NOVARTIS

Clinical Development

FTY720D (Fingolimod)

Study protocol 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

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List of abbreviations

ADEM	Acute disseminated encephalomyelitis
AE	Adverse event
ALT	Alanine aminotransferase
ARR	Annualized relapse rate
AST	Aspartate aminotransferase
AV	Atrio-ventricular
CI	Confidence interval
CNS	Central nervous system
CRF	Case Report/Record Form
CPO	Country pharma organization
CRO	Contract research organization
D_LCO	Carbon monoxide diffusing capacity
DMT	Disease-modifying therapy
DS&E	Drug safety & epidemiology
EDC	Electronic data capture
EDSS	Expanded disability status scale
EU	Europe / European
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume within 1 second
FVC	Forced vital capacity
GPP	Good pharmacoepidemiology practices
HR	Hazard ratio
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent ethics committee
IFN	Interferon
i.m.	intra-muscular
IN	Investigator notification
i.v.	intra-venous
IRB	Institutional review board

MRI	Magnetic resonance imaging
MS	Multiple sclerosis
PASS	Post-authorization safety study
PML	Progressive multiform leucoencephalopathy
PPMS	Primary progressive multiple sclerosis
PRES	Posterior reversible encephalopathy syndrome
PRMS	Progressive relapsing multiple sclerosis
REB	Research ethics board
RRMS	Relapsing remitting multiple sclerosis
SAE	Serious adverse event
s.c.	sub-cutaneous
SPMS	Secondary progressive multiple sclerosis
ULN	Upper limit of normal
WBC	White blood cell

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Glossary of terms

Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting collection of any data described in the protocol)
Parallel cohort	Patients treated at time of study entry with an approved disease modifying therapies for MS other than fingolimod.
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Stop study participation	Point/time at which the patient came in for a final evaluation visit
Treatment of interest	Either fingolimod or another MS disease-modifying therapy
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Protocol synopsis

Title of study: 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

Purpose and rationale: Purpose is to explore the overall safety profile of fingolimod under condition of routine medical practice. This is a post approval commitment study to health authorities

Objectives: To explore the overall safety profile of fingolimod over the long term in patients with relapsing forms of MS under conditions of routine medical practice

Population: This study will include patients with relapsing MS who either have been recently initiated with fingolimod by their treating physician or who are being treated with other approved disease-modifying therapies as part of their MS treatment in accordance with the respective local prescribing information and routine clinical practice

Inclusion/Exclusion criteria:

Inclusion criteria

- Patients starting fingolimod treatment at study entry or within the last 3 months prior to study entry, or patients who are being treated currently with another MS disease-modifying therapy as part of their routine clinical care and according to the locally approved label.
- For EU countries, patients treated with other MS DMT should be on or starting their second or more approved MS therapy or should present with rapidly evolving severe RRMS.

Exclusion criteria

- Patients who already received fingolimod more than 3 months prior study entry

Treatment of interest: The prescription of fingolimod is at the sole discretion of the prescribing physicians, is not part of the study plan and will not be provided by the study sponsor.

Patients treated with other approved disease modifying therapies for MS will constitute a parallel control cohort.

Study design: Non-interventional, parallel-cohort, long-term safety study

Key data collection:

- AEs and SAEs
- Vital signs
- Local laboratory blood results
- Ophthalmic examination results
- Pulmonary function test results

- Relapses

Data analysis: The purpose of this study is to explore the overall safety profile of fingolimod over the long-term and provide the systematic data on the incidence rates (IRs) of selected safety-related outcomes in the target population.

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum. Summary statistics for discrete variables will be presented in terms of absolute and relative frequencies here.

1 Introduction

1.1 Background

Multiple Sclerosis (MS) is a chronic, immune-mediated disease of the central nervous system characterized by inflammation, demyelination and axonal/neuronal destruction, ultimately leading to severe disability. MS affects ~ 2.5 million individuals worldwide. At diagnosis, approximately 85% of patients have relapsing-remitting MS (RRMS), characterized by recurrent, acute episodes (relapses) of neurological symptoms. After 6-10 years, 30-40% of patients with RRMS have progressed to secondary progressive MS (SPMS), when a less inflammatory, and more neurodegenerative, course of disease takes precedence. SPMS can also be segregated based on whether patients continue to experience relapses (relapsing form of SPMS) or not (purely progressive SPMS). About 10-15% of MS patients present with a primary progressive course (PPMS) defined by a continuous accumulation of neurological disability from symptom onset without superimposed exacerbations or remissions. Progressive relapsing MS (PRMS; chronic progressive from onset with infrequent relapses) is the least frequent form of MS.

Several therapies are approved for patients with RRMS and fall within 5 classes of products: interferon (IFN)β (1a and 1b), glatiramer acetate (amino acid copolymer), natalizumab (selective adhesion molecule inhibitor), mitoxantrone (chemotherapeutic), and fingolimod (S1P receptor modulator). All are considered as immunomodulatory or immunosuppressive medications. Beta interferons have multiple immune actions but the means by which the drugs are effective in MS remains unknown. They have shown modest (~30%) effect on relapses and in the case of IFNβ-1a, on disability (Goodin et al. 2002). Relatively minor differences in efficacy, based on dose frequency, exist between IFNβ products. Glatiramer acetate, a random mixture of amino acid copolymers has an effect on relapses similar to IFN-β but has not shown an effect on disability (Goodin et al. 2002). Natalizumab blocks lymphocyte migration into the CNS by inhibiting interaction of alpha-4 integrins on lymphocytes with the endothelial receptor VCAM-1 leading to significant reductions in relapse rate (68%) and disability (42%) (Polman et al. 2006). The risk of progressive multiform leucoencephalopathy (PML) limits use of this product predominantly to second-line situations (Ransohoff, 2007). Whether patients negative for antibodies to the JC virus (causal agent of PML) will have a lower risk of PML than those positive for antibodies (as appears likely based on preliminary reports) remains to be determined. Likewise, mitoxantrone, a chemotherapeutic agent, while demonstrating efficacy on relapses, is associated with risks of cardiac and hematological events that substantially restrict its use (Goodin et al. 2002). All of the above medications are given by injection (SC, IM or IV).

Fingolimod (FTY720) is a new chemical entity for once daily oral administration which has been submitted to health authorities in the USA and in Europe late 2009 and subsequently in other countries worldwide to obtain market authorization. Since August 2010, fingolimod has been approved in several countries for treatment of patients with relapsing of MS and is currently under review by other health authorities.

The efficacy profile of fingolimod was evaluated in three main studies. In one of the phase III clinical trials, study CFTY720D2302 (acronym TRANSFORMS), a large active controlled study vs. intramuscular interferon beta-1a, fingolimod showed a significant reduction in relapse rate reduction over the 12-month treatment period and reduced magnetic resonance imaging (MRI) lesion counts and rate of brain atrophy (Cohen et al. 2010). In another Phase III trial, Study CFTY720D2301 (acronym FREEDOMS), a 2-year placebo-controlled study, fingolimod demonstrated reduction of relapse rate, disability progression, MRI lesion counts and rate of brain atrophy (Kappos et al. 2010). Study CFTY720D2201E1, a long-term phase II open-label extension trial, where data up to 7 years of exposure showed sustained low levels of MS disease activity as manifest by low relapse rates, low lesion counts on brain MRI and low rate of disability progression.

The safety profile of fingolimod has been well characterized with over 9,300 MS patients treated with fingolimod in the context on clinical studies, comprising approximately 14,000 patient years of exposure by 31 Aug 2011. During the course of the fingolimod clinical development several areas were identified as safety areas of note: bradyarrhythmias upon treatment initiation or on restarting after an interruption of fingolimod therapy of more than 14 days, liver transaminase elevations, hypertension and macular edema.

Initiation of fingolimod treatment results in a transient decrease in heart rate and infrequently induces atrio-ventricular (AV) block. In MS clinical trials the mean maximal decrease in heart rate after the first dose intake was ~ 8 bpm and was seen at ~5 hours post-dose. Heart rates below 40 beats per minute were rarely observed in patients on fingolimod 0.5 mg/day. Heart rate progressively returned to baseline within 1 month of dose initiation despite continued dosing. In addition, a mild increase in blood pressure of approximately 1-2 mmHg diastolic and 2-3 mmHg systolic on average. This onset after approximately 2 months of treatment initiation persisted with continued treatment but reversed upon cessation of therapy. Hypertension was reported as an adverse event in 6.1% of patients on fingolimod 0.5 mg/day and in 3.8 % of patients on placebo in the 2-years placebo controlled study.

Liver enzyme elevations were seen in clinical trials. Asymptomatic elevations in serum levels of hepatic transaminases ≥3x ULN and ≥5x ULN, were observed in 8.5% and 1.9% of patients treated with fingolimod 0.5 mg/day respectively compared to 1.7% and 1.0% for patients receiving placebo. The majority of elevations occurred within 6-9 months of therapy and returned to normal, generally within 2-3 months of discontinuation of therapy.

Macular edema occurred in 0.4% of patients treated with fingolimod 0.5 mg/day. Approximately 75% of cases occurred within the first 3-4 months of therapy. The macular edema generally improved or resolved spontaneously after drug discontinuation. The risk of developing macular edema appears to be increased in MS patients with a history of uveitis. There is limited data on fingolimod in MS patients with diabetes mellitus. In earlier renal transplant clinical studies where patients with diabetes mellitus were included, therapy with fingolimod 2.5 mg/day and 5 mg/day resulted in a 2-fold increase in the incidence of macular edema. MS patients with diabetes mellitus are therefore expected to be at a higher risk for macular edema.

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. The overall rate of infections (in study D2301 72% on

fingolimod vs. 72% on placebo) and serious infections (in study D2301 1.6% on fingolimod vs. 1.9% on placebo) at the 0.5 mg/day dose, fingolimod was similar to placebo. However, lower respiratory tract infections, primarily bronchitis, were more common in fingolimod treated patients (in study D2301 8.0% on fingolimod vs. 3.6% on placebo for bronchitis and 0.5% on vs. 0.2% for pneumonia). One fatal primary disseminated varicella zoster infection and one fatal herpes simplex encephalitis case have occurred in patients receiving the 1.25 mg/day dose.

As part of a post-approval commitment to several health authorities Novartis is conducting this non-interventional post-authorization safety study (PASS) in order evaluate the overall long-term safety profile of fingolimod in a real-life setting in addition to further monitor safety areas of note described earlier. In addition this study will allow collection of safety information including, but not limited to infections, cardiac and vascular events (e.g. stroke, myocardial infarction, angina pectoris and peripheral vascular disease, second and third degree AV conduction block, hypertension), malignancies, pulmonary events, seizures, atypical MS relapses, and atypical severe neurological events.

As the study will be conducted in the target population under conditions of routine clinical care, it will also provide relevant safety information in populations that had not been included in the clinical development program such as elderly patients or patients with diabetes. It will allow further relevant safety information to be collected in addition to the already well-established safety profile based on the clinical trial database. An analogous study is also conducted in North America (CFTY720D2403).

This study will also collect data in a similar manner in a parallel-cohort in which patients will receive other approved disease-modifying therapies (DMT). This cohort will be used as an internal benchmark dataset for selected events and will supplement comparisons based on available external benchmarking databases. In the EU countries, the parallel cohort will only enroll patients already on, or starting, their second or more approved MS therapy or should present with rapidly evolving severe RRMS.

1.2 Purpose & rationale

The purpose of this multi-country, prospective, non-interventional (observational), parallel-cohort post-approval safety study in patients with relapsing MS, either recently (as defined by at study entry or within 3 months prior) initiated treatment with fingolimod or receiving another DMT, is to explore the overall safety profile of fingolimod under conditions of local label and routine medical practice.

2 Study objectives

2.1 Main objectives

To explore the overall safety profile of fingolimod, as measured by adverse events and vital signs, over the long term in patients with relapsing forms of MS under conditions of routine medical practice.

2.2   Other objectives

To investigate the incidence of selected safety outcomes including, but not limited to cardiac and vascular events (e.g. stroke, myocardial infarction, angina pectoris and peripheral vascular disease, second and third degree AV block, hypertension), symptomatic bradyarrhythmias on treatment initiation or on re-starting after an interruption in fingolimod therapy, eye events (e.g. macular edema), liver events, infections, pulmonary events, malignancies (e.g. lymphoma), seizures, atypical MS relapses and other atypical severe neurological events (e.g. PRES and ADEM) in the target population that recently initiated fingolimod according to the approved product label.

To put the fingolimod results on selected safety outcomes into context by using an internal parallel cohort whenever applicable or external benchmarking databases for less frequent events.

This study will also observe long-term MS disease activity of fingolimod in patients with MS, as measured by MS relapse, EDSS, and MRI qualitative changes.

3   Study design

3.1   Study design

This is a multi-country multi-center, long-term, prospective, non-interventional, parallel-cohort study to monitor and further describe the long-term safety of fingolimod. This study will be conducted in compliance with both an FDA post marketing requirement and Volume 9a of The Rules Governing Medicinal Products in the European Union (EudraLex Volume 9a, version September 2008), and is aligned with various guidelines and recommendations for good epidemiological practice for non-interventional studies and internationally accepted guidelines (FDA 2002), (EMEA 2005), (Glicklich & Dreyer 2007), (International Society of Pharmacoepidemiology 2008).

Patients eligible for participation in this study will, as part of their routine medical care, receive either fingolimod (fingolimod-cohort) or another approved disease-modifying therapy (parallel-cohort). It is anticipated that a minimum of 2000 patients recently initiated with fingolimod and 1000 patients treated with other approved MS DMT, will be included in this study in line with the study's inclusion and exclusion criteria. Patients will be followed in the study until the last patient enrolled is followed five years. Based on a mean follow-up time of 4 years (to account for the drop-out), for a minimum of 2000 included fingolimod patients a total exposure time of approximately 8,000 person years is anticipated. For some of the safety outcomes where considered feasible, data will be pooled from CFTY720D2403. The pooled data would include up to 4000 fingolimod patients (and 2000 control patients) with a total anticipated exposure of approximately 16,000 person-years.

Recommended data collection timepoints are intended to be aligned with most local labels and patterns of care that most patients will receive in routine clinical practice. Since this is a non-interventional study, there are no special protocol–mandated visits or procedures associated with the study. However whenever applicable, evaluations documented in the eCRF are expected to be aligned with the local prescribing information recommendations and

individual clinician practice. Information on safety areas of specific interest (see section 5.4) will be specifically collected.

During the course of the study, patients will be allowed to switch DMT (i.e. fingolimod or other DMT) while remaining in the study unless they are converted to an investigational DMT. Whenever possible, the patient should be followed for safety-related information approximately 6 months after this treatment discontinuation. Irrespective of which approved MS therapy they start after stopping fingolimod/original DMT, patients will remain in their original cohort.

The parallel cohort will deliver benchmark data for specific endpoints of interest such as hypertension, asthma or dyspnea. This approach allows the same data collection methods in the fingolimod and the parallel cohorts for this specific information and ensures simultaneous collection in a prospective manner.

For less frequent safety events such as cancer, or myocardial infarction, external databases are more appropriate to estimate the background risk that would be expected in the target population and provide more relevant comparisons than the internal cohort.

3.2   Interim analyses

A descriptive summary of the data of this non-interventional study will be compiled on a periodic basis (at least yearly) in addition to the regular periodic safety updates that are required by the health authorities after market approval has been granted.

4   Population and setting

This study will include patients with relapsing MS who either have been recently initiated with fingolimod by their treating physician or who are treated or starting with other DMT as part of their MS treatment in accordance with the respective local prescribing information and routine clinical practice.

Participating sites will be encouraged to enroll patients in both cohorts in a consecutive manner when patients come for their regular visit in order to minimize bias in patient selection.

During the fingolimod clinical development some population considered at risk were not necessarily studied. As part of this study, participating sites are highly encouraged to enroll patients with diabetes mellitus, cardiovascular risk factors, asthma, COPD or other pulmonary risk factors in order to better describe the overall safety profile of fingolimod in such population.

4.1   Inclusion criteria

Patients eligible for inclusion in this study have to fulfill the following criteria:
- Patients starting fingolimod treatment at study entry or within the last 3 months prior to study entry, or patients who are treated or starting with another MS DMT as part of their routine clinical care and according to the locally approved label.

- For EU countries, patients treated with other MS DMT should be on or starting their second or more approved MS therapy or should present with rapidly evolving severe RRMS.
- Patients, or legal representative of the patient, must provide written informed consent.

Treating physicians are encouraged whenever possible, to enroll in the parallel cohort, patients who have only recently initiated their new MS DMT.

4.2   Exclusion criteria

- Patients who already received fingolimod more than 3 months prior study entry.

4.3   Study completion

The study will be considered completed once the last patient enrolled in the study will have been followed for five years.

Participation in this study has no impact on the type of medical care that the patient will receive during study as well as post-study participation.

4.4   Change in medications of interest and premature study discontinuation

During the course of the study, a patient may discontinue his/her MS DMT:

- If this patient then starts another approved MS DMT or remains off DMT, this patient may remain in the study. If possible, data should then be captured at the time of this change in MS therapy (either to another DMT or stopping DMTs entirely), 6 months later and thereafter as per the recommended data collection schedule until the end of the study.

- If this patient is to receive an investigational MS DMT, this patient will have to stop study participation. If possible, data should then be captured at the time of this change in MS therapy and 6 months later. This last time point will constitute the end-of-study data collection point for this patient.

Patients may voluntarily withdraw from the study for any reason at any time.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the treating physician should contact the patient in accordance with their own routine clinical practice.

5   Data collection

There are no mandatory visits in the context of this non-interventional study. Patients will be followed according to the local prescribing information and practice in terms of visit frequency and type of assessments performed and only these data will be collected as part of this study. It is expected that individual patient data reported in this study should be in line with local label recommendations wherever applicable. Below is the recommended data collection schedule that is intended to mirror the patterns of routine clinical care of most patients being treated with fingolimod or other DMT (parallel cohort), and the differences in local labels (Table 5-1). It is highly recommended that patients should be evaluated at least

once a year and at completion of the study. If this is not happening, a phone call with the patient might be attempted in order to capture vital status and occurrence of adverse events. Note that a number of the recommended examinations for fingolimod patients (e.g. ophthalmic examinations) will not be obtained in the parallel-cohort unless they are performed as part of routine clinical care.

Table 5-1   Recommended data collection schedule

Visit	Baseline	Month 1	Month 3	Month 6	Month 9	Month 12 Every 6 months	Change in MS therapy[8]	6-month fup[9]	End of study
Assessments and data collection page									
Informed consent (mandatory)	X								
Demographic	X								
Risk factors and co-morbidity	X								
MS history	X								
MS disease-modifying therapy record	X			Record as needed					
1st dose observation[1]	X			Record as needed					
Pregnancy status (female of childbearing potential only)	X			Record as needed					
Vital signs	X	X	X	X	X	X	X	X	X
Selected Adverse Events [2]		X	X	X	X	X	X	X	X
MS status[3]		X	X	X	X	X	X	X	X
Ophthalmic examination[4]	X		when performed		Record as needed				
Hematology & Biochemistry[5]	X	X	X	X	X	Record as needed			
Dermatological examination[6]	X			Record as needed					
Pulmonary function tests				Record as needed					
Adverse events[7]				Record as needed					
Serious Adverse Events[7]				Record as needed					
Concomitant medication				Record as needed					
Study completion									X

1. Patients who newly initiate fingolimod therapy or are re-starting fingolimod after an interruption of more than 14 days should be observed for 6-hours after treatment initiation depending on local label.

2. Selected AEs include cardiac and vascular events (e.g. stroke, myocardial infarction, angina pectoris and peripheral vascular disease, second and third degree AV block, hypertension), symptomatic bradyarrhythmias on treatment initiation or on re-starting after an interruption in fingolimod therapy, eye events (e.g. macular edema), liver events, any infection, pulmonary events (e.g. dyspnea, asthma), malignancies (e.g. lymphoma), seizures, atypical MS relapse, and other atypical severe neurological events (e.g. ADEM, PRES).

3. MS status will capture when available, MS relapses, EDSS and MRI changes.

4. Fundoscopy and visual acuity are the recommended evaluations. For patients new to fingolimod therapy, the ophthalmic exam is recommended 3-4 months after treatment initiation as per local label. It is recommended that MS patients with diabetes mellitus or a

Visit	Baseline	Month 1	Month 3	Month 6	Month 9	Month 12 Every 6 months	Change in MS therapy[8]	6-month fup[9]	End of study
Assessments and data collection page									

history of uveitis undergo an ophthalmologic evaluation prior to initiating fingolimod therapy and have follow-up evaluations while receiving fingolimod therapy.

5. Hematology & biochemistry only local laboratory results are being captured. Measurements especially total WBC and liver function test whether normal or abnormal could be captured in the CRF if performed For Baseline data collection point, the last results available (maximum 6-months old) should be entered irrespective if abnormal or not. Liver enzymes should be measured and results captured as per local label. For ischemic type of events, results of prothrombin time/partial thromboplastin time, homocysteine, Activated protein C Resistance, lupus anticoagulant, antiphospholipid antibody, protein C, protein S fibrinogen and antithrombin III should be collected if performed.

Hematology panel includes hemoglobin, hematocrit, platelets, white blood cells, absolute neutrophils, absolute lymphocytes, absolutes eosinophils, absolute basophils and absolute monocytes.

Biochemistry panel includes glucose, calcium, sodium, potassium, magnesium, creatinine, urea, BUN, uric acid, albumin, total protein, alkaline phosphatase, ALT (SGPT), AST (SGOT) total bilirubin, GGT, total cholesterol and triglycerides.

6. Dermatological examination should be performed according to local label

7. All events meeting the criteria for an AE or SAE should be reported on the "Adverse events" eCRF page.

8. While in the study, patients who are changing approved MS DMT may document in the CRF any evaluation performed at the time stopping the previous MS therapy.

9. When patients are discontinuing their previous DMT, whenever available data should be collected 6 months after discontinuation. For patients changing to investigational therapy, this should actually be replaced by their End of study data collection visit.

5.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the participating site. Upon signing the informed consent form, the patient is assigned a patient number by the treating physician. At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third patient is assigned patient number 3). Once assigned to a patient, a patient number will not be reused.

5.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients includes: date of birth, age, sex, race, and ethnicity (where legally possible). Relevant medical history/current medical condition data will be captured using the Risk factors and comorbidity eCRF. Where possible, diagnoses, and not symptoms, should be recorded.

Baseline characteristics will also include, MS history including MS treatment.

5.3 Treatments of interest

The treatments of interest in this study are:
- For the fingolimod cohort: fingolimod 0.5 mg/day
- For the parallel-cohort: other approved MS DMT (e.g. beta interferon-1a, natalizumab).

The choice of treatment, as well as the decision to discontinue treatment, are at the sole discretion of the prescribing physician and the patients and are independent from participation in this study.

Any change in DMT (i.e. dose, frequency or treatment) should be captured in the MS disease-modifying therapy record CRF.

Patients are allowed to switch MS therapy while remaining in the study.

5.4 Variables of interest

One of the interests in this study relates to the occurrence of selected adverse events. Therefore data regarding new onset or worsening of the following selected adverse events will be specifically collected at each visit:

- Cardiac and vascular events (e.g. stroke, myocardial infarction, angina pectoris and peripheral vascular disease, second and third degree AV block, hypertension)
- Symptomatic bradyarrhythmias
- Eye events (e.g. Macular edema)
- Liver events
- Any infection
- Pulmonary events
- Malignancies (e.g. lymphoma)
- Seizures
- Atypical MS relapses - If, in the judgment of the treating physician, an MS relapse is unusually severe, atypical or unexpected and warrants specific notification, then it should be recorded as an adverse event. Appropriate additional investigations to determine a specific etiology are recommended.
- Other atypical severe neurological events (e.g. ADEM, PRES)

5.5 Safety related measurements

The following information should be collected in the context of this study in line with the different local label recommendations and whenever available:

- Physical examination
- Vital signs (heart rate, blood pressure)
- Laboratory evaluations results (e.g. white blood cell counts, including differential, and liver function tests)
- Ophthalmologic examinations results
- Pulmonary function tests results (FEV1, FVC and DLCO)
- Dermatological examination results

5.5.1 Physical examination

A physical examination may be performed at a routine clinical visit and may include an assessment of skin, head and neck, lymph nodes, breast, heart, lungs, abdomen, back and/or comments on general appearance. A neurological examination may also be a part of the physical examination. All significant findings that are present prior to start of the study should be reported on the Risk factors and co-morbidity CRF. Significant findings made after the

start of the study which meet the definition of an AE as defined per this protocol (See Section 6.1)) should be recorded on the Adverse Event eCRF.

5.5.2 Vital signs

Vital signs may be recorded at a routine clinical visit. Vital signs may include sitting pulse rate, sitting systolic and diastolic blood pressure.

5.5.3 Height and weight

Height should only be recorded at baseline while body weight may be recorded at each routine clinical visit.

5.5.4 Laboratory evaluations

Baseline laboratory evaluations should capture the last local laboratory results available prior study entry (maximum 6 months old). Afterwards, during the course of the study, only locally available clinically relevant laboratory results (normal or abnormal) should be collected.

Hematology and biochemistry measurements, especially total WBC and liver function tests (ALT, AST, and bilirubin and alkaline phosphatase) should be collected locally as per the local label and when available, the results should be recorded in the Laboratory eCRF pages.

In case of ischemic type of events, results of prothrombin time/partial thromboplastin time, homocysteine, Activated protein C Resistance, lupus anticoagulant, antiphospholipid antibody, protein C, protein S fibrinogen and antithrombin III may also be collected if performed.

5.5.5 Pulmonary function tests

Pulmonary Function tests evaluating forced expiratory volume within 1 second (FEV1) and forced vital capacity (FVC) and carbon monoxide diffusing capacity (D_LCO) should be performed when clinically indicated while a patient is taking fingolimod or another disease modifying therapy.

5.5.6 Ophthalmic evaluation

Ophthalmic examinations should be performed during the course of this study for the purpose of detecting macular edema according to local label.

5.5.7 Dermatological evaluation

Dermatological examinations should be performed where applicable according to local label prior to the start of treatment with fingolimod, and regularly thereafter.

5.5.8 Pregnancy

For fingolimod treated patients, pregnancy should be excluded for all women of childbearing potential, in accordance with the local product label, prior to entering this study. If a patient becomes pregnant during the study, the patient should immediately inform her treating physician to discuss management options. In addition, patients taking fingolimod will have the opportunity to participate in a pregnancy registry (see section 6.3).

5.6   Other measurements

In order to characterize disease evolution and its potential impact on safety events, MS status including MS relapses, EDSS, walking ability and MRI qualitative changes should be collected within the normal visit data collection whenever available.

6   Safety monitoring

6.1   Adverse events

In this study, Novartis is interested in collecting key selected adverse events (See Section 5.4). In addition, any additional events that meet the criteria for an AE should also be reported on the "Adverse events" eCRF. An adverse event is defined as the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after signing the informed consent, even if the event is not considered to be related to fingolimod or to the disease modifying therapy. Medical conditions/diseases present at study entry are only considered adverse events if they worsen after signing the ICF.

The occurrence of these selected adverse events and other reported adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events CRF with the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to fingolimod or to a DMT (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

A SAE is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (e.g. hospitalization for relapse treatment)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the study start
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Information about adverse reactions observed in relation to fingolimod can be found in the local product labeling.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 6.2.

6.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 12 weeks after the patient has stopped study participation (defined as time of last visit) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 12 weeks period should only be reported to Novartis if the treating physician suspects a causal relationship to the treatment of interest.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the treating physician receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form for post marketing surveillance study. The treating physician must assess the relationship of any SAE to treatment of interest, complete the SAE report form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety and Epidemiology (DS&E) Department. The telephone and telecopy number of the contact persons in the local department of Clinical Safety and Epidemiology, specific to the site, are listed in the treating physician/ investigator folder provided to each site. The original copy of the SAE report form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE report form was sent, using a new SAE report form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in Package Insert (new occurrence) and is thought to be related to the fingolimod, a DS&E Department associate may urgently require further information from the treating physician for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all treating physicians involved in any study with the same drug that this SAE has been reported.

6.3 Pregnancy reporting

To ensure patient safety, each pregnancy in a patient on fingolimod or another DMT must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy should be recorded on a Post-Marketing

Surveillance Study Pregnancy Form and reported by the treating physician to the local Novartis DS&E Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to fingolimod or another DMT of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE report form.

Any patient taking fingolimod that becomes pregnant during the course of this study will be encouraged to participate in the Gilenya Pregnancy Exposure Registry. Details surrounding participation in this registry will be provided to the patient at the time the pregnancy is reported.

7 Data analysis

The purpose of this study is to explore the overall safety profile of fingolimod over the long-term in the target populations under conditions of routine clinical care and provide the systematic data on the incidence rates (IRs) of selected safety-related outcomes in the target population.

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum. Summary statistics for discrete variables will be presented in terms of absolute and relative frequencies.

For selected safety outcomes, incidence rates with respective 95% confidence intervals (CI) will be calculated when applicable.

All results will be reported separately for the 2 cohorts (fingolimod and other DMT).

Interim results will be included in the periodic safety updates that are required by the health authorities. A final analysis will be performed at end of the study including IRs and adjusted Hazard Ratio (HRs) using a Cox proportional hazards regression model.

To gain more power in estimating the incidence of selected safety outcomes between the fingolimod cohort and other DMT cohort, safety data will be pooled together with the same data from study CFTY720D2403. The pooled data will include up to 4000 fingolimod patients and 2000 patients from other DMT. IRs as well as adjusted HRs for the selected safety outcomes will be provided for the pooled safety data. Homogeneity of the pooled data will be examined. Details of the pooling will be included in the statistical analysis plan.

Statistical analysis of all data will be performed using SAS® statistical software (SAS Institute, Cary, NC, USA).

7.1 Patient demographic and other baseline characteristics

Patient demographic and baseline characteristic data will be described by means of absolute and relative frequencies for categorical variables and mean, standard deviation minimum and maximum for continuous variables. Categorical variables will include sex, race, ethnicity, country, year of birth (grouped) and age (grouped). Continuous variables will include age, height and weight.

Relevant medical history/current medical condition data and any medications taken to treat these conditions; MS history and MS treatment data will also be summarized by frequency of

this conditions and treatments. Duration of MS and duration of previous MS treatment at baseline will be described with mean, median, standard deviation minimum and maximum.

7.2 Treatment exposure

Daily dose of fingolimod and the other DMT will be described with mean, standard deviation, minimum and maximum.

Duration on fingolimod or any of the other DMT will be summarized by mean, standard deviation, minimum and maximum. Drug exposure after patients switch from fingolimod to other DMT or vice versa will not be included in the calculation of duration for the two cohorts. Details for the calculation of exposure after patients switch medication will be described in the statistical analysis plan.

Percentage of patients discontinuing fingolimod and percentage of patients switching from other DMT to fingolimod will be reported.

Reason for stopping fingolimod or other DMT will be described.

7.3 Analysis of the main variables

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

7.3.1 Variables

The overall safety profile of fingolimod will be assessed based on adverse events and vital signs.

7.3.2 Statistical model, hypothesis and method of analysis

Data for the main variables will be presented using descriptive statistics and no statistical tests are planned.

Adverse Events:

The incidence of adverse events (new or worsened from baseline) and suspected treatment of interest related adverse events will be summarized as frequency count and percentage of patients with adverse events by primary system organ class, and preferred term.

In addition, the incidence of death, SAEs, AEs leading to discontinuation, and other significant AEs will be summarized separately by primary system organ class and preferred term.

All information pertaining to adverse events noted during the study will be listed by center and patient number.

Vital Signs:

Vital sign data will be summarized as descriptive statistics for change from baseline value. The incidence rates of notable vital sign abnormalities will be summarized.

7.3.3   Handling of missing values/censoring/discontinuations

Reasonable attempts should be made to limit the amount of missing data related to safety to ensure that important information related to the main objective of the study, evaluation of the long-term safety of fingolimod, is captured. No imputation will be made on the eCRFs for missing data.

7.4   Analysis of other variables

7.4.1   Safety-related outcomes of interest

Other safety-related outcomes of interest will include cardiac and vascular event (e.g. stroke, myocardial infarction, angina pectoris and peripheral vascular disease, second and third degree AV block, hypertension), symptomatic bradyarrhythmias, eye events (e.g. macular edema), liver events, infections, pulmonary events, malignancies (e.g. lymphomas), seizures atypical MS relapses, and other atypical severe neurological events (e.g. ADEM, PRES).

Descriptive statistics will be used to summarize all safety criteria. Basically, IRs per person-years of observation and 95% CI will be calculated assuming a Poisson distribution. Person-years are calculated as follows. If the AE is distal outcome like cancer/malignancies, all the time the patient is enrolled in the registry as time at risk or until the first occurrence of the cancer will be considered. However, if the AE is considered an acute AE then the follow-up time will end 90 days after either discontinuation of the drug, the onset of the specific AE, or the disenrollment from the registry, whichever comes first. For selected AEs of special interest, the person-time at risk for each patient will be computed separately for each AE. For those selected adverse events, patients will be censored at time of event. For adverse events not included in the selected list, person-time years would be calculated for the whole duration of follow-up (up to 90 days after last exposure) or the discontinuation from the study, whatever comes first. No censoring will be performed for these non-selected AEs at time of event(s).

At the end of the study a Cox proportional hazards regression model will be used to assess differences in risk of selected safety outcomes between the fingolimod cohort and the parallel cohort, adjusting for baseline covariate variables. Details will be included in the statistical analysis plan.

To ensure a valid descriptive comparison of the estimated incidence rates, data will be stratified into relevant subgroups by MS status, duration of treatment exposure, age, gender, ethnicity and geographic region in order to get homogeneous subgroups with respect to the background risk. Incidence rates will also be presented within each subgroup for each cohort.

7.4.2   Effectiveness variables

The following long-term effectiveness data will be evaluated as other objectives in this study.

MS Relapse: The Annual Relapse Rate (ARR) will be presented. Data on time to relapse will also be summarized.

EDSS: Descriptive statistics on absolute EDSS scores and change from baseline will be presented.

7.5 Sample size calculation

It is planned to include 2000 patients on fingolimod and 1000 in the parallel cohort and conduct a five-year follow-up. Sample size consideration is based on feasibility of patient recruitment. Power for detecting increased risk with fingolimod cohort vs. the external database and parallel cohort for the selected safety outcomes will be calculated given the assumed sample size. Allowing a 20% reduction in patient-years in order to account for patients lost to follow-up or discontinuing the study, the power calculations assume 8,000 fingolimod patient-years exposure based on a mean follow-up period of 4 years for the 2000 fingolimod patients to be enrolled in this study.

Table 12-1 in Appendix 1 shows the increased risk associated with fingolimod treatment that could be detected with adequate power using this sample size compared to background rates obtained from external databases.

For example, based on the cited incidence rates for myocardial infarction of 160 per 100,000 person-years, the power to detect a 1.8, 2.0 or 2.2 fold increase would be 69.4%, 84.5% or 93.3%, respectively.

Table 12-2 in Appendix 1 shows the power to detect an increased risk in hypertension dyspnea and asthma associated with fingolimod treatment based on a direct comparison with estimates from the parallel cohort.

The assumed incidence rates for the parallel cohort are estimated from the observed incidence rates of 1900, 2250, and 500 per 100,000 person-years for hypertension, dyspnea, and asthma from the placebo MS patients group in CFTY720D2301 study.

For example, based on the assumed incidence rate for hypertension of 1900 per 100,000 person- years for the parallel cohort, the power to detect a 1.4, 1.45 or 1.5 fold increase would be 75.7%, 84.5% or 90.8%, respectively.

No power calculations were performed for PRES and ADEM, as the background incidence rate for PRES derived from an US claims database study is extremely small (around 3 per 100,000 person-years), and no available literature could be identified reporting the incidence rate for ADEM in the adult population.

Power analysis based on pooled data (CFTY720D2403 and CFTY720D2406)

As study CFTY720D2403 will collect similar data, data from both studies D2403 and D2406 will be pooled in order to gain more power to detect differences in the incidence of selected safety outcomes between the fingolimod cohort and other DMT cohort. Therefore, the pooled data could include up to 4,000 fingolimod patients and 2,000 patients from other DMT. Allowing a 20% reduction in patient years in order to account for patients lost to follow up or discontinuing the study, the power calculations assume 16,000 fingolimod patient years exposure based on a mean follow-up period of 4 years for the 4,000 fingolimod patients to be enrolled in this study.

Table 13-1 and 13-2 from Appendix 2 show the greater power that is obtained when comparing the incidence rates for fingolimod cohort with the external database, and with the parallel cohort based on the pooled data. For example, based on the background incidence rate from an external database for myocardial infarction of 160 per 100,000 person-years and a

sample size of 4,000 pooled fingolimod patients, the power to detect a 1.6, 1.7, 1.8 times increase would be 75.4%, 85.9% or 92.6%, respectively. To obtain similar power with a sample size of 2,000 fingolimod patients, we would be able to detect a 1.8, 2.0, 2.2 fold increase in risk (Table 12-1).

7.6 Interim analysis

Interim reports will be generated yearly starting approximately half a year after start of enrolment, according to reporting requirements. The enrolment numbers and baseline characteristics of patients will be described as well as incidence of events reported.

8 Data review and database management

8.1 Site monitoring

Depending on country regulations, formal site monitoring may or may not be performed in this study. However, Novartis (or designee) may perform informal monitoring or auditing occasionally and may request additional information on patients from participating physicians.

The Novartis data management or designated CRO will assure compliance monitoring. Monitoring activity will include reviews of the progress of the study and compliance with protocol, SOPs and GPP guidelines.

8.2 Data capture and document retention

Site staff will enter protocol defined data into a web based Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before being saved in the database of the CRO working on behalf of Novartis. At the end of the study, the treating physician must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the treating physician will receive a CD-ROM or paper copies of the patient data for archiving at the site.

In all scenarios, the physician must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. All information entered in the CRF must be traceable to these source documents in the patient's file. The physician must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).The physician must give Novartis (or designee) access to all relevant source documents to confirm their consistency with the CRF entries. No information in source documents about the identity of the patients will be disclosed.

8.3 Data quality assurance

The Novartis data management or designated CRO will assure database auditing. An audit review of data contained upon source documents and CRFs vs. that entered into the study database will occur (data auditing).

8.4   Data coding

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

9   Limitations

Given that this is an observational, non-randomized study, different biases can obscure any true causal association. Systematic differences between the fingolimod cohort and the parallel-cohort may exist, influenced by clinical decisions of the treating physicians that may assign patients to different drugs based on disease severity, disease duration, presence of co morbidities, and other factors. These differences can potentially introduce channeling bias and confound the association between treatment and the risk of the safety outcome.

10   Ethical considerations

10.1   Regulatory and ethical compliance

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well being of patients participating in non-interventional studies are protected; consistent with the principles that have their origin in the Declaration of Helsinki; and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke, et al 2008), and with the ethical principles laid down in the Declaration of Helsinki.

10.2   Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before collecting any data described in this study protocol. The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to treating physicians in a separate document a proposed informed consent form that complies with the ICH GPP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by

the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

10.3   Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/IEC or equivalent board reviewing specifically non-interventional study protocol, before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the treating physician is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4   Early termination of the study

The study can be terminated at any time for any reason by Novartis in agreement with health authorities. The treating physician may be informed of procedures to be followed in order to assure that adequate consideration is given to the protection of the patient's interests. The participating physician will be responsible for informing the IRB/IEC of the early termination of the study.

10.5   Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, at least upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of study results.

10.6   Protocol adherence and amendment

Treating physician or other involved health care professionals will apply due diligence to avoid protocol deviations. The protocol should be amended and updated as needed throughout the course of the study. Any change or addition to the protocol requires a written protocol amendment that must be approved by Novartis, the treating physician and the relevant IRB/IEC/REB before implementation. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB must be kept informed of such administrative changes.

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12   Appendix 1: Power calculations based on sample size of 3000 patients

The following power analysis was performed using nQuery version 7.0 Two Group Fisher's Exact Test of Equal Proportions based on a sample size of 3000 patients, including 2000 patients for the fingolimod cohort and 1000 patients for the parallel cohort. Person-year based incidence rate was converted to person based incidence rate (assuming 4-year follow-up) before calculation in nQuery. A range of values for 'Increase magnitude' were listed for each safety-specific outcome to provide different scenarios for power.

Table 12-1   Power calculation for selected safety-specific outcomes under different assumptions for comparing fingolimod cohort (N=2000) vs. external databases assuming mean of 4 years follow-up

Background incidence rate from external databases	fingolimod, assumed incidence rate (N=2000)	Increase magnitude in fingolimod vs. external data	Power (%)
Melanoma skin cancer (SEER data)[1]			
19 per 100,000 PY	76 per 100,000 PY	4.0	72.6
19 per 100,000 PY	86 per 100,000 PY	4.5	81.2
19 per 100,000 PY	95 per 100,000 PY	5.0	87.6
Myocardial infarction[2]			
160 per 100,000 PY	288 per 100,000 PY	1.8	69.4
160 per 100,000 PY	320 per 100,000 PY	2.0	84.5
160 per 100,000 PY	352 per 100,000 PY	2.2	93.3
Stroke[3]			
129 per 100,000 PY	258 per 100,000 PY	2.0	75.0
129 per 100,000 PY	271 per 100,000 PY	2.1	81.5
129 per 100,000 PY	284 per 100,000 PY	2.2	86.6
Breast cancer (SEER data)[4]			
123 per 100,000 PY	271 per 100,000 PY	2.2	68.4
123 per 100,000 PY	295 per 100,000 PY	2.4	79.1
123 per 100,000 PY	332 per 100,000 PY	2.7	89.9
Seizures[5]			
61 per 100,000 PY	159 per 100,000 PY	2.6	72.1
61 per 100,000 PY	171 per 100,000 PY	2.8	80.2
61 per 100,000 PY	183 per 100,000 PY	3.0	86.4
Lymphoma[1]			
22 per 100,000 PY	88 per 100,000 PY	4.0	70.5
22 per 100,000 PY	99 per 100,000 PY	4.5	80.2
22 per 100,000 PY	110 per 100,000 PY	5.0	87.2

[1] SEER database, http://seer.cancer.gov/, 2003-2007 data: Melanoma skin cancer and lymphoma for all age groups. It was adapted to the gender distribution of the MS population.

[2] Data derived from www.heartstats.org. Source of incidence table: Unit of Health-care Epidemiology, Department of Public Health, University of Oxford (2010). Data from Scotland from 2009 of all age groups was used and was adapted to the gender distribution of the MS population.

Background incidence rate from external databases	fingolimod, assumed incidence rate (N=2000)	Increase magnitude in fingolimod vs. external data	Power (%)

[3] Data was derived from Stroke statistics 2009 by the British heart foundation for all age groups: Source of incidence table: Hippisley-Cox et al, 2004. It was adapted to the gender distribution of the MS population.

[4] SEER database, http://seer.cancer.gov/, 2003-2007 data: Breast cancer data of women for all age groups. As the MS population consists of two-thirds women power was calculated only for 5,333 patient-years in order to account for gender distribution in the study.

[5] Nyquist PA, Cascino GD, McClelland, et al (2002) Incidence of seizures in patients with MS: a population-based study. Mayo Clin Proc; 77(9):910-2.

Table 12-2 **Power calculation for selected safety outcomes under different assumptions for comparing fingolimod cohort (N=2000) vs. parallel cohort (N=1000) assuming mean of 4 years follow-up**

Parallel cohort Assumed incidence (N=1000)	fingolimod Assumed incidence rate (N=2000)	Increase magnitude in fingolimod vs. parallel cohort	Power (%)
Hypertension (FTY720D2301)[1]			
1,900 per 100,000 PY	2,660 per 100,000 PY	1.40	75.7
1,900 per 100,000 PY	2,755 per 100,000 PY	1.45	84.5
1,900 per 100,000 PY	2,850 per 100,000 PY	1.50	90.8
Dyspnea (FTY720D2301)[1]			
2250 per 100,000 PY	3,038 per 100,000 PY	1.35	73.1
2250 per 100,000 PY	3,150 per 100,000 PY	1.40	83.5
2250 per 100,000 PY	3,263 per 100,000 PY	1.45	90.7
Asthma (FTY720D2301)[1]			
500 per 100,000 PY	900 per 100,000 PY	1.8	66.6
500 per 100,000 PY	950 per 100,000 PY	1.9	76.0
500 per 100,000 PY	1,000 per 100,000 PY	2.0	83.6

[1]Data from placebo group of 2 year study FTY720D2301 reporting a cumulative incidence in 2 years of follow-up of 3.8% for Hypertension, 4.5% for Dyspnea and1.0% for Asthma.

13 Appendix 2: Power calculations based on sample size of 6000 patients

The following power analysis was performed using nQuery version 7.0 Two Group Fisher's Exact Test of Equal Proportions based on a sample size of 6000 patients from pooled D2403 and D2406 data, including 4000 patients for the fingolimod cohort and 2000 patients for the parallel cohort. Person-year based incidence rate was converted to person based incidence rate (assuming 4-year follow-up) before calculation in nQuery. A range of values for 'Increase magnitude' were listed for each safety-specific outcome to provide different scenarios for power.

Table 13-1   **Power calculation for selected safety-specific outcomes under different assumptions for comparing fingolimod cohort (N=4000) vs. external databases assuming mean of 4 years follow-up**

Background incidence rate from external databases	fingolimod, assumed incidence rate (N=4000)	Increase magnitude in fingolimod vs. external data	Power (%)
Melanoma skin cancer (SEER data)[1]			
19 per 100,000 PY	57 per 100,000 PY	3.0	69.0
19 per 100,000 PY	67 per 100,000 PY	3.5	83.2
19 per 100,000 PY	76 per 100,000 PY	4.0	91.8
Myocardial infarction[2]			
160 per 100,000 PY	256 per 100,000 PY	1.6	75.4
160 per 100,000 PY	272 per 100,000 PY	1.7	85.9
160 per 100,000 PY	288 per 100,000 PY	1.8	92.6
Stroke[3]			
129 per 100,000 PY	206 per 100,000 PY	1.6	66.2
129 per 100,000 PY	232 per 100,000 PY	1.8	86.5
129 per 100,000 PY	258 per 100,000 PY	2.0	95.9
Breast cancer (SEER data)[4]			
123 per 100,000 PY	221 per 100,000 PY	1.8	66.4
123 per 100,000 PY	234 per 100,000 PY	1.9	75.4
123 per 100,000 PY	246 per 100,000 PY	2.0	82.7
Seizures[5]			
61 per 100,000 PY	122 per 100,000 PY	2.0	74.7
61 per 100,000 PY	134 per 100,000 PY	2.2	86.1
61 per 100,000 PY	146 per 100,000 PY	2.4	93.0
Lymphoma[2]			
22 per 100,000 PY	66 per 100,000 PY	3.0	72.7
22 per 100,000 PY	77 per 100,000 PY	3.5	86.5
22 per 100,000 PY	88 per 100,000 PY	4.0	94.1

[1] SEER database, http://seer.cancer.gov/, 2003-2007 data: Melanoma skin cancer and lymphoma for all age groups. It was adapted to the gender distribution of the MS population.

[2] Data derived from www.heartstats.org. Source of incidence table: Unit of Health-care Epidemiology, Department of Public Health, University of Oxford (2010). Data from Scotland from 2009 of all age groups was used and was adapted to the gender distribution of the MS population.

[3] Data was derived from Stroke statistics 2009 by the British heart foundation for all age groups: Source of incidence table: Hippisley-Cox et al, 2004. It was adapted to the gender distribution of the MS population.

[4] SEER database, http://seer.cancer.gov/, 2003-2007 data: Breast cancer data of women for all age groups. As the MS population consists of two-thirds women power was calculated only for 10,700 patient-years in order to account for gender distribution in the study.

[5] Nyquist PA, Cascino GD, McClelland, et al (2002) Incidence of seizures in patients with MS: a population-based study. Mayo Clin Proc; 77(9):910-2.

Table 13-2   **Power calculation for selected safety outcomes under different assumptions for comparing fingolimod cohort (N=4000) vs. parallel cohort (N=2000) assuming mean of 4 years follow-up**

Parallel cohort Assumed incidence (N=2000)	fingolimod Assumed incidence (N=4000)	Increase magnitude in fingolimod vs. parallel cohort	Power (%)

Parallel cohort Assumed incidence (N=2000)	fingolimod Assumed incidence (N=4000)	Increase magnitude in fingolimod vs. parallel cohort	Power (%)
Hypertension (FTY720D2301)[1]			
1,900 per 100,000 PY	2,375 per 100,000 PY	1.25	68.0
1,900 per 100,000 PY	2,470 per 100,000 PY	1.30	82.6
1,900 per 100,000 PY	2,660 per 100,000 PY	1.40	96.9
Dyspnea (FTY720D2301)[1]			
2250 per 100,000 PY	2700 per 100,000 PY	1.20	57.5
2250 per 100,000 PY	2813 per 100,000 PY	1.25	76.3
2250 per 100,000 PY	2925 per 100,000 PY	1.30	89.1
Asthma (FTY720D2301)[1]			
500 per 100,000 PY	700 per 100,000 PY	1.4	43.7
500 per 100,000 PY	750 per 100,000 PY	1.5	61.0
500 per 100,000 PY	800 per 100,000 PY	1.6	76.0

[1]Data from placebo group of 2 year study FTY720D2301 reporting a cumulative incidence in 2 years of follow-up of 3.8% for Hypertension, 4.5% for Dyspnea and1.0% for Asthma.