NOVARTIS

Chief Medical Office & Patient Safety

Fingolimod

FTY720

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Fingolimod
Product(s) concerned (brand name(s)):	Gilenya®
Document status:	Final
Version number:	18.0
Data lock point for this RMP	11-Aug-2017 Clinical data of pediatric patients from D2311 28-Feb-2020 Post marketing data and clinical data of adult patients
Date of final sign off	16-Nov-2020

Rationale for submitting an updated RMP: The Risk Management Plan, EU RMP version 18.0, has been updated based on the PRAC Recommendations for the review of Gilenya Global PSUR 13 (EU-PSUR 12; period 01-Mar-2019 to 28-Feb-2020) in procedure EMEA/H/C/PSUSA/00001393/202002.

In addition, the targeted follow-up checklists for pregnancy were updated to be harmonized with those used for Mayzent (siponimod) and Kesimpta (ofatumumab).

All changes in the RMP are detailed in the table below which shows the modifications/changes for the consolidated RMP v18.0 from the previous RMP version 17.0.

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v 17.0
Part I	None
Part II	Module SV: Post-authorization exposure data updated with new PSUR data lock point (01-Mar-2019 to 28-Feb-2020).
Part III	Other forms of routine pharmacovigilance activities was updated for important identified risk - Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection).
Part IV	None
Part V	Summary of risk minimization meassure table was updated. Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection was updated for important identified risk - Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection).
Part VI	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection was updated for important identified risk - Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection).
Part VII	Annex 1: None Annex 2: None. Annex 3: None Annex 4: Follow up checklists were updated for identified Risk: Reproductive toxicity; Missing information: Lactating women and Suspected Progressive Multifocal Leukoencephalopathy. Annex 5: None Annex 6 Updated key safety messages. Annex 7: None Annex 8: Updated with summary of changes for Version 18.0

Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within procedure number
None		

Details of the currently approved RMP:

Version number: 17.0

Approved with procedure: EMEA/H/C/002202/IB/0065

Date of approval: 07-Aug-2020

QPPV name: [redacted]

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.

Table of contents

List of tables

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
AST	Aspartate aminotransferase
AUC	Area under 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	Custom MedDRA Queries
CNS	Central Nervous System
CSR	Clinical study report
CYP	Cytochrome P450
DMT	Disease-modifying therapy
DOD	Department of Defense
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EEA	European Economic Area
EPAR	European Public Assessnment Reports
EMA	European Medicines Agency
eNOS	endothelial nitric oxide synthase
ERR	even rate ratio
EU	European Union
FPFV	first patient first visit
GFAP	Glial Fibrillary Acidic Protein
GIRK	G-protein-gated inwardly rectifying K+ channels
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
ISS	Integrated Summary of Clinical Safety
JCV	John Cunningham virus
KLH	Keyhole limpet hemocyanin
LPLV	Last patient last visit
ME	Macular edema

MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MS	Multiple sclerosis
NMQ	Novartis MedDRA Queries
NO	Nitric oxide
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 Program
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
S(m)PC	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 Product Overview

Active substance(s) (INN or common name)	Fingolimod
Pharmacotherapeutic group(s) (ATC Code)	L04AA Selective immunosuppressants (ATC code L04AA27)
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	[Proposed SmPC] [Current approved SmPC]
	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.
	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?	Yes

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 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 males and females 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 Pantagonia, 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 (El-Salem 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 (Koutsourasi 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 environment 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 HLA-DRB1 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 parent-of-origin effect, with an excess of maternal transmission observed when examining half-sibling 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 (eg, 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 fumurate (Tecfidera)
- Alemtuzumab (Lemtrada)
- Peginterferon (Plegridy)
- Ocrelizumab (Ocrevus)
- Cladribine (Mavenclad)

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 USA, 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, Grytten-Thorkildsen et al 2008, Kingwell et al 2012b). Furthermore, highly disabled MS patients Expanded Disability Status Scale (EDSS) 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 (Brønnum-Hansen 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 United States 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 years 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 even 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 a tentatively elevated risk for falls (SMR = 1.3; 95% CI = 0.8, 2.1). They had a particularly high 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, Brønnum-Hansen 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) (Brønnum-Hansen 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 2.5 mg/kg, representing an approximate 50-fold margin based on the human systemic exposure, Area under 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 0.25 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 (10 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 0.1 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 1 mg/kg and higher and a decrease in viable fetuses at 3 mg/kg. Fingolimod was not teratogenic in the rabbit, where an increased embryo-fetal mortality was seen at doses of 1.5 mg/kg and higher, and a decrease in viable fetuses, as well as fetal growth retardation, at 5 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 ≥0.15 mg/kg, i.e. approximately 3.5-fold higher exposure, based on systemic exposure (area under curve, AUC), compared to exposure in patients treated with fingolimod doses of 0.5 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.	
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.
Nervous system:	
Sporadic findings were observed in the nervous system in toxicity studies at high oral doses	

Key Safety findings (from non-clinical studies)	Relevance to human usage
(≥10 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 30 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 10 mg/kg, brain findings similar to those seen at 30 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 10 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 10 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 (up to 3 mg/kg) or 52 week study (up to 10 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 (MBP) 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 10 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. 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 (5.0 mg/kg, p.o.) to a	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 reported pregnancies in fingolimod-treated patients is in line with community estimates.

Key Safety findings (from non-clinical studies)	Relevance to human usage
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 (7.5 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.	It is not known if fingolimod is excreted in human milk. Reproductive toxicity is an important identified risk in the RMP (please see Table 8-12Clinical 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 0.25 and/or 2.5 mg/kg when compared to placebo. These latter findings are not considered toxicologically 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	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
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 (0.5 µM) of fingolimod or fingolimod-phosphate was seen, there was no indication of QT prolongation in as 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 (0.3 mg/kg, 1.5 mg/kg, or 7.5 mg/kg). In mice, treated for 13 weeks at 5 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 10 mg/kg), dogs up to 26 weeks (high dose 10 mg/kg), or monkeys up to 52 weeks (high dose 10 mg/kg). In addition, FTY720, when given at an oral dose of 0.5 mg/kg for 4 weeks in a spontaneous hypertensive (SH) rats in combination with a salt (sodium)-depleted (SD) 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.
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 10 mg/kg. In another 26-week rat study, no	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

Key Safety findings (from non-clinical studies)	Relevance to human usage
findings in the liver were observed up to the highest dose tested, i.e., 7.5 mg/kg. In a 4 week dog study, at 30 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 10 mg/kg in a 26 week toxicity study in dogs, or following 52 weeks of treatment at 10 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.	at very high doses which are likely not relevant for patients at the therapeutic dose of 0.5 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 are discussed in Module SVII and / or Part II of Module SVIII.

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-2018, approximately 23,626 patients received fingolimod treatment in Novartis-sponsored interventional studies with a total exposure of more than 28,592 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 65,992patient-years in approximately 36,490, MS patients. From these, approximately 26,609 patients (with 57,500.96 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.

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-2018) the VDW contained data from 30,443 enrolled patients from 26 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 ongoing observational studies CFTY720D2403, CFTY720D2405 and CFTY720D2406 (PASSAGE). 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). There was no change in group D in the review period (01-Sep-2013 to 28-Feb-2017).
- **Group E** consists of all fingolimod-treated patients from all completed double-or rater-blind, randomized, controlled studies in adult patients with RRMS 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-Sep-2013 to 28-Feb-2017).
- **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
- Ongoing observational trials CFTY720D1401, CFTY720DDE02, CFTY720D2403, CFTY720D2405, CFTY720D2406 and CFTY720D2409
- The long-term Umbrella extension study CFTY720D2399 (Part 2 ongoing, Part-1 completed)

- **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 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-2018)

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	
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		1914		1914		0	1226		3140	
2405*	0		0		637		637		0	0		637	
2406*	0		0		3153		3153		0	1328		4481	
1401*+	0		0		1007		1007		0	0		1007	
DE02*+	0		0		4203		4203		0	0		4203	
DE17*+	0		0		6997		6997		0	0		6997	
IT03+	0		0		998		998		0	0		998	
US01+	0		0		789		789		0	263		1052	
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	(.)	.
2309E1	0	(.)	308	(105)	324	(107)	632	(212)	0	(.)	0	(.)	.
US01	0	(.)	0	(.)	193	(193)	193	(193)	0	(.)	0	(.)	.

Study	FTY720 5 mg		FTY720 1.25 mg		FTY720 0.5 mg		FTY720 Any dose		Placebo	INF and Other DMTs			Total enrolled
Umbrella extension													
2399E1	0	(.)	0	(.)	63	(31)	63	(.)	0	(.)	0	(.)	.
2399*	0	(.)	0	(.)	4088	(969)	4088	(71)	0	(.)	0	(.)	.
Total 1													30443
Total 2	94		1523		24029		25646		1545	3252			.
Total 3	137		2010		25683		26896		1545	3252			.

-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).

+ Country Pharmaceutical organization (CO).

- Source: Appendix 7 of PSUR 11, Table 2-8, VDW 28-Feb-2018:

For the studies in Table 4-1 above, the overall exposure by dose is presented in the table below. The overall estimated long-term exposure to fingolimod in completed and ongoing studies includes more than 12000 MS patients who have received fingolimod treatment for at least one year and more than 3000 MS patients more than five years. More than one hundred patients have now already been treated with fingolimod for more than 10 years.

Table 4-2 Actual exposure to fingolimod in clinical studies by duration for completed and ongoing MS studies

Duration of Exposure	FTY720 5 mg N=94	FTY720 1.25 mg N=1514	FTY720 0.5 mg N=23661	FTY720 any dose N=25269	Placebo N=1531	INF and Other DMTs N=3081
≥ 1 day	135	2046	25891	26605	1530	4241
≥ 180 days	110	1763	15070	15609	1235	3309
≥ 360 days (1 year)	88	1433	12570	13098	1057	2725
≥ 720 days (2 years)	0	952	10038	10459	746	1826
≥ 1080 days (3 years)	0	351	8130	8440	320	1074
≥ 1800 days (5 years)	0	72	4262	4439	5	65
≥ 3600 days (10 years)	0	0	25	152	0	0
Patient-years	147.4	3896.4	53465.4	57509.2	2772.6	7758.6

- N=Number of patients initially randomized/assigned to this treatment and actually treated.

Duration of Exposure	FTY720 5 mg N=94	FTY720 1.25 mg N=1514	FTY720 0.5 mg N=23661	FTY720 any dose N=25269	Placebo N=1531	INF and Other DMTs N=3081
- *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 11, Table 2-9 VDW 28-Feb-2018:						

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 Duration of exposure to study drug, by treatment, Safety set (D2311)

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

Duration of Exposure	FTY720 N=107 n (%)	IFNß-1a N=107 n (%)	Total N=214 n (%)
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 Periodic Safety Update Report (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 3866 patients in completed double-blind studies alone (group E), 3138 patients have had at least one year of exposure to fingolimod, with 1652 patients at least five years (table below).

Table 4-4 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=1876	FTY720 any dose N=3866
≥ 1 day	135	1899	3177	3865
≥ 180 days	110	1635	2902	3423
≥ 360 days (1 year)	88	1396	2627	3138
≥ 720 days (2 years)	0	952	2202	2613
≥ 1080 days (3 years)	0	351	1881	2178
≥ 1800 days (5 years)	0	72	1479	1652
≥ 2160 days (6 years)	0	43	1249	1523
≥ 2520 days (7 years)	0	0	656	1334
Patient-years	147.4	3781.1	13838.5	17767.0
- *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 and 0.5 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 11, Tabel 2-10, VDW 28-Feb-2018				

A majority of patients (approximately 70%) 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, a single female patient younger than 18 years of age 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 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	3	12	0	15
18-30	282	633	915	1635	3971	0	5606
31-40	434	954	1388	2606	5890	0	8496
41-55	420	1129	1549	3112	7840	0	10952
56-65	2	11	13	442	1023	0	1465
>65	0	0	0	23	97	0	120
Missing	0	0	0	7	18	2	27
Total	1138	2728	3866	7828	18851	2	26681

*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)
- 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 FTY720D2301_0606_0009 was aged 17 years at the time of core baseline.
-Source: Appendix 7 of PSUR 11, Table 2-11

The vast majority (approximately 90%) of patients from completed studies were Caucasian, approximately 5% were Asian (including "oriental") and approximately 2% 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 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	14.6	29.2	0	43.8
18-30	1475.4	2715.8	4191.2	3781.6	7704.3	0	11485.9
31-40	2177.7	4540.8	6718.5	6279.0	13312.9	0	19591.9
41-55	1831.6	4958.8	6790.5	6624.1	17112.6	0	23736.7
56-65	24.1	58.8	82.9	820.1	1596.6	0	2416.7
>65	0	0	0	48.5	156.4	0	204.9
Missing	0	0	0	32.8	50.7	9.9	93.4
Total	5508.8	12282.9	17791.8	17600.7	39962.7	9.9	57573.3

*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)
- 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.
- Patient FTY720D2301_0606_0009 was aged 17 years at the time of core baseline.
- Source: Appendix 7 of PSUR 11, Table 2-12

Table 4-7 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	3459	16490.8	18983	33627.3
Asian	188	519.8	1317	4179.2
Black	89	244.7	524	807.9
Other	130	536.5	816	1261.8
Missing	0	0	5041	17697.1
Total	3866	17791.8	26681	57573.3

-All doses of fingolimod are included (5mg, 1.25 mg, 0.5 mg)
Source: Appendix 7 of PSUR 11, Table 2-13

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

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

		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

		FTY720 N=107		IFNß-1a N=107	
Age	**Sex**	**n (%)**	**Patient-years**	**n (%)**	**Patient-years**
	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 Duration of exposure to study drug, by race and treatment, Safety set (D2311)

	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 4100 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 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%	5.9	0.1%	6.4	<0.1%	12.3	0.0%
18-30	528.3	17.0%	1273.3	17.6%	2624.4	14.1%	5948.0	13.9%	8572.4	14.0%
31-40	1176.0	37.9%	2386.9	33.1%	6129.6	32.9%	12323.0	28.8%	18452.6	30.1%
41-55	1320.1	42.6%	3330.5	46.1%	8121.8	43.6%	20448.8	47.9%	28570.6	46.5%
>55	75.5	2.4%	227.4	3.2%	1460.2	7.8%	4931.9	8.1%	4931.9	8.0%
Missing					305.0	1.6%	847.3	1.2%	847.3	1.4%
Total	3099.9	100%	7218.2	100%	18646.9	100%	42730.4	100%	61387.1	100%

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

- Patient FTY720D2301_0606_0009 was aged 17 years 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 11, Table 2-14

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 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	Yes	
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: Yes	Reproductive toxicity is an important identified risk.
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.	Yes	
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	Yes	

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
	transient, spontaneously resolving complete Atrio-Ventricular (AV) block.		
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	Yes	

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 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	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

Type of special population	Exposure/Representation in Clinical Trial Program
	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.
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

Type of special population	Exposure/Representation in Clinical Trial Program
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 cll 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 744,645.31 patient-years from approximately 299,378 country reported patients. This estimate is calculated based on the worldwide sales volume in kilograms (kg) of active substance to date and the defined daily dose (DDD).

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	Total Aug 2010-Feb 2020
Exposure*	905.66	16603.28	37333.42	59964.19	79733.39	94922.89	107317.05	111500.07	116,556.21	119809.15	744645.31

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-2019 to 28-Feb-2020) of approximately 21.9 kg (active ingredient), the estimated interval exposure is 110,515.7 patient-years.

Out of the above-mentioned country-reported total to date, the numbers of patients treated with fingolimod are shown in the tables below.

Table 6-2 Global cumulative post-marketing commercial exposure (number of patients)

Country/Region	Patient years	Number of Patients
US	205,731.55	111,086
Non-US	538,913.76	188,292
Total	744,645.31	299,378

Table 6-3 Non-US cumulative post-marketing commercial exposure (number of patients)

Country/Region	Patient years	Number of Patients
Region Europe (EEA)	344,229.43	126,372
Region Europe (Non-EEA)	51,066.17	11,511
Canada	20,297.87	6,648
Japan	21,254.93	6,459
Rest of the World	102,065.36	37,302
Total Non-US	538,913.76	188,292

Table 6-4 Cumulative post-marketing commercial exposure in the European region, and in EU-EEA by country (number of patients)

Country/Region	Number of Patients
Germany	48,457
Italy	16,087
France	13,777
Spain	7,660
United Kingdom	9,226
Greece	5,226
Austria	2,667
Belgium	3,255
Netherlands	2,308
Denmark	1,973
Ireland	2,315
Norway	1,856
Sweden	1,691
Czech Republic	2,101
Portugal	1,928
Finland	1,152
Poland	1,171
Slovakia	872
Hungary	966
Bulgaria	326
Slovenia	315

Country/Region	Number of Patients
Luxembourg	286
Cyprus	291
Lithuania	311
Estonia	46
Latvia	40
Malta	29
Total EU EEA-countries	126,372
Turkey	6,150
Switzerland	4,886
Russia	475
Total Region Europe	137,833

Table 6-5 Cumulative exposure from marketing experience

	EEA	USA and Canada	Japan	ROW
Patients	126,372	117734	6,45921,254.93	37,302
Patient Treatment Years (PTYs)	344,229.43	226,029.42		102,065.36

EEA: European Economic Area; ROW: Rest of the World; USA: United States of America.
This table includes cumulative data obtained from date of drug approval to 28-Feb-2020.
Source of data: PSUR-13

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

None

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

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)

	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 (%)**
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)
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

Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	**Details**
	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 • 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

Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	**Details**
	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 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).

Important Identified Risk: Hypertension

Table 8-3 Clinical trial data of Hypertension

	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 (%)**
Hypertension (SMQ) (narrow)					
Number of subjects with at least one event	95 (7.0)	37 (3.8)	1.88 [1.26;2.85]	2 (1.9)	4 (3.7)
Severity					
Mild	58 (4.3)	22 (2.3)		0 (0.0)	4 (3.7)
Moderate	36 (2.6)	15 (1.6)		2 (1.9)	0 (0.0)
Severe	1 (0.1)	0		0	0
SAEs	0	1 (0.1)	<1/100	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 0.5mg 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 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 Hypertension: Other details

Hypertension	Details
Potential mechanisms	At present it is not possible to definitively explain why Blood pressure (BP) is increased on fingolimod treatment. However, preclinical pharmacological data indicate that S1P acts as both a constrictor and a dilator via SMC and endothelial cells (EC), respectively, to maintain vascular homeostasis (Brinkmann 2007). Stimulation of S1P receptors in cultures of SMCs leads to increased intracellular Ca2+, activation of myosin light chain kinase (MLCK) and resulting smooth muscle contraction. Activation of S1P3 receptors on endothelial cells (ECs) results in vasodilation through activation of endothelial nitric oxide synthase (eNOS) with increased nitric oxide (NO) production (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 8-3Clinical trial data of Hypertension above. Impact on quality of life: Most cases of increased blood pressure resolved spontaneously. In some patients that may have confounding factors, regular blood pressure monitoring may be required and some may require pharmacologic treatment.
Risk factors and risk groups	None identified for fingolimod.
Preventability	The SmPC recommends monitoring of blood pressure as part of first dose monitoring; hypertension is included in section .4.4 (Special warnings and precautions for use) and Section 4.8 (Undesirable effects) of the SmPC and it is recommended that blood pressure should be regularly monitored during treatment with Gilenya. The SmPC does not recommend the use of fingolimod in patients with uncontrolled hypertension (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 hypertension.
Public health impact	Potential long-term risk in relatively young MS populations for known complications of hypertension. However, it is expected that these risks can be adequately controlled by standard antihypertensive therapy.

Important Identified Risk: Liver transaminase elevation

Table 8-5 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 8-6 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.
Characterization of the risk:	See Table 8-5Clinical trial data of Liver transaminase elevation above. The majority of patients were asymptomatic and recovered from liver transaminase elevation after the drug was discontinued without the need for treatment. Isolated serious cases may require supportive treatment and medical intervention.
Risk factors and risk groups	None identified for fingolimod.
Preventability	The SmPC states that patients with severe pre-existing hepatic injury should not be treated with Gilenya. Physicians are also advised to closely monitor transaminase and bilirubin levels and Gilenya should be discontinued if liver transaminases elevation above 5 times the ULN is confirmed. Initiation of Gilenya should be delayed in patients with active viral hepatitis until resolution. 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 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.

Important Identified Risk: Posterior Reversible Encephalopathy Syndrome (PRES)

Clinical trial data of Posterior Reversible Encephalopathy Syndrome (PRES)

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

Table 8-7 Important identified risk Posterior Reversible Encephalopathy Syndrome (PRES): Other details

Posterior Reversible Encephalopathy Syndrome (PRES)	Details
Potential mechanisms	PRES has been associated with the use of several immunosuppressive and immunomodulating agents which can cause endothelial dysfunction, e.g. cyclosporine, tacrolimus (Wong et al 2003).
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:	Rare cases of PRES have been reported at the 0.5 mg dose in clinical trials and in the post-marketing setting (see SmPC Sections 4.4, 4.8) Impact on quality of life: Symptomatic treatment should be given immediately and the causative factors corrected without delay. Life-supporting treatments may be required and appropriate treatment is expected to ensure a full recovery.
Risk factors and risk groups	None identified for fingolimod.
Preventability	Currently unknown. No apparent pattern for patient's features to prevent/predict the Adverse drug reactions (ADRs). 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 PRES.
Public health impact	Not expected to be clinically significant based on the data available and potential public health impact is considered to be low.

Important Identified Risk: Macular edema

Table 8-8 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

	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 (%)
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

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 8-9 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 8-8Clinical trial data of Macular edema 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.

Macular edema	Details
Preventability	The SmPC recommends that all patients have ophthamological 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.
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.

Important Identified Risk: Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection)

Table 8-10 Clinical trial data of Infections, including opportunistic infections (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)

	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 (%)
Moderate	17 (1.2)	5 (0.5)		0	0
Severe	4 (0.3)	1 (0.1)		0	0
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 8-11 Important identified risk: Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection): Other details

Infections, including opportunistic infections (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

Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection)	Details
	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. 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. The issue of reactivation is important because the cells responsible for surveillance for such infections, the effector memory T-cells, are not affected by fingolimod therapy (Mehling et al 2008, Brinkmann et al 2009, Johnson et al 2010), and thus theoretically, and in practice to date, PML would not be expected to occur with fingolimod. The reason for development of PML with natalizumab is not totally understood, but indiscriminate blockade of lymphocyte migration into the CNS (i.e. an effect on all lymphocyte subsets, including effector memory cells) may play a differentiating role for natalizumab vs. fingolimod. Additionally, natalizumab leads to extrusion of CD38+ cells from bone marrow, cells that are purported to harbor latent John Cunningham virus (JCV) infection. No such effect is seen with fingolimod.
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 8-10Clinical trial data of Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection) 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 VZV infection may cause serious debilitation, require hospitalization and more aggressive treatment, and could potentially lead to death. Herpes viral infections other than VZV

Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection)	**Details**
	Herpes viral infections other than VZV may cause serious debilitation, require hospitalization and more aggressive treatment, and could potentially lead to death. 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. 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).

Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection)	**Details**
	In people who are immunosuppressed, JC virus can reactivate and cause PML which is usually fatal. Cases of PML have been reported with another MS drug, natalizumab, a monoclonal antibody that blocks lymphocyte migration into the CNS (i.e. an effect on all lymphocyte subsets, including effector memory cells). Additionally, natalizumab has effects, such as mobilization of JC virus-carrying bone marrow precursor cells and splenic marginal zone B cells, which are not seen with fingolimod. The natalizumab label describes 3 risk factors that are known to increase the risk of PML in patients under therapy with natalizumab: treatment duration longer than 2 years, prior treatment with an immunosuppressant and presence of anti-JCV antibodies. Patients with all 3 known risk factors have an estimated risk of PML of 11/1,000. When evaluating the potential/theoretical risk with fingolimod, the specific risk factors should be considered: The presence of anti-JCV antibodies Switching to fingolimod after treatment with natalizumab for >2 years and duration of washout of natalizumab. Prior treatment with an immunosuppressant medication (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide).
Preventability	Vigilance for signs or symptoms of infections overall including opportunistic infections, is recommended. 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 cryptococcal meningitis) or bacterial (e.g. atypical mycobacterium), have been reported. See Table 12-1 for details on the SmPC. Varicella-zoster virus infections Vigilance for signs or symptoms of infections is recommended. Gilenya is contraindicated in patients with Known immunodeficiency syndrome, Increased risk for opportunistic infections, including immunocompromised patients. Severe active infections, active chronic infections (hepatitis, tuberculosis). A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with Gilenya (see Section 4.8). Initiation of treatment with Gilenya should be postponed for 1 month to allow full effect of vaccination to occur. When switching patients from another disease modifying therapy to Gilenya, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimising the risk of disease reactivation.

Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection)	**Details**
	Herpes viral infections other than VZV Increased vigilance for infections, including reactivation of chronic viral infections. During treatment, patients receiving Gilenya should be instructed to report symptoms of infection to their physician. Gilenya is contraindicated in patients with Known immunodeficiency syndrome, Increased risk for opportunistic infections, including immunocompromised patients. Severe active infections, active chronic infections (hepatitis, tuberculosis). When switching patients from another disease modifying therapy to Gilenya, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimising the risk of disease reactivation Progressive Multifocal Leukoencephalopathy (PML) Currently unknown
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 (PML, VZV, herpes viral infections other than VZV, fungal infection)
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. Varicella-zoster virus infections 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. One fatal case of disseminated varicella zoster infection occurred in a patient receiving fingolimod 0.5 mg with additional confounding factors. Herpes viral infections other than VZV 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

Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection)	Details
	risk factors which may pre-dispose to severe infection e.g. concomitant immunosuppressive therapy. Progressive Multifocal Leukoencephalopathy (PML) 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.

Important Identified Risk: Reproductive toxicity

Table 8-12 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 8-13 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 8-12Clinical trial data of Reproductive toxicity above 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.
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. 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.

Important Identified Risk: Bronchoconstriction

Table 8-14 Clinical trial data of Bronchoconstriction

	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 (%)**
Asthma/ bronchospasm (SMQ) (broad)					
Number of subjects with at least one event	27 (2.0)	22 (2.3)	0.87 [0.47;1.61]	6 (5.6)	2 (1.9)
Severity					
Mild	19 (1.4)	13 (1.3)		4 (3.7)	2 (1.9)
Moderate	7 (0.5)	7 (0.7)		2 (1.9)	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 (%)
Severe	1(0.1)	2 (0.2)		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 identified risk Bronchoconstriction: Other details

Bronchoconstriction	Details
Potential mechanisms	Preclinical data suggest a direct constrictor effect of S1P on airways smooth muscle, but a release of constrictor molecules from S1P1/S1P3-activated endothelium is also not excluded. In toxicological studies, there were no morphological changes in bronchi, either at the level of smooth muscle or epithelium, on long-term treatment with fingolimod up to high dose levels resulting in large exposure multiples (≥50) compared to the maximum dose currently used in man, i.e. 1.25 mg.
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 8-14Clinical trial data of Bronchoconstriction above. Impact on quality of life: Most cases will require supportive and/or medical intervention. Isolated cases have been reported that required ventilator assistance.
Risk factors and risk groups	No specific risk factors have been identified to predict the occurrence of bronchoconstriction in individual patients. Patients with pre-existing pulmonary conditions such as severe respiratory disease, pulmonary fibrosis, tuberculosis, and asthma requiring daily therapies (see Section 5.3 for complete list) were excluded from the pivotal MS studies.
Preventability	Currently unknown. No apparent pattern for patient's features to prevent/predict the ADR. Per the SmPC, caution is advised in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease. 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 Bronchoconstriction.
Public health impact	The increased mild airway resistance associated with fingolimod treatment is in part reversible with inhaled albuterol, a β-agonist. This finding provides evidence that in the clinic, inhaled β-agonist may be of value in treating symptomatic increased airway resistance associated with fingolimod treatment.

Bronchoconstriction	Details
	In renal transplant and MS studies, there is no evidence of pulmonary toxicity. Therefore, no clinically significant effect is expected, particularly at daily doses of fingolimod 1.25 mg or less. The results of Study FTY720D2102 indicate that fingolimod treatment can be safely started in patients with moderate asthma.

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

Table 8-16 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	
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 8-17 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 8-16 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. 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,

Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)	**Details**
	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.

Important Identified Risk: Convulsions

Table 8-18 Clinical trial data of Convulsions

	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 (%)**
Convulsions (SMQ) (broad)					
Number of subjects with at least one event	7 (0.5)	3 (0.3)	1.66 [0.38;9.95]	6 (5.6)	1 (0.9)
Severity					
Mild	1 (0.1)	0		1 (0.9)	1 (0.9)
Moderate	1 (0.1)	1 (0.1)		2 (1.9)	
Severe	5 (0.4)	2 (0.2)		3 (2.8)	
SAEs	5 (0.4)	2 (0.2)	1.77 [0.29;18.65]	4 (3.7)	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 8-19 Important Identified risk Convulsions: Other details

Convulsions	**Details**
Potential mechanisms	Mechanism currently unknown. It is unknown whether reported cases of seizure are due to Multiple Sclerosis, which has a higher background rate of seizures relative to the non-MS population, or due to fingolimod, or a combination of both.
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 8-18Clinical trial data of Convulsions above.

Convulsions	Details
	Seizure severity can impact a patient's quality of life affecting social and cognitive functioning as well as activities of daily living (e.g. driving and employment) (Noe 2011, Harden 2007).
Risk factors and risk groups	Seizures have been reported in patients with both underlying history and those without. In the Pediatric Study D2311 the rate of reported seizure was 5.6% with fingolimod. This is higher than rates reported in Phase III controlled trials in adults. The prevalence in MS pediatric population is higher than prevalence in MS adult population (5.5% vs 1.3%) (Durmus 2013)
Preventability	Currently unknown. No apparent pattern for patient's features to prevent/predict the occurrence.
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 risk of Convulsions.
Public health impact	The potential public impact is considered to be low. Seizures occur in about 2–3% of all patients with MS (Koch et al 2008, Kelley and Rodriguez 2009). The rate of convulsions observed in the fingolimod MS clinical trials is believed to be in line with the epidemiological experience. The prevalence in MS pediatric population is higher than prevalence in MS adult population (5.5% vs 1.3%) (Durmus 2013).

Important Potential Risk: Acute disseminated encephalomyelitis-like (ADEM-like) events

Clinical trial data of Acute disseminated encephalomyelitis-like (ADEM-like) events

No ADEM-like events were reported for adult patients (Group D), or pediatric patients (D2311).

Table 8-20 Important potential risk Acute disseminated encephalomyelitis-like (ADEM-like) events: Other details

Acute disseminated encephalomyelitis-like (ADEM-like) events	Details
Potential mechanisms	No mechanism for ADEM-like events in fingolimod treated patients has been identified.
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:	Rare events involving the nervous system occurred in patients treated with fingolimod at higher doses (1.25 or 5.0 mg) including ADEM-like events (see SmPC Section 4.8). Impact on quality of life: Most patients recover with treatment. Sequelae can include ataxia and paresis.
Risk factors and risk groups	Since this is a potential risk, no attributable increase 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 occurrence.

Acute disseminated encephalomyelitis-like (ADEM-like) events	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 ADEM.
Public health impact	The incidence of ADEM with fingolimod, and therefore the public health impact, is expected to be low on the basis of data currently available.

Important Potential Risk: Lymphoma

Clinical trial data of Lymphoma

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

Table 8-21 Important potential 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 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:	There have been cases of lymphoma of different varieties, in both clinical studies 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.

Lymphoma	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 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.

Important Potential Risk: Other malignant neoplasms

Table 8-22 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)					
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

	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	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 8-23 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 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 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 8-22. 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.

Other malignant neoplasms	Details
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.

Important Potential Risk: Thrombo-embolic events

Table 8-24 Clinical trial data of Thrombo-embolic events

	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 (%)**
All thromboembolic events (NMQ)					
Number of subjects with at least one event	19 (1.4)	22 (2.3)	0.61 [0.31;1.18]	0	2 (1.9)
Severity					
Mild	8 (0.6)	10 (1.0)		0	0
Moderate	7 (0.5)	7 (0.7)		0	2 (1.9)
Severe	4 (0.3)	5 (0.5)		0	0
SAEs	5 (0.4)	7 (0.7)	0.50 [0.13;1.85]	0	0
Leading to death	0	1 (0.1)	<1/100	0	0
All strokes (NMQ) (broad)					
Number of subjects with at least one event	10 (0.7)	5 (0.5)	1.42 [0.44;5.31]	0	1 (0.9)
Severity					
Mild	5 (0.4)	3 (0.3)		0	0
Moderate	2 (0.1)	1 (0.1)		0	1 (0.9)
Severe	3 (0.2)	1 (0.1)		0	0
SAEs	2 (0.1)	2 (0.2)	0.71 [0.05;9.78]	0	0
Leading to death	0	0		0	0
Embolic and thrombotic events (SMQ)					

	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	7 (0.5)	9 (0.9)	0.55 [0.17;1.66]	0	1 (0.9)
Severity					
Mild	2 (0.1)	2 (0.2)		0	0
Moderate	2 (0.1)	4 (0.4)		0	1 (0.9)
Severe	3 (0.2)	3 (0.3)		0	0
SAEs	3 (0.2)	5 (0.5)	0.42 [0.07;2.18]	0	0
Leading to death	0	1 (0.1)	<1/100	0	0
Ischemic heart disease (SMQ) (broad)					
Number of subjects with at least one event	8 (0.6)	14 (1.4)	0.40 [0.15;1.03]	0	0
Severity					
Mild	3 (0.2)	6 (0.6)		0	0
Moderate	4 (0.3)	4 (0.4)		0	0
Severe	1 (0.1)	4 (0.4)		0	0
SAEs	2 (0.1)	5 (0.5)	0.28 [0.03;1.73]	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 8-25 Important potential risk Thrombo-embolic events: Other details

Thrombo-embolic events	Details
Potential mechanisms	Mechanism currently unknown. In a 1-month, double blind, randomized, parallel design Study FTY720D2113 in healthy volunteers receiving placebo (n=29) or steady-state dosing of either fingolimod 0.5 mg (n=29) or 1.25 mg (n=29) daily, fingolimod treatment did not affect either cerebral vessel flow or reactivity. In addition, fingolimod treatment did not affect either platelet adhesion or stimulated platelet aggregometry.
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 8-24 above: Depending on the event type and severity, patients may fully recover, experience sequelae (e.g. paresis, heart failure) affecting their ability to perform activities, or the event may result in fatality.

Thrombo-embolic events	Details
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	No specific risk factors have been identified to predict the occurrence of thrombo-embolic events in individual patients receiving fingolimod. A description of cases of peripheral arterial occlusive disease is included in the SmPC. 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 Thrombo-embolic events.
Public health impact	Magnitude of risk (if any) cannot be fully delineated based on current data. Long-term observation of patients treated with fingolimod post-approval should help to better delineate the risk.

Important Potential Risk: QT interval prolongation

Table 8-26 Clinical trial data of QT interval prolongation

	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 (%)
Torsade De Pointes/QT prolongation (SMQ) (broad)					
Number of subjects with at least one event	24 (1.8)	16 (1.7)	1.06 [0.54;2.15]	5 (4.7)	2 (1.9)
Severity					
Mild	11 (0.8)	8 (0.8)		3 (2.8)	2 (1.9)
Moderate	7 (0.5)	6 (0.6)		1 (0.9)	0
Severe	6 (0.4)	2 (0.2)		1 (0.9)	0
SAEs	5 (0.4)	3 (0.3)	1.18 [0.23;7.62]	0	0
Leading to death	0	0		0	0
QT interval prolongation (specific) (CMQ)					
Number of subjects with at least one event	2 (0.1)	2 (0.2)	0.71 [0.05;9.78]	2 (1.9)	1 (0.9)
Severity					
Mild	2 (0.1)	2 (0.2)		2 (1.9)	1 (0.9)
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.

	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 (%)

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 8-27 Important potential risk QT interval prolongation: Other details

QT interval prolongation	Details
Potential mechanisms	In preclinical ion channel studies there was no signal of a fingolimod effect on cardiac repolarization. Fingolimod had no effect on hERG channel currents at concentrations <250 ng/mL and only a slight effect at 500 ng/mL-potentially related to cytotoxicity. The following findings were reported from in vivo telemetry studies: Conscious dog: no effects on QT interval up to a maximum oral dose of 10 mg/kg (C_{max} approximately 500 ng/mL; in man C_{max} is less than 5 ng/mL at doses of fingolimod 1.25 mg). Conscious monkey: no effects on QT interval up to a maximum oral dose of 10 mg/kg (plasma concentration approximately 300 ng/mL). Anesthetized Guinea pig: no QT effects up to a maximum iv-dose of 1 mg/kg. QT interval prolongation is believed to be an indirect effect due to compensatory increase in adrenergic tone secondary to fingolimod induced reduction of heart rate.
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 8-26Clinical trial data of QT interval prolongation above. Impact on quality of life: QT prolongation can be life-threatening; however, have been no cases with a fatal outcome reported.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to fingolimod has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Preventability	Use of Gilenya is not recommended in patients with significant QT prolongation (QTc>470msec (female) or >450msec (male). An ECG prior to and 6 hour after treatment initiation is recommended. Continuous ECG monitoring is recommended during the first dose monitoring. Extended monitoring is recommended if after 6 hours, the ECG shows a QTc interval ≥500 msec. Gilenya should not be used concomitantly with class Ia and Class III antiarrhythmics. 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 potential risk of QT interval prolongation.

QT interval prolongation	Details
Public health impact	Transient effect seen shortly after commencing fingolimod treatment and not expected to result in clinically significant cardiac arrhythmias.

8.3.2 SVII.3.2. Presentation of the missing information

Table 8-28 Missing information

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.
Elderly patients (≥65 years)	This population was not studied in the clinical trial development program. No age-related significant difference in safety and efficacy has been observed in clinical studies. Further data could characterize the safety of fingolimod use in elderly patients (> 65 years).
Lactating women	Fingolimod was excreted in milk of treated animals during lactation. This population was not studied in the clinical trial development program. It is not known if fingolimod is excreted in human milk. Further data could be used to determine the incidence, nature, severity and outcome of any adverse events in babies breastfed by patients taking fingolimod.
Patients with diabetes mellitus	Patients with diabetes were excluded in the clinical trial program. Further data could be used to ensure that patients with diabetes mellitus are appropriately managed while receiving fingolimod therapy.
Patients with cardiovascular conditions*	Patients with cardiovascular conditions were excluded in the clinical trial program. Further data could be used to ensure that fingolimod therapy is safely initiated in patients with underlying cardiovascular disease and to evaluate and characterize the safety of fingolimod use in patients with cardiovascular conditions.
Long-term risk of cardiovascular morbidity/mortality	The clinical trial program had a limited duration of follow-up of subjects. Further data could be used to better delineate the risk, if any, of cardiovascular (including cerebrovascular) events in patients treated with fingolimod
Long-term risk of malignant neoplasms	The clinical trial program had a limited duration of follow-up of subjects. Further data could be used to better delineate the risk, if any, of the long-term risk of malignant neoplasms
Unexplained death	It is currently unknown if fingolimod is associated with increased risk of unexplained death. Further data could be used to better delineate the risk, if any, of unexplained death in patients treated with fingolimod.
Switch from other disease modifying therapy	No studies have been conducted to date to evaluate the safety and efficacy of switches from newly marketed agents, some of which have been approved several years after Gilenya. Further data could be used to better delineate the risk, if any, of the switch from other disease modifying therapy in patients treated with fingolimod.

*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

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.
Elderly patients (≥65 years)	This population was not studied in the clinical trial development program. No age-related significant difference in safety and efficacy has been observed in clinical studies. Further data could characterize the safety of fingolimod use in elderly patients (> 65 years).
Lactating women	Fingolimod was excreted in milk of treated animals during lactation. This population was not studied in the clinical trial development program. It is not known if fingolimod is excreted in human milk. Further data could be used to determine the incidence, nature, severity and outcome of any adverse events in babies breastfed by patients taking fingolimod.
Patients with diabetes mellitus	Patients with diabetes were excluded in the clinical trial program. Further data could be used to ensure that patients with diabetes mellitus are appropriately managed while receiving fingolimod therapy.
Patients with cardiovascular conditions*	Patients with cardiovascular conditions were excluded in the clinical trial program. Further data could be used to ensure that fingolimod therapy is safely initiated in patients with underlying cardiovascular disease and to evaluate and characterize the safety of fingolimod use in patients with cardiovascular conditions.
Long-term risk of cardiovascular morbidity/mortality	The clinical trial program had a limited duration of follow-up of subjects. Further data could be used to better delineate the risk, if any, of cardiovascular (including cerebrovascular) events in patients treated with fingolimod
Long-term risk of malignant neoplasms	The clinical trial program had a limited duration of follow-up of subjects. Further data could be used to better delineate the risk, if any, of the long-term risk of malignant neoplasms
Unexplained death	It is currently unknown if fingolimod is associated with increased risk of unexplained death. Further data could be used to better delineate the risk, if any, of unexplained death in patients treated with fingolimod.
Switch from other disease modifying therapy	No studies have been conducted to date to evaluate the safety and efficacy of switches from newly marketed agents, some of which have been approved several years after Gilenya. Further data could be used to better delineate the risk, if any, of the switch from other disease modifying therapy in patients treated with fingolimod.

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 Table Part II SVIII.1: Summary of safety concerns

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

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
   - Gilenya Cardiac rate and rhythm disorders checklist
2. Important Identified risk: Bronchoconstriction
   - Gilenya Breathlessness checklist
3. Important Identified risk: Liver transaminase elevation
   - Liver injury checklist
4. Important Identified risk: Macular edema
   - S1P Modulator Macular edema checklist
5. Important Identified Risk: Infections, including opportunistic infections (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 check list
6. Important Identified risk: Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)
   - S1P Modulator and Skin Cancer checklist
7. Important Identified Risk: Reproductive toxicity; Missing information: Lactating women
   - Multiple Sclerosis- Pregnancy baseline follow up checklist
   - Multiple Sclerosis–Pregnancy Outcome (Estimated Date of Delivery+ one month) follow-up checklist
   - Multiple Sclerosis – Infant Health status follow-up during first year following drug exposure in pregnancy
8. Important Identified risk: Convulsions
   - Seizures checklist
9. Important Potential risks: Other malignant neoplasms; Lymphoma
   - Malignancy & Neoplasm checklist
   - Cervical dysplasia/cervical cancer checklist
10. Important Potential risk: Thrombo-embolic events
    - Stroke checklist
    - Ischemic heart disease/myocardial infarction checklist
11. Missing information: Unexplained death
    - Gilenya Sudden/unexplained death 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) 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 intramuscular 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: within 2 months from the European Commission Decision for procedure EMEA/H/C/002202/X/0044/G

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

FTY720D2409 summary

Study short name and title:

Study assessing the long-term cardiovascular risks in patients treated with fingolimod Long-term, open-label, multicenter study assessing long-term cardiovascular risks in patients treated with fingolimod.

Rationale and study objectives:

This study is a post-authorization follow-up measure to assess the long-term cardiovascular risk of fingolimod in patients who experience a serious cardiovascular event during the first 24-hours of fingolimod treatment initiation in study FTY720D2406.

The primary objective of this study is to estimate the long-term cardiovascular risk of fingolimod, as defined by the incidence of selected cardiovascular events over the course of the study, in patients who experienced a cardiovascular event during treatment initiation in Study 2406.

Study design:

This is a single-arm, open-label, long-term safety study.

Study population:

The study was planned to enroll up to 40 MS patients who sustained a serious cardiovascular event during their fingolimod treatment initiation in the FTY720D2406 study.

Milestones:

FPFV: 3Q 2014

LPFV: 2Q 2019

LPLV: 1Q 2020

Final study report planned: 30-Apr-2021

FTY720D2403 summary

Study short name and title:

Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy.

Rationale and study objectives:

The purpose of this multi-national prospective parallel-cohort study in patients with relapsing forms of MS, either newly treated with fingolimod or receiving another disease-modifying therapy, is to further monitor the overall safety profile of fingolimod under conditions of routine medical practice and to explore the incidence of selected safety-related outcomes.

Patients enrolled in this study will have the option to complete PRO questionnaires, as part of an optional PRO sub-study under conditions of routine medical practice. The purpose of collecting these PRO data is to evaluate outcomes that are important to patients which include disability, health-related quality of life, productivity, and treatment satisfaction and preference. The PRO sub-study will help describe the effect of treatment on long-term outcomes under conditions of routine medical practice which is important to understand the real-world value of fingolimod treatment.

The primary objective of this study is to further explore the overall safety profile of fingolimod over the long term in patients with relapsing MS under conditions of routine medical practice.

Study design:

This is a multi-national, long-term, prospective, parallel-cohort study to monitor and further describe the long-term safety of fingolimod.

Study population:

This study will include patients with relapsing forms of MS that have been newly initiated on fingolimod by their treating physician or patients that are treated with other disease-modifying therapies as part of their MS treatment in accordance with the respective local prescribing information and routine clinical practice.

It is estimated that approximately 2400 patients newly initiated on fingolimod and 1200 patients treated with other approved MS disease-modifying therapies, will be included in this study.

Milestones:

FPFV: 3Q 2011

LPFV: 2Q 2015

LPLV: 1Q 2020

Final study report planned: 30-Apr-2021

FTY720D2404 summary

Study short name and title:

Multi-National Gilenya Pregnancy Exposure Registry in Multiple Sclerosis.

Rationale and study objectives:

The purpose of the Multi-National Gilenya Pregnancy Exposure Registry in Multiple Sclerosis (MS) is to continuously monitor, evaluate, and assess for major and minor teratogenic effects

in the offspring of women exposed to fingolimod before (up to 8 weeks before last menstrual period (LMP)) and during pregnancy in routine clinical practice. The overall aim is to collect and evaluate data on maternal, fetal, and infant outcomes and compare it with reference populations.

The primary objective of the registry is to describe the overall frequency of major and minor congenital malformations associated with exposure to fingolimod during pregnancy.

Study design:

The Gilenya Pregnancy Exposure Registry is a (at least) six-year, multinational, prospective observational study.

Study population:

The targeted patient population is pregnant women with MS exposed to fingolimod during pregnancy or up to 8 weeks before last menstrual period.

Milestones:

FPFV: 4Q 2011

LPFV: 2Q 2029

LPLV: 4Q 2030

Final study report planned: 2Q 2031

FTY720D2406 summary

Study short name and title:

Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS newly initiated on fingolimod once daily or treated with another approved disease-modifying therapy.

Rationale and study objectives:

Purpose is to monitor the overall safety profile of fingolimod under conditions of routine medical practice and to explore the incidence of selected safety-related outcomes. This is a post approval commitment study to health authorities.

The primary objective of the registry is to explore the overall safety profile of fingolimod over the long term in patients with relapsing MS under conditions of routine medical practice.

Study design:

Long-term, prospective, non-interventional, parallel-cohort, safety study.

Study population:

This study is planned to include patients with relapsing MS who either are starting treatment with fingolimod at time of study entry or have recently (within 6 months) started other disease modifying therapy (DMT) as part of their MS treatment, in accordance with the routine clinical practice.

Milestones:

FPFV: 2Q 2012

LPFV: 4Q 2015

LPLV: 1Q 2020

Final study report planned: 30-Apr-2021

10.3 Part III.3Summary 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				
Study: CFTY720D2409: The primary objective is to estimate the long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event after the first dose. Status: Ongoing	To estimate the long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event after the first dose	• Bradyarrhythmia • Hypertension • Thrombo-embolic events • QT interval prolongation • Patients with cardiovascular conditions* • Long-term risk of cardiovascular morbidity/mortality • Unexplained death	Protocol submission	2Q-2014
			Final report submission	30-Apr-2021
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 proposed				

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
CFTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Status: Ongoing	To further explore the overall safety profile and incidence of selected safety-related outcomes of fingolimod under conditions of routine medical practice. To observe long-term effectiveness outcomes. To evaluate safety and effectiveness of switch from other disease modifying therapies.	• Bradyarrhythmia • Hypertension • Liver transaminase elevation • PRES • Macular edema • Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection) • Bronchoconstriction • Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma) • ADEM like events • Lymphoma • Other malignant neoplasms • Thrombo embolic events • QT interval prolongation • Convulsions • Patients with diabetes mellitus • Patient with cardiovascular conditions*	Annual update	Progress reports on enrolment and intermediate analysis results will be provided yearly in Q3.
			Final report submission	Final report: 30-Apr-2021

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
		• Long-term risk of cardiovascular morbidity/mortality • Long term risk of malignant neoplasms • Unexplained death • Switch from other disease modifying therapy		
CFTY720D2404: Prospective, observational study in pregnant MS patients with confirmed or suspected maternal exposure to fingolimod any time during pregnancy or shortly before pregnancy (up to 8 weeks before last menstrual period). Status: Ongoing	To collect data regarding fingolimod exposure during pregnancy and maternal, fetal and infant outcomes	• Reproductive toxicity	Annual update	Progress reports on enrollment and intermediate analysis results will be provided yearly in Q3.
			Final report submission	2Q 2031

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Study CFTY720D2406: Long-term prospective non interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Status: Ongoing	To further explore the overall safety profile and incidence of selected safety-related outcomes of fingolimod under conditions of routine medical practice. To observe long-term effectiveness outcomes. To evaluate safety and effectiveness of switch from other disease modifying therapies.	• Bradyarrhythmia • Hypertension • Liver transaminase elevation • PRES • Bronchoconstriction • Macular edema • Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection) • Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma) • ADEM like events • Lymphoma • Other malignant neoplasms • Thrombo-embolic events • QT interval prolongation • Convulsions • Patients with diabetes mellitus • Patients with cardiovascular conditions* • Long-term risk of cardiovascular	Annual update	Progress reports on enrollment and intermediate analysis results will be provided yearly in Q3.
			Final report submission	30-Apr-2021

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
		morbidity/mortality • Long-term risk of malignant neoplasms • Unexplained death • Switch from other disease modifying therapy		
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 intramuscular 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	Long-term use in pediatric patients, including impact on growth and development (including cognitive development)	Revised protocol	Within 2 months from the European Commission Decision for procedure EMEA/H/C/002202/X/0044/G
			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
	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.			

*This includes 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

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 Table 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
Hypertension	**Routine risk communication** Risks addressed in SmPC Sections 4.4 and 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 to monitor blood pressure regularly during treatment with Gilenya. **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

Safety concern	Routine risk minimization activities
	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
Posterior reversible encephalopathy syndrome (PRES)	**Routine risk communication** Risk is addressed in SmPC Section 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, describes symptoms of PRES and recommends the Gilenya be discontinued if PRES is suspected. **Other routine risk minimization measures beyond the Product Information:** None
Macular edema	**Routine risk communication** 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
Infections, including opportunistic infections (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 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

Safety concern	Routine risk minimization activities
	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 (WCBP) 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. **Other routine risk minimization measures beyond the Product Information:** None
Bronchoconstriction	**Routine risk communication** Risk is addressed in SmPC Sections 4.4, 4.8, and 5.1: Warning in Section 4.4 Listed as an ADR in Section 4.8 Pharmacodynamic effects stated in Section 5.1: Pharmacodynamic properties **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **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

Safety concern	Routine risk minimization activities
	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
Convulsions	**Routine risk communication** Risk is addressed in SmPC Sections 4.4 and 4.8, Listed as an ADR in Section 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Acute disseminated encephalomyelitis-like (ADEM-like) events	**Routine risk communication** Potential risk is addressed in SmPC Section 4.8. Listed as an ADR in Section 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Lymphoma	**Routine risk communication** Potential 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:**

Safety concern	Routine risk minimization activities
	None
Thrombo-embolic events	**Routine risk communication** Potential risk addressed in SmPC Section 4.8. Listed as an ADR in Section 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
QT interval prolongation	**Routine risk communication** Potential risk addressed in SmPC Sections 4.4 and 4.9. Warning in Section 4.4 Overdose in Section 4.9 **Routine risk minimization activities recommending specific clinical measures to address the risk:** The SmPC includes the recommendation if after 6 hours of the first dose, the heart rate is <45 bpm, or the ECG shows new onset second degree or higher grade AV block or a QTc interval ≥500 msec, extended monitoring (at least overnight monitoring), should be performed, and until the findings have resolved. **Other routine risk minimization measures beyond the Product Information:** None
Long-term use in pediatric patients, including impact on growth and development (including cognitive development)	**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 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Elderly patients (≥65 years)	**Routine risk communication** Missing information addressed in Sections 4.2 and 5.2 of the SmPC Posology and method of administration in Section 4.2 Pharmacokinetic properties in Section 5.2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Lactating women	**Routine risk communication** Missing information addressed in Section 4.6 of the SmPC: Fertility, pregnancy and lactation

Safety concern	Routine risk minimization activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: None **Other routine risk minimization measures beyond the Product Information:** None
Patients with diabetes mellitus	**Routine risk communication** Missing information addressed in Sections 4.2, 4.4 and 4.8 of the SmPC Section Diabetic patients addressed in Section 4.2 Posology and method of administration 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 4.2, includes the recommendation for regular ophthalmological examinations should be conducted in these patients to detect macular oedema. **Other routine risk minimization measures beyond the Product Information:** None
Patients with cardiovascular conditions*	**Routine risk communication** Missing information addressed in Section 4.3, 4.4 of the SmPC Contraindication in Section 4.3 Warning in Section 4.4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** The SmPC, Section 4.3 includes the following contraindications, "Patients with myocardial infarction (MI), unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure in the previous 6 months (see Section 4.4). Patients with severe cardiac arrhythmias requiring anti-arrhythmic treatment with class Ia and class III anti-arrhythmic drugs (see Section 4.4). Patients with second-degree Mobitz type II atrioventricular (AV) block or third-degree AV block, or sick-sinus syndrome, if they do not wear a pacemaker (see Section 4.4). Patients with a baseline QTc interval ≥500 msec (see Section 4.4). Section 4.4, includes the following recommendation, “Due to the risk of serious rhythm disturbances, Gilenya should not be used in patients with a history of symptomatic bradycardia or recurrent syncope, or in patients with significant QT prolongation (QTc>470msec (female) or >450msec (male)). Since significant bradycardia may be poorly tolerated in patients with a history of cardiac arrest, uncontrolled hypertension or severe sleep apnoea, Gilenya should not be used in these patients (see also Section 4.3). In such patients, treatment with Gilenya should be considered only if the anticipated benefits outweigh the potential risks. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate

Safety concern	Routine risk minimization activities
	monitoring, at least overnight extended monitoring is recommended for treatment initiation." **Other routine risk minimization measures beyond the Product Information:** None
Long-term risk of cardiovascular morbidity/mortality	**Routine risk communication** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Long-term risk of malignant neoplasms	**Routine risk communication** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Unexplained death	**Routine risk communication** Missing information addressed in Section 4.8 of the SmPC Listed as an ADR in Section 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Switch from other disease modifying therapy	**Routine risk communication** Missing information addressed in Sections 4.4, 4.5 and 5.1 of the SmPC. Warning in Section 4.4 Interaction with other medicinal products in Section 4.5 Pharmacodynamic properties in Section 5.1 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None

*This includes 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

12.2 Part V.2. Additional Risk minimization measures

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

Objective

To provide physicians and patients with educational information on 8 safety areas of interest:

- Bradyarrhythmias upon treatment initiation
- Infections, including PML, varicella zoster and cryptococcal infections (including cryptococcal meningitis)
- 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)
- Seizures
- 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:

- The Summary of Product Characteristics
- The Physician's checklist for adult and pediatric patients prior to prescribing GILENYA, including information about the Gilenya Pregnancy Exposure Registry (GPR)
- 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 the Women of Child Bearing Potential (WCBP), 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.

Removal of additional risk minimization activities

Not applicable

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 shall contain the following key messages:

- 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 the doctor before treatment. It must be repeated at suitable intervals
- Effective contraception is needed while on treatment and for 2 months after discontinuation
- Doctors will provide counselling before treatment initiation and regularly
- Counselling in the event of pregnancy and evaluation of the outcome of any pregnancy
- While on treatment, women must not become pregnant. 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

- Women exposed to GILENYA during pregnancy are encouraged to join pregnancy exposure registry that monitors outcomes of pregnancy

Addition in the EU PI of a contraindication in pregnant women and in WCBP not using effective contraception (SmPC and Package leaflet)

Dispatch of a Direct Healthcare Professional Communication (DHPC) informing the healthcare providers in the EU of this label update (EU Only).

Monitor birth outcome in patients who have become pregnant, in the Gilenya Pregnancy Registry (Study D2404) Patients who have become pregnant are encouraged to enroll in the Gilenya Pregnancy Registry.

The scope of this prevention for Gilenya is to ensure that WCBP (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.

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: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another disease-modifying therapy. Study FTY720D2406: Long-term prospective non interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2409: The primary objective is to estimate the long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose
Hypertension	Routine risk minimization measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: No additional risk minimization measures	Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2409: The primary objective is to estimate the long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.
Liver transaminase elevation	Routine risk minimization measures: SmPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2 Additional risk minimization measures: Educational materials for physicians and patients: - Physician's checklist for adult and 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: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
Posterior Reversible Encephalopathy Syndrome (PRES)	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 Additional risk minimization measures: No additional risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel cohort study monitoring safety in patients with MS newly started with fingolimod 0.5 mg capsule once daily or treated with

Safety concern	Risk minimization measures	Pharmacovigilance activities
		another approved disease-modifying therapy Study FTY720D2406: Long-term prospective non- interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy
Macular edema	Routine risk minimization measures: SmPC 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: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection)	Routine risk minimization measures: SmPC Sections 4.3, 4.4 and 4.8 Additional risk minimization measures: Educational materials for physicians and patients: - Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Independent review of cases of suspected PML by External Adjudication Committee Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

Safety concern	Risk minimization measures	Pharmacovigilance activities
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 Sending a DHPC in the EU to inform healthcare professionals regarding the label update and pregnancy prevention	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Study FTY720D2404: The Multinational Pregnancy Gilenya Exposure Registry in Multiple Sclerosis to prospectively collect outcome data on the babies born to women treated with fingolimod.
Bronchoconstriction	Routine risk minimization measures: SmPC Sections 4.4, 4.8 and 5.1 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: Study FTY720D2403: Long-term, prospective, multinational, parallel cohort study monitoring safety in patients with MS newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term prospective non interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
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: Educational materials for physicians and patients:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with

Safety concern	Risk minimization measures	Pharmacovigilance activities
	- Physician's checklist for adult and pediatric population - Patient/Parent/Caregiver guide	MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
Convulsions	Routine risk minimization measures: SmPC Sections 4.4 (pediatric patients) 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: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
Acute disseminated encephalomyelitis-like (ADEM-like) events	Routine risk minimization measures: SmPC Section 4.8 Additional risk minimization measures: No additional risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel cohort study monitoring safety in patients with MS newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term prospective non- interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
Lymphoma	Routine risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	SmPC Sections 4.8 and 5.3 Additional risk minimization measures: No additional risk minimization measures	Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy
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: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
Thrombo-embolic events	Routine risk minimization measures: SmPC Section 4.8 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: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study

Safety concern	Risk minimization measures	Pharmacovigilance activities
		monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.
QT interval prolongation	Routine risk minimization measures: SmPC Sections 4.4 and 4.9 Additional risk minimization measures: No additional risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate the long-term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.
Long-term 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.
Elderly patients (≥65 years)	Routine risk minimization measures: SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: No additional risk minimization measure	None Additional pharmacovigilance activities: None
Lactating women	Routine risk minimization measures: SmPC Sections 4.6 Additional risk minimization measures: No additional risk minimization measure	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None
Patients with diabetes mellitus	Routine risk minimization measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimization measures: No additional risk minimization measure	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, parallel-cohort study monitoring safety in patients with MS, either recently initiated on fingolimod or receiving another DMT according to local label and exclude patients previously treated with Natalizumab. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
Patients with cardiovascular conditions*	Routine risk minimization measures: SmPC sections 4.3, 4 .4 Additional risk minimization measures: No additional risk minimization measure	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate the long-term incidence of serious cardiovascular

Safety concern	Risk minimization measures	Pharmacovigilance activities
		adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.
Long-term risk of cardiovascular morbidity/mortality	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate the long-term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.
Long-term risk of malignant neoplasms	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.
Unexplained death	Routine risk minimization measures: SmPC Section 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: No additional risk minimization measure	Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate the long-term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.
Switch from other disease modifying therapy	Routine risk minimization measures: SmPC sections 4.4, 4.5 and 5.1 Additional risk minimization measures: No additional risk minimization measure	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy

*This includes 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

13 Part VI: Summary of the risk management plan- 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 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 in the 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 by 0.25 mg/day or 0.5 mg/day oral hard capsule.

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

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: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another disease-modifying therapy.

	Study FTY720D2406: Long-term prospective non interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2409: The primary objective is to estimate the long-term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose

Table 13-3 Important Identified Risk: Hypertension

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: No additional risk minimization measures
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2409: The primary objective is to estimate the long-term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.

Table 13-4 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: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

Table 13-5 Important Identified Risk: Posterior Reversible Encephalopathy Syndrome (PRES)

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: No additional risk minimization measures
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel cohort study monitoring safety in patients with MS newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease-modifying therapy Study FTY720D2406: Long-term prospective non- interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy

Table 13-6 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: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

Table 13-7 Important Identified Risk: Infections, including opportunistic infections (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. **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. In people who are immunosuppressed, JC virus can reactivate and cause PML which is usually fatal. Cases of PML have been reported with another MS drug, natalizumab, a monoclonal antibody that blocks lymphocyte migration into the CNS (i.e. an effect on all lymphocyte subsets, including effector memory cells). Additionally, natalizumab has effects, such as mobilization of JC virus-carrying bone marrow precursor cells and splenic marginal zone B cells, which are not seen with fingolimod. The natalizumab label describes 3 risk factors that are known to increase the risk of PML in patients under therapy with natalizumab: treatment duration longer than 2 years, prior treatment with an immunosuppressant and presence of anti-JCV antibodies. Patients with all 3 known risk factors have an estimated risk of PML of 11/1,000. When evaluating the potential/theoretical risk with fingolimod, the specific risk factors should be considered: The presence of anti-JCV antibodies Switching to fingolimod after treatment with natalizumab for >2 years and duration of washout of natalizumab Prior treatment with an immunosuppressant medication (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide).
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: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

Table 13-8 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'scisian's Check-list for adult and pediatric population - Patient/Parent/Caregiver guide - Pregnancy-specific patient reminder card Sending a DHPC in the EU to inform health professionals regarding label update and pregnancy prevention
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Study FTY720D2404: The Multinational Pregnancy Gilenya Exposure Registry in Multiple Sclerosis to prospectively collect outcome data on the babies born to women treated with fingolimod.

Table 13-9 Important Identified Risk: Bronchoconstriction

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	No specific risk factors have been identified to predict the occurrence of bronchoconstriction in individual patients. Patients with pre-existing pulmonary conditions such as severe respiratory disease, pulmonary fibrosis, tuberculosis, and asthma requiring daily therapies were excluded from the pivotal MS studies.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.4, 4.8 and 5.1 Additional risk minimization measures: No additional risk minimization measures
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel cohort study monitoring safety in patients with MS newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term prospective non interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

Table 13-10 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: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

Table 13-11 Important identified risk: Convulsions

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 4.4 (pediatric patients) 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: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy.

	Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

Table 13-12 Important potential risk: Acute disseminated encephalomyelitis-like (ADEM-like) events

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 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 4.8 Additional risk minimization measures: No additional risk minimization measures
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel cohort study monitoring safety in patients with MS newly started with fingolimod 0.5 mg capsule once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term prospective non- interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

Table 13-13 Important potential 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: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy

	Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy

Table 13-14 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: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

Table 13-15 Important potential risk: Thrombo-embolic events

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 4.8 Additional risk minimization measures: No additional risk minimization measures
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with

	MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate long term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.

Table 13-16 Important potential risk: QT interval prolongation

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 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 4.4 and 4.9 Additional risk minimization measures: No additional risk minimization measures
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate the long-term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.

Table 13-17 Important 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.

Table 13-18 Important Missing information: Elderly patients (≥65 years)

Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2 and 5.2 Additional risk minimization measures: No additional risk minimization measure

Table 13-19 Important Missing information: Lactating women

Risk minimization measures	Routine risk minimization measures: SmPC Section 4.6 Additional risk minimization measures: No additional risk minimization measure
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 13-20 Important Missing information: Patients with diabetes mellitus

Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimization measures: No additional risk minimization measure
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, parallel-cohort study monitoring safety in patients with MS, either recently initiated on fingolimod or receiving another DMT according to local label and exclude patients previously treated with Natalizumab. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

Table 13-21 Important Missing information: Patients with cardiovascular conditions*

Risk minimization measures	Routine risk minimization measures: SmPC sections 4.3 and 4.4 Additional risk minimization measures:

	No additional risk minimization measure
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate the long-term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.

*Cardiovascular conditions includes 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.Multiply table for each important risk/ missing information.

Table 13-22 Important Missing information: Long-term risk of cardiovascular morbidity/mortality

Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate the long-term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.

Table 13-23 Important Missing information: Long-term risk of malignant neoplasms

Risk minimization measures	No risk minimization measures

Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.

Table 13-24 Important Missing information: Unexplained death

Risk minimization measures	Routine risk minimization measures: SmPC Section 4.8 Additional risk minimization measures: No additional risk minimization measure
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy. Study FTY720D2409: The primary objective is to estimate the long-term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event during the first dose.

Table 13-25 Important Missing information: Switch from other disease modifying therapy

Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4, 4.5 and 5.1 Additional risk minimization measures: No additional risk minimization measure
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study FTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy.

	Study FTY720D2406: Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy

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

Table 13-26 Studies which are conditions of the marketing authorization

Study short name: **Study CFTY720D2409:** The primary objective is to estimate the long-term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event after the first dose.	**Purpose of the study:** This study is a post-authorization follow-up measure to assess the long-term cardiovascular risk of fingolimod in patients who experience a serious cardiovascular event during the first 24-hours of fingolimod treatment initiation in study FTY720D2406. The primary objective of this study is to estimate the long-term cardiovascular risk of fingolimod, as defined by the incidence of selected cardiovascular events over the course of the study, in patients who experienced a cardiovascular event during treatment initiation in Study 2406.

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

Table 13-27 Other studies in the post-authorization development plan

Study short name: CFTY720D2403: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy.	**Rationale and study objectives:** The purpose of this multi-national prospective parallel-cohort study in patients with relapsing forms of MS, either newly treated with fingolimod or receiving another disease-modifying therapy, is to further monitor the overall safety profile of fingolimod under conditions of routine medical practice and to explore the incidence of selected safety-related outcomes. Patients enrolled in this study will have the option to complete PRO questionnaires, as part of an optional PRO sub-study under conditions of routine medical practice. The purpose of collecting these PRO data is to evaluate outcomes that are important to patients which include disability, health-related quality of life, productivity, and treatment satisfaction and preference. The PRO sub-study will help describe the effect of treatment on long-term outcomes under conditions of routine medical practice which is important to understand the real-world value of fingolimod treatment. The primary objective of this study is to further explore the overall safety profile of fingolimod over the long term in patients with relapsing MS under conditions of routine medical practice.
Study short name: CFTY720D2404: Prospective, observational study in pregnant MS patients with confirmed or suspected maternal exposure to fingolimod any time during pregnancy or shortly before pregnancy (up to 8 weeks before last menstrual period).	**Rationale and study objectives:** The purpose of the Multi-National Gilenya Pregnancy Exposure Registry in Multiple Sclerosis (MS) is to continuously monitor, evaluate, and assess for major and minor teratogenic effects in the offspring of women exposed to fingolimod before (up to 8 weeks before last menstrual period (LMP)) and during pregnancy in routine clinical practice. The overall aim is to collect and evaluate data on maternal, fetal, and infant outcomes and compare it with reference populations. The primary objective of the registry is to describe the overall frequency of major and minor congenital malformations associated with exposure to fingolimod during pregnancy.

Study short name: Study CFTY720D2406: Long - term prospective non interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy.	**Rationale and study objectives:** Purpose is to monitor the overall safety profile of fingolimod under conditions of routine medical practice and to explore the incidence of selected safety-related outcomes. This is a post approval commitment study to health authorities. The primary objective of the registry is to explore the overall safety profile of fingolimod over the long term in patients with relapsing MS under conditions of routine medical practice.

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) 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 intramuscular 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 1 – EudraVigilance Interface

Available in electronic format only.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study program

Table 14-1 Planned and ongoing studies

Study	Summary of objectives	Safety concerns addressed	Milestones
[CFTY720D2409]: The primary objective is to estimate the long-term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event after the first dose. **Category 1**	To estimate the long-term incidence of serious cardiovascular adverse events in fingolimod treated patients who experienced a serious cardiovascular event after the first dose	• Bradyarrhythmia • Hypertension • Thrombo-embolic events • QT interval prolongation • Patients with cardiovascular conditions* • Long-term risk of cardiovascular morbidity/mortality • Unexplained death	Interim reports: annually 3Q Final report: 30-Apr-2021
[CFTY720D2403]: Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy. **Category 3**	To further explore the overall safety profile and incidence of selected safety-related outcomes of fingolimod under conditions of routine medical practice. To observe long-term effectiveness outcomes. To evaluate safety and effectiveness of switch from other disease modifying therapies.	• Bradyarrhythmia • Hypertension • Liver transaminase elevation • PRES • Macular edema • Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection) • Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma) • Bronchoconstriction • ADEM like events • Lymphoma • Other malignant neoplasms • Thrombo embolic events	Interim reports: annually 3Q Final report: 30-Apr-2021

Study	Summary of objectives	Safety concerns addressed	Milestones
		• QT interval prolongation • Convulsions • Patients with diabetes mellitus • Patient with cardiovascular conditions* • Long-term risk of cardiovascular morbidity/mortality • Long term risk of malignant neoplasms • Unexplained death • Switch from other disease modifying therapy	
[CFTY720D2404]: Prospective, observational study in pregnant MS patients with confirmed or suspected maternal exposure to fingolimod any time during pregnancy or shortly before pregnancy (up to 8 weeks before last menstrual period). **Category 3**	To collect data regarding fingolimod exposure during pregnancy and maternal, fetal and infant outcomes	• Reproductive toxicity	Interim reports: annually (3Q) Final report: 2Q 2031
[CFTY720D2406]: Long -term prospective non-interventional multinational parallel cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or	To further explore the overall safety profile and incidence of selected safety-related outcomes of fingolimod under conditions of routine medical practice. To	• Bradyarrhythmia • Hypertension • Liver transaminase elevation • PRES • Bronchoconstriction • Macular edema • Infections, including opportunistic infections (PML,	Interim reports: annually 3Q Final report: 30-Apr-2021

Study	Summary of objectives	Safety concerns addressed	Milestones
treated with another approved disease-modifying therapy. **Category 3**	observe long-term effectiveness outcomes. To evaluate safety and effectiveness of switch from other disease modifying therapies.	VZV, herpes viral infections other than VZV, fungal infection) • Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma) • ADEM like events • Lymphoma • Other malignant neoplasms • Thrombo-embolic events • QT interval prolongation • Convulsions • Patients with diabetes mellitus • Patients with cardiovascular conditions* • Long-term risk of cardiovascular morbidity/mortality • Long-term risk of malignant neoplasms • Unexplained death • Switch from other disease modifying therapy	
[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	**Core Phase** The primary objective of the Core Phase of the study was to evaluate the efficacy of fingolimod relative to intramuscular IFN β-1a in reducing the frequency of relapses as	• Long-term use in pediatric patients, including impact on growth and development (including cognitive development	Revised protocol: within 2 months from the European Commission Decision for procedure EMEA/H/C/002202/X/0044/G Interim reports: Annually (1st report by 31-Dec-2020) Extension Phase final report: 3Q 2027

Study	Summary of objectives	Safety concerns addressed	Milestones
weekly in pediatric patients with multiple sclerosis, with a five-year fingolimod Extension Phase. **Category 3**	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		

*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.

Table 14-2 Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission / Study report
CFTY720D2399: A single arm, open-label, multicenter study evaluating the long-term safety and tolerability of 0.5 mg fingolimod (FTY720) administered orally	To monitor the safety in patients with MS who received 0.5 mg fingolimod orally once daily	Lymphoma Other malignant neoplasms Long term risk of malignant neoplasms	Clinical Study Report (CSR) published 27-Nov-2017

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission / Study report
once daily in patients with relapsing forms of MS. **Category 3**			
CFTY720D2121 Investigation of 2 different dose-titration regimens of fingolimod on the negative chronotropic effect of fingolimod in healthy subjects. **Category 3**	To investigate 2 different dose-titration regimens of fingolimod on the negative chronotropic effect of fingolimod in healthy subjects.	Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose	**Clinical Study Report (CSR) published 15-Aug-2012**
CFTY720D2316 Tolerability, safety and health outcomes of fingolimod in patients with relapsing forms of MS. **Category 3**	To explore tolerability and safety and health outcomes of fingolimod in patients with relapsing forms of MS.	Bradyarrhythmia (including conduction defects) occurring post-first dose Macular edema	**CSR published 29-Jun-2012**
Physician Survey The effectiveness of the Physician's checklist was assessed using a questionnaire for GILENYA prescribers in selected EU countries. **Category 3**	To assess the knowledge and the stated behavior of the physician with respect to the educational material information on the risk minimization interventions required for the safe use of Gilenya.	• Bradyarrhythmia • Macular edema • Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection) • Liver transaminase • Reproductive toxicity	**14-Oct-2013**
PRIM: Gilenya Pregnancy outcomes Intensive Monitoring (enhanced pharmacovigilance data collection). **Category 3**	To collect data regarding fingolimod exposure during pregnancy and maternal, fetal and infant outcomes	Reproductive toxicity	**Completed 3Q 2019** Enhanced pharmacovigilance data will continu to be represented in the PSURs.

Annex 3 - Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this first or updated version of the RMP.

None

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP.

None

Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority.

Table 14-3 Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority

Study number, Study name (version number)	Procedure number in which protocol was approved
Category 1 and 2 studies in PV plan that were approved	
[CFTY720D2409] (Protocol version 8): Long-term, open-label, multicenter study assessing long-term cardiovascular risks in patients treated with fingolimod.	ANX 11.7
Category 3 studies in PV plan that were not requested to be reviewed	
[FTY720D2403] (Protocol version 2): Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started with fingolimod once daily or treated with another approved disease-modifying therapy.	Not applicable
[FTY720D2404] (Protocol version 2): The Multinational Pregnancy Gilenya Exposure Registry in Multiple Sclerosis.	FUM 014
[FTY720D2406] (Protocol version 3): Long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS recently initiated with fingolimod once daily or treated with another approved disease-modifying therapy	MEA 11.5
[FTY720D2311] (Protocol version 7) 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.	Not applicable

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:

Targeted follow-up checklists:

Identified risk: Bradyarrhythmia (including conductiondefects and bradycardia complicated by hypotension) occurring post first dose

Gilenya Cardiac rate and rhythm disorders checklist

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? ☐ No☐ Yes *(please specify)*

Did the patient receive treatment for the event? ☐ No☐ Yes *(please specify)*

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*)☐ Echocardiogram

☐ Holter monitor (*please include baseline*)☐ Coronary angiography

☐ Blood tests (*e.g. electrolytes*)☐ Electrophysiology study (EPS)

☐ Stress test ☐ Others (*please specify*)

☐ Cardiac biomarkers (specify e.g., creatinine kinase-MB, troponin)

☐ None of the above

Patient history:

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)*☐ Syncope

☐ Valvular disease *(please specify)*☐ Symptomatic bradycardia

☐ Pacemaker (specify if temporary or permanent)

☐ Cardiovascular disease (e.g. angina, CAD, MI, CHF)

☐ Wolff-Parkinson-White syndrome (*please specify*)

☐ Other (e.g. COPD, sleep apnea, hyperthyroidism) (*please specify)*

☐ Congenital heart disease☐ None of the above

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

☐ Antipsychotics/Antidepressants☐ Theophylline

☐ Beta blockers☐ Drugs of abuse (*e.g. cocaine*)

☐ Cholinomimetics *(e.g. metoclopramide)* ☐ Others (*please specify*)

☐ Antiarrhythmics (e.g. quinidine, digoxin, beta-blockers, calcium channel blockers)

☐ Anticonvulsants (e.g. phenytoin, gabapentin, topiramate)

☐ Calcium channel blockers (dihydropyridine or non-)

☐ None of the above

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

- First dose of Gilenya: 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 Gilenya (*fingolimod*) 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*):

Identified risk: Liver transaminase elevation

Liver injury checklist

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
- ☐ 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
☐ Valproic 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
☐ Nicotinic acid ☐ Methotrexate ☐ Other (specify)
☐ None

Identified risk: Bronchoconstriction

Gilenya Breathlessness checklist

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. Signs / symptoms
3. Were any of the following diagnostic tests performed? ►**If yes, please specify which test(s), dates and results**

- ☐ Physical exams
- ☐ Pulmonary Function Tests
- ☐ Imaging studies (e.g. Chest x-ray, CT, MRI, ventilation-perfusion scan)
- ☐ ECG
- ☐ Echocardiography
- ☐ Cardiac biomarkers (e.g., troponin I and CK-MB)
- ☐ Others (specify)
- ☐ None

Does the patient have a history of any of the following?

- ☐ Respiratory diseases (e.g., Asthma, COPD, Interstitial lung disease)
- ☐ Cardiovascular disorders (e.g., acute coronary syndrome, heart failure)
- ☐ Obesity
- ☐ Smoking
- ☐ Familial history of lung disease
- ☐ Occupational or environmental toxins exposure
- ☐ Others (specify)
- ☐ None

Has the patient recently (i.e. within the past 6 months) taken any of the following?

- ☐ NSAIDs
- ☐ Beta Blockers
- ☐ Radiation therapy
- ☐ Chemotherapy (specify)
- ☐ Others (Specify)
- ☐ None

Identified risk: Macular edema

S1P Modulator Macular edema checklist

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-Gilenya®) 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, Optical coherence tomography (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: Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection)

Suspected Progressive Multifocal Leukoencephalopathy checklist

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 report and/or summarize below)* ☐ **No** ☐ **Unknown**

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		

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

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/orage of the patient*) ☐ Yes☐ No☐ Unknown

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

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

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

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 fingolimod/siponimod: ☐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)?
☐ Subacute Headache☐ Nausea/Vomiting☐ Others (*please specify*)
☐ Confusion☐ Seizure(s)_____
☐ Lethargy ☐ Cranial nerve palsies_____
☐ Coma☐ Papilledema
☐ Fever☐ Neck stiffness ☐ None of the above

CBC (specifically absolute lymphocyte 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 fingolimod/Siponimod?

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

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

S1P Modulator and Skin Cancer checklist

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

☐ Location and clinical description of the skin lesion

☐ Biopsy results

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

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

Is the patient a smoker?

☐ Yes ☐ No

►If yes, provide:
- Smoking duration in years
- Number cigarettes a day

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

Identified Risk: Reproductive toxicity; Missing information: Lactating women

Multiple sclerosis- Pregnancy baseline FU checklist

- Please enter dates in DD/MM/YY format
- If the mother experienced an adverse event during pregnancy, please complete Adverse Event Report Form

1. To be populated by Novartis Country Organization		
Report type: ☐ study ☐ spontaneous	for study case:	Study number: Centre number: Patient number:
Country:		

2. Parental demographics		
Who took the drug? ☐ Mother ☐ Father		
	Mother	**Father** (required only if father took the drug)
Race/ Ethnicity:	☐ Asian ☐ Black ☐ Caucasian ☐ Hispanic ☐ Other, specify:	☐ Asian ☐ Black ☐ Caucasian ☐ Hispanic ☐ Other, specify:
Date of birth:		
Age	years	years
Height:	unit: ☐ cm ☐ in	unit: ☐ cm ☐ in
Weight	unit: ☐ kg ☐ lb (at LMP)	unit: ☐ kg ☐ lb

3. Maternal information	
Date of last menstrual period (LMP):	Expected date of delivery (EDD):
Method of EDD calculation: ☐ LMP ☐ Ultrasound ☐ Other, specify:	
Number of fetuses:	

4a. Suspected Novartis medication taken during or just before pregnancy									
Medication name	Dose/ times a day	Route of administration	Indication	If exact dates are unknown, enter gestation period, e.g. '2 weeks prior to last menstrual period'		Exposure by trimester*: enter yes, No, UNK (unknown)			
				Start date	Stop Date	Pre**	1st	2nd	3rd

4b. Other medications taken by the mother during pregnancy (including over-the-counter products)									

* 1st: week 0-12 2nd: week 13-26 3rd: week 27 onwards
** ''Pre'' refers to washout period of drug after stopping the medicine: for fingolimod = 8 weeks (2months), siponimod = 10 days, ofatumumab = 6 months

5. Contraception

Was contraception used? ☐ Yes ☐ No ☐ Unknown

Method of contraception
☐ oral contraceptive, specify name:
☐ intra-uterine device ☐ transdermal ☐ subcutaneous implant
☐ condom ☐ spermicide ☐ other, specify:

Do you think there was a failure in contraception? ☐ Yes ☐ No ☐ Unknown
Cause/reason for failure:

6. Prenatal tests

Prenatal test name	Test date	Abnormal results?			Test result (specify any abnormality)
		Yes	No	Not available	
		☐	☐	☐	
		☐	☐	☐	
		☐	☐	☐	

7. Maternal risk factors or conditions that may affect the outcome of the current pregnancy

☐ Smoking	
☐ Alcohol	
☐ Recreational drugs	Specify drugs used:
☐ Hypertension	
☐ Heart disease	Specify disease:

☐ Seizure	
☐ Diabetes	Specify type:
☐ Eclampsia	
☐ Pre-eclampsia	
☐ Thyroid disorder	Specify disorder:
☐ Infections	Specify infection:
☐ Environmental or occupational exposure	Specify exposure:
☐ History of infertility	
☐ Fertility treatment	Specify treatment:
☐ Autoimmune disease	Specify:
☐ Other	Specify:

8. Multiple sclerosis (MS) history

Duration of MS disease :

Is the patient mobile? ☐ Yes ☐ No EDSS:

Relapse just before or during current pregnancy

☐ Yes, date: ☐ No ☐ Unknown

Treatment given for the relapse (e.g. corticosteroid):

Current course of MS

☐ Primary progressive ☐ Secondary progressive

☐ Relapsing remitting ☐ Other, specify:

9. Previous obstetric history (provide details on all previous pregnancies below, including abortion or stillbirth)

Total number of prior pregnancies:

#	Gestation weeks at end of pregnancy	Outcome of pregnancy		Fetal/neonatal abnormalities or complications
1		☐ live birth ☐ spontaneous abort.	☐ therapeutic abort. ☐ elective termination	
2		☐ live birth ☐ spontaneous abort.	☐ therapeutic abort. ☐ elective termination	
3		☐ live birth ☐ spontaneous abort.	☐ therapeutic abort. ☐ elective termination	
4		☐ live birth ☐ spontaneous abort.	☐ therapeutic abort. ☐ elective termination	

10. Family history

	Fetal malformations or other poor pregnancy outcomes (e.g. congen. anomaly or mental retardation) in the immediate family	Family side	Relationship
1		☐ maternal ☐ paternal	

2		☐ maternal ☐ paternal	
3		☐ maternal ☐ paternal	

11. Any additional comments:

12. In order for us to maintain complete product safety information, we would like to obtain additional medical details concerning this case therefore, with patient consent, we would like to contact the treating physician(s) concerning this report. If you agree, please provide the following information:	
Role:	Name, Address, phone number, email:
☐ Obstetrician ☐ Midwife ☐ other specialist, specify:	

13. Reporter Information	
Name, Address:	
Phone number:	
Reporter type: ☐ Obstetrician ☐ Other physician ☐ Non-healthcare professional ☐ Paediatrician ☐ Midwife ☐ other, specify:	
Date:	Signature:

Please contact Novartis as soon as possible after the pregnancy has ended.

Multiple Sclerosis–Pregnancy Outcome (Estimated Date of Delivery+ one month) Follow-up Checklist

- Please enter dates in DD/MM/YY format
- If the mother experienced an adverse event during pregnancy, please complete Adverse Event Report Form

1. To be populated by Novartis Country Organization		
Report type:☐ study ☐ spontaneous	for study case:	Study number: Centre number: Patient number:
Country:		

2a. Suspected Novartis medication taken during or just before pregnancy									
Medication name	Dose/ times a day	Route of administration	Indication	If exact dates are unknown, enter gestation period, e.g. '2 weeks prior to last menstrual period'		Exposure by trimester*: enter yes, No, UNK (unknown)			
				Start date	Stop Date	Pre**	1st	2nd	3rd
2b. Other medications taken by the mother during pregnancy (including over-the-counter products)									

* 1st: week 0-12 2nd: week 13-26 3rd: week 27 onwards
** ''Pre'' refers to washout period of drug after stopping the medicine: for fingolimod = 8 weeks (2months), siponimod = 10 days, ofatumumab = 6 months

3. Prenatal tests					
Prenatal test name	Test date	Abnormal results?			Test result (specify any abnormality)
		Yes	No	Not available	
		☐	☐	☐	
		☐	☐	☐	
		☐	☐	☐	

Pregnancy outcome		
☐ **4. Live birth**	Date of birth:	Gestation weeks at birth:
	Timing of delivery: ☐ Full-term (between 37 and 42 weeks of gestation) ☐ Premature (before 37 completed weeks of gestation) ☐ Post-mature (after 42 weeks of gestation)	
	Normal (healthy) baby ☐ Yes ☐ No	
	Neonate demographics (at birth): Sex: ☐ male ☐ female Length: unit: ☐ cm ☐ in ☐ percentile: Weight: unit: ☐ kg ☐ lb ☐ percentile: Head circumference: unit: ☐ cm ☐ in Small for gestational age: ☐ Yes☐ No Apgar scores: 1 min : 5 mins : 10 mins :	
	Is the baby still alive?☐ Yes ☐ No, date of death: Cause of death and autopsy result (if available):	
☐ **5.Termination** (up to 22 completed weeks gestation)	Date of termination:	Gestation weeks at termination:
	Type of termination: ☐ spontaneous abortion / miscarriage ☐ induced termination ☐ therapeutic reason (maternal or fetal complication) ☐ elective termination	
	Medical problems: ☐ Blighted ovum ☐ Molar pregnancy / Hydatidiform mole ☐ Ectopic pregnancy ☐ Other, specify:	
☐ **6.Stillbirth** (after 22 completed weeks gestation)	Date of stillbirth:	Gestation weeks at stillbirth:
	Was an autopsy performed? ☐ Yes ☐ No ☐Unknown If yes, please provide the result attached to this form and give brief details here:	

7. Anomalies in the baby or fetus
Were any anomalies noted for the baby or fetus? ☐ Yes ☐ No ☐Unknown
Describe all anomalies:
Were any of the anomalies of known genetic origin: ☐ No ☐ Yes please specify:
If there were congenital malformation was at least one major? (i.e. requires medical or surgical treatment, has serious adverse effect on health/development or has significant cosmetic impact): ☐ Yes ☐ No, only minor ☐None ☐ Unknown

8. Delivery/Labour
Mode of delivery: ☐ Normal delivery ☐ Caesarean section ☐ Others, specify:

9. Complication during or after delivery
☐ None ☐ Intrauterine death ☐ Other, specify:

10. Causal relationship
What is the causal relationship between reported medication and **the outcome of the pregnancy?** ☐ Not suspected ☐ Suspected ☐ Not assessable

11. Any additional comments:

12. In order for us to maintain complete product safety information, we would like to obtain additional medical details concerning this case therefore, with patient consent; we would like to contact the treating physician(s) concerning this report. If you agree, please provide the following information:	
Role:	Name, Address, phone number, email:
☐ Obstetrician ☐ Midwife ☐ Other specialist, specify:	

13. Reporter Information	
Name, Address:	
Phone number:	
Reporter type: ☐ Obstetrician ☐ Other physician ☐ Non-healthcare professional ☐ Paediatrician ☐ Midwife ☐ other, specify:	
Date:	Signature:

Multiple Sclerosis- – Infant Health status follow-UP During first year following drug exposure in pregnancy

- Please enter dates in DD/MM/YY format

1. To be populated by Novartis Country Organization		
Report type: ☐ study ☐ spontaneous	for study case:	Study number: Centre number: Patient number:
Country:		

2. Infant Demographics		
Status ☐ living	Infant date of birth:	Infant gender:
	Date of measurement:	Infant age at measurement(in months):
	Weight: unit: ☐ kg ☐ lb ☐ percentile specify:	
	Length: unit: ☐ cm ☐ in ☐ percentile specify:	
	Head circumference: unit: ☐ cm ☐ in	
☐ deceased	Date of death:	Infant age at death in months:
	Cause of death (please provide autopsy report if available):	

3. Infant Health Status		
Have any congenital malformations been identified since birth? ☐ Yes ☐ No ☐ Unknown	If yes, please specify:	Diagnosis date:
Did malformations reported at or since birth resolve by themselves? ☐ Yes ☐ No ☐ Unknown	If no, please indicate the details including any medical intervention or surgical treatment:	
Has the infant experienced infection requiring hospitalization?	Please specify diagnosis, labs and infection site if known:	Event start date and end date:

☐ Yes ☐ No ☐ Unknown	Treatment given and outcome:	

4. Breastfeeding
Is the infant breast-fed? (Including partially) ☐ yes, currently ☐ has been weaned, date or infant age at weaning: ☐ no ☐ unknown

5. Developmental Delay			
Has the doctor diagnosed the child with any developmental delay?	☐ Yes ☐ No ☐ Unknown	Age at diagnosis (in months):	If yes, is it: ☐ physical ☐ mental/cognitive Please provide more details:

6. Infant Vaccination		
Has the baby received all vaccinations as recommended?	☐ Yes ☐ No ☐ Unknown	**If No,** please provide details:
Has the child had any reaction after vaccination that needed medical care/ to be seen by a doctor?	☐ Yes ☐ No ☐ Unknown	If yes, Please specify:

7. Any additional comments:

8. In order for us to maintain complete product safety information, we would like to obtain additional medical details concerning this case therefore, with patient consent; we would like to contact the treating physician(s) concerning this report. If you agree, please provide the following information:	
Role:	Name, Address, phone number, email:
☐ Pediatrician ☐ General physician ☐ Other specialist, specify:	

9. Reporter Information	
Name, Address:	
Phone number:	
Reporter type: ☐ Obstetrician ☐ Other physician ☐ Non-healthcare professional ☐ Paediatrician ☐ Midwife ☐ other, specify:	
Date:	Signature:

Identified Risk: Convulsions

Seizures checklist

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

EVENT DESCRIPTION: Did the patient present with any of the following signs/symptoms? Check/circle all that apply and please describe

Aura

☐ Visual disturbance ☐ Headache ☐ Nausea/Abdominal Sensation

☐ Depression/irritability/ sleep disruption ☐ Déjà vu/ jamais vu/ smell/ sound/taste

☐ Fear/ Panic

☐ Changes in bodily sensations, ability to interact, unfamiliarity with outside world

☐ No Aura

☐ Dizziness/lightheadedness

Post-ictal: ☐ Memory loss ☐ Confusion ☐ Weakness ☐ Somnolence ☐ Lethargy

Classification of current seizure: Please check all that apply

Generalized Seizures (produced by the entire brain)

Seizure classification	Symptoms
☐ "Grand Mal" or Generalized tonic-clonic	☐ Unconsciousness, convulsions, muscle rigidity
☐ Absence	☐ Brief loss of consciousness
☐ Myoclonic	☐ Sporadic (isolated), jerking movements
☐ Clonic	☐ Repetitive, jerking movements
☐ Tonic	☐ Muscle stiffness, rigidity
☐ Atonic	☐ Loss of muscle tone

Focal Seizures (produced by a small area of the brain)

Seizure classification	Symptoms
☐ Aura (formerly simple somatosensory)	☐ Jerking, muscle rigidity, spasms, head-turning
☐ Motor	☐ Unusual sensations affecting either the vision, hearing, smell taste or touch
☐ Autonomic	☐ Memory or emotional disturbances
	☐ Dyscognitive (formerly complex) ☐ Automatisms such as lip smacking, chewing,

fidgeting, walking and other repetitive, involuntary but coordinated movements

☐ Focal seizure secondarily generalized

☐ Symptoms initially associated with a preservation of consciousness that evolves into a loss of consciousness and convulsions

Were the seizures witnessed? ☐ Unknown ☐ No ☐ Yes *(please describe and if possible, include type and duration)*

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

☐ Neurological investigations (e.g. EEG, CT scan, MRI scan, PET, SPECT, video-EEG, lumbar puncture) ☐ Other (specify)

☐ General investigations (e.g. CBC, blood chemistry, urinalysis, alcohol screen, toxic screen)
☐ None of the above

Did the patient have a prior history of seizure? If yes, please provide classification and description:

_____
_____
_____

Relevant medical history (concurrent and pre-existing conditions)

(Please specify medical condition and date of onset)

☐ Temporary condition (exposure to drugs, drug withdrawal, high fever, abnormal sodium, calcium or glucose levels)

☐ Genetic disease or familial predisposition

☐ Idiopathic seizures

☐ Use of barbiturates/benzodiazepines

☐ Drugs of abuse (e.g. Cocaine)

☐ Brain tumor or other structural brain lesion (e.g. bleeding)

☐ Congenital brain defects

☐ Kidney or liver failure

☐ Traumatic brain injury, stroke, or a transient ischemic attack

☐ Peri or postpartum brain injury

☐ Phenylketonuria (PKU)

☐ Stopping alcohol after drinking heavily on most days

☐ Dementia (e.g. Alzheimer's disease)

☐ Sleep disorders

☐ Infections (brain abscess, meningitis, encephalitis, neurosyphilis, AIDS)

☐ Illness resulting in brain deterioration

☐ Psychiatric disorders

☐ Hyperventilation

☐ Emotional stress

☐ Migraines with focal symptoms or aura

☐ Menstrual cycle *(please specify (e.g. day 1, ovulation, second half cycle)*

☐ None

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

☐ Antibiotics (e.g., penicillin, ampicillin, carbenicillin, cephalosporin)☐ Antidepressants (e.g. bupropion, tricyclics)

☐ Analgesics (e.g., Fentanyl, mefenamic acid, tramadol, meperidine)☐ Drugs of abuse

☐ Antineoplastic agents (e.g., busulfan, carmustine, chlorambucil, methotrexate)

☐ Phenothiazines

☐ Antipsychotic medications (e.g. chlorpromazine, haloperidol, clozapine, atypicals)

☐ Metoclopramide

☐ Bronchial agents (e.g., aminophylline, theophylline)

☐ Lithium

☐ Sympathomimetics (e.g., ephedrine, phenylpropanolamine, terbutaline)

☐ General/local anesthetics (e.g., enflurane, ketamine, methohexital, bupivacaine, lidocaine, procaine)

☐ OTC and/or natural remedies (please specify)

☐ Immunosuppressants (steroids, cyclosporine)

☐ Anticonvulsants

☐ None of the above

Potential risks: Other malignant neoplasms; Lymphoma

Malignancy & Neoplasm checklist

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
- Symptoms
- Location
- Is the cancer localized? If not, please provide details on further locations:
- Location of biopsy site(s) and result (**for lymphomas, please provide lymph node biopsy or an English summary 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:
- Status of patient/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 checklist

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

1. Has the patient been vaccinated for HPV?

   ☐ Yes: Date: ____/____/____

   ☐ No

   ☐ Don't know

2. 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 _____

   ☐ No

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: _____

    ☐ Cancer Type: _____

☐ Don't know

☐ 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? _____

Potential risk: Thrombo-embolic events

Stroke checklist

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

Event Description:

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

☐ Unexplained change in the pattern of headaches

☐ Difficulty understanding when spoken to/Receptive aphasia

☐ Difficulty walking or an unexplained fall

☐ Cerebral topographical localization *(please specify)*

☐ Sensory deficit☐ Difficulty swallowing

☐ Blurred or poor vision in one or both eyes☐ Unexplained dizziness

☐ Motor deficit (e.g. paralysis, paresis)☐ Unconsciousness

☐ Headache (severe or of abrupt onset) ☐ Dysarthria

☐ Difficulty speaking/Expressive aphasia☐ Loss of balance or coordination

☐ Disorientation to place, time, person☐ Confusion

☐ Other *(please specify)*☐ None of the above

What type of stroke(s) was/were reported? (*please specify,* e.g., ischemic, hemorrhagic, TIA)

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

☐ Electroencephalogram (EEG)☐ Electrocardiogram (ECG)

☐ Imaging studies (i.e. CT scan, MRI scan, magnetic resonance angiography)

☐ Blood or urine tests☐ None of the above

Patient History:

Did the patient have a history of any of the following prior to the start of the suspect drug? **Check all that apply**

☐ Hypertension☐ Diabetes

☐ Peripheral vascular disease☐ Head injury

☐ Smoking☐ Hyperlipidaemia

☐ Migraine☐ Malignancy or neoplasm

☐ Cerebral Vascular Attacks or Transient Ischemic Attacks *(please explain)*

☐ Cardiovascular disease including cardiac arrhythmias, rheumatic heart disease, or recent myocardial infarction (MI) *(please explain)*

☐ Hypercoaguable disease/disorder (e.g. polycythaemia, sickle cell anemia, dysproteinemia)

☐ Drug abuse (i.e. cocaine, amphetamines, heroin)

☐ None of the above

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

☐ Ergotamines ☐ Antihypertensive agents

☐ Lipid lowering agents☐ Anticoagulants

☐ Oral contraceptives/Hormone therapy☐ None of the above

Ischemic heart disease/myocardial infarction checklist

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

Event Description:

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

☐ Angina pectoris (chest pain on exertion or stress) ☐ Nausea/Vomiting

☐ Choking pain ☐ Oedema in extremities

☐ Tightness or squeezing in the chest ☐ Restlessness

☐ Pain in left arm ☐ Fatigue

☐ Cold, clammy or pale skin ☐ Sweating

☐ Pain in jaw ☐ Pallor

☐ Decreased urine output ☐ Fever

☐ Shortness of breath ☐ Palpitation

☐ Loss of consciousness ☐ Musculoskeletal pain

☐ Dizziness ☐ None of the above

When did the symptoms begin?

☐ During exercise ☐ At rest ☐ During sleep ☐ Other *(please specify)*

What was the duration of the symptoms?

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

☐ ECG ☐ Echocardiogram ☐ Stress test ☐ Chest x-ray

☐ Blood test (e.g. cholesterol levels, thyroid function tests, blood glucose, CPK levels, troponin)

☐ Coronary angiography/Cardiac catheterization ☐ None of the above

Patient History:

Does the patient have a history of any of the following prior to the start of the suspect drug? **Check all that apply.**

☐ Diabetes ☐ Hypertension ☐ Hyperlipidemia ☐ Hyperthyroidism

☐ Obesity ☐ Hypothyroidism ☐ Alcohol abuse ☐ Sleep apnea

☐ Smoker ☐ Myocardial infarction ☐ Bradycardia ☐ Syncope

☐ Drugs of abuse (e.g. cocaine) ☐ Transient ischemic attack/Stroke

☐ Prolonged QT interval ☐ Obliterating arteriopathy of the lower limb

☐ Limited physical activity *(please specify)*

☐ Family history of myocardial infarction *(please specify)*

☐ None of the above

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

☐ Antihypertensives ☐ Ergotamines and derivatives

☐ Beta-Blockers ☐ Antiarrhythmic agents

☐ Antipsychotics (e.g. haloperidol, pimozide) ☐ Oral contraceptives

☐ Calcium channel blockers (please specify dihydropyridine or non-dihydropyridine)

☐ Antibiotics (e.g. erythromycin, clarithromycin) ☐ None of the above

Missing information: Unexplained death

Gilenya Sudden/unexplained death checklist

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

Event Description:

DD	MM	YYYY

Date of death

Autopsy performed? ☐ Yes (please include results) ☐ No

Cause of death (if patient was hospitalized, provide relevant information):_____

Circumstance of the death

- Was death related to neurological complications/directly related to MS? ☐ Yes ☐ No
- Was the death witnessed? ☐ Yes ☐ No (please include date and any information about the health of the patient when last seen alive)
- Was death self-inflicted? ☐ Yes (suicide) ☐ Yes (accidental) ☐ No
- Was death inflicted by others? ☐ Yes (euthanasia) ☐ Yes (accidental) ☐ Yes (criminal) ☐ No
- Were any symptoms or signs noted at the time patient was last seen? (e.g. convulsions, foaming at the mouth, confusion, tongue biting, etc.) ☐ Yes (please specify) ☐ No
- Was a collapse/loss of consciousness witnessed? ☐ Yes (please describe any signs or symptoms) ☐ No
- Were there any attempts to resuscitate the patient? ☐ Yes (please describe the initial response to treatment if applicable) ☐ No
- What was the initial cardiac rhythm noted? (e.g. ventricular fibrillation, Torsades de Pointes, etc.)
- Were any of the following diagnostic tests performed? Check all that apply and please specify which test(s), dates and results

☐ Relevant recent investigations during life (e.g. positive stress ECG, angiograms, ECG, Holter monitor, investigations for epilepsy, electrolytes, etc.)

☐ Death certificate, and/or post-mortem findings

☐ Recent blood work ☐ None of the above

Patient History:

Does the patient have a history of any of the following? **Check all that apply**

☐ Unexplained syncope ☐ Asthma/COPD

☐ Alcohol intake, drugs of abuse (please specify) ☐ Diabetes

☐ Cardiovascular disease (*please specify*)☐ Obesity

☐ Family history of sudden death*(please specify)*☐ Thyrotoxicosis

☐Sleep apnea ☐ Major surgery

☐ Epilepsy/Seizures☐ Malignancies

☐ Thromboembolic or haemorrhagic events including CVA, TIA

☐ Psychiatric disorders (e.g. schizophrenia or psychosis)

☐ Other relevant history *(please specify)* ☐ None of the above

Describe all concomitant medication taken by the patient (describe therapy dates, indication, dose and posology):

Fingolimod therapy:

Dates of treatment initiation, interruption and reason

Start date			Stop date			Reason for interruption
DD	MM	YYYY	DD	MM	YYYY	

If treatment started (or restarted after interruption of more than 2 weeks) at any time prior to death, please provide first dose details:

All available hourly heart rate, blood pressure, ECG/Holter with date/time

Heart rate at baseline: Date: ____/____/____Rate: _____ bpm

The minimum heart rate measured during the first dose observation period: _____ bpm

The time interval between the last dose of Gilenya (fingolimod) and the minimum heart rate: _____ minutes / hours / days / weeks (please specify units)

Did the patient experience any symptoms during first dose observation period?

☐ Yes (please list the symptoms and provide the blood pressure at the time of the event)

☐ No

Did the patient experience any cardiovascular event during first dose observation period?

☐ Yes (please specify, indicate if any treatment for the event was administered and provide details on any ECG abnormalities observed)

☐ No

Annex 5 - Protocols for proposed and ongoing studies in RMP part IV

There are no proposed or ongoing studies in the post authorization efficacy development plan as stated in RMP Part IV.

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

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

Approved Key Messages of the Additional Risk Minimization Measures

Physician's checklist

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

- Monitoring requirements at treatment initiation

  Before first dose

  - Perform baseline ECG prior to the first dose of GILENYA
  - Perform blood pressure measurement prior to the first dose of GILENYA
  - Perform liver function test, including transaminases and bilirubin, prior to (within 6 months) treatment initiation
  - Arrange ophthalmological assessment before starting GILENYA treatment in patients with diabetes mellitus or with a history of uveitis
  - A negative pregnancy test result must be confirmed prior to starting treatment

  Until 6 hours after first dose

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

  >6 to 8 hours after first dose

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

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

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

monitoring at treatment initiation/re-initiation. Repeat the first dose monitoring after the second dose of GILENYA.

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

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

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

- If GILENYA treatment is considered in these patients anticipated benefits must outweigh potential risks and a cardiologist must be consulted to determine appropriate monitoring, at least overnight extended monitoring is recommended.
- GILENYA is not recommended in patients concomitantly taking medicines known to decrease the heart rate. If GILENYA treatment is considered in these patients anticipated benefits must outweigh potential risks and a cardiologist must be consulted to switch to non heart-rate-lowering therapy or, if not possible, to determine appropriate monitoring. At least overnight extended monitoring is recommended.
- GILENYA reduces peripheral blood lymphocyte counts. Peripheral lymphocyte count (CBC) should be checked in all patients prior to initiation (within 6 months or after discontinuation of prior therapy) and monitored during treatment with GILENYA. Treatment should be interrupted if lymphocyte count is confirmed as $<0.2x10^9$/L. The approved dosing of 0.5 mg once daily (or 0.25 mg once daily in pediatric patients 10 years of age and above with a body weight of ≤ 40 kg) when restarting Gilenya should be administered. Other dosing regimens have not been approved.
- GILENYA has an immunosuppressive effect that predisposes patients to an infection risk, including opportunistic infections that can be fatal, and increases the risk of developing lymphomas (including mycosis fungoides) and other malignancies, particularly those of the skin. Surveillance should include vigilance for both skin malignancies and mycosis fungoides. Physicians should carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis.
    - Treatment initiation in patients with severe active infection should be delayed until the infection is resolved. Suspension of treatment during serious infections should be considered. Anti-neoplastic, immunomodulatory or immunosuppressive therapies should not be co-administered due to the risk of additive immune system effects. For the same reason, a decision to use prolonged concomitant treatment with corticosteroids should be taken after careful consideration.
    - Vigilance for basal cell carcinoma and other cutaneous neoplasms including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma is recommended, with skin examination prior to treatment initiation and then every 6 to 12 months taking into consideration clinical judgement. Patients should be referred to a dermatologist if suspicious lesions are detected. Caution patients against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

- Specific recommendations regarding vaccination for patients initiating GILENYA treatment.
    - Check varicella zoster virus (VZV) antibody status in patients without a healthcare professional confirmed history of chickenpox or documentation of a full course of varicella vaccination. If negative, a full course of vaccination with varicella vaccine is

recommended and treatment initiation should be delayed for 1 month to allow full effect of vaccination to occur.

- Patients should be instructed to report signs and symptoms of infections immediately to their prescriber during and for up to two months after treatment with GILENYA.
  - Prompt diagnostic evaluation should be performed in patient with symptoms and signs consistent with encephalitis, meningitis or meningoencephalitis; appropriate treatment, if diagnosed, should be initiated.
  - Serious, life-threatening, and sometimes fatal cases of encephalitis, meningitis or meningoencephalitis caused by herpes simplex virus (HSV) and VZV were reported while on GILENYA treatment.
  - Reports of cryptococcal meningitis (sometimes fatal) have been received after approximately 2-3 years of treatment, although an exact relationship with the duration of treatment is unknown
  - Cases of progressive multifocal leukoencephalopathy (PML) have occurred after approximately 2-3 years of monotherapy treatment although an exact relationship with the duration of treatment is unknown. Physicians should be vigilant for clinical symptoms or MRI findings suggestive of PML. If PML is suspected, treatment with GILENYA should be suspended until PML has been excluded.
  - Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported in the post-marketing setting. Cancer screening, including Pap test, and vaccination for HPV-related cancer is recommended for patients, as per standard of care.
- A full ophthalmological assessment should be considered:
  - 3-4 months after starting GILENYA therapy for the early detection of visual impairment due to drug-induced macular edema.
  - During treatment with GILENYA in patients with diabetes mellitus or with a history of uveitis.
- GILENYA is teratogenic. It is contraindicated in women of childbearing potential (including female adolescents) not using effective contraception and in pregnant women,
  - A negative pregnancy test result must be confirmed prior to starting treatment, and it must be repeated at suitable intervals.
  - Women of child-bearing potential, including adolescent females, their parents (or legal representatives), and caregivers, should be counselled before treatment initiation and regularly thereafter about the serious risks of GILENYA to the foetus, facilitated by the pregnancy-specific patient reminder card.
  - Women of childbearing potential must use effective contraception during treatment and for two months following treatment discontinuation.
  - While on treatment, women must not become pregnant. If a woman becomes pregnant while on treatment, GILENYA must be discontinued. When stopping GILENYA therapy due to pregnancy or for planning a pregnancy, the possible return of disease activity should be considered. Medical advice should be given regarding the risk of

harmful effects to the foetus associated with GILENYA treatment and ultrasonography examinations should be performed.
  - GILENYA must be stopped 2 months before planning a pregnancy.
  - Physicians are encouraged to enroll pregnant patients, or pregnant women may register themselves in the GILENYA pregnancy registry.

- Some cases of acute liver failure requiring liver transplant and clinically significant liver injury have been reported. Therefore, liver function should be monitored carefully.
  - Before initiation of treatment, recent (i.e. within last 6 months) transaminase and bilirubin levels should be available;
  - During treatment, in the absence of clinical symptoms, liver transaminases and serum bilirubin should be monitored at months 1, 3, 6, 9 and 12 on therapy and periodically thereafter until 2 months after Gilenya discontinuation;
  - 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;
- The approved dosing of 0.5 mg daily (or 0.25 mg once daily in pediatric patients 10 years of age and above with a body weight of ≤40 kg) should be administered. Other dosing regimens have not been approved.
- In the post-marketing setting, severe exacerbation of disease has been observed rarely in some patients stopping GILENYA. The possibility of recurrence of exceptionally high disease activity should be considered.
- Cases of seizure, including status epilepticus, have been reported. Physicians should be vigilant for seizures and especially in those patients with underlying conditions or with a pre-existing history or family history of epilepsy.
- Physicians should reassess on an annual basis the benefit of GILENYA treatment versus risk in each patient, especially pediatric patients.
- Physicians should provide patients/parents/caregivers with the patients/parents/caregiver's guide and with the pregnancy-specific patient reminder card.

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

Specifically, with pediatric patients, physicians should also:
- Assess Tanner staging and measure height and weight as per standard of care;
- Perform cardiovascular monitoring;
- Take precautions when the first dose is administered / patients are switched from 0.25 to 0.5 mg daily, due to the potential for bradyarrhythmia;

- Monitor the patient for sign and symptoms of depression and anxiety;
- Emphasize treatment compliance and misuse to patients, especially about treatment interruption and the importance of repeating cardiovascular monitoring;
- Emphasize GILENYA immunosuppressive effects;
- Consider a complete vaccination schedule before starting GILENYA;
- Provide guidance on seizure monitoring.

Patient/Parent/Caregiver's guide

The patient/parents/caregiver guide shall contain the following key messages:

- What GILENYA is and how it works;
- What multiple sclerosis is;
- Patients should read the package leaflet thoroughly before starting treatment and should keep it in case they need to refer to it again during treatment;
- Importance of reporting adverse reactions;
- Patients should have a baseline ECG and blood pressure measurement prior to receiving the first dose of GILENYA.
- Heart rate should be monitored for 6 or more hours after the first dose of GILENYA, including hourly pulse and blood pressure checks. Patients may be monitored with a continuous ECG during the first 6 hours. An ECG at 6 hours should also be performed and, in some circumstances, monitoring may involve an overnight stay.
- Patients should call their doctor in case of treatment interruption as the 1st dose monitoring may need to be repeated, depending on duration of interruption and time since starting of GILENYA treatment.
- Patients should report immediately symptoms indicating low heart rate (such as dizziness, vertigo, nausea or palpitations) after the first dose of GILENYA.
- GILENYA is not recommended in patients with cardiac disease or those taking medicines concomitantly known to decrease heart rate, and they should tell any doctor they see that they are being treated with GILENYA.
- Signs and symptoms of infection, which should be immediately reported to the prescriber physician during and up to two months after GILENYA treatment, including the following:
    - Headache accompanied by stiff neck, sensitivity to light, fever, flu-like symptoms, nausea, rash, shingles and/or confusion or seizures (fits) (may be symptoms of meningitis and/or encephalitis, either caused by a fungal or viral infection);
    - Symptoms such as weakness, visual changes, or new/worsening MS symptoms (may be symptoms of progressive multifocal leukoencephalopathy [PML]).

- The need to undergo cancer screening, including Pap test, and vaccination for HPV-related cancer, as per standard of care, will be assessed by the prescriber physician.
- Any symptoms of visual impairment should be reported immediately to the prescriber during and for up to two months after the end of treatment with GILENYA.
- GILENYA is teratogenic. Women of child-bearing potential, including adolescent females, should:

  - Be informed before treatment initiation and regularly thereafter by their physician about GILENYA's serious risks to the foetus, and about the contraindication in pregnant women and in women of childbearing potential not using effective contraception, facilitated by the pregnancy-specific patient reminder card.
  - Have a negative pregnancy test before starting GILENYA;
  - Be using effective contraception during and for at least two months following discontinuation of GILENYA treatment;
  - Report immediately to the prescribing physician any (intended or unintended) pregnancy during and up to two months following discontinuation of GILENYA treatment;
- A liver function test should be performed prior to treatment initiation; liver function monitoring should be performed at months 1, 3, 6, 9 and 12 during GILENYA therapy and periodically thereafter, until 2 months after Gilenya discontinuation. Patients should inform their doctor if they notice yellowing of their skin or the whites of their eyes, abnormally dark urine, pain on the right side of the stomach area, tiredness, feeling less hungry than usual or unexplained nausea and vomiting as these can be signs of liver injury;
- Skin cancers have been reported in multiple sclerosis patients treated with GILENYA. Patients should inform their doctor immediately if any skin nodules (e.g., shiny, pearly nodules), patches or open sores that do not heal within weeks are noted. Symptoms of skin cancer may include abnormal growth or changes of skin tissue (e.g., unusual moles) with a change in colour, shape or size over time;
- Seizure may occur. The doctor should be informed about a pre-existing history or family history of epilepsy;
- Stopping GILENYA therapy may result in return of disease activity. The prescribing physician should decide whether and how the patient should be monitored after stopping GILENYA.

Specifically for Pediatric patients:

The following should be considered:

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

Pregnancy-specific patient reminder card

The pregnancy-specific patient reminder card shall contain the following key messages:

- GILENYA is contraindicated during pregnancy and in women of childbearing potential not using effective contraception;
- Doctors will provide counselling before treatment initiation and regularly thereafter regarding the teratogenic risk of GILENYA and required actions to minimise this risk.
- Patients must use effective contraception while taking GILENYA;
- A pregnancy test must be carried out and negative results verified by the doctor before starting treatment. It must be repeated at suitable intervals;
- Patients will be informed by their doctor of the need foreffective contraception while on treatment and for 2 months after discontinuation;
- Doctors will provide counselling in the event of pregnancy and evaluation of the outcome of any pregnancy;
- While on treatment, women must not become pregnant. If a woman becomes pregnant or wants to become pregnant, GILENYA must be discontinued;
- Patients should inform their doctor straight away if there is worsening of multiple sclerosis after stopping treatment with GILENYA;
- Women exposed to GILENYA during pregnancy are encouraged to join the pregnancy exposure registry that monitors outcomes of pregnancy.

Annex 7 - Other supporting data (including referenced material)

Brief Statistical Description and Supportive Outputs

The [Brief Statistical Description portion and Supportive Outputs of Annex 7] is presented separately.

MedDRA Search terms for clinical trial data

Bradyarrhythmia and bradycardia, hypotension and malaise (Novartis MedDRA query; NMQ): Bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ), PTs: Bradycardia, Electrocardiogram RR interval prolonged, Heart rate decreased, Syncope; Hypotension [GILENYA] (NMQ): PTs: Blood pressure ambulatory decreased, Blood pressure decreased, Blood pressure diastolic decreased, Blood pressure immeasurable, Blood pressure orthostatic decreased, Blood pressure systolic decreased, CT hypotension complex, Diastolic hypotension, Dizziness postural, Hypotension, Mean arterial pressure decreased, Neonatal hypotension, Orthostatic hypotension, Procedural hypotension, Altered state of consciousness, Blood pressure abnormal, Blood pressure ambulatory abnormal, Blood pressure diastolic abnormal, Blood pressure fluctuation, Blood pressure inadequately controlled, Blood pressure orthostatic abnormal, Blood pressure systolic abnormal, Blood pressure systolic inspiratory decreased, Consciousness fluctuating, Depressed level of consciousness, Dizziness, Dizziness exertional, Labile blood pressure, Loss of consciousness, Presyncope, Schellong test, Syncope, Tilt table test positive; PT: Malaise

Bradyarrhythmias and bradycardia NMQ (narrow): PTs: Accessory cardiac pathway, Adams-Stokes syndrome, Agonal rhythm, Atrial conduction time prolongation, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Atrioventricular conduction time shortened, Atrioventricular dissociation, Bifascicular block, Bradyarrhythmia, Bradycardia, Brugada syndrome, Bundle branch block, Bundle branch block bilateral, Bundle branch block left, Bundle branch block right, Conduction disorder, Defect conduction intraventricular, Electrocardiogram delta waves abnormal, Electrocardiogram PQ interval prolonged, Electrocardiogram PQ interval shortened, Electrocardiogram PR prolongation, Electrocardiogram PR shortened, Electrocardiogram QRS complex prolonged, Electrocardiogram QT prolonged, Electrocardiogram 3 epolarization abnormality, Electrocardiogram RR interval prolonged, Heart rate decreased, Lenegre’s disease, Long QT syndrome, Nodal arrhythmia, Nodal rhythm, Paroxysmal atrioventricular block, Sinoatrial block, Sinus arrest, Sinus arrhythmia, Sinus bradycardia, Sinus node dysfunction, Trifascicular block, Ventricular asystole, Ventricular dyssynchrony, Wandering pacemaker, Wolff-Parkinson-White syndrome

Liver transaminase elevation: SMQs (broad): Cholestasis and jaundice of hepatic origin, Drug related hepatic disorders-severe events only, Liver related investigations, signs and symptoms

Posterior Reversible Encephalopathy Syndrome (PRES): PT Posterior reversible encephalopathy syndrome

Macular oedema (NMQ) (narrow): PTs Cystoid macular oedema, diabetic retina oedema, macular cyst, macular oedema, retinal oedema, optical coherence tomography abnormal and subretinal fluid.

Pregnancy (PSUR) (NMQ): Pregnancy and neonatal topics (SMQ), PTs: Ectopic pregnancy under hormonal contraception, Exposure via body fluid, Failed forceps delivery, Forceps delivery Vacuum extractor delivery

Skin cancer (BCC) (CMQ): PTs: Basal cell carcinoma, Basosquamous carcinoma of skin

Skin cancer (MELANOMA) (CMQ): PTs: Acral lentiginous melanoma, Acral lentiginous melanoma stage I, Acral lentiginous melanoma stage II, Acral lentiginous melanoma stage III, Acral lentiginous melanoma stage IV, Desmoplastic melanoma, Lentigo maligna, Lentigo maligna recurrent, Lentigo maligna stage I, Lentigo maligna stage II, Lentigo maligna stage III, Lentigo maligna stage IV, Malignant blue naevus, Malignant melanoma, Malignant melanoma in situ, Malignant melanoma of eyelid, Malignant melanoma stage I, Malignant melanoma stage II, Malignant melanoma stage III, Malignant melanoma stage IV, Melanoma recurrent, Metastatic malignant melanoma, Nodular melanoma, Superficial spreading melanoma stage I, Superficial spreading melanoma stage II, Superficial spreading melanoma stage III, Superficial spreading melanoma stage IV, Superficial spreading melanoma stage unspecified

Skin cancer (SCC) (CMQ); PTs: Bowen's disease Squamous cell carcinoma of skin

Other malignant neoplasms (cervical cancer) (CMQ): PTs: Adenocarcinoma of the cervix, Adenosquamous carcinoma of the cervix, Cervix cancer metastatic, Cervix carcinoma, Cervix carcinoma recurrent, Cervix carcinoma stage 0, Cervix carcinoma stage I, Cervix carcinoma stage II, Cervix carcinoma stage III, Cervix carcinoma stage IV, Small cell carcinoma of the cervix, Squamous cell carcinoma of the cervix

All thromboembolic events (NMQ): PTs: Acute aortic syndrome, Acute coronary syndrome. Acute myocardial infarction, Administration site thrombosis, Adrenal thrombosis, Agnosia, Amaurosis, Amaurosis fugax, Angina pectoris, Angina unstable, Anginal equivalent, Angiogram abnormal, Angiogram cerebral abnormal, Angiogram peripheral abnormal, Angioplasty, Aortic bypass, Aortic embolus, Aortic surgery, Aortic thrombosis, Aortogram abnormal, Aphasia, Application site thrombosis, Arterectomy, Arterectomy with graft replacement, Arterial bypass occlusion, Arterial bypass operation, Arterial bypass thrombosis, Arterial graft, Arterial occlusive disease, Arterial stent insertion, Arterial therapeutic procedure, Arterial thrombosis, Arteriogram abnormal, Arteriogram carotid abnormal, Arteriogram coronary abnormal, Arteriosclerosis coronary artery, Arteriospasm coronary, Arteriotomy, Arteriovenous fistula occlusion, Arteriovenous fistula thrombosis, Arteriovenous graft thrombosis, Artificial blood vessel occlusion, Atherectomy, Atherosclerotic plaque rupture, Atrial thrombosis, Axillary vein thrombosis, Balint's syndrome, Basal ganglia haematoma, Basal ganglia haemorrhage, Basal ganglia infarction, Basal ganglia stroke, Basilar artery aneurysm, Basilar artery occlusion, Basilar artery perforation, Basilar artery stenosis, Basilar artery thrombosis, Blindness transient, Blood creatine phosphokinase abnormal, Blood creatine phosphokinase increased, Blood creatine phosphokinase MB abnormal, Blood creatine phosphokinase MB increased, Bone infarction, Brachiocephalic arteriosclerosis, Brachiocephalic artery occlusion, Brachiocephalic artery stenosis, Brachiocephalic vein occlusion, Brachiocephalic vein thrombosis, Brain hypoxia, Brain injury, Brain stem embolism,

Brain stem haematoma, Brain stem haemorrhage, Brain stem infarction, Brain stem ischaemia, Brain stem microhaemorrhage, Brain stem stroke, Brain stem thrombosis, Budd-Chiari syndrome, Capsular warning syndrome, Cardiac stress test abnormal, Cardiac ventricular scarring, Cardiac ventricular thrombosis, Cardiopulmonary exercise test abnormal, Carotid aneurysm rupture, Carotid angioplasty, Carotid arterial embolus, Carotid arteriosclerosis, Carotid artery aneurysm, Carotid artery bypass, Carotid artery calcification, Carotid artery disease, Carotid artery dissection, Carotid artery insufficiency, Carotid artery occlusion, Carotid artery perforation, Carotid artery restenosis, Carotid artery stenosis, Carotid artery stent insertion, Carotid artery stent removal, Carotid artery thrombosis, Carotid endarterectomy, Carotid revascularization, Catheter site thrombosis, Catheterisation venous, Cavernous sinus thrombosis, Central nervous system haemorrhage, Central pain syndrome, Central venous catheterization, Cerebellar artery occlusion, Cerebellar artery thrombosis, Cerebellar embolism, Cerebellar haematoma, Cerebellar haemorrhage, Cerebellar infarction, Cerebellar ischaemia, Cerebellar microhaemorrhage, Cerebellar stroke, Cerebral aneurysm perforation, Cerebral aneurysm ruptured syphilitic, Cerebral arteriosclerosis, Cerebral arteriovenous malformation haemorrhagic, Cerebral artery embolism, Cerebral artery occlusion, Cerebral artery perforation, Cerebral artery restenosis, Cerebral artery stenosis, Cerebral artery thrombosis, Cerebral congestion, Cerebral endovascular aneurysm repair, Cerebral gas embolism, Cerebral haematoma, Cerebral haemorrhage, Cerebral haemorrhage foetal, Cerebral haemorrhage neonatal, Cerebral haemosiderin deposition, Cerebral hypoperfusion, Cerebral infarction, Cerebral infarction foetal, Cerebral ischaemia, Cerebral microembolism, Cerebral microhaemorrhage, Cerebral reperfusion injury, Cerebral revascularization, Cerebral septic infarct, Cerebral small vessel ischaemic disease, Cerebral thrombosis, Cerebral vascular occlusion, Cerebral vasoconstriction, Cerebral venous thrombosis, Cerebral ventricular ruptura, Cerebrospinal thrombotic tamponade, Cerebrovascular accident, Cerebrovascular accident prophylaxis, Cerebrovascular disorder, Cerebrovascular insufficiency, Cerebrovascular operation, Cerebrovascular stenosis, Charcot-Bouchard microaneurysms, Choroidal infarction, Coeliac artery occlusion, Collateral circulation, Compression garment application, Computerised tomogram coronary artery abnormal, Congenital hemiparesis, Coronary angioplasty, Coronary arterial stent insertion, Coronary artery bypass, Coronary artery disease, Coronary artery dissection, Coronary artery embolism, Coronary artery insufficiency, Coronary artery occlusion, Coronary artery reocclusion, Coronary artery restenosis, Coronary artery stenosis, Coronary artery thrombosis, Coronary brachytherapy, Coronary bypass stenosis, Coronary bypass thrombosis, Coronary endarterectomy, Coronary no-reflow phenomenon, Coronary ostial stenosis, Coronary revascularization, Coronary vascular graft occlusion, Coronary vascular graft stenosis, CSF bilirubin positive, CSF red blood cell count positive, Deep vein thrombosis, Deep vein thrombosis postoperative, Delayed ischaemic neurological deficit, Device embolisation, Device occlusion, Device related thrombosis, Diplegia, Directional Doppler flow tests abnormal, Dissecting coronary artery aneurysm, Disseminated intravascular coagulation, Disseminated intravascular coagulation in newborn, Dysarthria, ECG electrically inactive area, ECG signs of myocardial infarction, ECG signs of myocardial ischaemia, Electrocardiogram Q wave abnormal, Electrocardiogram ST segment abnormal, Electrocardiogram ST segment depression, Electrocardiogram ST segment elevation, Electrocardiogram ST-T segment abnormal, Electrocardiogram ST-T segment depression, Electrocardiogram ST-T segment elevation, Electrocardiogram T wave abnormal, Electrocardiogram T wave inversión, Embolia cutis medicamentosa, Embolic cerebral

infarction, Embolic pneumonia, Embolic stroke, Embolism, Embolism arterial, Embolism venous, Endarterectomy, Epidural haemorrhage, Exercise electrocardiogram abnormal, Exercise test abnormal, External counterpulsation, Extra-axial haemorrhage, Extradural haematoma, Femoral artery embolism, Foetal cerebrovascular disorder, Graft thrombosis, Haemorrhage coronary artery, Haemorrhage intracranial, Haemorrhagic cerebral infarction, Haemorrhagic infarction, Haemorrhagic stroke, Haemorrhagic transformation stroke, Haemorrhoids thrombosed, Hemianaesthesia, Hemiasomatognosia, Hemiparaesthesia, Hemiparesis, Hemiparesis, Hemiplegia, Heparin-induced thrombocytopenia, Hepatic artery embolism, Hepatic artery occlusion, Hepatic artery thrombosis, Hepatic infarction, Hepatic vascular thrombosis, Hepatic vein embolism, Hepatic vein occlusion, Hepatic vein thrombosis, Homans' sign positive, Hypothenar hammer syndrome, Hypoxic-ischaemic encephalopathy, Iliac artery embolism, Iliac artery occlusion, Iliac vein occlusion, Implant site thrombosis, Incision site vessel occlusion, Infarction, Inferior vena cava syndrome, Inferior vena caval occlusion, Infusion site thrombosis, Injection site thrombosis, Inner ear infarction, Instillation site thrombosis, Internal carotid artery kinking, Intestinal infarction, Intra-aortic balloon placement, Intracardiac mass, Intracardiac thrombus, Intra-cerebral aneurysm operation, Intracerebral haematoma evacuation, Intracranial aneurysm, Intracranial artery dissection, Intracranial haematoma, Intracranial tumour haemorrhage, Intracranial venous sinus thrombosis, Intraoperative cerebral artery occlusion, Intraventricular haemorrhage, Intraventricular haemorrhage neonatal, Ischaemic cardiomyopathy, Ischaemic cerebral infarction, Ischaemic mitral regurgitation, Ischaemic stroke, Jugular vein occlusion, Jugular vein thrombosis, Kounis syndrome, Lacunar infarction, Lacunar stroke, Lateral medullary syndrome, Left atrial appendage occlusion, Leriche syndrome, Mahler sign, May-Thurner syndrome, Medical device site thrombosis, Meningorrhagia, Mesenteric arterial occlusion, Mesenteric arteriosclerosis, Mesenteric artery embolism, Mesenteric artery stenosis, Mesenteric artery stent insertion, Mesenteric artery thrombosis, Mesenteric vascular insufficiency, Mesenteric vascular occlusion, Mesenteric vein thrombosis, Mesenteric venous occlusion, Microembolism, Microvascular coronary artery disease, Migrainous infarction, Millard-Gubler syndrome, Modified Rankin score decreased, Monoparesis, Monoplegia, Moyamoya disease, Myocardial hypoxia, Myocardial infarction, Myocardial ischaemia, Myocardial necrosis, Myocardial necrosis marker increased, Myocardial reperfusion injury, Myocardial stunning, NIH stroke scale abnormal, NIH stroke scale score decreased, NIH stroke scale score increased, Obstetrical pulmonary embolism, Obstructive shock, Ophthalmic vein thrombosis, Optic nerve infarction, Ovarian vein thrombosis, Paget-Schroetter syndrome, Pancreatic infarction, Papillary muscle infarction, Paradoxical embolism, Paralysis, Paraneoplastic thrombosis, Paraparesis, Paraplegia, Paresis, Pelvic venous thrombosis, Penile artery occlusion, Penile vein thrombosis, Percutaneous coronary intervention, Perinatal stroke, Peripheral arterial occlusive disease, Peripheral arterial reocclusion, Peripheral artery angioplasty, Peripheral artery bypass, Peripheral artery occlusion, Peripheral artery stent insertion, Peripheral artery thrombosis, Peripheral embolism, Peripheral endarterectomy, Peripheral revascularization, Periprocedural myocardial infarction, Periventricular haemorrhage neonatal, Phlebectomy, Pituitary haemorrhage, Pituitary infarction, Placental infarction, Pneumatic compression therapy, Popliteal artery entrapment syndrome, Portal shunt procedure, Portal vein cavernous transformation, Portal vein occlusion, Portal vein thrombosis, Portosplenomesenteric venous thrombosis, Post angioplasty restenosis, Post cardiac arrest syndrome, Post procedural myocardial infarction, Post procedural pulmonary embolism, Post

procedural stroke, Post stroke depression, Post thrombotic syndrome, Postinfarction angina, Postoperative thrombosis, Postpartum thrombosis, Postpartum venous thrombosis, Precerebral arteriosclerosis, Precerebral artery occlusion, Precerebral artery thrombosis, Prinzmetal angina, Profundaplasty, Prosthetic vessel implantation, Pulmonary artery occlusion, Pulmonary artery therapeutic procedure, Pulmonary artery thrombosis, Pulmonary embolism, Pulmonary endarterectomy, Pulmonary infarction, Pulmonary microemboli, Pulmonary thrombosis, Pulmonary vein occlusion, Pulmonary veno-occlusive disease, Pulmonary venous thrombosis, Putamen haemorrhage, Quadriparesis, Quadriplegia, Renal artery angioplasty, Renal artery occlusion, Renal artery thrombosis, Renal embolism, Renal infarct, Renal vascular thrombosis, Renal vein embolism, Renal vein occlusion, Renal vein thrombosis, Retinal artery embolism, Retinal artery occlusion, Retinal artery thrombosis, Retinal infarction, Retinal vascular thrombosis, Retinal vein occlusion, Retinal vein thrombosis, Reversible cerebral vasoconstriction syndrome, Reversible ischaemic neurological deficit, Right hemisphere deficit syndrome, Ruptured cerebral aneurysm, Scan myocardial perfusion abnormal, Shunt occlusion, Shunt thrombosis, SI QIII TIII pattern, Silent myocardial infarction, Spinal artery embolism, Spinal artery thrombosis, Spinal cord haematoma, Spinal cord haemorrhage, Spinal cord infarction, Spinal epidural haematoma, Spinal epidural haemorrhage, Spinal subarachnoid haemorrhage, Spinal subdural haematoma, Spinal subdural haemorrhage, Splenic artery thrombosis, Splenic embolism, Splenic infarction, Splenic thrombosis, Splenic vein occlusion, Splenic vein thrombosis, Stoma site thrombosis, Stress cardiomyopathy, Stress echocardiogram abnormal, Stroke in evolution, Subarachnoid haematoma, Subarachnoid haemorrhage neonatal, Subclavian artery embolism, Subclavian artery occlusion, Subclavian artery thrombosis, Subclavian coronary steal syndrome, Subclavian steal syndrome, Subclavian vein occlusion, Subclavian vein thrombosis, Subdural haematoma, Subdural haematoma evacuation, Subdural haemorrhage, Subdural haemorrhage neonatal, Subendocardial ischaemia, Superficial siderosis of central nervous system, Superior mesenteric artery syndrome, Superior sagittal sinus thrombosis, Superior vena cava occlusion, Superior vena cava syndrome, Surgical vascular shunt, Testicular infarction, Thalamic infarction, Thalamus haemorrhage, Thrombectomy, Thromboangiitis obliterans, Thromboembolectomy, Thrombolysis, Thrombophlebitis, Thrombophlebitis migrans, Thrombophlebitis neonatal, Thrombophlebitis superficial, Thrombosed varicose vein, Thrombosis, Thrombosis corpora cavernosa, Thrombosis in device, Thrombosis mesenteric vessel, Thrombosis prophylaxis, Thrombotic cerebral infarction, Thrombotic microangiopathy, Thrombotic stroke, Thrombotic thrombocytopenic purpura, Thyroid infarction, Transient ischaemic attack, Transverse sinus thrombosis, Troponin I increased, Troponin increased, Troponin T increased, Truncus coeliacus thrombosis, Tumour embolism, Tumour thrombosis, Ultrasonic angiogram abnormal, Ultrasound Doppler abnormal, Umbilical cord occlusion, Umbilical cord thrombosis, Vaccination site thrombosis, Vascular access site thrombosis, Vascular encephalopathy, Vascular graft, Vascular graft occlusion, Vascular graft thrombosis, Vascular operation, Vascular pseudoaneurysm thrombosis, Vascular stent insertion, Vascular stent occlusion, Vascular stent restenosis, Vascular stent stenosis, Vascular stent thrombosis, Vasodilation procedure, Vein of Galen aneurysmal malformation, Vena cava embolism, Vena cava filter insertion, Vena cava filter removal, Vena cava thrombosis, Venogram abnormal, Venoocclusive disease, Venoocclusive liver disease, Venous angioplasty, Venous occlusion, Venous operation, Venous recanalisation, Venous repair, Venous stent insertion, Venous thrombosis, Venous thrombosis in pregnancy, Venous thrombosis limb, Venous thrombosis neonatal, Vertebral artery aneurysm, Vertebral artery

dissection, Vertebral artery occlusion, Vertebral artery perforation, Vertebral artery stenosis, Vertebral artery thrombosis, Vertebrobasilar insufficiency, Vessel puncture site occlusion, Vessel puncture site thrombosis, Visceral venous thrombosis, Visual acuity reduced transiently, Visual agnosia, Visual midline shift syndrome, Wall motion score index abnormal

All strokes (NMQ) (broad): Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ) PTs: Basal ganglia haematoma, Basal ganglia haemorrhage, Brain stem haematoma, Brain stem haemorrhage, Brain stem microhaemorrhage, Central nervous system haemorrhage, Cerebellar haematoma, Cerebellar haemorrhage, Cerebellar microhaemorrhage, Cerebellar stroke, Cerebral haematoma, Cerebral haemorrhage, Cerebral microhaemorrhage, Extra-axial haemorrhage, Haemorrhage intracranial, Haemorrhagic cerebral infarction, Haemorrhagic stroke, Haemorrhagic transformation stroke, Intracranial haematoma, Intraventricular haemorrhage, Putamen haemorrhage, Subarachnoid haematoma, Subarachnoid haemorrhage, Thalamus haemorrhage, Basal ganglia infarction, Basal ganglia stroke, Basilar artery thrombosis, Brain stem infarction, Brain stem ischaemia, Brain stem stroke, Cerebellar infarction, Cerebellar ischaemia, Cerebellar stroke, Cerebral infarction, Cerebral ischaemia, Cerebral microembolism, Cerebral vascular occlusion, Cerebral venous thrombosis, Cerebrovascular accident, Delayed ischaemic neurological deficit, Embolic cerebral infarction, Embolic stroke, Ischaemic cerebral infarction, Ischaemic stroke, Lacunar infarction, Lacunar stroke, Post cardiac arrest syndrome, Precerebral arteriosclerosis, Retinal artery occlusion, Stroke in evolution, Thalamic infarction, Thrombotic cerebral infarction, Thrombotic stroke

QT interval prolongation (specific) (CMQ): PTs: Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged, Long QT syndrome, Torsade de pointes

Table 14-4 Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection)

Type	Risk name	Search criteria
Main risk	Infection	SOC “Infections and infestations”
Main risk	VZV infections for Clinical Trial database	Varicella-Zoster virus infections overall search includes all the PTs under the following sub categories. This search is a subset of the ARGUS search with specific PTs related to VZV only: **Varicella/chickenpox (primary infection)** PTs: Congenital varicella infection, Encephalitis post varicella, Varicella, Varicella post vaccine, Varicella zoster virus infection **Herpes Zoster/shingles (reactivation)** ***Disseminated HZ infections (reactivation)*** PTs: Herpes zoster cutaneous disseminated, Herpes zoster disseminated, Herpes zoster infection neurological, Herpes zoster meningitis, Herpes zoster meningoencephalitis, Herpes zoster meningomyelitis, Herpes zoster pharyngitis, Varicella zoster gastritis, Varicella zoster oesophagitis, Varicella zoster pneumonia, Disseminated varicella zoster vaccine virus infection ***Non-disseminated HZ infections (reactivation)*** PTs: Genital herpes zoster, Herpes zoster, Herpes zoster necrotising retinopathy, Herpes zoster oticus, Ophthalmic herpes zoster, Varicella keratitis

Type	Risk name	Search criteria
Main risk	HVIs other than VZV for Clinical Trial database	'HVIs other than VZV' overall search includes all the PTs under the following sub categories. This search is a subset of the ARGUS search with specific PTs to related to respective types of HVIs: **Herpes simplex virus infections** Eczema herpeticum, Herpes simplex colitis, Herpes simplex encephalitis, Herpes simplex gastritis, Herpes simplex hepatitis, Herpes simplex meningitis, Herpes simplex meningoencephalitis, Herpes simplex meningomyelitis, Herpes simplex necrotising retinopathy, Herpes simplex oesophagitis, Herpes simplex otitis externa, Herpes simplex pharyngitis, Herpes simplex pneumonia, Herpes simplex sepsis, Herpes simplex visceral, Meningoencephalitis herpes simplex neonatal, Ophthalmic herpes simplex, Congenital herpes simplex infection, Genital herpes simplex, Herpes simplex, Herpes simplex cervicitis,Herpes simplex virus conjunctivitis neonatal, Kaposi's varicelliform eruption, Neonatal mucocutaneous herpes simplex, Oral herpes **Epstein-Barr virus infection** Epstein-Barr viraemia, Epstein-Barr virus associated lymphoma, Epstein-Barr virus associated lymphoproliferative disorder, Epstein-Barr virus infection, Hepatitis infectious mononucleosis, Infectious mononucleosis, Oral hairy leukoplakia, Post transplant lymphoproliferative disorder, X-linked lymphoproliferative syndrome **Cytomegalovirus infections** Congenital cytomegalovirus infection, Cytomegalovirus chorioretinitis, Cytomegalovirus colitis, Cytomegalovirus duodenitis, Cytomegalovirus enteritis, Cytomegalovirus enterocolitis, Cytomegalovirus gastritis, Cytomegalovirus gastroenteritis, Cytomegalovirus gastrointestinal infection, Cytomegalovirus hepatitis, Cytomegalovirus infection, Cytomegalovirus mononucleosis, Cytomegalovirus mucocutaneous ulcer, Cytomegalovirus myelomeningoradiculitis, Cytomegalovirus myocarditis, Cytomegalovirus oesophagitis, Cytomegalovirus pancreatitis, Cytomegalovirus pericarditis, Cytomegalovirus syndrome, Cytomegalovirus urinary tract infection, Cytomegalovirus viraemia, Disseminated cytomegaloviral infection, Encephalitis cytomegalovirus, Pneumonia cytomegaloviral **Human herpes virus HHV-6, -7 and -8 infections** Exanthema subitum, Human herpesvirus 6 infection, Human herpesvirus 7 infection, Human herpesvirus 8 infection, Roseola
Main risk	PML	PTs: Progressive Multifocal Leukoencephalopathy, Leukoencephalopathy, Leukoencephalomyelitis, JC virus granule cell neuronopathy
Sub-risk	RCNVI	PTs: 'Acute pulmonary histoplasmosis', 'Adrenal gland tuberculosis', 'African trypanosomiasis', 'American trypanosomiasis', 'Atypical mycobacterial infection', 'Atypical mycobacterial lymphadenitis', 'Atypical mycobacterial pneumonia', 'Atypical mycobacterium pericarditis', 'Blastomycosis', 'Bone tuberculosis', 'Borderline leprosy', Bovine tuberculosis', 'Cerebral toxoplasmosis', 'Choroid tubercles', 'Chronic pulmonary histoplasmosis', 'Coccidioides encephalitis', 'Coccidioidomycosis', 'Congenital toxoplasmosis', 'Congenital tuberculosis', 'Conjunctivitis tuberculous', 'Cryptococcal cutaneous infection', 'Cryptococcal fungaemia', 'Cryptococcosis', 'Cutaneous coccidioidomycosis', 'Cutaneous leishmaniasis', 'Cutaneous

Type	Risk name	Search criteria
		tuberculosis', Disseminated Bacillus Calmette-Guerin infection, 'Disseminated cryptococcosis', 'Disseminated tuberculosis', 'Ear tuberculosis', 'Endocarditis histoplasma' Epididymitis blastomyces', 'Epididymitis tuberculous', 'Erythema induratum', 'Extrapulmonary tuberculosis',' Eye infection toxoplasmal', 'Female genital tract tuberculosis', 'Gastroenteritis cryptococcal', 'Hepatitis toxoplasmal', 'Histoplasmosis', 'Histoplasmosis cutaneous', 'Histoplasmosis disseminated', 'Immune reconstitution inflammatory syndrome associated tuberculosis', 'Indeterminate leprosy', 'Joint tuberculosis', 'Latent tuberculosis', 'Leishmaniasis', 'Lepromatous leprosy', 'Leprosy', 'Lupus vulgaris', 'Lymph node tuberculosis', 'Male genital tract tuberculosis', 'Meningitis coccidioides', 'Meningitis cryptococcal', 'Meningitis histoplasma', 'Meningitis toxoplasmal', 'Meningitis trypanosomal', 'Meningitis tuberculous', 'Mucocutaneous leishmaniasis', 'Mycobacterial infection', 'Mycobacterium abscessus infection', 'Mycobacterium avium complex immune restoration disease', 'Mycobacterium avium complex infection', 'Mycobacterium chelonae infection', 'Mycobacterium fortuitum infection', 'Mycobacterium kansasii infection', 'Mycobacterium marinum infection', 'Mycobacterium ulcerans infection', 'Myocarditis toxoplasmal', 'Neurocryptococcosis', 'Oesophageal tuberculosis', 'Oral tuberculosis', 'Osteomyelitis blastomyces', 'Paracoccidioides infection', 'Pericarditis histoplasma', 'Pericarditis tuberculous', 'Peritoneal tuberculosis', 'Pneumocystis jiroveci infection', 'Pneumocystis jiroveci pneumonia', 'Pneumonia blastomyces', 'Pneumonia cryptococcal', 'Pneumonia toxoplasmal', 'Presumed ocular histoplasmosis syndrome', 'Prostatitis tuberculous', 'Pulmonary tuberculoma', 'Pulmonary tuberculosis', 'Renal tuberculosis', 'Retinitis histoplasma', 'Salpingitis tuberculous', 'Silicotuberculosis', 'Spleen tuberculosis', 'Strongyloidiasis', 'Thyroid tuberculosis', 'Toxoplasmosis', 'Trypanosomiasis', 'Tuberculoid leprosy', 'Tuberculoma of central nervous system', 'Tuberculosis', 'Tuberculosis bladder', 'Tuberculosis gastrointestinal', 'Tuberculosis liver', 'Tuberculosis of central nervous system', 'Tuberculosis of eye', 'Tuberculosis of genitourinary system', 'Tuberculosis of intrathoracic lymph nodes', 'Tuberculosis of peripheral lymph nodes', 'Tuberculosis ureter', 'Tuberculous endometritis', 'Tuberculous laryngitis', 'Tuberculous pleurisy', 'Tuberculous tenosynovitis', 'Type 1 lepra reaction', 'Type 2 lepra reaction', 'Visceral leishmaniasis'.
Sub-risk	RCVI (Reactivation of chronic viral infections)	Congenital varicella infection, Encephalitis post varicella, Varicella, Varicella post vaccine,Disseminated varicella zoster vaccine virus infection, Herpes zoster cutaneous disseminated, Herpes zoster disseminated, Herpes zoster infection neurological, Herpes zoster meningitis, Herpes zoster meningoencephalitis, Herpes zoster meningomyelitis, Herpes zoster pharyngitis, Varicella zoster gastritis, Varicella zoster oesophagitis, Varicella zoster pneumonia, Gastritis herpes, Herpes oesophagitis, Herpes pharyngitis, Herpes sepsis, Meningitis herpes, Meningoencephalitis herpetic, Meningomyelitis herpes, Pneumonia herpes viral, Genital herpes zoster, Herpes zoster, Herpes zoster necrotising retinopathy, Herpes zoster oticus, Ophthalmic herpes zoster, Genital herpes, Herpes dermatitis, Herpes ophthalmic, Herpes virus infection, Necrotising herpetic retinopathy, Post herpetic neuralgia, Varicella virus test positive, Congenital varicella infection, Encephalitis post varicella, Varicella, Varicella post

Type	Risk name	Search criteria
		vaccine, Varicella zoster virus infection, Herpes zoster cutaneous disseminated, Herpes zoster disseminated, Herpes zoster infection neurological, Herpes zoster meningitis, Herpes zoster meningoencephalitis, Herpes zoster meningomyelitis, Herpes zoster pharyngitis, Varicella zoster gastritis, Varicella zoster oesophagitis, Varicella zoster pneumonia, Varicella keratitis Genital herpes zoster, Herpes zoster, Herpes zoster necrotising retinopathy, Herpes zoster oticus, Ophthalmic herpes zoster, Eczema herpeticum, Herpes simplex colitis, Herpes simplex encephalitis, Herpes simplex gastritis, Herpes simplex hepatitis, Herpes simplex meningitis, Herpes simplex meningoencephalitis, Herpes simplex meningomyelitis, Herpes simplex necrotising retinopathy, Herpes simplex oesophagitis, Herpes simplex otitis externa, Herpes simplex pharyngitis, Herpes simplex pneumonia, Herpes simplex sepsis, Herpes simplex visceral, Meningoencephalitis herpes simplex neonatal, Ophthalmic herpes simplex, Congenital herpes simplex infection, Genital herpes simplex, Herpes simplex, Herpes simplex cervicitis, Herpes simplex virus conjunctivitis neonatal, Kaposi's varicelliform eruption, Neonatal mucocutaneous herpes simplex, Oral herpes, Colitis herpes, Gastritis herpes, Herpes oesophagitis, Herpes ophthalmic, pharyngitis, Herpes sepsis, Meningitis herpes, Meningoencephalitis herpetic, Meningomyelitis herpes, Necrotising herpetic retinopathy, Pneumonia herpes viral, Proctitis herpes, Genital herpes, Herpes dermatitis, Herpes virus infection, Herpes simplex test positive, Epstein-Barr viraemia, Epstein-Barr virus associated lymphoma, Epstein-Barr virus associated lymphoproliferative disorder, Epstein-Barr virus infection, Hepatitis infectious mononucleosis, Infectious mononucleosis, Oral hairy leukoplakia, Post transplant lymphoproliferative disorder, X-linked lymphoproliferative syndrome, Epstein-Barr virus antibody positive, Epstein-Barr virus antigen positive, Epstein-Barr virus test positive, heterophile test positive, Mononucleosis syndrome, Congenital cytomegalovirus infection, Cytomegalovirus chorioretinitis, Cytomegalovirus colitis, Cytomegalovirus duodenitis, Cytomegalovirus enteritis, Cytomegalovirus enterocolitis, Cytomegalovirus gastritis, Cytomegalovirus gastroenteritis, Cytomegalovirus gastrointestinal infection, Cytomegalovirus gastrointestinal ulcer, Cytomegalovirus hepatitis, Cytomegalovirus infection, Cytomegalovirus gastrointestinal ulcer, Cytomegalovirus mononucleosis, Cytomegalovirus mucocutaneous ulcer, Cytomegalovirus myelomeningoradiculitis, Cytomegalovirus myocarditis, Cytomegalovirus oesophagitis, Cytomegalovirus pancreatitis, Cytomegalovirus pericarditis, Cytomegalovirus syndrome, Cytomegalovirus urinary tract infection, Cytomegalovirus viraemia, Disseminated cytomegaloviral infection, Encephalitis cytomegalovirus, Pneumonia cytomegaloviral, Cytomegalovirus test positive, Exanthema subitum, Human herpesvirus 6 infection, Human herpesvirus 7 infection, Human herpesvirus 8 infection, Roseola, Human herpes virus 6 serology positive, Human herpes virus 8 test positive, Meningitis herpes, Meningoencephalitis herpetic, Meningomyelitis herpes, Roseolovirus test positive, Eczema herpeticum, Herpes simplex colitis, Herpes simplex encephalitis, Herpes simplex gastritis, Herpes simplex hepatitis, Herpes simplex meningitis, Herpes simplex meningoencephalitis, Herpes simplex meningomyelitis, Herpes

Type	Risk name	Search criteria
		simplex necrotising retinopathy, Herpes simplex oesophagitis, Herpes simplex otitis externa, Herpes simplex pharyngitis, Herpes simplex pneumonia, Herpes simplex sepsis, Herpes simplex visceral, Meningoencephalitis herpes simplex neonatal, Ophthalmic herpes simplex, Congenital herpes simplex infection, Genital herpes simplex, Herpes simplex, Herpes simplex virus conjunctivitis neonatal, Kaposi's varicelliform eruption, Neonatal mucocutaneous herpes simplex, Oral herpes, Epstein-Barr viraemia, Epstein-Barr virus associated lymphoma, Epstein-Barr virus associated lymphoproliferative disorder, Epstein-Barr virus infection, Hepatitis infectious mononucleosis, Infectious mononucleosis, Oral hairy leukoplakia, Post transplant lymphoproliferative disorder, X-linked lymphoproliferative syndrome, Congenital cytomegalovirus infection, Cytomegalovirus chorioretinitis, Cytomegalovirus colitis, Cytomegalovirus duodenitis, Cytomegalovirus enteritis, Cytomegalovirus enterocolitis, Cytomegalovirus gastritis, Cytomegalovirus gastroenteritis, Cytomegalovirus gastrointestinal infection, Cytomegalovirus hepatitis, Cytomegalovirus infection, Cytomegalovirus mononucleosis, Cytomegalovirus mucocutaneous ulcer, Cytomegalovirus myelomeningoradiculitis, Cytomegalovirus myocarditis, Cytomegalovirus oesophagitis, Cytomegalovirus pancreatitis, Cytomegalovirus pericarditis, Cytomegalovirus syndrome, Cytomegalovirus urinary tract infection, Cytomegalovirus viraemia, Disseminated cytomegaloviral infection, Encephalitis cytomegalovirus, Pneumonia cytomegaloviral, Exanthema subitum, Human herpesvirus 6 infection, Human herpesvirus 7 infection, Human herpesvirus 8 infection, Roseola Eczema herpeticum, Herpes simplex colitis, Herpes simplex encephalitis, Herpes simplex gastritis, Herpes simplex hepatitis, Herpes simplex meningitis, Herpes simplex meningoencephalitis, Herpes simplex meningomyelitis, Herpes simplex necrotising retinopathy, Herpes simplex oesophagitis, Herpes simplex otitis externa, Herpes simplex pharyngitis, Herpes simplex pneumonia, Herpes simplex sepsis, Herpes simplex visceral, Meningoencephalitis herpes simplex neonatal, Ophthalmic herpes simplex, Congenital herpes simplex infection, Genital herpes simplex, Herpes simplex, Herpes simplex virus conjunctivitis neonatal, Kaposi's varicelliform eruption, Neonatal mucocutaneous herpes simplex, Oral herpes, Colitis herpes, Gastritis herpes, Herpes oesophagitis, Herpes ophthalmic, pharyngitis, Herpes sepsis, Meningitis herpes, Meningoencephalitis herpetic, Meningomyelitis herpes, Necrotising herpetic retinopathy, Pneumonia herpes viral, Proctitis herpes, Viral keratouveitis, Genital herpes, Herpes dermatitis, Herpes simplex DNA test positive, Herpes simplex serology positive, Herpes virus infection, Simplex virus test positive, Epstein-Barr viraemia, Epstein-Barr virus associated lymphoma, Epstein-Barr virus associated lymphoproliferative disorder, Epstein-Barr virus infection, Hepatitis infectious mononucleosis, Infectious mononucleosis, Oral hairy leukoplakia, Post transplant lymphoproliferative disorder, X-linked lymphoproliferative syndrome, Epstein-Barr virus antibody positive, Epstein-Barr virus antigen positive, Epstein-Barr virus test positive, heterophile test positive, Mononucleosis syndrome, Congenital cytomegalovirus infection, Cytomegalovirus chorioretinitis, Cytomegalovirus colitis, Cytomegalovirus duodenitis, Cytomegalovirus enteritis, Cytomegalovirus enterocolitis, Cytomegalovirus gastritis, Cytomegalovirus gastroenteritis, Cytomegalovirus gastrointestinal

Type	Risk name	Search criteria
		infection, Cytomegalovirus gastrointestinal ulcer, Cytomegalovirus hepatitis, Cytomegalovirus infection, Cytomegalovirus gastrointestinal ulcer, Cytomegalovirus mononucleosis, Cytomegalovirus mucocutaneous ulcer, Cytomegalovirus myelomeningoradiculitis, Cytomegalovirus myocarditis, Cytomegalovirus oesophagitis, Cytomegalovirus pancreatitis, Cytomegalovirus pericarditis, Cytomegalovirus syndrome, Cytomegalovirus urinary tract infection, Cytomegalovirus viraemia, Disseminated cytomegaloviral infection, Encephalitis cytomegalovirus, Pneumonia cytomegaloviral, Cytomegalovirus test positive,Exanthema subitum, Human herpesvirus 6 infection, Human herpesvirus 7 infection, Human herpesvirus 8 infection, Roseola, Human herpes virus 6 serology positive, Human herpes virus 8 test positive, Meningitis herpes, Meningoencephalitis herpetic, Meningomyelitis herpes, Roseolovirus test positiveAcute hepatitis B, Acute hepatitis C, Adenoviral hepatitis, Asymptomatic viral hepatitis, Chronic hepatitis, Chronic hepatitis B, Chronic hepatitis C, Congenital hepatitis B infection, Cytomegalovirus hepatitis, Hepatitis, Hepatitis A,Hepatitis A antibody positive, Hepatitis A antigen positive, Hepatitis A virus test positive, Hepatitis acute, Hepatitis B, Hepatitis B antibody positive, Hepatitis B antigen positive, Hepatitis B core antibody positive, Hepatitis B core antigen positive, Hepatitis B e antibody positive, Hepatitis B e antigen positive, Hepatitis B surface antibody positive, Hepatitis B surface antigen positive, Hepatitis B virus test positive, Hepatitis C, Hepatitis C antibody positive, Hepatitis C core antibody positive, Hepatitis C RNA increased, Hepatitis C RNA positive, Hepatitis chronic active,Hepatitis chronic persistent, Hepatitis D antibody positive,Hepatitis D antigen positive, Hepatitis D RNA positive,Hepatitis D virus test positive, Hepatitis E, Hepatitis E antibody positive, Hepatitis E antigen positive, Hepatitis E virus test positive,Hepatitis F, Hepatitis fulminant, Hepatitis G, Hepatitis H, Hepatitis infectious, Hepatitis infectious mononucleosis, Hepatitis mumps, Hepatitis neonatal, Hepatitis non-A non-B, Hepatitis non-A non-B non-C, Hepatitis post transfusion, Hepatitis viral, Hepatitis viral test positive, Hepatitis virus-associated nephropathy,Viral hepatitis carrier
Sub-risk	Sepsis	Abdominal sepsis, Amniotic infection syndrome of Blane, Anthrax sepsis, Bacterial sepsis, Biliary sepsis, Brucella sepsis,Burkholderia cepacia complex sepsis, Campylobacter sepsis, Candida sepsis, Cerebral septic infarct,Citrobacter sepsis, Clostridial sepsis, Corynebacterium bacteraemia, Corynebacterium sepsis, Device related sepsis, Disseminated Bacillus Calmette-Guerin infection, Enterobacter sepsis, Enterococcal sepsis, Escherichia sepsis, Fungal sepsis, Group B streptococcus neonatal sepsis, Haemophilus sepsis, Helicobacter sepsis, Herpes sepsis,Herpes simplex sepsis, Herpes zoster disseminated, Infantile septic granulomatosis, Intestinal sepsis, Klebsiella sepsis, Listeria sepsis, Meningococcal sepsis, Micrococcal sepsis, Myocarditis septic, Neutropenic sepsis, Nocardia sepsis, Pelvic sepsis, Plague sepsis, Pneumococcal sepsis, Post procedural sepsis, Postpartum sepsis, Pseudallescheria sepsis, Pseudomonal sepsis, Pulmonary sepsis, Salmonella sepsis, Sepsis, Sepsis neonatal, Sepsis pasteurella, Sepsis syndrome, Septic arthritis haemophilus, Septic arthritis neisserial, Septic arthritis staphylococcal, Septic arthritis streptobacillus,Septic arthritis streptococcal, Septic embolus, Septic encephalopathy, Septic necrosis, Septic phlebitis,

Type	Risk name	Search criteria
		Septic rash, Septic shock, Septic vasculitis, Serratia sepsis, Staphylococcal sepsis, Stenotrophomonas sepsis, Streptococcal sepsis, Thrombophlebitis septic, Umbilical sepsis, Urosepsis, Viral sepsis, Wound sepsis, Yersinia sepsis, Acinetobacter bacteraemia, Bacillus bacteraemia, Bacteraemia, Bacterial toxaemia, Bacterial translocation, Bacteroides bacteraemia, Blood culture positive, Clostridium bacteraemia, Cronobacter bacteraemia, Cryptococcal fungaemia, Cytomegalovirus viraemia, Disseminated cryptococcosis, Disseminated cytomegaloviral infection, Disseminated tuberculosis, Disseminated varicella zoster vaccine virus infection, Endotoxaemia, Endotoxic shock, Enterobacter bacteraemia, Enterococcal bacteraemia, Epstein-Barr viraemia, Escherichia bacteraemia, Fungaemia, Granulicatella bacteraemia, Haemophilus bacteraemia, Histoplasmosis disseminated, HIV viraemia, Klebsiella bacteraemia, Meningococcal bacteraemia, Nocardiosis, Pneumococcal bacteraemia, Pseudomonal bacteraemia, Salmonella bacteraemia, Serratia bacteraemia, Staphylococcal bacteraemia, Staphylococcal toxaemia, Streptococcal bacteraemia, Systemic candida, Systemic infection, Systemic mycosis, Toxic shock syndrome, Toxic shock syndrome staphylococcal, Toxic shock syndrome streptococcal, Viraemia, Yersinia bacteraemia.
Sub-risk	Cellulitis	PTs ‘Anorectal cellulitis’, ‘Application site cellulitis’, ‘Breast cellulitis’, ‘Catheter site cellulitis’, ‘Cellulitis’, ‘Cellulitis enterococcal’, ‘Cellulitis gangrenous’, ‘Cellulitis laryngeal’, ‘Cellulitis of male external genital organ’, ‘Cellulitis orbital’, ‘Cellulitis pasteurella’, ‘Cellulitis pharyngeal’, ‘Cellulitis staphylococcal’, ‘Cellulitis streptococcal’, ‘Eosinophilic cellulitis’, ‘External ear cellulitis’, ‘Implant site cellulitis’, ‘Incision site cellulitis’, ‘Infusion site cellulitis’, ‘Injection site cellulitis’, ‘Lacrimal sac cellulitis’, ‘Periorbital cellulitis’, ‘Post procedural cellulitis’, ‘Vaccination site cellulitis’, ‘Vaginal cellulitis’ and ‘Vulval cellulitis’

Table 14-5 Search criteria for Opportunistic Infections

Opportunistic Infection type	PTs categorized as OIs under infection type
Adenoviral infections	Meningoencephalitis adenoviral
Allescheria infections	Allescheriosis
Aspergillus infections	Aspergilloma, Aspergillus infection,Aspergillosis, Aspergillosis oral, Bronchopulmonary aspergillosis, Cerebral aspergillosis, Meningitis aspergillus, Oro-pharyngeal aspergillosis, Sinusitis aspergillus
Atypical mycobacterial infections	Atypical mycobacterial infection, Atypical mycobacterial lower respiratory tract infection, Atypical mycobacterial pneumonia, Atypical mycobacterium pericarditis, Mycobacterial infection, Mycobacterial peritonitis, Mycobacterium avium complex infection, Mycobacterium chelonae infection, Mycobacterium fortuitum infection, Mycobacterium kansasii infection, Mycobacterium marinum infection, Mycobacterium ulcerans infection, Superinfection mycobacterial
Bacterial infections NEC	Burkholderia gladioli infection, Burkholderia infection

Opportunistic Infection type	PTs categorized as OIs under infection type
Candida infections	Candida endophthalmitis, Candida osteomielitis, Candida retinitis, Candida sepsis, Endocarditis candida, Gastrointestinal candidiasis, Hepatic candidiasis, Hepatosplenic candidiasis, Meningitis candida, Mucocutaneous candidiasis, Neonatal candida infection, Oesophageal candidiasis, Peritoneal candidiasis, Splenic candidiasis, Systemic candida
Coccidioides infections	Coccidioides encephalitis, Coccidioidomycosis, Cutaneous coccidioidomycosis, Meningitis coccidioides
Cryptococcal infections	Cryptococcal fungaemia, Cryptococcosis, Disseminated cryptococcosis, Meningitis cryptococcal, Neurocryptococcosis
Cryptosporidia infections	Biliary tract infection cryptosporidial, Cryptosporidiosis infection
Cytomegaloviral infections	Cytomegalovirus chorioretinitis, Cytomegalovirus colitis, Cytomegalovirus duodenitis, Cytomegalovirus enteritis, Cytomegalovirus enterocolitis, Cytomegalovirus gastritis, Cytomegalovirus gastroenteritis, Cytomegalovirus gastrointestinal infection, Cytomegalovirus gastrointestinal ulcer, Cytomegalovirus hepatitis, Cytomegalovirus mononucleosis, Cytomegalovirus mucocutaneous ulcer, Cytomegalovirus myelomeningoradiculitis, Cytomegalovirus myocarditis, Cytomegalovirus oesophagitis, Cytomegalovirus pancreatitis, Cytomegalovirus pericarditis, Cytomegalovirus proctocolitis, Cytomegalovirus viraemia, Disseminated cytomegaloviral infection, Encephalitis cytomegalovirus, Pneumonia cytomegaloviral
Fungal infections NEC	Alternaria infection, Cerebral fungal infection, Encephalitis fungal, Exserohilum infection, Fungal abscess central nervous system, Fusarium infection, Meningitis exserohilum, Mucormycosis, Necrotising fasciitis fungal, Phaehyphomycosis, Scedosporium infection, Trichosporon infection, Zygomycosis
Herpes virus infection	Herpes simplex meningoencephalitis, Herpes simplex meningomyelitis, Herpes simplex necrotising retinopathy, Herpes zoster cutaneous disseminated, Herpes zoster meningitis, Herpes zoster meningoencephalitis, Herpes zoster meningomyelitis, Herpes zoster necrotising retinopathy, Meningomyelitis herpes, Herpes simplex meningitis, Herpes zoster cutaneous disseminated, Encephalitis post varicella, Herpes simplex encephalitis, Herpes zoster disseminated, Lower respiratory tract herpes infection, Meningitis herpes, Meningoencephalitis herpetic, Necrotising herpetic retinopathy
Histoplasma infections	Endocarditis histoplasma, Histoplasmosis, Histoplasmosis cutaneous, Histoplasmosis disseminated, Meningitis histoplasma, Pericarditis histoplasma, Presumed ocular histoplasmosis syndrome, Retinitis histoplasma
Infections NEC	Opportunistic infection
Isospora infections	Isosporiasis

Opportunistic Infection type	PTs categorized as OIs under infection type
Leishmania infections	Cutaneous leishmaniasis, Leishmaniasis, Mucocutaneous leishmaniasis, Visceral leishmaniasis
Listeria infections	Listeria encephalitis, Listeria sepsis, Listeriosis, Meningitis listeria
Nocardia infections	Nocardia sepsis Nocardiosis
Paracoccidioides infections	Paracoccidioides infection
Parvoviral infections	Erythema infectiosum, Parvovirus infection, Parvovirus B19 infection
Plasmodia infections	Cerebral malaria, Malarial myocarditis
Pneumocystis infections	Pneumocystis jirovecii infection, Pneumocystis jirovecii pneumonia
Polyomavirus infections	Progressive multifocal leukoencephalopathy
Pseudallescheria infections	Pseudallescheria infection, Pseudallescheria sepsis
Pseudomonas infections	Pseudomonas aeruginosa meningitis
Respiratory syncytial virus infections	Pneumonia respiratory syncytial viral, Respiratory syncytial virus bronchiolitis, Respiratory syncytial virus bronchitis, Respiratory syncytial virus infection
Salmonella infections	Meningitis salmonella
Toxoplasma infections	Cerebral toxoplasmosis, Meningitis toxoplasmal, Toxoplasmosis
Tuberculous infections	Adrenal gland tuberculosis, Bone tuberculosis, Choroid tubercles, Congenital tuberculosis, Conjunctivitis tuberculous, Cutaneous tuberculosis, Disseminated Bacillus Calmette-Guerin infection, Disseminated tuberculosis, Epididymitis tuberculous, Extrapulmonary tuberculosis, Female genital tract tuberculosis, Immune reconstitution inflammatory syndrome associated tuberculosis, Intestinal tuberculosis, Joint tuberculosis, Lupus vulgaris, Lymph node tuberculosis, Male genital tract tuberculosis, Meningitis tuberculous, Oesophageal tuberculosis, Oral tuberculosis, Pericarditis tuberculous, Peritoneal tuberculosis, Prostatitis tuberculous, Renal tuberculosis, Salpingitis tuberculous, Spleen tuberculosis, Thyroid tuberculosis, Tuberculoma of central nervous system, Tuberculosis, Tuberculosis bladder, Tuberculosis gastrointestinal, Tuberculosis liver, Tuberculosis of central nervous system, Tuberculosis of eye, Tuberculosis of genitourinary system, Tuberculosis of intrathoracic lymph nodes, Tuberculosis of peripheral lymph nodes, Tuberculosis ureter, Tuberculous endometritis, Tuberculous laryngitis, Tuberculous pleurisy, Tuberculous tenosynovitis

References List

External references

Abdelkefi A, Ben Jamil W, Torjman L, et al (2009) Hemophagocytic syndrome after hematopoietic stem cell transplantation: a prospective observational study. International journal of hematology; 89(3):368-73.

Achiron A, Garty BZ, Menascu S, et al (2012) Multiple sclerosis in Israeli children: incidence, an clinical, cerebrospinal fluid and magnetic resonance imaging findings. Isr Med Assoc J; 14(4):234-9.

Aksamit AJ (2006) Review of progressive multifocal leukoencephalopathy and natalizumab. Neurologist; 12:293-8.

Al Ghamdi G, Awada A, Tanimu DZ, et al (1998) Neurological disorders in renal transplant recipients. Saudi J Kidney Dis Transplant; 9:435-99.

Alajbegovic A, Loga N, Tiro N, et al (2011) Depression in multiple sclerosis patients. Med Arh; 65(2):115-8.

Allende ML, Yamashita T, Proia RL (2003) G-protein-coupled receptor S1P1 acts within endothelial cells to regulate vascular maturation. Blood; 102(10):3665-7.

Alonso A, Hernán MA (2008) Temporal trends in the incidence of multiple sclerosis: a systematic review. Neurology; 71:129-35

Alshubaili AF, Alramzy K, Ayyad YM, et al (2005) Epidemiology of multiple sclerosis in Kuwait: new trends in incidence and prevalence. Eur Neurol; 53(3):125-31.

Bagert BA (2009) Epstein-Barr virus in multiple sclerosis: Current neurology and neuroscience reports; 9(5):405-10.

Bamer AM, Cetin K, Johnson KL, et al (2008) Validation study of prevalence and correlates of depressive symptomatology in multiple sclerosis. Gen Hosp Psychiatry; 30(4):311-7.

Bazelier MT, van Staa T, Uitdehaag BM, et al (2011) The risk of fracture in patients with multiple sclerosis: the UK general practice research database. J Bone Miner Res; 26(9):2271-9.

Beiske AG, Svensson E, Sandanger I, et al (2008) Depression and anxiety amongst multiple sclerosis patients. Eur J Neurol; 15(3):239-45.

Boström I, Callander M, Kurtzke JF, et al (2009) High prevalence of multiple sclerosis in the Swedish county of Värmland. Mult Scler; 15(11):1253-62.

Brew BJ, Davies NWS, Cinque P, et al (2010) Progressive multifocal leukoencephalopathy and other forms of JC virus disease. Nat Rev Neurol; 6:667-79.

Brinkmann V (2007) Sphingosine 1-phosphate receptors in health and disease: mechanistic insights from gene deletion studies and reverse pharmacology. Pharmacol Ther; 115:84-105.

Brinkmann V (2009) FTY720 (fingolimod) in Multiple Sclerosis: therapeutic effects in the immune and the central nervous system. Br J Pharmacol; 158:1173-82.

Brønnum-Hansen H, Koch-Henriksen N, Hyllested K (1994) Survival of patients with multiple sclerosis in Denmark: a nationwide, long-term epidemiologic survey. Neurology; 44(10):1901-7.

Brønnum-Hansen H, Koch-Henriksen N, et al (2004) Trends in survival and cause of death in Danish patients with multiple sclerosis. Brain; 127(Pt 4):844-50.

Brønnum-Hansen H, Stenager E, Stenager EN, et al (2005) Suicide among Danes with multiple sclerosis. J Neurol Neurosurg Psychiatry; 76(10):1457-9.

Brønnum-Hansen H, Hansen T, Koch-Henriksen N, et al (2006) Fatal accidents among Danes with multiple sclerosis. Mult Scler; 12(3):329-32.

Canna SW, Behrens EM et al (2012) Making Sense of the Cytokine Storm: A Conceptual Framework for Understanding, Diagnosing, and Treating Hemophagocytic Syndromes. Pediatric clinics of North America; 59 (2):329-44.

Cattaneo D, De Nuzzo C, Fascia T, et al (2002) Risk of falls in subjects with multiple sclerosis. Arch Phys Med Rehabil; 83(6):864-7.

Chabolla DR, Wszolek ZK (2006) Pharmacologic management of seizures in organ transplant. Neurology; 67(12 Suppl 4), 34S-38S.

Cheng Q, Miao L, Zhang J, et al (2007) A population-based survey of multiple sclerosis in Shanghai, China. Neurology; 68(18):1495-500.

Chitnis T, Glanz B, Jaffin S, et al (2009) Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. Mult Scler; 15(5):627-31.

Chuang HC, Lay JD, Hsieh WC, et al (2007) Pathogenesis and mechanism of disease progression from hemophagocytic lymphohistiocytosis to Epstein-Barr virus-associated T-cell lymphoma: nuclear factor-kappa B pathway as a potential therapeutic target. Cancer Sci; 98(9):1281-7

Cocco E, Sardu C, Massa R, Mamusa E, et al (2011) Epidemiology of multiple sclerosis in south-western Sardinia. Mult Scler; 17(11):1282-9.

D'Amico E, Zanghi A, Leone C, et al (2016) Treatment-related progressive multifocal leukoencephalopathy in multiple sclerosis: a comprehensive review of current evidence and future needs. Drug Saf; 39(12):1163-1174.

Da Silva AM, Vilhena E, Lopes A, et al (2011) Depression and anxiety in a Portuguese MS population: associations with physical disability and severity of disease. J Neurol Sci; 306(1-2):66-70.

Dahl OP, Stordal E, Lydersen S, et al (2009) Anxiety and depression in multiple sclerosis. A comparative population-based study in Nord-Trøndelag County, Norway. Mult Scler; 15(12):1495-501.

De Jager PL, Jia X, Wang J, et al (2009) Meta-analysis of genome scans and replication identify CD6, IRF8 and TNFRSF1A as new multiple sclerosis susceptibility loci. Nat Genet; 41(7):776-85.

de Sèze M, Ruffion A, Denys P, et al (2007) The neurogenic bladder in multiple sclerosis: review of the literature and proposal of management guidelines. Mult Scler; 13(7):915-28.

Donaghy M (1999) Neurologic Considerations of Organ Transplantation. In: Ginns L, Cosimi AB, Morris PJ (eds), Organ Transplantation. New Jersey (USA): Wiley-Blackwell, p 696-708.

Ebers GC, Sadovnick AD, Dyment DA, et al (2004) Parent-of-origin effect in multiple sclerosis: observations in half-siblings. Lancet; 363:1773-4.

Ekestern E and Lebhart G (2004) Mortality from multiple sclerosis in Austria 1970–2001: dynamics, trends, and prospects. Eur J Neurol; 11(8):511-20.

El-Salem K, Al-Shimmery E, Horany K, et al (2006) Multiple sclerosis in Jordan: a clinical and epidemiological study. J Neurol; 253(9):1210-6.

Feinstein A (2004) The neuropsychiatry of multiple sclerosis. Can J Psychiatry; 49(3):157-63.

Finlayson ML, Peterson EW, Cho CC (2006) Risk factors for falling among people aged 45 to 90 years with multiple sclerosis. Arch Phys Med Rehabil; 87(9):1274-9.

Forrest M, Sun SY, Hajdu R, et al (2004) Immune cell regulation and cardiovascular effects of sphingosine 1-phosphate receptor agonists in rodents are mediated via distinct receptor sub-types. J Pharmacol Exp Ther; 309:758-68.

Fredrikson S, Cheng Q, Jiang GX, et al (2003) Elevated suicide risk among patients with multiple sclerosis in Sweden. Neuroepidemiology; 22(2):146-52.

Friese MA, Jakobsen KB, Friis L, et al (2008) Opposing effects of HLA class I molecules in tuning autoreactive CD8+ T cells in multiple sclerosis. Nat Med; 14(11):1227-35.

Gadoth N (2003) Multiple sclerosis in children. Brain Dev; 25(4):229-32.

Gajofatto A, Stefani A, Turatti M, et al (2013) Bianchi MR, Lira MG, Moretto G, Salviati A, Benedetti MD. Prevalence of multiple sclerosis in Verona, Italy: an epidemiological and genetic study. Eur J Neurol; 20(4):697-703

Gray OM, McDonnell GV, Hawkins SA (2008) Factors in the rising prevalence of multiple sclerosis in the north-east of Ireland. Mult Scler; 14(7):880-6.

Grimaldi LM, Palmeri B, Salemi G, et al (2007) High prevalence and fast rising incidence of multiple sclerosis in Caltanissetta, Sicily, southern Italy. Neuroepidemiology; 28(1):28-32.

Goodin DS, Reder AT, Ebers GC, et al (2012) Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNβ-1b trial. Neurology; 78(17):1315-22

Grytten-Torkildsen N, Lie SA, Aarseth JH, et al (2008) Survival and cause of death in multiple sclerosis: results from a 50-year follow-up in Western Norway. Mult Scler; 14(9):1191-8.

Gupta G, Gelfand JM, Lewis JD (2005) Increased risk for demyelinating diseases in patients with inflammatory bowel disease. Gastroenterology; 129:819-26.

Hader WJ, Yee IM (2007) Incidence and prevalence of multiple sclerosis in Saskatoon, Saskatchewan. Neurology; 69(12):1224-9.

Hedström AK, Hillert J, Olsson T, Alfredsson L et al (2013). Smoking and multiple sclerosis susceptibility. Eur J Epidemiol; 28(11):867-74.

Hernán MA, Olek MJ, Ascherio A (1999) Geographic variation of MS incidence in two prospective studies of US women. Neurology; 53:1711-8.

Herrera BM, Ramagopalan SV, Orton S, et al (2007) Parental transmission of MS in a population based Canadian cohort. Neurology; 69:1208.

Herrera BM, Ramagopalan SV, Lincoln MR, et al (2008) Parent-of-origin effects in MS: observations from avuncular pairs. Neurology; 71:799.

Hirst C, Ingram G, Pickersgill T, et al (2009) Increasing prevalence and incidence of multiple sclerosis in south east Wales. J Neurol Neurosurg Psychiatry; 80(4):386-91.

Hirst C, Swingler R, Compston DA, et al (2008) Survival and cause of death in multiple sclerosis: a prospective population-based study. J Neurol Neurosurg Psychiatry; 79(9):1016-21.

Hoppenbrouwers IA, Liu F, Aulchenko YS, et al (2008) Maternal transmission of multiple sclerosis in a dutch population. Arch Neurol; 65:345.

Hupperts R, Broadley S, Mander A, et al (2001) Patterns of disease in concordant parent-child pairs with multiple sclerosis. Neurology; 57:290.

Internal Novartis analyses in US Department of Defense database (database reference: [Dorrance K, Ramchandani S, Neil N, Fisher H. (2013)] Leveraging the military health system as a laboratory for health care reform. Military Medicine; 178:142-145).

International Multiple Sclerosis Genetics Consortium, Hafler DA, Compston A, et al (2007) Risk alleles for multiple sclerosis identified by a genomewide study. N Engl J Med; 357:851.

International Multiple Sclerosis Genetics Consortium, Wellcome Trust Case Control Consortium 2, Sawcer S, et al (2011) Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. Nature; 476:214.

Islam T, Gauderman WJ, Cozen W, et al (2007) Childhood sun exposure influences risk of multiple sclerosis in monozygotic twins. Neurology; 69:381.

Jadidi E, Mohammadi M, Moradi T (2013) High risk of cardiovascular diseases after diagnosis of multiple sclerosis. Mult Scler; 0(0):1-5

Janka GE (2012) Familial and acquired hemophagocytic lymphohistiocytosis. Annu Rev Med; 63:233-246

Joensen P.(2010) Multiple sclerosis incidence in the Faroe Islands 1986-2007. Acta Neurol Scand; 121(5):348-53.

Joffe RT, Lippert GP, Gray TA, et al (1987) Mood disorder and multiple sclerosis. Arch Neurol; 44(4):376-8.

Johnson TA, Shames I, Keezer M, et al (2010) Reconstitution of circulating lymphocyte counts in FTY720-treated MS patients. Clin Immunol; 137(1):15-20

Kantarci OH, Barcellos LF, Atkinson EJ, et al (2006) Men transmit MS more often to their children vs women: the Carter effect. Neurology; 67:305.

Kantarci OH, Spurkland A (2008) Parent of origin in multiple sclerosis: understanding inheritance in complex neurologic diseases. Neurology; 71:786.

Kargarfard M, Eetemadifar M, Mehrabi M, et al (2012) Fatigue, depression, and health-related quality of life in patients with multiple sclerosis in Isfahan, Iran. Eur J Neurol; 19(3):431-7

Kelley BJ and Rodriguez M (2009) Seizures in patients with multiple sclerosis. Epidemiology, pathophysiology and management. CNS Drugs; 23(10):805-15.

Kim NH, Kim HJ, Cheong HK, et al (2010) Korean Multiple Sclerosis Study Group. Prevalence of multiple sclerosis in Korea. Neurology; 75 (16):1432-8.

Kingwell E, van der Kop M, Zhao Y, et al (2012b) Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. J Neurol Neurosurg Psychiatry; 83(1):61-6.

Koch M, Uyttenboogaart M, Polman S, et al (2008) Seizures in multiple sclerosis. Epilepsia; 49(6):948-53.

Koch-Henriksen N, Sørensen PS (2010) The changing demographic pattern of multiple sclerosis epidemiology. Lancet Neurol; 9:520.

Koutsouraki E, Costa V, Baloyannis S. Epidemiology of multiple sclerosis in Europe: a review. Int Rev Psychiatry. 2010; 22(1):2-13.

Lai C-H, Tseng H-F (2009) Population-based epidemiological study of neurological diseases in Taiwan: I. Creutzfeldt-Jakob disease and multiple sclerosis. Neuroepidemiology; 33(3):247-53.

Lalmohamed A, Bazelier MT, Van Staa TP, Uitdehaag BM, Leufkens HG, De Boer A, De Vries F. Causes of death in patients with multiple sclerosis and matched referent subjects: a population-based cohort study. Eur J Neurol. 2012 Jul; 19(7):1007-14.

Langer-Gould A, Brara SM, Beaber BE, Zhang JL. Incidence of multiple sclerosisin multiple racial and ethnic groups. Neurology. 2013 May 7; 80 (19):1734-9

Leray E, Morrissey SP, Yaouanq J, et al (2007) Long-term survival of patients with multiple sclerosis in West France. Mult Scler; 13(7):865-74.

Lincoln MR, Montpetit A, Cader MZ, et al (2005) A predominant role for the HLA class II region in the association of the MHC region with multiple sclerosis. Nat Genet; 37:1108-12.

Lings S (2002) Driving accident frequency increased in patients with multiple sclerosis. Acta Neurol Scand; 105(3):169-73.

Maakaroun NR, Moanna A, Jacob JT, et al (2010) Viral infections associated with haemophagocytic syndrome. Reviews of medical virology 2010 Mar; 20 (2):93-105.

Mackenzie IS, Morant SV, Bloomfield GA, MacDonald TM, O'Riordan J (2014) Incidence and prevalence of multiple sclerosis in the UK 1990-2010: a descriptive study in the General Practice Research Database. J Neurol Neurosurg Psychiatry; 85(1):76-84.

Marrie RA, Horwitz R, Cutter G, et al (2009) The burden of mental comorbidity in multiple sclerosis: frequent, underdiagnosed, and undertreated. Mult Scler; 15(3):385-92.

Marrie RA, Yu N, Blanchard J, et al (2010) The rising prevalence and changing age distribution of multiple sclerosis in Manitoba. Neurology; 74(6):465-71.

Mehling M, Brinkmann V, Antel J, et al (2008) FTY720 therapy exerts differential effects on T cell subsets in multiple sclerosis. Neurology; 71:1261-7.

Melcon MO, Gold L, Carrá A, et al (2008) Argentine Patagonia: prevalence and clinical features of multiple sclerosis. Mult Scler; 14(5):656-62.

Mizugishi K, Yamashita T, Olivera A, et al (2005) Essential role for sphingosine kinases in neural and vascular development. Mol Cell Biol; 25(24):11113-21.

Multiple Sclerosis International Federation (2013), "Atlas of MS 2013" Detailed data queries: http://www.atlasofms.org/index.aspx (accessed: 06-Mar-2014).

Nielsen NM, Westergaard T, Frisch M, et al (2006b) Type 1 diabetes and multiple sclerosis: A Danish population-based cohort study. Arch Neurol; 63:1001.

O'Connor P (2007) Natalizumab and the role of α4-integrin antagonism in the treatment of multiple sclerosis. Expert Opin Biol Ther; 7:123-36.

Orton SM, Wald L, Confavreux C, et al (2011) Association of UV radiation with multiple sclerosis prevalence and sex ratio in France. Neurology; 76:425-31.

Ojeda E, Díaz-Cortes D, Rosales D, et al (2013) Prevalence and clinical features of multiple sclerosis in Latin America. Clin Neurol Neurosurg. 2013 Apr; 115(4):381-7

Papathanasopoulos P, Gourzoulidou E, Messinis L, et al (2008) Prevalence and incidence of multiple sclerosis in western Greece: a 23-year survey. Neuroepidemiology; 30(3):167-73.

Patten SB, Beck CA, Williams JVA, et al (2003) Major depression in multiple sclerosis. A population-based perspective. Neurology; 61(11):1524-7.

Pender MP (2009) Does Epstein-Barr virus infection in the brain drive the development of multiple sclerosis? Brain; 132:3196-8.

Peterson EW, Cho CC, von Koch L, et al (2008) Injurious falls among middle aged and older adults with multiple sclerosis. Arch Phys Med Rehabil; 89(6):1031-7.

Pohl D (2008) Epidemiology, immunopathogenesis and management of pediatric central nervous system inflammatory demyelinating conditions. Curr Opin Neurol; 21(3):366-72.

Pugliatti M, Rosati G, Carton H, et al (2006) The epidemiology of multiple sclerosis in Europe. Eur J Neurol; 13(7):700-22.

Ragonese P, Aridon P, Salemi G, et al (2008) Mortality in multiple sclerosis: a review. Eur J Neurol; 15(2):123-7.

Ragonese P, Aridon P, Mazzola MA, et al (2010) Multiple sclerosis survival: a population-based study in Sicily. Eur J Neurol; 17(3):391-7.

Ramagopalan SV, Handel AE, Giovannoni G, et al (2011) Relationship of UV exposure to prevalence of multiple sclerosis in England. Neurology; 76:1410-4.

Redelings MD, McCoy L, Sorvillo F (2006) Multiple sclerosis mortality and patterns of comorbidity in the United States from 1990 to 2001. Neuroepidemiology; 26(2):102-7.

Reinhardt K, Weiss S, Rosenbauer J, et al (2014) Multiple sclerosis in children and adolescents: incidence and clinical picture - new insights from the nationwide German surveillance (2009-2011). Eur.J.Neurol; 21 (4):654-659.

Sadovnick AD, Eisen K, Ebers GC, et al (1991) Cause of death in patients attending multiple sclerosis clinics. Neurology; 41(8):1193-6.

Sadovnick AD, Ebers GC, Wilson RW, et al (1992) Life expectancy in patients attending multiple sclerosis clinics. Neurology; 42(5):991-4.

Salzer J, Hallmans G, Nyström M, et al (2012) Vitamin D as a protective factor in multiple sclerosis. Neurology; 79:2140.

Sardu C, Cocco E, Mereu A, et al (2012) Population based study of 12 autoimmune diseases in Sardinia, Italy: prevalence and comorbidity. PLoS One; 7(3):e32487.

Smestad C, Sandvik L, Celius EG (2009) Excess mortality and cause of death in a cohort of Norwegian multiple sclerosis patients. Mult Scler; 15(11):1263-70.

Stern M (2005) Aging with multiple sclerosis. Phys Med Rehabil Clin N Am; 16(1):219-34.

Stenager EN, Jensen B, Stenager M, et al (2011) Suicide attempts in multiple sclerosis. Mult Scler; 17(10):1265-8.

Storer RD, Sistare FD, Reddy MV, et al (2010) An industry perspective on the utility of short-term carcinogenicity testing in transgenic mice in pharmaceutical development. Toxicol Pathol; 38:51-61.

Sumelahti M-L, Tienari PJ, Wikstrom J, et al (2002) Survival of multiple sclerosis in Finland between 1964 and 1993. Mult Scler; 8(4):350-5.

Sumelahti ML, Hakama M, Elovaara I, et al (2010) Causes of death among patients with multiple sclerosis. Mult Scler; 16(12):1437-42.

Thacker EL, Mirzaei F, Ascherio A (2006) Infectious mononucleosis and risk for multiple sclerosis: a meta-analysis. Ann Neurol; 59:499.

The Australia and New Zealand Multiple Sclerosis Genetics Consortium (ANZgene) (2009) Genome-wide association study identifies new multiple sclerosis susceptibility loci on chromosomes 12 and 20. Nat Genet; 41(7):824-30.

The International Multiple Sclerosis Genetics Consortium (2007) Risk alleles for multiple sclerosis identified by a genomewide study. N Engl J Med; 357:851-62.

The International Multiple Sclerosis Genetics Consortium and the Wellcome Trust Case Control Consortium 2 (2011) Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. Nature; 476:214-9.

Toro J, Sarmiento OL, Díaz del Castillo A, et al (2007) Prevalence of multiple sclerosis in Bogotá, Colombia. Neuroepidemiology; 28(1):33-8.

Van der Mei IAF, Ponsonby AL, Dwyer T, et al (2003) Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study. BMJ; 327:316 (Internet) Available from: <http://www.bmj.com/content/327/7410/316> (Accessed 15 March 2013).

Williamson DM, Henry JP, Schiffer R, et al (2007) Prevalence of multiple sclerosis in 19 Texas counties, 1998-2000. J Environ Health; 69(10):41-5.

Willer CJ, Dyment DA, Sadovnick AD, et al (2005) Timing of birth and risk of multiple sclerosis: population based study. BMJ; 330:120.

Wingerchuk DM (2012). Smoking: effects on multiple sclerosis susceptibility and disease progression. Ther Adv Neurol Disord; 5(1):13-22.

Wong R, Beguelin GZ, de Lima M, Giralt SA, et al (2003) Tacrolimus-associated posterior reversible encephalopathy syndrome after allogeneic haematopoietic stem cell transplantation. Br J Haematol; 122:128-34.

World Health Organization (2004) The world health report 2004-changing history. Statistical Annex: Annex Table 2 Deaths by cause, sex, and mortality stratum in WHO regions, estimates for 2002 (Internet) Available from: http://www.who.int/entity//whr/2004/annex/topic/en/annex_2_en.pdf (Accessed 19 Aug 2008).

Novartis internal references

[Internal Novartis analyses in US Department of Defense database (database reference: Dorrance K, Ramchandani S, Neil N, Fisher H. (2013)] Leveraging the military health system as a laboratory for health care reform. Military Medicine; 178:142-145.

PSUR-11: Gilenya PSUR 29-Feb-2017 to 28-Feb-2018

Study CFTY720D2311

[PSUR-13: Gilenya PSUR 29-Feb-2019 to 28-Feb-2020]

Annex 8 – Summary of changes to the risk management plan over time

Table 14-6 Summary of changes to the risk management plan over time

Version	Date	Safety Concerns	Comment
2.0	Procedure approval date: 17-Mar-2011	Identified risks: Bradyarrhythmia (including conduction defects) occurring post-first dose Hypertension Liver transaminase elevation Macular edema Infections Leukopenia and lymphopenia Reproductive toxicity Bronchoconstriction Potential risks: Skin cancer Posterior Reversible Encephalopathy Syndrome (PRES) Other malignant neoplasms Thrombo-embolic events QT interval prolongation Convulsions Progressive multifocal leukoencephalopathy (PML) Reactivation of chronic viral infections Off-label use Pulmonary edema Decreased renal function Interaction with Ketoconazole Interaction with Atenolol Missing information: Elderly patients Pediatric patients Pregnant and lactating women Patients with diabetes mellitus Patients with cardiovascular conditions including myocardial infarction, angina pectoris, Raynaud's phenomenon, cardiac failure or severe cardiac disease, increased QTc interval, uncontrolled hypertension	

Version	Date	Safety Concerns	Comment
		Long-term risk of cardiovascular morbidity/mortality Long-term risk of malignant neoplasms	
3.2	Procedure approval date: 18-Jun-2012	No change to risks	Procedure approval date: 18-Jun-2012 Changes to Pharmacovigilance commitments: New studies FTY720D2403 and FTY720D2406 added to replace Post-approval 5-year safety study. New Proposed substudy added. New Study FTY720D2121 added. Targeted follow-up for cases of lymphoma changed to cases of non-cutaneous malignancies. Targeted follow-up added for cases of cardiac rate and rhythm disorders, stroke, ischemic cardiac events, and unexplained death events. Changes to Risk minimization commitments: In the Physician's Checklist, the statement, "Check liver transaminases at months 1, 3, and 6 of therapy and periodically thereafter or at any time if there are signs or symptoms of hepatic dysfunction" was changed to include monitoring at 9 and 12 months. In the Patient Reminder Card, the statement, "The need for a liver function test prior to treatment initiation and for liver function monitoring at months 1, 3, and 6 during GILENYA therapy and periodically thereafter" was changed to include monitoring at 9 and 12 months.
4.0	24-Apr-2012	Posterior Reversible Encephalopathy Syndrome (PRES) separated from Acute Disseminated encephalomyelitis-like (ADEM-like) events and changed to an identified risk.	Procedure approval date: 31-Aug-2012 No change to Pharmacovigilance or Risk minimization commitments.
5.0	04-Nov-2012	New potential interaction added for Class Ia or Class III antiarrhythmics medicinal products.	Procedure approval date: 26-Apr-2013

Version	Date	Safety Concerns	Comment
			Changes to Pharmacovigilance commitments: Studies FTY720D2121 and FTY720D2316 completed. Study FTY720D2399E1 replaced with Study FTY720D2399. No changes to Risk minimization commitments.
6.1	07-Sep-2013	New potential risk added called Interaction with Carbamezapine. The name of the potential risk called “Interaction with Atenolol” changed to “Interaction with Beta Blockers”. The name of the important identified risk called “Bradyarrhythmia (including conduction defects) occurring post-first dose” changed to “Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose”. Two new important potential risks called “Atypical MS relapse” and “Hemophagocytic syndrome” added.	Procedure approval date: 24-Oct-2013 Key safety messages in EU RMP educational materials updated regarding bradyarrythmia and first dose monitoring One new pharmacovigilance activity added to address potential risk of Hemophagocytic Syndrome (HPS). Monthly internal company safety database search for potentially undiagnosed cases of HPS. Potential HPS cases will be independently reviewed and adjudicated by External Adjudication Committee.
7.0	01-Nov-2013	One new important identified risk called “Varicella zoster virus” (VZV) infection was added. This risk was previously addressed under the existing important potential risk of “Reactivation of chronic viral infections” (RCVI), which was renamed “Herpes viral infections other than VZV” One new important potential risk called “Lymphoma” was added. This risk was previously addressed under the existing important potential risk of “Other malignant neoplasms”.	Procedure approval date: Not applicable
7.3	10-Apr-2014	The indication has been updated to include treatment with Gilenya after other disease modifying agents.	Procedure approval date: 26 May 2014 (EC Decision date) Changes to Pharmacovigilance commitments:

Version	Date	Safety Concerns	Comment
		New missing information called “Switch from other disease modifying agent” has been added. New important potential risk added called “Hypersensitivity”. “Hypersensitivity” changed to important identified risk. Missing information called “Switch from other disease modifying agent” has been changed to “Switch from other disease modifying therapy” to align with SmPC.	Studies FTY720D2403 and FTY720D2406 will also address new missing information topic called “Switch from other disease modifying therapy”. New routine pharmacovigilance targeted follow-up checklist added for new risk called “Hypersensitivity”. No changes to Pharmacovigilance Plan or Risk minimization commitments.
8.0	05-May-2014	Important identified risk called “Bronchoconstriction” and important potential risk called “Decreased renal function” were removed.	Procedure approval date: Not Applicable New enhanced pharmacovigilance program for collecting additional pregnancy related information and monitoring of pregnancy outcomes was added. The key safety messages in the Physician’s checklist educational material have been updated. There are no changes to the key safety messages in the Patient reminder card. The pharmacovigilance activity called Physicians Survey (CHMP-FUM16) is now completed and was removed. Direct Healthcare Professional Communications (DHPC) was removed as this activity was completed.
8.1	05-Sep-2014	Bronchoconstriction	Procedure approval date: Pending Re-introduction of Bronchoconstriction” as an important identified risk in all relevant sections
9.0	24-Feb-2015	Infections, updated to add “Cryptococcal infections, including cryptococcal meningitis”.	“Cryptococcal infections, including cryptococcal meningitis” were added under the existing identified risk “Infections” and relevant sections of the RMP version 9.0 were updated accordingly.
10.0	12-May-2015	Infections: Opportunistic infections will be included under the existing important identified risk of Infections. Infections as an important identified risk, which already includes cryptococcal infections, was	

Version	Date	Safety Concerns	Comment
		updated by combining the important identified risk of Varicella Zoster Virus infections (VZV) and important potential risks of Progressive multifocal leukoencephalopathy (PML) and Herpes viral infections other than VZV. 'Basal cell carcinoma (BCC)' was added as an important identified risk and the important potential risk of 'Skin cancer' was changed to 'Skin cancer other than BCC'. Pulmonary edema: was removed as an important potential risk and will continue to be monitored with routine pharmacovigilance.	
11.0	17-Jul-2015	This update includes information on PML case (without prior Tysabri use) and supplementary text was added in line with Pharmacovigilance Risk Assessment Committee (PRAC) recommendation for PML which was already covered under existing identified risk of infection.	Respective RMP sections are also updated with texts in line SmPC 'warning and precautions section'.
12.0	05-Jul-2016	The name of the important identified risk, "Infections" is updated to "Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection)", in line with the information recently approved in the EU Product Information.	The due dates of the final study/program reports for the additional pharmacovigilance activities, FTY720D2403, FTY720D2404 and PRIM are updated from 4Q 2020, 4Q 2017 and 2Q 2016 to 2Q 2023, 2Q 2031 and 1Q 2020, respectively. This RMP version includes updated clinical trial and post-marketing data for all risks from Periodic Safety Update Report (PSUR 9) (EU PSUR 8) (data lock point 28-Feb-2016) and also includes editorial changes.
13.0	16-Oct-2017	"Convulsions", previously classified as important potential risk is reclassified as important identified risk. "Pediatric patients", previously classified as missing information is removed from the list of safety concerns.	Updated with clinical trial data of pediatric patients from study FTY720D2311 with data lock point (DLP) (11-Aug-2017). Updated post marketing data and clinical data of adult patients updated with DLP (28-Feb-2017). Specific adverse event targeted follow-up checklists used to collect additional data for the Gilenya RMP risks were

Version	Date	Safety Concerns	Comment
			updated to include all checklists currently in use for Gilenya. Proposed SmPC provided with this updated EU RMP
14.0	07-Dec-2017	The safety concerns for Gilenya were reviewed in light of the updated GVP Module V. Some safety concerns previously classified as important are removed from the list of safety concerns. The Important identified risk of 'Basal cell carcinoma' was changed to 'Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)' and the Important potential risk of 'Skin cancer other than BCC was removed from the list of safety concerns	This version has been updated with the completion of Catergory 3 study FTY720D2399. Proposed educational program for Gilenya (fingolimod), which includes a Physician's checklist and a Patient reminder card were updated.
14.1	03-Apr-2018	Based on the AR on EU RMP V14.0, the following safety concerns proposed for removal in RMP V14.0 were requested to be maintained in the RMP **Identified risk:** Hypertension Posterior Reversible Encephalopathy Syndrome (PRES) Bronchoconstriction **Potential risk:** Acute disseminated encephalomyelitis-like (ADEM-like) events QT interval prolongation missing information: Patients with diabetes mellitus • Elderly patientsIn • In the same AR, Novartis was also requested to remove 'Atypical MS relapse' and 'Hemophagocytic syndrome' from the important potential risks, as those safety concerns are not addressed by any of the listed additional	EMA procedure number: EMEA/H/C/002202/II/47.

Version	Date	Safety Concerns	Comment
		pharmacovigilance activities, in line with GVP module V (Revision 2).	
13.1	10-May-2018	"Long-term use in pediatric patients' was added as new missing information and Study FTY720D2311 is added as new additional PV activity. Educational materials for physicians and patients, Physician's checklist for adult and pediatric population, and Patient / Parent / Caregiver reminder card were updated to include new additional risk minimization measure for the missing information "Long-term use in pediatric patients'.	Updated v13.0 based on the response to AR for EMA procedure EMEA/H/C/002202/X/0044/G.
13.2	14-Aug-2018	• Updated the wording of the missing information "Long-term use in pediatric patients" by Long-term use in pediatric patients, including impact on growth and development (including cognitive development) • Updated the milestones and due dates for the study D2311	Updated v13.1 based on the response to the AR for EMA procedure EMEA/H/C/002202/X/0044/G.
15.0	20-Sep-2018	Consolidated version of the EU RMP 14.1 and the EU RMP v13. .2.	First draft dated 20-Aug-2018 has been updated as per Rapporteur's recommendation on September 17, 2018
16.0	26-Mar-2019	The risk minimisation measures for the Important identified risk 'Reproductive toxicity' are updated. Important Potential Risks 'Interaction with Class Ia or Class III antiarrhythmic medicinal products' and 'Interaction with Beta blockers' are removed. Study D2403 timelines were updated	Updated based on the Final Assessment Report for procedure EMEA/H/C/002202/LEG/037
16.1	03-Sep-2019	Renamed the 'Patient / Parent / Caregiver reminder card' to 'Patient / Parent / Caregiver guide'.	Updated 16.0 based on the 2nd Request for Supplementary Information for EMA procedure EMEA/H/C/002202/II/0053

Version	Date	Safety Concerns	Comment
		Updated key messages in the Patient / Parent / Caregiver guide. Renamed the 'Pregnancy-specific patient card' to include the word "reminder". Updated key messages of the Pregnancy-specific patient reminder card. Updated 'Pregnancy Prevention Programme (PPP)' to 'Pregnancy prevention'. The 'Pregnancy outcomes Intensive Monitoring' programme (PRIM) is removed from the additional pharmacovigilance activities.	
17.0	07-Aug-2020	No changes to risks	Updated the milestones for the studies (CFTY720D2409/ CFTY720D2406/ CFTY720D2403) from 15-Dec-2020 to 30-Apr-2021
18.0		Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection was updated for important identified risk - Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection). The targeted follow-up checklists for pregnancy/PML were updated to be harmonized with those used for Mayzent (siponimod) and Kesimpta (ofatumumab)	Update based on the PRAC Recommendation for the review of Gilenya Global PSUR 13 (EU-PSUR 12; period 01-Mar-2019 to 28-Feb-2020) in procedure EMEA/H/C/PSUSA/00001393/202002) Updated post marketing data based on DLP of 28-Feb-2020