25 April 2014
EMA/195551/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Gilenya

International non-proprietary name: FINGOLIMOD

Procedure No. EMEA/H/C/002202/II/0021

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

List of abbreviations

AE	Adverse Events
ALT	Alanine Aminotransferase
ARR	Annualised Relapse Rate
AV	Atrioventricular
BCC	Basal Cell Carcinoma
CHMP	Committee for Human Medicinal Product
CI	Confidence Interval
DLP	Data Lock Point
DMT	Disease Modifying Therapy
EDSS	Expanded Disability Status Scale
ERA	Environmental Risk Assessment
EU	European Union
FAS	Full Analysis Dataset
GA	Glatiramer acetate
Gd	Gadolinium
GGT	gammaglutamyl-transferases
HR	Hazard Ratio
IFN	Interferon
MAA	Marketing Authorisation Application
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NB	Negative Binomial
PEC	Predicted Environmental Concentration
PML	Progressive multifocal leukoencephalopathy
PRAC	Pharmacovigilance Risk Assessment
PSUR	Periodic Safety Update Report
S1P	Sphingosine-1-Phosphate
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SOC	System Organ Class
WBC	White Blood Cells

1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 10 July 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Gilenya	FINGOLIMOD	See Annex A

The following variation was requested:

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

The MAH proposed to modify the indication (section 4.1) of Gilenya to extend the patient population from patients with high disease activity despite treatment with a beta-interferon (IFN) to patients with high disease activity despite treatment with a disease modifying therapy (DMT). Section 1 of the Package Leaflet has been amended accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Rapporteur: Pierre Demolis

1.2. Steps taken for the assessment

Submission date:	10 July 2013
Start of procedure:	26 July 2013
Rapporteur's preliminary assessment report circulated on:	20 September 2013
CoRapporteur's preliminary assessment report circulated on:	23 September 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 October 2013
MAH's responses submitted to the CHMP on:	20 December 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	3 February 2014
Rapporteurs' joint assessment report on the MAH's responses circulated on:	10 February 2014
Rapporteurs' final joint assessment report on the MAH's responses circulated on:	14 February 2014
Follow on Request for supplementary information and extension of timetable adopted by the CHMP on:	20 February 2014
MAH's responses submitted to the CHMP on:	26 February 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	28 March 2014
PRAC RMP Advice and assessment overview	10 April 2014
CHMP opinion:	25 April 2014

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/117/2013 on the agreement of a paediatric investigation plan (PIP).

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

2. Scientific discussion

2.1. Introduction

Fingolimod, a sphingosine 1-phosphate receptor modulator is a selective immunosuppressant. It is metabolised by sphingosine kinase to the active metabolite fingolimod phosphate. Fingolimod phosphate, binds at low nanomolar concentrations to sphingosine 1-phosphate (S1P) receptors 1, 3, and 4 located on lymphocytes, and readily crosses the blood-brain barrier to bind to S1P receptors 1, 3, and 5 located on neural cells in the central nervous system. 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, rather than depletion, of lymphocytes. This redistribution is believed to reduce the infiltration of pathogenic lymphocyte cells into the central nervous system, where they would be involved in nerve inflammation and nervous tissue damage.

Fingolimod (Gilenya) was authorised in the European Union (EU) on 17 March 2011 for the treatment of multiple sclerosis (MS).The recommended dose of Gilenya is one 0.5 mg capsule taken orally once daily. As of May 2013, Gilenya has been approved in more than 70 countries worldwide. The approved wording for the indication in the EU is as follows:

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

- Patients with high disease activity despite treatment with a beta-interferon.

  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 beta-interferon. 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.

Interferon-β (IFN-β) and glatiramer acetate (GA) were the currently approved first-line therapies in the EU for the treatment of patients with relapsing MS at the time of this variation submission. Other treatments available for relapsing MS include oral fingolimod, administered once daily, and natalizumab (Tysabri), administered via monthly intravenous infusions. These therapies offer improved efficacy over current first-line therapies but are also associated with some risks and are approved as second-line therapy in the EU. Additionally, newer MS drugs, dimethyl fumarate (Tecfidera), teriflunomide (Aubagio) and alemtuzumab (Lemtrada), received positive opinions by the CHMP recommending the granting of the Marketing Authorisation for their use in broader RRMS population.

The European Commission (EC) Decisions on the Marketing Authorisation were issued in August and September 2013 for Aubagio and Lemtrada, and January 2014 for Tecfidera.

Available data indicate that the IFN-β agents and GA have comparable efficacy (Cadavid et al 2007, Mikol et al 2007, Limmroth et al 2011), providing about a 30% to 35% reduction in the relapse rate compared to placebo, and modest effect on slowing disability progression in patient with RRMS (Goodin et al 2002). In the literature, data from observational studies indicate that switching from a first-line DMT to another DMT (first- or second-line) is generally beneficial but do not indicate that switching from GA to IFN-β would offer significant benefits over a switch from IFN-β to GA (Oreja-Guevara et al 2009, Gajofatto et al 2009). According to expert opinion, the definitions of high disease activity despite treatment with IFN-β, would similarly apply to prior treatment with GA (Fazekas et al 2013).

On this basis, the MAH applied for the following variation:

Modification of the indication (section 4.1) of Gilenya to extend the patient population from patients with high disease activity despite treatment with a beta-interferon to patients with high disease activity despite treatment with a disease modifying therapy (DMT). The Package Leaflet was proposed to be updated in accordance.

2.2. Non-clinical aspects

An updated ERA was submitted to support this application at the CHMP request. As the target patient population remains those with highly-active disease, the exposure of fingolimod is not expected to be increased substantially according to the proposed indication update. Based on the maximum recommended daily dose of 0.5 mg fingolimod and using the default market penetration factor of 1% given in the current ERA guideline (EMEA/CHMP/SWP/4447/00), the predicted environmental concentration (PEC) is 0.0025 µg/L for fingolimod which maintains below the trigger value for Phase II studies(< 0.01 µg/L). A risk for the environment is therefore not anticipated for fingolimod.

2.3. Clinical efficacy

No new efficacy data have been submitted in this application. Additional efficacy post-hoc analyses have been performed by the MAH to support the proposed modification of the indication using data from phase III completed studies D2301, D2302 and D2309. D2301 and D2302 studies were previously submitted as part of the initial MAA dossier. D2309 study was submitted as part of a post-authorisation measure (FUM 9).

2.3.1. Methods – analysis of data submitted

Phase III studies used for the efficacy analyses are presented in Table 1.

Table 1. Overview of the clinical studies

Study No.	Study objective, population	Number of randomized patients	Treatment duration	Dosage	Primary efficacy endpoint
Phase III					
[Study D2301] (placebo-controlled)	Fingolimod pivotal efficacy and safety in patients with RRMS	1250 (planned) 1272 (actual)	24 months	Fingolimod 1.25 mg orally qd Fingolimod 0.5 mg orally qd Placebo	ARR up to 24 months
[Study D2309] (placebo-controlled)	Fingolimod pivotal efficacy and safety in patients with RRMS	1080 (planned) 1083 (actual)	24 months	Fingolimod 1.25 mg orally qd Fingolimod 0.5 mg orally qd Placebo	ARR up to 24 months
[Study D2302] (active-controlled)	Fingolimod pivotal efficacy and safety in patients with RRMS	1275 (planned) 1292 (actual)	12 months	Fingolimod 1.25 mg orally qd Fingolimod 0.5 mg orally qd IFN-β1a 30 µg im once/week	ARR up to 12 months

RRMS = relapsing remitting multiple sclerosis; ARR = annualized relapse rate; qd = once daily.

For efficacy analyses, the following 4 populations were defined from the Phase III placebo- and active-controlled studies: 1) Pooled data from Studies D2301 and D2309, 2) Data from Study D2301,3) Data from Study D2309 and 4) Data from Study D2302. According to the MAH, given the similar trial designs of studies D2301 and D2309 (2-year placebo-controlled), these 2 studies were pooled for efficacy analyses. Hence this allows for a meta-analysis model for pooling Studies D2301 and D2309 with study and treatment as fixed effects. Study D2302 utilised a different design (1-year, IFN-β1a active-controlled) and was analyzed separately to provide supportive evidence. For individual Studies D2301 and 2309, only summary statistics and/or frequencies were provided.

Subpopulation definitions

Four subpopulations were defined for those patients who were previously treated with GA and for those previously treated with IFN for evaluation of efficacy: 1) Patients previously treated with GA at any time (**Group GA**), 2) Patients previously treated with GA in the 1 year prior to Screening, defined as those who were on GA at any time during the year prior to the Screening visit (**Group GA1**), 3) Patients previously treated with IFN at any time (**Group IFN**) and 4) Patients previously treated with IFN in the 1 year prior to Screening, defined as those who were on any of the 3 IFN-β treatments at any time during the year prior to the Screening visit (**Group IFN1**).

Subgroup definitions

For the **Group GA1** subpopulation, 2 key subgroups were defined: 1) **GA failures** (patients previously treated with GA in the 1 year prior to Screening with relapse in the year before Screening and with either at least 1 Gd-enhancing T1 lesion or at least 9 T2 lesions at Baseline) and 2) **GA non-responders** (patients previously treated with GA in the 1 year prior to Screening with equal or more relapses in the year before Screening than in the previous year, ie, 2 years before Screening).

Similarly, for the **Group IFN1** subpopulation, 2 key subgroups were defined: 1) **IFN failures** (patients previously treated with IFN in the 1 year prior to Screening with relapse in the year before Screening and with either at least 1 Gd-enhancing T1 lesion or at least 9 T2 lesions at Baseline) and 2) **IFN non-**

responders (patients previously treated with IFN in the 1 year prior to Screening with equal or more relapses in the year before Screening than in the previous year, ie, 2 years before Screening).

In addition to these key subgroups, the following subgroups were also defined **for both Group GA1 and Group IFN1**: 1) Combined failures and non-responders to previous GA/IFN treatment: patients fulfilling any or both of the definitions of failure or non-responder, 2) Patients previously treated with GA/IFN in the 1 year prior to Screening with relapse in the year before Screening and at least 1 Gd-enhancing T1 lesion or a T2 lesion volume ≥ 0.5 mL at Baseline, 3) Patients with ≤ 2 relapses during the past 2 years prior to Screening, 4) Patients with ≥ 3 relapses during the past 2 years prior to Screening, 5) Patients previously treated with GA/IFN in the 1 year prior to Screening with a baseline EDSS score of 0 and 6) Patients previously treated with GA/IFN in the 1 year prior to Screening with a baseline EDSS score >0.

Efficacy variables

These were as follows:

• ARR (confirmed relapses only) up to Month 12 and 24 (pooled Studies D2301/D2309, Study D2301, and Study D2309) and ARR (confirmed relapses only) up to Month 12 (Study D2302)

• Proportion of relapse-free patients up to Month 24 (pooled Studies D2301/D2309, Study D2301, and Study D2309) and proportion of relapse-free patients up to Month 12 (Study D2302)

• 3-month confirmed disability progression up to Month 24 based on EDSS (pooled Studies D2301/D2309, Study D2301, and Study D2309) and 3-month confirmed disability progression up to Month 12 based on EDSS (Study D2302)

• 6-month confirmed disability progression up to Month 24 based on EDSS (pooled Studies D2301/D2309, Study D2301, and Study D2309)

• Number of Gd-enhancing T1 lesions at Month 24 (pooled Studies D2301/D2309, Study D2301, and Study D2309) and number of Gd-enhancing T1 lesions at Month 12 (Study D2302)

• Total volume of Gd-enhancing T1 lesions at Month 24 (pooled Studies D2301/D2309,Study D2301, and Study D2309) and total volume of Gd-enhancing T1 lesions at Month12 (Study D2302)

• Number of new/newly enlarged T2 lesions at Month 24 (pooled Studies D2301/D2309,Study D2301, and Study D2309) and number of new/newly enlarged T2 lesions at Month12 (Study D2302)

• Change and percent change from baseline in total volume of T2 lesions at Month 24 (pooled Studies D2301/D2309, Study D2301, and Study D2309) and change and percent change from baseline in total volume of T2 lesions at Month 12 (Study D2302)

• Percent change from baseline in normalized brain volume at Month 24 (pooled StudiesD2301/D2309, Study D2301, and Study D2309) and percent change from baseline in normalized brain volume at Month 12 (Study D2302)

Results of the analysis when pooling the studies D2301/D2309 are presented below, as relevant for the CHMP discussion.

2.3.2. Results

2.3.2.1. Patient disposition

The number of patients as per subpopulation and subgroup definitions are presented in Table 2.

Table 2. Number of patients by subpopulation and main subgroups for pooled studies D2301/D2309, Study D2301, Study D2309, and study D2302

	FTY720 1.25 mg n (%)	FTY720 0.5 mg n (%)	Placebo n (%)	Total n (%)
Pooled Studies D2301/D2309	N = 799	N = 783	N = 773	N = 2355
Treatment-naïve patients*	342 (42.8)	338 (43.2)	345 (44.6)	1025 (43.5)
Previously-treated patients	457 (57.2)	445 (56.8)	428 (55.4)	1330 (56.5)
Previously treated with GA	221 (27.7)	171 (21.8)	190 (24.6)	582 (24.7)
Previously treated with GA in the 1 year prior to Screening (Group GA1)	98 (12.3)	76 (9.7)	90 (11.6)	264 (11.2)
Failures**	75 (76.5)	57 (75.0)	76 (84.4)	208 (78.8)
Non-responders***	80 (81.6)	65 (85.5)	79 (87.8)	224 (84.8)
Previously treated with IFN	370 (46.3)	345 (44.1)	324 (41.9)	1039 (44.1)
Previously treated with IFN in the 1 year prior to Screening (Group IFN1)	172 (21.5)	178 (22.7)	156 (20.2)	506 (21.5)
Failures**	128 (74.4)	146 (82.0)	124 (79.5)	398 (78.7)
Non-responders***	148 (86.0)	151 (84.8)	134 (85.9)	433 (85.6)
Study D2301	N = 429	N = 425	N = 418	N = 1272
Treatment-naïve patients*	259 (60.4)	244 (57.4)	249 (59.6)	752 (59.1)
Previously-treated patients	170 (39.6)	181 (42.6)	169 (40.4)	520 (40.9)
Previously treated with GA	52 (12.1)	42 (9.9)	44 (10.5)	138 (10.8)
Previously treated with GA in the 1 year prior to Screening (Group GA1)	26 (6.1)	20 (4.7)	20 (4.8)	66 (5.2)
Failures**	21 (80.8)	15 (75.0)	16 (80.0)	52 (78.8)
Non-responders***	22 (84.6)	18 (90.0)	15 (75.0)	55 (83.3)
Previously treated with IFN	125 (29.1)	127 (29.9)	115 (27.5)	367 (28.9)
Previously treated with IFN in the 1 year prior to Screening (Group IFN1)	56 (13.1)	69 (16.2)	64 (15.3)	189 (14.9)
Failures**	45 (80.4)	57 (82.6)	52 (81.3)	154 (81.5)
Non-responders***	48 (85.7)	60 (87.0)	54 (84.4)	162 (85.7)
Study D2309	N = 370	N = 358	N = 355	N = 1083
Treatment-naïve patients*	83 (22.4)	94 (26.3)	96 (27.0)	273 (25.2)
Previously-treated patients	287 (77.6)	264 (73.7)	259 (73.0)	810 (74.8)
Previously treated with GA	169 (45.7)	129 (36.0)	146 (41.1)	444 (41.0)
Previously treated with GA in the 1 year prior to Screening (Group GA1)	72 (19.5)	56 (15.6)	70 (19.7)	198 (18.3)
Failures**	54 (75.0)	42 (75.0)	60 (85.7)	156 (78.8)
Non-responders***	58 (80.6)	47 (83.9)	64 (91.4)	169 (85.4)
Previously treated with IFN	245 (66.2)	218 (60.9)	209 (58.9)	672 (62.0)
Previously treated with IFN in the 1 year prior to Screening (Group IFN1)	116 (31.4)	109 (30.4)	92 (25.9)	317 (29.3)
Failures**	83 (71.6)	89 (81.7)	72 (78.3)	244 (77.0)
Non-responders***	100 (86.2)	91 (83.5)	80 (87.0)	271 (85.5)
	FTY720 1.25 mg n (%)	**FTY720 0.5 mg n (%)**	**IFN-β1a n (%)**	**Total n (%)**
Study D2302	N = 426	N = 431	N = 435	N = 1292
Treatment-naïve patients*	170 (39.9)	184 (42.7)	186 (42.8)	540 (41.8)
Previously-treated patients	256 (60.1)	247 (57.3)	249 (57.2)	752 (58.2)
Previously treated with GA	67 (15.7)	57 (13.2)	67 (15.4)	191 (14.8)
	FTY720 1.25 mg n (%)	**FTY720 0.5 mg n (%)**	**Placebo n (%)**	**Total n (%)**
Previously treated with GA in the 1 year prior to Screening (Group GA1)	36 (8.5)	32 (7.4)	47 (10.8)	115 (8.9)
Failures**	32 (88.9)	28 (87.5)	43 (91.5)	103 (89.6)
Non-responders***	34 (94.4)	29 (90.6)	45 (95.7)	108 (93.9)
Previously treated with IFN	209 (49.1)	219 (50.8)	207 (47.6)	635 (49.1)
Previously treated with IFN in the 1 year prior to Screening (Group IFN1)	179 (42.0)	190 (44.1)	168 (38.6)	537 (41.6)
Failures**	145 (81.0)	160 (84.2)	150 (89.3)	455 (84.7)
Non-responders***	155 (86.6)	166 (87.4)	139 (82.7)	460 (85.7)

GA = glatiramer acetate; IFN = interferon.
* Defined as not receiving any of the approved MS DMTs or any other MS medications.
** Defined as with at least 1 relapse in the past year and either at least 1 Gd-enhancing T1 lesion at Baseline or baseline T2 lesion count ≥ 9.
*** Defined as with equal or more relapses in year -1 than in year -2.
Source: [SCE-Appendix 1-Table 3.1-1a, Table 3.1-1b, Table 3.1-1c, Table 3.1-1d]

In the pooled studies D2301/D2309, the majority (68.6% and 74.5%) of patients in both Group GA1 and Group IFN1 completed the study, with the highest percentage (75.0% and 83.1%) in the fingolimod 0.5 mg treatment groups. In both Group GA1 and Group IFN1, the most frequently reported reasons for discontinuation were withdrawal of consent and adverse events (AEs); both more frequently reported in the placebo groups than in the fingolimod 0.5 mg groups. For the subgroups of failures and non-responders, the percentage of patients who completed the study was similar for Group GA1 (69.2% and 67.0%, respectively) and Group IFN1 (76.9% and 73.0%, respectively). As for the overall groups GA1 and IFN1, the highest percentages of patients who completed the study in the subgroups of failures and non-responders were in the fingolimod 0.5 mg groups (77.2% and 84.2% respectively). The most frequently reported reasons for study discontinuation in both subgroups were withdrawal of consent and AEs, with AEs more frequently reported in the placebo groups than in the fingolimod 0.5 mg groups.

Patient disposition for pooled studies D2301/D2309 is presented in Table 3.

Table 3. Patient disposition by subpopulation (Group GA1 and Group IFN1) and by subgroup (failures and non-responders), pooled studies D2301/D2309, pooled randomised population

	Group GA1				Group IFN1			
	FTY720 1.25 mg n (%)	FTY720 0.5 mg n (%)	Placebo n (%)	Total n (%)	FTY720 1.25 mg n (%)	FTY720 0.5 mg n (%)	Placebo n (%)	Total n (%)
Overall	**N' = 98**	**N' = 76**	**N' = 90**	**N' = 264**	**N' = 172**	**N' = 178**	**N' = 156**	**N' = 506**
Completed study	64 (65.3)	57 (75.0)	60 (66.7)	181 (68.6)	118 (68.6)	148 (83.1)	111 (71.2)	377 (74.5)
On study drug*	57 (58.2)	50 (65.8)	53 (58.9)	160 (60.6)	109 (63.4)	132 (74.2)	100 (64.1)	341 (67.4)
Off study drug**	7 (7.1)	7 (9.2)	7 (7.8)	21 (8.0)	9 (5.2)	16 (9.0)	11 (7.1)	36 (7.1)
Discontinued from the study	34 (34.7)	19 (25.0)	30 (33.3)	83 (31.4)	54 (31.4)	30 (16.9)	45 (28.8)	129 (25.5)
Abnormal laboratory value(s)	3 (3.1)	3 (3.9)	0 (0.0)	6 (2.3)	12 (7.0)	7 (3.9)	1 (0.6)	20 (4.0)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.4)	1 (0.6)	2 (1.1)	0 (0.0)	3 (0.6)
Administrative problems	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.4)	2 (1.2)	2 (1.1)	3 (1.9)	7 (1.4)
AE(s)	7 (7.1)	4 (5.3)	8 (8.9)	19 (7.2)	11 (6.4)	5 (2.8)	7 (4.5)	23 (4.5)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	4 (4.1)	4 (5.3)	4 (4.4)	12 (4.5)	7 (4.1)	1 (0.6)	7 (4.5)	15 (3.0)
Protocol violation	3 (3.1)	0 (0.0)	1 (1.1)	4 (1.5)	1 (0.6)	3 (1.7)	1 (0.6)	5 (1.0)
Subject withdrew consent	11 (11.2)	7 (9.2)	9 (10.0)	27 (10.2)	12 (7.0)	7 (3.9)	16 (10.3)	35 (6.9)
Subject's condition no longer requires study drug	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.4)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Unsatisfactory therapeutic effect	6 (6.1)	1 (1.3)	5 (5.6)	12 (4.5)	7 (4.1)	3 (1.7)	10 (6.4)	20 (4.0)
Failures	**N = 98 N' = 75**	**N = 76 N' = 57**	**N = 90 N' = 76**	**N = 264 N' = 208**	**N = 172 N' = 128**	**N = 178 N' = 146**	**N = 156 N' = 124**	**N = 506 N' = 398**
Completed study	47 (62.7)	44 (77.2)	53 (69.7)	144 (69.2)	95 (74.2)	123 (84.2)	88 (71.0)	306 (76.9)
On study drug*	42 (56.0)	38 (66.7)	46 (60.5)	126 (60.6)	88 (68.8)	109 (74.7)	78 (62.9)	275 (69.1)
Off study drug**	5 (6.7)	6 (10.5)	7 (9.2)	18 (8.7)	7 (5.5)	14 (9.6)	10 (8.1)	31 (7.8)
Discontinued from the study	28 (37.3)	13 (22.8)	23 (30.3)	64 (30.8)	33 (25.8)	23 (15.8)	36 (29.0)	92 (23.1)
Abnormal laboratory value(s)	3 (4.0)	2 (3.5)	0 (0.0)	5 (2.4)	7 (5.5)	5 (3.4)	0 (0.0)	12 (3.0)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.5)	1 (0.8)	2 (1.4)	0 (0.0)	3 (0.8)
Administrative problems	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.5)	2 (1.6)	2 (1.4)	3 (2.4)	7 (1.8)
AE(s)	6 (8.0)	2 (3.5)	6 (7.9)	14 (6.7)	6 (4.7)	4 (2.7)	6 (4.8)	16 (4.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	3 (4.0)	3 (5.3)	3 (3.9)	9 (4.3)	4 (3.1)	0 (0.0)	5 (4.0)	9 (2.3)
Protocol violation	3 (4.0)	0 (0.0)	1 (1.3)	4 (1.9)	0 (0.0)	1 (0.7)	1 (0.8)	2 (0.5)
Subject withdrew	7 (9.3)	5 (8.8)	6 (7.9)	18 (8.7)	8 (6.3)	6 (4.1)	12 (9.7)	26 (6.5)

	Group GA1				Group IFN1			
	FTY720 1.25 mg n (%)	FTY720 0.5 mg n (%)	Placebo n (%)	Total n (%)	FTY720 1.25 mg n (%)	FTY720 0.5 mg n (%)	Placebo n (%)	Total n (%)
consent								
Subject's condition no longer requires study drug	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	6 (8.0)	1 (1.8)	4 (5.3)	11 (5.3)	5 (3.9)	3 (2.1)	9 (7.3)	17 (4.3)
Non-responders	**N = 98 N' = 80**	**N = 76 N' = 65**	**N = 90 N' = 79**	**N = 264 N' = 224**	**N = 172 N' = 148**	**N = 178 N' = 151**	**N = 156 N' = 134**	**N = 506 N' = 433**
Completed study	50 (62.5)	50 (76.9)	50 (63.3)	150 (67.0)	102 (68.9)	123 (81.5)	91 (67.9)	316 (73.0)
On study drug*	45 (56.3)	43 (66.2)	44 (55.7)	132 (58.9)	94 (63.5)	110 (72.8)	82 (61.2)	286 (66.1)
Off study drug**	5 (6.3)	7 (10.8)	6 (7.6)	18 (8.0)	8 (5.4)	13 (8.6)	9 (6.7)	30 (6.9)
Discontinued from the study	30 (37.5)	15 (23.1)	29 (36.7)	74 (33.0)	46 (31.1)	28 (18.5)	43 (32.1)	117 (27.0)
Abnormal laboratory value(s)	3 (3.8)	1 (1.5)	0 (0.0)	4 (1.8)	11 (7.4)	6 (4.0)	1 (0.7)	18 (4.2)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.4)	0 (0.0)	2 (1.3)	0 (0.0)	2 (0.5)
Administrative problems	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.4)	2 (1.4)	2 (1.3)	3 (2.2)	7 (1.6)
AE(s)	7 (8.8)	3 (4.6)	8 (10.1)	18 (8.0)	10 (6.8)	5 (3.3)	7 (5.2)	22 (5.1)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	3 (3.8)	3 (4.6)	4 (5.1)	10 (4.5)	5 (3.4)	1 (0.7)	6 (4.5)	12 (2.8)
Protocol violation	2 (2.5)	0 (0.0)	1 (1.3)	3 (1.3)	1 (0.7)	3 (2.0)	1 (0.7)	5 (1.2)
Subject withdrew consent	10 (12.5)	7 (10.8)	9 (11.4)	26 (11.6)	11 (7.4)	6 (4.0)	16 (11.9)	33 (7.6)
Subject's condition no longer requires study drug	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.4)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)
Unsatisfactory therapeutic effect	5 (6.3)	1 (1.5)	4 (5.1)	10 (4.5)	5 (3.4)	3 (2.0)	9 (6.7)	17 (3.9)

AE = adverse event.
For the overall population, N′ = number of patients in this subpopulation, n = number of patients in this category (%): the denominator is the number of patients in the subpopulation. For the subgroups of failures and non-responders, N′ = number of patients in this subgroup, n = number of patients in this category (%): the denominator is the number of patients in the subgroup.
* 'On study drug': patients who took study drug until study completion.
** 'Off study drug': patients who completed the study but discontinued the drug prematurely.

Source: [SCE-Appendix 1-Table 3.1-2a, Table 3.1-2e, Table 3.1-2i]

Overall, for both studies D2301 and D2309, taken individually, patient disposition in the subpopulations and subgroups was consistent with pooled Studies D2301/D2309. The main reasons for study discontinuation were AEs, patient withdrawing consent, and unsatisfactory therapeutic effect. Same consistent findings were observed for study D2302. It is noted that the numbers of patients discontinuing in Group GA1 compared to Group IFN1 were low, making difficult comparison between treatment groups and across populations.

2.3.2.2. Baseline data

Demographics were similar across subpopulations, subgroups, and treatment groups. The mean age was approximately 39 years, there were notably more women (mean: 76.1 for group IFN1 and 77.7% in group GA1), and the majority of patients were Caucasian (88.6% and 90.7%, respectively); these results are consistent with demographics typically seen for a relapsing MS population. Overall, the duration of MS since first symptom and the baseline EDSS score were similar across subpopulations (Group GA1 and Group IFN1), subgroups and treatment groups. The mean duration of MS was 9.82 (7.473) to 11.24 (7.344) across all subgroups. Mean EDSS score was 2.46 (1.237) to 2.89 (1.414). The mean number of relapses in the last 1 year tended to be higher in all treatment groups for both the failure and non-responder subgroups in Group GA1 (1.5 to 1.8) compared to Group IFN1 (1.4 to 1.6). The baseline characteristics were similar across the subgroups and treatment, although Group IFN1 was slightly more active than Group GA1. The proportion of patients free of Gd-enhancing T1 lesions tended to be slightly higher in Group GA1 and the GA1 subgroups of failures and non-responders compared to Group IFN1 and Group IFN1 subgroups of failures and non-responders. The number of Gd-enhancing lesions was slightly higher in the Group IFN1 than in group GA1.

Baseline data are presented in Tables 4, 5 and 6.

Table 4. Demographics by subpopulation (Group GA1 and Group IFN1) and subgroup (failures and non responders), pooled studies D2301/2309 pooled randomised population

		Group GA1				Group IFN1			
		FTY720 1.25 mg	FTY720 0.5 mg	Placebo	Total	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	Total
Overall		**N′ = 98**	**N′ = 76**	**N′ = 90**	**N′ = 264**	**N′ = 172**	**N′ = 178**	**N′ = 156**	**N′ = 506**
Age (years)	Mean (SD)	38.3 (9.40)	39.7 (9.17)	40.4 (8.37)	39.4 (9.00)	39.7 (9.53)	39.2 (8.65)	38.2 (8.23)	39.1 (8.84)
	Median (Range)	40.0 (18 - 55)	40.0 (19 - 55)	39.5 (20 - 55)	40.0 (18 - 55)	41.0 (18 - 55)	39.0 (20 - 55)	39.0 (19 - 55)	40.0 (18 - 55)
Sex, n (%)	Male	24 (24.5)	17 (22.4)	18 (20.0)	59 (22.3)	39 (22.7)	43 (24.2)	39 (25.0)	121 (23.9)
	Female	74 (75.5)	59 (77.6)	72 (80.0)	205 (77.7)	133 (77.3)	135 (75.8)	117 (75.0)	385 (76.1)
Race*, n (%)	Caucasian	83 (84.7)	70 (92.1)	81 (90.0)	234 (88.6)	156 (90.7)	164 (92.1)	139 (89.1)	459 (90.7)
Failures		**N = 98 N′ = 75**	**N = 76 N′ = 57**	**N = 90 N′ = 76**	**N = 264 N′ = 208**	**N = 172 N′ = 128**	**N = 178 N′ = 146**	**N = 156 N′ = 124**	**N = 506 N′ = 398**
Age (years)	Mean (SD)	38.4 (9.52)	39.4 (9.51)	39.8 (8.27)	39.2 (9.06)	39.2 (9.74)	39.6 (8.81)	38.0 (8.36)	38.9 (8.99)
	Median (Range)	40.0 (18 - 54)	40.0 (19 - 55)	38.5 (20 - 54)	40.0 (18 - 55)	41.0 (18 - 55)	39.0 (20 - 55)	39.0 (19 - 55)	39.0 (18 - 55)
Sex, n (%)	Male	20 (26.7)	15 (26.3)	16 (21.1)	51 (24.5)	30 (23.4)	38 (26.0)	29 (23.4)	97 (24.4)
	Female	55 (73.3)	42 (73.7)	60 (78.9)	157 (75.5)	98 (76.6)	108 (74.0)	95 (76.6)	301 (75.6)
Race*, n (%)	Caucasian	60 (80.0)	51 (89.5)	68 (89.5)	179 (86.1)	116 (90.6)	134 (91.8)	109 (87.9)	359 (90.2)
Non-responders		**N = 98 N′ = 80**	**N = 76 N′ = 65**	**N = 90 N′ = 79**	**N = 264 N′ = 224**	**N = 172 N′ = 148**	**N = 178 N′ = 151**	**N = 156 N′ = 134**	**N = 506 N′ = 433**
Age (years)	Mean (SD)	38.8 (8.97)	39.8 (9.61)	40.3 (8.50)	39.6 (8.99)	39.4 (9.74)	39.2 (8.82)	38.6 (8.08)	39.0 (8.92)
	Median (Range)	40.0 (18 - 55)	40.0 (19 - 55)	39.0 (20 - 55)	40.0 (18 - 55)	40.5 (18 - 55)	39.0 (20 - 55)	39.0 (19 - 55)	40.0 (18 - 55)
Sex, n (%)	Male	20 (25.0)	17 (26.2)	15 (19.0)	52 (23.2)	33 (22.3)	37 (24.5)	38 (28.4)	108 (24.9)
	Female	60 (75.0)	48 (73.8)	64 (81.0)	172 (76.8)	115 (77.7)	114 (75.5)	96 (71.6)	325 (75.1)
Race*, n (%)	Caucasian	69 (86.3)	60 (92.3)	71 (89.9)	200 (89.3)	134 (90.5)	138 (91.4)	118 (88.1)	390 (90.1)

For the overall population, N′ = number of patients in this subpopulation. All percentages use N′ as the denominator. For the subgroups of failures and non-responders, N′ = number of patients in this subgroup. All percentages use N′ as the denominator.
* Results for all categories of race are included in the post-text tables.
Source: [SCE-Appendix 1-Table 3.1-4a, Table 3.1-4e, Table 3.1-4i]

Table 5. MS disease history and EDSS score at baseline, by subpopulation (Group GA1 and Group IFN1) and subgroup (failures and non- responders), pooled studies D2301/D2309, pooled randomised population

	Group GA1				Group IFN1			
	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	Total	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	Total
Overall	**N' = 98**	**N' = 76**	**N' = 90**	**N' = 264**	**N' = 172**	**N' = 178**	**N' = 156**	**N' = 506**
Duration of MS since first symptom (years)								
n	98	76	90	264	172	178	156	506
Mean (SD)	10.56 (7.890)	9.82 (7.473)	10.31 (8.620)	10.26 (7.335)	10.20 (7.928)	10.16 (7.709)	10.09 (7.282)	10.15 (7.642)
Median (Range)	8.95 (1.1 - 36.1)	7.95 (0.7 - 32.0)	8.90 (0.9 - 29.0)	8.70 (0.7 - 36.1)	7.90 (0.8 - 36.7)	8.70 (0.8 - 49.1)	8.40 (0.9 - 40.1)	8.50 (0.8 - 49.1)
Number of relapses in the last year								
n	98	76	90	264	172	178	156	506
Mean (SD)	1.6 (0.97)	1.5 (0.99)	1.8 (1.09)	1.6 (1.02)	1.4 (0.83)	1.4 (0.83)	1.5 (0.97)	1.5 (0.87)
Median (Range)	1.0 (0 - 6)	1.0 (0 - 5)	1.5 (0 - 7)	1.0 (0 - 7)	1.0 (0 - 5)	1.0 (0 - 5)	1.0 (0 - 7)	1.0 (0 - 7)
EDSS score at Baseline								
n	98	76	90	264	172	178	156	506
Mean (SD)	2.72 (1.409)	2.53 (1.249)	2.56 (1.333)	2.61 (1.336)	2.57 (1.299)	2.46 (1.237)	2.74 (1.447)	2.58 (1.328)
Median (Range)	3.00 (0.0 - 5.5)	2.50 (0.0 - 5.5)	2.50 (0.0 - 6.0)	2.50 (0.0 - 6.0)	2.50 (0.0 - 6.0)	2.50 (0.0 - 5.5)	2.50 (0.0 - 5.5)	2.50 (0.0 - 6.0)
Failures	**N' = 75**	**N' = 57**	**N' = 76**	**N' = 208**	**N' = 128**	**N' = 146**	**N' = 124**	**N' = 398**
Duration of MS since first symptom (years)								
n	75	57	76	208	128	146	124	398
Mean (SD)	11.24 (7.344)	10.07 (7.103)	9.97 (6.432)	10.46 (6.947)	10.52 (8.101)	10.64 (7.867)	10.58 (7.580)	10.58 (7.836)
Median (Range)	9.60 (1.2 - 32.9)	9.00 (0.7 - 30.5)	8.70 (0.9 - 29.0)	9.15 (0.7 - 32.9)	8.70 (0.8 - 36.7)	9.00 (0.8 - 49.1)	8.50 (0.9 - 40.1)	8.85 (0.8 - 49.1)
Number of relapses in the last year								
n	75	57	76	208	128	146	124	398
Mean (SD)	1.6 (0.85)	1.6 (0.88)	1.8 (1.13)	1.7 (0.97)	1.5 (0.77)	1.5 (0.76)	1.6 (0.86)	1.5 (0.80)
Median (Range)	1.0 (1 - 4)	1.0 (1 - 4)	2.0 (1 - 7)	1.0 (1 - 7)	1.0 (1 - 4)	1.0 (1 - 5)	1.0 (1 - 5)	1.0 (1 - 5)
EDSS score at Baseline								
n	75	57	76	208	128	146	124	398
Mean (SD)	2.79 (1.343)	2.53 (1.269)	2.52 (1.396)	2.62 (1.343)	2.63 (1.312)	2.48 (1.272)	2.83 (1.476)	2.64 (1.355)
Median (Range)	3.00 (0.0 - 5.5)	2.50 (0.0 - 5.5)	2.50 (0.0 - 6.0)	2.50 (0.0 - 6.0)	2.50 (0.0 - 6.0)	2.50 (0.0 - 5.5)	2.50 (0.0 - 5.5)	2.50 (0.0 - 6.0)

	Group GA1				Group IFN1			
	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	Total	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	Total
Non-responders	**N' = 80**	**N' = 65**	**N' = 79**	**N' = 224**	**N' = 148**	**N' = 151**	**N' = 134**	**N' = 433**
Duration of MS since first symptom (years)								
n	80	65	79	224	148	151	134	433
Mean (SD)	10.74 (7.126)	10.62 (7.699)	10.24 (6.557)	10.53 (7.077)	10.23 (8.189)	10.59 (7.874)	10.60 (7.551)	10.47 (7.869)
Median (Range)	9.50 (1.1 - 32.9)	8.90 (0.7 - 32.0)	8.90 (0.9 - 29.0)	9.05 (0.7 - 32.9)	7.75 (0.8 - 36.7)	8.90 (0.8 - 49.1)	8.95 (0.9 - 40.1)	8.70 (0.8 - 49.1)
Number of relapses in the last year								
n	80	65	79	224	148	151	134	433
Mean (SD)	1.8 (0.99)	1.7 (0.95)	1.8 (1.13)	1.8 (1.03)	1.5 (0.82)	1.5 (0.82)	1.6 (0.95)	1.5 (0.86)
Median (Range)	2.0 (1 - 6)	1.0 (1 - 5)	2.0 (1 - 7)	1.5 (1 - 7)	1.0 (1 - 5)	1.0 (1 - 5)	1.0 (1 - 7)	1.0 (1 - 7)
EDSS score at Baseline								
n	80	65	79	224	148	151	134	433
Mean (SD)	2. 89 (1.414)	2.58 (1.227)	2.53 (1.374)	2.67 (1.351)	2.54 (1.303)	2.49 (1.287)	2.80 (1.442)	2.60 (1.346)
Median (Range)	3.00 (0.0 - 5.5)	2.50 (0.0 - 5.5	2.50 (0.0 - 6.0)	2.50 (0.0 - 6.0)	2.50 (0.0 - 6.0)	2.50 (0.0 - 5.5)	2.50 (0.0 - 5.5)	2.50 (0.0 - 6.0)

EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.
For the overall group, N' is the number of patients in the subpopulation. n refers to the number of patients in the subpopulation with non-missing values for the parameter. For the subgroups of failures and non-responders, N' is the number of patients in the subgroup. n refers to the number of patients in the subgroup with non-missing values for the parameter.
Source: [SCE-Appendix 1-Table 3.1-6a, Table 3.1-7a, Table 3.1-6e, Table 3.1-6i, Table 3.1-7e, Table 3.1-7i]

Table 6 MRI parameters at baseline, by subpopulation (Group GA1 and Group IFN1) and subgroup (failures and non- responders), pooled studies D2301/D2309, pooled randomised population

	Group GA1				Group IFN1			
	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	Total	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	Total
Overall	**N' = 98**	**N' = 76**	**N' = 90**	**N' = 264**	**N' = 172**	**N' = 178**	**N' = 156**	**N' = 506**
Proportion of patients free of Gd-enhancing T1 lesions								
n'	97	76	90	263	169	178	156	503
n (%)	67 (69.1)	52 (68.4)	62 (68.9)	181 (68.8)	113 (66.9)	108 (60.7)	94 (60.3)	315 (62.6)
Number of Gd-enhancing T1 lesions								
n	97	76	90	263	169	178	156	503
Mean (SD)	1.1 (3.30)	1.2 (3.70)	1.3 (3.65)	1.2 (3.52)	1.8 (4.74)	2.1 (7.40)	1.4 (3.10)	1.8 (5.46)
Median (Range)	0.0 (0 - 22)	0.0 (0 - 28)	0.0 (0 - 25)	0.0 (0 - 28)	0.0 (0 - 26)	0.0 (0 - 84)	0.0 (0 - 25)	0.0 (0 - 84)
Total volume of Gd-enhancing T1 lesions (mm^3)								
n	97	76	90	263	169	178	156	503
Mean (SD)	111.89 (294.367)	129.64 (317.048)	138.06 (410.247)	125.97 (343.255)	147.87 (408.276)	207.01 (688.165)	162.12 (435.515)	173.22 (531.023)
Median (Range)	0.0 (0.0 - 1997.2)	0.0 (0.0 - 1834.1)	0.0 (0.0 - 2970.0)	0.0 (0.0 - 2970.0)	0.0 (0.0 - 3075.9)	0.0 (0.0 - 6849.8)	0.0 (0.0 - 2970.0)	0.0 (0.0 - 6849.8)
Total volume of T2 lesions (mm^3)								
n	97	76	89	262	169	178	155	502
Mean (SD)	5019.99 (6388.987)	4664.64 (6072.102)	5999.42 (7190.570)	5249.62 (6584.277)	5524.07 (8028.945)	6381.49 (8514.654)	6376.73 (8363.001)	6091.37 (8300.139)
Median (Range)	2218.70 (0.0 - 39076.0)	2480.71 (0.0 - 32049.0)	3479.30 (40.1 - 35754.4)	2668.12 (0.0 - 39076.0)	2329.10 (0.0 - 40524.1)	3452.12 (0.0 - 42652.9)	3130.23 (0.0 - 43628.6)	3081.57 (0.0 - 43628.6)
Normalized brain volume (cc)								
n	96	76	90	262	168	178	156	502
Mean (SD)	1529.491 (78.4311)	1517.240 (97.5797)	1510.486 (81.1362)	1519.409 (85.3592)	1516.875 (88.1500)	1515.827 (86.5256)	1503.196 (97.7358)	1512.253 (90.7065)
Median (Range)	1547.594 (1355.96 - 1718.75)	1522.051 (1143.65 - 1733.71)	1506.915 (1275.04 - 1716.15)	1526.180 (1143.65 - 1733.71)	1521.257 (1320.57 - 1763.83)	1523.390 (1143.65 - 1697.72)	1506.793 (1229.79 - 1712.96)	1519.686 (1143.65 - 1763.83)
Failures	**N' = 75**	**N' = 57**	**N' = 76**	**N' = 208**	**N' = 128**	**N' = 146**	**N' = 124**	**N' = 398**
Proportion of patients free of Gd-enhancing T1 lesions								
n'	74	57	76	207	127	146	124	397
n (%)	44 (59.5)	34 (59.6)	49 (64.5)	127 (61.4)	74 (58.3)	77 (52.7)	64 (51.6)	215 (54.2)
Number of Gd-enhancing T1 lesions								
n	74	57	76	207	127	146	124	397
Mean (SD)	1.5 (3.71)	1.6 (4.20)	1.5 (3.93)	1.5 (3.91)	2.2 (5.14)	2.5 (8.10)	1.7 (3.38)	2.2 (6.01)
Median (Range)	0.0 (0 - 22)	0.0 (0 - 28)	0.0 (0 - 25)	0.0 (0 - 28)	0.0 (0 - 26)	0.0 (0 - 84)	0.0 (0 - 25)	0.0 (0 - 84)

	Group GA1				Group IFN1			
	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	Total	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	Total
Total volume of Gd-enhancing T1 lesions (mm^3)								
n	74	57	76	207	127	146	124	397
Mean (SD)	146.67 (329.822)	170.94 (357.041)	162.93 (442.344)	159.32 (380.186)	171.36 (383.114)	250.13 (752.959)	202.37 (480.498)	210.01 (571.926)
Median (Range)	0.0 (0.0 - 1997.2)	0.0 (0.0 - 1834.1)	0.0 (0.0 - 2970.0)	0.0 (0.0 - 2970.0)	0.0 (0.0 - 2206.0)	0.0 (0.0 - 6849.8)	0.0 (0.0 - 2970.0)	0.0 (0.0 - 6849.8)
Total volume of T2 lesions (mm^3)								
n	74	57	76	207	127	146	124	397
Mean (SD)	6346.31 (6765.374)	6091.28 (6406.122)	6852.46 (7433.958)	6461.92 (6898.914)	6782.50 (8249.390)	7334.17 (8767.126)	7543.66 (8813.309)	7223.13 (8603.620)
Median (Range)	3672.44 (343.3 - 39076.0)	3762.54 (497.9 - 32049.0)	4040.11 (377.7 - 35754.4)	3874.13 (343.3 - 39076.0)	4166.00 (343.3 - 40524.1)	4186.04 (454.9 - 42652.9)	4115.90 (180.3 - 43628.6)	4166.00 (180.3 - 43628.6)
Normalized brain volume (cc)								
n	74	57	76	207	126	146	124	396
Mean (SD)	1523.129 (82.7206)	1503.771 (92.9816)	1505.354 (84.2585)	1511.273 (86.2488)	1512.702 (89.1302)	1507.665 (88.5955)	1492.628 (100.8747)	1504.559 (92.9159)
Median (Range)	1534.042 (1355.96 - 1718.75)	1485.737 (1143.65 - 1733.71)	1504.761 (1275.04 - 1716.15)	1510.591 (1143.65 - 1733.71)	1517.429 (1320.57 - 1763.83)	1516.680 (1143.65 - 1697.72)	1495.214 (1229.79 - 1712.96)	1508.319 (1143.65 - 1763.83
Non-responders								
	N' = 80	**N' = 65**	**N' = 79**	**N' = 224**	**N' = 148**	**N' = 151**	**N' = 134**	**N' = 433**
Proportion of patients free of Gd-enhancing T1 lesions								
n'	79	65	79	223	146	151	134	431
n (%)	55 (69.6)	44 (67.7)	55 (69.6)	154 (69.1)	100 (68.5)	92 (60.9)	79 (59.0)	271 (62.9)
Number of Gd-enhancing T1 lesions								
n	79	65	79	223	146	151	134	431
Mean (SD)	1.0 (2.75)	1.3 (3.97)	1.3 (3.86)	1.2 (3.53)	1.6 (4.37)	2.3 (7.99)	1.4 (3.24)	1.8 (5.66)
Median (Range)	0.0 (0 - 20)	0.0 (0 - 28)	0.0 (0 - 25)	0.0 (0 - 28)	0.0 (0 - 26)	0.0 (0 - 84)	0.0 (0 - 25)	0.0 (0 - 84)
Total volume of Gd-enhancing T1 lesions (mm^3)								
n	79	65	79	223	146	151	134	431
Mean (SD)	111.51 (287.952)	127.58 (318.809)	133.01 (418.338)	123.81 (346.426)	126.82 (338.455)	230.94 (742.928)	175.62 (464.137)	178.47 (547.423)
Median (Range)	0.0 (0.0 - 1997.2)	0.0 (0.0 - 1834.1)	0.0 (0.0 - 2970.0)	0.0 (0.0 - 2970.0)	0.0 (0.0 - 2206.0)	0.0 (0.0 - 6849.8)	0.0 (0.0 - 2970.0)	0.0 (0.0 - 6849.8)
Total volume of T2 lesions (mm^3)								
n	79	65	79	223	146	151	134	431
Mean (SD)	5044.86 (6730.421)	4853.76 (5856.967)	5783.21 (6704.172)	5250.72 (6462.128)	4939.60 (7413.899)	6283.67 (8499.722)	6662.86 (8804.286)	5946.26 (8261.758)
Median (Range)	1937.08 (0.0 - 39076.0)	2643.81 (0.0 - 32049.0)	3453.30 (40.1 - 30257.9)	2692.43 (0.0 - 39076.0)	2027.20 (0.0 - 40524.1)	3416.40 (0.0 - 42652.9)	3137.36 (0.0 - 43628.6)	2804.00 (0.0 - 43628.6)

	Group GA1				Group IFN1			
	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	Total	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	Total
Normalized brain volume (cc)								
n	78	65	79	222	145	151	134	430
Mean (SD)	1529.260 (81.1963)	1509.937 (94.7547)	1514.179 (77.1031)	1518.236 (84.0499)	1519.245 (89.3133)	1518.266 (88.1241)	1499.790 (99.4317)	1512.839 (92.3873)
Median (Range)	1540.699 (1355.96 - 1718.75)	1493.292 (1143.65 - 1733.71)	1511.333 (1363.84 - 1716.15)	1518.786 (1143.65 - 1733.71)	1521.333 (1320.57 - 1763.83)	1530.141 (1143.65 - 1697.72)	1503.134 (1229.79 - 1712.96)	1521.126 (1143.65 - 1763.83)

Gd = Gadolinium.
For the overall group, N' = number of patients in the subpopulation. n' = number of patients with an evaluable MRI scan at Baseline. For the subgroups of failures and non-responders, N' = number of patients in the subgroup. n' = number of patients with an evaluable MRI scan at Baseline.
Percentages use the number of patients with an evaluable MRI scan as the denominator.
Source: [SCE-Appendix 1-Table 3.1-8a, Table 3.1-8e, Table 3.1-8i, Table 3.1-9a, Table 3.1-9e, Table 3.1-9i]

Overall, for both studies D2301 and D2309, taken individually, baseline data in the subpopulations and subgroups were consistent with pooled Studies D2301/D2309. Same consistent findings were observed for study D2302.

2.3.2.3. Efficacy results

Results from the pooled studies are presented in Tables 7 to 13.

Efficacy analysis from the pooled studies D2301/D2309 showed significant reductions for the ARR ratio for fingolimod 0.5 mg vs. placebo for both subgroups of failures and non-responders in Group IFN1 and in Group GA1, with the reduction slightly being larger in Group IFN1 than in Group GA1 (see Table 7). In Group GA1, a similar relative reduction for fingolimod 0.5 mg vs. placebo was observed for subgroups of failures (ARR ratio: 0.518; 95% CI: 0.306, 0.877; p = 0.014 ; reduction of 48%) and non-responders (ARR ratio: 0.500; 95% CI: 0.294, 0.850; p = 0.011; reduction of 50%). In Group IFN1, a slightly greater reduction for fingolimod 0.5 mg vs. placebo was observed for subgroups of failures (ARR ratio: 0.437, 95% CI: 0.300, 0.637; p < 0.001; reduction of 56%) and non-responders (ARR ratio: 0.372; 95% CI: 0.255, 0.545; p < 0.001; reduction of 63%). Globally, the effects on ARR ratio are similar in GA1 and IFN1 groups, in failures and non-responders groups and similar to the overall results. In addition, an increased proportion of relapse-free patients was observed for fingolimod 0.5 mg versus placebo for both subgroups of failures and non-responders in Group IFN1 and Group GA1 (see Table 8), although statistical significance was not reached in GA1 subgroup (failure group: odds ratio= 1.93; 95% CI: 0.853, 4.378; p = 0.114 and non-responders group: odds ratio= 2.10; 95% CI: 0.948, 4.635; p = 0.068) as opposed to INF1 group (failures group: odds ratio= 2.62; 95% CI: 1.575, 4.345; p < 0.001 and non-responders group: odds ratio= 3.23; 95% CI: 1.946, 5.363; p < 0.001).

Table 7. Aggregate ARR up to month 24, Group GA1 and IFN1, by subgroup (failures and non- responders) and treatment, pooled studies D2301/D2309, pooled FAS

	Group GA1			Group IFN1		
	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
Overall	n* = 98	n* = 76	n* = 90	n* = 172	n* = 178	n* = 156
Model estimates from NB model**						
ARR	0.268	0.229	0.521	0.168	0.234	0.516
95% CI	(0.191; 0.377)	(0.152; 0.345)	(0.388; 0.700)	(0.122; 0.231)	(0.180; 0.304)	(0.414; 0.643)
Comparison to placebo						
ARR ratio to placebo	0.515	0.440		0.325	0.454	
95% CI	(0.328; 0.808)	(0.266; 0.728)		(0.220; 0.479)	(0.323; 0.639)	
P-value	0.004	0.001		< 0.001	< 0.001	
Failures	n* = 75	n* = 57	n* = 76	n* = 128	n* = 146	n* = 124
Model estimates from NB model**						
ARR	0.257	0.280	0.542	0.164	0.234	0.536
95% CI	(0.174; 0.380)	(0.183; 0.429)	(0.397; 0.739)	(0.113; 0.236)	(0.176; 0.312)	(0.421; 0.682)
Comparison to placebo						
ARR ratio to placebo	0.475	0.518		0.305	0.437	
95% CI	(0.289; 0.781)	(0.306; 0.877)		(0.197; 0.474)	(0.300; 0.637)	
P-value	0.003	0.014		< 0.001	< 0.001	
Non-responders	n* = 80	n* = 65	n* = 79	n* = 148	n* = 151	n* = 134
Model estimates from NB model**						
ARR	0.228	0.247	0.495	0.155	0.200	0.538
95% CI	(0.153; 0.340)	(0.162; 0.376)	(0.357; 0.685)	(0.110; 0.221)	(0.148; 0.270)	(0.426; 0.679)
Comparison to placebo						
ARR ratio to placebo	0.461	0.500		0.289	0.372	
95% CI	(0.276; 0.771)	(0.294; 0.850)		(0.190; 0.440)	(0.255; 0.545)	
P-value	0.003	0.011		< 0.001	< 0.001	

ARR = annualized relapse rate; NB = negative binomial.
n* = number of patients in this subgroup, ** NB regression model, log-link, adjusted for study, treatment, and treatment by study interaction for the overall result, and for study, treatment, subgroup, treatment by study

interaction, and treatment by subgroup interaction for subgroup analyses. Log(time on study in days) was used as an offset variable.
Source: [SCE-Appendix 1-Table 3.2-1b, Table 3.2-1d]

Table 8. Proportion of relapse-free patients up to month 24 , Group GA1 and IFN1, by subgroup (failures and non- responders) and treatment, pooled studies D2301/D2309, pooled FAS

	Group GA1			Group IFN1		
	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
Overall	n* = 98	n* = 76	n* = 90	n* = 172	n* = 178	n* = 156
Relapse free, n (%)	70 (71.4)	54 (71.1)	44 (48.9)	137 (79.7)	126 (70.8)	74 (47.4)
Model estimates from logistic regression**						
Odds ratio to placebo	2.70	2.59		4.32	2.66	
95% CI	(1.341, 5.449)	(1.227, 5.456)		(2.606; 7.172)	(1.683; 4.214)	
P-value	0.005	0.012		< 0.001	< 0.001	
Failures	n* = 75	n* = 57	n* = 76	n* = 128	n* = 146	n* = 124
Relapse free, n (%)	55 (73.3)	37 (64.9)	37 (48.7)	100 (78.1)	103 (70.5)	59 (47.6)
Model estimates from logistic regression**						
Odds ratio to placebo	3.07	1.93		3.95	2.62	
95% CI	(1.416, 6.643)	(0.853, 4.378)		(2.252, 6.920)	(1.575, 4.345)	
P-value	0.004	0.114		< 0.001	< 0.001	
Non-responders	n* = 80	n* = 65	n* = 79	n* = 148	n* = 151	n* = 134
Relapse free, n (%)	61 (76.3)	45 (69.2)	41 (51.9)	119 (80.4)	113 (74.8)	64 (47.8)
Model estimates from logistic regression**						
Odds ratio to placebo	3.04	2.10		4.49	3.23	
95% CI	(1.399, 6.598)	(0.948, 4.635)		(2.595, 7.763)	(1.946, 5.363)	
P-value	0.005	0.068		< 0.001	< 0.001	

n* = number of patients in this subgroup.
** Logistic regression model adjusted for study, treatment, and treatment by study interaction for the overall model, and for study, treatment, subgroup, treatment by study interaction, and treatment by subgroup interaction for subgroup analyses. For subgroup analyses where the model did not converge, the logistic regression was estimated within the subgroup of interest and thus reduced only to include treatment, study, and treatment by study interaction.

Source: [SCE-Appendix 1-Table 3.2-3b, Table 3.2-3d]

Regarding disability parameters, the reduction in risk of 3-month disability progression up to month 24 for fingolimod 0.5 mg compared to placebo was greater for Group GA1 than for Group IFN1 for both subgroups of failures and non-responders (see Table 9). In Group GA1, treatment with fingolimod 0.5 mg resulted in a reduction in risk of 3-month disability progression up to Month 24 compared to placebo of 66.1% for failures (HR: 0.339, 95% CI: 0.138, 0.832) and 55.7% for non-responders (HR: 0.443, 95% CI: 0.193, 1.014). In Group IFN1, treatment with fingolimod 0.5 mg resulted in a small reduction in risk of 3- month disability progression up to Month 24 compared to placebo of 6.4% for failures (HR: 0.936, 95% CI: 0.500, 1.754) and 15.4% for non-responders (HR: 0.846, 95% CI: 0.460, 1.554). Overall, there was a trend towards beneficial effect of fingolimod 0.5 mg on 3- month disability progression in GA1 and IFN1 groups both in failures and non-responders; however statistical significance is only reached in the GA1 failures subgroup. A reduction of the risk for 6-month confirmed disability progression in all subgroups and the reduction for fingolimod 0.5 mg versus placebo was also observed and almost similar in both subgroups of failures and non-responders in group GA1 (33.8% and 39.6%) and in group IFN1 (44%). However, none of the comparison reaches statistical significance (see Table 10).

Table 9. Proportion of patients free of 3-month confirmed disability progression at Month 24 , pooled studies D2301/D2309

	FTY720 0.5 mg	Placebo	HR (95%CI)
Group GA1			
Failures	84.7%	61.6 %	0.339 (0.138,0.832)
	P=0.007		
Non responders	80.7%	63.3%	0.443 (0.193,1.014)
	P= 0.026		
Group INF1			
Failures	77.9%	75.3%	0.936 (0.500, 1.754)
	P=0.727		
Non responders	77.3%	72.4%	0.846 (0.460, 1.554)
	P=0.377		

Table 10. Proportion of patients free of 6-month confirmed disability progression at month 24 , pooled studies D2301/D2309

	FTY720 0.5 mg	Placebo	HR (95%CI)
Group GA1			
Failures	84.7%	74.5 %	0.662 (0.255, 1.715)
	P=0.172		
Non responders	86.2%	74.6%	0.604 (0.232, 1.571)
	P=0.104		
Group INF1			
Failures	84.4%	82.6%	0.560 (0.250, 1.255)
	P=0.241		
Non responders	87.1%	80.4%	0.559 (0.260, 1.205)
	P=0.163		

Regarding MRI parameters, the number of new/newly T2 lesions and the number of GD enhancing lesions were significantly reduced for fingolimod 0.5 mg versus placebo in failures and non-responders subgroups of both groups GA1 and INF1. These differences were statistically significant (see Tables 11 and 12).

Table 11. Number of new/newly enlarged T2 lesions at month 24, Group GA1 and IFN1, by subgroup (failures and non- responders) and treatment, pooled studies D2301/D2309, pooled FAS

	Group GA1			Group IFN1		
	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
Overall	**N′ = 98**	**N′ = 76**	**N′ = 90**	**N′ = 172**	**N′ = 178**	**N′ = 156**
	n* = 65	n* = 56	n* = 63	n* = 120	n* = 144	n* = 112
Model estimates from NB model**						
Estimated lesion count	0.799	0.698	4.387	0.713	1.468	3.514
95% CI	(0.399; 1.601)	(0.333; 4.466)	(2.263; 8.505)	(0.456; 1.114)	(1.016; 2.120)	(2.375; 5.279)
Lesion count ratio to placebo	0.182	0.159		0.201	0.414	
95% CI	(0.070; 0.476)	(0.059; 0.430)		(0.111; 0.366)	(0.241; 0.713)	
p-value	< 0.001	< 0.001		< 0.001	< 0.001	
Failures	**N′ = 75**	**N′ = 57**	**N′ = 76**	**N′ = 128**	**N′ = 146**	**N′ = 124**
	n* = 47	n* = 43	n* = 54	n* = 93	n* = 117	n* = 90
Model estimates from NB model**						
Estimated lesion count	1.077	0.898	5.099	0.834	1.594	3.937
95% CI	(0.537; 2.160)	(0.434; 1.859)	(2.745; 9.471)	(0.507; 1.370)	(1.065; 2.385)	(2.551; 6.075)
Lesion count ratio to placebo	0.211	0.176		0.212	0.405	
95% CI	(0.083; 0.536)	(0.068; 0.458)		(0.110; 0.410)	(0.224; 0.732)	
p-value	0.001	< 0.001		< 0.001	0.003	
Non-responders	**N′ = 80**	**N′ = 65**	**N′ = 79**	**N′ = 148**	**N′ = 151**	**N′ = 134**
	n* = 51	n* = 49	n* = 53	n* = 104	n* = 119	n* = 92
Model estimates from NB model**						
Estimated lesion count	0.514	0.801	5.436	0.753	1.405	3.531
95% CI	(0.249; 1.060)	(0.375; 1.714)	(2.571; 11.493)	(0.468; 1.212)	(0.927; 2.130)	(2.252; 5.537)
Lesion count ratio to placebo	0.094	0.147		0.213	0.398	
95% CI	(0.033; 0.268)	(0.051; 0.428)		(0.111; 0.411)	(0.216; 0.734)	
p-value	< 0.001	< 0.001		< 0.001	0.003	

NB = negative binomial.
N′ = number of patients in this subgroup
n* = number of observations considered in this analysis: non-missing, T2 assessments at Month 24.
** NB regression model, log-link, adjusted for treatment, study, and treatment by study interaction for the overall result, and for treatment, study, subgroup, treatment by study interaction, and treatment by subgroup interaction for subgroup analyses. For subgroup analyses where the model does not converge, the estimates within the subgroup of interest are based on the reduced model adjusted for treatment, study, and treatment by study interaction.
Source: [SCE-Appendix 1-Table 3.2-12b, Table 3.2-12d]

Table 12. Number of Gd-emhancing T1 lesions at month 24, Group GA1 and IFN1, by subgroup (failures and non- responders) and treatment, pooled studies D2301/D2309, pooled FAS

	Group GA1			Group IFN1		
	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
Overall	N′ = 98 n* = 67	N′ = 76 n* = 56	N′ = 90 n* = 64	N′ = 172 n* = 121	N′ = 178 n* = 145	N′ = 156 n* = 113
Model estimates from NB model**						
Estimated lesion count	0.151	0.099	1.363	0.111	0.409	1.000
95% CI	(0.042; 0.540)	(0.028; 0.343)	(0.565; 3.286)	(0.052; 0.238)	(0.252; 0.666)	(0.614; 1.628)
Comparison to placebo						
Lesion count ratio to placebo	0.110	0.072		0.111	0.409	
95% CI	(0.023; 0.521)	(0.016; 0.333)		(0.045; 0.274)	(0.206; 0.816)	
P-value	0.005	< 0.001		< 0.001	0.011	
Failures	N′ = 75 n* = 49	N′ = 57 n* = 43	N′ = 76 n* = 55	N′ = 128 n* = 93	N′ = 146 n* = 118	N′ = 124 n* = 91
Model estimates from NB model**						
Estimated lesion count	0.207	0.127	1.581	0.121	0.421	1.165
95% CI	(0.057; 0.755)	(0.037; 0.439)	(0.683; 3.659)	(0.052; 0.279)	(0.249; 0.713)	(0.679; 2.000)
Comparison to placebo						
Lesion count ratio to placebo	0.131	0.080		0.104	0.361	
95% CI	(0.028; 0.612)	(0.018; 0.359)		(0.038; 0.281)	(0.170; 0.768)	
P-value	0.010	< 0.001		<0.001	0.008	
Non-responders	N′ = 80 n* = 53	N′ = 65 n* = 49	N′ = 79 n* = 54	N′ = 148 n* = 105	N′ = 151 n* = 120	N′ = 134 n* = 93
Model estimates from NB model**						
Estimated lesion count	0.103	0.113	1.548	0.109	0.384	1.017
95% CI	(0.028; 0.372)	(0.035; 0.371)	(0.659; 3.637)	(0.048; 0.247)	(0.221; 0.668)	(0.582; 1.778)
Comparison to placebo						
Lesion count ratio to placebo	0.066	0.073		0.108	0.378	
95% CI	(0.014; 0.311)	(0.017; 0.315)		(0.040; 0.289)	(0.172; 0.829)	
P-value	< 0.001	< 0.001		<0.001	0.015	

NB = negative binomial.
N′ = number of patients in this subgroup. n* =number of observations considered in this analysis: nonmissing Gd + T1 assessments at Month 24; scans obtained less than 30 days after the last use of steroids to treat MS are excluded from this analysis.
** NB regression model, log-link, adjusted for study, treatment, and treatment by study interaction for the overall result, and for study, treatment, subgroup, treatment by study interaction, and treatment by subgroup interaction for subgroup analyses. For subgroup analyses were the model does not converge, the estimates within the subgroup of interest are based on the reduced model adjusted for treatment, study, and treatment by study interaction.
Source: [SCE-Appendix 1-Table 3.2-8b, Table 3.2-8d]

Regarding the change from baseline in volume of T2 lesions, the mean change from baseline was numerically lower for fingolimod 0.5 mg compared to placebo across all subgroups, although none of these achieved statistical significance for any subgroup in a non-parametric analysis for the Group GA1. In Group IFN1, treatment with fingolimod 0.5 mg resulted in a statistically significant reduction from baseline to Month 24 in the volume of T2 lesions compared to placebo for both subgroups of failures and non- responders. The percent change from baseline in the volume of T2 lesions was statistically significant for fingolimod 0.5 mg compared to placebo for all subgroups (see Table 13).

Table 13. Change from baseline in volume T2 lesions at month 24, Group GA1 and IFN1, by subgroup (failures and non- responders) and treatment, pooled studies D2301/D2309, pooled FAS

	Group GA1			Group IFN1		
	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
Overall	N′ = 98	N′ = 76	N′ = 90	N′ = 172	N′ = 178	N′ = 156
Change from Baseline (mm^3)	n* = 67	n* = 56	n* = 63	n* = 119	n* = 145	n* = 111
Median (mean)	-108.70 (-205.29	-54.33 (-190.07)	-15.12 (1037.85)	-151.65 (-421.79)	-45.78 (6.46)	303.29 (802.93)
p-value vs. placebo (Wilcoxon)	0.012	0.101		< 0.001	< 0.001	
Percent change from Baseline	n* = 64	n* = 53	n* = 63	n* = 117	n* = 144	n* = 108
Median (mean)	-9.08 (-2.93)	-6.79 (-0.64)	-0.53 (10.57)	-8.00 (-1.63)	-2.89 (28.79)	7.64 (19.94)
p-value vs. placebo (Wilcoxon)	0.004	0.036		< 0.001	< 0.001	
Failures	N′ = 75	N′ = 57	N′ = 76	N′ = 128	N′ = 146	N′ = 124
Change from Baseline (mm^3)	n* = 49	n* = 43	n* = 55	n* = 92	n* = 118	n* = 90
Median (mean)	-231.76 (-254.35)	-80.12 (-228.78)	-2.90 (1205.41)	-258.93 (-367.29)	-55.70 (4.95)	482.13 (886.72)
p-value vs. placebo (Wilcoxon)	0.005	0.064		< 0.001	< 0.001	
Percent change from Baseline	n* = 49	n* = 43	n* = 55	n* = 92	n* = 118	n* = 90
Median (mean)	-9.76 (-1.67)	-4.02 (2.33)	-0.14 (13.64)	-8.12 (-2.00)	-1.71 (4.72)	10.30 (22.41)
p-value vs. placebo (Wilcoxon)	0.003	0.070		< 0.001	< 0.001	
Non-responders	N′ = 80	N′ = 65	N′ = 79	N′ = 148	N′ = 151	N′ = 134
Change from Baseline (mm^3)	n* = 53	n* = 49	n* = 54	n* = 103	n* = 120	n* = 92
Median (mean)	-163.09 (-413.41)	-62.95 (-213.32)	-14.71 (1218.27)	-131.62 (-261.18)	-50.07 (6.66)	267.57 (783.84)
p-value vs. placebo (Wilcoxon)	0.002	0.062		< 0.001	< 0.001	
Percent change from Baseline	n* = 52	n* = 47	n* = 54	n* = 101	n* = 119	n* = 90
Median (mean)	-9.08 (-7.05)	-5.10 (0.40)	-0.21 (11.73)	-8.05 (-0.62)	-2.96 (32.99)	5.81 (20.87)
p-value vs. placebo (Wilcoxon)	0.002	0.073		< 0.001	< 0.001	

N′ = number of patients in this subgroup.
n* = number of patients with non-missing change from Baseline in total volume of T2 lesions at Month 24.
Source: [SCE-Appendix 1-Table 3.2-14b, Table 3.2-15b, Table 3.2-14d, Table 3.2-15d]

Treatment with fingolimod 0.5 mg also resulted in statistically significant differences in percent change from Baseline in normalized brain volume at Month 24 compared to placebo for the subgroups of failures and non-responders for Group GA1 and Group IFN1 based on non-parametric and parametric analyses (see Table 14).

Table 14. Percent change from baseline in normalised brain volume at month 24, Group GA1 and IFN1, by subgroup (failures and non- responders) and treatment, pooled studies D2301/D2309, pooled FAS

	Group GA1			Group IFN1		
	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
Overall	N′ = 98 n* = 67	N′ = 76 n* = 55	N′ = 90 n* = 62	N′ = 172 n* = 118	N′ = 178 n* = 143	N′ = 156 n* = 111
Median (mean)	-0.47 (-0.50)	-0.68 (-0.77)	-1.55 (-1.71)	-0.46 (-0.51)	-0.72 (-0.81)	-1.12 (-1.44)
p-value vs. placebo (Wilcoxon)	< 0.001	< 0.002		< 0.001	< 0.001	
Failures	N′ = 75 n* = 49	N′ = 57 n* = 42	N′ = 76 n* = 54	N′ = 128 n* = 90	N′ = 146 n* = 117	N′ = 124 n* = 90
Median (mean)	-0.54 (-0.64)	-0.85 (-0.95)	-1.58 (-1.71)	-0.50 (-0.52)	-0.77 (-0.88)	-1.19 (-1.64)
p-value vs. placebo (Wilcoxon)	0.001	0.035		< 0.001	< 0.001	
Non-responders	N′ = 80 n* = 53	N′ = 65 n* = 48	N′ = 79 n* = 53	N′ = 148 n* = 102	N′ = 151 n* = 119	N′ = 134 n* = 92
Median (mean)	-0.47 (-0.49)	-0.69 (-0.68)	-1.57 (-1.70)	-0.45 (-0.49)	-0.71 (-0.77)	-1.13 (-1.49)
p-value vs. placebo (Wilcoxon)	< 0.001	0.002		< 0.001	< 0.001	

N′ = number of patients in this subgroup.
n* = number of patients with non-missing percent change from Baseline in normalized brain volume at Month 24.
Source: [SCE-Appendix 1-Table 3.2-18b, Table 3.2-18d]

2.3.3. Discussion

The efficacy post-hoc analyses of the individual studies D2301, D2302, D2309 based on the subgroup of patients either treatment-naïve or previously-treated with glatiramer acetate or interferon-beta, were already reviewed by the CHMP as part of the initial MAA and FUM 9. All of these studies showed lower aggregate ARRs for fingolimod 0.5 mg when compared to placebo for both patients with or without prior MS DMT (either treatment-naïve or previously-treated with glatiramer acetate or interferon-beta), and these findings were consistent with the overall results of each of the study, when analysed individually. In addition, in all treatment groups, previously-treated patients (with glatiramer acetate or interferon-beta) showed higher ARRs than treatment-naïve patients.

The new post-hoc efficacy analysis presented in this application relates to the pooling of studies D2301/D2309. Description of the results is presented in 2.3.2.

Overall, the presented results appeared to show beneficial effects of fingolimod 0.5 mg in the subgroup of patients previously treated with GA and these were found to be consistent with the effects observed in the overall study populations and with those patients previously treated with beta-interferon and subsequently treated with fingolimod. However, the CHMP noted some limitations in these post-hoc analyses such as the relatively small number of patients previously treated with GA or IFN (which was further reduced when the MAH selected only those patients who were exposed to GA or IFN treatment during the last year prior to screening for the fingolimod trial), the overlap between treatment failures and non-responders definitions making these subgroup analyses of limited relevance. Prior to concluding on the presented analyses, a number of concerns were raised by the CHMP regarding the need to discuss on how the differences in the placebo group between GA1 and IFN1 subgroups could affect the interpretation of the results and to provide information regarding treatment duration with IFN or GA as well as the reasons for discontinuation of these treatments (e.g lack of efficacy, tolerability issue).These concerns were adequately addressed by the MAH and therefore the CHMP was

of the opinion that the benefit-risk profile of Gilenya in RRMS patients with high disease activity despite treatment with glatiramer acetate was favourable.

Whilst concerns were initially raised regarding the absence of data in patients previously treated with other MS drugs that recently became available (e.g teriflunomide, dimethyl fumarate, alemtuzumab) or even natalizumab, the CHMP acknowledged the availability of new treatment alternatives for MS patients with efficacy comparable to well-established interferon beta or glatiramer acetate (GA) therapies, thus possibly broadening the options for neurologists at treatment initiation or in case of treatment failure. According to the MAH, because of the wording of the indication as currently approved, MS patients with high disease activity while being treated with IFN or GA can be switched to any approved DMT except fingolimod, a switch only possible for those failing IFN treatment. In the current situation, patients with high disease activity treated with new oral agents, Tecfidera (DMF) or Aubagio (teriflunomide), are not eligible for treatment with fingolimod (or natalizumab). Both products have demonstrated superiority to placebo but not to an active comparator. If these patients fail their prescribed therapy and require greater efficacy, they must undertake an additional year of therapy with IFN (or either IFN or GA for natalizumab), even if they are experiencing the effects of high disease activity before they could be prescribed fingolimod or natalizumab. However, there is currently no efficacy or safety data to support the clinical benefit of this mandatory step, while there is evidence that ongoing clinical or imaging disease activity may lead to irreversible neurological deficits in the long-term. The only alternative for potentially more efficacious treatment for these patients becomes de facto alemtuzumab (which has also demonstrated superiority to an active comparator), although there is similarly no efficacy or safety data to support this algorithm.

Given the current situation and the available therapeutic options in clinical practice, the CHMP considered that it would be unreasonable to expect separate data to be provided in patients treated with each of the marketed drugs. Taking into consideration the different mechanisms of action of fingolimod, teriflunomide and dimethyl fumarate, the CHMP was of the view that there was a reasonable scientific plausibility in the assumption that even if treatment with teriflunomide and/or dimethyl fumarate failed due to lack of efficacy, the treatment with fingolimod would be effective. In addition, the CHMP considered that the possibility to introduce potentially more effective treatment earlier, without unnecessary testing of similar alternatives in terms of efficacy in a stepwise procedure, will be beneficial for patients.

Therefore the CHMP considered that the proposed change of the indication to reflect the possible therapeutic options for Gilenya, could be acceptable, provided that amendments in section 4.1 of the SmPC are made in line with the CHMP recommendations. The final recommended wording by the CHMP is as follows:

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

- Patients with 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."

The CHMP also recommended the MAH to submit a proposal for gathering additional data on the safety and efficacy of Gilenya treatment in MS patients who were previously treated with at least one DMT , including teriflunomide, dimethyl fumarate, alemtuzumab, natalizumab. This proposal was submitted as part of the risk management plan and was considered acceptable by the PRAC/CHMP (see 2.5).

2.3.4. Conclusions

On the basis of the available data, the CHMP concluded that the proposed change in the wording of the indication (section 4.1) were acceptable.

2.4. Clinical safety

The safety profile for fingolimod 0.5 mg has been characterized during the Phase III program and in the post marketing setting since its launch, including over 63,000 MS patients who have been exposed to fingolimod for a total of more than 73,000 patient-years as of DLP of February 2013. To support the proposed modification of the indication, the MAH presented safety analysis using the same studies as for the efficacy analysis (D2301, D2309, D2301). Study D2316 was also included in the analysis to support the safety profile of fingolimod in the extended population applied for.

2.4.1. Methods – analysis of data submitted

Datasets from the clinical studies used for the safety analysis are presented in Table 15.

Table 15. Population and subpopulation groupings for safety assessment

Database	Studies	Number of patients (safety population)	Safety topics	Population/ Subpopulations
Pooled placebo-controlled safety dataset (all double-blind, placebo-controlled studies ≥ 24 months duration)	D2301 and D2309	2355	Deaths SAEs AEs leading to study drug discontinuation All AEs.	**Overall population**, and **Group GA1** - GA at any time in the 1 year prior to the screening visit **Group IFN1** - IFN-β at any time in the 1 year prior to the screening visit **Group GA** - Patients previously treated with GA at any time
Study D2302 (double-blind active-controlled, double-dummy, studies ≥ 12 months duration)	D2302	1280	Deaths SAEs AEs leading to study drug discontinuation All AEs.	**Overall population**, and **Group GA1** - GA at any time in the 1 year prior to the screening visit **Group IFN1** - IFN-β at any time in the 1 year prior to the screening visit **Group GA** - Patients previously treated with GA at any time
Study D2316 (uncontrolled, open-label study ≥ 16 weeks duration)	D2316	2415	Deaths SAEs AEs leading to study drug discontinuation All AEs.	**Overall population**, and **Group GA1** - GA at any time in the 6 months prior to enrollment

GA = glatiramer acetate IFN-β = interferon beta

Note: In Study D2302, 12 patients were excluded from the Safety population because they were randomized in error and did not receive study drug [Study D2302-Table 14.1-1.4].

2.4.2. Results

2.4.2.1. Patient exposure

Patient exposure is presented in Tables 16 and 17.

Table 16 Duration of exposure to study drug by subpopulation and treatment (Pooled studies D2301/D2309 safety population: Groups GA1 and IFN1)

Duration of exposure (days) Statistic	Group GA1			Group IFN1		
	FTY720 1.25 mg N' = 98	FTY720 0.5 mg N' = 76	Placebo N' = 90	FTY720 1.25 mg N' = 172	FTY720 0.5 mg N' = 178	Placebo N' = 156
N	98	76	90	172	178	156
Mean (SD)	528.9 (265.62)	570.8 (251.98)	533.6 (254.34)	553.3 (255.96)	620.6 (215.97)	577.2 (238.43)
Median	688.0	718.0	699.5	714.5	720.0	721.0
Min – max	1 - 831	2 - 831	9 - 836	1 - 836	9 - 881	9 – 890
Patient years	141.9	118.8	131.5	260.5	302.5	246.5

Group GA1 = Patients previously treated with GA at any time in the 1 year prior to Screening.
Group IFN1 = Patients previously treated with IFN (any of the 3 IFN-β treatments) at any time in the 1 year prior to Screening
N'= number of patients in this subpopulation.
Duration of exposure - the total actual days patients took the study medication
Patient years - the sum of the number of days on study drug for all patients in each treatment group divided by 365.25.

Table 17 Duration of exposure to study drug by subpopulation and treatment (study D2302 safety population: Groups GA1 and IFN1)

Duration of exposure (days) Statistic	Group GA1			Group IFN1		
	FTY720 1.25 mg N = 36	FTY720 0.5 mg N = 31	IFN-β1a N = 47	FTY720 1.25 mg N = 176	FTY720 0.5 mg N = 190	IFN-β1a N = 167
n	36	31	47	175 *	190	167
Mean (SD)	317.3 (117.47)	335.0 (83.26)	350.0 (60.11)	332.8 (90.47)	344.8 (74.32)	328.1 (93.36)
Median	370.5	364.0	365.0	364.0	365.0	362.0
Min – max	2 – 392	61 – 402	88 – 427	1 – 428	3 – 409	6 – 400
Patient years	31.3	28.4	45.0	159.4	179.4	150.0

2.4.2.2. Adverse Events

These are presented in Tables 18 and 19.

Table 18 Number (%) of patients with AEs (at least 10% in any treatment group) by preferred term and treatment (pooled Studies D2301/D2309 safety population: Groups GA1 and IFN1)

	Group GA1			Group IFN1		
Preferred term	FTY720 1.25 mg N' = 98 n (%)	FTY720 0.5 mg N' = 76 n (%)	Placebo N' = 90 n (%)	FTY720 1.25 mg N' = 172 n (%)	FTY720 0.5 mg N' = 178 n (%)	Placebo N' = 156 n (%)
Any preferred term	94 (95.9)	74 (97.4)	88 (97.8)	165 (95.9)	175 (98.3)	148 (94.9)
Nasopharyngitis	28 (28.6)	21 (27.6)	23 (25.6)	52 (30.2)	51 (28.7)	43 (27.6)
Headache	26 (26.5)	15 (19.7)	26 (28.9)	47 (27.3)	49 (27.5)	40 (25.6)
Upper respiratory tract infection	22 (22.4)	15 (19.7)	26 (28.9)	36 (20.9)	40 (22.5)	33 (21.2)
Cough	8 (8.2)	13 (17.1)	11 (12.2)	29 (16.9)	27 (15.2)	17 (10.9)
Nausea	17 (17.3)	13 (17.1)	15 (16.7)	21 (12.2)	25 (14.0)	21 (13.5)
Pain in extremity	6 (6.1)	11 (14.5)	13 (14.4)	18 (10.5)	20 (11.2)	13 (8.3)
Dizziness	11 (11.2)	10 (13.2)	9 (10.0)	21 (12.2)	22 (12.4)	18 (11.5)
Fatigue	10 (10.2)	9 (11.8)	11 (12.2)	17 (9.9)	16 (9.0)	16 (10.3)
Arthralgia	9 (9.2)	8 (10.5)	10 (11.1)	13 (7.6)	18 (10.1)	17 (10.9)
Hypertension	12 (12.2)	8 (10.5)	1 (1.1)	20 (11.6)	13 (7.3)	8 (5.1)
Influenza	7 (7.1)	8 (10.5)	12 (13.3)	15 (8.7)	16 (9.0)	9 (5.8)
Migraine	9 (9.2)	8 (10.5)	8 (8.9)	9 (5.2)	12 (6.7)	4 (2.6)
Urinary tract infection	13 (13.3)	8 (10.5)	17 (18.9)	12 (7.0)	18 (10.1)	25 (16.0)
Diarrhoea	12 (12.2)	7 (9.2)	14 (15.6)	23 (13.4)	25 (14.0)	15 (9.6)
Sinusitis	10 (10.2)	7 (9.2)	8 (8.9)	17 (9.9)	24 (13.5)	14 (9.0)
Bronchitis	11 (11.2)	7 (9.2)	6 (6.7)	13 (7.6)	14 (7.9)	8 (5.1)
Dyspnoea	8 (8.2)	6 (7.9)	9 (10.0)	21 (12.2)	15 (8.4)	14 (9.0)
Lymphopenia	6 (6.1)	5 (6.6)	0 (0.0)	20 (11.6)	14 (7.9)	0 (0.0)
Back pain	9 (9.2)	5 (6.6)	9 (10.0)	18 (10.5)	12 (6.7)	9 (5.8)
Melanocytic naevus	8 (8.2)	5 (6.6)	8 (8.9)	10 (5.8)	14 (7.9)	21 (13.5)
Insomnia	5 (5.1)	5 (6.6)	9 (10.0)	7(4.1)	13(7.3)	14(9.0)
Depression	6 (6.1)	4 (5.3)	8 (8.9)	16 (9.3)	19 (10.7)	12 (7.7)
Rash	7 (7.1)	4 (5.3)	9 (10.0)	7 (4.1)	8 (4.5)	8 (5.1)

Group GA1 = Patients previously treated with GA at any time in the 1 year prior to Screening.
Group IFN1 = Patients previously treated with IFN (any of the 3 IFN-β treatments) at any time in the 1 year prior to Screening.
N'= number of patients in this subpopulation. All percentages use N' as the denominator.

Preferred terms are sorted in descending frequency in the Group GA1 FTY720 0.5 mg arm.
A patient with multiple adverse events (AEs) within a preferred term is counted only once in the preferred term for that treatment.

Table 19 Number (%) of patients with AEs (at least 10% in any treatment group) by preferred term and treatment (study D2302 safety population: Groups GA1 and IFN1)

	Group GA1			Group IFN1		
	FTY720 1.25 mg N' = 36	FTY720 0.5 mg N' = 31	IFN-β1a N' = 47	FTY720 1.25 mg N' = 176	FTY720 0.5 mg N' = 190	IFN-β1a N' = 167
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any preferred term	34 (94.4)	28 (90.3)	45 (95.7)	159 (90.3)	168 (88.4)	149 (89.2)
Nasopharyngitis	11 (30.6)	12 (38.7)	7 (14.9)	31 (17.6)	39 (20.5)	36 (21.6)
Headache	6 (16.7)	7 (22.6)	7 (14.9)	46 (26.1)	51 (26.8)	32 (19.2)
Back pain	2 (5.6)	5 (16.1)	2 (4.3)	12 (6.8)	13 (6.8)	7 (4.2)
Nausea	2 (5.6)	4 (12.9)	4 (8.5)	11 (6.3)	22 (11.6)	11 (6.6)
Dizziness	1 (2.8)	4 (12.9)	1 (2.1)	10 (5.7)	13 (6.8)	11 (6.6)
Hypoaesthesia	1 (2.8)	4 (12.9)	3 (6.4)	7 (4.0)	3 (1.6)	6 (3.6)
Diarrhoea	4 (11.1)	2 (6.5)	4 (8.5)	13 (7.4)	15 (7.9)	11 (6.6)
Fatigue	7 (19.4)	2 (6.5)	4 (8.5)	21 (11.9)	21 (11.1)	18 (10.8)
Alanine aminotransferase increased	4 (11.1)	2 (6.5)	0 (0.0)	6 (3.4)	8 (4.2)	3 (1.8)
Myalgia	0 (0.0)	2 (6.5)	5 (10.6)	7 (4.0)	5 (2.6)	17 (10.2)
Dry eye	4 (11.1)	1 (3.2)	1 (2.1)	1 (0.6)	1 (0.5)	0 (0.0)
Influenza like illness	1 (2.8)	1 (3.2)	20 (42.6)	4 (2.3)	6 (3.2)	44 (26.3)
Arthralgia	0 (0.0)	1 (3.2)	6 (12.8)	8 (4.5)	7 (3.7)	11 (6.6)
Toothache	4 (11.1)	0 (0.0)	0 (0.0)	5 (2.8)	6 (3.2)	4 (2.4)
Pyrexia	0 (0.0)	0 (0.0)	13 (27.7)	8 (4.5)	9 (4.7)	16 (9.6)
Melanocytic naevus	4 (11.1)	0 (0.0)	1 (2.1)	15 (8.5)	11 (5.8)	12 (7.2)

Group GA1 = Patients previously treated with GA at any time in the 1 year prior to Screening.
Group IFN1 = Patients previously treated with IFN (any of the 3 IFN-β treatments) at any time in the 1 year prior to Screening.
N' = number of patients in this subpopulation. All percentages use N' as the denominator.
Preferred terms are sorted in descending frequency in the Group GA1 FTY720 0.5 mg arm.
A patient with multiple adverse events (AEs) within a preferred term is counted only once in the preferred term for that treatment.
Source: [SCS-Appendix 1-Table 1.1-2c, Table 1.1-2d]

In study 2316, adverse events were reported in 331 of 438 patients (75.6%) in Group GA1, which could be possibly related to the shorter treatment period of 16 weeks compared to the other analysed studies. The highest incidence of patients with AEs was reported in the SOC infections and infestations, with 36.5% of patents in Group GA1. The preferred terms with the highest incidence were nasopharyngitis (14.6%) and influenza (4.1%). Nervous system disorders were reported in 25.3% of patients, with 11.6% reporting headache. Other commonly reported AEs (preferred terms) were fatigue in 9.4% of patients and lymphopenia in 7.1% of patients.

2.4.2.3. Serious adverse event/deaths/other significant events

Number of patients with SAEs (at least 2 patients in any treatment group) are presented in Tables 20 and 21.

Table 20. Number (%)of patients with SAEs (at least 2 patients in any treatment group) by preferred term and treatment (Pooled studies D2301/D2309 safety population: Group GA1 and IFN1)

	Group GA1			Group IFN1		
	FTY720 1.25 mg N = 98	FTY720 0.5 mg N = 76	Placebo N = 90	FTY720 1.25 mg N = 172	FTY720 0.5 mg N = 178	Placebo N = 156
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any preferred term	19 (19.4)	15 (19.7)	14 (15.6)	30 (17.4)	23 (12.9)	18 (11.5)
Syncope	0 (0.0)	2 (2.6)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)
Nephrolithiasis	0 (0.0)	2 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple sclerosis relapse	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	2 (1.1)	3 (1.9)
Bradycardia	1 (1.0)	0 (0.0)	1 (1.1)	5 (2.9)	0 (0.0)	0 (0.0)
Basal cell carcinoma	2 (2.0)	0 (0.0)	3 (3.3)	1 (0.6)	4 (2.2)	1 (0.6)
Abdominal pain	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.6)	2 (1.1)	0 (0.0)
Chest pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)

Table 21. Number (%)of patients with SAEs (at least 2 patients in any treatment group) by preferred term and treatment (Study D2302 safety population: Group GA1 and IFN1)

	Group GA1			Group IFN1		
	FTY720 1.25 mg N = 36	FTY720 0.5 mg N = 31	IFN-β1a N = 47	FTY720 1.25 mg N = 176	FTY720 0.5 mg N = 190	IFN-β1a N = 167
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any preferred term	2 (5.6)	3 (9.7)	2 (4.3)	23 (13.1)	17 (8.9)	11 (6.6)
Atrioventricular block second degree	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.5)	0 (0.0)
Bradycardia	1 (2.8)	0 (0.0)	0 (0.0)	4 (2.3)	1 (0.5)	0 (0.0)
Sinus bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.5)	0 (0.0)
Malignant melanoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)

Six deaths were reported during the study periods presented in this submission. Three deaths were reported in study 2301, 1 patient in the fingolimod 1.25 mg treatment arm and 2 patients in the placebo arm, none of these patients were included in any of the subpopulations based on prior treatment. One patient in the placebo arm died on Day 269 (65 days after last dose) in study D2309. Two deaths were reported, both in the fingolimod 1.25 mg arm in study D2302. One patient was included in Group IFN1. This death occurred more than 60 days after last study dose, and was attributed to Herpes simplex encephalitis, which began during study treatment following a course of high-dose corticosteroids for an MS relapse and was complicated by a delay in antiviral treatment. Two additional patient deaths were reported after the database lock. In study D2316, one death was reported in the fingolimod 0.5 mg arm of this single-arm study in a patient that was not included in the subpopulation presented.

2.4.2.4. Laboratory findings

Results of laboratory examinations for the individual subgroups were not included in this submission. The safety evaluation between the subgroups is limited to the AE analyses which were considered acceptable by the CHMP, taking into account that clinically significant laboratory abnormalities would be reported as AEs by the investigator and discussed in 2.4.2.2.

2.4.2.5. Safety in special population

No new analyses were performed in special populations to support to the present application.

2.4.2.6. Discontinuation due to adverse events

These are presented in Tables 22 and 23.

Table 22. Number (%) of patients with AEs leading to study drug discontinuttion (at least 2 patients in any treatment group) by preferred term and treatment (Pooled studies D2301/D2309 safety population: Group GA1 and IFN1)

	Group GA1			Group IFN1		
	FTY720 1.25 mg N = 98	FTY720 0.5 mg N = 76	Placebo N = 90	FTY720 1.25 mg N = 172	FTY720 0.5 mg N = 178	Placebo N = 156
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any preferred term	16 (16.3)	15 (19.7)	13 (14.4)	32 (18.6)	21 (11.8)	12 (7.7)
Gamma-glutamyltransferase increased	0 (0.0)	4 (5.3)	0 (0.0)	1 (0.6)	6 (3.4)	0 (0.0)
Dyspnoea	2 (2.0)	3 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphopenia	0 (0.0)	2 (2.6)	0 (0.0)	5 (2.9)	1 (0.6)	0 (0.0)
Liver function test abnormal	1 (1.0)	2 (2.6)	0 (0.0)	2 (1.2)	0 (0.0)	1 (0.6)
Basal cell carcinoma	2 (2.0)	1 (1.3)	3 (3.3)	1 (0.6)	2 (1.1)	1 (0.6)
Alanine aminotransferase increased	1 (1.0)	1 (1.3)	0 (0.0)	3 (1.7)	4 (2.2)	1 (0.6)
Aspartate aminotransferase increased	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.6)
Bradycardia	1 (1.0)	0 (0.0)	1 (1.1)	2 (1.2)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)	1 (1.1)	2 (1.2)	0 (0.0)	0 (0.0)
Hepatic enzyme increased	1 (1.0)	0 (0.0)	0 (0.0)	3 (1.7)	0 (0.0)	0 (0.0)

Table 23. Number (%) of patients with AEs leading to study drug discontinuation (at least 2 patients in any treatment group) by preferred term and treatment (Study D2302 safety population: Group GA1 and IFN1)

	Group GA1			Group IFN1		
	FTY720 1.25 mg N = 36	FTY720 0.5 mg N = 31	IFN-β1a N = 47	FTY720 1.25 mg N = 176	FTY720 0.5 mg N = 190	IFN-β1a N = 167
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any primary SOC	5 (13.9)	2 (6.5)	0 (0.0)	19 (10.8)	11 (5.8)	7 (4.2)
Hepatic enzyme increased	0 (0.0)	1 (3.2)	0 (0.0)	1 (0.6)	3 (1.6)	1 (0.6)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	2 (1.1)	1 (0.6)
Transaminases increased	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)
Malignant melanoma	0 (0.0)	0 (0.0) *	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)

In study 2316, AEs resulting in study drug discontinuation were reported in a similar proportion of patients in Group GA1 and the overall population, with the highest incidence in the investigations SOC due to liver enzyme abnormalities.

2.4.2.7. Additional data

During the evaluation, the MAH presented additional data on switching from natalizumab to fingolimod from post-marketing experience and clinical trial (study D2324). According to the MAH, about 10 to 15% of all fingolimod-treated patients had previously been treated and switched from natalizumab. The post-marketing data did not show any increased reporting of serious adverse events (SAEs) in patients who switched from natalizumab to fingolimod. In particular, there is no pattern of any increase for any type of potential opportunistic infections with the exception of Progressive multifocal leukoencephalopathy (PML). Few patients were reported with PML within the first months of switching from natalizumab to fingolimod, during fingolimod treatment. These cases of PML were attributed to previous natalizumab treatment.

Study D2324 investigated disease control and safety in patients switching from natalizumab to fingolimod after different washout periods (8, 12, and 16 weeks). Although the study was terminated

early (n = 142 instead of n = 600) based on the publication of data after the start of this study, that addressed the return of MS disease after stopping the treatment with natalizumab, it contains useful information regarding the optimal interval of switching from natalizumab to fingolimod with respect to both risk of disease recurrence (disease control) and overall safety. Switching to fingolimod after 16 weeks washout was associated with notably higher disease activity on MRI when compared to 8 to 12 weeks washout. The reported results did not demonstrate substantial difference between washout period of 8 or 12 weeks in terms of efficacy or safety parameters. However, patients in the 8 weeks washout group had lower mean number of active T2 lesions (primary objective; 8 weeks – 1.9, 12 weeks - 4.1 and 16 weeks – 7.7) when adjusted for the observational period. Similarly, changes in key secondary variables had tendency for a better outcome in a group with 8 weeks washout period. The mean number (SD) of active (new or newly enlarging) T2 lesions, adjusted for the duration of the washout period, was the lowest in the 8 weeks group (0.4 [2.71]), followed by the 12 weeks group (2.1 [11.15]) and the highest in the 16 weeks group (3.6 [7.54]). The mean number (SD) of active (new or newly enlarging) T2 lesions during the first 8 weeks of fingolimod treatment was the lowest in the 8 weeks group (1.5 [4.56]), followed by the 12 weeks group (2.1 [5.50]) and the highest in the 16 weeks group (4.2 [10.24]). Overall, the least MRI activity was seen in patients who had a washout period of 8 weeks. More patients switching to fingolimod within less than 16 weeks remained relapse-free. Most relapses occurred between 4 and 5 months after discontinuation of natalizumab. There were no unusually severe relapses. No new safety or tolerability signals emerged from this study. Particularly, there was no difference in AE profile, SAE, or discontinuation rates between the various washout groups. The infection rates, types of infections and severe infections did not notably differ between groups and there were no differences compared to the established safety profile of fingolimod. There was no difference across groups with respect to abnormal liver function tests (LFTs). There was no case of PML or death.

Literature data (F. Rinaldi et al., 2012, MSJ, 18 (11) 1640-1643) also reported disease reactivation in 11 out of 22 patients switched to fingolimod after 3 months washout period.

2.4.3. Discussion

In pooled studies D2301/D2309, the safety data reported in Groups GA1 and IFN1 were generally consistent with the known fingolimod safety profile. The most commonly reported SOC were ‘infections and infestations’, ‘nervous system disorders’ and ‘gastro-intestinal disorders’. The overall incidence of patients with SAEs was low, but was slightly higher in patients treated with fingolimod 0.5 mg compared to placebo in both pooled Group GA1 (19.7% vs 15.6%) and Group IFN1 (12.9% vs 11.5%).

The incidence of SAEs was higher in Group GA1 across treatment arms, including the placebo arm compared to Group IFN1 and the overall pooled safety population. The frequency of AEs leading to discontinuation of study drug was low, but consistently slightly higher in patients treated with fingolimod 0.5 mg compared to placebo across both Groups GA1 and IFN1. Similar to SAEs, the incidence of AEs leading to study drug discontinuation was slightly higher across the fingolimod 0.5 mg and placebo arms in Group GA1 compared to Group IFN1. Of the 6 deaths reported for the studies included in this application, none occurred on fingolimod 0.5 mg, and one death in Group IFN1 with fingolimod 1.25 mg dose, more than 60 days after last study dose was attributed to Herpes simplex encephalitis, which began during study participation.

Some specific AEs that were reported more commonly in MS patients treated with fingolimod 0.5 mg than in placebo-treated patients were: infections (nasopharyngitis, bronchitis, herpes infections), liver enzyme elevations (most often reported as increases in ALT and gamma-glutamyltransferase (GGT)), lymphopenia, hypertension, respiratory AEs (primarily driven by cough). No increases in neoplasms

(overall) were seen in the comparison of fingolimod 0.5 mg to placebo for Group GA1 or Group IFN1. No cases of macular edema were reported in fingolimod 0.5 mg treated patients in Group GA1 or Group IFN1. There was an increase in the incidence of migraine with fingolimod 0.5 mg compared to placebo in both subpopulations, which was more pronounced in Group IFN1, however at a lower incidence overall in this subpopulation compared to Group GA1. Vascular disorder events were more frequent in patients treated with fingolimod 0.5 mg compared to placebo in both Group GA1 and Group IFN1. This was primarily driven by the proportion of patients reporting hypertension, a known side effect of fingolimod. The difference was more pronounced in Group GA1 due to a considerably lower incidence of hypertension in the placebo arm in GA1 (1.1%) than in Group IFN1 (5.1%). More cases of BCC (Basal Cell Carcinoma) were reported on fingolimod 0.5 mg (4 patients; 2.2%) than on placebo (1 patient; 0.6%) in Group IFN1; in Group GA1 more cases of BCC were reported on placebo (3 patents; 3.3%) than on fingolimod 0.5 mg (1 patient; 1.3%). Non-BCC skin malignancies were rare in all subpopulations and were too infrequent to draw meaningful conclusions.

Overall, slight increases in some specific AEs were observed in Group IFN1 (lymphopenia, headache, diarrhea) and in Group GA1 (cardiac events driven by higher incidence of palpitation AEs, hypertension, nausea, respiratory disorders). Isolated seizure events were reported in all treatment arms in Group GA1, without evidence of a dose response or a particular seizure type predominating. However these specific AEs are consistent with the known safety profile of fingolimod. The presented safety analyses did not suggest any clinically-relevant differences in the comparisons of Group GA1 and Group IFN1. Rates of WBC decrease reported as AEs overall were comparable between the fingolimod 0.5 mg arms in Groups IFN1 and GA1. Bradycardia was rarely reported (0-1 patient in the fingolimod 0.5 mg or placebo arms in Groups GA1 and IFN1). There were no reports of atrioventricular (AV) blocks in Group GA1, and only rare reports of first-degree AV block in Group IFN1 reported (2-3 patients in the fingolimod 0.5 mg or placebo arms).

As mentioned by the MAH, for study D2302, the number of patients in Group GA1 was small. There was also a considerable imbalance in the number of patients in the fingolimod 0.5 mg and IFN-β1a arms, in both the Group GA1 and IFN1 subpopulations, making difficult the interpretation of the analysis. Nevertheless, the overall findings were consistent with the safety data from the pooled studies and therefore, the CHMP considered these data as supportive of the safety profile in the analysed populations, ie patients previously treated with IFN and GA.

As compared to IFN and GA, the safety profile of other DMTs (e.g teriflunomide, dimethyl fumarate, alemtuzumab) in the MS population, is less known and safety information regarding switching from another first line DMT is limited. During the evaluation, the MAH proposed to maintain their proposed indication by introducing different levels of risk minimisation regarding certain DMTs (e.g teriflunomide, alemtuzumab), based on their pharmacodynamic/pharmacokinetic and safety profiles. Because alemtuzumab has profound and prolonged immunosuppressive effects and the actual duration of these effects is unknown, the MAH proposed to not recommend initiating treatment with Gilenya after alemtuzumab unless the benefits of such treatment clearly outweigh the risks for the individual patient. This was considered acceptable by the CHMP. The CHMP also agreed that the additional data presented for the switching from natalizumab supported the existing SmPC warning in section 4.4 that concomitant immune effects, could occur for up to 2-3 months following discontinuation of natalizumab. For the other DMTs, the proposal for risk minimisations were also considered acceptable, provided amendments are made in section of the SmPC in line with the CHMP recommendations (see 2.6). The CHMP also recommended the MAH to submit a proposal for gathering additional data on the safety and efficacy of Gilenya treatment in MS patients who were previously treated with at least one DMT including teriflunomide, dimethyl fumarate, alemtuzumab, natalizumab, prior to final conclusions are made on this variation. This proposal was submitted as part of the risk management plan and was considered acceptable by the PRAC/CHMP (see 2.5).

2.4.4. Conclusions

On the basis of the available data, the CHMP concluded that the proposed warnings (section 4.4) to support the proposed change in the indication (section 4.1), were acceptable (see 2.6).

2.4.5. PSUR cycle

The CHMP, having considered the data submitted in the application and following the update of the RMP (version 7.3), was of the opinion that the PSUR cycle should remain unchanged.

2.5. Risk management plan

During the evaluation, the CHMP agreed with the introduction of different levels of risk minimisation regarding certain DMTs (e.g teriflunomide, alemtuzumab) as discussed in detailed above. In addition the CHMP requested the MAH to submit a proposal (e.g registry) for systematically gathering additional data on the safety and efficacy of Gilenya treatment in MS patients who were previously treated with at least one DMT including teriflunomide, dimethyl fumarate, alemtuzumab, natalizumab.

Subsequently, the MAH submitted an updated RMP, version 7.1 to address the above recommendations.

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 7.1 the PRAC considers by consensus that the risk management system for fingolimod (GILENYA) in the treatment of highly active relapsing remitting multiple sclerosis in

- adult patients with high disease activity despite treatment with a ~~beta-interferon~~ disease modifying agent. 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 beta-interferon~~ with a disease modifying agent. 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 on-going severe relapses, as compared to the previous year;

or

- adult 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;

is acceptable. The following point should be taken into account with the next update:

- The MAH proposed as additional pharmacovigilance studies to evaluate the safety and efficacy of Gilenya in patients switching from other disease modifying agents to amend the protocol for the on-going post-authorisation safety study FTY720D2406. The MAH should submit an updated protocol taking into account the comments (amendment of inclusion criteria: patients switching from disease modifying therapies to fingolimod, study objectives, statistical analysis plan) together with sample size calculation based on assumptions regarding the number of patients expected in each newly defined group.

Advice on conditions of the marketing authorisation

The PRAC do not advise any changes to the current conditions of the Marketing Authorisation.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Table 24. Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose • Hypertension • Liver transaminase elevation • Posterior Reversible Encephalopathy Syndrome (PRES) • Macular oedema • Infections • Leucopenia and lymphopenia • Reproductive toxicity • Bronchoconstriction • Varicella-Zoster virus infections
Important potential risks	• Skin cancer • Acute disseminated encephalomyelitis-like (ADEM-like) events • Lymphoma • Other malignant neoplasms • Thromboembolic events • QT interval prolongation • Convulsions • Progressive multifocal leukoencephalopathy (PML) • Herpes viral infections other than VZV • Off-label use • Pulmonary oedema • Decreased renal function • Atypical MS relapse • Hemophagocytic syndrome • Hypersensitivity
Potential interactions	• Ketoconazole • Carbamazepine • Beta blockers • Class Ia or Class III anti-arrhythmic medicinal products
Missing information	• Elderly patients • Paediatric patients • Pregnant and lactating women • Patients with diabetes mellitus • Patients with cardiovascular conditions including myocardial

Summary of safety concerns	
	infarction, angina pectoris, Raynaud's phenomenon, cardiac failure or severe cardiac disease, increased QTc interval, uncontrolled hypertension, patients at risk for bradyarrhythmia and who may not tolerate bradycardia, patients with second degree Mobitz type 2 or higher AV block, sick-sinus syndrome, sino-atrial heart block, history of cardiac arrest, cerebrovascular disease and severe sleep apnea) • Long-term risk of cardiovascular morbidity/mortality • Long-term risk of malignant neoplasms • Unexplained death • Switch from other disease modifying agent

The PRAC agreed.

Pharmacovigilance plans

Table 25. Ongoing and planned studies in the pharmacovigilance development plan

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status	Date for submission of final reports
Study FTY720D2399 A single arm, open-label, multicenter study evaluating the long-term safety, tolerability and efficacy of 0.5 mg fingolimod (FTY720) administered orally once daily in patients with multiple sclerosis. Category 3	To monitor evaluate the long-term the safety and tolerability of fingolimod 0.5 mg/day in patients with MS who received fingolimod 0.5 mg/day	• Other malignant neoplasms • Long-term risk of malignant neoplasms • Lymphoma	Ongoing	2Q 2017
Study FTY720D2403 Long-term, prospective, multinational, parallel cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease modifying therapy. Category 3	To further explore the overall safety profile and incidence of selected safety related outcomes of fingolimod under conditions of routine medical practice. To observe long- term effectiveness outcomes. To evaluate safety and effectiveness of switch from other disease modifying therapies.To further explore the overall safety profile of	• Bradyarrhythmia (including conduction defects) occurring post-first dose • Hypertension • Liver transaminase elevation • Posterior Reversible Encephalopathy Syndrome (PRES) • Macular oedema • Infections • Varicella-Zoster Virus infections • Herpes viral infections other than VZV	Ongoing	Interim reports: annually 3Q; Final report: 4Q 2020

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status	Date for submission of final reports
	fingolimod over the long term, as measured by adverse events and vital signs in patients with relapsing MS under conditions of routine medical practice.	• Bronchoconstriction • Skin cancer • Acute disseminated encephalomyelitis-like (ADEM-like) events • Lymphoma • Other malignant neoplasms • Thromboembolic events • QT interval prolongation • Convulsions • Progressive multifocal leukoencephalopathy (PML) • Pulmonary oedema • Patients with diabetes mellitus • Patients with cardiovascular conditions • Long-term risk of cardiovascular morbidity/mortality • Long-term risk of malignant neoplasms • Unexplained death Switch from other disease modifying agent		
Study FTY720D2404 The Multinational Pregnancy Gilenya Exposure Registry in Multiple Sclerosis to prospectively collect outcome data on the babies born to women treated with fingolimod. Category 3	To collect data Regarding fingolimod Exposure during Pregnancy and maternal, fetal and infant outcomesTo describe the overall frequency of major and minor congenital mal-formations associated with exposure to fingolimod during pregnancy.	• Reproductive toxicity • Pregnant and lactating women	Ongoing	Interim reports: annually 3Q; Final report: 1Q 2018
Study FTY720D2406 Long-term, prospective, non-interventional, multi-national, parallel-cohort study monitoring safety in	To further explore the overall safety profile and incidence of selected safety-related outcomes of fingolimod , as	• Bradyarrhythmia (including conduction defects) occurring post-first dose • Hypertension	Ongoing	Interim reports: annually 3Q; Final report: 4Q 2020

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status	Date for submission of final reports
patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Category 3	measured by adverse events and vital signs, over the long term in patients with relapsing forms of MS under conditions of routine medical practice. To observe long-term effectiveness outcomes. To evaluate safety and effectiveness of switch from other disease modifying therapies.	• Liver transaminase elevation • Posterior Reversible Encephalopathy Syndrome (PRES) • Macular oedema • Infections • Varicella-Zoster Virus infections • Herpes viral infections other than VZV • Bronchoconstriction • Skin cancer • Acute disseminated encephalomyelitis-like (ADEM-like) events • Lymphoma • Other malignant neoplasms • Thromboembolic events • QT interval prolongation • Convulsions • Progressive multifocal leukoencephalopathy (PML) • Pulmonary oedema • Patients with diabetes mellitus • Patients with cardiovascular conditions • Long-term risk of cardiovascular morbidity/mortality • Long-term risk of malignant neoplasms • Unexplained death • Switch from other disease modifying agent		
Study FTY720D2409 Long-term, open-label, multicenter, prospective study to assess potential long term cardiovascular risks in fingolimod treated patients.	To estimate the long term potential cardiovascular risk of fingolimod in patients who experienced a serious cardiovascularac event during	• Bradyarrhythmia (including conduction defects) occurring post-first dose • Hypertension • Thromboembolic events • QT interval prolongation	Planned	4Q 2020

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status	Date for submission of final reports
Category 1	treatment initiation, as defined by the incidence of serious cardiovascular events.the first dose.	• Patients with cardiovascular conditions • Long-term risk of cardiovascular morbidity/mortality • Unexplained death		

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that the MAH should submit an updated protocol FTY720D2406 taking into account the comments (amendment of inclusion criteria: patients switching from disease modifying therapies to fingolimod, study objectives, statistical analysis plan) together with sample size calculation based on assumptions regarding the number of patients expected in each newly defined group.

The PRAC also considered that the studies in the post-authorisation development plan are sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 26. Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Identified risks		
Bradyarrhythmia (including conduction defects and bradycardia complicated by hyotension) occurring post-first dose	*SmPC Sections 4.4, 4.5 and 4.8:* First dose monitoring requirements and recommendation not to use Gilenya in patients on concurrent heart rate lowering medications, patients on Class Ia and Class III anti-arrythmics and those with certain underlying cardiovascular or cerebrovascular conditions. Bradycardia and atrioventricular block are identified as common undesirable effects in the SmPC Section 4.8.	Educational material materials for physicians and patients: - Physician's checklist - Patient reminder card
Hypertension	*SmPC Sections 4.4 and 4.8:* Blood pressure should be regularly monitored during treatment with fingolimod that may require treatment with antihypertensive	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	agents or discontinuation of Gilenya. Gilenya should not be used in patients with uncontrolled hypertension. Hypertension is identified as a common undesirable effect in the SmPC Section 4.8.	
Liver transaminase elevation	*SmPC Sections 4.2, 4.4, 4.8 and 5.2:* Liver transaminases levels should be monitored at months 1, 3, 6, 9 and 12 on therapy and periodically thereafter with more frequent monitoring for elevations above 5 times the ULN. Recommendation to discontinue treatment if significant liver injury confirmed. ALT (very common), GGT, hepatic enzyme increased, liver function test abnormal are identified as common undesirable effects in the SmPC Section 4.8.	Educational material materials for physicians and patients: - Physician's checklist - Patient reminder card
Posterior Reversible Encephalopathy Syndrome (PRES)	*SmPC Sections 4.8:* PRES is identified as a rare undesirable effect in the SmPC Section 4.8.	None.
Macular oedema	*SmPC Sections 4.4 and 4.8:* An ophthalmological evaluation is recommended at 3- 4 months after treatment initiation. Macular edema is identified as an uncommon undesirable effect in the SmPC Section 4.8	Educational material materials for physicians and patients: - Physician's checklist - Patient reminder card
Infections	*SmPC Sections 4.4 and 4.8:* Obtain recent complete blood count (CBC) (i.e. within 6 months) prior to treatment initiation and periodically during treatment, and in case of signs of infections. Infections are identified as common undesirable effects in the SmPC Section 4.8.	Educational material materials for physicians and patients: - Physician's checklist - Patient reminder card
Leucopenia and lymphopenia	*SmPC Sections 4.4 and 4.8:* Further information relating to this risk is provided under infections above. Lymphopenia and leucopenia are identified as common undesirable	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	effects in the SmPC Section 4.8.	
Reproductive toxicity	*SmPC Section 4.6:* SmPC recommendation for effective contraception during treatment with fingolimod and for 2 months post-drug discontinuation and a negative pregnancy test before initiation of treatment in women of childbearing potential and discontinuation of fingolimod if pregnancy confirmed.	Educational material materials for physicians and patients: - Physician's checklist - Patient reminder card
Bronchoconstriction	*SmPC Sections 4.4, 4.8 and 5.1:* Fingolimod should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease. This risk is also mentioned in Section 4.8 of the SmPC.	None.
Varicella-Zoster virus infections	*SmPC Sections 4.4:* Before initiating Gilenya therapy, patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV. VZV vaccination of antibody negative patients should be considered prior to commencing treatment with Gilenya, following which initiation of treatment with Gilenya should be postponed for 1 month to allow full effect of vaccination to occur.	None.
Potential risks		
Skin cancer	None.	None.
Acute disseminated encephalomyelitis-like (ADEM-like) events	Potential risk addressed in SmPC Section 4.8 and 5.3.	None.
Lymphoma	Potential Risk addressed in SmPC Section 4.8 and 5.3. Lymphoma cases presented in Section 4.8. Animal findings presented in Section 5.3 Preclinical safety data.	None.
Other malignant neoplasms	Potential Risk addressed in SmPC Section 4.8 and 5.3.	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Lymphoma cases presented in Section 4.8. Animal findings presented in Section 5.3 Preclinical safety data.	
Thromboembolic events	Potential risk of peripheral peripheral arterial occlusive disease and ischemic strokes are mentioned in Section 4.8 of the SmPC.	None.
QT interval prolongation	Potential risk of QT prolongation is mentioned in Sections 4.4 and 5.1 of the SmPC.	None.
Convulsions	None.	None.
Progressive multifocal leukoencephalopathy (PML)	None.	None.
Herpes viral infections other than VZV	Potential risk addressed in SmPC Sections 4.4 and 4.8 (see section on infections above).	None.
Off-label use	None.	None.
Pulmonary oedema	None.	None.
Decreased renal function	This potential risk is addressed SmPC Section 4.2	None.
Atypical MS relapse	None.	None.
Hemophagozytic syndrome	Labeling currently undergoing with a change to include hemophagozytic syndrome in SmPC Section 4.8	DHPC to raise awareness about hemophagozytic syndrome as one time activity.
Hypersensitivity	None.	None.
Potential interactions		
Ketoconazole	This potential risk is addressed in SmPC Section 4.5.	None.
Carbamazepine	This potential risk is addressed in SmPC Section 4.5.	None.
Beta blockers	This potential risk is addressed in SmPC Section 4.4 and 4.5.	None.
Class Ia or Class III anti-arrhythmic medicinal products	This potential risk is addressed in SmPC Section 4.4 and 4.5.	None.
Missing information		
Elderly patients	According to SmPC Section 4.2, fingolimod should be used with caution in patients aged 65 years and over due to insufficient data on safety and efficacy.	None.
Paediatric patients	The paucity of data is described in	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	the SmPC Sections 4.2 and 5.2 “The safety and efficacy of fingolimod in children aged 0 to 18 years have not yet been established”.	
Pregnant and lactating women	Addressed in SmPC Section 4.6	Educational material materials for physicians and patients: - Physician’s checklist - Patient reminder card
Patients with diabetes mellitus	This item is addressed the SmPC Section 4.2 and 4.4 regarding necessity for patients with diabetes mellitus to undergo an ophthalmologic evaluation prior to initiating fingolimod therapy and have follow-up evaluations while receiving fingolimod therapy. The paucity of data is described in SmPC Section 4.2, “fingolimod has not been studied in MS patients with concomitant diabetes mellitus. It should be used with caution in patients with diabetes mellitus due to a potential increased risk of macular edema”.	None.
Patients with cardiovascular conditions	This item is addressed in the SmPC Section 4.4.	None.
Long-term risk of cardiovascular morbidity/mortality	None.	None.
Long-term risk of malignant neoplasms	This item is addressed in the SmPC Section 4.8.	None.
Unexplained death	This item is addressed in the SmPC Section 4.8.	None.
Switch from other disease modifying agent	This item is addressed in the SmPC Section 4.4.	None.

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

The CHMP endorsed this advice without changes and also recommended to include separate analyses according to the type of therapy previously used (teriflunomide, dimethyl fumarate, alemtuzumab, natalizumab) in the updated protocol for study FTY720D2406.

In addition, the MAH proposed to upgrade “hypersensitivity” from “potential” to “identified” risk to comply with the latest PRAC recommendation on the PSUR (April 2014) in an updated version 7.3 of the RMP. The CHMP considered version 7.3 acceptable.

2.6. Update of the product information

The MAH initially proposed the following changes to the Product Information (new text=underlined, deleted text= strikethrough):

Summary of the Product Characteristics

- **Section 4.1**

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

- Patients with high disease activity despite treatment with a disease modifying therapy ~~beta-interferon.~~

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 a disease modifying therapy ~~interferon~~. 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.

During the procedure, the MAH proposed to introduce different levels of risk minimisation regarding certain DMTs (e.g teriflunomide, alemtuzumab), based on their pharmacodynamic/pharmacokinetic and safety profiles as discussed in detailed above, (new text=underlined, deleted text= strikethrough):

- **Section 4.2**

~~Patients can switch directly from beta interferon or glatiramer acetate to Gilenya provided there are no signs of relevant treatment-related abnormalities, e.g. neutropenia.~~

- **Section 4.4**

Prior treatment with immunosuppressants

When switching patients from another disease modifying therapy to Gilenya, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimising the risk of disease reactivation. A CBC is recommended prior to initiating Gilenya to ensure that immune effects of the previous therapy (i.e. cytopenia) have resolved.

Gilenya can generally be started immediately after discontinuation of interferon, glatiramer acetate or dimethyl fumarate~~to Gilenya, a washout is not necessary, assuming any immune effects (i.e. cytopenia) of such therapies have resolved~~.

Due to the long half-life of natalizumab, elimination usually takes ~~concomitant exposure, and thus concomitant immune effects, could occur for~~ up to 2-3 months following discontinuation~~natalizumab if~~

~~Gilenya was immediately started. Therefore caution is required when switching patients from natalizumab to Gilenya.~~ Teriflunomide is also eliminated slowly from the plasma. Without an accelerated elimination procedure, clearance of teriflunomide from plasma can take from several months up to 2 years. An accelerated elimination procedure is defined in the teriflunomide summary of product characteristics. Caution regarding potential concomitant immune effects is required when switching patients from natalizumab or teriflunomide to Gilenya.

Alemtuzumab has profound and prolonged immunosuppressive effects. As the actual duration of these effects is unknown, initiating treatment with Gilenya after alemtuzumab is not recommended unless the benefits of such treatment clearly outweigh the risks for the individual patient.~~When switching from other immunosuppressive medications, the duration and mode of action of such substances must be considered when initiating Gilenya to avoid additive immune suppressive effects.~~

The CHMP, having considered the above, made the following recommendations:

- The wording of the indication (section 4.1) should state “despite treatment with at least one DMT therapy” because of the safety profile of Gilenya.

- The deletion of section 4.2 is considered acceptable;

- The MAH proposed to start treatment with fingolimod directly after dimethyl fumarate discontinuation based on a short half life of its active metabolite MMF. However, lymphocytes count in patients treated with dimethyl fumarate is decreased by <30% and increase of lymphocyte count is observed only four weeks after stopping the drug, albeit not returning to baseline levels. Having in mind that fingolimod also reduces lymphocytes count (reduction to 20-30% of baseline) though likely due to another mechanism, it would be recommended to reconsider the duration of washout period. The duration of washout period allowing recovery of the CBC counts might be appropriate. Recommendations should take into consideration the CBC counts following discontinuation of dimethyl fumarate treatment and prior to initation of fingolimod treatment;

- The MAH did not provide clear recommendations for the washout period for teriflunomide except of pointing to very long elimination period (up to 2 years). In MS patients, the median half life (t1/2z) was approximately 19 days after repeated doses of 14 mg of teriflunomide. If a decision is made to stop treatment with Aubagio, during the interval of 5 half-lives (approximately 3.5 months although may be longer in some patients), starting other therapies will result in concomitant exposure to Aubagio. This may lead to an additive effect on the immune system and caution is, therefore, indicated, especially since fingolimod can even further reduce white blood cell counts. Having in mind that pharmacodynamic effects of teriflunomide on white blood cell counts (reduction of WBC count <15%) might be even further exagerated if fingolimod is introduced within the period shorter than 3.5 months after teriflunomide discontinuation, more clear recommendations on duration of washout period based on pharmacokinetic data as well as white blood cells counts should be made.

The final wording recommended by the CHMP and agreed with the MAH for sections 4.1 and 4.4 is as follows:

- **Section 4.1**

Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis 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.

- **Section 4.4**

Infections

[…]

Before initiating treatment with Gilenya, a recent complete blood count (CBC) (i.e. within 6 months or after discontinuation of prior therapy) should be available. Assessments of CBC are also recommended periodically during treatment, at month 3 and at least yearly thereafter, and in case of signs of infection. Absolute lymphocyte count <0.2x109/l, if confirmed, should lead to treatment interruption until recovery, because in clinical studies, fingolimod treatment was interrupted in patients with absolute lymphocyte count $<0.2x10^9$/l.

[…]

Prior treatment with immunosuppressive or immunomodulatory therapies

There have been no studies performed to evaluate the efficacy and safety of Gilenya when switching patients from teriflunomide, dimethyl fumarate or alemtuzumab treatment to Gilenya. When switching patients from another disease modifying therapy to Gilenya, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimising the risk of disease reactivation. A CBC is recommended prior to initiating Gilenya to ensure that immune effects of the previous therapy (i.e. cytopenia) have resolved.

Gilenya can generally be started immediately after discontinuation of interferon or glatiramer acetate.

For dimethyl fumarate, the washout period should be sufficient for CBC to recover before treatment with Gilenya is started.

Due to the long half-life of natalizumab, elimination usually takes up to 2-3 months following discontinuation. Teriflunomide is also eliminated slowly from the plasma. Without an accelerated elimination procedure, clearance of teriflunomide from plasma can take from several months up to 2 years. An accelerated elimination procedure as defined in the teriflunomide summary of product characteristics is recommended or alternatively washout period should not be shorter than 3.5 months. Caution regarding potential concomitant immune effects is required when switching patients from natalizumab or teriflunomide to Gilenya.

Alemtuzumab has profound and prolonged immunosuppressive effects. As the actual duration of these effects is unknown, initiating treatment with Gilenya after alemtuzumab is not recommended unless the benefits of such treatment clearly outweigh the risks for the individual patient.

Package Leaflet

The Package Leaflet initially proposed an update in section 1 of the Package Leaflet. Following additional updates in section 4.4 of the SmPC, sections 2 and 3 were also amended in line with the SmPC. The final recommended wording by the CHMP is as follows:

- **Section 1**

What Gilenya is used for

Gilenya is used in adults to treat relapsing-remitting multiple sclerosis (MS), more specifically in:

Patients who have failed to respond despite treatment with an MS treatment.

or

Patients who have rapidly evolving severe MS.

Gilenya does not cure MS, but it helps to reduce the number of relapses and to slow down the progression of physical disabilities due to MS.

- **Section 2**

Other medicines and Gilenya

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Tell your doctor if you are taking any of the following medicines:

- **Medicines that suppress or modulate the immune system**, including **other medicines used to treat MS**, such as beta interferon, glatiramer acetate, natalizumab, mitoxantrone, teriflumomide, dimethyl fumarate or alemtuzumab. You must not use Gilenya together with such medicines as this could intensify the effect on the immune system (see also 'Do not take Gilenya').

- **Section 3**

Your doctor may switch you directly from beta interferon, glatiramer acetate or dimethyl fumarate to Gilenya if there are no signs of abnormalities caused by your previous treatment. Your doctor may have to do a blood test in order to exclude such abnormalities. After stopping natalizumab you may have to wait for 2-3 months before starting treatment with Gilenya. To switch from teriflunomide, your doctor may advise you to wait for a certain time or to go through an accelerated elimination procedure. If you have been treated with alemtuzumab, a thorough evaluation and discussion with your doctor is required to decide if Gilenya is appropriate for you.

3. Benefit-risk balance

3.1.1. Beneficial effects

Post-hoc analyses in patients previously treated with glatiramer acetate in the year prior to treatment with fingolimod showed beneficial effects of fingolimod 0.5 mg consistent with the effects of fingolimod in the overall study populations and with those patients previously treated with beta-interferon and subsequently treated with fingolimod.

In pooled studies D2301/D2309, post-hoc results showed effects in favour of fingolimod 0.5 mg compared to placebo in all subgroups (failures and non-responders patients treated with glatiramer acetate or interferon-beta at any time in the year prior to screening) for all efficacy variables as measured by the ARR, proportion of relapse-free patients, disability and MRI parameters, although not all results were statistically significant.

3.1.2. Uncertainty in the knowledge about the beneficial effects

No efficacy data are available in patients previously treated with other DMTs (e.g teriflunomide, dimethyl fumarate, alemtuzumab, or even natalizumab) prior to fingolimod 0.5 mg, and under the current conditions in clinical practice it would be unreasonable to request such data to be provided for all the available drugs on the market.

In addition, limitations in the presented post-hoc analyses were noted (e.g inclusion of relatively small number of patients in treatment groups, overlap of the failures and non -responder definitions).

3.2. Risks

3.2.1. Unfavourable effects

Although the number of patients included in the analysis was small, the safety profile of fingolimod in patients previously treated with glatiramer acetate is similar to the safety profile of fingolimod in patients previously treated with interferon beta and generally consistent with the known profile of fingolimod.

3.2.2. Uncertainty in the knowledge about the unfavourable effects

No safety data are available in patients previously treated with other DMTs (e.g teriflunomide, dimethyl fumarate, alemtuzumab) prior to fingolimod 0.5 mg. Given the long lasting immunosuppressant properties of these MS therapies, this raised a concern on the possible potentiation of immunosuppressive activities when switching between these drugs, and for that reason detailed recommendations, on how this should be done in clinical practice, were introduced in the SmPC. The CHMP recommended different levels of risk minimisation regarding the different DMTs (e.g teriflunomide, alemtuzumab, dimethyl fumarate), based on their pharmacodynamic/pharmacokinetic and safety profiles. Such measures were considered adequate to ensure safe and effective use in the proposed indication.

3.3. Benefit-risk balance

3.3.1. Importance of favourable and unfavourable effects

The efficacy of Gilenya in patients switching from glatiramer acetate treatment is supported by the available data. No new safety signal emerged and the overall safety profile of Gilenya is considered acceptable in this population. Due to safety concerns, Gilenya (fingolimod) was originally restricted to high disease activity and for one part of the indication after failure to interferon-beta, similarly to Tysabri, and the indication of the latter has been updated to include RRMS patients with high disease activity who failed to respond to glatiramer acetate.

Whilst concerns were initially raised regarding the absence of data in patients previously treated with other MS drugs that recently became available (e.g teriflunomide, dimethyl fumarate, alemtuzumab) or even natalizumab, the CHMP acknowledged the availability of new treatment alternatives for MS patients with efficacy comparable to well-established interferon beta or glatiramer acetate (GA) therapies, thus possibly broadening the options for neurologists at treatment initiation or in case of treatment failure. The CHMP also considered that given the current situation and the available therapeutic options in clinical practice, it would be unreasonable to expect separate data to be provided in patients treated with each of the marketed drugs. Taking into consideration the different mechanisms of action of fingolimod, teriflunomide and dimethyl fumarate, the CHMP was of the view

that there was a reasonable scientific plausibility in the assumption that even if treatment with teriflunomide and/or dimethyl fumarate failed due to lack of efficacy, the treatment with fingolimod would be effective. In addition, the CHMP considered that the possibility to introduce potentially more effective treatment earlier, without unnecessary testing of similar alternatives in terms of efficacy in a stepwise procedure, will be beneficial for patients. The CHMP therefore concluded that the currently approved wording of the indication was not reflecting the possible therapeutic options for Gilenya and should be amended accordingly.

Additionally, as part of supplementary measures to ensure the effective and safe use of the product in the intended indication, data on the efficacy and safety of Gilenya treatment in MS patients who were previously treated with at least one DMT, including teriflunomide, dimethyl fumarate, alemtuzumab, natalizumab, are to be collected as part of an ongoing long term study.

3.3.2. Benefit-risk balance

The overall benefit-risk balance of Gilenya is positive for the following indication:

"Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis 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."

4. Recommendations

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

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

Modification of the indication (section 4.1) of Gilenya to extend the patient population to patients with high disease activity despite treatment with at least one disease modifying therapy (DMT). Consequential changes were made in section 4.4 of the SmPC to include safety information relevant to switching from other immunosuppressive or immunomodulatory therapies to Gilenya. The Package Leaflet has been amended accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.