NOVARTIS

Patient Safety & Pharmacovigilance

Fingolimod

FTY720

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Fingolimod
Product(s) concerned (brand name(s)):	Gilenya®
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Date of final sign off	23-Jul-2025

Rationale for submitting an updated RMP:

The Risk Management Plan (RMP), EU RMP version 21.1, has been prepared in response to Request for Supplementary Information received in the Committee for Medicinal Products for Human Use (CHMP) assessment report (with Procedure No.: EMEA/VR/0000257758), and to correct a typographical error in Annex 6 Physician's checklist. Additionally, the RMP is updated to reflect the completion of the pregnancy-related pharmacovigilance activities and subsequent discontinuation/removal of enhanced pharmacovigilance data collection using the PRegnancy outcomes Intensive Monitoring (PRIM) specific follow-up checklists. The collection of the pregnancy specific pharmacovigilance data will be continued using the marketing authorization holder's standard follow-up checklists for pregnancy and the data will continue to be presented in the Periodic Safety Update Report (PSURs) as a part of routine pharmacovigilance activities.

Summary of significant changes in this RMP:

Key changes made compared to RMP version 21.0:

Part	Major changes compared to RMP v 21.0
Part I	Updated reference to the proposed SmPC
Part II	Section 8.3.1, Module SVII.3.1. Presentation of important identified risks and important potential risks: Updated the risk characterization table (8.3.1.5, Table 8-10) for the important identified risk 'Reproductive toxicity'
Part III	Section 10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection: Removed pregnancy specific follow-up questionnaires for important identified risk 'Reproductive toxicity'
Part IV	None
Part V	Section 12.3, Part V.3 Summary of risk minimization measures: Removed pregnancy specific follow-up questionnaires from the routine pharmacovigilance activities for important identified risk 'Reproductive toxicity' (Table 12-2)
Part VI	Section 13.2.2 Part VI - II B: Summary of important risks: Removed pregnancy specific follow-up questionnaires from the routine pharmacovigilance activities for important identified risk 'Reproductive toxicity' (Table 13-6)
Part VII	Annex 4: Removed pregnancy specific follow-up questionnaires for important identified risk 'Reproductive toxicity'. Annex 6: Corrected the term 'macular degeneration' to 'macular edema' in the Physician's checklist (Table 14-4) to address a typographical error

Other RMP versions under evaluation

No RMPs are currently under evaluation.

Details of the currently approved RMP:

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QPPV name: Dr. Justin Daniels PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

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List of abbreviations

ADR	Adverse Drug Reaction
ADEM-like	Acute Disseminated Encephalomyelitis-like events
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
AJ	Adherens Junctions
ALT	Alanine Aminotransferase
AR	Assessment Report
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AV	Atrio-Ventricular
BP	Blood Pressure
BPM	Beats Per Minute (heart rate)
BRB	Blood Retinal Barrier
CBC	Complete Blood Count
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMQ	Customized MedDRA Queries
CNS	Central Nervous System
CSR	Clinical Study Report
CYP	Cytochrome P450
DMT	Disease-Modifying Therapy
DOD	Department of Defense
DHPC	Direct Healthcare Professional Communications
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Reports
ERR	Event Rate Ratio
EU	European Union
EUROCAT	European Registration of Congenital Anomalies and Twins
FPFV	First Patient First Visit
GFAP	Glial Fibrillary Acidic Protein
GIRK	G-protein-gated Inwardly Rectifying K+ channels
GPR	Gilenya Pregnancy Registry
GVP	Good Pharmacovigilance Practices
hERG	Human Ether-a-go-go Related Gene
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HVI	Herpes Viral Infections
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IM	Intramuscular

ISS	Integrated Summary of Clinical Safety
JCV	John Cunningham virus
KLH	Keyhole Limpet Hemocyanin
LPLV	Last Patient Last Visit
MACDP	Metropolitan Atlanta Congenital Defects Program
MCM	Major Congenital Malformation
ME	Macular Edema
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MTD	Maximum Tolerated Dose
NMQ	Novartis MedDRA Queries
OCT	Optical Coherence Tomography
OR	Odds Ratio
PML	Progressive Multifocal Leukoencephalopathy
PPMS	Primary Progressive Multiple Sclerosis
PRES	Posterior Reversible Encephalopathy Syndrome
PRIM	PRegnancy Outcomes Intensive Monitoring
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PY	Patient-Years
RCVI	Reactivation Of Chronic Viral Infections
RMP	Risk Management Plan
RR	Relative Risk
RRMS	Relapsing Remitting Multiple Sclerosis
S1P	Sphingosine-1-Phosphate
SAE	Serious Adverse Event
SMC	Smooth Muscle Cell
SMH	Smooth Muscle Cell Hypertrophy
SmPC	Summary of Product Characteristics
SMR	Standardized Mortality Rate
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SPMS	Secondary Progressive Multiple Sclerosis
SRs	Spontaneous Adverse Events Reports
TJ	Tight Junctions
ULN	Upper Limit of Normal
UTI	Urinary Tract Infection
VDW	Virtual Data Warehouse
VSMCs	Vascular Smooth Muscle Cells
VZV	Varicella Zoster Virus
WBC	White Blood Cell
WHO	World Health Organization

1 Part I: Product(s) Overview

Table 1-1 Part I.1 - Product Overview

Active substance(s) (INN or common name)	Fingolimod
Pharmacotherapeutic group(s) (ATC Code)	L04AE Immunosuppressants, sphingosine-1-phosphate (S1P) receptor modulators (ATC code L04AE01)
Marketing Authorization Holder	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Gilenya®
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Fingolimod is a sphingosine-1-phosphate (S1P) receptor modulator.
	Summary of mode of action: Fingolimod is metabolized by sphingosine kinase to the active metabolite fingolimod phosphate. Fingolimod phosphate binds at low nanomolar concentrations to sphingosine 1-phosphate (S1P) receptor 1 located on lymphocytes, and readily crosses the blood-brain barrier to bind to S1P receptor 1 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 reduces the infiltration of pathogenic lymphocyte cells into the central nervous system, where they would be involved in nerve inflammation and nervous tissue damage. Animal studies and *in vitro* experiments indicate that fingolimod may also act via interaction with S1P receptors on neural cells.
	Important information about its composition: None.
Hyperlink to the Product Information	[Current approved SmPC] [Proposed SmPC]
Indication(s) in the EEA	Current: Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and paediatric patients aged 10 years and older: - Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (for exceptions and information about washout periods see sections 4.4 and 5.1 of the SmPC). 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.
	Proposed: None.
Dosage in the EEA	Current: Adults: One 0.5 mg capsule taken orally once daily Paediatric patients (10 years and above): - Paediatric patients with body weight ≤ 40 kg: one 0.25 mg capsule daily taken orally. - Paediatric patients with body weight > 40 kg: one 0.5 mg capsule daily taken orally.
	Proposed: None.
Pharmaceutical form(s) and strengths	Current: Gilenya 0.25 mg hard capsules Gilenya 0.5 mg hard capsules
	Proposed: None.
Is/will the product be subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indication

Relapsing-remitting Multiple Sclerosis [RRMS]

Incidence:

Globally, the estimated median annual incidence of multiple sclerosis (MS) in 2013 was 4.0 per 100,000 (interquartile range: 1.5 to 7.5) according to estimates from the (Multiple Sclerosis International Federation 2013). On a regional level, Europe had the highest estimated median annual incidence in 2013 (5.5 per 100,000), followed by the Asia (3.0 per 100,000), Africa (1.0 per 100'000), and the Americas (0.6 per 100,000). Countries reporting the highest estimated median annual incidence of MS included Canada (13.4 per 100,000), Latvia (11.6 per 100,000), and Czech Republic (11.0 per 100,000) (Multiple Sclerosis International Federation 2013).

A literature review of publications during the period 2000-2009 on the European epidemiology of MS by (Koutsouraki et al 2010) reported that the estimated mean annual MS incidence is 4.3 per 100,000. The overall sex-specific incidence density of MS for females and males was reported to be 3.6 and 2.0 per 100'000 patient-years (PY), respectively (Koutsouraki et al 2010).

Pediatric patients:

It is estimated that up to 3-10% of MS cases manifest in childhood and adolescence; up to 2% of incident MS diagnoses manifest before the age of 10 years. The gender ratio in pediatric MS varies with a female preponderance among the pediatric population. However, the age of onset of disease is similar for both males and females in the pediatric population (Pohl 2008, Chitnis et al 2009). Estimates of pediatric MS incidence vary. The lack of uniform criteria to define pediatric MS could account for some of the variability. Current estimates are likely to be influenced by regional and ethnic differences in MS incidences, as well as the source population. Data from studies in different countries published since 2005 reported the following (only studies with more than 100 MS patients were considered):

Europe: In the UK, data from the GPRD from 2010 yielded an estimated incidence rate of 0.1 per 100,000 PY in those 0 to 9 years old and 1.7 per 100,000 PY in those 10 to 19 years old (Mackenzie et al 2014). In Sicily, Italy, the average annual incidence rate between 1993 and 2002 was 6.1 per 100,000 PY (95% Confidence Interval (CI) = 4.1 - 8.1) in those 0 to 24 years old (Grimaldi et al 2007). In a nationwide prospective surveillance in Germany, an incidence rate of 0.64 per 100,000PY (95% CI 0.56−0.73) was reported in those less than 16 years old. The incidence in children below 11 years was 0.09 per 100,000PY (95% CI 0.06−0.14), 1.1 per 100,000PY (95% CI 0.87−1.37) in the 11 to 13 years old age group and 2.64 per 100,000PY (95% CI 2.20−3.14) in the 14 to 15 years age group (Reinhardt et al 2014)

In Sardinia, from 2003 to 2007, the crude incidence in those 0 to 14 years old was 0 (95% CI=0.0-21.9) (Cocco et al 2011). The incidence of MS in Faroe Island during the period from 1986 to 2007 in those 0 to 19 years old was 0 (Joensen 2010).

In a study conducted in Israel, from 1995 to 2009, using the MS Center Database and the Israeli Health Statistics Census Data, the mean annual incidence of MS in children <12 years old was

0.1/100,000 (ranged across study years from 0.0 per 100,000 to 0.5 per 100,000). The mean annual incidence of juvenile MS (from 12 to 18 years old) was 2.6 per 100,000 for the studied period (Achiron et al 2012).

North America: An incidence rate of MS of 2.8 per 100,000 PY (95% CI = 2.3-3.4) with a female to male rate ratio of 7.1 for those ≤ 24 years old was reported in Manitoba, Canada using provincial administrative claims data from 1996 to 2006 (Marrie et al 2010). A population -based registry, in which data was collected over a 35-year period in Saskatoon, Canada showed an average annual incidence rate of 0.15 per 100,000 population in those 0 to 14 years old (Hader and Yee 2007).

Asia: In Taiwan, MS cases were identified from the National Health Insurance Database (2001 to 2005) and population data used for incidence calculation showed that the incidence rate in those <15 years old was 0.15 per 100,000 PY and in those 15 to 19 years old, it was 0.41 per 100,000 PY (Lai and Tseng 2009).

Elderly patients (≥65 years)

No worldwide data on incidence, prevalence, and mortality of MS in elderly people was identified. Therefore, only epidemiological data from studies in different countries published since 2005 are reported (only studies with more than 100 MS patients were considered). Estimates vary depending on the geographical area and the source of data.

Europe: In the UK, data from the GPRD from 2010 yielded an estimated incidence rate of MS of 11.5 per 100,000 person-years (PY) in those 60 to 69 years old, 8.8 per 100,000 PY in those 70 to 79 years old, 7.3 per 100,000 PY in those 80 to 89 years old, and 5.5 per 100,000 PY in those ≥90 years old (Mackenzie et al 2014). In a study from Caltanissetta, Sicily, Italy, the calculated incidence rate was 0 per 100,000 PY in those ≥65 years old (Grimaldi et al 2007).

North America: Incidence rates of MS of 8.7 (95% CI 5.9-11.4) per 100,000 PY in those 60 to 64 years old and 1.3 (95% CI = 0.7-1.9) per 100,000 PY in those ≥65 years old were reported in Manitoba, Canada using provincial administrative claims data from 1996 to 2006. Female to male rate ratio was 1.4 in those 60 to 64 years old and 1.5 in those ≥65 years old (Marrie et al 2010). A population based registry operating over 35 years in Saskatoon, Canada showed an incidence rate of 0.7 per 100,000 population in those 65 to 74 years old and 0 per 100,000 population in those over 75 years old (Hader and Yee 2007).

Asia: In Taiwan, MS cases were identified from the National Health Insurance Database (2001 to 2005) and population data used for incidence calculation, which showed that incidence rates in those 60 to 64 years old was 1.1 per 100,000 PY; in those 65 to 69 years old and those 70 to 74 years old, it was 1.0 per 100,000 PY for both; in those 75 to 79 years old, it was 0.8 per 100,000 PY, and in those ≥80 years old, it was 0.5 per 100,000 PY (Lai and Tseng 2009).

Prevalence:

Globally, the estimated median prevalence of MS in 2013 was 33.0 per 100,000 (interquartile range: 5.2 to 91.1). On a regional level, Europe has the highest estimated median prevalence (101.0 per 100,000), followed by Asia (16.0 per 100,000), the Americas (5.7 per 100,000), and Africa (3.0 per 100,000). Countries reporting the highest estimated prevalence of MS include Canada (291.0 per 100,000), Sweden (189.0 per 100,000), and Hungary (176.0 per 100,000).

MS is more common among women than men, with an estimated global mean female/male ratio of 2.3, ranging from 1.0 to 9.0 (Multiple Sclerosis International Federation 2013).

A literature review on epidemiology of MS in Europe by (Koutsouraki et al 2010) reported that the total estimated European MS prevalence rate for the past 3 decades was 83.0 per 100,000. A decreasing north-to-south gradient in the distribution of MS prevalence rates across Europe is observed, even though assessment biases may play a role.

Two recent European studies reported higher prevalence rates. In the UK, data from the General Practice Research Database (GPRD) yielded an overall period prevalence of 203.4 per 100,000 in 2010 (Mackenzie et al 2014). In a population-based study conducted in Sardinia, MS prevalence of 224 per 100,000 (95%CI=170-290) individuals was observed (Sardu et al 2012).

In a systematic review of the literature for all clinical studies of MS in Latin American populations up to May 2011, the prevalence of MS in Latin American countries ranged between 1.6 and 19.6 per 100,000 population (Ojeda et al 2013).

Pediatric patients:

As cited in Gadoth (2003), the worldwide prevalence of childhood MS was estimated as 1.4 to 2.5 per 100,000 populations. However, for infants and young children, it was 0.4 to 1.4 per 100,000 populations.

North America, South America, and Europe: An estimated prevalence of MS of 0 per 100,000 persons (95% CI = 0 - 5) in those 0 to 14 years old and of 18.9 per 100,000 persons (95% CI=11-33) in those 15 to 24 years old was reported in South East Wales, UK using different sources (GP notifications, hospital episode statistics, consultant neurologists, prevalence study in the year 1985, and large departmental database), which was very similar to the 35 year population based registry in Saskatoon, Canada (Hader and Yee 2007, Hirst et al 2009).

In Patagonia, Argentina, using multiple case-finding methods, and in Bogota, Colombia, using clinical hospital records, the prevalence of MS was similar in those 0 to 14 years old compared to data from the UK and Canada. However, prevalence was lower in those 15 to 24 years old with 5.4 cases per 100,000 inhabitants in Patagonia, Argentina and 0.5 per 100,000 population (95% CI = 0.1-1.5) in Bogota, Colombia (Toro et al 2007, Melcon et al 2008).

In Western Greece, in those 15 to 24 years old, a prevalence rate of 23.08 per 100,000 populations was reported using hospital patient records (Papathanasopoulos et al 2008). In Galtanissetta, Sicily, Italy, an estimated prevalence in 2002 in those 0 to 14 years old was 0 cases per 100,000 inhabitants; but it was higher in those 15 to 24 years old with 76 cases per 100,000 inhabitants (Grimaldi et al 2007). In the county of Värmland, in Sweden, the prevalence of MS in those 15 to 24 years old was lower with 9.6 per 100,000 population (data derived from hospital and general practice medical files) (Boström et al 2009).

In Sardinia, in 2007, the crude prevalence in those 0 to 14 years old was 0.0 (95% CI=0.0-23.9) (Cocco et al 2011). Likewise, for the age group 0 to 14, the point prevalence of MS in Verona, Italy on 31-Dec-2001 was 0.0 (no 95% CI reported) (Gajofatto et al 2013). The prevalence of MS in the north-east region of Northern Ireland was 0.0 per 100,000 (95% CI = 0.0-12.0) in those 0 to 14 years old, and 18.4 (95% CI, 4.8-47.6) in those 15 to 24 years old (Gray et al 2008).

In Jordan, in a retrospective cohort study, the MS prevalence ranged between 22 to 24 per 100,000 population in those 0 to 14 years old and between 71 to 125 per 100,000 population in those 15 to 24 years old (ElSalem et al 2006). In Kuwait, a retrospective study of medical records revealed a prevalence of 14.2 per 100,000 population (95% CI = 10.2, 18.3) in those 10 to 19 years old (Alshubaili et al 2005).

Asia: In Shanghai, China, in 2004, prevalence rates were low with 0.24 per 100,000 inhabitants in those 0 to 9 years old, and 0.28 per 100,000 inhabitants in those 10 to 19 years old (data derived from hospital inpatient registers at hospitals and network of physicians) (Cheng et al 2007).

In Korea, age- and sex specific prevalence per 100,000 inhabitants for MS was: 0 in those 0 to 4 years old; 0.53 in those 5 to 9 years old, 1.25 in those 10 to 14 years old; and 2.14 in those 15 to 19 years old (Kim et al 2010).

Elderly patients (≥65 years)

Europe: Data from the GPRD yielded UK-specific period prevalence estimates for the year 2010 as follows (by age group and per 100'000 population): 60 to 69, 446.4; 70-79, 268.7; 80-89, 124.4; ≥90, 67.0 (Mackenzie et al 2014). In Western Greece, in those 65 to 74 years old, a prevalence of 26.5 per 100,000 was reported and in those ≥75 years old, a prevalence of 4.1 per 100,000 was reported using hospital patient records (Papathanasopoulos et al 2008). In Galtanissetta, Sicily, Italy, reported prevalence in those 65 to 74 year old was higher, with 66.5 per 100,000 and lower in those over 70 years old with 0 per 100,000 (Grimaldi et al 2007). In the county of Värmland, in Sweden, the prevalence of MS in those 65 to 74 years old was higher with 201.9 per 100,000; in those 75 to 84 years old it was 62.5 per 100,000, and in those above 85 years old, it was 0 per 100,000 (data derived from hospital and general practice medical files) (Boström et al 2009).

North America: A population-based registry operating over 35 years in Saskatoon, Canada showed a prevalence of 520.9 per 100,000 in those 65 to 74 years old and 294.7 per 100,000 in those over 75 years old (Hader and Yee 2007). Prevalence in counties of Texas in the US was much lower, with 55.4 per 100,000 (95% CI=32.3-88.7) in those 60 to 69 years old and 10.7 per 100,000 (95% CI=2.9-27.4) in those over 70 years old (multiple case -finding methods used) (Williamson et al 2007).

Asia: In Shanghai, China, in 2004, prevalence estimates were low with 1.8 per 100,000 inhabitants in those 60 to 69 years old and 0.8 per 100,000 inhabitants in those ≥70 years old (data derived from hospital inpatient registers at hospitals and network of physicians) (Cheng et al 2007).

South America: In Patagonia, Argentina, using multiple case finding methods, prevalence of MS was even lower with 0 cases per 100,000 inhabitants in those older than 65 years (Melcon et al 2008). In Bogota, Colombia, using clinical hospital records, the prevalence of MS was higher: 8.7 per 100,000 population (95% CI = 4.6 - 14.8) in those 60 to 64 years old; 1.8 per 100,000 population (95% CI = 0.2 - 6.4) in those 65-69 years old; 2.5 per 100,000 population (95% CI = 0.3 - 9.0) in those 70 to 74 years old; 1.8 per 100,000 population (95% CI = 0.0 10.0) in those 75 to 80 years old; and 0 per 100,000 population in those older than 80 years old (Toro et al 2007).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Globally, the interquartile range for age of onset of MS symptoms is between 28.2 and 32.0 years, with an average age of onset of 30.0 years. Regionally, the average age of onset is lowest in Asia (28.3), followed by similar average age of onset in Africa (29.3), Europe (29.2), and the Americas (29.4) (Multiple Sclerosis International Federation 2013). A literature review on the epidemiology of MS in Europe by (Koutsouraki et al 2010) reported that the highest MS prevalence rate in Europe was estimated for the age group 35 to 64 years old for both sexes. Globally, the median estimated female/male ratio is 2.1 (with an interquartile range of 1.8 to 2.6). Regionally, the median estimated female/male ratio is reported to be lowest in Africa (1.8) and Europe (2.0) and highest in Asia (2.1) and the Americas (2.3). Among European countries, the female/ male ratio varied between 1.2 and 2.6 (Multiple Sclerosis International Federation 2013).

There are differences in MS prevalence among different ethnic groups: MS is very rare in Samis, Turkmen, Uzbeks, Kazakhs, Kirgizis, native Siberians, North and South Amerindians, Canadian Hutterites, Chinese, Japanese, African blacks, and New Zealand Maoris; while there is a high risk for MS among Sardinians, Parsis, and Palestinians (Koutsouraki et al 2010). A US population-based study using healthcare records between 2008 and 2010 in Southern California found an overall increased incidence of MS in blacks compared with whites, which appears to be driven by a higher risk in black vs. white women; black men had a similar risk of MS compared with white men; in contrast, Hispanics and Asians had a lower risk of MS compared with whites regardless of sex (Langer-Gould et al 2013).

Risk factors of the disease:

To date, a number of risk factors or potential risk factors for MS are known (the most important ones being summarized below):

- **Other autoimmune disorders:** a large Danish study found that patients with type 1 diabetes mellitus had an increased risk for developing MS compared with the general population (Nielsen et al 2006b). Another large, well designed cohort study found that patients with inflammatory bowel disease have an increased risk for demyelinating diseases, including MS (Gupta et al 2005).
- **Viral infections:** Epstein Barr Virus (EBV), which causes infectious mononucleosis, is considered a possible cause or trigger of MS (Bagert 2009, Pender 2009). In a meta analysis of 14 case control and cohort studies, the risk of MS was increased after infectious mononucleosis (relative risk = 2.3; 95% CI = 1.7, 3.0) (Thacker et al 2006).
- **Geographical factors:** There is also a widely held belief of an association between latitude and MS, with the risk of MS increasing from south to north (Alonso and Hernán 2008). In an analysis from the Nurses' Health Study, for example, the adjusted rate ratios were 3.5 for the northern United States and 2.7 for the middle tiers relative to the southern tier (Hernán et al 1999). However, the universal association between latitude and risk of MS has been challenged by findings from a 2010 systematic review and meta-analysis of epidemiologic studies of MS (Koch-Henriksen and Sørensen 2010). The results showed that while the prevalence of MS increased with geographic latitude in Western Europe, North America, and Australia/New Zealand, the incidence of MS increased with latitude only in Australia/New Zealand and not in Western Europe or North America. Thus, there was no

latitudinal gradient for MS incidence in the northern hemisphere. In the absence of association with incidence, the observed latitudinal gradient of MS prevalence could be explained by other factors, such as survival time, diagnostic accuracy, and ascertainment probability.

- **Lack of sunlight and low vitamin D level:** A number of studies have found an inverse relationship between sun exposure, ultraviolet radiation exposure or vitamin D serum levels, and the risk or prevalence of MS (Islam et al 2007, Orton et al 2011, Ramagopalan et al 2011, Salzer et al 2012, van der Mei et al 2003).
- **Other environmental factors:** Smoking is a well-established risk factor for MS. A recent meta-analysis of published data on MS risk and smoking revealed a risk ratio of 1.48 (95% CI: 1.35–1.63) (Wingerchuk 2012). Furthermore, in two Swedish population-based case-control analyses, researchers observed a clear dose response association between cumulative dose of smoking and MS risk (Hedström et al 2013). Month of birth has been implicated as a possible risk factor for MS. A large population -based study found that the risk of MS is increased for those born in May and decreased for those born in November, suggesting that the gestational or neonatal environment influences the risk of MS later in life (Willer et al 2005).
- **Genetic factors:** The risk of developing MS is associated with certain class I and class II alleles of the major histocompatibility complex (MHC), particularly the HLADRB1 locus (Australia and New Zealand Multiple Sclerosis Genetics Consortium (ANZgene) 2009, De Jager et al 2009, Friese et al 2008, International Multiple Sclerosis Genetics Consortium 2007, International Multiple Sclerosis Genetics Consortium 2011, Lincoln et al 2005). Furthermore, data suggests that transmission of MS is influenced by the sex of the parent (Ebers et al 2004, Herrera et al 2007, Herrera et al 2008, Hoppenbrouwers et al 2008, Hupperts et al 2001, Kantarci et al 2006, Kantarci and Spurkland 2008). Most studies have found a maternal parentoforigin effect, with an excess of maternal transmission observed when examining halfsibling pairs with MS and unaffected parents, patients with MS in extended pedigrees, or avuncular pairs of patients with MS (Ebers et al 2004, Herrera et al 2008, Hoppenbrouwers et al 2008). In contrast, studies of parent child pairs with MS have found that paternal transmission is equal to or greater than maternal transmission (Hupperts et al 2001, Kantarci et al 2006, Herrera et al 2007). The explanation for this discrepancy is unclear, but epigenetic mechanisms (e.g., DNA modifications, such as histone acetylation and DNA methylation, which do not modify the DNA sequence) transmitted through cell division may be involved in direct transmission from an affected parent (Kantarci and Spurkland 2008).

The main existing treatment options:

To date, the following disease modifying therapies are approved for MS:

- Interferon beta-1b (Betaseron, Extavia)
- Interferon beta-1a (Avonex, Rebif)
- Glatiramer acetate (Copaxone)
- Natalizumab (Tysabri)
- Fingolimod (Gilenya)
- Mitoxantrone (Novantrone)
- Teriflunomide (Aubagio)

- Dimethyl fumarate (Tecfidera)
- Alemtuzumab (Lemtrada)
- Peginterferon (Plegridy)
- Ocrelizumab (Ocrevus)
- Cladribine (Mavenclad)
- Siponimod (Mayzent)
- Ofatumumab (Kesimpta)
- Ozanimod (Zeposia)
- Ponesimod (Ponvory)
- Ublituximab (Briumvi)

Natural history of the indicated condition in the population, including mortality and morbidity:

Multiple Sclerosis Patients

The World Health Organization 2004 estimated that the annual death rate of MS patients was 0.3 per 100,000 per year.

Mortality rates per 100,000 from 1990 to 1994 in different European countries were as follows: Austria 0.8, Belgium 1.0, Bulgaria 0.5, Croatia 0.8, Estonia 1.3, Finland 0.9, Greece 0.4, Hungary 1.1, Ireland 1.1, Netherlands 0.6, Norway 1.5, Portugal 0.4, Romania 0.7, Slovenia 1.3, Spain 0.4, and Sweden 1.1 (Ekestern and Lebhart 2004). A literature review on epidemiology of MS in Europe by (Pugliatti et al 2006) reported that mortality rates in Europe ranged from 0.5 to 3.6 per 100,000. In the US, Caucasians had a higher crude mortality rate (1.7 per 100,000) than Hispanics (0.2 per 100,000), Blacks (1.0 per 100,000), Asian/Pacific Islanders (0.1 per 100,000), and Native American/Alaska Native (0.3 per 100,000) (Redelings et al 2006).

In some countries, the mortality rates were decreasing. WHO reported the following estimated rates for 2002: in Scotland, 1.8 per 100,000 persons; in Switzerland, 1.2 per 100,000 persons; in Germany, 0.7 per 100,000 persons; and 1.0 per 100,000 persons in the Netherlands (Ragonese et al 2008). In Austria, the average annual mortality rates decreased between the periods of 1970 - 1979 to 1990 - 2001 from 1.4 to 0.7 per 100,000 persons, respectively (Ekestern and Lebhart 2004). Standardized mortality rates (SMR) were 1.4 in the US between 1990 and 2001, 1.4 to 1.6 in Canada between 1980 and 1991, 2.9 in Denmark between 1949 and 1998, and 2.8 in South Wales, England, in 1985 (Hirst et al 2008, Ragonese et al 2008). Comparison of all causes of mortality in MS patients versus the general population indicates an approximately 2- to 3-fold greater risk of mortality associated with MS in Europe and North America. These studies typically observed MS cohorts over a very long follow up period (Sadovnick et al 1992, Brønnum-Hansen et al 2004, Leray et al 2007, Smestad et al 2009, Ragonese et al 2010, Sumelahti et al 2010, GryttenThorkildsen et al 2008, Kingwell et al 2012b). Furthermore, highly disabled MS patients with an Expanded Disability Status Scale (EDSS) of 8 or 9 had an 8-fold increased mortality risk compared to the general French (age, gender, and calendar year matched) population. (Leray et al 2007). Age at onset also plays an important role: patients in Denmark in whom MS began before the age of 20 years had an excess death rate (observed

minus expected number of deaths per 1,000 person years of observation) of 8.6 which increased to 19.1 for the age of onset ≥50 years (BrønnumHansen et al 1994).

A comparison of the risk of all-cause mortality was made in 15684 MS patients and 78420 age/sex-matched non-MS patients in the US Department of Defense (DoD) database. This indicated a mortality rate ratio of 2.93 (95% CI 2.67 -3.22) (Internal Novartis analyses in US DoD database).

Mean age at death of MS patients was 65.3 years (95% CI = 63.4 - 67.1) in a study from South Wales, England in 1985, and 60.9 years in the US between 1990 and 2001 (Redelings et al 2006, Hirst et al 2008). Median survival time in England was 33 years from date of diagnosis and 38 years from symptom onset. The majority of studies report that 60 to 70% of deaths occurring in MS patients are attributable to the disease itself or its complications (Hirst et al 2008).

In a follow-up study conducted in the US among patients initially randomized to placebo in the pivotal IFNB-1b trial, 30.6% had died after 21 years of follow up (Goodin et al 2012).

Elderly Patients (≥65 years)

North America: National multiple causes of death (MCOD) data in the US revealed a crude MS mortality rate of 4.9 per 100,000 population in those 65 to 74 years old, 5.0 per 100,000 population in those 75 to 84 years old and 3.0 per 100,000 population in those older than 85 years old (Redelings et al 2006).

Pediatric Patients

North America and Europe: A study of 386 MS patients in Oslo, Norway revealed that younger age of onset was significantly associated with longer survival (relative risk = 0.46; 95% CI = 0.31 - 0.57) when compared to patients with older age of onset; in those with an age of onset between 0 and 19 years old, there was a 87% survival 25 years after onset of MS (Smestad et al 2009). Data from the MCOD in the US revealed a crude MS mortality rate of 0.01 per 100,000 population in those less than 1 year old, 0.00 per 100,000 population in those 1 to 4 years old, as well as in those 5 to 14 years old (Redelings et al 2006).

Important co-morbidities:

Co-morbidity of Cardiovascular Disease in the target population

In a large, population-based cohort study conducted between 1987 and 2009 using the Swedish National Inpatient Register, researchers reported elevated, age-and sex-adjusted IRRs in the MS- versus general-population for stroke (1.71, 95% CI 1.46-2.00), MI (1.85, 95% CI 1.59-2.15), and heart failure (1.97, 95% CI 1.52-2.56), but a reduced IRR for atrial fibrillation/flutter in MS patients versus the general population (0.63, 95% CI 0.46-0.87) (Jadidi et al 2013).

A comparison of the risk of all coronary artery disorders (i.e., comprising diagnoses for angina pectoris, acute myocardial infarction (AMI), myocardial infarction (MI), coronary artery embolism/thrombosis, ischemic coronary artery disorder, and ischemic heart disease) was made in 15684 MS patients and 78420 age/sex-matched non-MS patients in the United States DoD database. This study yielded a crude event rate ratio (ERR) for all coronary artery disorders of

2.31 (95% CI 2.21-2.42). The same study yielded elevated crude ERRs for the diagnosis categories of all vascular hypertensive disorders, all cardiac arrhythmias, and all thromboembolic events (1.45 (95% CI 1.41 -1.49), 1.91 (95% CI 1.84-1.98), and 2.77 (95% CI 2.68-2.86), respectively) (Internal Novartis analyses in US Department of Defense database).

From a cohort study using the UK GPRD and national death certificates between 2001 and 2008, (Lalmohamed et al 2012) reported an elevated incidence rate ratio (IRR) of death due to cardiovascular disease in MS patients versus age- and sex-matched non-MS controls: IRR 2.42 (95% CI 1.47-3.97).

Co-morbidity of Depression in the target population

Lifetime prevalence rates of major depression between 42% and 50% and annual prevalence of 25.7% was reported from patients attending MS clinics. An elevated risk for depression among persons with MS compared to those without MS was shown (adjusted odds ratio (OR) = 2.3, 95% CI = 1.6 - 3.3) (Joffe et al 1987, Patten et al 2003, Feinstein 2004).

In Norway, 31% of MS patients reported depression compared to 16.1% in the general population (Beiske et al 2008).

In a sample of 50 randomly selected patients with various types of MS, 56% had depressive disorder (Alajbegovic et al 2011).

Reported levels of depression using a self-rating questionnaire were significantly higher ($p < 0.001$) for MS patients ($n = 325$) than healthy subjects ($n = 183$) (MS patients: mean = 5.6 vs. healthy subjects: mean = 3.8) (da Silva et al 2011). In a Norwegian sample of 172 MS patients and 56,000 controls, depression was reported by 26.2% of the men with MS compared with 10.8% of the controls ($p < 0.001$). The corresponding figures for women were 25.2% versus 10.4% ($p < 0.001$). Overall, 25.6% of MS patients versus 10.6% of controls reported depression (Dahl et al 2009).

Two cross-sectional surveys revealed a prevalence of mild depressive symptoms between 45% and 51% in MS patients and a registry showed a depression prevalence of 46% in the US, which is higher than in the general US population (16.2%) (Bamer et al 2008, Marrie et al 2009).

In a study conducted in Iran in 2009, severe depression (per Beck depression inventory (BDI)) among MS patients was present in 24.4% of subjects with RMS, 48.3% of those with Primary progressive multiple sclerosis (PPMS) and 45.8% of those with Secondary progressive multiple sclerosis (SPMS). Moderate depression was found in 33% of those with RMS, 31% of those with PPMS, and 30.6% of those with SPMS (Kargarfard et al 2012).

Falls, accidents and suicide in the target population

The risk for death by accidents in Denmark was 37% higher in MS patients than in the general population (SMR = 1.37; 95% CI = 1.1, 1.7). MS patients had an elevated risk for falls (SMR = 1.3; 95% CI = 0.8, 2.1). They had a higher risk for deaths from burns (SMR = 8.9; 95% CI = 5.2, 14.3) and suffocation (SMR = 5.6; 95% CI = 2.8, 10.0) (Brønnum-Hansen et al 2006). In Denmark, drivers with MS were 3.4 times more often treated in the emergency department after an accident than drivers without MS (Lings 2002). Furthermore, 52.3% to 54.0% of MS patients reported falls in the last 6 and 2 months, respectively (Cattaneo et al 2002, Finlayson et al 2006). In another study, 39.3% of the MS patients reported to have had recent falls that required

medical attention more than 6 months ago and 11.9% reported falls in the last 6 months (Peterson et al 2008). A study in the GPRD in the UK revealed that MS patients had a 1.2-fold increased risk of any fracture compared to the year of birth, gender and practice-matched general population (adjusted Hazard Ratio (HR) = 1.23; 95% CI = 1.09, 1.38) (Bazelier et al 2011).

As MS is associated with depression, MS patients have a higher risk of attempted and completed suicides. A comparison of the risk of attempted suicide was made in 15684 MS patients and 78420 age/sex-matched non-MS patients in the United States DoD database. This study yielded a crude event rate ratio for attempted suicide of 2.41 (95% CI 1.29-4.49) (Internal Novartis analyses in US Department of Defense database). In Denmark, persons with MS compared to the general population had more than twice the risk to commit suicide (SMR = 2.1; 95% CI = 1.8, 2.6) which is similar to data from Sweden (SMR = 2.3, 95% CI = 1.9, 2.8), and Finland (SMR = 1.7; 95% CI = 0.9, 2.7) (Fredrikson et al 2003, BrønnumHansen et al 2005, Sumelahti et al 2010). The risk was particularly high the first year after diagnosis (SMR = 3.2, 95% CI = 1.4, 6.0) (BrønnumHansen et al 2005). In Canada, the proportion of suicide among MS deaths was 7.5 times that for the age matched general population (Sadovnick et al 1991). Suicide rates seem to increase with age and completed suicide is more common in men (Stern 2005). Crude suicide rate among MS patients in Sweden was 71 per 100,000 PY and significantly higher in males than in females (Fredrikson et al 2003). Nevertheless, in studies in Finland and Denmark, no elevated risk of suicide was observed in MS patients (Sumelahti et al 2002, Stenager et al 2011)

Co-morbidity of UTI in the target population

A comparison of the risk of Urinary tract infection (UTI) was made in 15684 MS patients and 78420 age/sex-matched non-MS patient in the United States DoD database. This indicated an ERR of 2.23 (95% CI 2.17-2.30) (Internal Novartis analyses in US DoD database).

A publication by (de Sèze et al 2007) reported median incidence of upper UTI in MS patients to be 8% (ranging from 0% to 23%); however, the applicable time period (i.e. yearly, biennially, etc.) for this estimate is not explicitly mentioned therein.

Lower UTI was reported on average in 30% of MS patients and ranged from 13% to 80%. Prevalence of upper UTI in MS patients was reported to be between 2.2% and 22.8% (de Sèze et al 2007).

MS patients had a much higher risk of fatal UTI compared to matched controls (odds ratio (OR) = 11.3) (95% CI = 10.1 – 12.6) (Redelings et al 2006).

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

An extensive program of toxicological studies served as a basis for the safe use of fingolimod in humans. Non-clinical evaluations to support the administration of fingolimod in humans included safety pharmacology; genotoxicity; repeat-dose toxicity in mice, rats, dogs, and monkeys; reproductive toxicity in rats and rabbits; developmental toxicity in rats; carcinogenicity studies in mice and rats; and a number of mechanistic studies in various *in vitro* or *in vivo* models.

Non-clinical safety findings have been addressed by numerous clinical assessments.

The major target organs were the lymphoid system (lymphopenia and lymphoid atrophy), lungs (increased weight, smooth muscle hypertrophy at the bronchio-alveolar junction), and heart (negative chronotropic effect, increase in blood pressure (BP), perivascular changes and myocardial degeneration) in several species; blood vessels (vasculopathy) in rats only; and pituitary, forestomach, liver, adrenals, gastrointestinal tract and nervous system at high doses only (often associated with signs of general toxicity) in several species.

No evidence of carcinogenicity was observed in a 2-year bioassay in rats at oral doses of fingolimod up to the maximally tolerated dose of [redacted] mg/kg, representing an approximate 50-fold margin based on the human systemic exposure, Area under the curve (AUC) at the 0.5 mg dose. However, in a 2-year mouse study, an increased incidence of malignant lymphoma was seen at doses of [redacted] mg/kg and higher, representing an approximate 6-fold margin based on the human systemic exposure (AUC) at a daily dose of 0.5 mg.

Fingolimod was not mutagenic in an Ames test and in a L5178Y mouse lymphoma cell line *in vitro*. No clastogenic effects were seen *in vitro* in V79 Chinese hamster lung cells. Fingolimod-induced numerical (polyploidy) chromosomal aberrations were seen in V79 cells at concentrations of 3.7 µg/mL and above. Fingolimod was not clastogenic in the *in vivo* micronucleus tests in mice and rats.

Fingolimod had no effect on sperm count/ motility nor on fertility in male and female rats up to the highest dose tested ([redacted] mg/kg); representing an approximate 150-fold margin based on the human systemic exposure (AUC) at a daily dose of 0.5 mg.

Fingolimod was teratogenic in the rat when given at doses of [redacted] mg/kg or higher. The most common fetal visceral malformations included persistent truncus arteriosus and ventricular septum defect. An increase in post-implantation loss was observed in rats at [redacted] mg/kg and higher and a decrease in viable fetuses at [redacted] mg/kg. Fingolimod was not teratogenic in the rabbit, where an increased embryo-fetal mortality was seen at doses of [redacted] mg/kg and higher, and a decrease in viable fetuses, as well as fetal growth retardation, at [redacted] mg/kg.

In rats, F1 generation pup survival was decreased in the early postpartum period at doses that did not cause maternal toxicity. However, F1 body weights, development, behavior, and fertility were not affected by treatment with fingolimod. In a study in young rats which were treated from weaning through sexual maturity, slight changes in bone mineral density and persistent neurobehavioral impairment (altered auditory startle) were observed at all doses. Delayed sexual maturation was noted in females at the highest dose tested and in males at all doses. Repeated stimulations with Keyhole Limpet Hemocyanin (KLH) showed a moderately

decreased response during the treatment period, but a clear tendency towards fully functional immune reactions at the end of an 8-week recovery period. Fingolimod was excreted in milk of treated animals during lactation. Fingolimod and its metabolites crossed the placental barrier in pregnant rabbits.

Table 3-1 highlights some of the toxicological findings for which a clinical correlation has not been found. Some findings were only seen in a single animal species or strain following treatment with fingolimod, such as generalized vasculopathy in Wistar rats or an increased incidence of malignant lymphomas in mice.

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	Relevance to human usage
Repeat-dose toxicity	
Vasculopathy:	
Repeat-dose toxicity studies in mice, Sprague-Dawley rats, Wistar rats, dogs and monkeys showed generalized vasculopathy only in Wistar rats (in a life-time assay findings were seen at doses [redacted] mg/kg, i.e. approximately 3.5-fold higher exposure, based on systemic exposure (AUC), compared to exposure in patients treated with fingolimod doses of [redacted] mg/day). In dogs, fingolimod-related changes were seen exclusively in the heart (vascular wall thickening and perivascular and focal perimysial fibrosis of the left ventricular papilla in the heart) and were not associated with an inflammatory component.	In clinical studies to date, no evidence of drug-related vasculopathy in humans has been observed.
Hemodynamic and immunomodulatory effects of fingolimod and an increased susceptibility of Wistar rats to develop vascular lesions may have contributed to the lesions in comparison to Sprague-Dawley rats. In contrast, hemodynamic effects alone may have led to the development of the lesions seen in the heart of dogs.	
Lungs:	
A potential for broncho-constriction and increased sensitivity induced by agents known to induce bronchoconstriction was found in experimental settings in animals. In addition, smooth muscle cell hypertrophy (SMH) was observed in the terminal bronchioli in rats and monkeys. The SMH induced by fingolimod is a minimal to mild stable lung lesion without any sign of progression over the analyzed treatment periods of up to 52 weeks in monkeys, or 2 years in rats. A study in juvenile rats showed that these animals appeared to be less sensitive to develop SMH. The SMH lesion showed a clear trend to reversibility after drug discontinuation.	Extensive respiratory monitoring has been performed in clinical studies with fingolimod and no evidence of drug-induced lung fibrosis has been observed.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Nervous system:	
Sporadic findings were observed in the nervous system in toxicity studies at high oral doses ([redacted] mg/kg). High tissue accumulation with lung over blood ratios between 40 and 400 at steady state conditions were demonstrated in animals. In a 4-week toxicity study in dogs, at an oral dose of [redacted] mg/kg/day, perivascular mononuclear cell infiltration in the gray matter of the brain, peripheral nerve degeneration (axon and Schwann cells) in the heart, and ganglion cell vacuolation of Auerbach's plexus in the stomach were noted. It was concluded that fingolimod caused activation of microglial cells, which are the subpopulation of normal brain residents, and macrophages infiltrating from the circulating peripheral blood. In a 26-week toxicity study in dogs, at the high dose of [redacted] mg/kg, brain findings similar to those seen at [redacted] mg/kg/day following 4 weeks of treatment were seen. Electron microscopical examinations revealed proliferation and swelling of processes of astrocytes in the affected brains but no effects on neurons. The dose of [redacted] mg/kg in that study was considered to have been above the maximum tolerated dose (MTD), as 3 animals had to be sacrificed (weeks 7, 10, 25) and one male died in week 23. All animals showed a history of clinical signs for a prolonged period of time including decrease in food consumption, emaciation and hypothermia. In a 13 week toxicity study in monkeys, an increased number of Glial fibrillary acidic protein (GFAP) positive astrocytes in the cerebral gray matter were observed in one male in the [redacted] mg/kg group, indication an early activation of astrocytes. There were no effects on the central or peripheral nervous system in a 39 week study ([redacted] mg/kg) or 52 week study (up to [redacted] mg/kg) in monkeys treated with fingolimod. A special examination of the brain in the 52-week monkey study did not show any changes in the densities of GFAP or Myelin Basic Protein in the cerebral white matter.	The sporadic Central Nervous System (CNS) effects observed at high doses in toxicology studies are unlikely to have any human correlate at the therapeutic dose of 0.5 mg.
Reproductive Toxicity	
Fingolimod had no effect on the fertility and early embryonic development in rats up to [redacted] mg/kg (highest dose tested). In rats, fingolimod increased post-implantation loss, and decreased viable fetuses. In rabbits, fingolimod increased embryo-fetal mortality, decreased the number of viable fetuses and induced fetal growth retardation.	Based on cumulative analysis of post-marketing data there is an increased risk of major and of major + minor congenital anomalies in prospective cases with maternal exposure during pregnancy as compared with general population. The pattern of malformation reported for fingolimod is similar to that observed in the general population. The proportion of spontaneous abortion in prospectively

Key Safety findings (from non-clinical studies)	Relevance to human usage
Fingolimod was teratogenic in rats (including persistent truncus arteriosus, ventricular septal defect) but not in rabbits. Fingolimod and its metabolites cross the placental barrier in pregnant rabbits ([redacted] mg/kg, p.o.) to a limited extent. The radioactivity concentrations in the fetuses were approximately 4-fold lower than in maternal blood. The fetuses and the dams were exposed mainly to oxidative metabolites (predominantly M3, butanoic acid metabolite) and less to parent compound and fingolimod-phosphate. Fingolimod and its metabolites were transferred into the milk of lactating rats ([redacted] mg/kg, p.o.). About 2% of the administered radioactive dose was secreted in the milk within 48 hours mainly as fingolimod and fingolimod-phosphate.	reported pregnancies in fingolimod-treated patients is in line with general population. It is not known if fingolimod is excreted in human milk. Reproductive toxicity is an important identified risk in the RMP (please see Table 8-9 Clinical trial data of Reproductive toxicity) and is also highlighted in the Summary of Product Characteristics (SmPC) Section 4.3, 4.4 and 4.6.
Developmental toxicity	
In rats, F1 generation pup survival was decreased in the early postpartum period at doses that did not cause maternal toxicity. However, F1 body weights, development, behavior, and fertility were not affected by treatment with fingolimod. In a juvenile rat study fingolimod caused treatment-related effects comparable to those seen in adult rats with the exception of the absence of smooth muscle hypertrophy in the lungs of the juvenile rats. In another study, slight changes in bone mineral density and persistent neurobehavioral impairment (altered auditory startle) were observed at all doses. Delayed sexual maturation was noted in females at the highest dose tested and in males at all doses. Repeated stimulations with KLH showed a moderately decreased response during the treatment period, but a clear tendency towards fully functional immune reactions at the end of an 8 week recovery period.	Paediatric (10 years and above) safety monitoring has been performed in clinical studies with fingolimod and study results support a positive benefit-risk profile of fingolimod as the first oral therapy in pediatric MS patients.
Genotoxicity	
Fingolimod was not mutagenic, clastogenic or aneugenic in any of the *in vitro* or *in vivo* studies performed	No mutagenic risk for patients anticipated based on preclinical data.
Carcinogenicity	
In a 2-year study, mice in the high dose groups developed an increased incidence of malignant lymphomas, believed to be related to systemic immunosuppression. Systemic exposures were approximately 2-20 times the systemic exposure seen in man. There was a statistically significant increase in the incidence of histiocytic sarcomas, hemangiomas and hemangiosarcomas at [redacted] and/or [redacted] mg/kg when compared to placebo. These latter findings are not considered toxicologically	In the completed Phase 3 MS studies (Study FTY720D2301 and Study FTY720D2302) and the completed core Phase 2 Study FTY720D2201, there was no evidence of increased risk of malignancy in patients treated with fingolimod.

Key Safety findings (from non-clinical studies)	Relevance to human usage
relevant, as the incidence of these tumors was within the historical control range of that mouse strain used in carcinogenicity studies at Novartis Pharma. A 2-year bioassay in rats showed no tumorigenic potential. No increased incidence of lymphoma was observed in the rat carcinogenicity study or in the long-term primate toxicology study up to the highest doses tested, providing substantial exposure margins of more than 50- or 150-fold in rats and monkeys, respectively.	
General safety pharmacology: **-cardiovascular (including potential for QT interval prolongation)**	
Fingolimod induces a transient decrease in heart rate and increase in blood pressure, both of which was not associated with relevant findings in long-term toxicology studies, although histopathological findings in the heart in dogs at high doses in chronic toxicity studies may have been related to hemodynamic factors. Effects on heart rate were characterized further and are related to an effect of fingolimod-phosphate on G-protein-gated inwardly rectifying K+ (GIRK) channels. Although a slight inhibition of human Ether-a-go-go Related Gene (hERG) channel activity at the solubility limit ([redacted] µM) of fingolimod or fingolimod-phosphate was seen, there was no indication of QT prolongation in series of *in vitro* or *in vivo* studies up to high concentrations and/or doses.	The transient effect on heart rate has also been studied and confirmed in human. In clinical studies to date, no evidence of drug related cardiopathy in humans has been observed. The effects observed at high doses in dog studies are unlikely to have any human correlate at the therapeutic dose of 0.5 mg A slight QT prolongation was observed in man which based on the studies performed could not be reproduced in preclinical experiments.
Mechanisms for drug interactions	None identified preclinically.
Other toxicity-related information or data **Nephrotoxicity:**	
Kidney changes, consisting of basophilic tubuli (severity grade minimal) were seen in a 26-week study in Wistar rats at all treated groups ([redacted] mg/kg, [redacted] mg/kg, or [redacted] mg/kg). In mice, treated for 13 weeks at [redacted] mg/kg, an increased incidence of interstitial inflammation accompanied by increased numbers of basophilic tubules and intratubular hyaline casts in male animals was found. Transient decreases in renal function were also noted in dogs and a decrease in urine output was observed in rats. However, no findings in kidneys was seen in Sprague Dawley rats up to 26 weeks (high dose [redacted] mg/kg), dogs up to 26 weeks (high dose [redacted] mg/kg), or monkeys up to 52 weeks (high dose [redacted] mg/kg). In addition, FTY720, when given at an oral dose of [redacted] mg/kg for 4 weeks in spontaneous hypertensive rats in combination with a salt (sodium)-depleted diet, was not nephrotoxic.	The kidney effects observed in toxicology studies are unlikely to have any human correlate at the therapeutic dose of 0.5 mg.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Hepatotoxicity:	
Minimal hepatocellular necrosis in individual females and slight increases in Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) and total bilirubin was seen in a 26-week toxicity study in rats at [redacted] mg/kg. In another 26-week rat study, no findings in the liver were observed up to the highest dose tested, i.e., [redacted] mg/kg. In a 4 week dog study, at [redacted] mg/kg, there was an increase in AST and ALT and a decrease in γ globulin; microscopically there was brown pigment in the Kupffer cells in the liver and single cell necrosis of hepatocytes. No liver findings were seen at [redacted] mg/kg in a 26 week toxicity study in dogs, or following 52 weeks of treatment at [redacted] mg/kg in cynomolgus monkeys. Overall, effects on the liver were not consistently seen in animal toxicity studies and were mild and did only occur at high dose levels in some studies in combination with general clinical signs (e.g., body weight and food consumption), indicating that the MTD may have been exceeded. There was no evidence in animals for cholestasis.	Increase in ALT and AST have also been observed in patients. These changes in animals were not linked with clinically meaningful effects on liver histology except at very high doses which are likely not relevant for patients at the therapeutic dose of [redacted] mg. A direct correlation of the effects on liver seen in animals with the findings in clinical trials is unlikely. Increase in ALT and AST have also been observed in patients. Bilirubin levels were not impacted by fingolimod

Important identified risks from non-clinical data and confirmed by clinical data are bradyarrhythmia, hypertension, liver transaminase elevation, infections, bronchoconstriction and reproductive toxicity. These risks have been discussed in Module SVII and / or Part II of Module SVIII up to RMP v18, and have been re-categorized with RMP v19 (removal of hypertension, infections, bronchoconstriction).

There are no other important potential risks identified in non-clinical safety studies which would not have been refuted by clinical data or which would be of unknown significance. Furthermore, there is no missing information identified in the non-clinical safety program.

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

As of 28-Feb-2023, approximately 25,400 patients received fingolimod treatment in Novartis-sponsored interventional studies with a total exposure of more than 35,200 patient years cumulatively since the Development IBD (DIBD).

In the terminated renal transplant clinical program, 1,606 renal transplant patients received fingolimod, the large majority of them at doses (2.5 or 5.0 mg/day) higher than those used in MS patients, in combination primarily with cyclosporine and corticosteroids (in the context of de novo renal transplantation), with an estimated 1,420.4 patient-years of exposure to fingolimod.

In the MS indication (including trials with commercial drug use and estimated data from ongoing blinded trials and local studies), the total exposure to fingolimod in clinical studies is estimated as 71449.35 patient-years in approximately 39344 MS patients. From these, approximately 28669 patients (with 58270.70 patient-years) are derived from patient-level clinical study drug data.

Exposure of the remainder is estimated based on the reported number of enrolled patients and the randomization rate. The locked and unblinded study FTY720D2306 in primary progressive MS contributes approximately 1346 patient-years in approximately 483 fingolimod-treated MS patients. FTY720D2306 study is completed and will no longer have any updates in the patient exposure details.

Exposure and patient demographics (age, gender, race distribution) of patients exposed to fingolimod and comparator treatments are summarized on the basis of the data available in the common data repository virtual data warehouse (VDW) and are discussed in light of the expected characteristics of the target population. At the cut-off date (28-Feb-2023) the VDW contained data from 35,200 enrolled patients from 29 core and/or extension studies. It contained all data from all completed global clinical trials, plus data from selected ongoing or completed global or local studies including the observational studies, CFTY720D2405, CFTY720D2403 (PASSAGE-US) and CFTY720D2406 (PASSAGE-EU). An overview is provided in Table 4-1.

Exposure to fingolimod is summarized for groups D, E, F and G as also used for the reporting of safety data in fingolimod treated patients:

- **Group D** consists of all patients from all completed double-or rater-blind, randomized, controlled studies in adult patients with RRMS (all core data from studies CFTY720D1201, CFTY720D2201, CFTY720D2301, CFTY720D2302, CFTY720D2309, CFTY720D2312 and CFTY720D2320). There was no change in group D in the review period (01-Mar-2021 to 28-Feb-2023).

- **Group E** consists of all fingolimod-treated patients from all completed double-or rater-blind, randomized, controlled studies in adult patients with RRMS (Group D) or their completed extensions. It only contains patients treated with fingolimod from Novartis global drug supply. There was no change in group E in the review period (01-Mar-2021 to 28-Feb-2023).

- **Group F** consists of an extended fingolimod-treated safety population: it includes fingolimod-treated patients from all available studies in the VDW. In addition to the studies in group E, group F includes:
  - Completed studies CFTY720D2306, CFTY720D2316, CFTY720D2324, CFTY720D2325, CFTY720IT03, CFTY720DDE17 and CFTY720US01 and its extension, CFTY720DDE02, CFTY720D2403, CFTY720D2405, CFTY720D2406 CFTY720D1401, CFTY720D2399 (Part 1, E1, and Part 2) and CFTY720D2409
  - Ongoing studies (not available in VDW): CFTY720D2311 (completed core and ongoing extension (E1) phase in pediatric MS) and CFTY720D2419 (ongoing local China post approval commitment study). Additionally, fingolimod is used as comparator treatment in an ongoing, double-blinded study in pediatric MS (CBAF312D2301).

- **Group G:** All patients in all available completed and ongoing studies in the virtual data warehouse in the broader MS indication (incl. PPMS, RRMS, RMS, acute optic neuritis).

An overview of overall patient enrollment is provided in the table below.

Table 4-1 SIII.1: Summary of the number of patients enrolled and assigned to study drug in all available studies in the data repository, all completed and ongoing clinical studies are included (28-Feb-2022)

Study	FTY720 5 mg	FTY720 1.25 mg	FTY720 0.5 mg	FTY720 Any dose	Placebo	INF and Other DMTs	Total enrolled
Initial study							
1201	0	57	57	114	57	0	171
2201	94	94	0	188	93	0	281
2301	0	429	425	854	418	0	1272
2302	0	426	431	857	0	435	1292
2306	0	147	336	483	487	0	970
2309	0	370	358	728	355	0	1083
2312**	0	0	352	719**	0	342	1061
2316	0	0	2417	2417	0	0	2417
2320	0	0	95	95	43	0	138
2324	0	0	50	50	92	0	142
2325	0	0	162	162	0	0	162
2403*	0	0	2243	2243	0	1223	3466
2405	0	0	637	637	0	0	637
2406*	0	0	3128	3128	0	1318	4446
1401*+	0	0	1007	1007	0	0	1007
DE02+	0	0	4133	4133	0	0	4133

Study	FTY720 5 mg		FTY720 1.25 mg		FTY720 0.5 mg		FTY720 Any dose		Placebo	INF and Other DMTs		Total enrolled	
DE17*+	0		0		6997		6997		0	0		6997	
IT03+	0		0		998		998		0	0		998	
US01+	0		0		789		789		0	263		1052	
US09	0		0		436		436		0	439		875	
Extensions													
1201E1	0	(.)	64	(23)	79	(32)	143	(50)	0	(.)	0	(.)	.
2201E1	123	(43)	127	(40)	0	(.)	250	(83)	0	(.)	0	(.)	.
2301E1	0	(.)	434	(145)	486	(155)	920	(300)	0	(.)	0	(.)	.
2302E1	0	(.)	504	(174)	523	(167)	1027	(341)	0	(.)	0	(.)	.
2306E1	0	(.)	0	(.)	571	(375)	571	(301)	0	(.)	0	(.)	.
2309E1	0	(.)	308	(105)	324	(107)	632	(212)	0	(.)	0	(.)	.
US01	0	(.)	0	(.)	193	(193)	193	(193)	0	(.)	0	(.)	.
Umbrella extension													
2399E1	0	(.)	0	(.)	63	(31)	63	(.)	0	(.)	0	(.)	.
2399	0	(.)	0	(.)	4089	(969)	4089	(71)	0	(.)	0	(.)	.
2399P2	0	(.)	0	(.)	661	(.)	661	(.)	0	(.)	0	(.)	.
Total 1													32600
Total 2	94		1523		25051		27035		1545	4020		.	
Total 3	137		2010		27080		28586		1545	4020		.	

-Numbers represent patients assigned to the treatment at the start of the study phase. Numbers in parenthesis represent the number of patients newly assigned to this treatment at the start of an extension or long-term extension study phase. Patients may appear under more than one treatment column if they have been reassigned.

-Total 1: The total number of patients enrolled.

-Total 2: The total number of patients initially assigned to this treatment.

-Total 3: The total number of patients eventually assigned to this treatment.

- Completed studies are defined by a published study report at the cutoff date.

* Studies ongoing as of the data cutoff for this reporting period (numbers reflect the status of the database).

** 367 patients took 0.25 mg per day

+ Country Pharmaceutical organization (CPO).

Study	FTY720 5 mg	FTY720 1.25 mg	FTY720 0.5 mg	FTY720 Any dose	Placebo	INF and Other DMTs	Total enrolled
- Source: Appendix 7 of PSUR 15, Table 6, VDW 28-Feb-2022							

For the studies in Table 4-1 above, the overall exposure by dose is presented in the Table 4-2. The overall estimated long-term exposure to fingolimod in completed studies includes more than 13500 MS patients who have received fingolimod treatment for at least one year and more than 4800 MS patients more than five years. More than 400 patients have now been treated with fingolimod for more than 10 years.

Table 4-2 SIII.2: Actual exposure to fingolimod in clinical studies by duration for completed and ongoing MS studies (interventional and non-interventional)

Duration of Exposure	FTY720 5 mg N=94	FTY720 1.25 mg N=1514	FTY720 0.5 mg N=24689	FTY720 0.25 mg N=366	FTY720 any dose N=26663	Placebo N=1531	INF and Other DMTs N=3860
≥ 1 day	135	2046	27588	366	28668	1530	5865
≥ 180 days	110	1763	16262	329	17130	1235	4187
≥ 360 days (1 year)	88	1433	12839	156	13523	1057	3118
≥ 720 days (2 years)	0	952	9594	0	10015	746	1996
≥ 1080 days (3 years)	0	351	7299	0	7604	320	1498
≥ 1800 days (5 years)	0	72	4597	0	4834	5	500
≥ 3600 days (10 years)	0	0	186	0	460	0	0
Patient-years	147.4	3896.4	53924.1	324.9	58292.7	2772.6	10711.3

- N=Number of patients initially randomized/assigned to this treatment and actually treated.
- *Actual exposure to study drug according to the drug administration panel. Patient-years of exposure correspond to the actual time patients were treated with the specific medication. Dosing errors of fingolimod are counted in the “any dose” column, but not in the specific dose columns. Dosing errors are periods during which the drug administration panel suggests that the patient has taken fingolimod, but not at the assigned dose.
- Patients can appear under more than one treatment if they were re-assigned.
- Patients are cumulatively counted at each level of exposure.
- Because of definitional difference between group G and F, the actual exposure for fingolimod in this table differs from the actual exposure in Group F by one patient.
-Source: Appendix 7 of PSUR 15, Table-7, VDW 28-Feb-2022

Of the 214 patients who received at least one dose of study drug in the pediatric study (D2311) 107 were assigned to fingolimod. Further, 102 (95.3%) of these patients had at least one year of exposure and 74 (69.2%) had at least 1 ½ years (i.e. ≥ 540 days) exposure to fingolimod. The mean fingolimod exposure time was 600.9 ± 149.27 days (Table 4-3).

Table 4-3 SIII.3: Duration of exposure to study drug, by treatment, Safety set (D2311 – Core Study)

Duration of Exposure	FTY720 N=107 n (%)	IFNß-1a N=107 n (%)	Total N=214 n (%)
≥ 1 days	107 (100)	107 (100)	214 (100)
≥ 7 days	107 (100)	107 (100)	214 (100)
≥ 14 days	106 (99.1)	107 (100)	213 (99.5)
≥ 30 days	106 (99.1)	107 (100)	213 (99.5)
≥ 60 days	105 (98.1)	106 (99.1)	211 (98.6)
≥ 90 days	105 (98.1)	105 (98.1)	210 (98.1)
≥ 180 days	103 (96.3)	99 (92.5)	202 (94.4)
≥ 270 days	103 (96.3)	93 (86.9)	196 (91.6)
≥ 360 days	102 (95.3)	88 (82.2)	190 (88.8)
≥ 450 days	97 (90.7)	81 (75.7)	178 (83.2)
≥ 540 days	74 (69.2)	55 (51.4)	129 (60.3)
≥ 630 days	55 (51.4)	37 (34.6)	92 (43.0)
≥ 720 days	30 (28.0)	19 (17.8)	49 (22.9)
≥ 750 days	2 (1.9)	1 (0.9)	3 (1.4)
Mean	600.9	523.7	562.3
Standard deviation (SD)	149.27	187.29	173.32
Min	9	30	9
Q1	510.0	451.0	482.0
Median	634.0	547.0	587.0
Q3	721.0	711.0	716.0
Max	767	750	767
Patient-years	176.0	153.4	329.5

Each subject is counted in the category of maximum duration as well as in each lower category.
The duration of exposure for a subject is the number of days on study drug, with all interruptions excluded.
Patient-years is (the sum of the number of days on study drug for all subjects in the group)/365.25.
Source: Attachment to Annex 7 of RMP v 13, CFTY720D2311 Table 14.3-1.1

Patient exposure according to the Integrated Summary of Safety (ISS) rules grouped patients according to the highest dose of fingolimod received. To disentangle the different doses and to account for treatment switching (e.g. patients were re-assigned to lower doses of fingolimod when higher doses were discontinued), a more elaborate algorithm than the one used in the Integrated Summary of Safety (ISS) was introduced, replacing the previous patient numbers

presented before PSUR 7. This explains the slight difference in the overall estimate compared to exposure tables that use ISS rules but represents a more accurate patient exposure.

Of the 4577 patients in completed double-blind studies alone (group E), 3428 patients have had at least one year of exposure to fingolimod, with 1652 patients at least five years (table below).

Table 4-4 SIII.4: Actual exposure to study medication by duration for completed RRMS studies (Group E)

Duration of Exposure*	FTY720 5 mg N=137	FTY720 1.25 mg N=1853	FTY720 0.5 mg N=2224	FTY720 0.25 mg N=363	FTY720 any dose N=4577
≥ 1 day	135	1899	3522	366	4576
≥ 180 days	110	1635	3209	329	4059
≥ 360 days (1 year)	88	1396	2761	156	3428
≥ 720 days (2 years)	0	952	2202	0	2613
≥ 1080 days (3 years)	0	351	1881	0	2178
≥ 1800 days (5 years)	0	72	1479	0	1652
≥ 2160 days (6 years)	0	43	1276	0	1530
≥ 2520 days (7 years)	0	0	944	0	1346
Patient-years	147.4	3781.1	15043.4	324.9	19296.7

- *Actual exposure to study drug according to the drug administration panel. Patient-years of exposure correspond to the actual time patients were treated with the specific medication.
- N=Number of patients initially randomized/assigned to this treatment and actually treated.
- 'Any dose' of fingolimod include all doses (5 mg, 1.25 mg, 0.5 mg, 0.25 mg)
- Patient years correspond to the actual time patients were treated with the specific study drug; patients can appear under more than one study drug if they were reassigned. It is defined as the sum of the number of days on a specific study drug across all patients, divided by 365.25.

Source: Appendix 7 of PSUR 15, Table-8, VDW 28-Feb-2022

A majority of patients (approximately 71%) from completed double-blind studies (group E) were female (Table 4-5), reflecting the fact that MS is more common in women than men; the result is similar when expressed in patient-years of exposure (Table 4-6).

Most patients were between 18 and 55 years of age at the inclusion into the initial study which corresponds to the inclusion criteria used in the Phase 3 studies. Although, per protocol, patients younger than 18 years were not to be included, [redacted] was included in Study FTY720D2301. Table 4-5 and Table 4-6 provide summaries by the patient's age at baseline of the first study in which the patient participated.

Table 4-5 SIII.5: Exposure (number of patients) to fingolimod from MS studies, by age and gender (ISS rules)

Age*	Group E			Group F			
	Male	Female	Total	Male	Female	Missing	Total
<18	0	1	1	4	13	0	17
18-30	332	760	1092	1743	4243	0	5986
31-40	491	1101	1592	2779	6273	0	9052
41-55	479	1348	1827	3345	8475	0	11820
56-65	15	50	65	530	1185	0	1715
>65	0	0	0	23	105	0	128
Missing	0	0	0	4	9	3	16
Total	**1317**	**3260**	**4577**	**8428**	**20303**	**3**	**28734**

*Age refers to the age at baseline of the first study (not the age at the first dose of fingolimod).
-All doses of fingolimod are included (5 mg, 1.25 mg, 0.5 mg, and 0.25 mg)
- The duration of exposure is the total number of days patients took study medication (ISS-rules=same definition as also used in the integrated summary of safety).
- [redacted] at the time of core caseline.
-Source: Appendix 7 of PSUR 15, Table-9, VDW: 28-Feb-2022

The vast majority (approximately 87%) of patients from completed studies (Group E) were Caucasian, approximately 4% were Asian (including “oriental”) and approximately 4% were Black, with the rest of the patients falling into other categories (Table 4-7). The clinical study population reflects that MS is predominantly a disease of the Caucasian population.

Table 4-6 SIII.6: Exposure (patient-years) to fingolimod from MS studies, by age and gender (ISS rules)

Age*	Group E			Group F			
	Male	**Female**	**Total**	**Male**	**Female**	**Missing**	**Total**
<18	0	8.7	8.7	6.5	27.1	0	33.6
18-30	1623.2	2960.9	4584.1	3895.8	7764.0	0	11659.8
31-40	2328.8	4920.2	7249.0	6325.3	13451.0	0	19776.3
41-55	1958.7	5395.6	7354.4	6719.2	17316.0	0	24035.3
56-65	33.2	94.0	127.2	870.8	1727.0	0	2597.9
>65	0	0	0	32.6	164.5	0	197.1
Missing	0	0	0	6.8	19.6	7.9	34.3
Total	5943.9	13379.4	19323.4	17857.0	40469.2	7.9	58334.2

*Age refers to the age at baseline of the first study (not the age at the first dose of fingolimod).

-All doses of fingolimod are included (5 mg, 1.25 mg, 0.5 mg. 0.25 mg)

- The duration of exposure is the total number of days patients took study medication (ISS-rules=same definition as also used in the integrated summary of safety).

- Patient-years are defined as the sum of the number of days on study drug for all patients in each treatment group, divided by 365.25.

- [redacted] at the time of core baseline.

- Source: Appendix 7 of PSUR 15, Table-10, VDW: 28-Feb-2022

Table 4-7 SIII.7: Exposure (number of patients and patient-years) to fingolimod from MS studies, by race)

Race	Group E		Group F	
	Number of patients	Patient-years	Number of patients	Patient-years
Caucasian	3998	17832.6	20694	39820.2
Asian	189	532.9	1327	2183.3
Black	165	308.4	756	1094.3
Other	225	649.5	972	1679.7
Missing	0	0	4985	13556.7
Total	4577	19323.4	28734	58334.2
-All doses of fingolimod are included (5mg, 1.25 mg, 0.5 mg, 0.25 mg) Source: Appendix 7 of PSUR 15, Table 11, VDW: 28-Feb-2022				

A breakdown of exposure to fingolimod in the pediatric study (D2311) by age and gender is shown in Table 4-8.

Table 4-8 SIII.8: Duration of exposure to study drug, by age, gender and treatment, Safety set (D2311 - Core Study)

		FTY720 N=107		IFNß-1a N=107	
Age	**Sex**	**n (%)**	**Patient-years**	**n (%)**	**Patient-years**
Total	Total	107 (100)	176.0	107 (100)	153.4
	Male	37 (34.6)	58.6	43 (40.2)	63.0
	Female	70 (65.4)	117.4	64 (59.8)	90.5
Age ≤12 years	Total	13 (12.1)	20.0	9 (8.4)	9.7
	Male	8 (7.5)	11.5	7 (6.5)	7.4
	Female	5 (4.7)	8.4	2 (1.9)	2.3
Age >12 years	Total	94 (87.9)	156.1	98 (91.6)	143.8
	Male	29 (27.1)	47.1	36 (33.6)	55.6
	Female	65 (60.7)	109.0	62 (57.9)	88.2
N=number of subjects in the safety set; n=number of subjects in the subgroup from the safety set; %=n/N Patient-years is (the sum of the number of days on study drug for each subject in each category a group)/365.25. Source: Attachment to Annex 7 of RMP v 13, CFTY720D2311-Table 14.3-1.1b					

A breakdown of exposure to fingolimod in the pediatric study (D2311) by race is shown in Table 4-9.

Table 4-9 SIII.9: Duration of exposure to study drug, by race and treatment, Safety set (D2311-Core Study)

	FTY720 N=107		IFNß-1a N=107	
Race	**n (%)**	**Patient-years**	**n (%)**	**Patient-years**
White	100 (93.5)	166.0	97 (90.7)	142.9
Black or African American	1 (0.9)	1.7	3 (2.8)	1.9
Asian	1 (0.9)	1.4	0	0
American Indian or Alaska Native	3 (2.8)	3.9	2 (1.9)	2.7
Other	2 (1.9)	3.1	5 (4.7)	6.0

N=number of subjects in the safety set; n=number of subjects in the subgroup from the safety set; %=n/N

Patient-years is (the sum of the number of days on study drug for each subject in each category a group)/365.25.

Source: Attachment to Annex 7 of RMP v 13, CFTY720D2311-Table 14.3-1.1c

The time spent at-risk from the first dose of fingolimod is more relevant than the age at baseline due to:

- increasing age of individual patients within studies; there are already patients with more than 10 years of exposure within the study data
- some patients randomized/assigned to comparator treatment in the original study switching to fingolimod in a later extension study

The time spent at-risk from the first dose of fingolimod categorized by the age at which that drug exposure was experienced is provided in Table 4-10.

In particular it shows that, patients have spent more than 5500 patient-years in the >55-year age category (Group F). The increase in exposure in patients older than 55 years in the review period is partly caused by aging of the original study population, and partly due to the inclusion of observational studies which do not have an age restriction into Group F.

Table 4-10 SIII.10: Time-at-risk (in patient-years) in patients assigned to any dose of fingolimod in MS studies, by age-group and gender

Age*	**Group E**				**Group F**					
	Male		**Female**		**Male**		**Female**		**Total**	
<18	0	0%	0.1	<0.1%	5.8	<0.1%	6.4	<0.1%	12.2	<0.1%
18-30	800.2	12.7%	1844.3	13.4%	2665.6	13.9%	6038.7	13.8%	8704.2	13.8%
31-40	2267.9	36.0%	4094.4	28.6%	6920.4	32.8%	12503.3	28.5%	18793.7	29.8%
41-55	2935.2	46.6%	7313.3	51.1%	8458.2	44.1%	21165.8	48.2%	29624.0	47.0%

Age*	Group E				Group F					
	Male		Female		Male		Female		Total	
>55	301.5	4.8%	1047.5	7.3%	1651.8	8.6%	3933.3	9.0%	5585.2	8.9%
Missing					119.2	0.6%	225.2	0.5%	325.7	0.6%
Total	6304.8	100%	14299.7	100%	19191.0	100%	43872.6	100%	63071.9	100%

-All doses of fingolimod are included (5 mg, 1.25 mg, 0.5 mg. 0.25 mg)

*The time-at-risk corresponds to the time patients spent at-risk and could have contributed to the collection of adverse events, including treatment interruptions and up to 45-days after study drug discontinuation (approx. 5 times the elimination half-life of fingolimod). The time-at-risk is calculated as the sum of days patients spent at risk within each age category (patients can contribute to more than one category as they age), divided by 365.25.

- [redacted] at the time of core baseline

- The total column might contain slightly more patient exposure than in the respective gender or age categories combined due to missing gender or age data for some patients

- Source: Appendix 7 of PSUR 15, Table-12, VDW: 28-Feb-2022

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 SIV.1: Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Long-term use in pediatric patients, including impact on growth and development (including cognitive development)	There is limited data on long term use in pediatric patients.	Yes	
Pediatric Patients (age 10 to below 18 years)	Pediatric patients were excluded from enrollment in the pivotal studies	No	Completion of the Core Phase of Study D2311
Elderly patients (≥65 years)	Based on epidemiology, MS is not a disease of elderly, patients above 55 years old were excluded from the pivotal studies	No	Safety profile in elderly patients is similar to adult patients and no additional safety concerns are observed. The reported AEs in the elderly population corresponded to the symptoms of MS or to the known pharmacological effects of fingolimod.
Pregnant and lactating women	Fingolimod and its metabolites crossed the placental barrier in pregnant rabbits (5.0 mg/kg, p.o.) to a limited extent. Fingolimod and its metabolites were transferred into the milk of lactating rats.	Use in pregnancy: No Use in lactating women: No	Reproductive toxicity is an important identified risk. The cases received cumulatively did not add significant information on fingolimod exposure via breast milk over the past 10 years in the post-marketing setting. In the limited number of female patients with

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
			information on breast-fed babies, no events suggesting a possible impact on the fetal immune system were reported.
Patients with diabetes mellitus	Patients with diabetes mellitus are at increased risk of developing macular edema. In renal transplant clinical studies in which patients with diabetes mellitus were included, therapy with fingolimod 2.5 mg and 5 mg resulted in a 2 fold increase in the incidence of macular edema.	No	As per VDW Diabetes safety set, 11 patients (2.3%) in FTY group (n=482) and 1 patient (0.8%) in no FTY group (n=125) presented with macular edema as new event. Cumulative data so far have not revealed any specific trend in the incidence of AEs for patients with diabetes mellitus. An analysis to assess the risk of occurrence of macular edema in MS patients with diabetes based on pooled fingolimod trials in VDW revealed a numerically increased risk of macular edema with fingolimod treatment compared with no fingolimod treatment which was not statistically significant.
Patients with cardiovascular conditions	Initiation of fingolimod treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays, including the occurrence of isolated reports of transient, spontaneously resolving complete Atrio-Ventricular (AV) block.	No	No long-term serious CV events observed in fingolimod treated patients who experienced a cardiac event during first dose observation period in the PASSAGE studies and also in the PM setting. The risk is mitigated by adequate guidance on the use of fingolimod in patients with underlying CV conditions and

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
			monitoring guidance during FDO.
Hepatic impairment	Patients with hepatic impairment (cirrhosis, chronic active hepatitis or chronic persistent hepatitis, or patients with persistent ALT/AST or alkaline phosphatase (AP) levels more than 2.5 × Upper limit of normal (ULN), serum creatinine >2.0 × ULN, serum bilirubin >2 × ULN) were excluded from enrollment in the clinical program.	No	Liver transaminase elevation is an important identified risk.
Long-term risk of malignant neoplasms	The clinical trial program excluded patients with diagnosed malignancies besides of BCC and SCC	No	The review of PASSAGE data did not reveal any new information safety signals. No increased risk of malignancies other than skin malignancies consistent with the findings from previous clinical trials and PM setting. The information on risk of malignancies with long term use is covered under the potential risk malignancies.

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions due to exposure limitations during a set course of the studies. Rare adverse reactions or adverse reactions with a long latency or those caused by prolonged/cumulative exposure become evident with continuing safety monitoring in the post-marketing setting.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 SIV.2: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure/Representation in Clinical Trial Program
Pregnant women	Not included in the clinical development program
Breastfeeding women	

Type of special population	Exposure/Representation in Clinical Trial Program
	Fingolimod is not recommended for use in pregnant and lactating women and has, therefore, not been formally studied in this population.
Patients with relevant comorbidities: Patients with hepatic impairment	Not included in the clinical development program Patients with severe liver impairment (Child-Pugh class C) are contraindicated. The pharmacokinetics of fingolimod and fingolimod-phosphate was compared in 6 healthy control subjects versus 6 subjects with severe hepatic impairment of Child-Pugh class C Study A2204. Severe hepatic impaired subjects had a similar fingolimod C_{max}, doubled AUC, and 50% prolonged elimination half-life. Plasma protein binding was not altered by severe hepatic impairment. Fingolimod is contra-indicated in patients with severe hepatic impairment (Child-Pugh class C).
Patients with cardiovascular impairment	Initiation of fingolimod treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays, including the occurrence of isolated reports of transient, spontaneously resolving complete AV block. The patients with the following conditions were excluded from the pivotal studies: myocardial infarction within the past 6 months prior to enrollment or current unstable ischemic heart disease history of angina pectoris due to coronary spasm or history of Raynaud's phenomenon cardiac failure at time of Screening (Class III, according to NYHA Classification) or any severe cardiac disease as determined by the investigator history or presence of a second degree atrioventricular (AV) block or a third degree AV block or an increased QTc interval >440 ms on Screening electrocardiogram (ECG) arrhythmia requiring current treatment with Class III antiarrhythmic drugs (e.g., amiodarone, bretylium, sotalol, ibulitide, azimilide, dofelitide) history of cardiac arrest, symptomatic bradycardia, resting pulse rate <55 beats per minute (bpm) prior to randomization, sick sinus syndrome or sino-atrial heart block, a positive tilt test during workup for vasovagal syncope
Pulmonary conditions	Patients with severe respiratory disease or pulmonary fibrosis, tuberculosis, abnormal chest High resolution computed tomography (HRCT) or chest X-ray suggestive of active pulmonary disease, abnormal pulmonary function tests (Forced expiratory volume in 1 second (FEV_1) and Forced vital capacity (FVC) values lower than 70% of predicted value, Diffusing capacity of the lung for carbon monoxide (D_LCO) values lower than 60% of predicted value) or asthmatic patients requiring daily (chronic) therapies were excluded from the pivotal studies based on the preclinical finding of minimal to slight hypertrophy/hyperplasia of Smooth muscle cells (SMCs) in the broncho-alveolar junction in rats and monkeys.

Type of special population	Exposure/Representation in Clinical Trial Program
Patients with Diabetes Mellitus and Macular edema	A known or 'new' diagnosis of diabetes mellitus (if screening blood glucose is suspicious for diabetes [≥126 mg/dL or ≥7 mmol/L if fasting and ≥200 mg/dL or 11.1 mmol/L if random testing] were excluded from the pivotal studies due to increased risk of developing macular edema. In renal transplant clinical studies in which patients with diabetes mellitus were included, therapy with fingolimod 2.5 mg and 5 mg resulted in a 2-fold increase in the incidence of macular edema. Patients with a history of macular edema during screening visit were excluded from entering the pivotal studies. Patients with diagnosed macular edema during the studies, had to discontinue fingolimod
Immunocompromised patients	Patients with history of chronic disease of the immune system other than MS or a known immunodeficiency syndrome, patients received total lymphoid irradiation or bone marrow transplantation were excluded from the pivotal studies
Active systemic bacterial, viral, or fungal infections	Patients with severe active infections or active chronic infections (diagnosis of Acquired immunodeficiency syndrome (AIDS), hepatitis B, or hepatitis C infection (defined as a positive human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen, or hepatitis C antibody test, respectively), tuberculosis were excluded from the pivotal studies
History or presence of malignancy	Patients with known active malignancies; except for patients with cutaneous basal cell carcinoma and squamous cell carcinoma were excluded from the pivotal studies
Patients with a disease severity different from inclusion criteria in clinical trials	Primary progressive MS and Secondary progressive MS patients were excluded from the clinical trial program. Fingolimod is currently approved for relapsing MS patients.
Population with relevant different ethnic origin	No exclusion based on ethnic origin. The racial distribution in the updated clinical trial database stands at: 64% Caucasians, 2% Blacks, 4% Asians (including Orientals), and 29% others. Dedicated Japanese studies (FTY720D1201) were the basis for the approval in Japan. A long-term extension of the study (FTY720D1201E) has also been read out.
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Elderly	Based on epidemiology, MS is not a disease of elderly. The upper age limit for inclusion of patients in the Phase 3 clinical development program in MS was 55 years of age for the majority of the studies, 60 years in Study FTY720D2201 and 65 years in Study FTY720D2316. Therefore, experience in the use of fingolimod in the elderly MS patient population, especially above the age range of 65, is currently limited.

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

The number of patients exposed to fingolimod in the commercial setting is based on reported numbers from each country organization. The number of patients reported may include patients who have previously discontinued from a clinical trial and have switched to commercial drug. For this reason, the overall estimate of the number of patients exposed to fingolimod is calculated as the sum of the number of patients in the commercial setting and the number of patients in ongoing clinical trials (patients who discontinued from a previous trial are not counted to avoid any double counting).

Exposure in terms of patient-years is calculated from the sales volume of active substance sold during the interval period and the defined daily dose in one capsule (0.5 mg). The number of capsules divided by 365.25 provides the patient-years of exposure. The sales volume of active substance includes that used for trials which use commercial drug, these trials are excluded from the clinical trial estimate to avoid double-counting of exposure.

6.1.2 Part II Module SV.1.2. Exposure

The cumulative commercial patient exposure since the first launch of the product in MS, excluding clinical study exposure, is estimated to be approximately 1,088,631 patient-years (cut-off date: 28-Feb-2024). This estimate is calculated based on the worldwide sales volume in kilograms (kg) of active substance to date and the defined daily dose.

Table 6-1 Post-marketing (PM) exposure to commercial drug in patient years by reporting period

	Aug 2010 - Feb 2011	Mar 2011 - Feb 2012	Mar 2012 - Feb 2013	Mar 2013 - Feb 2014	Mar 2014 - Feb 2015	Mar 2015 - Feb-2016	Mar 2016 - Feb 2017	Mar 2017 - Feb 2018	Mar 2018 - Feb 2019	Mar 2019 - Feb 2020	Mar-2020 – Feb 2021	Mar 2021 - Feb-2023	Mar 2023-Feb 2024	Total Aug 2010 - Feb 2024
Exposure*	905.66	16,603.28	37,333.42	59,964.19	79,733.39	94,922.89	107,317.05	111,500.07	116,556.21	119,809.15	110,997.02	181,326.19	51,662.47	1,088,631

Source: Worldwide reported sales volume in kilogram (kg) of active substance at the time of the DLP
*Current review period exposure as calculated from sales data and is estimated with more precision than in earlier reporting periods and does differ slightly.

Based on the sales volume of fingolimod, in the latest review period (01-Mar-2023 to 28-Feb-2024) of approximately 9.4 kg (active ingredient), the estimated interval exposure was 51,662.47 patient-years.

Out of the above-mentioned country-reported total to date, the distribution by region and country of the exposure in patient treated with fingolimod are presented in Table 6-2 and Table 6-3.

Table 6-2 Global cumulative post-marketing commercial exposure

Country/Region	Patient years
US	[redacted]
Non-US	[redacted]
Total	1,088,631.00

Table 6-3 Non-US cumulative post-marketing commercial exposure

Country/Region	Patient years
Region Europe (EEA)	522,655.45
Region Europe (Non-EEA)	82,071.05
[redacted]	[redacted]
[redacted]	[redacted]
Rest of the World	159,005.25
Total Non-US	[redacted]

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

A possible risk of misuse or dependence on fingolimod is not anticipated on the basis of its mechanism of action and lack of psychopharmacologic effects. While no clinical studies have been carried out to specifically investigate abuse potential, no evidence has emerged from clinical trials which would suggest a potential for abuse or dependence with fingolimod.

A review of all complete and incomplete spontaneous reports of abuse and misuse, with or without associated adverse reactions, did not reveal any use patterns or other safety information relevant to the benefit-risk assessment for fingolimod.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II SVII.1. Identification of safety concerns in the initial RMP submission

This section is not applicable, the RMP was already approved.

8.2 Part II SVII.2: New safety concerns and reclassification with a submission of an updated RMP

There was no change in safety concerns since the last update.

8.3 Part II SVII.3: Details of important identified risks, important potential risks, and missing information

8.3.1 SVII.3.1. Presentation of important identified risks and important potential risks

8.3.1.1 Important Identified Risk: Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose

Table 8-1 Clinical trial data of Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose

	Adult (Group D)			Pediatric (D2311)*	
	FTY720 0.5 mg N=1364 n (%)	**Placebo N=966 n (%)**	**Odds-ratio**	**FTY720 N=107 n (%)**	**IFNβ-1a N=107 n (%)**
Bradyarrhythmia and bradycardia, hypotension and malaise (NMQ)					
Number of subjects with at least one event	175 (12.8)	122 (12.6)	1.02 [0.79;1.32]	13 (12.1)	11 (10.3)
Severity					
Mild	116 (8.5)	80 (8.3)		9 (8.4)	7 (6.5)
Moderate	45 (3.3)	34 (3.5)		2 (1.9)	3 (2.8)
Severe	14 (1.0)	8 (0.8)		2 (1.9)	1 (0.9)
SAEs	15 (1.1)	5 (0.5)	2.14 [0.73;7.54]	1 (0.9)	1 (0.9)
Leading to death	0	0		0	0
Bradyarrhythmias and bradycardia NMQ (narrow)					
Number of subjects with at least one event	50 (3.7)	21 (2.2)	1.71 [1.00;3.02]	4 (3.7)	2 (1.9)
Severity					
Mild	36 (2.6)	13 (1.3)		3 (2.8)	1 (0.9)

	Adult (Group D)			Pediatric (D2311)*	
	FTY720 0.5 mg N=1364 n (%)	Placebo N=966 n (%)	Odds-ratio	FTY720 N=107 n (%)	IFNβ-1a N=107 n (%)
Moderate	9 (0.7)	7 (0.7)		0 (0.0)	1 (0.9)
Severe	5 (0.4)	1 (0.1)		1 (0.9)	0 (0.0)
SAEs	12 (0.9)	3 (0.3)	2.85 [0.77;15.77]	1 (0.9)	0 (0.0)
Leading to death	0	0		0	0

* No inferential statistics were performed due to the small sample size

Numbers (n) represent counts of subjects.

Case Retrieval Strategy: Group D MedDRA version 19.1, D2311 MedDRA version 20.0.
Source: Attachment to Annex 7 of RMP v 14 and 13, Group D: TRSK D 3-1.2, TRSK D 3-2.1, TRSK D 3-1.3; D2311: Table 14.3.1-1.2a, Table 14.3.1-1.5a, Table 14.3.1-1.15

Table 8-2 Important identified risk Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose: Other details

Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	Details
Potential mechanisms	The mechanism of fingolimod's effect on heart rate and atrioventricular conduction is linked to an activation of GIRK channels in atrial myocytes and a hyperpolarization of cell membranes that transiently reduces the excitability of the cells (Brinkmann 2007). A similar GIRK channel modulation can be produced through stimulation of muscarinic receptors by acetylcholine and, consistent with the mechanism, the effects are reversible by β-receptor agonists. Although experiments with S1P3-deficient mice suggest a dominant role of S1P3 in this process (Forrest et al 2004), data suggest that in humans, S1P1 (rather than S1P3) may play a dominant role in the regulation of atrial myocyte function, AV conduction and heart rate (Brinkmann 2007)
Evidence source(s) and strength of evidence	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Characterization of the risk:	See Table 8-1 above. Most of cases of bradyarrhythmia are asymptomatic and resolve spontaneously. There have been isolated reports of atrioventricular blocks that require pharmacologic treatment and other treatment measures.
Risk factors and risk groups	Patients with particular medical history and/or co-medications in whom bradycardia may be poorly tolerated or might be at increased risk for bradycardia. This includes patients with: • second degree Mobitz type II or higher AV block, • sick-sinus syndrome

Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	**Details**
	• sino-atrial heart block, • history of symptomatic bradycardia or recurrent syncope, • significant QT prolongation (QTc>470msec (female) or >450msec (male)). Avoid in patients with risk factors for QT prolongation such as hypokalemia, hypomagnesemia or congenital QT prolongation • known ischemic heart disease (including angina pectoris), • cerebrovascular disease, • history of myocardial infarction, • congestive heart failure, • history of cardiac arrest, • uncontrolled hypertension • severe sleep apnea, Other potential risk factors include concomitant administration with: • Class Ia (e.g. quinidine, dysopyramide) or Class III (e.g. amiodarone, sotalol) anti-arrhythmic medicinal products. • beta blockers, • heart-rate-lowering calcium channel blockers (such as verapamil, diltiazem or ivabradine), or other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic agents or pilocarpine)
Preventability	The SmPC contains contraindications and recommendations for activities during first dose administration and the need for appropriate first dose monitoring and additional observation (see Table 12-1).
Impact on the benefit-risk balance of the product	The benefit-risk profile of fingolimod in the indication of relapsing MS remains positive, as the benefits of stronger and sustained efficacy as compared to placebo and a standard of care continue to outweigh the well-characterized and manageable risk of bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose.
Public health impact	Reduction in heart rate is a pharmacodynamic effect which is expected to occur in most patients at treatment initiation. The effect is clinically benign and, as demonstrated in Study A0114, the negative chronotropic effect of fingolimod 5.0 mg, a dose 10 times greater than the proposed dose for registration, is similar to that of atenolol 50 mg in terms of mean nadir heart rate. A small number of patients have developed atrioventricular conduction abnormalities post-first dose which resolved without sequelae within 24-48 hours. If therapy is needed, bradyarrhythmia is responsive to atropine or intravenous β-agonists. In the post-marketing setting, isolated reports of transient, spontaneously resolving complete AV block have been observed during the 6-hour monitoring period with Gilenya (SmPC). Apart from the transient effects observed following first dose administration, fingolimod does not appear to be associated with any

Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	**Details**
	significant changes in heart rate or atrioventricular conduction based on mid- and long-term follow-up data available. In the post-marketing setting, isolated delayed onset events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose. These cases have been confounded by concomitant medicinal products and/or pre-existing disease. The relationship of such events to fingolimod is uncertain (SmPC).

8.3.1.2 Important Identified Risk: Liver transaminase elevation

Table 8-3 Clinical trial data of Liver transaminase elevation

	Adult (Group D)			**Pediatric (D2311)***	
	FTY720 0.5 mg N=1364 n (%)	**Placebo N=966 n (%)**	**Odds-ratio**	**FTY720 N=107 n (%)**	**IFNβ-1a N=107 n (%)**
Liver transaminase elevation					
Number of subjects with at least one event	213 (15.6)	52 (5.4)	3.25 [2.36;4.55]	9 (8.4)	6 (5.6)
Severity					
Mild	86 (6.3)	31 (3.2)		6 (5.6)	3 (2.8)
Moderate	99 (7.3)	16 (1.7)		2 (1.9)	2 (1.9)
Severe	28 (2.1)	5 (0.5)		1 (0.9)	1 (0.9)
SAEs	2 (0.1)	1 (0.1)	1.42 [0.07;83.69]	1 (0.9)	0
Leading to death	0	0		0	0

* No inferential statistics were performed due to the small sample size

Numbers (n) represent counts of subjects.

Case Retrieval Strategy: Group D MedDRA version 19.1, D2311 MedDRA version 20.0.
Source: Attachment to Annex 7 of RMP v 14 and v 13, Group D: TRSK D 3-1.2, TRSK D 3-2.1, TRSK D 3-1.3; D2311: Table 14.3.1-1.2a, Table 14.3.1-1.5a, Table 14.3.1-1.15

Table 8-4 Important identified risk Liver transaminase elevation: Other details

Liver transaminase elevation	**Details**
Potential mechanisms	Currently unknown, mechanism of action has not been elucidated
Evidence source(s) and strength of evidence	Considered ‘important’ as a change in the risk could have an impact on the risk-benefit balance of the product.

Liver transaminase elevation	Details
Characterization of the risk:	See Table 8-3 Clinical trial data of Liver transaminase elevation above. The majority of patients experienced asymptomatic elevation in serum levels of ALT of ≥3x ULN (upper limit of normal) and ≥5x ULN, respectively. Recurrence of liver transaminase elevations has occurred upon re-challenge in some patients, supporting a relationship to the medicinal product. Isolated serious cases may require supportive treatment and medical intervention.
Risk factors and risk groups	None identified for fingolimod.
Preventability	The SmPC states that during treatment, in the absence of clinical symptoms, if liver transaminases are greater than 3 but less than 5 times the upper limit of normal (ULN) without increase in serum bilirubin, more frequent monitoring including serum bilirubin and alkaline phosphatase (ALP) measurement should be instituted to determine if further increases occur and in order to discern if an alternative aetiology of hepatic dysfunction is present. If liver transaminases are at least 5 times the ULN or at least 3 times the ULN associated with any increase in serum bilirubin, Gilenya should be discontinued. Hepatic monitoring should be continued. If serum levels return to normal (including if an alternative cause of the hepatic dysfunction is discovered), Gilenya may be restarted based on a careful benefit-risk assessment of the patient.
Impact on the benefit-risk balance of the product	The benefit-risk profile of fingolimod in the indication of relapsing MS remains positive, as the benefits of stronger and sustained efficacy as compared to placebo and a standard of care continue to outweigh the well-characterized and manageable risk of Liver transaminase elevation.
Public health impact	Not expected to be clinically significant based on the data available and potential public health impact is considered to be low.

8.3.1.3 Important Identified Risk: Macular edema

Table 8-5 Clinical trial data of Macular edema

	Adult (Group D)			Pediatric (D2311)*	
	FTY720 0.5 mg N=1364 n (%)	Placebo N=966 n (%)	Odds-ratio	FTY720 N=107 n (%)	IFNβ-1a N=107 n (%)
Macular oedema (NMQ) (narrow)					
Number of subjects with at least one event	7 (0.5)	4 (0.4)	1.24 [0.31;5.80]	1 (0.9)	0
Severity					
Mild	1 (0.1)	0		1 (0.9)	0
Moderate	3 (0.2)	3 (0.3)		0	0
Severe	3 (0.2)	1 (0.1)		0	0
SAEs	2 (0.1)	1 (0.1)	1.42 [0.07;83.69]	0	0
Leading to death	0	0		0	0

* No inferential statistics were performed due to the small sample size

	Adult (Group D)			Pediatric (D2311)*	
	FTY720 0.5 mg N=1364 n (%)	Placebo N=966 n (%)	Odds-ratio	FTY720 N=107 n (%)	IFNβ-1a N=107 n (%)

Numbers (n) represent counts of subjects.

Case Retrieval Strategy: Group D MedDRA version 19.1, D2311 MedDRA version 20.0.
Source: Attachment to Annex 7 of RMP v14 and v 13, Group D: TRSK D 3-1.2, TRSK D 3-2.1, TRSK D 3-1.3; D2311: Table 14.3.1-1.2a, Table 14.3.1-1.5a, Table 14.3.1-1.15

Table 8-6 Important identified risk Macular edema: Other details

Macular edema	Details
Potential mechanisms	S1P and its receptors S1P1 and S1P3 play a key role in the regulation of endothelial and epithelial barriers (Brinkmann 2007). The cellular components of the blood retinal barrier (BRB-endothelial cells, epithelial cells, astrocytes) express S1P receptors and these receptors tightly control endothelial and epithelial barriers. The BRB contains both tight junctions (TJ) and adherens junctions (AJ) between its cellular compartments. This suggests that pharmacological activation of S1P receptors on the BRB may at the same time increase/protect AJ between cells (via S1P1 receptor agonism), thereby strengthening the barrier, but may also reduce TJ between the cellular components (via S1P3 receptor agonism), thereby reducing barrier function. A reduction of TJ via S1P receptors may be of particular concern in cases of pre-damage, e.g. in diabetic retinopathy. In vivo studies have shown that fingolimod signals endothelial S1P1 to protect mice from vascular endothelial growth factor-induced vascular leakage. The increase in endothelial barrier function by the drug may relate to the 10-fold higher affinity of the biologically active fingolimod-phosphate to S1P1 compared to S1P3 (Brinkmann 2007). Co-administration of cyclosporine A suppressed the barrier-protective effects of fingolimod on AJ in peripheral vessels but did not modulate effects of fingolimod on the BRB, suggesting that the antagonistic regulation of AJ by fingolimod and cyclosporine A may be of lesser importance for the development of ME.
Evidence source(s) and strength of evidence	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Characterization of the risk:	See Table 8-5 above. Most of the patients are asymptomatic; however, discontinuation of Gilenya is needed when macular edema is diagnosed. In most cases, macular edema resolves spontaneously after the drug is withdrawn. More serious cases that manifest as decreased visual acuity may require pharmacological intervention and some may require surgery.
Risk factors and risk groups	Patients with diabetes and history of uveitis are considered at increased risk of developing macular edema. Such patients should undergo an ophthalmic evaluation prior to initiating Gilenya therapy and have follow-up evaluations while receiving Gilenya therapy.
Preventability	The SmPC recommends that all patients have ophthalmological examination 3-4 months after treatment initiation. Patients with diabetes mellitus or a history of uveitis should undergo an ophthalmological evaluation prior to initiating therapy and have follow-up evaluations while receiving therapy. See Table 12-1 for details.

Macular edema	Details
Impact on the benefit-risk balance of the product	The benefit-risk profile of fingolimod in the indication of relapsing MS remains positive, as the benefits of stronger and sustained efficacy as compared to placebo and a standard of care continue to outweigh the well-characterized and manageable risk of Macular edema.
Public health impact	No significant effect expected, particularly at doses of fingolimod 0.5 mg daily. Macular edema can be readily detected by appropriate clinical examinations and subsequent discontinuation of fingolimod therapy has been shown to result in resolution of the condition without long-term visual impairment.

8.3.1.4 Important Identified Risk: Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection

Table 8-7 Clinical trial data of Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection

	Adult (Group D)			Pediatric (D2311)*	
	FTY720 0.5mg N=1364 n (%)	Placebo N=966 n (%)	Odds-ratio	FTY720 N=107 n (%)	IFNβ-1a N=107 n (%)
Infections and infestations (SOC)					
Number of subjects with at least one event	867 (63.6)	638 (66.0)	0.90 [0.75;1.07]	64 (59.8)	60 (56.1)
Severity					
Asymptomatic	5 (0.4)	7 (0.7)		NA	NA
Mild	418 (30.6)	317 (32.8)		53 (49.5)	51 (47.7)
Moderate	399 (29.3)	283 (29.3)		9 (8.4)	9 (8.4)
Severe	45 (3.3)	31 (3.2)		2 (1.9)	0
SAEs	19 (1.4)	13 (1.3)	1.04 [0.48;2.29]	4 (3.7)	2 (1.9)
Leading to death	0	0		0	0
Opportunistic infections (CMQ)					
Number of subjects with at least one event	0	0		0	0
Varicella-zoster virus Infections (NMQ) (broad)					
Number of subjects with at least one event	36 (2.6)	15 (1.6)	1.72 [0.91;3.40]	1 (0.9)	1 (0.9)
Severity					
Mild	15 (1.1)	9 (0.9)		1 (0.9)	1 (0.9)
Moderate	17 (1.2)	5 (0.5)		0	0
Severe	4 (0.3)	1 (0.1)		0	0

	Adult (Group D)			Pediatric (D2311)*	
	FTY720 0.5mg N=1364 n (%)	Placebo N=966 n (%)	Odds-ratio	FTY720 N=107 n (%)	IFNβ-1a N=107 n (%)
SAEs	3 (0.2)	1 (0.1)	2.13 [0.17;111.78]	0	0
Leading to death	0	0		0	0
Infections (HVI other than VZV-broad)					
Number of subjects with at least one event	61 (4.5)	52 (5.4)	0.82 [0.55;1.23]	2 (1.9)	2 (1.9)
Severity					
Mild	43 (3.2)	38 (3.9)		2 (1.9)	2 (1.9)
Moderate	16 (1.2)	14 (1.4)		0	0
Severe	2 (0.1)	0		0	0
SAEs	1 (0.1)	0	>100	0	0
Leading to death	0	0		0	0

* No inferential statistics were performed due to the small sample size

Numbers (n) represent counts of subjects.

Case Retrieval Strategy: Group D MedDRA version 19.1, D2311 MedDRA version 20.0.
Source: Attachment to Annex 7 of RMP v 14 and v 13, Group D: TRSK D 3-1.2, TRSK D 3-2.1, TRSK D 3-1.3; D2311: Table 14.3.1-1.2a, Table 14.3.1-1.5a, Table 14.3.1-1.15

Table 8-8 Important identified risk: Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection : Other details

Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection	Details
Potential mechanisms	A key pharmacodynamic effect of fingolimod is a dose-dependent reduction of peripheral lymphocyte count to 20 - 30% of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues. Lymphocyte counts typically return to normal range within 1-2 months of stopping. Fingolimod down regulates S1P1 receptors rendering lymphocytes unable to respond to the S1P gradient and egress from lymph nodes. The resultant sequestration of T and B lymphocytes in lymphoid tissues results in marked reduction of lymphocytes, but not myeloid leukocytes, in the blood. This process is reversible; lymphocytes reappear in the blood after the cessation of treatment, indicating that fingolimod does not kill lymphocytes. The absence of a significant increase in overall infection rates (including serious infections) with fingolimod therapy, despite the reduction in peripheral blood lymphocyte count, may be related to the fact that the memory effector subset of T-cells do not appear to be affected by fingolimod, remaining in the peripheral circulation. In addition, fingolimod effects on peripheral blood neutrophil counts are less marked, being reduced by less than 20% from baseline values.

Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection	**Details**
	To date, the known pharmacodynamic and toxicology data for fingolimod do not support a rationale for the observed increased rates of opportunistic infections including cryptococcal infections in patients with MS treated with Gilenya. Varicella-zoster virus (VZV) infections and Herpes viral infections other than VZV Progressive Multifocal Leukoencephalopathy (PML) PML is a reactivation of latent JC virus in a host with immune suppression.
Evidence source(s) and strength of evidence	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Characterization of the risk:	See Table 8-7 above. The majority of the non-serious respiratory infections and urinary tract infections only require supportive treatment, but other serious infections may require medical intervention such as treatment with antibiotics. Isolated cases of infections including opportunistic infections may require hospitalization and more aggressive systemic antimicrobial treatment. Cryptococcal meningitis may lead to fatality in case of delay in diagnosis and delayed/inappropriate treatment. Varicella-zoster virus infections Serious, life-threatening, and sometimes fatal cases of encephalitis, meningitis or meningoencephalitis caused by herpes simplex and varicella zoster viruses have occurred with Gilenya at any time during treatment. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with Gilenya. Herpes viral infections other than VZV Serious, life-threatening, and sometimes fatal cases of encephalitis, meningitis or meningoencephalitis caused by herpes simplex virus were reported while on GILENYA treatment. If herpes encephalitis, meningitis or meningoencephalitis occur, Gilenya should be discontinued and appropriate treatment for the respective infection should be administered Progressive Multifocal Leukoencephalopathy (PML) This serious infection carries a mortality rate in excess of 20% based on the experience with natalizumab cases (D'Amico et al 2016).At present there is no treatment or cure for PML (Aksamit 2006, O'Connor 2007). Early diagnosis is important to clinical outcome and to prevent disability (Brew et al 2010).
Risk factors and risk groups	Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies) and those with severe active infections including active chronic infections (hepatitis, tuberculosis) should not receive Gilenya.

Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection	**Details**
	Varicella-zoster virus infections Patients receiving concomitant immunosuppressive therapy may be at increased risk for VZV infections. The patient who died because of disseminated varicella zoster infection reported no history of varicella infection, no previous vaccination against varicella zoster (VZ) virus and was VZ virus-IgG negative. Therefore, patients with negative VZ virus-IgG results may be at increased risk of developing severe forms of primary infection with VZ virus, particularly in the context where they receive additional high-dose steroid therapy, e.g. in case of an MS relapse. Herpes viral infections other than VZV Patients receiving concomitant immunosuppressive therapy may be at increased risk for Herpes viral infections other than VZV. Progressive Multifocal Leukoencephalopathy (PML) PML primarily affects individuals with suppressed immune systems. In recent years, the most common underlying immunosuppressive illness has been AIDS. However, a variety of non-AIDS immunosuppressive illnesses has been associated with the occurrence of PML. These include lymphoreticular malignancy, most commonly chronic lymphocytic leukemia or non-Hodgkin lymphoma. JC virus is a double-stranded DNA human polyomavirus acquired in childhood. After infection, it remains latent in the body. 50-70% of the adult population is seropositive. It is believed that all seropositive individuals harbor latent virus in kidney, lymphoreticular tissue, or brain. PML is considered a reactivation infection. Whether the reactivation occurs systemically, with immunosuppression causing dissemination to the brain at that time, or the reactivation occurs from latent virus in the brain remains unclear (Aksamit 2006). In people who are immunosuppressed, JC virus can reactivate and cause PML which is usually fatal. PML has been reported under fingolimod treatment since marketing authorization. The majority of PML cases have occurred after 2 or more years of fingolimod treatment. When evaluating the risk with fingolimod, these potential risk factors should be considered: Duration of fingolimod exposure Prior treatment with an immunosuppressant medication (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide) or an immunomodulator medication Severe lymphopenia (<0.5x10^9/l).
Preventability	The immune system effects of Gilenya may increase the risk of infections, including opportunistic infections. In the post-marketing setting cases of infections with opportunistic pathogens, such as viral (e.g. VZV, JCV, Herpes simplex virus (HSV)), fungal (e.g. cryptococci including

Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection	Details
	cryptococcal meningitis) or bacterial (e.g. atypical mycobacterium), have been reported. See Table 12-1 for details on the SmPC. Fingolimod is contraindicated in patients with immunodeficiency syndrome, immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies), severe active and chronic infections (hepatitis, tuberculosis) and in patients with suspected or confirmed PML. Refer to Section 4.4 of SmPC: The immune system effects of Gilenya may increase the risk of infections, including opportunistic infections. Vigilance for signs or symptoms of infections overall including opportunistic infections, is recommended. Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. Patients at increased risk of PML should be closely monitored for any signs or symptoms. Annual MRI may be considered as part of increased vigilance especially in these patients at increased risk of PML. If PML is suspected, MRI should be performed immediately for diagnostic purposes and treatment with fingolimod should be suspended until PML has been excluded. If PML is confirmed, treatment with fingolimod must be permanently discontinued. After stopping Gilenya in the setting of PML, monitor for the development of immune reconstitution inflammatory syndrome (PML-IRIS). Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with S1P receptors modulators, including Gilenya, who developed PML, and subsequently discontinued treatment. IRIS presents as a clinical decline in the patient's condition that may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic changes on MRI. The time to onset of IRIS in patients with PML was usually from weeks to months after S1P receptor modulator discontinuation. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken. Initiation of treatment with fingolimod should be delayed in patients with severe active infection until resolution. Suspension of treatment with fingolimod, should be considered if a patient develops a serious infection. Because residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 2 months after discontinuation of fingolimod, vigilance for infection should be continued throughout this period.
Impact on the benefit-risk balance of the product	The benefit-risk profile of fingolimod in the indication of relapsing MS remains positive, as the benefits of stronger and sustained efficacy as compared to placebo and a standard of care continue to outweigh the well-characterized and manageable risk of Infections, including opportunistic infections

Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection	**Details**
Public health impact	In the completed Phase 3 studies, the incidence rates of infections on fingolimod 0.5 mg was similar to that in patients receiving interferon β-1a i.m. or placebo. Both fatal cases of infection (herpes simplex encephalitis and disseminated varicella zoster infection) occurred in patients receiving fingolimod 1.25 mg with additional confounding factors. The potential public health impact in patients receiving fingolimod 0.5 mg is considered to be low although care is needed in patients who have other risk factors which may pre-dispose to severe infection e.g. concomitant immunosuppressive therapy. Other Opportunistic infection including cryptococcal meningitis The potential public health impact in patients receiving fingolimod 0.5 mg is considered to be low although care is needed in patients who have other risk factors which may pre-dispose to severe infection e.g. concomitant immunosuppressive therapy.

8.3.1.5 Important Identified Risk: Reproductive toxicity

Table 8-9 Clinical trial data of Reproductive toxicity

	Adult (Group D)			**Pediatric (D2311)***	
	FTY720 0.5mg N=1364 n (%)	**Placebo N=966 n (%)**	**Odds-ratio**	**FTY720 N=107 n (%)**	**IFNβ-1a N=107 n (%)**
Pregnancy (PSUR) (NMQ)					
Number of subjects with at least one event	22 (1.6)	25 (2.6)	0.62 [0.33;1.15]	1 (0.9)	0
Severity					
Mild	17 (1.2)	18 (1.9)		1 (0.9)	0
Moderate	3 (0.2)	5 (0.5)		0	0
Severe	2 (0.1)	2 (0.2)		0	0
SAEs	3 (0.2)	6 (0.6)	0.35 [0.06;1.66]	0	0
Leading to death	0	0		0	0

* No inferential statistics were performed due to the small sample size

Numbers (n) represent counts of subjects.

Case Retrieval Strategy: Group D MedDRA version 19.1, D2311 MedDRA version 20.0.
Source: Attachment to Annex 7 of RMP v 14 and v 13, Group D: TRSK D 3-1.2, TRSK D 3-2.1, TRSK D 3-1.3; D2311: Table 14.3.1-1.2a, Table 14.3.1-1.5a, Table 14.3.1-1.15

Table 8-10 Important identified risk Reproductive toxicity: Other details

Reproductive toxicity	Details
Potential mechanisms	Not known. S1P1 signaling is involved in embryonic neural and vascular development. Accordingly, S1P1 receptor-deficient mice showed defects in neurogenesis (Mizugishi et al 2005), and blood vessels were incompletely covered by vascular smooth muscle cells (VSMCs) (Allende et al 2003). Conditional deletion of S1P1 in ECs mimicked the vascular effect (Allende et al 2003), indicating that vessel coverage by VSMCs is directed by the activity of the S1P1 receptor in ECs.
Evidence source(s) and strength of evidence	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Characterization of the risk:	See Table 8-9 Clinical trial data of Reproductive toxicity. Due to the potential toxicity observed in animals, women of childbearing potential are recommended to use effective contraception with Gilenya and two months after drug discontinuation. Results from CFTY720D2404 (Gilenya Pregnancy Registry, "GPR"): The prevalence of major congenital malformations (MCMs) in prospective live births in the GPR, using both the EUROCAT (6.7%; 95% CI: 3.4, 11.7) and MACDP (9.1%; 95% CI: 5.2, 14.6) classification systems, was higher than in the general population (1.77% and 3.0%, respectively), with non-overlapping CIs. The most frequently reported major malformations involved the following: congenital heart defects, renal abnormalities and musculoskeletal abnormalities. However, compared to EUROCAT data, a fingolimod-specific malformation pattern cannot be described based on these results. Important study limitations include no adjustment for confounders, no re-adjudication in case of spontaneous resolution, lack of an internal comparator cohort and small sample size. A majority of participants reported at least one risk factor for MCM, which contributed to the observed increased MCM prevalence. The prevalence of spontaneous abortions was at the lower end and that of still births was in line with what would be expected in the general population and in women with MS in studies of similar designs. In the fingolimod prospective pharmacovigilance data, including data from the PRIM program (PRegnancy outcomes Intensive Monitoring), the prevalence of MCMs among 700 live births, stillbirths or terminations of pregnancy due to fetal anomaly from women who were exposed to fingolimod (including women treated with fingolimod up to 8 weeks before pregnancy and during pregnancy) was 3.6% (95% CI: 2.3-5.2). The most frequently reported MCMs were congenital heart defects, nervous system and renal abnormalities. Compared to EUROCAT data, only congenital heart defects appear more frequently. Important program limitations include possible under reporting, loss to follow-up, no adjustment for confounders, and lack of an internal comparator cohort.
Risk factors and risk groups	Females of childbearing potential not using an effective form of contraception. Fingolimod is excreted in milk of treated animals during lactation. Because of the potential for serious ADRs in nursing infants from fingolimod, women receiving Gilenya should not breast feed.
Preventability	In the EU, the use of fingolimod in women of childbearing potential not using effective contraception and in pregnant women is contraindicated.

Reproductive toxicity	Details
	The SmPC also states that fingolimod should not be used during breastfeeding. Women of childbearing potential must use effective contraception. A negative pregnancy test result is required before treatment initiation. See Table 12-1 for details.
Impact on the benefit-risk balance of the product	The benefit-risk profile of fingolimod in the indication of relapsing MS remains positive, as the benefits of stronger and sustained efficacy as compared to placebo and a standard of care continue to outweigh the well-characterized and manageable risk of reproductive toxicity.
Public health impact	No significant effect is expected if effective contraceptive measures are used in females of childbearing potential.

8.3.1.6 Important Identified Risk: Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)

Table 8-11 Clinical trial data of Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)

	Adult (Group D)		
	FTY720 0.5mg N=1364 n (%)	**Placebo N=966 n (%)**	**Odds-ratio**
Skin cancer (BCC) (CMQ)			
Number of subjects with at least one event	17 (1.2)	5 (0.5)	2.43 [0.85;8.44]
Severity			
Mild	3 (0.2)	2 (0.2)	
Moderate	7 (0.5)	0	
Severe	7 (0.5)	3 (0.3)	
SAEs	15 (1.1)	4 (0.4)	2.67 [0.85;11.10]
Leading to death	0	0	
SKIN CANCER (MELANOMA) (CMQ)			
Number of subjects with at least one event	4 (0.3)	2 (0.2)	1.42 [0.20;15.70]
Severity			
Mild	0	1 (0.1)	
Moderate	0	0	
Severe	4 (0.3)	1 (0.1)	
SAEs	4 (0.3)	1 (0.1)	2.84 [0.28;139.92]
Leading to death	0	0	
Skin cancer (SCC) (CMQ)			
Number of subjects with at least one event	1 (0.1)	0	>100
Moderate	1 (0.1)	0	
SAEs	0	0	

	Adult (Group D)		
	FTY720 0.5mg N=1364 n (%)	Placebo N=966 n (%)	Odds-ratio
Leading to death	0	0	

Numbers (n) represent counts of subjects.

Case Retrieval Strategy: Group D MedDRA version 19.1

Source: Attachment to Annex 7 of RMP v 14, Group D: TRSK D 3-1.2, TRSK D 3-2.1, TRSK D 3-1.3

Table 8-12 Important identified risk Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma): Other details

Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)	Details
Potential mechanisms	Unknown. A hypothetical mechanism would be related to systemic immunosuppression and reduced immunosurveillance.
Evidence source(s) and strength of evidence	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Characterization of the risk:	See Table 8-11 above. Basal cell carcinoma is a superficial, slowly growing papule or nodule that derives from certain epidermal cells. Metastasis is rare, but local growth can be highly destructive. Treatment may involve curettage and electrodesiccation, surgical excision, cryosurgery, topical chemotherapy, or, occasionally, radiation therapy or drug therapy [Merck Manual accessed 08-Apr-2015]. The effect of skin cancer on the individual patient is variable depending on the type and extent of the skin cancer. Treatment of the lesion (e.g. excision, cryosurgery, topical chemotherapy) is needed and monitoring for potential recurrence is recommended. Metastatic disease requires further intervention (e.g. radiation). Patients should be monitored for recurrence and may need to make lifestyle changes to alter exposure to the sun [Merck Manual accessed 09-Apr-2015], [Burdon-Jones D (2010)].
Risk factors and risk groups	None identified for fingolimod.
Preventability	The SmPC includes: Section 4.4: Cutaneous neoplasms: Basal cell carcinoma (BCC) and other cutaneous neoplasms, including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma, have been reported in patients receiving Gilenya (see Section 4.8). Vigilance for skin lesions is warranted and a medical evaluation of the skin is recommended at initiation, and then every 6 to 12 months taking into consideration clinical judgement. The patient should be referred to a dermatologist in case suspicious lesions are detected.

Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)	**Details**
	Since there is a potential risk of malignant skin growths, patients treated with fingolimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy. BCC, Kaposi's sarcoma, malignant melanoma, Merkel cell carcinoma and SCC are listed as ADRs with common frequency in Section 4.8 of SmPC. See Table 12-1 for details on the SmPC.
Impact on the benefit-risk balance of the product	The benefit-risk profile of fingolimod in the indication of relapsing MS remains positive, as the benefits of stronger and sustained efficacy as compared to placebo and a standard of care continue to outweigh the well-characterized and manageable risk of Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)
Public health impact	The long-term incidence cannot be fully estimated based on the currently available data.

8.3.1.7 Important Identified Risk: Lymphoma

Clinical trial data of Lymphoma

No events of Lymphoma were reported for adult patients (Group D) or pediatric patients (D2311).

Table 8-13 Important identified risk Lymphoma: Other details

Lymphoma	**Details**
Potential mechanisms	Fingolimod has not shown genotoxic potential and is, therefore, not considered a directly DNA damaging agent. Unlike classical tumor promoters which induce cell division and/or inhibit apoptosis, there is no evidence that fingolimod produces proliferation either in vitro or in toxicology studies. In a 2-year study, mice developed an increased incidence of malignant lymphomas, believed to be related to systemic immunosuppression. Systemic exposures were approximately 2-20 times the systemic exposure seen in man. A 2-year bioassay in rats showed no tumorigenic potential. There are fundamental species differences between mice and man, with a greater preponderance of lymphomas in mice, a species which is particularly prone to develop this type of tumor (Storer et al 2010). No increased incidence of lymphoma was observed either in the rat carcinogenicity study or in the long-term non-human primate toxicology study up to the highest doses tested, providing substantial exposure margins of more than 50 or 150-fold in rats and monkeys, respectively.
Evidence source(s) and strength of evidence	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.

Lymphoma	Details
Characterization of the risk:	There have been cases of lymphoma of different varieties, in extension phases of clinical trials and the post-marketing setting (see SmPC Section 4.8) Depending on the type, location, and extent of the lymphoma and the treatment and interventions required (including surgery and hospitalization), the patient's overall comfort and ability to perform normal activities of daily living can be affected.
Risk factors and risk groups	Since this is a potential risk, no attributable increase due to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Preventability	Currently unknown. No apparent pattern for patient's features to prevent/predict the event. See Table 12-1 for details in SmPC.
Impact on the benefit-risk balance of the product	The benefit-risk profile of fingolimod in the indication of relapsing MS remains positive, as the benefits of stronger and sustained efficacy as compared to placebo and a standard of care continue to outweigh the potential risk of Lymphoma.
Public health impact	Although the incidence is expected to be low on the basis of data currently available, the long-term incidence cannot be fully estimated based on the currently available data.

8.3.1.8 Important Potential Risk: Other malignant neoplasms

Table 8-14 Clinical trial data of Other malignant neoplasms

	Adult (Group D)			Pediatric (D2311)*	
	FTY720 0.5mg N=1364 n (%)	Placebo N=966 n (%)	Odds-ratio	FTY720 N=107 n (%)	IFNβ-1a N=107 n (%)
Malignant or unspecified tumours (SMQ)					
Number of subjects with at least one event	28 (2.1)	17 (1.8)	1.17 [0.61;2.29]	0	0
Severity					
Mild	4 (0.3)	3 (0.3)		0	0
Moderate	9 (0.7)	4 (0.4)		0	0
Severe	15 (1.1)	10 (1.0)		0	0
SAEs	24 (1.8)	15 (1.6)	1.14 [0.57;2.34]	0	0
Leading to death	0	0		0	0
Nervous system neoplasms and unspecified NEC (HLGT)					
Number of subjects with at least one event	0	0		0	0
Breast and nipple neoplasms malignant (HLT)					

	Adult (Group D)			Pediatric (D2311)*	
	FTY720 0.5mg N=1364 n (%)	**Placebo N=966 n (%)**	**Odds-ratio**	**FTY720 N=107 n (%)**	**IFNβ-1a N=107 n (%)**
Number of subjects with at least one event	3 (0.2)	3 (0.3)	0.71 [0.09;5.29]	0	0
Moderate	0	2 (0.2)		0	0
Severe	3 (0.2)	1 (0.1)		0	0
SAEs	3 (0.2)	3 (0.3)	0.71 [0.09;5.29]	0	0
Leading to death	0	0		0	0
Other malignant neoplasms (cervical cancer) (CMQ)					
Number of subjects with at least one event	0	1 (0.1)	<1/100	0	0
Severe	0	1 (0.1)		0	0
SAEs	0	1 (0.1)	<1/100	0	0
Leading to death	0	0		0	0
Thyroid neoplasms malignant (HLT)					
Number of subjects with at least one event	1 (0.1)	1 (0.1)	0.71 [0.01;55.63]	0	0
Moderate	0	1 (0.1)		0	0
Severe	1 (0.1)	0		0	0
SAEs	1 (0.1)	1 (0.1)	0.71 [0.01;55.63]	0	0
Leading to death	0	0		0	0

* No inferential statistics were performed due to the small sample size

Numbers (n) represent counts of subjects.

Case Retrieval Strategy: Group D MedDRA version 19.1, D2311 MedDRA version 20.0.
Source: Attachment to Annex 7 of RMP v 14 and v 13, Group D: TRSK D 3-1.2, TRSK D 3-2.1, TRSK D 3-1.3; D2311: Table 14.3.1-1.2a, Table 14.3.1-1.5a, Table 14.3.1-1.15

Table 8-15 Important potential risk Other malignant neoplasms: Other details

Other malignant neoplasms	Details
Potential mechanisms	Fingolimod has not shown genotoxic potential and is, therefore, not considered a directly DNA damaging agent. Unlike classical tumor promoters which induce cell division and/or inhibit apoptosis, there is no evidence that fingolimod produces proliferation either in vitro or in toxicology studies. In a 2-year study, mice developed an increased incidence of malignant lymphomas, believed to be related to systemic immunosuppression. Systemic exposures were approximately 2-20 times the systemic exposure seen in man. A 2-year bioassay in rats showed no tumorigenic potential. There are fundamental species differences between mice and man, with a greater

Other malignant neoplasms	Details
	preponderance of lymphomas in mice, a species which is particularly prone to develop this type of tumor (Storer et al 2010). No increased incidence of lymphoma was observed either in the rat carcinogenicity study or in the long-term non-human primate toxicology study up to the highest doses tested, providing substantial exposure margins of more than 50 or 150-fold in rats and monkeys, respectively.
Evidence source(s) and strength of evidence	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Characterization of the risk:	See Table 8-14 above. Depending on the type, location, and extent of the malignancy and the treatment and interventions required (including surgery and hospitalization), the patient's overall comfort and ability to perform normal activities of daily living can be affected.
Risk factors and risk groups	Since this is a potential risk, no attributable increase due to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Preventability	Currently unknown. No apparent pattern for patient's features to prevent/predict the event. The SmPC includes a mention of cases of lymphoma and a description of carcinogenicity studies. See Table 12-1 for details.
Impact on the benefit-risk balance of the product	The benefit-risk profile of fingolimod in the indication of relapsing MS remains positive, as the benefits of stronger and sustained efficacy as compared to placebo and a standard of care continue to outweigh the potential risk of Other malignant neoplasms.
Public health impact	Although the incidence is expected to be low on the basis of data currently available, the long-term incidence cannot be fully estimated based on the currently available data.

8.3.2 SVII.3.2. Presentation of the missing information

Table 8-16 Missing information: Long-term use in pediatric patients, including impact on growth and development (including cognitive development)

Missing information	Characterization
Long-term use in pediatric patients, including impact on growth and development (including cognitive development)	The clinical trial program for pediatric population had a flexible duration design and not all patients had been followed up for the entire two years in the core phase of the Study D2311. Five years extension phase has been added to the study to gather further safety data long term.

*Cardiovascular conditions include myocardial infarction, angina pectoris, Raynaud's phenomenon, cardiac failure or severe cardiac disease, increased QTc interval, uncontrolled hypertension, patients at risk for bradyarrhythmia and who may not tolerate bradycardia, patients with second degree Mobitz type 2 or higher AV block, sick-sinus syndrome, sino-atrial heart block, history of cardiac arrest, cerebrovascular disease and severe sleep apnea.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Part II SVIII.1: Summary of safety concerns

Important identified risks	Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose Liver transaminase elevation Macular edema Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection Reproductive toxicity Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma) Lymphoma
Important potential risks	Other malignant neoplasms
Missing information	Long-term use in pediatric patients, including impact on growth and development (including cognitive development)

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up questionnaires for risks:

Specific adverse event follow-up checklists will be used to collect further data to help further characterize and/or closely monitor each of the respective risks specified below:

1. Important Identified risk: Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post first dose
   - S1P modulator and cardiac rate and rhythm disorders checklist
2. Important Identified risk: Liver transaminase elevation
   - Liver injury checklist
3. Important Identified risk: Macular edema
   - S1P Modulator Macular edema checklist
4. Important Identified Risk: Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection
   - Suspected Progressive Multifocal Leukoencephalopathy checklist
   - Varicella Zoster Virus (VZV) infections checklist
   - Cryptococcal meningitis for Multiple Sclerosis Products checklist
5. Important Identified risk: Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)
   - Multiple sclerosis product and skin cancer checklist
6. Important Identified Risk: Lymphoma; Important Potential risks: Other malignant neoplasms
   - Malignancy and Neoplasm checklist
   - Cervical dysplasia/cervical cancer checklist

Other forms of routine pharmacovigilance activities for risks

Independent review of cases of suspected PML and other opportunistic infections (OIs) by an External Adjudication Committee.

Objectives: To further characterize the important identified risk of PML, an independent adjudication committee will review and adjudicate potential PML cases from clinical trials and post-marketing reports identified by Novartis. The case reports will be reviewed individually and in aggregate by members of the expert Panel on an ongoing basis. The panel will also review cases involving other OIs on an ongoing basis.

Milestones: Expert comments from External Adjudication Committee review will be incorporated in the assessment of the cases and will be presented in each PSUR.

10.2 Part III.2. Additional pharmacovigilance activities

FTY720D2311 summary

Study short name and title:

A two-year, double-blind, randomized, multicenter, active-controlled Core Phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a (IFN β-1a) intramuscular (IM) once weekly in pediatric patients with multiple sclerosis, with a five-year fingolimod Extension Phase.

Rationale and study objective:

Core Phase

The primary objective of the Core Phase of the study was to evaluate the efficacy of fingolimod relative to IM IFN β-1a in reducing the frequency of relapses as assessed by the annualized relapse rate (ARR) in children/adolescent MS patients aged 10 to < 18 years when treated for up to 24 months.

The key secondary objective was to evaluate the efficacy of fingolimod relative to IFN β-1a in reducing the number of new/newly enlarging T2 (n/neT2) lesions in children/adolescent MS patients aged 10 to < 18 years treated for up to 24 months.

Extension Phase:

To examine long-term safety, tolerability and efficacy parameters in patients treated with Fingolimod

Study design:

This double-blind, double-dummy, randomized, multicenter, active-controlled study is divided into a Core Phase, which includes the pre-randomization period and the double-blind treatment period, and an Extension Phase in which all patients will be treated with fingolimod.

Study population:

Approximately 270 patients were planned to be screened (~30% screen-failure rate) at approximately 105 sites worldwide in order to randomize 190 patients. Approximately 25 to 30 additional patients in the younger cohort (≤12 years of age or patients ≤40 kg or patients with Tanner stage <2) are planned for enrollment.

Milestones:

FPFV (Core Phase): 3Q 2013

LPFV (Core Phase): 2Q 2016

LPLV (Core Phase): 3Q 2017

Final study report (Core Phase): 4Q 2017

LPFV (Extension phase): 3Q 2017; for young cohort: 1Q 2022

LPLV (Extension Phase) planned: 3Q 2022; for young cohort: 1Q 2027

Revised protocol: Q3 2019 (additional recruitment of younger cohort)

Final study report (Extension Phase) planned: 3Q 2027

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
CFTY720D2311: A two-year, double-blind, randomized, multicenter, active-controlled Core Phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a (IFN β-1a) IM once weekly in pediatric patients with multiple sclerosis, with a five-year fingolimod Extension Phase.	• **Core Phase:** The primary objective of the study was to evaluate the efficacy of fingolimod relative to IM IFN β-1a in reducing the frequency of relapses as assessed by the annualized relapse rate (ARR) in children/adolescent MS patients aged 10 to <18 years when treated for up to 24 months. • The key secondary objective was to evaluate the efficacy of fingolimod relative to IFN β-1a in reducing the number of new/newly enlarging T2 (n/neT2) lesions in children/adolescent MS patients aged 10 to <18 years treated for up to 24 months. • **Extension Phase**: To examine long-	Long-term use in pediatric patients, including impact on growth and development (including cognitive development)	Revised protocol	21-Aug-2019
			Annual update	Annually (1st report by 31-Dec-2020)
			Extension Phase final report	3Q 2027

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	term safety, tolerability and efficacy parameters in patients treated with fingolimod.			

11 Part IV: Plans for post-authorization efficacy studies

Not Applicable.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	**Routine risk communication** Risks addressed in SmPC Sections 4.3, 4.4, 4.5 and 4.8 Contraindications included in Section 4.3 Warning, including first dose monitoring in Section 4.4 Interaction with other medicinal products in Section 4.5 Listed as ADRs in Section 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** The SmPc, Section 4.3 includes contraindications in patients with specific cardiac conditions. Section 4.4, includes the recommendation for ECG and blood pressure measurements to be performed prior to and 6 hours after the first dose of Gilenya. All patients should be monitored for a period of 6 hours for signs and symptoms of bradycardia with hourly heart rate and blood pressure measurement. Continuous (real time) ECG monitoring during this 6 hour period is recommended. The SmPC also includes recommendations regarding post-dose bradyarrhythmia-related symptoms and extended monitoring. **Other routine risk minimization measures beyond the Product Information:** None
Liver transaminase elevation	**Routine risk communication** Risk addressed in SmPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2 Hepatic impairment addressed in Section 4.2: Posology and method of administration Contra-indication in severe liver impairment in Section 4.3 Warning in Section 4.4 Listed as an ADR in Section 4.8 Characteristics in specific groups (hepatic impairment) of patients: 5.2 Pharmacokinetic properties **Routine risk minimization activities recommending specific clinical measures to address the risk:** The SmPC, Section 4.4, includes the recommendation for liver function monitoring and provides guidance for discontinuing and resuming treatment. **Other routine risk minimization measures beyond the Product Information:** None
Macular edema	**Routine risk communication**

Safety concern	Routine risk minimization activities
	Risk addressed in SmPC Sections 4.4, 4.8. Warning in Section 4.4 Listed as an ADR in Section 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** The SmPC, Section 4.4, includes the recommendation for an ophthalmological evaluation at 3-4 months after treatment initiation and if patients report visual disturbances at any time while on therapy. **Other routine risk minimization measures beyond the Product Information:** None
Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection	**Routine risk communication** The risk is addressed in SmPC Sections 4.3, 4.4 and 4.8 Contraindication for patients with severe/chronic active infections or at increased risk for opportunistic infections and for patients with suspected or confirmed progressive multifocal leukoencephalopathy (PML), in Section 4.3 Warnings in Section 4.4 Listed as ADRs in Section 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** The SmPC, Section 4.4, instructs physicians to carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis. This section also includes the recommendation for a complete blood count before starting Gilenya, periodically during treatment and in case of signs of infection and to delay treatment initiation in patients with severe active infections. In addition, recommendations are provided regarding varicella immunity and opportunistic infections including instructing patients to report symptoms of infection to their physician. **Other routine risk minimization measures beyond the Product Information:** None
Reproductive toxicity	**Routine risk communication** The risk is addressed in SmPC Sections 4.3, 4.4 and 4.6. Contraindication in pregnant women and in women of childbearing potential not using effective contraception in Section 4.3. Warnings in Section 4.4 Risk addressed in SmPC Section 4.6: regarding the increased risk of malformation and the malformations types. **Routine risk minimization activities recommending specific clinical measures to address the risk:** The SmPC states that fingolimod should not be used during breastfeeding. Women of childbearing potential must use effective contraception. A negative pregnancy test result is required before treatment initiation.

Safety concern	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information: None
Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)	**Routine risk communication** Risk is addressed in SmPC Sections 4.4, 4.8 Warning in Section 4.4 Listed as ADRs in Section 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** The SmPC, Section 4.4, instructs physicians to carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis. This section also includes the recommendation for a medical evaluation of the skin at initiation of treatment with Gilenya, and then every 6 to 12 months taking into consideration clinical judgement. The patient should be referred to a dermatologist in case suspicious lesions are detected. **Other routine risk minimization measures beyond the Product Information:** None
Lymphoma	**Routine risk communication** Risk addressed in SmPC Section 4.8 and 5.3. Listed as an ADR in Section 4.8 Preclinical safety data in Section 5.3 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Other malignant neoplasms	**Routine risk communication** Potential risk addressed in SmPC Section 4.4 Warning in Section 4.4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** The SmPC includes the recommendation that physicians should carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis. **Other routine risk minimization measures beyond the Product Information:** None
Long-term use in pediatric patients, including impact on	**Routine risk communication** Missing information addressed in Sections 4.2 and 5.2 of the SmPC. Posology and method of administration addressed in Section 4.2

Safety concern	Routine risk minimization activities
growth and development (including cognitive development)	**Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None

12.2 Part V.2. Additional Risk minimization measures

Physician's checklist, Patient/ Parent / Caregiver guide, and Pregnancy-specific patient reminder card

Objective

To provide physicians and patients with educational information on 7 safety areas of interest:

- Bradyarrhythmias upon treatment initiation
- Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection,
- Reproductive toxicity & prevention of pregnancy
- Macular edema
- Liver transaminase elevation
- Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)
- Long-term use in pediatric patients

The goal is for this information to assist the physician in managing and counselling patients who are either currently being treated with GILENYA, or in whom therapy with GILENYA is proposed as well as for educating patients about the risks while using GILENYA. Local Marketing Authorisation Holders will distribute the educational materials to physicians involved in treatment with GILENYA.

Rationale for the additional risk minimization activity

In order to increase understanding of the safe and effective use of GILENYA, physicians will be provided with a physician information pack containing the following elements:

- Product information
- The Physician's checklist for adult and pediatric patients prior to prescribing GILENYA.
- The Patient / Parent / Caregiver guide to be provided to all patients, their parents (or legal representatives), and caregivers.
- The Pregnancy-specific patient reminder card to be provided to all patients, their parents (or legal representatives), and caregivers, as applicable.

Target audience and planned distribution path

Target audience: Physicians who are managing and counselling patients who are either currently being treated with GILENYA, or in whom therapy with GILENYA is proposed. The specific risk regarding Reproductive toxicity will be communicated to women of child-bearing potential using the 'pregnancy-specific patient reminder card'.

Distribution path: Local Marketing Authorisation Holders will distribute the educational materials to physicians involved in treatment with GILENYA.

Evaluation of the effectiveness of proposed educational program

The effectiveness of the Physician's checklist was assessed using a questionnaire for GILENYA prescribers in selected EU countries. This survey was conducted in May 2013 and is now a completed activity.

Distribution of the Physician's checklist and of the Patient / Parent / Caregiver guide and the pregnancy-specific patient reminder card, will be monitored as a process indicator for effectiveness. Periodic review of pregnancy specific data will continue to be presented in PSURs.

Pregnancy Prevention

The following set of interventions aims at minimising pregnancy exposure and is intended to inform the prescribers and patients about the teratogenic risk associated with the use of fingolimod during pregnancy and required actions to minimize this risk:

Physician's checklist with mention of the following key messages:

- Confirmation of a negative pregnancy test result and Counselling on the need for effective contraception in women of childbearing age
- Risk of teratogenicity information and reproductive risk with GILENYA
- Contraindication and the need for counselling women of child-bearing potential, including adolescent females, their parents (or legal representatives), and caregivers before treatment initiation and regularly, facilitated by the pregnancy-specific patient reminder card.
- Cross reference to 'pregnancy-specific patient reminder card'

Patient/Parent/Caregiver's guide with mention of the following key message messages:

- Information regarding the contraindication
- Cross reference to the pregnancy-specific patient reminder card

Pregnancy-specific patient reminder card contains the following key messages:

While on treatment, women must not become pregnant.

- Patients will be informed by their doctor about the teratogenic risk and required actions to minimise this risk
- Need for effective contraception while taking GILENYA
- Ensure that a pregnancy test is carried out and negative results are verified by your doctor before treatment. It must be repeated at suitable intervals
- Effective contraception is needed while on treatment and for 2 months after discontinuation
- Your treating physician will provide counselling before treatment initiation and regularly
- Your treating physician will provide counselling in the event of pregnancy and evaluation of the outcome of any pregnancy

- If a woman becomes pregnant or wants to become pregnant while on treatment, GILENYA must be discontinued
- Patients should inform their doctor straight away if there is worsening of multiple sclerosis after stopping treatment with GILENYA

As per the EU SmPC, use of fingolimod is contraindicated in pregnant women and in women of child-bearing potential not using effective contraception (SmPC and Package leaflet).

This is to ensure that women of child-bearing potential (including adolescent females), are not pregnant when starting therapy and do not become pregnant during the course of and/or soon after stopping the therapy.

Removal of additional risk minimization activities

The key messages concerning "Convulsions" were deleted from Physician's checklist and Patient/ Parent / Caregiver guide.

12.3 Part V.3 Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	Routine risk minimization measures: SmPC Sections 4.3, 4.4, 4.5 and 4.8 Additional risk minimization measures: Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None
Liver transaminase elevation	Routine risk minimization measures: SmPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2 Additional risk minimization measures: Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None.

Safety concern	Risk minimization measures	Pharmacovigilance activities
Macular edema	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 Additional risk minimization measures: Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None.
Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection	Routine risk minimization measures: SmPC Sections 4.3, 4.4 and 4.8 Additional risk minimization measures: Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire for PML, CM and VZV; PML case adjudication by independent expert panel Additional pharmacovigilance activities: None.
Reproductive toxicity	Routine risk minimization measures: SmPC Sections 4.3, 4.4 and 4.6 Additional risk minimization measures: Pregnancy Prevention and Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide - Pregnancy-specific patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None.
Skin cancer (Basal Cell Carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 Additional risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide	Additional pharmacovigilance activities: None.
Lymphoma	Routine risk minimization measures: SmPC Sections 4.8 and 5.3 Additional risk minimization measures: No additional risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None.
Other malignant neoplasms	Routine risk minimization measures: SmPC Section 4.4 Additional risk minimization measures: No additional risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None.
Long-term use in pediatric patients, including impact on growth and development (including cognitive development)	Routine risk minimization measures: SmPC sections 4.2 and 5.2 Additional risk minimization measures: Educational materials for physicians and patients: - Physician's checklist for adult and pediatric patients - Patient / Parent / Caregiver guide	Study FTY720D2311: A two-year, double-blind, randomized, multicenter, active-controlled Core Phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a (IFN β-1a) IM once weekly in pediatric patients with multiple sclerosis, with a five-year fingolimod Extension Phase.

13 Part VI: Summary of the risk management plan for Gilenya® (Fingolimod)

This is a summary of the risk management plan (RMP) for Gilenya®. The RMP details important risks of Gilenya, how these risks can be minimized, and how more information will be obtained about Gilenya's risks and uncertainties (missing information).

Gilenya's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Gilenya should be used.

This summary of the RMP for Gilenya should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which are part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Gilenya's RMP.

13.1 Part VI: I. The medicine and what it is used for

Gilenya is authorized for a single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and paediatric patients aged 10 years and older in the European Economic Area (EEA) (see SmPC for the full indication):

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

or

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

It contains fingolimod (a sphingosine-1-phosphate (S1P) receptor modulator) as the active substance and it is given as 0.25 mg/day or 0.5 mg/day hard capsule by oral route.

Further information about the evaluation of Gilenya benefits can be found in Gilenya's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine’s webpage.

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Gilenya, together with measures to minimize such risks and the proposed studies for learning more about Gilenya's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Gilenya, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment so that

immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Gilenya is not yet available, it is listed under ‘missing information’ below.

13.2.1 Part VI – II.A: List of important risks and missing information

Important risks of Gilenya are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Gilenya. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 13-1 List of important risks and missing information

Important identified risks	Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose Liver transaminase elevation Macular edema Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection Reproductive toxicity Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma) Lymphoma
Important potential risks	Other malignant neoplasms
Missing information	Long-term use in pediatric patients, including impact on growth and development (including cognitive development)

13.2.2 Part VI - II B: Summary of important risks

Table 13-2 Important Identified Risk: Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Patients with particular medical history and/or co-medications in whom bradycardia may be poorly tolerated or might be at increased risk for bradycardia. This includes patients with: • second degree Mobitz type II or higher AV block, • sick-sinus syndrome • sino-atrial heart block, • history of symptomatic bradycardia or recurrent syncope, • significant QT prolongation (QTc>470msec (female) or >450msec (male)). Avoid in patients with risk factors for QT prolongation such as hypokalemia, hypomagnesemia or congenital QT prolongation • known ischemic heart disease (including angina pectoris), • cerebrovascular disease, • history of myocardial infarction, • congestive heart failure,

	• history of cardiac arrest, • uncontrolled hypertension • severe sleep apnea, Other potential risk factors include concomitant administration with: Class Ia (e.g. quinidine, dysopyramide) or Class III (e.g. amiodarone, sotalol) anti-arrhythmic medicinal products. • beta blockers, • heart-rate-lowering calcium channel blockers (such as verapamil, diltiazem or ivabradine), or other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic agents or pilocarpine).
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.3, 4.4, 4.5 and 4.8 Additional risk minimization measures: Educational materials for physicians and patients: -Physician's checklist for adult and pediatric population -Patient/Parent/Caregiver guide
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: None

Table 13-3 Important Identified Risk: Liver transaminase elevation

Table	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	None identified for fingolimod.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2 Additional risk minimization measures: Educational materials for physicians and patients: -Physician's checklist for adult and pediatric population -Patient/Parent/Caregiver guide
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: None.

Table 13-4 Important Identified Risk: Macular edema

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Patients with diabetes and history of uveitis are considered at increased risk of developing macular edema. Such patients should undergo an ophthalmic evaluation prior to initiating Gilenya therapy and have follow-up evaluations while receiving Gilenya therapy.

Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 Additional risk minimization measures: Educational materials for physicians and patients: -Physician's checklist for adult and pediatric population -Patient/Parent/Caregiver guide
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: None.

Table 13-5 Important Identified Risk: Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies) and those with severe active infections including active chronic infections (hepatitis, tuberculosis) should not receive Gilenya.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.3, 4.4, and 4.8 Additional risk minimization measures: Educational materials for physicians and patients: -Physician's checklist for adult and pediatric population -Patient/Parent/Caregiver guide
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Independent review of cases of suspected PML by External Adjudication Committee Additional pharmacovigilance activities: None.

Table 13-6 Important Identified Risk: Reproductive toxicity

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Females of childbearing potential not using an effective form of contraception. Fingolimod is excreted in milk of treated animals during lactation. Because of the potential for serious ADRs in nursing infants from fingolimod, women receiving Gilenya should not breast feed.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.3, 4.4 and 4.6. Additional risk minimization measures: Pregnancy prevention Educational materials for physicians and patients: - Physician's Checklist for adult and pediatric population

	- Patient/Parent/Caregiver guide - Pregnancy-specific patient reminder card
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None.

Table 13-7 Important Identified Risk: Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	None identified for fingolimod.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 Additional risk minimization measures: Educational materials for physicians and patients: -Physician's checklist for adult and pediatric population -Patient/Parent/Caregiver guide
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: None.

Table 13-8 Important identified risk: Lymphoma

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.
Risk factors and risk groups	Since this is a potential risk, no attributable increase due to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.8 and 5.3 Additional risk minimization measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: None

Table 13-9 Important potential risk: Other malignant neoplasms

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the risk-benefit balance of the product.

Risk factors and risk groups	Since this is a potential risk, no attributable increase due to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: None.

Table 13-10 Missing information: Long-term use in pediatric patients, including impact on growth and development (including cognitive development)

Risk minimization measures	Since this is a missing information, no attributable increase due to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified. Routine risk minimization measures: SmPC sections 4.2 and 5.2 Additional risk minimization measures: Educational materials for physicians and patients: -Physician's checklist for adult and pediatric population -Patient/Parent/Caregiver guide
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2311: A two-year, double-blind, randomized, multicenter, active-controlled Core Phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a (IFN β-1a) IM once weekly in pediatric patients with multiple sclerosis, with a five-year fingolimod Extension Phase.

13.2.3 Part VI – II C: Post-authorization development plan

13.2.3.1 II.C.1 Studies which are conditions of the marketing authorization

None.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

Table 13-11 Other studies in the post-authorization development plan

Study short name:	Rationale and study objectives:
CFTY720D2311: A two-year, double-blind, randomized, multicenter, active-controlled Core Phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a (IFN β-1a) intramuscular (IM) once weekly in pediatric patients with multiple sclerosis, with a five-year fingolimod Extension Phase.	**Core Phase** The primary objective of the Core Phase of the study was to evaluate the efficacy of fingolimod relative to IM IFN β-1a in reducing the frequency of relapses as assessed by the annualized relapse rate (ARR) in children/adolescent MS patients aged 10 to <18 years when treated for up to 24 months. The key secondary objective was to evaluate the efficacy of fingolimod relative to IFN β-1a in reducing the number of new/newly enlarging T2 (n/neT2) lesions in children/adolescent MS patients aged 10 to <18 years treated for up to 24 months. **Extension Phase:** To examine long-term safety, tolerability and efficacy parameters in patients treated with Fingolimod.

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

This annex contains the specific adverse event targeted follow-up checklists used to collect additional data for the following Gilenya RMP risks:

1. Important Identified risk: Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post first dose
   - S1P modulator and cardiac rate and rhythm disorders checklist
2. Important Identified risk: Liver transaminase elevation
   - Liver injury checklist
3. Important Identified risk: Macular edema
   - S1P Modulator Macular edema checklist
4. Important Identified Risk: Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection
   - Suspected Progressive Multifocal Leukoencephalopathy checklist
   - Varicella Zoster Virus (VZV) infections checklist
   - Cryptococcal meningitis for Multiple Sclerosis Products checklist
5. Important Identified risk: Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)
   - Multiple sclerosis product and skin cancer checklist
6. Important Identified Risk: Lymphoma; Important Potential risks: Other malignant neoplasms
   - Malignancy and Neoplasm checklist
   - Cervical dysplasia/cervical cancer checklist

Targeted follow-up checklists:

Important identified risk: Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose

S1P modulator and cardiac rate and rhythm disorders checklist (version 4.0 / January 2021)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed for first dose events and/or other events.

Event description:

Did the patient experience any symptoms?Did the patient receive treatment for the event?

☐ Yes *(please specify)* ☐ Yes *(please specify)*
☐ No ☐ No

Were any of the following diagnostic tests performed? **Check all that apply and please specify which test(s), dates and results**

☐ ECG (*please include baseline*)
☐ Holter monitor (*please include baseline*)
☐ Coronary angiography
☐ Electrophysiology study (EPS)
☐ Stress test
☐ Echocardiogram
☐ Blood tests (*e.g. electrolytes*)
☐ Others (*please specify*)

☐ Cardiac biomarkers (specify e.g., creatinine kinase-MB, troponin)
☐ None of the above

Relevant medical history (concurrent and pre-existing conditions)

(Please specify medical condition and date of onset) Did the patient have a history of any of the following prior to the start of the suspect drug? **Check all that apply**

☐ ECG abnormalities *(please specify)*
☐ Valvular disease *(please specify)*
☐ Symptomatic bradycardia
☐ Congenital heart disease
☐ Pacemaker (*specify if temporary or permanent*)
☐ Syncope
☐ Cardiovascular disease (e.g. angina, CAD, MI, CHF)
☐ Wolff-Parkinson-White syndrome (*please specify*)
☐ Other (e.g. COPD, sleep apnea, hyperthyroidism) (*please specify)*
☐ None of the above

Was the patient taking any of the following drugs? **Check all that apply**

☐ Antipsychotics/Antidepressants
☐ Theophylline
☐ Antiarrhythmics (*e.g. quinidine, digoxin, beta-blockers, calcium channel blockers*)
☐ Anticonvulsants (*e.g. phenytoin, gabapentin, topiramate*)
☐ Beta blockers
☐ Calcium channel blockers (dihydropyridine or non-)
☐ Drugs of abuse (*e.g. cocaine*)
☐ Cholinomimetics *(e.g. metoclopramide)*
☐ Others (*please specify*)
☐ None of the above

First dose observation (FDO) period: Please provide details of events occurring during/post FDO.

- First dose of S1P Modulator: Date: ____/____/____Time: _____

- Heart rate at baseline: Date: ____/____/____Time: _____Rate: _____ bpm
- The minimum heart rate measured during the event: _____ bpm
- The time interval between the first dose of S1P modulator and the minimum heart rate:
  _____ minutes / hours / days / weeks (*please specify units*)
- ECGs performed at time of event? If yes, please provide details on any abnormalities noted other than bradycardia.
- Did the patient receive any treatment for the event?

☐ Yes – pharmacological (*e.g. atropine, please specify*)
☐ Yes – non-pharmacological (*e.g. IV fluids, please specify*)
☐ No

- Vital signs during observation period (*hourly heart rate and BP*):

Important identified risk: Liver transaminase elevation

Liver injury checklist (version 3.0 / May 2021)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Event Description:

1. Diagnosis and date of diagnosis_____

2. Did the patient present with any of the following signs or symptoms? Check all that apply:

☐ Jaundice ☐ Ascites ☐ Asterixis (flapping tremor)
☐ Dark urine ☐ Fever ☐ Altered mental status
☐ Pale stool ☐ Fatigue ☐ Abdominal pain (specify location)
☐ Pruritus ☐ Bleeding (specify location) ☐ Anorexia
☐ Nausea ☐ Spider angiomata ☐ Variceal Bleeding
☐ Caput medusa ☐ Peripheral edema ☐ Fetor hepaticus
☐ Gynecomastia ☐ Muscle wasting ☐ Other (specify)
☐ None

3. Were any of the following diagnostic tests performed?

►If yes, please specify the dates and results including reference range and pre- and post-treatment values:

☐ Liver function tests
☐ Serology & PCR testings for Hepatitis A, B, C &/or E virus
☐ Autoantibody tests
☐ Abdominal or hepatobiliary ultrasound (with or without Doppler's)
☐ Abdominal CT scan / MRI
☐ Liver biopsy
☐ Liver transplant (planned or completed)
☐ Other (specify)
☐ None

4. Does the patient have a history of any of the following prior to the start of the suspect drug? Check all that apply and include date(s) of onset as well as status (i.e. active/inactive) and details:

☐ Previously elevated liver enzymes ☐ Tattoos
☐ Hepatitis ☐ Transfusion or blood product administration
☐ Other hepatobiliary disease or dysfunction ☐ Gilbert's disease
☐ Autoimmune disease (specify type) ☐ Alcohol intake (quantify if possible) ☐ Active or chronic pancreatitis ☐ Drug abuse

☐ Diabetes mellitus (Type I or II) ☐ Foreign travel
☐ Non-alcoholic steatohepatitis☐ Active gall bladder disease
☐ Cirrhosis☐ Portal hypertension
☐ Ascites☐ Variceal bleeding/esophageal varices☐ Spider angiomata☐ Thrombocytopenia
☐ None ☐ Other (specify)

5. Has the patient recently (i.e. within the past 6 months) taken any of the following? Check all that apply:
☐ Sulfonamides ☐ Furosemide ☐ ACE Inhibitors
☐ Amoxicillin / clavulanic acid ☐ NSAIDS (e.g. ibuprofen) ☐ Estrogens (oral contraceptives) ☐ Metronidazole ☐ Acetaminophen/Paracetamol ☐ Amiodarone
☐ COX II inhibitors(e.g. celecoxib) ☐ Tetracycline ☐ Steroids
☐ Thiazide diuretics ☐ 6-Mercaptopurine ☐ Statins
☐ Valproic acid ☐ Methotrexate ☐ Other (specify)

☐None

Important identified risk: Macular edema

S1P Modulator Macular edema checklist (version 2.1 / May 2021)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Relevant medical history (concurrent and pre-existing conditions)
(Please specify medical condition and date of onset)
☐ Eye diseases (e.g., uveitis, optic neuritis) ►If yes (specify)
☐ Intraocular surgery►If yes (provide type and date of surgery)
☐ Diabetes mellitus ►If yes, provide:

- Date of diagnosis
- Was there evidence of retinopathy prior to starting the drug? ☐ Yes, grade ____ ☐ No

☐ Other (specify)
☐ None

Has the patient recently (i.e. within the past 6 months) taken any other medications?
☐ Yes (specify) ☐ No

Event description:
1. Date of diagnosis: ____/____/____
2. Was macular edema diagnosed in☐ Left eye☐ Right eye☐ Both eyes
3. Did the patient experience any symptoms due to the macular edema? ☐ Yes (list the symptoms) ☐ No
4. Were any of the following diagnostic tests performed? ►If yes, please specify the dates and results at baseline (i.e. pre- **fingolimod/siponimod**) and at the time of the event:
☐ Fundoscopy
☐ Optical Coherence Tomography (OCT)
☐ Fluorescein angiography (FA)
☐ Visual acuity
☐ Other: _____

Course of the event after diagnosis:
5. Details of any treatment prescribed for the macular edema:
Right eye☐ Photocoagulation / Laser☐ Intravitreal steroid injection☐ Surgery
☐ Other (specify)☐ None

Left eye☐ Photocoagulation / Laser☐ Intravitreal steroid injection☐ Surgery
☐ Other (specify)☐ None

6. Current status of the macular edema

☐ Resolved☐ Improving☐ Unchanged☐ Deteriorated
☐ Results of tests performed (e.g., fundoscopy, OCT, FA, specify the dates and results)
7. Current status of vision impairment related to macular edema (if any)?
☐ Resolved☐ Improving☐ Unchanged☐ Deteriorated
☐ Visual acuity (specify the dates and results)

Important identified risk: Opportunistic infections including PML, VZV, herpes viral infections other than VZV, fungal infection

Suspected Progressive Multifocal Leukoencephalopathy checklist (version 5.1 / November 2024)

Please provide the following information in addition to routine information request forms.

Did the patient present with any of the following signs or symptoms? Check all that apply.

☐ Hemiparesis ☐ Cognitive impairment ☐ Weakness ☐ Headaches

☐ Hemianopia ☐ Personality changes ☐ Aphasia ☐ None of the above

☐ Brainstem deficits ☐ Dysarthria ☐ Visual impairment ☐ Others (*please specify*)

☐ Clumsiness/ Cerebellar deficits ☐ Sensory deficits ☐ Fever_____

Was brain MRI/MRA performed? ☐ **Yes** *(provide recent and prior reports and/or summarize below)* ☐ **No** ☐ **Unknown**

Date/Results:_____
_____
_____
_____
_____

CSF JCV analysis ☐ **Yes** *(provide results below)* ☐ **No** ☐ **Unknown**

Type of test (PCR, JCV antibody)	**Test date**	**Result**

Please include results of other relevant tests

Type of test	**Test date**	**Result**
JCV (serum or urine)		
Anti JCV antibody index		
Absolute lymphocyte count		
WBC – including lymphocyte subsets (e.g., CD4, CD8)		
Brain biopsy		

Other		

Absolute lymphocyte counts (please provide up to 12 months prior to PML onset)

Date	Absolute lymphocyte counts	Date	Absolute lymphocyte counts

PML-IRIS

Did this patient receive a diagnosis of IRIS (Immune Reconstitution Inflammatory Syndrome)?

☐ Yes - onset date (DD/MMM/YYYY) ☐ No ☐ **Unknown**

What is the outcome of the patient's PML-IRIS?

☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Fatal ☐ Unknown

Provide the date of the assessed outcome of PML-IRIS (DD/MMM/YYYY):

Patient History:

Does the patient have a history of any immunosuppressive disorders prior to the start of the suspect drug (eg, HIV infection; malignancy, e.g., leukemia, lymphoma, myeloproliferative diseases; sarcoidosis; other disturbances of the immune system, e.g., history of low CD4/CD8 ratio; other)? ☐ Yes *(summarize below)* ☐ No ☐ Unknown

Immune disorder	Date of onset	Status (active, inactive)	Other details

List prior MS therapies:

Drug	Dose	Start date	Stop date

Has the patient taken any of the following medications in the past or currently? Check all that apply and include dates of starting and completing and indication the medication in the space below.

☐ Chemotherapy/ Cytoreductive therapy *please specify* ☐ Corticosteroids *specify dose and duration*

☐ Other immunosuppressant drugs *please specify* ☐ Radiation therapy

☐ None of the above

Additional details:

_____
_____
_____

Varicella Zoster Virus (VZV) infections checklist (version 5.0 / May 2020)

Event Description

1. Confirm the type of varicella zoster virus infection:

☐ Primary infection (e.g. varicella/chickenpox) ☐Reactivation (e.g. herpes zoster/shingles)

☐Unknown/undetermined

2. Specify diagnosis (including complications, if any), the date the diagnosis was made (e.g. radiculitis, post-herpetic neuralgia, polyneuritis, facial paralysis, etc.) and current clinical status.

3. Infection location:

Skin: ☐ Yes ☐ No ☐ Unknown

If yes, provide clinical description and specify the involved dermatome(s):

If yes, any complication? ☐ Eye ☐ Ear ☐ Post-herpetic neuralgia

Disseminated infection: ☐ Yes ☐ No ☐ Unknown

If yes: ☐ Cutaneous dissemination; ☐ CNS dissemination ☐ Visceral dissemination.

If applicable: CNS:☐ Meningitis ☐ Myelitis ☐ Encephalitis ☐ Vasculitis ☐ Other (*please specify*)

Other: ☐ Yes (*please specify*)☐ No☐ Unknown

4. Treatment for this event, including response (*please provide treatment drugs, dose, route and dates of treatment*)

5. Were any of the following diagnostic tests performed? ►**If yes, please specify the dates and results.**

Serum/blood CSF Vesicles/skin lesion

☐ VZV IgM/IgG☐ VZV PCR☐ VZV PCR

☐ VZV PCR☐ Other (specify) ☐ Other (specify)

☐ Other (specify)☐ None☐ None

☐ None

Patient history

6. Does the patient have a history of VZV exposure (infection and/or vaccination)?

History of varicella (*please provide date and/or age of the patient*) ☐ Yes ☐ No ☐ Unknown

History of shingles (*please provide number of episodes (if recurrent), date and/or*☐ Yes ☐ No ☐ Unknown

age of the patient)

Varicella vaccination (*please provide number of doses, date and/or age of the patient*☐ Yes ☐ No ☐ Unknown

at the time of vaccination).

Shingles vaccination (*please provide date and/or age of the patient at the time of* ☐ Yes ☐ No ☐ Unknown

vaccination).

7. Has the patient recently (i.e. within the past 6 months) taken any immunosuppressive therapies? (*specify dose and duration of therapy*)

☐ Corticosteroids ☐ Yes ☐ No ☐ Unknown

☐ Other immunosuppressive or immunomodulator therapies☐ Yes ☐ No ☐ Unknown

☐ Cytotoxics ☐ Yes ☐ No ☐ Unknown

☐ Other ☐ Yes ☐ No ☐ Unknown

☐ None ☐ Yes ☐ No ☐ Unknown

Cryptococcal Meningitis for Multiple Sclerosis Products checklist (version 2.0 / June 2020)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Part I: Critical Information – Please provide the following

Approximate onset date of symptoms that led to the diagnosis: _____

Action taken with suspect drug: ☐Discontinued ☐Continued ☐Unknown

Event Outcome: ☐Complete recovery ☐Recovered with sequelae ☐Condition improving

☐Condition unchanged ☐Condition deteriorating ☐Fatal ☐Unknown

What were the initial presenting symptom(s)?

☐ Headache ☐ Nausea/Vomiting☐ Others (*please specify*)

☐ Confusion ☐ Seizure(s)_____

☐ Lethargy ☐ Cranial nerve palsies_____

☐ Coma ☐ Papilledema

☐ Fever ☐ Neck stiffness ☐ None of the above

CBC (specifically WBC and absolute lymphocyte and neutrophil counts):

Test	**Date**	**Result (please provide units)**

Please indicate Cryptococcus diagnostic testing:

CSF cryptococcus antigen test ☐ Positive (titer)☐ Negative☐ Not done

Serum cryptococcus antigen test ☐ Positive (titer)☐ Negative☐ Not done

India inkmicroscopy ☐ Positive☐ Negative☐ Not done

Fungal culture results:_____

Part II: Additional Information that is helpful if available

Anti-Cryptococcal Treatment:

Drug	**Dose**	**Start and stop dates of therapy**

Patient History, Concurrent Conditions, and Relevant Therapy:

Does the patient have a history of any of the following prior to the start of suspect therapy?

Check all that apply and please include date(s) of onset as well as status (i.e. active/ inactive) and details

☐ HIV Infection☐ Malignancy (e.g. Leukemia, Lymphoma, Myeloproliferative disease)

☐ Sarcoidosis☐ Other disturbances of the immune system (e.g. history of low CD4/CD8 ratio)

☐ Close contact with birds☐ Contact with eucalyptus trees ☐Other relevant history *(please specify)*☐ None of the above

_____

_____

_____
_____

How long has the patient had Multiple Sclerosis (years/months or specific date of diagnosis) _____

List all MS treatments and duration:

Drug	**Dose**	**Start and stop dates of therapy**

List all concomitant or prior immunosuppressive therapies (e.g., monoclonal antibodies, cancer chemotherapy or cytoreductive treatments, corticosteroids, radiation therapy):

Drug/Intervention	**Dose**	**Start and Stop dates of therapy**

Important identified risk: Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)

Multiple sclerosis product and Skin Cancer (version 3.0 / January 2021)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

1. Event description:

☐ Diagnosis and date of diagnosis

☐ Signs /symptoms

☐ Anatomical Location and clinical description of the skin lesion

☐ Biopsy done ☐ Biopsy not done

If done, provide pathological stage of tumor _____

2. Patient history prior to the start of the drug:

Does the patient have a history of skin cancer?

☐ Squamous cell carcinoma ☐ Basal cell carcinoma ☐ Melanoma ☐ Other (specify) ☐ None

►If yes, provide:

- Source of diagnosis (biopsy/ clinical only)
- Date of diagnosis
- Location of the lesion and treatment

Does the patient have a family history of skin cancer?

☐ Squamous cell carcinoma ☐ Basal cell carcinoma ☐ Melanoma ☐ Other (specify)

☐ None

Does the patient have skin moles or pre-cancerous lesions like actinic keratosis?

☐ Yes ☐ No

►If moles, provide:

- Number of moles
- Location of the moles

► If pre-cancerous skin lesion, please specify:_____

Does the patient have any risk factors for decreased immune system?

☐ Yes ☐ No

- Has the patient previously been treated with immunosuppresors/ immunomodulators,

☐ Yes☐ No

►If yes, please provide the following information:

- Reason (MS or other than MS -specify)
- Drug generic name
- Treatment duration
- Dose

- Has the patient previously been treated with Chemotherapy/radiation ☐ Yes ☐ No

►If yes, please specify:

- Does the patient have any immune system disorders like HIV/AIDS or any other autoimmune condition?

☐ Yes ☐ No

►If yes, please specify:

•

Is the patient a smoker?

☐ Yes ☐ No

►If yes, provide:

- Smoking duration in years
- Number cigarettes a day

Does the patient have a history of prolonged sun/ultraviolet ray exposure?

☐ Yes ☐ No

Does patient use sunscreen regularly?

☐ Yes ☐ No

Does the patient have a history of exposure to carcinogens (e.g. arsenic, industrial tar, coal, paraffin)

☐ Yes☐ No

3. Please select one item in each column of the table below to identify the patient's skin type (Fitzpatrick 1975)

Skin type	**Sunburn Tendency**	**Tan tendency**	**Skin, hair and eye color**
I	☐ Always sunburns	☐ Never tans	☐ White skin, freckles, blond or red hair,

			blue or green eyes
II	☐ Usually sunburns	☐ Sometimes tans	☐ White skin, blond hair, blue or green eyes
III	☐ Seldom sunburns	☐ Usually tans	☐ White skin, usually dark hair, brown eyes
IV-VI	☐ Never sunburns	☐ Always tans darkly.	☐ Brown to dark skin/ brown or black hair brown eyes

Important identified risk: Lymphoma

Important potential risk: Other malignant neoplasms

Malignancy and Neoplasm (version 6.0 / April 2024)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Description of the event (malignancy / neoplasm):

- Diagnosis/date of diagnosis
- Location
  - Is the cancer localized? If not, please provide details on further locations (metastases):
  -
- Location of biopsy site(s) and result **(for lymphomas, please provide lymph node biopsy as well as gene rearrangement studies if performed):**
- Histological typing of cancer including immunophenotyping and molecular profile **(please provide a copy of report or an English summary):**
- Staging of the neoplasm (TNM):
- ECOG status /Current treatment plan:

Were any of the following diagnostic tests performed? Check all that apply and specify which test(s), dates and results

☐ Biopsies
☐ Bone marrow aspiration
☐ Blood test, urine test, biomarkers
☐ Imaging tests (e.g. x-ray, CT scan, MRI scan, PET scan, mammogram, PSA screening)
☐ Exploratory surgery (planned or completed)
☐ EBV serology test
☐ Other viral serology tests (e.g. HIV, HCV)
☐ None of the above

Relevant medical history (concurrent and pre-existing conditions)

(Please specify medical condition and date of onset)

Check all that apply and provide details as applicable:

☐ Infection☐ UV exposure, PUVA/UVB
☐ Smoking☐ Alcohol abuse
☐ Personal history of malignancy☐ Family history of malignancy
☐ Immunosuppression condition (e.g. HIV, transplantation)☐ Immunosuppression therapy
☐ Autoimmune disease (e.g. psoriasis, Sjogren Syndrome, rheumatoid arthritis)
☐ Exposure to carcinogens (environmental, occupational)☐ None of the above

Cervical dysplasia/cervical cancer (version 2.0 / June 2020)

A. Event description

Current diagnosis _____ Date ___/____/_____

PAP results (date) _____ ☐ Not done ☐ Unknown

Biopsy results (date) _____ ☐ Not done ☐ Unknown

Current HPV results, genotype_____ Test date ___/____/_____

B. Patient history

1. How often has the subject had PAP tests? _____ Date of last PAP test (before current one): ___ / ___ / _____
   a. Was it normal? ☐ Yes ☐ No ☐ Unknown
   b. If not normal: What were PAP results? _____ ☐ Not done ☐ Unknown
      What were biopsy results? _____ _____ ☐ Not done ☐ Unknown
2. When was the last normal PAP test (date)? _____ ☐ Not done ☐ Unknown
3. Has the patient ever been tested for HPV (Human papilloma virus) ___☐ Yes ☐ No ☐ Unknown
   a. HPV test results and genotype_____ _ ☐ Unknown.
4. Has the patient been vaccinated for HPV?
   ☐ Yes: Date of completion: ____/____/____
   Name of vaccine: _____
   ☐ No
   ☐ Don't know
5. Smoking status:
   ☐ Current smoker How long _____
   ☐ Never smoked
   ☐ Smoked in past: How long ____ Quit date_____
6. Has the patient ever used contraceptive pills?
   ☐ Yes How long _____
9. Is there a family history of cervical cancer?
   ☐ Yes: Relationship: _____
   ☐ No
   ☐ Don't know
10. Has the patient had a sexually transmitted disease?
    (Gonorrhea, Chlamydia, Trichomoniasis, Herpes, other)
    ☐ Yes: Specify: _____Date_____
    ☐ No
    ☐ Don't know
11. Does the patient have (or have history of) the following?
    ☐ HIV Date: _____

☐ No

☐ Don't know

☐ Cancer Type: _____

☐ Autoimmune disease Type: _____

7. How many pregnancies has the patient had? _____

How many live births: _____

How many miscarriages: _____

How many elective abortions: _____

8. Age of patient at first pregnancy? _____

12. Has the patient taken immunosuppressant medications?

☐ Yes: Specify: _____Date_____

☐ No

☐ Don't know

13. How many sexual partners in patient's lifetime? _____

14. Age when patient became sexually active? _____

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

This annex contains key safety messages of the proposed educational program for Gilenya (fingolimod), which includes a Physician's checklist for adult and pediatric patients (Table 14-4), a Patient / Parent / Caregiver guide (Table 14-5), and a Pregnancy-specific patient reminder card (Table 14-6).

Approved Key Messages of the Additional Risk Minimization Measures

Table 14-4 Physician's checklist

Safety Topics	HCP Key Safety Messages
Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	• Do not initiate GILENYA in patients with a cardiac condition or who are taking medicinal products for which GILENYA is contraindicated. • Prior to initiating GILENYA in patients with underlying medical conditions or who are concomitantly taking medicinal products which carry an increased risk of serious rhythm disturbance or bradycardia, ensure the anticipated benefits outweigh the potential risks and seek advice from a cardiologist regarding appropriate monitoring (at least overnight extended monitoring for treatment initiation) and/or adjustment of the concomitant medicinal product. • Monitor all patients for signs and symptoms of bradycardia for a period of at least 6 hours after the first dose of GILENYA, including performing an electrocardiogram (ECG) and blood pressure measurement prior to and 6 hours after first dose. • If post-dose signs and symptoms of bradyarrhythmia occur, extend first dose monitoring per guidelines until resolution; be familiar with criteria (i.e. need for pharmacological intervention, age-specific heart rate limits, new ECG findings) that would warrant overnight monitoring. • Follow first-dose monitoring recommendations after treatment interruption or increase in daily dose.
Liver transaminase elevation	• Do not initiate GILENYA in patients with severe liver impairment (Child-Pugh class C) • Transaminase and bilirubin levels should be obtained prior to initiation of GILENYA, monitored every 3 months for the first year on therapy, and periodically thereafter, up to 2 months after GILENYA discontinuation. • For asymptomatic elevations in liver function tests (LFTs), perform LFTs more frequently if increases in transaminase are greater than 3 times to less than 5 times upper limit of normal (ULN) without increase in serum bilirubin. Discontinue GILENYA for transaminase increase at least 5 times the ULN or at least 3 times the ULN associated with any increase in serum bilirubin. Restart GILENYA only after careful consideration of benefit-risk. • For patients with clinical symptoms of liver dysfunction, evaluate promptly and discontinue GILENYA if significant liver injury is confirmed. If serum levels return to normal (including if an alternative cause of the liver dysfunction is discovered), GILENYA may be restarted based on a careful benefit-risk assessment of the patient.

Macular edema	• Obtain an ophthalmological assessment before starting GILENYA in patients with diabetes or a history of uveitis. • Obtain an ophthalmological assessment in all patients 3 to 4 months after initiating GILENYA. • It is recommended to discontinue GILENYA in patients who develop macular edema. Restart GILENYA only after careful consideration of benefit-risk.
Opportunistic infections including varicella zoster virus (VZV), herpes viral infections other than VZV, fungal infections	• Do not initiate GILENYA in patients with immunodeficiency syndrome, increased risk for opportunistic infections including immunocompromised patients or severe active or active chronic infections (i.e. hepatitis or tuberculosis). • GILENYA may be initiated in patients who have had severe active infection that has resolved. • Anti-neoplastic, immunomodulatory or immunosuppressive therapies should not be co-administered due to the risk of additive immune system effects. Carefully consider any decision regarding prolonged concomitant corticosteroids use. • Monitor peripheral blood lymphocyte counts prior to and during treatment with GILENYA. Interrupt treatment for lymphocyte count $<0.2x10^9$/L until recovery. • Instruct patients to report signs and symptoms of infections during, and for up to two months after, treatment with GILENYA. • For potentially serious infection, evaluate the patient promptly and consider an infectious disease referral. Consider suspending GILENYA and the benefit-risk of any subsequent reinitiation. • Be aware that serious, life-threatening and sometimes fatal cases of opportunistic infections of the central nervous system (CNS) have occurred on GILENYA treatment, including herpes viral infection (encephalitis, meningitis and meningo-encephalitis; observed at any time), and cryptococcal meningitis, (observed after approximately 2-3 years). • GILENYA should be discontinued in patients with CNS herpes infections. GILENYA should be suspended in patients with cryptococcal meningitis with careful consideration with a specialist before reinitiating. • Inform patients that during GILENYA treatment, they should not receive live attenuated vaccines and that other vaccines may be less effective. • Prior to initiation of GILENYA, check varicella status and recommend a full course of vaccination for VZV in anti-body negative patients. Postpone initiation of treatment for 1 month to allow the full effect of vaccination. • Recommend vaccination against human papilloma virus (HPV) prior to initiation of treatment.
Progressive multifocal leukoencephalopathy (PML)	• Do not treat with GILENYA in patients with suspected or confirmed PML. • Be aware that PML has been predominantly observed after 2 or more years of fingolimod treatment. • Ensure patients have a baseline Magnetic Resonance Imaging (MRI) usually within 3 months before initiating GILENYA. Annual MRIs may be considered especially in patients with multiple risk factors generally associated with PML.

	If there is suspicion of PML, perform a diagnostic MRI immediately and suspend GILENYA until PML has been excluded. If PML is confirmed, treatment with GILENYA must be permanently discontinued. • Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with S1P receptors modulators, including fingolimod, who developed PML and subsequently discontinued treatment. The time to onset of IRIS in patients with PML was usually from weeks to months after S1P receptor modulator discontinuation. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken.
Reproductive toxicity	• GILENYA is teratogenic and contraindicated in women of childbearing potential not using effective contraception or who are pregnant. • Women of childbearing potential must use effective contraception during treatment and for two months following treatment discontinuation. • Before initiating treatment and regularly thereafter, counsel women of childbearing potential, including adolescent females, their parents or legal representatives, about the risks to a foetus and to use effective contraception during treatment and for two months after discontinuation. • Confirm a negative pregnancy test prior to starting treatment and repeat at suitable intervals. • Discontinue GILENYA if a woman becomes pregnant and consider the possible return of disease activity. • Instruct patient to stop GILENYA two months before attempting to become pregnant.
Skin cancer (basal cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell carcinoma, squamous cell carcinoma)	• Perform skin examination prior to treatment initiation and every 6 to 12 months. • Refer patients to a dermatologist if suspicious lesions are detected. • Caution against exposure to sunlight without protection. • Instruct patient to avoid concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.
Use in pediatric patients, including impact on growth and development	• All warnings and precautions and monitoring in adults also apply to pediatric patients. • Assess Tanner staging, height, and weight according to standard of care. • Ensure that vaccination status is up to date before initiation of GILENYA. • Monitor for signs and symptoms of depression and anxiety.

Table 14-5 Patient/Parent/Caregivers guide

Safety Topics	HCP Key Safety Messages
Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	• Inform your doctor if you have underlying cardiac conditions or are taking medicines known to decrease your heart rate. • Your doctor will perform an ECG and blood pressure measurement before the first dose of GILENYA.

	• Your doctor will monitor for heart rate after the first dose. Prolonged and overnight monitoring may be required. Follow-up monitoring may be required at treatment re-initiation. • Immediately inform your doctor of symptoms indicating low heart rate (such as dizziness, vertigo, nausea or palpitations), that develop after the first dose of GILENYA. • Call your doctor in case of missed doses as the first dose monitoring may need to be repeated.
Liver transaminase elevation	• Inform your doctor if you have liver problems. • Your doctor will perform liver function tests before starting treatment, at specified intervals during treatment and for up to 2 months after discontinuation. • Inform your doctor if you notice any of the signs of liver injury (such as yellowing of your skin or the whites of your eyes, abnormally dark urine, pain on the right side of the stomach area, unexplained nausea and vomiting).
Macular edema	• Your doctor may arrange an eye assessment before starting GILENYA and as required during treatment. A follow-up eye assessment may be done 3-4 months after starting GILENYA. • Immediately inform your doctor of any symptoms of visual changes during treatment and for up to two months after the end of treatment with GILENYA.
Opportunistic infections including varicella zoster virus (VZV), herpes viral infections other than VZV, fungal infections	• Your doctor will monitor blood lymphocyte counts prior to and during treatment with GILENYA. Treatment with GILENYA may be interrupted if blood lymphocyte count is too low. • Immediately inform your doctor of signs and symptoms of infection, during and up to two months after GILENYA treatment (such as fever, flu-like symptoms, headache accompanied by stiff neck, sensitivity to light, nausea, shingles and/or confusion or seizures [may be symptoms of meningitis and/or encephalitis]).
Progressive multifocal leukoencephalopathy (PML)	• PML is a rare brain disorder caused by an infection that may lead to severe disability or death. • Your doctor will arrange magnetic resonance imaging (MRI) scans before you start treatment and during treatment to monitor the risk of PML. • Immediately inform your physician if you believe your MS is getting worse or if you notice any new symptoms during and after treatment with Gilenya, for example changes in mood or behaviour, new or worsening weakness on one side of the body, changes in vision, confusion, memory lapses or speech and communication difficulties. These may be symptoms of PML or of an inflammatory reaction (known as immune reconstitution inflammatory syndrome or IRIS) that can occur in patients with PML as GILENYA is removed from their body after they stop taking it. • Speak with your partner or caregivers and inform them about your treatment. Symptoms might arise that you might not become aware of by yourself.
Skin cancer (basal cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell	• Immediately inform your doctor if any skin nodules (e.g. shiny, pearly nodules), patches or open sores that do not heal within weeks are noted. Skin cancers have been reported in multiple sclerosis patients treated with GILENYA. Symptoms of skin

carcinoma, squamous cell carcinoma)	cancer may include abnormal growth or changes of skin tissue (e.g. unusual moles) with a change in colour, shape or size over time.
Reproductive toxicity	• GILENYA must not be used in women who could become pregnant and are not using effective contraception or who are pregnant. • If you are a woman of childbearing potential, you must use effective contraception during treatment and for two months following treatment discontinuation. • Immediately report to your doctor any (intended or unintended) pregnancy during treatment and up to two months following discontinuation of GILENYA treatment.
Specifically for pediatric patients	All warnings and precautions and monitoring in adults also apply to pediatric patients. In addition: • Your doctor will assess height, weight, and puberty status according to standard of care. • Your doctor will ensure that your vaccination status is up to date before you start treatment with GILENYA. • Monitor for signs and symptoms of depression and anxiety.

Table 14-6 Pregnancy specific patient reminder card

• IF USED DURING PREGNANCY, GILENYA CAN HARM YOUR UNBORN BABY. GILENYA is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. It is important that you use effective contraception while taking GILENYA and for 2 months after you stop taking it to avoid becoming pregnant. Your doctor will provide counselling regarding effective contraception.
• Your doctor will provide counselling before treatment initiation and regularly thereafter regarding the risk of GILENYA harming an unborn baby and required actions to minimize this risk.
• A pregnancy test must be carried out and negative results verified by your doctor before starting treatment. A pregnancy test must be repeated at suitable intervals.
• Women must NOT become pregnant while on treatment. If you become pregnant or want to become pregnant, GILENYA must be discontinued.
• Inform your doctor immediately if you think you are pregnant. Your doctor will provide counselling in the event of pregnancy and evaluation of the outcome of any pregnancy.
• Immediately inform your doctor if there is worsening of multiple sclerosis after stopping treatment with GILENYA.