patients who had a Gd-enhancing T1 lesion at Baseline and no relapse during the 6 months prior to randomization).

Study D2302/D2302E1

Overall, MS disease history was similar across all 4 subgroups for patients included in the Study D2302/D2302E1 analysis. The mean duration of MS since first symptoms was slightly higher for the subgroup of "NO imaging AND WITH clinical features" (10.35 years) compared with the subgroups of "imaging AND clinical features" (7.50 years), "imaging OR clinical features" (7.31 years), and "imaging AND NO clinical features" (6.22 years). The mean number of relapses in the previous year ranged from 1.3 to 1.5 relapses, and the time of onset since the most recent relapse was approximately 6.5 months.

MRI baseline characteristics

Pooled Studies D2301 + D2309

Overall, MRI baseline characteristics were representative of the subgroups based on their respective definitions for pooled Studies D2301 + D2309. For example, for the subgroups of "imaging AND clinical features" and "imaging AND NO clinical features", all patients included in these subgroups by definition had a Gd-enhancing T1 lesion at Baseline, therefore, the proportion of patients free of Gd-enhancing T1 lesions at Baseline is 0 for both subgroups.

Similarly, for the subgroup of "NO imaging AND WITH clinical features", no patients in this subgroup were to have a Gd-enhancing T1 lesion at Baseline, therefore, the number and volume of Gd-enhancing T1 lesions at Baseline is 0 for this subgroup.

Study D2302

As noted for pooled Studies D2301 + D2309, MRI baseline characteristics were representative of the subgroups based on their respective definitions for Study D2302.

Study D2302/D2302E1

The majority of patients who were randomized in Study D2302 and are included in 4 defined subgroups did not have a Gd-enhancing T1 lesion at Baseline (the proportion of patients free of Gd-enhancing T1 lesions at Baseline is >50% in 3 of the 4 subgroups); however, patients did have notable T2 lesion burden (median lesion volume: 5164, 3395, 2712, and 3774 mm3 for "imaging AND clinical features", "imaging OR clinical features", "imaging AND NO clinical features", and "NO imaging AND WITH clinical features", respectively).

ARR by subgroup

The data in subsequent sections provide evidence that patients treated with fingolimod 0.5 mg in

subgroups defined by imaging and clinical features demonstrate treatment benefits based on reductions in ARR in placebo- and active-controlled studies and in patients who received 12 months of treatment with IFN-β1a and were re-randomized to receive fingolimod 0.5 mg.

As previously noted, no multiplicity adjustment was applied to these efficacy analyses. These post-hoc analyses as such, have limitations; data for the evaluation of efficacy for subgroups are reviewed in their totality.

Pooled Studies D2301 + D2309

A summary of ARR by subgroup for pooled Studies D2301 + D2309 is presented in Table 3-5;

Table 3-5 ARR, fingolimod 0.5 mg vs placebo, pooled Studies D2301 + D2309, by subgroup (FAS patients previously treated with any DMT 1 year prior to randomization)

Study/pool Size	n, ARR LS mean Fingolimod 0.5 mg	Placebo	Fingolimod 0.5 mg vs placebo ARR ratio (95% CI) % change (p-value*)
Imaging AND clinical features[1]			
Combined (fixed effects)			
D2301 + D2309	54	53	0.58 (0.37, 0.92)
N=2355, M=160	0.40	0.69	-41.5 (0.0193)
Imaging OR clinical features[2]			
Combined (fixed effects)			
D2301 + D2309	122	120	0.61 (0.41, 0.92)
N=2355, M=347	0.24	0.39	-38.5 (0.0177)
Imaging AND NO clinical features[3]			
Combined (fixed effects)**			
D2301 + D2309	44	42	0.25 (0.12, 0.52)
N=2355, M=118	0.11	0.46	-75.4 (0.0003)
NO imaging AND WITH clinical features[4]			
Combined (fixed effects)			
D2301 + D2309	78	78	0.87 (0.53, 1.43)
N=2355, M=229	0.30	0.35	-13.1 (0.5806)

ARR = annualized relapse rate; CI = confidence interval; DMT = disease-modifying therapy; FAS = full analysis set; LS = least square.

N(M)=number of FAS (subgroup) patients

Negative binomial regression of number of confirmed relapses with treatment as factor, covariates EDSS score at Baseline and number of relapses in the last 2 years prior to the study, adjusted by time on study (yielding ARR), with ln(time) used as offset.

[1] Patients previously treated with DMT, had Gd-enhancing T1 lesion at Baseline AND had ≥1 relapse during the 6 months prior to randomization.

[2] Patients previously treated with DMT, had Gd-enhancing T1 lesion at Baseline OR had ≥1 relapse during the 6 months prior to randomization.

[3] Patients previously treated with DMT, had Gd-enhancing T1 lesion at Baseline AND NO relapse during the 6 months prior to randomization.

[4] Patients previously treated with DMT, had NO Gd-enhancing T1 lesion at Baseline AND WITH ≥1 relapse during the 6 months prior to randomization.

* P-value for treatment contrast.

** Based on a reduced negative binomial regression model without the covariate of number of relapses in the last 2 years prior to the study due to non-convergence issue.

Patients with both “imaging AND clinical features” (representing the current SmPC) had a lower ARR when

treated with fingolimod 0.5 mg compared with placebo (41.5% reduction in ARR).

For patients representing the proposed SmPC who were previously treated with DMTs and who had MRI activity at Baseline or with relapse in the 6 months prior to randomization, not both ("imaging OR clinical features"), a lower ARR was observed when treated with fingolimod 0.5 mg compared with placebo (38.5% reduction in ARR).

Patients previously treated with DMTs who had MRI activity at Baseline and without relapse in the 6 months prior to randomization ("imaging AND NO clinical features") demonstrated the greatest reduction in ARR, with a lower ARR when treated with fingolimod 0.5 mg compared with placebo (75.4% reduction in ARR).

For the subgroup of patients without MRI activity at Baseline and with a relapse in the 6 months prior to randomization ("NO imaging AND WITH clinical features"), the treatment outcome on ARR for patients treated with fingolimod 0.5 mg was comparable to the other subgroups (ARR=0.30) and the reduction in ARR compared with placebo was 13.1%. The lower magnitude of the relative treatment effect may be explained by the fact that lower MRI disease burden is associated with less relapse activity evidenced by the outcome in the placebo group.

The results across all 4 subgroups demonstrate that all patients with imaging and/or clinical features at Baseline have a reduced ARR when switching from another DMT to fingolimod 0.5 mg.

Study D2302

A summary of ARR by subgroup for Study D2302 is presented in Table 3-6.

Table 3-6 ARR, fingolimod 0.5 mg vs IFN-beta1a, Study D2302, by subgroup (FAS patients previously treated with any DMT 1 year prior to randomization)

Study/pool Size	n, ARR LS mean		Fingolimod 0.5 mg vs IFN-β1a
	Fingolimod 0.5 mg	IFN-β1a	ARR ratio (95% CI) % change (p-value*)
Imaging AND clinical features[1]			
D2302	37	47	0.44 (0.21, 0.89)
N=1280, M=121	0.28	0.65	-56.4 (0.0221)
Imaging OR clinical features[2]			
D2302	109	93	0.46 (0.29, 0.75)
N=1280, M=307	0.26	0.55	-53.8 (0.0016)
Imaging AND NO clinical features[3]			
D2302	30	29	0.30 (0.13, 0.71)
N=1280, M=83	0.22	0.72	-69.8 (0.0061)
NO imaging AND WITH clinical features[4]			
D2302	79	64	0.58 (0.32, 1.04)
N=1280, M=224	0.27	0.47	-42.2 (0.0674)

ARR = annualized relapse rate; CI = confidence interval; DMT = disease-modifying therapy; FAS = full analysis set; IFN-β1a = interferon-β1a; LS = least square.

N(M)=number of FAS (subgroup) patients.

Negative binomial regression of number of confirmed relapses with treatment as factor, covariates EDSS score at Baseline and number of relapses in the last 2 years prior to the study, adjusted by time on study (yielding ARR), with ln(time) used as offset.

Patients with both "imaging AND clinical features" (matching the current SmPC) had a lower ARR when treated with fingolimod 0.5 mg compared with IFN-β1a (56.4% reduction in ARR).

For patients matching the proposed SmPC who were previously treated with DMTs and who had MRI activity at Baseline or with relapse in the 6 months prior to randomization, but not both ("imaging OR clinical features"), a lower ARR was observed when treated with

fingolimod 0.5 mg compared with IFN-β1a (53.8% reduction in ARR) in line with the results observed for the subgroup of patients with both "imaging AND clinical features".

Patients previously treated with DMTs who had MRI activity at Baseline and without relapse in the 6 months prior to randomization ("imaging AND NO clinical features") demonstrated the greatest reduction in ARR, with a lower ARR when treated with fingolimod 0.5 mg compared with IFN-β1a (69.8% reduction in ARR).

Similarly for patients without MRI activity at Baseline and with a relapses in the 6 months prior to randomization (NO imaging AND WITH clinical features), a reduction in ARR was observed for patients treated with fingolimod 0.5 mg compared with IFN-β1a (42.2% reduction in ARR).

Study D2302/D2302E1

A summary of ARR by subgroup for patients who received IFN-β1a during Study D2302 and then switched to fingolimod 0.5 mg during Study D2302E1 is presented in Table 3-7.

Table 3-7 ARR, within-subgroup comparison for Study D2302E1 by subgroups, Month 0 to 12 vs Month 12 to 24 (extension FAS for patients who switched from IFN-beta1a to fingolimod 0.5 mg)

	IFN-β1a / FTY720 0.5 mg Imaging AND clinical features[1]	IFN-β1a / FTY720 0.5 mg Imaging OR clinical features[2]	IFN-β1a / FTY720 0.5 mg Imaging AND NO clinical features[3]	IFN-β1a / FTY720 0.5 mg No imaging AND WITH clinical features[4]
	N=28	N=72	N=53	N=19
Month 0 to 12				
Number of relapses	38	27	0	27
Time in study (days)	10293	26648	19664	6984
ARR	1.348	0.370	0	1.412
ARR estimate from Poisson model	1.280	0.370	--	1.419
95%CI	1.055, 1.553	0.239, 0.575	--	1.167, 1.725
Month 12 to 24				
Number of relapses	17	16	7	9
Time in study (days)	9673	25358	18797	6561
ARR	0.642	0.230	0.136	0.501
ARR estimate from Poisson model	0.612	0.233	--	0.505
95%CI	0.411, 0.911	0.128, 0.423	--	0.245, 1.038
Month 12 to 24 vs Month 0 to 12				
ARR ratio	0.478	0.629	--	0.356
95% CI	0.302, 0.757	0.335, 1.180	--	0.175, 0.720
P-value	0.0027	0.1462	--	0.0065

ARR = annualized relapse rate; CI = confidence interval; FAS = full analysis set; IFN-β1a = interferon-β1a.

N=number of extension FAS patients (subgroup) who were switched from IFN-β1a to fingolimod 0.5 mg.

ARR estimates (95% CI), rate ratio, and p-values were obtained from a Poisson model (with repeated measures where treatment period is the main effect) adjusted for number of relapses in 2 years prior to enrollment. Log(time in study) is the offset variable.

Upon switching from IFN-β1a (Month 0 to 12) to fingolimod 0.5 mg (Month 12 to 24), a lower ARR was observed for the subgroup of "imaging AND clinical features" (0.642) with a substantial reduction in ARR

of 52.2%.

The subgroup of “imaging OR clinical features” comprises to a substantial degree the patients with no relapses and only imaging during Month 0 to 12, which leads to a reduced ARR for this subgroup. A reduction in ARR of 37.1% was observed (0.230) from Month 12 to 24.

Upon switching from IFN-β1a (Month 0 to 12) to fingolimod 0.5 mg (Month 12 to 24) a lower ARR was observed on fingolimod for the subgroup of “NO imaging AND WITH clinical features” (0.501) with a reduction in ARR of 64.4%.

The reduction in ARR is consistent across these 3 subgroups, demonstrating that patients defined by imaging and/or clinical features have a reduced ARR when switching from

IFN-β1a to fingolimod 0.5 mg.

It should be noted that for the subgroup of “imaging AND NO clinical features”, ARR was 0 due to the definition of this subgroup (patients had no relapses from Baseline to Month 12 of

Study D2302). Therefore, the ARR in these patients by definition could only numerically increase from Month 0 to 12 to Month 12 to 24. The ARR observed for this subgroup was low on fingolimod for Month 12 to 24 (0.136).

2.3.3. Discussion on clinical efficacy

Post-hoc analyses of data from previously submitted studies and a newly submitted study (D1201) have been performed to support the proposed indication of Gilenya.

The MAH has compared the results on ARR between two subpopulations corresponding respectively to the current restricted indication and to the proposed broader indication and extracted from the overall population of the abovementioned studies. In the pooled data analysis submitted by the applicant, the new conditions proposed for the broader indication provide a difference in size between the current restricted and proposed new indication sub-populations included in these data of only around 2%.

Regarding the results of the new data analysis proposed by the applicant, the clinical efficacy demonstrated in previously submitted studies are confirmed in the subpopulations and subgroups targeted in this new analysis. In both subpopulations (current restricted indication and proposed broader indication populations) of the pooled studies (D2301 + D2309), there was a significant percent reduction in ARR (45.7% and 44.8% reduction, respectively) in the fingolimod groups compared to placebo ($p<0.0001$). Additionally, a significant percent reduction in ARR was observed for the overall initial population (52.1%) in the fingolimod group compared to placebo ($p<0.0001$), with a similar reduction as was observed for both subgroups. The consistency between the subpopulations was also observed within the individual studies (Studies D1201, D2301, D2309, and D2302) except for study 1201, where the benefit was not clearly demonstrated in the defined current and proposed SmPC populations.

The applicant as well performed subgroup analyses, where 4 subgroups were defined according to the different examinations that triggered the treatment: 1) Imaging AND clinical features, 2) Imaging OR clinical features, 3) Imaging AND NO clinical features, 4) NO imaging AND WITH clinical features.

For the pooled studies D2301 + D2309, the analysis indicates that patients with both imaging AND clinical features are likely to have more active disease than those who have either imaging OR clinical features. The ARR ratio was similar for both subgroups. The results further indicate that, within these studies, there was no advantage with fingolimod 0.5 mg over placebo in the subgroup of patients with NO imaging activity AND WITH clinical features within the 6 month preceding start of trial medication. These patients

also had the lowest absolute risk of clinical relapses. For those patients with only imaging features (defined as subjects having Gd-enhancing T1 lesions at baseline) the absolute risk of relapse was highest and the ARR was 0.11 on fingolimod compared with 0.46 on placebo, showing a relative reduction with 75.4 % (p=0.0003). These results indicate that imaging activity without clinical activity had a higher risk of relapse than those without imaging activity, and the greatest relative effect of fingolimod was registered in this group.

In study D2302 there was only a slight increase of ARR in those with imaging AND clinical features compared to those with imaging OR clinical features. Again, for this subgroup with imaging AND NO clinical features, the effect size was larger than for those with NO imaging AND WITH clinical features, in analogy with the results for pooled studies D2301+D2309. Efficacy in those with clinical features AND NO imaging activity was of borderline significance over beta interferon.

For patients switching from Interferon to Gilenya in extension study D2302/D2302E1), the reduction in ARR was consistent across 3 subgroups (Imaging AND clinical features, Imaging OR clinical features, NO imaging AND WITH clinical features).

2.3.4. Conclusions on the clinical efficacy

The criteria for diagnosis of MS have been updated in 2001, 2005 and 2010. During recent years more emphasis has been put on the role of MRI and how MRI can measure disease activity in order to reach a diagnosis of MS. In a previous version of the criteria for MS diagnosis, reference was made to a specific number of 9 T2 hyperintense brain lesions; however this reference has been removed in the 2010 revision of the McDonald criteria. This reference can be considered outdated and it should be removed from the indication text.

To support the current variation application, the applicant has performed post-hoc analyses of data from previously conducted clinical studies with fingolimod. The applicant compared the ARR in the overall population and in subgroups defined according to the currently approved indication and the new proposed indication. Additional supportive post-hoc analyses were also performed. The results for the subgroups defined according to the current SmPC and the proposed SmPC indicated that patients with both imaging and clinical features are likely to have more active disease than those who have either imaging or clinical features. The positive results from the performed analyses in the subgroups confirm the efficacy of fingolimod in the intended population after the extension of indication which, as mentioned above, overlaps a great deal with the population covered in the current wording of the indication.

2.4. Clinical safety

Introduction

The current application seeks a modification to the Gilenya indication, to include patients with active MS disease defined by clinical or imaging features despite treatment with at least 1 DMT. To support the proposed change, the current submission presents the results of post-hoc analyses of safety data from all 4 completed, randomized, double-blind, controlled studies within the fingolimod Phase 2 and 3 clinical development programs which explored the fingolimod 0.5 mg dose for at least 6 months. Integrated long-term safety information is provided from the aforementioned core studies and from open-label extension studies. Safety data for the proposed Summary of Product Characteristics (SmPC) and current SmPC subpopulation was compared.

2.4.1. Safety analysis

- **Evaluation of SmPC subpopulations (Group D and Group F analyses)**

The key safety analyses for this submission are based on the following datasets:

- Group D Pooled data from 3 placebo-controlled core studies D1201, D2301, D2309 and active-controlled study D2302. For study D2302 only fingolimod data was included. These studies provided a pooled dataset (Group D) of 3818 patients from completed, randomized, controlled, double-blind studies of at least 6 months duration which tested the efficacy and safety of fingolimod 0.5 mg. An overview of the 4 controlled Phase 2 and 3 studies contributing to the post-hoc safety analyses is provided in Table 1-1 below.

- Group F Pooled integrated data from core and extension studies D1201, D2301, D2302, D2309, D1201E1, D2301E1, D2302E1, D2309E1, 2399E1, and D2399 (Study D2399 only contains patients from the 4 Group D core studies) that comprised 3458 patients. Only patients who had participated in the core studies and had fingolimod exposure will be included in the long-term safety analysis (Table 1-2).

Table 1-1 Phase 2/3 controlled studies (Group D) that contribute to the target indication

Study	Objective, population	No. of patients[1]	Treatment duration	Treatment dose/day
Placebo-controlled studies				
D1201	Efficacy and safety, RMS	171	6 months	FTY720 1.25 mg / once daily FTY720 0.5 mg / once daily placebo
D2301	Efficacy and safety, RRMS	1272	24 months	FTY720 1.25 mg / once daily FTY720 0.5 mg / once daily placebo
D2309	Efficacy and safety, RRMS	1083	24 months	FTY720 1.25 mg / once daily FTY720 0.5 mg / once daily placebo
Active-controlled study				
D2302	Efficacy and safety, RRMS	1292	12 months	FTY720 1.25 mg / once daily FTY720 0.5 mg / once daily IFN-β1a 30 µg im / once weekly

FTY720 = fingolimod; IFN-β1a = interferon-beta1a; RMS = relapsing multiple sclerosis; RRMS = relapsing remitting multiple sclerosis
[1]Number of patients randomized
Source: [Synopses of individual studies], [Tabular Listing of All Clinical Studies]

Table 1-2 Completed and ongoing long-term studies (Group F)

Study	Objective, population	No. of patients[1]	Treatment duration	Treatment dose/day
Individual extension studies				
D1201E1	Collect long-term safety and efficacy data on patients who completed double-blind 6 months treatment in patients with RMS	143	No predefined treatment period. Until fingolimod became commercially available in Japan.	FTY720 1.25 mg / once daily FTY720 0.5 mg / once daily
D2301E1	Compare efficacy and safety of FTY720 1.25 mg and FTY720 0.5 mg in patients with RRMS	920	No predefined treatment period for the extension study. Up to 5 years data was provided.	FTY720 1.25 mg / once daily FTY720 0.5 mg / once daily
D2309E1	To evaluate long-term safety and tolerability To evaluate long-term efficacy	632	No predefined treatment period. Treatment continues until FTY720 becomes available in the participating country or development is terminated.	FTY720 1.25 mg / once daily FTY720 0.5 mg / once daily
D2302E1	Obtain long-term safety and efficacy data in patients treated with fingolimod. Examine the safety of converting patients from IFN-β1a treatment in the core phase to fingolimod treatment in patients with RRMS	1030[2]	Up to 4 years	FTY720 1.25 mg / once daily FTY720 0.5 mg / once daily
D2399E1	Monitor and further describe the long-term safety and effectiveness of fingolimod in patients with RMS	63	Patient follow-up was expected to be at least 5 years. However, the study was terminated early and all patients were offered enrollment into the interventional follow-up Study D2399.	FTY720 0.5 mg / once daily
Pooled extension study				
D2399[3]	To evaluate the long-term safety and tolerability of fingolimod 0.5 mg/day in patients with relapsing forms of MS.	1704[4]	In countries where reimbursement does not become available during the course of the study, all patients (Phase 2/3 and other) will remain in the study maximally through 30-Jun-2016.	FTY720 0.5 mg / once daily

FTY720 = fingolimod; IFN-β1a = interferon-beta1a; MS = multiple sclerosis; RRMS = relapsing remitting multiple sclerosis

[1]Number of patients that entered the study

[2]Among these 1030 patients entering into the extension phase, 3 did not receive extension phase treatment

[3]Includes patients from several studies in the fingolimod development program, only patients from core studies D1201, D2301, D2302, and D2309 were considered in this submission

[4]Includes only patients from Studies D1201, D2301, D2302, and D2309

The consistency of safety was evaluated by the MAH for the overall safety population, and for the current and proposed SmPC subpopulations (Table 1-4), based on pooled study data (Table 1-3).

Table 1-3 Population groupings and safety assessments in pooled datasets – SmPC subpopulation

Database	Studies	Pooled treatment groups	Safety topics Populations/Subpopulations/Subgroup
Safety analysis – comparison of SmPC subpopulations			
Group D	D1201, D2301, D2302[1] and D2309	FTY720 1.25 mg FTY720 0.5 mg placebo	Topics: Disposition, demographics, MS disease history, baseline disease activity, exposure, AEs and risks Populations: SAF, SAF-proposed SmPC, and SAF-current SmPC
Group F[2]	D1201, D2301, D2309, D2302[1], D1201E1, D2301E1, D2309E1, D2302E1, D2399E1[3] and D2399[3]	FTY720 1.25 mg FTY720 0.5 mg	Topics: Disposition, demographics, exposure, AEs and risks Populations: SAF, SAF-proposed SmPC, and SAF-current SmPC

Note: Patients were grouped by the highest assigned dose of FTY720 treatment.

AEs = adverse events; FTY720 = fingolimod; MS = multiple sclerosis; SAF = safety set; SmPC = summary of product characteristics

[1]Patients treated with IFN β1a during core study D2302 were excluded from the dataset

[2]Data considered from first dose of FTY720, excludes control data prior to the first dose of fingolimod

[3]contains only patients from Studies D2301, D2302 and D2309

Table 1-4 Definitions of safety analysis populations based on the current and proposed SmPC subpopulations (Group D and Group F analyses)

Population	Definition
Randomized set	All patients who were assigned randomization numbers at the start of the core phase.
SAF (overall SAF)	All patients who took at least 1 dose of study medication. Patients were grouped according to the treatment actually received
SAF-proposed SmPC	All patients in SAF who fulfilled at least 1 of the following active MS criteria defined by clinical or imaging features: Patients who received ≥1 prior DMT during the year before treatment initiation and had either ≥1 Gd-enhancing T1 lesion at baseline and/or ≥1 relapse the year prior to screening Rapidly evolving severe RRMS: ≥2 relapses within the year before baseline and ≥1 Gd-T1 lesion at baseline
SAF-current SmPC	All patients in SAF who fulfilled at least 1 of the following 2 criteria in the current SmPC: Patients who received ≥1 prior DMT during the year before treatment initiation but: Had as many or more relapses in the year immediately before the study than in the preceding year, or Had at ≥1 relapse in the previous year plus at least either 1 Gd-enhancing T1 lesion or 9 T2 lesions at baseline Rapidly evolving severe RRMS: ≥2 relapses within the year before baseline and ≥1 Gd-T1 lesion at baseline

From the pooled dataset Group D, 1269 patients received treatment with fingolimod 0.5 mg. The SAF-current SmPC population accounted for more than 95% of the SAF-proposed SmPC population in the pooled studies of interest (Table 1-5).

Table 1-5 Analysis populations, by treatment, Group D analysis, D1201, D2301, D2302, and D2309 combined (Randomized)

Population Study	FTY720 0.5 mg N = 1271 n (%)	Placebo N = 830 n (%)	IFN-β1a N=435 n (%)	Total N=3818 [1] n (%)
Randomized population	1271 (100.0)	830 (100.0)	435 (100)	3818 (100)
D1201	57 (4.5)	57 (6.9)	-	171 (4.5)
D2301	425 (33.4)	418 (50.4)	-	1272 (33.3)
D2302[2]	431 (33.9)	-	435 (100)	1292 (33.8)
D2309	358 (28.2)	355 (42.8)	-	1083 (28.4)
Safety set	1269 (99.8)	830 (100.0)	431 (99.1)	3803 (99.6)
D1201	57 (4.5)	57 (6.9)	-	168 (4.4)
D2301	425 (33.4)	418 (50.4)	-	1272 (33.3)
D2302[2]	429 (33.8)	-	431 (99.1)	1280 (33.5)
D2309	358 (28.2)	355 (42.8)	-	1083 (28.4)
SAF-proposed SmPC	615 (48.4)	358 (43.1)	244 (56.1)	1831 (48.0)
D1201	23 (1.8)	27 (3.3)		73 (1.9)
D2301	159 (12.5)	142 (17.1)	-	440 (11.5)
D2302[2]	248 (19.5)	-	244 (56.1)	741 (19.4)
D2309	185 (14.6)	189 (22.8)	-	577 (15.1)
SAF-current SmPC	605 (47.6)	350 (42.2)	237 (54.5)	1786 (46.8)
D1201	23 (1.8)	27 (3.3)	-	71 (1.9)
D2301	158 (12.4)	140 (16.9)	-	432 (11.3)
D2302[2]	245 (19.3)	-	237 (54.5)	724 (19.0)
D2309	179 (14.1)	183 (22.0)	-	559 (14.6)

Table 1-6 Analysis populations, by treatment, Group F analysis, D1201, D1201E1, D2301, D2301E1, D2302, D2302E1, D2309, D2309E1, D2399E1, D2399 combined (SAF)

Population	FTY720 0.5 mg N = 1739 n (%)
Safety set (SAF)	1739 (100.0)
SAF-proposed SmPC	837 (48.1)
SAF-current SmPC	820 (47.2)

FTY720 = fingolimod; SAF = safety set; SmPC = Summary of product characteristics

Source: [SCS-Appendix 1-Table S1.1-2]

Safety analyses (based on a data lock point of 01-Oct-2014) were performed for pooled and individual study data using MedDRA 17.0. The safety analysis focuses on adverse events (AEs) and serious adverse events (SAEs), from the core phases (Group D) of controlled studies using incidence and exposure adjusted incidence rate (IR) of AEs/SAEs. All data for AEs while patients were on study drug and up to 45 days after the study drug discontinuation were included. For analyses in Group D, all data available in the clinical database for SAEs were included regardless of the 45-day cutoff, but excluding those after the first dose of an extension study if patients continued in an extension. For analyses in Group F, all data available in the clinical database for SAEs were included regardless of extension. All important identified and potential risk definitions were based on predefined risk search criteria. Level 1 corresponds to the overarching risk search term, which may have MedDRA substructures or NMQs (Level 2, 3, 4 or 5). These NMQs levels follow the same rules as SMQ levels. The priority focus of the safety information was the analysis of AEs of fingolimod in pooled core Studies D1201, D2301, D2302, D2309, and specifically the AEs classified as 'important identified risks' or 'important potential risks.

Patient disposition was summarized for all randomized patients in Group D and the safety set in Group F. MS disease baseline characteristics (including MS history) were summarized by treatment using

frequency distributions (for categorical variables) and summary statistics (for continuous variables) using the randomized set in Group D only.

- **Evaluation of subgroups based on imaging / clinical features**

Additional supportive analyses, in which patients were allocated to 4 subgroups based on imaging and/or clinical features at baseline, were performed using the following studies:

- Patients from pooled placebo-controlled Studies D2301 and D2309, and active-controlled study D2302 who were previously treated with DMT within 1 year prior to treatment initiation.

- Patients switching from IFN-β1a in core study D2302 to fingolimod 0.5 mg in extension study D2302E1

For safety, only the "imaging AND clinical features" and "imaging OR clinical features" subgroups are provided for the AE/SAE safety analyses for comparison. It should be noted that the "imaging OR clinical features" subgroup is pooled from the 2 subgroups which represent the opposite ends of the subgroup definition: "imaging AND NO clinical features" and "NO imaging AND WITH clinical features." Since the safety analysis focuses on comparison of patients under the current and proposed label, only the 2 subgroups that most closely matched these populations were analyzed. However, results are available from all 4 subgroups, for exposure, demographics, disposition, baseline MS disease history and baseline MS disease characteristics.

The additional safety information mentioned above from subgroup analyses of patients based on clinical and/or imaging features is included for completeness. For the safety results however, it needs to be taken into consideration that these are being based on a small number of patients and at the same time explore a high number of endpoints (ie different preferred terms), each with a relatively low frequency of occurrence. This multiplicity of events assessed in conjunction with the low within subgroup incidence rates increases the risk of chance findings.

Table 1-7 Subgroup analysis populations for core studies D2301/D2309 and D2302), (randomized set)

	FTY720 0.5 mg N=1214 n (%)	Placebo N=773 n (%)	IFN-β1a im N=435 n (%)	Total N=2422 n (%)
Safety Set (SAF)	1212 (99.8)	773 (100.0)	431 (99.1)	2416 (99.8)
SAF - Imaging **AND** clinical features	91 (7.5)	53 (6.9)	47 (10.8)	191 (7.9)
SAF - Imaging **OR** clinical features	231 (19.0)	120 (15.5)	93 (21.4)	444 (18.3)
SAF - Imaging **AND NO** clinical features	74 (6.1)	42 (5.4)	29 (6.7)	145 (6.0)
SAF - **NO** imaging **AND WITH** clinical features	157 (12.9)	78 (10.1)	64 (14.7)	299 (12.3)

Table 1-8 Number (%) of patients by subgroup, Interferon-beta1a im/FTY720 0.5 mg, D2302E1, Extension safety population 0 – 24 month analysis

Subgroup population	IFN-β1a/FTY720 0.5 mg N=167
Imaging AND clinical features	28 (16.8)
Imaging OR clinical features	72 (43.1)
Imaging AND NO clinical feature	53 (31.7)
NO imaging AND WITH clinical feature	19 (11.4)

2.4.2. Patient exposure

- **Exposure to treatment**

Exposure is defined as the sum of days spent in study minus the sum of days of all treatment interruptions irrespective of the identity and dose of the treatment medication. Patient-years are defined as the sum of the number of days on study drug for all patients in the group divided by 365.25. Exposure data is presented for Group D SAF-proposed SmPC and SAF-current SmPC (Table 1-9) and Group F SAF-proposed SmPC and SAF-current SmPC (Table 1-10).

- **Exposure in controlled studies (Group D analysis)**

Duration of exposure was similar between fingolimod 0.5 mg and placebo in the individual studies.

The mean duration of exposure was to some degree higher in the placebo arm compared to the fingolimod 0.5 mg arm for both the SAF proposed SmPC (488.2 days in the fingolimod 0.5 mg arm and 540.5 days in the placebo arm) and the SAF current SmPC (486.2 days in the fingolimod 0.5 mg arm and 536.2 days in the placebo arm). Since the 1 year Study D2302 was included only in the fingolimod 0.5 mg arm, there was a higher percentage of patients receiving treatment for ≥2 years in the placebo arm for both the SAF-proposed SmPC and the SAF-current SmPC (45.3% and 44.3%, respectively) when compared to the fingolimod 0.5 mg arm (27.6% and 27.3%, respectively). The median duration of exposure was higher for patients on placebo compared to the patients on fingolimod 0.5 mg for both the SAF-proposed SmPC (379.0 days in the fingolimod 0.5 mg and 710.0 days in the placebo), and the

SAF-current SmPC (378.0 days in the fingolimod 0.5 mg arm and 708.5 days in the placebo arm). The differences in median duration of exposure between fingolimod 0.5 mg and the placebo reflects the inclusion of Study D2302 for which only the patients on fingolimod 0.5 mg are included, while the patients treated with the active comparator IFN-β1a are not.

Since Study D2302 was only 1 year in duration, the median duration of exposure was noticeably impacted, while the mean duration of overall exposure decreased only to a minor degree (see Table 1-9). Exposure adjusted AE incidence rates were provided in addition to AE incidence to allow further comparison, as needed.

Table 1-9 Duration of exposure to study drug, by the randomized/initial treatment, Group D analysis (SAF-proposed and SAF-current SmPC)

	SAF-proposed SmPC		SAF-current SmPC	
	FTY720 0.5 mg N = 615 (%)	Placebo N = 358 (%)	FTY720 0.5 mg (N = 605)	Placebo (N = 350)
Duration of exposure (days)				
≥1	615 (100.0)	358 (100.0)	605 (100.0)	350 (100.0)
≥7	611 (99.3)	357 (99.7)	601 (99.3)	349 (99.7)
≥14	607 (98.7)	354 (98.9)	597 (98.7)	346 (98.9)
≥30	602 (97.9)	352 (98.3)	592 (97.9)	344 (98.3)
≥60	595 (96.7)	351 (98.0)	585 (96.7)	343 (98.0)
≥90	585 (95.1)	339 (94.7)	575 (95.0)	331 (94.6)
≥180	560 (91.1)	305 (85.2)	549 (90.7)	297 (84.9)
≥360 (1 yr)	466 (75.8)	256 (71.5)	457 (75.5)	248 (70.9)
≥720 (2 yrs)	170 (27.6)	162 (45.3)	165 (27.3)	155 (44.3)
≥1080 (3 yrs)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Summary				
n	615	358	605	350
Mean	488.2	540.5	486.2	536.2
SD	221.83	254.22	222.07	255.45
Median	379.0	710.0	378.0	708.5
Range	1 to 881	2 to 890	1 to 881	2 to 890
Patient-years	822.1	529.7	805.3	513.8

FTY720 = fingolimod; SAF = safety; SmPC = Summary of Product Characteristics

- **Exposure in the long-term safety population (Group F analysis)**

The durations of study drug exposure to fingolimod 0.5 mg in the Group F analysis for both the SAF-proposed SmPC and the SAF-current SmPC reflect the increased long-term safety study durations (Table 1-2) and allow for valid comparisons of safety.

The median duration of exposure was similar in the patients on fingolimod 0.5 mg for both the SAF-proposed SmPC (1358.0 days), and the SAF-current SmPC (1358.5 days; Table 1- 10). The mean study drug exposure for patients on fingolimod 0.5 mg was also similar between the SAF-proposed SmPC and the SAF-current SmPC. There was no meaningful difference between the PTYs of exposure in the fingolimod 0.5 mg arm for both the SAF-proposed SmPC (3342.6 PTYs) and the SAF-current SmPC (3277.7 PTYs).

Duration of actual exposure to study medication by administered study drug and dose for individual studies is presented in Table 1-10.

Table 1-10 Duration of exposure to study drug, by the highest assigned dose of fingolimod, Group F analysis (SAF-proposed SmPC and SAF-current SmPC)

	SAF-proposed SmPC	SAF-current SmPC
Duration of exposure (days)	SAF-proposed FTY720 0.5 mg N = 837 n (%)	SAF-current FTY720 0.5 mg N = 820 n (%)
≥1	837 (100.0)	820 (100.0)
≥7	833 (99.5)	816 (99.5)
≥14	828 (98.9)	811 (98.9)
≥30	822 (98.2)	805 (98.2)
≥60	809 (96.7)	792 (96.6)
≥90	794 (94.9)	777 (94.8)
≥180	763 (91.2)	746 (91.0)
≥360 (1 yr)	699 (83.5)	684 (83.4)
≥720 (2 yrs)	592 (70.7)	578 (70.5)
≥1080 (3 yrs)	494 (59.0)	483 (58.9)
≥1440 (4 yrs)	395 (47.2)	386 (47.1)
≥1800 (5 yrs)	340 (40.6)	333 (40.6)
≥2160 (6 yrs)	275 (32.9)	273 (33.3)
≥2520 (7 yrs)	198 (23.7)	196 (23.9)
≥2880 (8 yrs)	14 (1.7)	14 (1.7)
≥3240 (9 yrs)	0 (0.0)	0 (0.0)
Summary		
n	837	820
Mean	1458.6	1460.0
SD	946.90	951.27
Median	1358.0	1358.5
Range	1 to 3104	1 to 3104
Patient-years	3342.6	3277.7

- **Exposure in subgroups based on imaging/clinical features**
    - **Exposure in pooled D2301+D2309 studies**

The mean exposure was similar among all 4 subgroups. The number of PTYs varied proportionally with the number of patients in each of the 4 subgroups. For complete exposure data see [SCS-Appendix 1-Table S2.6-1.1a to Table S2.6-1.1d].

- **Exposure in Study D2302**

The mean exposure was similar among all 4 subgroups. The number of PTYs varied proportionally with the number of patients in each of the 4 subgroups. For complete exposure data see [SCS-Appendix 1-Table S2.6-1.2a to Table S2.6-1.2d].

- **Exposure in D2302/D2302E1**

The mean exposure was similar among all 4 subpopulations. The number of PTYs varied proportionally with the number of patients in each of the 4 subgroups. For complete exposure data see [SCS-Appendix 1-Table S3.6-1.1a to Table S3.6-1.1d].

- **Post-marketing exposure**

Combining the exposure information from MS clinical trials and sales information, it is conservatively estimated that approximately 104 757 MS patients have been exposed to fingolimod for a total of approximately 175 217 patient years (DSUR-FTY720-001 (Issue 4)).

2.4.3. Adverse events

2.4.3.1. Most frequently AEs

- **Most frequently AEs in SmPC subpopulations**

The most common AEs (≥5% incidence) observed in the SAF were as follows:

Table 2-1 Most commonly-occurring adverse events (at least 5.0 percent in either treatment group) by preferred term, by initial/randomized treatment, Group D combined SAF

Preferred term	FTY720 0.5 mg N = 1269 N' = 1269 n (%)	Placebo N = 830 N' = 830 n (%)
Nasopharyngitis	311 (24.5)	219 (26.4)
Headache	296 (23.3)	179 (21.6)
Upper respiratory tract infection	191 (15.1)	159 (19.2)
Nausea	146 (11.5)	92 (11.1)
Diarrhoea	134 (10.6)	77 (9.3)
Influenza	118 (9.3)	65 (7.8)
Fatigue	117 (9.2)	73 (8.8)
Cough	116 (9.1)	87 (10.5)
Urinary tract infection	108 (8.5)	102 (12.3)
Back pain	104 (8.2)	71 (8.6)
Alanine aminotransferase increased	100 (7.9)	23 (2.8)
Dizziness	97 (7.6)	66 (8.0)
Pain in extremity	96 (7.6)	57 (6.9)
Sinusitis	95 (7.5)	64 (7.7)
Depression	85 (6.7)	62 (7.5)
Bronchitis	85 (6.7)	35 (4.2)
Melanocytic naevus	84 (6.6)	62 (7.5)
Hypertension	79 (6.2)	28 (3.4)
Oropharyngeal pain	75 (5.9)	62 (7.5)
Insomnia	75 (5.9)	49 (5.9)
Dyspnoea	74 (5.8)	53 (6.4)
Arthralgia	73 (5.8)	72 (8.7)
Vomiting	44 (3.5)	46 (5.5)
Rash	43 (3.4)	46 (5.5)

Table 2-2 **Most commonly-occurring adverse events (at least 5.0 percent in either treatment group by preferred term), by initial/randomized treatment, Group D analysis, (SAF-proposed and SAF-current SmPC)**

	SAF-proposed SmPC		SAF-current SmPC	
Preferred term	**FTY720 0.5 mg N = 615 N'=615 n (%)**	**Placebo N=358 N'=358 n (%)**	**FTY720 0.5 mg N=605, N'=605 n (%)**	**Placebo N=350, N'=350 n (%)**
Nasopharyngitis	145 (23.6)	91 (25.4)	141 (23.3)	88 (25.1)
Headache	146 (23.7)	82 (22.9)	141 (23.3)	78 (22.3)
Upper respiratory tract infection	92 (15.0)	74 (20.7)	90 (14.9)	71 (20.3)
Nausea	75 (12.2)	45 (12.6)	70 (11.6)	42 (12.0)
Diarrhoea	66 (10.7)	36 (10.1)	65 (10.7)	35 (10.0)
Cough	63 (10.2)	33 (9.2)	62 (10.2)	31 (8.9)
Fatigue	63 (10.2)	32 (8.9)	62 (10.2)	30 (8.6)
Urinary tract infection	56 (9.1)	49 (13.7)	53 (8.8)	48 (13.7)
Back pain	52 (8.5)	27 (7.5)	52 (8.6)	26 (7.4)
Influenza	52 (8.5)	29 (8.1)	52 (8.6)	28 (8.0)
Dizziness	53 (8.6)	33 (9.2)	50 (8.3)	33 (9.4)
Pain in extremity	52 (8.5)	28 (7.8)	51 (8.4)	28 (8.0)
Sinusitis	50 (8.1)	27 (7.5)	48 (7.9)	27 (7.7)
Depression	47 (7.6)	28 (7.8)	46 (7.6)	28 (8.0)
Melanocytic naevus	41 (6.7)	30 (8.4)	40 (6.6)	30 (8.6)
Insomnia	39 (6.3)	26 (7.3)	39 (6.4)	26 (7.4)
Arthralgia	39 (6.3)	32 (8.9)	38 (6.3)	32 (9.1)
Bronchitis	41 (6.7)	15 (4.2)	38 (6.3)	15 (4.3)
Oropharyngeal pain	36 (5.9)	24 (6.7)	35 (5.8)	22 (6.3)
Hypertension	35 (5.7)	12 (3.4)	35 (5.8)	11 (3.1)
Alanine aminotransferase increased	35 (5.7)	8 (2.2)	35 (5.8)	8 (2.3)
Pharyngitis	34 (5.5)	11 (3.1)	34 (5.6)	11 (3.1)
Dyspnoea	32 (5.2)	24 (6.7)	31 (5.1)	23 (6.6)
Paraesthesia	31 (5.0)	13 (3.6)	30 (5.0)	13 (3.7)
Rash	27 (4.4)	23 (6.4)	27 (4.5)	23 (6.6)
Vomiting	21 (3.4)	23 (6.4)	21 (3.5)	22 (6.3)
Abdominal pain	22 (3.6)	19 (5.3)	21 (3.5)	19 (5.4)
Cystitis	19 (3.1)	18 (5.0)	17 (2.8)	18 (5.1)
Muscle spasms	17 (2.8)	18 (5.0)	17 (2.8)	17 (4.9)

For patients in the fingolimod 0.5 mg group, based on small numbers, only the incidence of the event "erythema" in the SAF-proposed SmPC subpopulation appeared to be twice the incidence in the SAF-current SmPC subpopulation: 0.5% (n=3) versus 0.2% (n=1) respectively.

The most common AEs (≥5% incidence) observed in the SAF were consistent with the known safety profile of fingolimod. In addition the incidences of the most common AEs did not show any relevant differences (of ≥1%) between the subpopulations. This is expected given the substantial patient overlap between the SmPC subpopulations.

- **Adverse events in imaging/clinical subgroups**

Pooled studies D2301+D2309

In the fingolimod 0.5 mg treatment group, some numeric differences in incidences were observed between the 2 subgroups of interest. However, there was no clear association between higher incidences and one particular subgroup, and it is concluded by the MAH that these variations are due to small sample sizes and random variation.

Study D2302/D2302E1

Some differences in types of AEs and incidences were observed between the 2 subgroups of interest. However, based on the small sample sizes, it is expected that variations were due to random variation according to the MAH.

2.4.3.2. Adverse events of special interest

The safety profile of fingolimod was also assessed based on the following AE risk terms listed as "important identified risks" or "important potential risks" in the current RMP [EU RMP version 8.1]:

- Bradyarrhythmia
- Hypertension
- Liver transaminase elevation
- Macular edema
- Infections
- Leucopenia and lymphopenia
- Reproductive toxicity
- Bronchoconstriction
- Hypersensitivity
- Skin cancer
- Other malignant neoplasms
- Thromboembolic events
- QT interval prolongation
- Convulsions
- Herpes zoster / varicella zoster virus (VZV)
- Herpes viral infections other than VZV
- Pulmonary edema
- Decreased renal function

Bradyarrhythmia

For Level 1 term 'bradyarrhythmia', the IR in the fingolimod 0.5 mg group in the core studies were similar for both the proposed-SmPC and current-SmPC subpopulations. In both SmPC subpopulations the IRs of bradyarrhythmia were marginally higher for the fingolimod 0.5 mg as compared to the placebo groups (11.4 (n=86) versus 10.6 (n=52) (IRR of 1.08) in the proposed-SmPC subpopulation; and 11.0 (n=82) versus 11.0 (n=52) (IRR of 1.01) in the current-SmPC subpopulation.

In the core studies, IRs and IRRs for Level 1 terms were comparable across the 2 SmPC subpopulations.

In the overall SAF, patients treated with fingolimod 0.5 mg in core studies had a higher IR of bradyarrhythmia than placebo patients: 10.4 (n=167) versus 9.4 (n=113), respectively, resulting in an IRR of 1.10 (SAF, Group D analysis, Level 1 term). This IR is dominated by occurrence after fingolimod treatment initiation. Thus, the bradyarrhythmia IR in the fingolimod 0.5 mg group decreased with longer exposure, from 10.4 (n=167) to 4.4 (n=282) (SAF, Group D versus Group F analysis).

No meaningful differences in IRs were observed between the SmPC subpopulations over longer exposure durations (Group D versus Group F analysis).

Hypertension

For the Level 1 term 'hypertension', and its Level 2 terms, the IRs in the fingolimod 0.5 mg group in the core studies were comparable for both the proposed-SmPC and current-SmPC subpopulations (5.0 (n=41) and 5.1 (n=41), respectively). The IRs with fingolimod 0.5 mg were higher than with placebo: 5.0 (n=41) versus 2.4 (n=13) in the SAF-proposed SmPC and 5.1 (n=41) versus 2.3 (n=12) in the SAF-current SmPC subpopulation. The apparently lower IRR versus placebo in the SAF-proposed SmPC subpopulation was due to a difference in the number of events in the placebo group; the number of Level 1 events in the fingolimod 0.5 mg group was the same in both SmPC subpopulations.

In the overall SAF, patients treated with fingolimod 0.5 mg in the core studies had a higher IR of hypertension than placebo patients: 5.4 (n=94) versus 2.8 (n=36), respectively, (IRR of 1.96) (SAF, Group D analysis, Level 1 term).

For fingolimod 0.5 mg, the IR decreased with longer exposure (from 5.4 (n=94) to 3.4 (n=231), IRR 0.63) (SAF, Group D versus Group F analysis).

No meaningful differences were observed between the SmPC groups over longer exposure durations (Group D versus Group F analysis).

Liver transaminase elevation

For the Level 1 term 'liver transaminase elevation', the IRs of fingolimod 0.5 mg in the core studies were comparable for both the proposed-SmPC and current-SmPC subpopulations (10.9 (n=86) versus 11.0 (n=85)). The IRRs in fingolimod versus placebo in the core studies were comparable in the SAF-proposed subpopulation and the SAF-current SmPC subpopulation: 2.77 versus 2.72, respectively. This was also the case for the Level 2 terms (Group D analysis).

In the overall SAF, patients treated with fingolimod 0.5 mg in the core studies had a higher IR of liver transaminase elevation than placebo patients: 12.8 (n=211) versus 3.8 (n=50) (IRR of 3.36) (SAF, Group D analysis, Level 1 term).

For fingolimod 0.5 mg the IR decreased with long term exposure, from 12.8 (n=211) to 5.5 (n=356), IRR 0.43 (SAF, Group D versus Group F analysis). These results are in line with what is discussed in [EU RMP version 8.1].

No meaningful differences were observed between the SmPC subpopulations over longer exposure durations (Group D versus Group F analysis).

Macular edema

Patients in the MS program underwent mandatory special assessments that included frequent examinations by an ophthalmologist including eye history, visual acuity, and dilated ophthalmoscopy, optical coherence tomography at Screening and end-of-treatment and at any time in case of suspicion of macular edema. Medical records of all potential macular edema cases were reviewed by the DSMB ophthalmologist, a retinal specialist. In the extension studies, ophthalmological monitoring was not as extensive.

For the term Macular edema, the IR of Level 1 and 2 terms in the fingolimod 0.5 mg group in the core studies were identical in both the SAF-proposed SmPC and the SAF-current SmPC subpopulations: 0.2 (n=2) and 0.2 (n=2), respectively. An apparent lower IRR versus placebo in the SAF-proposed SmPC subpopulation (0.43 versus 0.64) was due to a difference in the number of patients in the placebo group in the 2 SmPC subpopulations (n=3 versus n=2).

For the overall SAF, patients treated with fingolimod 0.5 mg in the core studies had a higher IR of macular edema than placebo patients, although the IR were low in both groups: 0.3 (n=6) versus 0.2 (n=3) (IRR

of 1.48) (SAF, Group D analysis, Level 1 term). For the fingolimod 0.5 mg group, the IR showed a slight decrease with longer observation, from 0.3 (n=6) to 0.2 (n=12), IRR 0.48 (SAF, Group D versus Group F analysis).

No meaningful differences were observed between the SmPC subpopulations over longer exposure durations (Group D versus Group F analysis)

Infections

For the Level 1 term 'infections', IR and IRRs versus placebo in the core studies were comparable for the SAF-proposed and SAF-current SmPC subpopulations. This was also the case for the Level 2 terms (Group D analysis).

As part of a previous health authority request related to PSUR, Novartis has been routinely assessing cellulitis infections as a subgroup of infections. For the Level 1 term 'infections (cellulitis)', the IRs and IRRs in fingolimod 0.5 mg versus placebo in the core studies were also comparable for the SAF-proposed and SAF-current SmPC subpopulations (Group D analysis).

In the overall SAF, patients treated with fingolimod 0.5 mg in the core studies had a similar IR of infections compared to placebo patients: 93.2 (n=827) versus 96.6 (n=586) (IRR of 0.96) (SAF, Group D analysis, Level 1 term). For fingolimod 0.5 mg the IR decreased with longer term exposure, from 93.2 (n=827) to 66.9 (n=1368) (IRR of 0.72) (SAF, Group D versus Group F analysis). These results are in line with what is discussed in [EU RMP version 8.1].

No meaningful differences were observed between the SmPC subpopulations over longer exposure durations (Group D versus Group F analysis).

Leukopenia and lymphopenia

For the Level 1 term 'leukopenia and lymphopenia', the IRs for fingolimod 0.5 mg in the core studies were marginally higher in the SAF-proposed subpopulation than in the SAF-current SmPC subpopulation (6.3 (n=51) versus 6.1 (n=49)). The IRR versus placebo in the core studies was also marginally higher in the SAF-proposed subpopulation than in the SAF-current SmPC subpopulation (17.38 versus 16.50). The IRs and IRRs for Level 2 terms were also higher in the SAF-proposed subpopulation than in the SAF-current SmPC subpopulation (Group D analysis).

For the overall SAF, patients treated with fingolimod 0.5 mg in the core studies had a higher IR of leucopenia and lymphopenia than placebo patients: 4.7 (n=82) versus 0.2 (n=3) (IRR 21.02) (SAF, Group D analysis, Level 1 term).

For fingolimod 0.5 mg, the IR increased with exposure, from (n=82) to 6.4 (n=395) (SAF, Group D versus Group F analysis). This is primarily due to the open label nature of the extension studies. In the core studies, investigators were blinded and only laboratory values which were lower than the threshold of 200 cells/mm3 were flagged to the investigator. In the noncontrolled extension studies, the investigators had access to laboratory values and were free to exercise medical judgment.

Leucopenia and lymphopenia are expected pharmacodynamic effects of fingolimod and thus have a higher incidence in the fingolimod group as compared to placebo. These results are in line with what is discussed in [EU RMP version 8.1].

No meaningful differences were observed between the SmPC subpopulations over longer exposure durations (Group D versus Group F analysis).

Bronchoconstriction

For Level 1 term ‘asthma/bronchospasm’, IRs and IRRs for fingolimod 0.5 mg versus placebo in the core studies were comparable for the SAF-proposed SmPC and SAF-current SmPC subpopulations. This was also the case for Level 2 terms (Group D analysis).

In the overall SAF, patients treated with fingolimod 0.5 mg in the core studies had a similar IR of asthma/bronchospasm to placebo: 1.5 (n=27) versus 1.6 (n=21), respectively, (IRR of 0.95) (SAF, Group D analysis, Level 1 term), The IR in the fingolimod 0.5 mg group remained stable, with a tendency to decrease (from 1.5 (n=27) to 1.1 (n=77)) with longer exposure (SAF, Group D versus Group F comparison).

No meaningful differences were observed between the SmPC subpopulations over longer exposure durations (Group D versus Group F analysis).

Hypersensitivity

For the Level 1 term of hypersensitivity there were no apparent differences in IR between patients on fingolimod 0.5 mg and placebo for both the SAF-proposed (10.6 (n=82) versus 13.3 (n=65)) and SAF-current (10.6 (n=80) versus 13.5 (n=64)) subpopulations.

In the overall SAF population, there was no difference in IR and IRR (0.80 for SAF-proposed versus 0.78 for SAF-current). There was no difference in the IRR between the Group D and F analyses for both SmPC subpopulations (10.6 (n=82) versus 5.7 (n=168) for SAF-proposed and 10.6 (n=80) versus 5.5 (n=161) for SAF-current). The results from the Group D versus Group F analysis align with what is observed in [EU RMP version 8.1].

Reproductive toxicity

For the Level 1 risk search term ‘pregnancy and neonatal topics (SMQ) (broad)’ and its associated Level 2 terms, the IRs and IRRs for fingolimod 0.5 mg versus placebo in the core studies were comparable in the SAF-proposed and SAF-current SmPC subpopulations (Group D analysis)

For the overall SAF, the IR of pregnancy and neonatal topics (SMQ) (broad) in the core studies was 1.2 (n=21) in the fingolimod 0.5 mg group and 1.9 (n=25) in the placebo group, (IRR of 0.62) (SAF, Group D analysis, Level 1 grouped terms. For fingolimod 0.5 mg the IR remained stable or decreased (from 1.2 (n=21) to 0.8 (n=61), IRR 0.71) (SAF, Group D versus Group F analysis).

These results are in line with what is discussed in [EU RMP version 8.1].

No meaningful differences were observed between the SmPC subpopulations over longer exposure durations (Group D versus Group F analysis)

Skin cancer

For the Level 1 term 'skin cancer', the IRs in the fingolimod 0.5 mg group in the core studies were similar for both the proposed-SmPC and current-SmPC subpopulations). Inboth subpopulations the IRs were marginally lower for the fingolimod 0.5 mg as compared to the placebo group (3.1 (n=26) versus 3.5 (n=19)and 3.0 (n=25) and 3.6 (n=19), respectively), resulting in an IRR of <1 in both SmPC subpopulations (0.88 and 0.83 respectively).

Overall, the IRs and IRRs for Level 1 and 2 terms were similar in the proposed-SmPC subpopulation and the current-SmPC subpopulations (Group D analysis, Table 2-23), with only the IRR for the Level 2 term Skin premalignant disorders (SMQ) being numerically slightly higher in the proposed-SmPC subpopulation than in the current-SmPC subpopulation (0.74 versus 0.68, respectively).

In the overall SAF however, the IR for fingolimod 0.5 mg was higher as compared with placebo (3.0 (n=54) versus 2.2 (n=29) respectively), resulting in an IRR of 1.38 (SAF, Group D analysis, Level 1 term). This is in line with what is discussed in [EU RMP version 8.1].

No meaningful differences in IRs or IRRs were observed between the SmPC subpopulations over longer exposure durations (Group D versus Group F analysis).

Other malignant neoplasms

For the Level 1 term 'other malignant neoplasms' and its associated Level 2 terms, the IRs and IRRs versus placebo in the core studies were similar in the SAF-proposed and SAF-current SmPC subpopulations (Group D analysis). This was also the case for the Level 1 term 'malignant neoplasms (cervical cancer)' and its Level 2 terms (Group D analysis).

For the overall SAF, patients treated with fingolimod 0.5 mg in the core studies had a similar IR to placebo patients: 1.5 (n=28) versus 1.3 (n=18) (IRR of 1.15) (SAF, Group D analysis, Level 1 term). For fingolimod 0.5 mg, the IR was stable or reduced with longer exposure (from 1.5 (n=28) to 1.1 (n=81), IRR 0.71) (SAF, Group D versus Group F analysis). The IR of other malignant neoplasms (cervical cancer) in the core studies were 0.3 (n=5) for patients treated with fingolimod 0.5 mg versus 0.1 (n=2) in the placebo group, IRR 1.85 (SAF, Group D analysis, Level 1 term. For fingolimod 0.5 mg, the IR was stable or reduced with longer exposure (from 0.3 (n=5) to 0.1 (n=9), IRR 0.44) (SAF, Group D versus Group F analysis).

QT interval prolongation

For the Level 1 term 'Torsade de pointes/QT interval prolongation' the IRs and IRRs for fingolimod 0.5 mg versus placebo in the core studies was similar for the proposed-SmPC and current-SmPC subpopulations. This was also the case for the Level 2 terms (Group D analysis).

In the overall SAF, the IRs for the Level 1 term in the core studies were comparable in the fingolimod 0.5 mg and placebo groups (1.3 (n=23) versus 1.1 (n=15), respectively, IRR 1.13) (SAF, Group D analysis, Level 1 term). The IR in the fingolimod 0.5 mg group decreased with longer exposure: from 1.3 (n=23) to

0.6 (n=48), IRR 0.51 (SAF Group D versus Group F comparison). This reduction is understandable as QTc prolongation was most often observed in the context of the first-dose observation. These results are in line with what is discussed in [EU RMP version 8.1].

No meaningful differences were observed between the SmPC subpopulations over longer exposure durations (Group D versus Group F analysis).

Thrombo-embolic events

For the Level 1 term 'thromboembolic events', the IRs for the fingolimod 0.5 mg in the core studies were comparable for both the proposed-SmPC and current-SmPC subpopulations; the IRRs versus placebo in the core studies were 1.08 and 1.20, respectively.

For the Level 2 term embolic and thromboembolic events (SMQ), the IRR versus placebo was lower in the proposed-SmPC subpopulation than in the current-SmPC subpopulation (0.81 versus 1.07, respectively). The IRRs for the other Level 2 terms were similar for the 2 SmPC subpopulations (Group D analysis).

In the overall SAF, patients treated with fingolimod 0.5 mg in the core studies had a lower IR of thromboembolic events than with placebo: 1.0 (n=18) versus 1.7 (n=22) respectively (IRR of 0.60) (SAF, Group D analysis, Level 1 term).

For fingolimod 0.5 mg, the IR remained stable with a tendency to decrease with longer exposure, from 1.0 (n=18) to 0.8 (n=59), IRR 0.80 (SAF, Group D versus Group F analysis). No meaningful differences were observed between the SmPC subpopulations over longer exposure durations (Group D versus Group F analysis.

For the Level 1 term 'thrombo-embolic events (all stroke)', the IRs in the fingolimod 0.5 mg group in the core studies were similarly low: 0.1 (n=1) in both the proposed-SmPC and current-SmPC subpopulations; IRR versus placebo was not calculated since no events were reported in the placebo group . This was also the case for the Level 2 terms. In the overall SAF, the IR for fingolimod 0.5 mg and placebo were both 0.1 (n=1 and n=2, respectively), with an IRR of 0.37 (SAF, Group D analysis, Level 1 term). For fingolimod 0.5 mg, the IR remained stable with longer exposure (0.1 (n=1) versus 0.1 (n=9), IRR 2.18 (SAF, Group D versus Group F analysis). No meaningful differences were observed between the SmPC subpopulations over longer exposure durations (Group D versus Group F analysis).

For the Level 1 term 'thromboembolic events (myocardial infarction)', the IRs and IRRs in the fingolimod 0.5 mg group in the core studies versus placebo were comparable in the proposed-SmPC and current-SmPC subpopulations. The IRs for Level 1 and 2 terms for myocardial infarction were comparable for the 2 SmPC subpopulations (Group D analysis). For the overall SAF, the IRs in the core studies were low: 0.4 (n=8) in the fingolimod 0.5 mg group versus 0.8 (n=11) in the placebo group, with an IRR of 0.54 (SAF, Group D analysis, Level 1 term).For fingolimod 0.5 mg, the IR remained stable with longer exposure (0.4 (n=8) versus 0.2 (n=16), IRR 0.48 (SAF, Group D versus Group F analysis).

No meaningful differences were observed between the SmPC subpopulations over longer exposure durations (Group D versus Group F analysis)

Convulsions

For Level 1 term 'convulsions (SMQ) (Broad)', the IRs with fingolimod 0.5 mg in the core studies were comparable in both the proposed-SmPC and current-SmPC subpopulation (0.6 (n=5) versus 0.5 (n=4)). In both SmPC subpopulations the IRs of convulsions in the core studies were higher for the fingolimod 0.5 mg group compared to the placebo group, but the actual incidences were low: 0.6 (n=5) versus 0.2 (n=1), (IRR of 3.24) in the proposed-SmPC subpopulation; and 0.5 (n=4) versus 0.2 (n=1), (IRR of 2.57) in the current-SmPC subpopulation. This difference in IRR is attributed to a difference of one additional patient with convulsions in the proposed SmPC subpopulation.

In the core studies, IRs and IRRs for Level 2 terms were comparable across the 2 SmPC subpopulations, except the IR for Level 2 term convulsions (PT) which was higher in the proposed-SmPC subpopulation versus the current-SmPC subpopulation (0.4 versus 0.2). This is attributed to a difference of just 1 patient with PT of convulsions between the groups.

In the overall SAF, the IRs of Level 1 term convulsions in the core studies were low in both groups, but higher in the fingolimod 0.5 mg group than in placebo patients: 0.4 versus 0.1 respectively (IRR of 2.59) (SAF, Group D analysis, Level 1 term). For fingolimod 0.5 mg, the IR did not show any meaningful change with longer exposure (from 0.4 to 0.3, IRR of 0.80) (SAF, Group D versus Group F analysis). These results are in line with what is discussed in [EU RMP version 8.1].

No meaningful differences in IRs were observed between the SmPC subpopulations over longer exposure durations (Group D versus Group F analysis.

Herpes zoster

For the Level 1 term 'herpes zoster infections', the IRs and IRRs versus placebo in the core studies were comparable for the SAF-proposed and SAF-current SmPC subpopulations. This was also the case for the Level 2 terms (Group D analysis). In the overall SAF, patients treated with fingolimod 0.5 mg in the core studies had a higher IR of herpes zoster infections than placebo patients: (n=19) versus 0.5 (n=7) (IRR 2.01) (SAF, Group D analysis, Level 1 term). For fingolimod 0.5 mg, the IR remained stable with longer exposure (1.1 (n=19) versus 1.1 (n=78), IRR 1.02 (SAF, Group D versus Group F analysis. No meaningful

differences were observed between the SmPC subpopulations over longer exposure durations (Group D versus Group F analysis)

For the Level 1 term 'herpes zoster without dissemination', the IRs and IRR versus placebo in the core studies were comparable for the SAF-proposed and SAF-current SmPC subpopulations. This was also the case for the Level 2 terms (Group D analysis,). In the overall SAF, patients treated with fingolimod 0.5 mg in core studies had a higher IR of Herpes zoster without dissemination than placebo patients: (n=19) versus 0.5 (n=7), respectively, resulting in an IRR of 2.01 (SAF, Group D analysis, Level 1 term). For fingolimod 0.5 mg, the IR remained stable with longer exposure (1.1 (n=19) versus 1.1 (n=77), incidence rate ratio 1.00 (SAF, Group D versus Group F analysis. For the Level 1 term 'herpes zoster disseminated', 2 cases were reported in the fingolimod 1.25 mg group in the core studies (SAF, Group D analysis, Level 1 term) and 1 case was reported in the fingolimod 0.5 mg group in the extension studies (SAF, Group D versus Group F analysis).

The results for herpes zoster infections are in line with what is discussed in [EU RMP version 8.1].

Herpes viral infections other than VZV

For the Level 1 term 'herpes viral infections other than VZV', the IRs and IRRs fingolimod 0.5 mg versus placebo in the core studies were comparable for the SAF-proposed and SAF-current SmPC subpopulations. This was also the case for the Level 2 terms (Group D Analysis. For the SAF, patients treated with fingolimod 0.5 mg in the core studies did not show any meaningful difference in IR of the Level 1 term 'herpes viral infections other than VZV' when compared to placebo patients: 3.3 (n=59) versus 3.7 (n=49), IRR 0.89. This was also the case for the Level 2 terms (SAF, Group D analysis);

For patients treated with fingolimod 0.5 mg in the SAF Group D versus Group F analysis, the IR tended to decrease with longer exposure (from 3.3 (n=59) to 2.6 (n=177), IRR 0.77. The results for the SAF are in line with what is discussed in [EU RMP version 8.1].

No meaningful differences in IRs were observed between the SmPC subpopulations over longer exposure durations (Group D versus Group F analysis).

Decreased renal function

Decreased renal function had been added as an important potential risk to the RMP based on renal transplant studies with fingolimod. The MAH considers that this potential risk has not been confirmed in MS patients and that there is no increased risk of renal dysfunction in patients treated with fingolimod. Most cases of "decreased renal function" in MS patients are nonserious and asymptomatic changes in laboratory parameters. Symptomatic cases are confounded by pre-existing comorbidities and/or acute illnesses.

Given the lack of clinical relevance of the reported cases and no change in the characterization of this risk over time, the MAH proposed to remove decreased renal function as an important potential risk from the RMP and continue to monitor with routine pharmacovigilance activities. However, decreased renal function was still included in the search criteria at the time of data cutoff for this submission, and is presented here for completeness.

For Level 1 term 'decreased renal function', the IRs in the fingolimod 0.5 mg group in the core studies were 0.4 (n=3) in both the proposed-SmPC and current-SmPC subpopulations. In both SmPC subpopulations the IR of decreased renal function in the core studies was marginally higher for the fingolimod 0.5 mg as compared to the placebo groups (0.4 (n=3) versus 0.2 (n=1), (IRR 1.94) in the proposed-SmPC subpopulation; and 0.4 (n=3) versus 0.2 (n=1), (IRR 1.92) in the current-SmPC subpopulation.

In the core studies, IRs and IRRs for Level 2 terms were similar for the proposed-SmPC and current-SmPC subpopulations.

For the overall SAF, patients treated with fingolimod 0.5 mg in the core studies had a higher IR of decreased renal function than placebo patients, although the overall rates were low in both groups: 0.3 (n=6) versus 0.1 (n=1) (IRR 4.44), (SAF, Group D analysis, Level 1 term.For fingolimod 0.5 mg, the incidence rate was stable or lower with extended exposure (from 0.3 (n=6) to 0.2 (n=17), (IRR 0.69) (SAF, Group D versus Group F analysis) .

No meaningful differences in IRs were observed between the SmPC subpopulations over longer exposure durations (Group D versus Group F

Pulmonary edema

For the Level 1 term 'pulmonary edema' and its associated Level 2 terms, the IRs and IRRs for fingolimod 0.5 mg group in the core studies, versus placebo, were similar in the SAF-proposed and SAF-current SmPC subpopulations (Group D analysis).

In the overall SAF, patients treated with fingolimod 0.5 mg in the core studies had a similar IR of pulmonary edema to placebo patients, and the overall rates were low in both groups: 0.2

(n=3) versus 0.1 (n=2) respectively, IRR 1.11 (SAF, Group D analysis, Level 1 grouped terms). For fingolimod 0.5 mg, the IR remained stable with longer exposure (0.2 (n=3) versus 0.1 (n=4), IRR 0.32) (SAF, Group D versus Group F analysis). These results are in line with what is discussed in [EU RMP version 8.1].

No meaningful differences were observed between the SmPC subpopulations over longer exposure durations (Group D versus Group F analysis).

2.4.4. Serious adverse events and deaths

- **Deaths in completed studies**

Across the studies, SAEs (including deaths) were required to be reported from the time the patient provided informed consent until up to 3 months after the patient stopped participating in the study. Deaths which occurred after this period were reported to Novartis at the discretion of the investigator. SAEs, including deaths that were reported to Novartis were recorded in the Drug Safety database (ARGUS) irrespective of protocol requirements.

- **Deaths in ongoing studies**

Study D2399 is the only ongoing study in this submission. Deaths for this study were reported in [PSUR 7] and the annual interim analysis report for this study.

- **Other serious adverse events**

The overall profile of SAEs in the pooled studies was consistent with that previously observed.

Overall, 10.4% of patients treated with fingolimod 0.5 mg and 12.5% of placebo patients experienced SAEs during the core studies D1201, D2301, D2302 and D2309 (SAF, Group D analysis).

In the core studies, the incidence of individual PTs in the fingolimod 0.5 mg group showed no meaningful differences between the current- and proposed-SmPC subpopulations: all PTs were below 1%, with the exception of basal cell carcinoma, which had an incidence of 1.2% in the fingolimod 0.5 mg group in the current-SmPC subpopulation and 1.1% in the proposed-SmPC subpopulation (Group D analysis.

Based on exposure adjusted incidence rates, the SAE profile for the fingolimod 0.5 mg group did not show any meaningful differences with longer exposure: the incidence rates for the majority of SAE PTs

remained stable or decreased. As would be expected, some SAEs were reported in the long-term extension studies which had not been observed previously in the core studies. However, in each case, the incidence rate change was from 0 to 0.1% (SAF, Group D versus Group F analysis). This was also the case for both the current and proposed SmPC subpopulations, and no meaningful differences were observed between the 2 subpopulations (Group D versus Group F analysis)

Serious adverse events based on identified and potential risks are presented for core and long-term studies. Group D and Group F comparisons are presented for identified and potential risks that could be impacted by duration of treatment or time. Since the composition of the SAF-proposed SmPC and SAF-current SmPC populations were similar no major differences in SAEs were expected.

Bradyarrhythmia

Patients treated with fingolimod 0.5 mg in core studies had a higher incidence rate of bradyarrhythmia SAEs than patients treated with placebo in both the SAF-proposed SmPC and SAF-current SmPC. The IRs and IRR for Level 1 and 2 terms were identical for the SAF-proposed SmPC and SAF-current SmPC.

In the overall SAF-population, the IR was higher for patients taking fingolimod compared to placebo. No meaningful differences in IRs or IRRs were observed between the SmPC groups in the comparison of core and long-term studies.

Bronchoconstriction

Patients treated with fingolimod 0.5 mg in core studies had a similarly low incidence rate of bronchoconstriction (asthma/bronchospasm) in both the SAF-proposed SmPC and SAF-current SmPC subpopulations (IR=0.1 (n=1) versus IR=0.1 (n=0) respectively; IRR versus placebo was not calculated since none of the patients in the placebo group had SAEs). The IRs and IRR for Level 1 and 2 terms were identical for the SAF-proposed SmPC and SAF-current SmPC.

In the overall SAF-population, the IR was similar for patients taking fingolimod 0.5 mg or placebo (IR=0.1 (n=1) versus IR=0.1 (n=1), respectively; IRR=0.74). No meaningful differences in IRs or IRRs were observed in the core and long-term studies for the overall SAF (IR=0.1 (n=1) versus IR=0.0

(n=1), IRR=0.24), or in each SmPC subpopulation).

Convulsions

The IR of SAEs for the risk search term of convulsions was higher in patients treated with fingolimod 0.5 mg compared to placebo in the SAF-proposed SmPC population (0.4 (n=3) versus 0.2 (n=1), IRR=1.94) but not in the SAF-current SmPC population (0.2 (n=2) versus 0.2 (n=1), IRR=1.28).

In the overall SAF-population, the IR was higher for patients taking fingolimod 0.5 mg compared to placebo (IR=0.3 (n=5) versus IR=0.1 (n=2), respectively; IRR=1.85).

The IR of convulsions was marginally lower in the long-term studies compared to core studies in the proposed SmPC subpopulation (IR=0.2 (n=7) versus (IR=0.4 (n=3), respectively); however, there was no difference between the long term and core studies in the current SmPC subpopulation (IR=0.2 (n=6) versus IR=0.2 (n=2).

There was no meaningful difference between the IRR of SAF-proposed and SAF-current SmPC subpopulations (IRR=0.56 versus 0.72).

Herpes zoster infections

The IR for herpes zoster infections similarly low in the SAF-proposed and SAF-current populations in Group D (IR=0.1 (n=1) in each SmPC subpopulation); IRR was not calculated since none of the patients in the placebo group had SAEs). For the overall SAF population, the IR was higher for patients on

fingolimod 0.5 mg compared to patients on placebo (IR=0.1 (n=2) versus IR=0.0 (n=0), respectively; IRR was not calculated since none of the patients in the placebo group had SAEs)). For the Group D and Group F comparison, there was no change in the IR and IRRs of herpes zoster infection in the long-term studies compared to core studies in the both SAF-proposed and SAF-current populations (IR=0.1 (n=4) versus IR=0.1 (n=1); IRR=0.96 in each SmPC subpopulation).

Herpes viral infections other than VZV

The IR of SAEs of herpes zoster infections other than VZV was similarly low for both SmPC subpopulations (IR=0.1 (n=1) versus IR=0.0 (n=0) in placebo; IRR was not calculated since none of the patients in the placebo group had SAEs). For the overall SAF, patients on fingolimod 0.5 mg had a higher IR than patients on placebo (IR=0.1 (n=1) versus IR=0.0 (n=0), respectively; IRR was not calculated since none of the patients in the placebo group had SAEs).

No meaningful differences were observed in the IR or IRRs in the Group D and Group F analysis in the both SAF-proposed and SAF-current SmPC populations (IR=0.1 (n=1) versus IR=0.1 (n=2); IRR=0.48 in each SmPC subpopulation).

Infections

Serious adverse events under the risk search term of infections were of similarly low incidence in the SAF-proposed and SAF-current SmPC populations (IR=1.1 (n=9) versus IR=1.1 (n=6) in placebo; IRR=0.97 versus 0.96, respectively). There was no obvious difference in the profile of serious infections between the 2 subpopulations. For the overall SAF, patients on fingolimod 0.5 mg had a marginally higher IR than patients on placebo (IR=1.1 (n=19) versus IR=0.9 (n=12), respectively; IRR=1.17). No meaningful differences in SAEs of infection were observed in the Group D versus Group F comparison between the SAF-proposed SmPC and the SAF-current SmPC subpopulations.

No serious cases of infections (cellulitis) were reported in Group D for both fingolimod 0.5 mg or placebo in both the SmPC subpopulations and overall SAF. No meaningful differences were observed in SAEs for infections (cellulitis) for groups D and F comparison (IR=0.0 (n=0) versus IR=0.0 (n=1), respectively in each SmPC subpopulation).

Hypertension

There were no SAEs of hypertension reported for the SAF-proposed SmPC or SAF-current SmPC in the core studies. This was also the case for the overall SAF in the fingolimod 0.5 mg group. For the Group D and F comparison, 2 patients in Group F experienced SAEs of hypertension but the IR remained similarly low in both the SAF-proposed and SAF-current population (IR=0.0 (n=1) in each SmPC subpopulation).

Hypersensitivity

The IR of hypersensitivity SAEs in patients treated with fingolimod 0.5 mg was marginally lower compared to placebo and was the same for both the subpopulations (IR=0.2 (n=2) versus IR=0.4 (n=2), respectively in each SmPC subpopulation; IRR=0.65 and 0.64 for SAF proposed and SAF-current SmPC subpopulations, respectively). In the overall SAF-population, the IR was the similar for patients taking fingolimod 0.5 mg or placebo (IR=0.1 (n=2) versus IR=0.2 (n=3), respectively; IRR=0.49).

For the Group D and F comparison there were no meaningful differences in IR or IRRs (IR=0.2 (n=2) versus IR=0.1 (n=4), IRR=0.48, in each SmPC subpopulation.

Leukopenia and Lymphopenia

Serious adverse events under the risk search term of leukopenia and lymphopenia were similarly low in both SmPC subpopulations (IR=0.1 (n=1) versus IR=0.0 (n=0) in each SmPC subpopulation; IRR was not calculated since none of the patients in the placebo group had SAEs). This was the case for overall

SAF-population (IR=0.1 (n=2) versus IR=0.0 (n=0), respectively). No meaningful differences in IRs or IRRs were observed between Group D and Group F in both SmPC subpopulations (IR=0.1 (n=1) versus IR=0.1 (n=5), IRR=1.20, in each SmPC subpopulation).

Liver transaminase elevation

Serious adverse events under the risk search term of liver transaminase elevation were of similarly low incidence in both SmPC subpopulations (IR=0.1 (n=1) in the fingolimod 0.5 mg group versus IR=0.0 (n=0) in the placebo group in each SmPC subpopulation; IRR was not calculated since none of the patients in the placebo group had SAEs). In the overall SAF-population, there were no meaningful differences in IR between fingolimod 0.5 mg and placebo (IR=0.1 (n=2) versus IR=0.1 (n=1), respectively; IRR=1.48). No meaningful differences in IRs or IRRs were observed between the Group D and Group F in both SmPC subpopulations (IR=0.1 (n=1) versus IR=0.1 (n=3), IRR=0.72, in each SmPC subpopulation.

Macular edema

Serious adverse events under the risk search term of macular edema were similar and low in both SmPC subpopulations for fingolimod 0.5 mg and placebo (IR=0.1 (n=1) versus IR=0.2 (n=1), respectively; IRR=0.65, SAF-proposed and 0.64, SAF-current). In the overall SAF, patients on fingolimod 0.5 mg had a similar IR to patients on placebo (IR=0.1 (n=2) versus IR=0.1 (n=1); IRR=1.48). No meaningful differences in IRs and IRRs were observed between Group D and Group F and between both the SmPC subpopulations (IR=0.1 (n=1) versus IR=0.0 (n=1), IRR=0.24, in each SmPC subpopulation).

Other malignant neoplasms

Serious adverse events under the risk search term of other malignant neoplasms were similar in both SmPC subpopulations with marginally higher IR in the fingolimod 0.5 mg compared to placebo (IR=1.2 (n=10) versus IR=1.6 (n=9), IRR=0.72, SAF-proposed; IR=1.2 (n=10) versus IR=1.7 (n=9), IRR=0.71, SAF-current). However, in the overall SAF population, there was no meaningful difference in the IR between fingolimod 0.5 mg and placebo (IR=1.3 (n=24) versus IR=1.1 (n=15); IRR=1.18).
No meaningful differences in IRs or IRRs were observed between Group D and Group F and between both SmPC populations (IR=1.2 (n=10) versus IR=0.9 (n=32), IRR=0.77, SAF-proposed; IR=1.2 (n=10) versus IR=0.9 (n=31), IRR=0.75, SAF-current).

Other malignant neoplasms (cervical cancer)

Serious adverse events under the risk search term of other malignant neoplasms (cervical cancer) were of similarly low incidence in both SmPC subpopulations in fingolimod 0.5 mg or placebo (IR=0.0 (n=0) versus IR=0.2 (n=1), respectively; IRR=0) (Table 2-50). This was also the case with overall SAF population (IR=0.0 (n=0) versus IR=0.1 (n=1), respectively; IRR=0). There were no serious cases of cervical cancer in the SAF-proposed and SAF-current Group D and Group F comparisons.

Skin cancer

Serious adverse events under the risk search term of skin cancer were of similarly low incidence in both SmPC subpopulations and were similar between fingolimod 0.5 mg and placebo (IR=1.2 (n=10) versus IR=1.1 (n=6), respectively in each SmPC subpopulation;

IRR=1.08 for SAF-proposed and 1.07 for SAF-current). For the overall SAF, patients on fingolimod 0.5 mg had a higher IR than patients on placebo (IR=1.2 (n=21) versus IR=0.5 (n=7), IRR=2.22).

No meaningful differences in IRs and IRRs were observed between Group D and Group F and between both the SmPC populations (IR=1.2 (n=10) versus IR=0.7 (n=24), IRR=0.58, SAF proposed; IR=1.2 (n=10) versus IR=0.7 (n=23), IRR=0.55, SAF-current).

Pulmonary edema

Serious adverse events under the risk search term of pulmonary edema were similar and of low incidence in both SmPC subpopulations for fingolimod 0.5 mg or placebo (IR=0.1 (n=1) versus IR=0.0 (n=0); IRR was not calculated since none of the patients in the placebo group had SAEs). This was also the case for overall SAF population. No meaningful differences in IRs and IRRs were observed between Group D and Group F and between both the SmPC subpopulations (IR=0.1

(n=1) versus IR=0.0 (n=1), IRR=0.24, in each SmPC subpopulation).

QT interval prolongation

Serious adverse events under the risk search term of QT interval prolongation were similar and low in both SmPC subpopulations for fingolimod 0.5 mg or placebo (IR=0.1 (n=1) versus IR=0.2 (n=1), respectively; IRR=0.64 in each SmPC subpopulation). In the overall SAF, IRs were similarly low between the fingolimod 0.5 mg and placebo groups (IR=0.3 (n=5) versus IR=0.2 (n=3), IRR=1.23). No meaningful differences in IRs or IRRSs were observed between Group D and Group F and between both SmPC populations (IR=0.1 (n=1) versus IR=0.1 (n=4), IRR=0.96, in each SmPC subpopulation).

Reproductive toxicity

Serious adverse events under the risk search term of pregnancy and neonatal topics (Level 1) were of similar and low incidence in both SmPC subpopulations for fingolimod 0.5 mg or placebo (IR=0.2 (n=2) versus IR=0.4 (n=2), respectively; IRR=0.65 for SAF-proposed and 0.64 for SAF-current) . In the overall SAF, IRs were similarly low in the fingolimod 0.5 mg and placebo groups (IR=0.2 (n=3) versus IR=0.4 (n=6), IRR=0.37). No meaningful differences in IRs or IRRs were observed between Group D and Group F in both SmPC populations (IR=0.2 (n=2) versus IR=0.2 (n=7), IRR=0.84, SAF proposed; IR=0.2 (n=2) versus IR=0.2 (n=6), IRR=0.72, SAF current).

Thrombo-embolic events

Serious adverse events under the risk search term of thrombo-embolic events were of similar and low incidence in both SmPC subpopulations for fingolimod 0.5 mg or placebo (IR=0.3 (n=3) versus IR=0.2 (n=1), IRR=1.94, SAF-proposed; IR=0.4 (n=3) versus IR=0.2 (n=1), IRR=1.92 SAF-current). In the overall SAF population, the IRs were similarly low (IR=0.2 (n=4) versus IR=0.5 (n=7), IRR=0.42.

No meaningful differences in IRs or IRRs were observed between Group D and Group F and between both SmPC populations (IR=0.3 (n=3) versus IR=0.3 (n=12), IRR=0.97, SAF-proposed; IR=0.4 (n=3) versus IR=0.3 (n=12), IRR=0.97, SAF-current).

Similarly, SAEs under the risk search term of thrombo-embolic events (myocardial infarction) were of low incidence both SmPC subpopulations in fingolimod 0.5 mg or placebo (IR=0.2 (n=2) versus IR=0.0 (n=0) in each SmPC subpopulation; IRR was not calculated since none of the patients in the placebo group had SAEs). In the overall SAF population, the IRs were similarly of low incidence IR=0.1 (n=2) versus IR=0.3 (n=4), IRR=0.37). No meaningful differences in IRs were observed between Group D and Group F, and between both SmPC populations (IR=0.2 (n=2) versus IR=0.1 (n=3), IRR=0.36) in each SmPC subpopulation.

Serious adverse events in imaging/clinical subgroups

- Pooled studies D2301/D2309

In the fingolimod 0.5 mg treatment group, some numeric differences in incidences were observed between the 2 subgroups of interest. However, there was no clear association between higher incidences and one particular subgroup, and it is concluded by the MAH that these variations are due to small sample sizes and random variation.

2.4.5. Laboratory findings

Post-hoc analyses of laboratory examinations were not performed for this submission.

However, in accordance with study protocols, all clinically significant laboratory abnormalities were to be reported as AEs by the investigator and are thus included in the current evaluation on this basis.

Post-hoc analyses of ECGs, vital signs, body weight or physical examinations were not performed for this submission. However, in accordance with study protocols, all clinically significant abnormalities in these parameters were to be reported as AEs by the investigator and are thus included in the current evaluation on this basis.

No new data have been generated in support of this extension of indication with regards to laboratory findings.

2.4.6. Safety in special populations

- Intrinsic factors

Results of analyses based on intrinsic factors for the original application were provided in the original application

- Extrinsic factors

Results of analyses based on extrinsic factors for the original application were provided in the original application

- Drug interactions

Drug interactions were discussed in the original application

- Use in pregnancy and lactation

Fertility, pregnancy and lactation were discussed in the original application

- Overdose

No new information about overdose has been generated in support of this application.

Overdose was discussed in the original application.

- Drug abuse

No new information about abuse/dependence potential has been generated in support of this application. No studies with fingolimod have been conducted to investigate drug abuse.

- Withdrawal and rebound

Withdrawal and rebound were discussed in the original application

No new information has been generated in support of this extension of indication with regards to safety in special groups and situations.

2.4.7. Safety related to drug-drug interactions and other interactions

N/A

2.4.8. Discontinuation due to adverse events

Adverse events leading to discontinuation in the individual studies have been described previously for Studies D1201, D2301, D2302, D2309, D1201E1, D2301E1, D2302E1, D2309E1 and D2399E1 were not part of the analyses for this submission.

No new information has been generated in support of this extension of indication with regards to discontinuation due to adverse events.

2.4.9. Post-marketing experience

Relevant publications containing important new safety information, a summary of significant findings from ongoing clinical studies, and estimated patient exposure and use patterns were provided in Global PSUR 7 and PSUR 8 (EUPSUR7).

2.4.10. Discussion on clinical safety

The main results for this submission were adverse events analysis based on safety data from the completed randomized controlled studies within the fingolimod phase 2 and 3 clinical development programs which explored the fingolimod 0.5 mg dose for at least 6 months. Only study D1201 has not been previously submitted for analysis neither in the original MAA nor in the subsequent applications. This study provides limited safety information as duration of exposure was 6 months and this study involved only 73 patients in the safety analysis set.

The analysis sets were of sufficient size for comparison of safety in the SAF-proposed SmPC (n=725), and FAS-current SmPC (n=710) subpopulations. However the FAS-current SmPC population accounted for more than 95% of the SAF-proposed SmPC population in the pooled studies of interest, with a difference in size between the new proposed SmPC population and the current one around 2% only, and an overlap between both groups. Therefore analyses by subpopulations subgroups provide a more relevant comparison as these subgroups were disjunctive without patients in common. However interpretation of results in this case was somewhat limited by the small sample sizes of the different subgroups.

Safety and tolerability were assessed based on AE/SAE results only. Treatment emergent adverse events (TEAEs) and adverse drug reactions (ADRs) were not presented through this application. This precludes an accurate analysis of causal relationship between AEs and study treatments, notably with fingolimod.

Some minor differences between the SmPC subpopulations were observed, with regards to convulsions, hypertension, leucopenia and lymphopenia, macular edema, skin cancer, thromboembolic events, however no firm conclusion can be drawn from these results due to the small size groups.

It should be considered that the strategy to extend the use of Gilenya to a broader population of relapsing/remitting MS patients, by relaxing the conditions of eligibility to the treatment, could potentially increase the risk to observe ADRs, notably the important risks previously reported with fingolimod.

Overall, the provided safety data confirmed that the safety profile remained consistent and comparable for patients with active MS selected according to the conditions of the proposed label and patients selected according to the current SmPC. The safety profile of fingolimod is unchanged for the targeted patient population and could be manageable as outlined in the current Risk Management Plan.

2.4.11. Conclusions on clinical safety

Post-hoc analyses have shown that the safety profile of Gilenya remains consistent in the two populations (current restricted indication and proposed new indication). Overall, no relevant differences were observed between the SmPC subpopulations, and the safety profile was consistent with the known safety profile of fingolimod.

2.4.12. PSUR cycle

The PSUR cycle remains unchanged.

The PSUR cycle for the medicinal product should follow a yearly cycle until otherwise agreed by the CHMP.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.5. Risk management plan

The CHMP considered that the current RMP (version 8.1) is considered equally applicable to the revised target population, and that no specific updates were considered necessary.

2.6. Update of the Product information

The MAH proposed to update section 4.1 of the SmPC 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 ~~high~~ active disease defined by clinical or imaging features ~~activity~~ 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).*

~~These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of at least one disease modifying therapy.~~

~~Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadoliniumenhancing lesion. A "nonresponder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.~~

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.*

No update in other sections of SmPC was proposed as well as no change in other annexes.

3. Benefit-Risk Balance

Benefits

Beneficial effects

As demonstrated in the phase III studies for the initial MAA, a relative reduction of the frequency by relapses by approximately 50 % versus placebo was observed in patients with RRMS in one 2-year and one 1-year study. Fingolimod also demonstrated a reduction in risk of disability progression relative to placebo over 2 years. In a comparative 1-year study against IFN-beta-1a, no statistically significant difference was seen for risk of disability progression between fingolimod and IFN-beta-1a.

The post-hoc analyses of data from previously submitted studies and a newly submitted study (D1201) have been performed and the obtained results (see Section 2.3.2.3.) have confirmed the conclusions on the benefits of Gilenya.

In the pooled data analysis submitted by the applicant, for the new conditions proposed for the broader indication a population size difference of only 2% was identified from the original group. The MAH has compared the results on ARR between two subgroups corresponding respectively to the current restricted indication and to the proposed broader indication and extracted from the overall population of the 4 studies mentioned. The performed analyses demonstrated the beneficial effects of Gilenya on ARR in the

constructed subgroups of patients defined according to the proposed broader indication. These benefits were expressed as a significant percent reduction in ARR in the fingolimod groups compared to placebo which was consistent between the sub-groups within the individual studies.

Uncertainty in the knowledge about the beneficial effects

The subgroups of patients with differing disease/imaging activity during the six months preceding treatment initiation in the relevant trials were small creating consequent uncertainty about the precision of estimates. The absolute risk of relapse within the relevant subgroups included in the proposed formal indication has not been defined nor has the absolute benefit of fingolimod within this full scope. Within the available data, it is notable that the effect on ARR in the total population was primarily driven by patients who had MRI activity, whereas those with only clinical relapses had less reduction of ARR.

From the presented literature no consensus could be distilled on the definition of treatment failure to first line therapies and on the definition of highly active disease as well as the role of MRI imaging in these. An increase in T2 lesion load in patients receiving a DMT could indeed represent a suboptimal response to DMT as it has been shown for interferon-beta, although no prospective data exist to validate a MRI measure of activity as a reliable predictor of a poor response in general. Thus the appropriateness of any changes in therapy, based only on MRI imaging without supportive clinical symptoms has not yet been established at the level of a therapeutic guideline or consensus and remains a subject of discussion.

The Committee recognized that clinical and MRI measures can be used in the detection of disease activity in RRMS patients receiving DMTs and that by combining these measures, clinicians might be able to more accurately predict which patients will need a switch or escalation of treatment. Their use in the process of evaluation of MS patients is supported by the increased use of a new composite outcome measure for the ultimate goal of complete remission that is the concept of “no evidence of disease activity”(NEDA - integrating relapse rate and disability progression on the clinical side and new or enlarging T2- or contrast enhancing lesions on the MRI side) and the currently validated RIO score (scoring system that consists of a combination of clinical and MRI parameters to predict suboptimal responders) (Rio and al Mult. Scler., 2009;15:848-853 and Sormani and al, Mult. Scler., 2013;19:605-612).

Notwithstanding this, it was also recognized that MRI is capable of detecting the continuous inflammation in MS patients which, even if not clinically manifesting itself as a relapse, is a known feature of the disease. Additionally, the data in literature suggests that MRI imaging correlates with the long-term outcome (Rudick et al, 2006) and that MS patients show higher recruitment of functional brain areas as compared to healthy controls in order to fulfil the same task as measured by functional MRI (Rachbauer et al, 2006), indicating the need to compensate for existing, but still subclinical brain damage. The CHMP was of the opinion that this suggests that disease activity in MS can lead to brain damage already before becoming clinically detectable as sustained disability and that MRI evidence of continuing disease activity without corresponding clinical symptoms could equally qualify, on a case-by-case basis, for active treatment.

Risks

Unfavourable effects

Unfavourable effects appear similar to effects described so far in the RMP for the approved indication or raised in last PSUR8 (EuPSUR7).

The most relevant effects for the current procedure are described in the effects table below, and include notably immunosuppression-related effects.

With the new wording of the indication, MS patients would probably switch to Gilenya at an earlier time in the course of their disease. To be treated at an earlier time by Gilenya could potentially result in the

earlier exposure of patients to the immunosuppressive effects of the drug and the risks associated with them. It will also extend the period of fingolimod exposure in general, and thus the occurrence of serious adverse events associated with prolonged immunosuppression. These unfavourable effects related to immunosuppression are described in the current RMP and most notably include opportunistic infections and PML.

Uncertainty in the knowledge about the unfavourable effects

Uncertainties about the unfavourable effects remain similar to those considered for the current population treated with fingolimod. In addition, uncertainties were increased with regard to the consequences of a potential prolonged immunosuppression further to fingolimod exposure. Lastly, uncertainties remain on the effect of fingolimod exposure to patients with false positive MRI response.

Effects table

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favorable Effects						
ARR (Annualized Relapse Rate	**Relapse defined as new or recurrent neurologic symptoms, not associated with fever or infection, lasting for at least 24 hours, and accompanied by new objective neurological findings upon examination by a neurologist at unscheduled visits**	**N/A**	**FAS-proposed SPC: 0.27**	**0.48**	**Ratio (95% CI) : 0.55(0.44,0.69) ;**	**D2301+D2309**
Unfavorable Effects						
Infections	**Pneumonia Tinea versicolour Bronchitis Herpes zoster**	Incidence Rate / 100 patient-years	**0.4 1.0 4.8 1.0**	**0.1 0.2 2.6 0.6**	**Events are dose dependent**	**MS clinical trial safety population**
Basal cell carcinoma		Incidence Rate / 100 patient-years	**0.9**	**0.4**		**cut-off of Feb-2015**

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Lymphopenia / leucopenia		Incidence Rate / 100 patient-years	**5.3**	**0.3**	**Events are dose dependent**	
Bradyarrhythmia	**Bradyarrhythmias and bradycardia (grouped terms)**	Incidence Rate / 100 patient-years	**3.7**	**2.0**		
Hypertension	**SMQ (narrow)**	Incidence Rate / 100 patient-years	**5.4**	**2.7**	**Events are dose dependent**	
Liver transaminase elevation		Incidence Rate / 100 patient-years	**12.7**	**3.8**		

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The demonstrated positive effect of fingolimod on ARR in the evaluated populations represents a clinically important benefit as the frequency of relapses is indicative of the activity of the disease and is closely related to the accumulation of disability in MS patients. It was recognized that to be treated at an earlier time by fingolimod would potentially mean an earlier exposure of patients to the immunosuppressive effects of the drug, thus potentially increasing the chances of experiencing the related adverse events. Among these, most notably the risk of infections would potentially be increased as exposure increases. Nevertheless, in reality, the target population within the new proposed indication will be similar to the current indication although is it acknowledged that a switch to fingolimod may occur at an earlier time in the natural course of the disease. Thus the safety profile for fingolimod with the new proposed indication will not change to any appreciable degree. Fingolimod is and will remain a second line drug and as such the CHMP did not consider that the risks associated with fingolimod will fundamentally change given the proposed wording of the new indication.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

In recent years, the treatment landscape for multiple sclerosis has changed with the introduction of several new pharmacological treatments. The monoclonal antibody natalizumab approved in 2006, and the oral MS medication fingolimod approved in 2011 both received a restricted second line indication mainly due to safety concerns. A second monoclonal antibody, alemtuzumab, approved in 2013, was

given a broader indication where it was specified that “patients with RRMS with active disease defined by clinical OR imaging features” could be treated. The current therapeutic indication for fingolimod in the EU is treatment of adult patients with high disease activity, defined by specific clinical (relapse) and imaging criteria, despite treatment with at least 1 disease modifying therapy (DMT), or patients with rapidly evolving severe RRMS.

The applicant has proposed to extend the second-line indication, notably, with this modification, fingolimod would remain a second-line therapy, with the exception of patients with rapidly evolving MS, which remains unchanged.

To support the presently proposed change in indication, the MAH for Gilenya has submitted the results of post-hoc analyses from controlled studies within the fingolimod development program with the aim to show that the efficacy and safety of fingolimod remains unchanged under the conditions of the current and the proposed definitions for active disease in the SmPC.

The data on efficacy have confirmed the postulated treatment benefits in both the population covered by the current and the proposed new indication. It was recognized that the strategy to extend the use of fingolimod to a broader population of relapsing/remitting MS patients, by modifying the conditions of eligibility to the treatment, could potentially increase the exposure and have an effect on the safety concerns reported with fingolimod. Nevertheless it was concluded that in reality the safety profile of fingolimod would not change to any appreciable degree. Taking into account all the above mentioned points, the CHMP concluded that the risk-benefit profile of fingolimod in the new extended indication remains favourable.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**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

Extension of Indication to update the Gilenya indication in second line use to ‘*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).*’
As a consequence, section 4.1 of the SmPC is updated.
In addition, the applicant took the opportunity to relocate documents from section 5.3.5.1 to 5.3.5.2.

The variation leads to amendments to the Summary of Product Characteristics.

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in

accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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

- **Additional risk minimisation measures**

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

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where GILENYA is marketed, at launch and after launch all physicians who intend to prescribe GILENYA are provided with an updated physician information pack containing the following elements:

- The Summary of Product Characteristics
- Physician's checklist prior to prescribing GILENYA
- Information about the Fingolimod Pregnancy Exposure Registry
- Patient reminder card

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

- Monitoring requirements at treatment initiation
  Before first dose
  - Perform baseline ECG prior to the first dose of GILENYA.
  - Perform blood pressure measurement prior to the first dose of GILENYA.
  - Perform a liver function test prior to treatment initiation.
  - Arrange ophthalmological assessment prior to initiation with GILENYA in patients with diabetes mellitus or with a history of uveitis.

  Until 6 hours after first dose
  - 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.
  - Perform an ECG at the end of the 6-hour monitoring period.

  >6 to 8 hours after first dose
  - 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-initiation of GILENYA therapy after treatment interruption

The same first dose monitoring as for treatment initiation is recommended when:
- o treatment is interrupted for one day or more during the first 2 weeks of treatment.
- o treatment is interrupted for more than 7 days during weeks 3 and 4 of treatment.
- o treatment is interrupted for more than 2 weeks after at least 1 month of treatment.

o Recommendation for overnight monitoring after the first dose (or if the first dose monitoring applies during treatment re-initiation)

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:
- o With third degree AV block occurring at any time.
- o Where at the 6-hour time point:
  - Heart rate <45 bpm.
  - New onset second degree or higher AV block.
  - QTc interval ≥500 msec.

o That GILENYA is not recommended in patients with:
- o Second degree Mobitz Type II or higher AV block
- o Sick-sinus syndrome
- o Sino-atrial heart block
- o QTc prolongation >470 msec (females) or >450 msec (males)
- o Ischaemic cardiac disease including angina pectoris
- o Cerebrovascular disease
- o History of myocardial infarction
- o Congestive heart failure
- o History of cardiac arrest
- o Severe sleep apnoea
- o History of symptomatic bradycardia
- o History of recurrent syncope
- o 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.

o GILENYA is not recommended in patients concomitantly taking Class Ia or Class III anti-arrhythmic medicines.

o GILENYA is not recommended in patients concomitantly taking medicines which are 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.

o GILENYA reduces peripheral blood lymphocyte counts. There is a need to check the patient's peripheral lymphocyte count (CBC) prior to initiation and to monitor during treatment with GILENYA.

o GILENYA may increase the risk of infections. 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.

o The need to instruct patients to report signs and symptoms of infections immediately to their prescriber during and for up to two months after treatment with GILENYA.

- Specific recommendations regarding vaccination for patients initiating or currently on GILENYA treatment.

- The need for a full ophthalmological assessment 3-4 months after starting GILENYA therapy for the early detection of visual impairment due to drug-induced macular oedema.

- The need for ophthalmological assessment during treatment with GILENYA in patients with diabetes mellitus or with a history of uveitis.

- The teratogenic risk of GILENYA: the importance of avoiding pregnancy when undergoing treatment with GILENYA and the need for a negative pregnancy test result prior to treatment initiation. This should be repeated at suitable intervals.

- The need to advise women of child-bearing potential on the serious risk to the foetus and the need to practice effective contraception during treatment and for at least two months following discontinuation of treatment with GILENYA.

- The need for liver function monitoring at months 1, 3, 6, 9 and 12 during GILENYA therapy and periodically thereafter.

- The need to provide patients with the patient reminder card.

The patient reminder card shall contain the following key messages:

- That they will have a baseline ECG and blood pressure measurement prior to the first dose of GILENYA.

- That their heart rate will need to 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 a continuous ECG during the first 6 hours. They will need an ECG at 6 hours and in some circumstances monitoring may involve an overnight stay.

- The need to call the doctor in case of treatment interruption as the 1st dose monitoring may need to be repeated depending on duration of the interruption and time since start of GILENYA treatment.

- The need to 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.

- The signs and symptoms of infection and the need to report these immediately to the prescriber during and up to two months after treatment with GILENYA.

- The need to report any symptoms of visual impairment immediately to the prescriber during and for up to two months after the end of treatment with GILENYA.

- That GILENYA is teratogenic so women with childbearing potential must:
  - Have a negative pregnancy test.
  - Be using effective contraception during and for at least two months following discontinuation of treatment with GILENYA.
  - Report any (intended or unintended) pregnancy during and two months following discontinuation of treatment with GILENYA immediately to the prescriber.

- The need for a liver function test prior to treatment initiation and for liver function monitoring at months 1, 3, 6, 9 and 12 during GILENYA therapy and periodically thereafter.

- **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