NOVARTIS

Clinical Development

FTY720 (Fingolimod)

CFTY720D2399 / NCT01201356

# A single arm, open-label, multicenter study evaluating the long-term safety and tolerability of 0.5 mg fingolimod (FTY720) administered orally once daily in patients with relapsing forms of multiple sclerosis

## RAP Module 3 – Detailed Statistical Methodology for D2399 final CSR full analysis – long-term follow-up study part I


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**Table of contents**

## List of abbreviations

| | |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| ARR | annual relapse rate |
| AST | aspartate aminotransferase |
| AV | atrioventricular |
| BPM | beats per minute |
| eCRF | electronic case report/record form |
| CPO | Country Pharma Organization |
| CRO | Contract Research Organization |
| $D_LCO$ | carbon monoxide diffusing capacity test |
| DS&E | Drug Safety & Epidemiology |
| ECG | electrocardiogram |
| EDC | electronic data capture |
| EDSS | expanded disability status scale |
| [redacted] | [redacted] |
| FDD | First dose of study drug (among all studies) |
| FDF | First dose of fingolimod |
| FEV1 | forced expiratory volume over 1 second test |
| FSH | follicle-stimulating hormone |
| FVC | forced vital capacity test |
| GGT | gamma-glutamyl-transferase |
| HbA1c | glycated hemoglobin |
| HCG | human chorionic gonadotropin |
| HR | heart rate |
| IB | investigator's brochure |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IFN | interferon |
| IN | Investigator Notification |

| | |
|---|---|
| IRB | Institutional Review Board |
| LN | lymph nodes |
| LUC | large unstained cells |
| MRI | magnetic resonance imaging |
| MS | multiple sclerosis |
| NPDR | non-proliferative diabetic retinopathy |
| OCT | optical coherence tomography |
| p.o. | by mouth |
| PFT | pulmonary function test |
| PPMS | primary progressive multiple sclerosis |
| [redacted] | [redacted] |
| RBC | red blood cell |
| RMP | risk management plan |
| RRMS | relapsing remitting multiple sclerosis |
| [redacted] | [redacted] |
| SAE | serious adverse event |
| s.c. | subcutaneously |
| [redacted] | [redacted] |
| SPMS | secondary progressive multiple sclerosis |
| SUSAR | suspected unexpected serious adverse reactions |
| [redacted] | [redacted] |
| ULN | upper limit of normal range |

# 1 Overview

Study CFTY720D2399 is a single arm, open-label, multicenter study evaluating the long-term, safety, tolerability and efficacy of 0.5 mg fingolimod (FTY720) administered orally once daily in patients with relapsing forms of multiple sclerosis (MS). This study allows MS patients who have participated in clinical studies with fingolimod to be transferred in, some patients who already complete CFTY720D2399 are eligible to re-enter if qualified. The term 'long-term follow-up' is used to define this CFTY720D2399 study throughout this document, indicating that CFTY720D2399 is the extension of all historical fingolimod studies. Prior fingolimod studies include CFTY720D2201/E1, CFTY720D2301/E1, CFTY720D2302/E1, CFTY720D2309/E1, CFTY720D2312, CFTY720D2316, CFTY720D2320, CFTY720D2324, CFTY720D2325, CFTY720D2399E1 and CFTY720D2402. Patients from other ongoing or newly starting fingolimod MS studies may roll over to the long-term follow-up study once they are eligible. Generally, a patient with previous fingolimod trial experience may participate the study series in the order of core study, extension study, the CFTY720D2399E1 study and the long-term follow-up study . Patients can transfer into the long-term follow-up study directly either from the core, extension or CFTY720D2399E1.

Note that CFTY720D2399E1 is an intermediate study, which occurs after a patient's core or extension study and before the long-term follow-up study. Patients from studies CFTY720D2302E1 and CFTY720D2309E1 may roll over directly into the long-term follow-up study, or they may roll over into the CFTY720D2399E1 study first, and then into the long-term follow-up study . The CFTY720D2399E1 study was closed out early due to a low enrollment rate.

Approximately 5000 patients who have completed ongoing or planned clinical trials in the MS development program with fingolimod are expected to be enrolled in >500 centers worldwide into this long-term follow-up study.

Upon signing the informed consent, patients will be transferred into this study from one of the ongoing fingolimod core/extension studies (CFTY720D2201/E1, CFTY720D2301/E1, CFTY720D2302/E1, CFTY720D2309/E1, etc.), as well as from designated ongoing or newly starting fingolimod MS studies. In addition, phase II/III patients that have already completed CFTY720D2399, CFTY720D2309/E1, or one of the phase II/III extension studies will be able to enroll into this study. Patients will be provided with fingolimod 0.5 mg/day once a day treatment until study completion.

Patients who participated in double-blind studies and are directly entering this study will remain blinded to the identity of the treatment in the previous study. In order to maintain the blind, the monitoring immediately after the first dose of study drug will be performed by a blinded first-dose administrator.

This study has two parts:

Part One will collect long-term safety, tolerability, efficacy, and health outcomes data through approximately 30-Jun-2016. Part Two will collect limited safety data until approximately 30-Jun-2018 from a subset of patients participating in Part One and other

eligible patients from ongoing fingolimod trials (e.g., CFTY720D2312). Eligibility for Part Two is defined as prior fingolimod study patients who are unable to obtain fingolimod outside a clinical trial.

By June 2016, investigators must determine commercial Gilenya eligibility for all active study patients (i.e., reimbursed for commercial Gilenya). Patients able to obtain commercial Gilenya will then have their End of Study (Part One) visit and exit the study, regardless of their post-study treatment decision (i.e., continuing on Gilenya commercially or transitioning to another treatment option). Patients discontinuing or completing the study at Part One who do not continue on commercial Gilenya must return for two follow-up study visits, 3-months and 6-months post-last dose of fingolimod. Patients who choose to continue on commercial Gilenya outside the study are exempted from the follow-up visits. Patients not eligible for reimbursed, commercial Gilenya will be offered continued study participation in Part Two until their scheduled study visit closest to 30-Jun-2018 (+/- 30 day visit window), with a reduced assessment schedule (see protocol Table 6-2), for the purpose of collecting additional long-term safety and tolerability data in support of the primary study objective. Patients discontinuing or completing the study after entering Part Two who do not continue on commercial Gilenya must return for one follow-up study visit, 3-months post-last dose of fingolimod. Patients who choose to continue on commercial Gilenya outside the study are exempted from the follow-up visit.

The duration of treatment of a patient in this trial is dependent on which study the patient participated in previously as well as the availability of reimbursement for commercially available fingolimod in the respective country. The study part I is planned to end by 30-Jun-2016 in order to collect 6 months or more of long-term safety data for the majority of Phase II/III patients. Guidance regarding scheduling of the Study Completion visit is provided in order to streamline the study closure processes, specifically designating the Study Completion visit to occur at or shortly after sixty months of study participation for those patients who would reach 60 months by 30-Jun-2016. Patients not reaching 60 months by 30-Jun-2016 will have their study completion on or around 30-Jun-2016 (+/- 30 day visit window), and patient who have already reached 60 months should have their Study Completion visit at their next six monthly visit, or 30-Jun-2016, whichever comes first.

This analysis plan will describe the analyses which will be conducted on the CFTY720D series studies (from initial core/extension study to the long-term follow-up study ) for Final CSR full analysis - long-term follow-up study part I. Patients participating in this study will provide clinical data of up to 15 years of exposure, which will provide information on the long-term safety, tolerability and efficacy profile of 0.5 mg fingolimod (FTY720) administered orally once daily in patients with relapsing forms of multiple sclerosis (MS) to help in therapeutic decision making. The full analysis will address safety updates for opportunistic infections and for basal cell carcinoma, since basal cell carcinoma has been reported in patients receiving fingolimod. Two follow-up visits (3-month and 6-month follow-up) are required after study completion to continuously monitor study safety.

Unless otherwise mentioned, all data collected from the first dose of fingolimod in the core/extension studies up to the end of the long-term follow-up study part I will be analyzed to evaluate the endpoints.

# 2 General strategies of data presentation

Statistical Analysis System (SAS) version 9.1 or higher will be used to perform all analyses.

In general, variables will be summarized using frequency distributions for categorical variables and summary statistics for continuous variables. Summary statistics for continuous variables will include n, mean, standard deviation, minimum, first quartile (Q1), median, third quartile (Q3) and maximum.

Note that, for CFTY720D2312 and CFTY720D2402 patients, the core study data is not included for any summary, and only information in the long-term follow-up study part I is included for listing purposes.

## 2.1 Allocated treatment

All patients during the long-term follow-up study are treated with fingolimod 0.5 mg per day. The summaries for data collected during the long-term follow-up study part I will only present one total group (the same as fingolimod any dose). However, patients may have been assigned a different dose (5 mg, 1.25 mg) in their initial fingolimod trial. The summaries for data collected from first dose of fingolimod among all studies will be presented by highest assigned dose of fingolimod; only two groups will be presented: fingolimod 0.5 mg and fingolimod any dose.

## 2.2 Precision rules

Whenever possible, the minimum and maximum values of the data will be presented to the same precision as the raw data; the mean, median, quartile 1, and quartile 3 will be presented to one more decimal place, and standard deviation will be presented to two more decimal places than the raw data.

## 2.3 Time frames, baseline, and visit windows

This section defines the study and data time frames, baseline, and rules for visit windows.

### 2.3.1 Database lock for Study part I

There are two database locks for this study. The analyses specified in this document include data from study part I with a database lock planned around 30$^{th}$ Jun 2017. All qualified patients will have end of study visit scheduled around 31$^{st}$ Oct 2016, which gives time for 6-month follow-up by end of Apr 2017. The 2$^{nd}$ data base lock is planned around 2018 for study part 2, in which patients from the long-term follow-up study are kept for another 2 years after finishing study part I. The analysis plan for study part II will be provided in a separate analysis plan.

### 2.3.2 Study day

The day of first administration of fingolimod study drug is defined as ***Day 1***. Day 1 does not need to occur in the long-term follow-up study.

All other study days will be labeled relative to Day 1. Thus, study day for a particular event date on or after Day 1 is calculated as: (*Date of event – Date of first dose of fingolimod study drug* + 1). An event that occurs prior to Day 1 is calculated as: (*Date of event – Date of first dose of fingolimod study drug*).

In addition to calculating study day with respect to the first dose date of fingolimod drug across all studies, study day will also be calculated relative to the first dose date of fingolimod during the long-term follow-up study.

The number of days after permanent study drug discontinuation will be calculated as (*Date of event – Date of last dose of fingolimod study drug*).

The duration of an event will be calculated as (*Event end date – Event start date* + 1). Day 0 will not be used.

### 2.3.3 Baseline and post-baseline

Unless otherwise specified, the baseline relative to the first dose of fingolimod (FDF) will be used throughout this study. It is defined as the last available measurement made prior to administration of the first dose of fingolimod among all studies a patient has participated in. The baseline can also be defined relative to the first dose of fingolimod during the long-term follow-up study in certain cases (i.e. ECG summary by visit), which is defined as the last available measurement made prior to administration of the first dose of fingolimod during the long-term follow-up study. The baseline relative to first dose of study drug in the core study (e.g. demographic information, core baseline characteristics) is also used for mentioned sections.

Post-baseline assessments are assessments made after the baseline assessment.

### 2.3.4 Variables Summarized by Visits

Below are the visit windowing rules used for visits as defined in the Virtual Data Warehouse (VDW) RAP M4 draft version 4.3.

Visit windows will be widely used to align visits across studies. They are based on the assessment schedule of the pivotal studies and comprise a set of days around the nominal visits. The same visit windows will apply to all studies. Visit-windows are non-overlapping; all together they cover the entire study period. Generally, visit-windows are not symmetrical around the nominal visit day. Among all the analysis, ECG, dose monitoring and ‘end of study’ summary for related panels will not use visit-window. Corresponding summaries are based on nominal visits.

Visit windows will be used to present summary statistics by visit. Efficacy data sets consider only scheduled visits, while safety datasets consider both scheduled and unscheduled visits. For efficacy analysis, if multiple assessments are available within a visit window, the record closest to the target day will be selected (if more than one assessment is equidistant to the target day, the later assessment will be used). For safety analysis, multiple assessments within a visit window will be averaged (for quantitative variables) or the worst record (for qualitative variables) will be selected. A follow-up visit-window will be used for data collected after last dose of fingolimod, which only consider scheduled assessments.

Similar rules (record selection either by date closest to target day or by averaging records within the same window) will be applied for efficacy and safety analysis respectively.

Unless otherwise specified, the following vital sign/lab visit windows are derived with respect to the first dose date of fingolimod among all studies.

**Table 1 Visit-windows for vital signs and laboratory values**

| Visit | Start day (time) | Target Day (time) | End day (time) |
|---|---|---|---|
| ***Week 2**** | 3 | 14 | 22 |
| ***Month 1*** | 23 | 30 | 45 |
| ***Month 2*** | 46 | 60 | 75 |
| ***Month 3*** | 76 | 91 | 136 |
| ***Month 6*** | 137 | 182 | 227 |
| ***Month 9*** | 228 | 273 | 319 |
| ***Month 12*** | 320 | 365 | 410 |
| … | | every 3 months | |
| ***Month X (row i)*** | $S_i$=Integerpart(($D_i$+$D_{i-1}$) /2)+1 | $D_i$ = Integerpart(X*365.25/12) | $E_i$=Integerpart(($D_{i+1}$+$D_i$) /2) |
| ... | ... | Every 3 months | ... |
| ***Month X (last row)*** | $S_{last}$ | $D_{last}$ | $E_{last}$=$D_{last}$+( $D_{last}$-$S_{last}$) |

- Unless otherwise specified, Day 1 is defined as the first dose day of fingolimod among all studies.
- Baseline will refer to the last value prior to the intake of the first dose of fingolimod. (Measurements labeled as “pre-dose” assessments will not be used as baseline values if the actual time variable suggests that the value has been obtained after the first dose of study medication: exceptions are body weight and temperature for which Day 1 records can be used as baseline irrespective of the actual time on day 1).
- Multiple results per patient within a visit window will be averaged for summary statistics by considering both scheduled and unscheduled visits..
- This visit windowing approach will only be used for summary statistics. (All individual assessments including unscheduled visits will be used to analyze notable and abnormal values, in shift tables and on listings.)
- ** Week 2 for laboratory values will include day 1 post-baseline as the start day.

**Table 2 Visit-windows for efficacy data (non-EDSS) domains**

| Visit | Start day (time) | Target Day (time) | End day (time) |
|---|---|---|---|
| ***Month 3*** | 1 | 91 | 136 |
| ***Month 6*** | 137 | 182 | 273 |
| ***Month 12*** | 274 | 365 | 547 |
| ***Month 24*** | 548 | 730 | 912 |
| ***Year 3 (M36)*** | 913 | 1095 | 1278 |
| ***Year 4 (M48)*** | 1279 | 1461 | 1643 |
| ***Year 5 M(60)*** | 1644 | 1826 | 2008 |
| ***Year 6 (M72)*** | 2009 | 2191 | 2373 |
| ***Year 7 (M84)*** | 2374 | 2556 | 2739 |
| ***Year8 (M96)*** | 2740 | 2922 | 3104 |
| ***Year 9*** | 3105 | 3287 | 3469 |
| ***Year 10*** | 3470 | 3652 | 3834 |
| ***Year 11*** | 3835 | 4017 | 4200 |

| | | | |
|---|---|---|---|
| … | | every 12 months | |
| ***Month X (row i)*** | $S_i$=Integerpart(($D_i$+$D_{i-1}$) /2)+1 | $D_i$ = Integerpart(X*365.25/12) | $E_i$=Integerpart(($D_{i+1}$+$D_i$) /2) |
| ... | ... | Every 12 months | ... |
| ***Month X (last row)*** | $S_{last}$ | $D_{last}$ | $E_{last}$=$D_{last}$+( $D_{last}$-$S_{last}$) |

- Day 1 is defined as the first dose day of fingolimod among all studies.
- Baseline will refer to the last MRI value prior to Day 1.
- For MRI: Visits 777 and 779 (study drug discontinuation assessments: the last scheduled scan is the reference scan), will be included in the visit windowing approach. However, 777 will only be used in a visit window if no other scheduled visit is available in the same window, if another scheduled visit is present, then the scheduled visit will take priority over 777.
- If multiple assessments are available within a visit window, the record closest to the target day will be selected (if more than one assessment is at the same distance to the target day, the later one will be used for summary statistics (after unscheduled visits are excluded).

## Table 3 Visit-windows for EDSS efficacy data

| Visit | Start day (time) | Target Day (time) | End day (time) |
|---|---|---|---|
| ***Month 3*** | 1 | 90 | 135 |
| ***Month 6*** | 136 | 180 | 225 |
| ***Month 9*** | 226 | 270 | 315 |
| ***Month 12*** | 316 | 360 | 405 |
| ***Month 15*** | 406 | 450 | 495 |
| ***Month 18*** | 496 | 540 | 585 |
| ***Month 21*** | 586 | 630 | 675 |
| ***Month 24*** | 676 | 720 | 765 |
| ***Month 27*** | 766 | 810 | 855 |
| ***Month 30*** | 856 | 900 | 945 |
| ***Month 33*** | 946 | 990 | 1035 |
| ***Month 36*** | 1036 | 1080 | 1125 |
| ***:*** | : | : | : |
| ***Month 72*** | 2116 | 2160 | 2205 |
| ***:*** | : | every 3 months | : |

- Day 1 is defined as the first dose day of fingolimod among all studies.
- Expanded Disability Status Scale (EDSS) scores will be summarized by visits occurring every 3 months from the date of first dose of study drug (for example at Month 3, Month 6, etc.).
- Baseline will refer to the last value prior to the intake of the first dose of fingolimod among all studies.
- If multiple assessments are available within a visit window, the record closest to the target day will be selected (if more than one assessment is at the same distance to the target day, the later one will be used for summary statistics (after unscheduled visits are excluded).

## Table 4 Follow-up visit windows (applicable to several panels: e.g. VSN, LAB, EDSS, MSFC, [redacted])

| Visit label | Start day (time) | Target Day (time) | End day (time) |
|---|---|---|---|
| ***FU (Month 3)*** | Day 1 p.l.d | Day 90 p.l.d | Day 135 p.l.d |
| ***FU (Month 6)*** | >= Day 136 p.l.d | Day 180 p.l.d | |

- Follow-up visit windows are defined relative to study drug discontinuation in the respective pool (unscheduled visits will be excluded).
- p.l.d = post last dose.

- Day 1 p.l.d is defined as the first day after the *last dose day of fingolimod*.

## 2.4 Imputation of Incomplete Dates

Incomplete or partial dates will be imputed (where appropriate, and will follow Virtual Data Warehouse (VDW) imputation rules – refer to VDW MAP M8) to decide on the inclusion or exclusion of related events in the summary tables. Each incomplete date will be split into its day, month, and year components, and an imputation rule will be applied. However in data listings, the dates as available in the database should be listed (without imputation).

General imputation rules from the VDW MAP M3, draft version 3.0 are given below.

Specific imputation rules may apply to certain panels (e.g. concomitant medications) and are described in the relevant sections. If no imputation rules are described then the general imputation rules apply to partially missing or impossible dates:

- If the year is missing or impossible (e.g. 12-Jan-1911), then the date will be imputed as missing.
- If the year is not missing and possible, but the month is impossible or missing (e.g. 17-XXX-2010), then the year will be kept and July 1st will be imputed (1-July-2010).
- If the year and the month are not missing and possible, but the Day is impossible or missing (e.g. 31-FEB-2009), then the year and month will be kept, the 15th will be imputed (15-FEB-2009).

## 2.5 Analysis sets

The following analysis sets will be defined.

- **Enrolled set:** The enrolled set will include all patients who entered the long-term follow-up study part I (excludes long-term follow-up study screen failures), but will exclude patients with protocol deviation severity code of 8 (8=exclude from all analyses) in the long-term follow-up study part I.
- **Safety set**: The safety set will include all patients who entered the long-term follow-up study part I and received at least one dose of fingolimod in any study, but will exclude patients with protocol deviation severity codes of 5 (5=exclude from all safety analyses) and 8 (8=exclude from all analyses) in the long-term follow-up study part I. Note that all data reported in the long-term follow-up study part I will be analyzed, including assessments or events which started before the long-term follow-up study part I.
- **Fingolimod safety set:** The fingolimod safety set will include all patients who entered the long-term follow-up study part I and received at least one dose of fingolimod in any study, but will exclude patients with protocol deviation severity codes of 5 (5=exclude from all safety analyses) and 8 (8=exclude from all analyses) during the core study prior to entry to the long-term follow-up study part I. For patients with such protocol deviations after the core study, record level data associated with the protocol deviations will be excluded from the analysis.

- **Fingolimod full analysis set:** The fingolimod full analysis set will include all patients who entered the long-term follow-up study part I and received at least one dose of fingolimod in any study but will exclude patients with protocol deviation severity codes of 0 (0=exclude from all efficacy analyses) and 8 (8=exclude from all analyses) during the core study prior to entry to the long-term follow-up study part I. For patients with such protocol deviations after the core study, record level data associated with the protocol deviations will be excluded from the analysis.
- **Follow-up set:** The follow-up set will consist of all patients in the safety set who have any follow-up visit data or at least one safety record after the study drug discontinuation. It will be used for summary of adverse events and concomitant medications with occurrences after last dose of fingolimod only.

Patient disposition, core study, protocol deviations, analysis sets, demographics, and baseline and history information will be summarized based on the enrolled set. Efficacy analyses will be summarized based on the fingolimod full analysis set. Safety summaries that include only long-term follow-up study part I data will be based on safety set, while other safety assessments that include data from the first dose of fingolimod among all studies, will be summarized based on fingolimod safety set.

A summary of the number and percentage of patients in each analysis set (enrolled set, safety set, fingolimod safety set, fingolimod full analysis set, and follow-up set) will be summarized. Percentages will be based on the enrolled set. A listing of patient assignment into each analysis set will also be displayed.

### 2.5.1 Subgroups

The following subgroups are defined for AE analysis:

1. Duration of fingolimod treatment up to the end of the long-term follow-up study part I (yearly interval):
    - Year 1 subgroup: patients on fingolimod treatment >= 0 year (>= 1 day)
    - Year 2 subgroup: patients on fingolimod treatment >= 1 year (>= 360 days)
    - Year 3 subgroup: patients on fingolimod treatment >= 2 year (>= 720 days)
    - Year 4 subgroup: patients on fingolimod treatment >= 3 year (>= 1080 days)
    - Year 5 subgroup: patients on fingolimod treatment >= 4 year (>= 1440 days)
    - Year N subgroup: patients on fingolimod treatment >= N -1 year (>= (N - 1) x 360 days)
2. Patients from Phase II/III studies: This subgroup includes patients who have enrolled in any of the following studies: D2201, D2301, D2302, and D2309 before entering the long-term follow-up study part I.

# 3 Patient Disposition

All screen failures in the long-term follow-up study will be listed along with their primary reason for failing screening.

The number and percentage of patients who completed the long-term follow-up study part I, and who discontinued the long-term follow-up study part I, along with the primary reason for discontinuation, will be summarized for the enrolled set. The number and percentage of patients who are expected to have follow-up visits and who returned for 3-month and 6-month follow-up visits will also be summarized.

The patients who discontinued from the long-term follow-up study part I and corresponding reasons will be listed for the enrolled set. Additionally, a similar listing will be provided for the enrolled set of patients from D2312 and D2402 studies who discontinued early from the long-term follow-up study part I .

# 4 Protocol Deviations

The number and percentage of patients in the enrolled set with each protocol deviation in the long-term follow-up study part I will be displayed by protocol deviation category. Additionally, patients with at least one protocol deviation during the long-term follow-up study part I and patients with at least one protocol deviation causing exclusion from any analysis set (deviation severity codes 0, 5, or 8) will be summarized.

The protocol deviation data will be listed as well.

Additionally, the investigator comments during the long-term follow-up study part I will be listed.

# 5 Background and demographic characteristics

## 5.1 Core study

The core study refers to the first fingolimod MS study the patient enrolled in. The number and percentage of patients in each core study prior to transfer into the long-term follow-up study will be provided.

## 5.2 Demographics

Using data collected from the patient's core study, the following demographic variables will be summarized for the enrolled set and the subgroup of enrolled set patients from phase II/III studies: sex, age (years), age groups [<18, 18-30, 31-40, 41-55, >55], race, ethnicity, baseline weight, baseline height, and baseline BMI. Baseline height and weight will be derived as the last non-missing assessment prior to first dose of any drug among all studies a patient has participated in. Baseline BMI will be derived based on baseline height and weight. Age will be calculated as the (core study's demographic screening or baseline visit date – patient's birth date +1) / 365.25.

Unless otherwise specified, age is presented in the listings in 3 ways: age 1 is the age at the visit where demographic data is collected (screening or baseline visit of core study); age 2 is the age at first dose of fingolimod among all studies; age 3 is the age at last dose of fingolimod.

## 5.3 MS disease history characteristics before enrollment in core study

Using data collected from the patient's core study, the following MS disease history characteristics will be summarized for the enrolled set: duration of MS since diagnosis in years, duration of MS since first symptoms in years, number of relapses in the last year prior to enrollment in the core study, number of relapses in the last 2 years prior to enrollment in the core study, time since the onset of the most recent relapse (in months) prior to enrollment in the core study, and duration from MS diagnosis date to last dose date of study drug (in years). The baseline EDSS score and the duration of exposure to fingolimod prior to first dose in the long-term follow-up study part I will also be summarized for the enrolled set. Note that not all parameters are collected across all studies.

The following definitions will be used in calculations involving MS disease history characteristics: one year is defined as 365.25 days and one month is defined as 30 days.

For the MS disease history summary, the variable *Duration of MS since diagnosis* (years) will be derived for each patient as: (first dose date of any study drug among all studies a patient has participated in – the MS diagnosis date + 1)/365.25. *Duration of MS since first symptom* (years) is calculated as (first dose date of any study drug among all studies a patient has participated in – the first MS symptom date +1) / 365.25. The *time since the onset of the most recent relapse* (months) is computed as (first dose date of any study drug among all studies a patient has participated in – the most recent relapse onset date prior to enrollment in the core study + 1)/30. The duration from MS diagnosis date to last dose date of study drug (in years) is calculated as (last dose date of any study drug among all studies a patient has participated in - the MS diagnosis date + 1)/365.25. Note that the first dose date of any study drug among all studies a patient has participated in may not be fingolimod.

## 5.4 MRI baseline characteristics

The MRI baseline characteristics will be summarized for number of Gd-enhanced T1 lesions, number of T2 lesions, total volume of T1 hypointense lesions, total volume of T2 lesions, volume of Gd-enhanced T1 lesions and normalized brain volume at both core baseline and fingolimod baseline if applicable. This summary is based on enrolled set.

## 5.5 MS medication history prior to enrollment in core study

For the MS medication history of disease-modifying drugs (DMDs), treatment-naïve patients are defined as those who never took MS disease-modifying medications prior to enrollment in core study. The number and percentage of treatment-naïve patients and patients who took categories of MS DMDs will be summarized for the enrolled set.

# 6 Study drug

## 6.1 Duration of exposure

The duration of exposure to fingolimod study drug will be defined as the number of days from first dose date of fingolimod among all studies to last dose date of the long-term follow-up study part I, excluding the days for which the patient did not take fingolimod (i.e., periods of temporary interruption). The number and percentage of patients being exposed for a minimum of ≥1 day, ≥90 days, ≥180 days, ≥360 days, etc. will be presented. Summary statistics of duration of exposure will also be provided. Patient-years of exposure will be reported and is calculated as the (sum of the total number of days on fingolimod study drug for all patients in the treatment group)/365.25. The above summaries will be presented for the fingolimod safety set and the subgroup of fingolimod safety set patients from Phase II/III studies.

Similar summaries will be provided for the duration of exposure to fingolimod study drug during the long-term follow-up study part I, which is defined as the number of days from first dose date of fingolimod in the long-term follow-up study to the last dose date, excluding the days for which the patient did not take fingolimod. Duration of exposure to fingolimod study drug during the long-term follow-up study part I will be presented for the safety set.

The fingolimod dose administration records during the long-term follow-up study part I will be listed for the safety set.

# 7 Concomitant medication

## 7.1 Imputation of concomitant medication start date

Missing or partial concomitant medication start dates are imputed following the VDW MAP Module 8 'Concomitant Medication Start Date Imputation (#IMPUTMED)' section (displayed below):

**Concomitant Medication Start Date Imputation (#IMPUTMED)**

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

| | Day | Month | Year |
|---|---|---|---|
| **Partial CMD Start Date** | Not used | MON | YYYY |
| **Treatment Start Date (TRTSTD)** | Not used | TRTM | TRTY |

The following matrix explains the logic behind the imputation.

| | MON MISSING | MON < TRTM | MON = TRTM | MON > TRTM |
|---|---|---|---|---|
| **YYYY MISSING** | **(C)** Uncertain | **(C)** Uncertain | **(C)** Uncertain | **(C)** Uncertain |
| **YYYY < TRTY** | **(D)** Before Treatment Start | **(A)** Before Treatment Start | **(A)** Before Treatment Start | **(A)** Before Treatment Start |

| | | | | |
|---|---|---|---|---|
| **YYYY = TRTY** | **(C)** Uncertain | **(A)** Before Treatment Start | **(C)** Uncertain | **(B)** After Treatment Start |
| **YYYY > TRTY** | **(E)** After Treatment Start | **(B)** After Treatment Start | **(B)** After Treatment Start | **(B)** After Treatment Start |

The following table is the legend to the logic matrix.

| | |
|---|---|
| **Relationship** | |
| **Before Treatment Start** | Partial date indicates CMD start date **prior** to Treatment Start Date |
| **After Treatment Start** | Partial date indicates CMD start date **after** Treatment Start Date |
| **Uncertain** | Partial date **insufficient to determine** relationship of CMD start date to Treatment Start Date |
| **Imputation Calculation** | |
| **NC / Blank** | No convention |
| **(A)** | 15MONYYYY |
| **(B)** | MAX( 01MONYYYY, TRTSTD+1 ) |
| **(C)** | IF CMDTYP1C IN (1, 3) THEN TRTSTD-1<br>ELSE IF CMDTYP1C IN (., 2) THEN TRTSTD+1 |
| **(D)** | 01JULYYYY |
| **(E)** | 01JANYYYY |

## 7.2 Imputation of concomitant medication end date

Partial or missing concomitant end dates will be imputed such that the imputed end date is the latest possible date (i.e. last day of month if day is missing, last day of year if both month and day are missing). These imputation rules will tend to consider medications with an unknown start and/or end date to be "concomitant". See VDW MAP Module 8 variable CMDEND1O specifications for details.

## 7.3 Concomitant medication analyses

Concomitant medications are defined as medications, other than the study drug, that are reported during the study. All medications recorded on the CFTY720D2399 concomitant medications / significant non-drug therapies CRF will be coded using the current Hybrid DTD_DDE Dictionary. Concomitant medications and significant non-drug therapies, which are recorded in the CFTY720D2399 database and taken at any time from first dose date of fingolimod among all studies to last dose date of fingolimod + 45 days, will be summarized for the safety set by Anatomical Therapeutic Chemical (ATC) class and preferred term. The summary will show the number and percentage of patients receiving at least one drug of a particular ATC class and at least one drug in a particular preferred term (PT). To determine if any particular treatment is needed after discontinuation of fingolimod, concomitant medications and significant non-drug therapies, which are recorded in the CFTY720D2399 database and taken after last dose date of fingolimod, will be summarized in the same way as above for the follow-up set.

Note that concomitant medications which are recorded on the CFTY720D2399 concomitant medications / significant non-drug therapies CRF can include medications that may have been taken during any gap between the completion of the prior study and enrollment into this long-term follow-up study, even if the medication is not ongoing at the time of enrollment.

All concomitant medications recorded during the long-term follow-up study part I will be listed. The concomitant medications taken after study drug discontinuation but up to or after 45 days will be flagged. Records for steroid treatment of MS relapse during the long-term follow-up study part I will be listed for the safety set.

# 8 Efficacy evaluation

The secondary objective of this study is to evaluate the long-term efficacy of fingolimod 0.5 mg in patients with relapsing forms of MS. [redacted] Long-term efficacy will be assessed in terms of MS relapse, MRIs, EDSS, MSFC, and health outcomes.

## 8.1 Analysis of MS Relapses

### 8.1.1 Relapse date imputations and handling of duplicate relapse records

The start date of a relapse should never be missing. However, missing or partial dates may be expected from some non-phase III trials where data checking may be less vigorous than in phase III trials. To avoid an artificial inflation of the number of relapses by low quality data, missing dates for relapses will only be imputed if the end date of the relapse is after the first dose of the initial study (i.e. if the relapse happened at least partially within the study). If partial or complete end dates are before the first dose date of the initial study, then no imputation will be done. If partial or complete relapse end dates are after the first dose of the initial study, the following algorithm will be applied:

**Firstly, drop blanks and impute missing or partially missing start dates**

1. Drop complete blanks: If the relapse onset date is invalid (e.g. “No”, “None”) or completely missing and there is no information recorded across all variables, the onset date will be set to missing.
2. Otherwise, if the record is not empty or the onset date is partially missing, check if another record may be available for the same relapse. Concretely:
    a. If a relapse onset date has a missing day-part (XX-MM-YYYY), where XX represents the missing or invalid part, the onset date will be imputed by the onset date of another treatment-emergent relapse record with a non-missing start date for the same patient within the same month and year, if such a relapse is available (choose the first one if more than one is available).
    b. If a relapse onset date has a missing day- and month part (XX-XX-YYYY, the onset date will be imputed by the onset date of another treatment-emergent relapse record for the same patient within the same year, if such a relapse is available (choose the first one if more than one is available).
3. Otherwise, if the onset date of a relapse is completely or partially missing, the onset will be imputed with the first possible day within the available non-missing date-part, or the first-dose date, or the relapse end-date minus 90, whatever occurs latest.

**Secondly, impute the end date**

The imputation of missing or partially missing end dates will be done after the imputation of start dates.

1. If the end date of a relapse is completely missing, it will be imputed as 90 days after the onset date.
2. If the end date of a relapse is partially missing, it will be imputed as the maximum of the relapse start day plus one or the minimum of either 90 days after the onset date, or as the last possible day based on the non-missing parts of the end-date (e.g. XXDEC2007 where XX indicated the missing end day would be imputed as 31-DEC-2007 if the onset date of the relapse was 26-NOV-2007).

**Thirdly, handle duplicate relapse records:**

After the imputation of start and end-dates is completed, records which refer to the same relapse (30-day rule) will be combined into a new artificial record. This step will help to consolidate core and extension databases where the same relapse may be recorded more than once, and it will help to ensure consistent relapse rules even for studies with a less vigorous date management.

1. For each patient relapses will be sorted by onset date (source or imputed).
2. **Combine relapses for which the distance between onset dates is <30 days:** Starting from the first relapse within each patient, the distance from each relapse to the next will be tested. If the onset date of a relapse is less than 30 days from the onset date of a previous one, an artificial record will be created using the "worst" or "most severe" information from both records (Conservative approach). The following rules apply:
   a. Onset date: use the *minimum* of the candidate dates with the highest degree of completeness. The degree of completeness is defined in descending order: 1. Original date, 2. Only day-part imputed, 3. Day and Month part imputed, 4. Day, Month and Year imputed.

      Example: an original date entered by the investigator has the higher degree of completeness compared to a partial/imputed date. An imputed date with just the day-part imputed has the higher degree of completeness compared to a completely imputed date. Rationale: amongst the candidate-dates with the highest reliability/completeness – choose the first/worst.

   b. End date: use the *maximum* of the candidate dates with the highest degree of completeness. The degree of completeness is defined in descending order: 1. Original date, 2. Only day-part imputed, 3. Day and Month part imputed, 4. Day, Month and Year imputed.

      Example: an original date entered by the investigator has the higher degree of completeness compared to a partial/imputed date. An imputed date with just the day-part imputed has the higher degree of completeness compared to a completely imputed date. Rationale: amongst the candidate-dates with the highest reliability/completeness – choose the last/worst.

c. When two records are combined from two consecutive phases (e.g. one from an initial study, the other one from an extension) the combined record will be considered as belonging to the first phase.

   Example: A relapse may have started at the end of an extension but ended in an Umbrella study. The same relapse may then be captured in the extension and also in the Umbrella study. When the two records are combined into one, the relapse – according to its start date – will be considered in the extension phase. Programmatically: Ext1n will take the minimum value of the two combined records.

d. Hospitalization: "yes" is worse than "no"

e. Severity: "severe" is worse than "moderate" is worse than "mild" is worse than "unknown"

f. Steroids: "yes" is worse than "no"

g. Relapse confirmed: "yes" is worse than "no"

h. Recovery: "none" is worse than "partial" is worse than "complete"

i. Daily activity: "affected" is worse than "not affected"

**Lastly, truncate the duration of all relapses to a maximum of 90 days**

1. For each relapse record, check whether the duration from onset to end date is less or equal to 90 days, if this is not the case do the following:
   a. Determine the degree of completeness of the start and end-date. The degree of completeness is defined in descending order: 1. Original date, 2. Only day-part imputed, 3. Day and Month part imputed, 4. Day, Month and Year imputed.

      Example: an original date entered by the investigator has the higher degree of completeness compared to a partial/imputed date. An imputed date with just the day-part imputed has the higher degree of completeness compared to a completely imputed date.

   b. Keep the date with the higher degree of completeness fixed and update the other date, so that the duration the relapse is maximized to 90 days

      Rationale: If one of the dates has to be replaced to keep truncate the duration of the relapse to 90 days, keep the date with the higher degree of completeness/reliability fixed (either the end- or the start date) and replace the other one.

   c. If the onset- and end-date have the same degree of completeness, keep the start date fixed and impute the end-date such that the duration of the relapse is maximized to 90 days.
2. If a relapse is recorded as ongoing at the final exam, impute an end date such that the duration is maximized to 90 days.

### 8.1.2 Annualized relapse rates

Annualized relapse rate (ARR) is defined as the *number of relapses* experienced during a specific period of time adjusted to a one-year period. The 'number of relapses' can refer to

either the number of *confirmed relapses* or the number of *all relapses* (including both confirmed and unconfirmed relapses).

Confirmation of relapses is not collected in the following studies: CFTY720D2316, CFTY720D2320, CTY720D2399E1, and the long-term follow-up study prior to protocol amendment 4. Therefore, the number of confirmed relapses during this time is not able to be reported. Additionally, confirmed relapses will not be reported for patients from the CFTY720D2324 study since it is a phase IIIb study and confirmation is not collected in the long-term follow-up study for patients coming from previous studies that are not phase II/III. The number of unconfirmed relapses is also not able to be reported for study CTY720D2399E1 since the study does not collect relapse start dates. However, note that the time during which number of relapses is not able to be counted and the time off study for patients who re-enrolled into the long-term follow-up study will still be included in the time in study, which can make the ARR appear lower than it actually is. If confirmation of a relapse is missing or not collected, the relapse will be treated as an unconfirmed relapse. Therefore, ARR based on all relapses (confirmed or unconfirmed) should be considered a more reliable estimation of relapse rate than ARR based on confirmed relapse.

The group level (aggregate) ARR will be calculated as follows: (total number of relapses) / (total number of days in the study for all patients for that specific period of time) x 365.25.

### 8.1.3 Time in study

For the analysis of ARR from first dose of fingolimod to end of study treatment, the time in study (days) is calculated as: last dose date of fingolimod – first dose date of fingolimod among all studies + 1 day. Similarly, the time in study from first dose of fingolimod among all studies to end of follow-up is calculated as: last available visit/evaluation date across all panels – first dose date of fingolimod among all studies + 1 day.

For the analysis of ARR from first dose of fingolimod among all studies to end of a particular month (i.e. “Month 6”, “Month 12”, “Month 24”, and every 12 months from then on), “Month 0 to X” time in study will be calculated as minimum of (first dose date of fingolimod + integerpart(X/12*365.25) where X denotes the month, last available visit/evaluation date across all panels) – first dose date of fingolimod + 1 day.

### 8.1.4 MS relapses analyses

MS relapses analyses will be conducted on the fingolimod full analysis set. All analyses will be done for all relapses (confirmed and unconfirmed) and for confirmed relapses.

A summary of ARRs will be presented by time period (cumulative time intervals: ‘Month 0 to Month 6’, ‘Month 0 to Month 12’, ‘Month 0 to Month 24’, ‘Month 0 to Month 36’, … incremented by 1 year for each successive interval, plus ‘Month 0 to end of study treatment’ and ‘Month 0 to end of follow-up’) from first dose of fingolimod among all studies. The summary will include number of patients summarized, number of relapses, time in study (days), and group level ARR. In addition, model based estimates of ARR and corresponding two-sided 95% confidence interval will be obtained by fitting a negative binomial regression model adjusted for the number of relapses in the last two years prior to

enrolment in the core study and EDSS score at first dose of fingolimod baseline, with the logarithm of the time in study as the offset variable.

A summary of relapse characteristics will be displayed by time period (consecutive yearly intervals: 'Month 0 to Month 12', 'Month 12 to Month 24', etc., plus 'End of study treatment to End of follow-up') from first dose of fingolimod among all studies. Relapse characteristics will be summarized at a patient level (the number and percent of patients with at least one relapse type) and at a relapse event level (the number and percent of a particular type of relapse out of the total number of relapses). The types of relapses being summarized include: relapses which affect daily activities, relapses which require steroids, and relapses which require hospitalization.

The time to first onset of relapse from first dose date of fingolimod among all studies will be analysed. Specifically, the number of patients at risk, the cumulative number of patients with relapse, the Kaplan-Meier (KM) estimate of the percent of patients without relapse and corresponding standard error and two-sided 95% CI will be provided at each yearly time point (1 year = 360 days). Patients with no relapse, patients for whom follow-up ends before a confirmed relapse occurs, and patients who drop out prior to the relapse will all be censored, i.e. the time to event for these patients will be the time in study (from first dose of fingolimod among all studies to last available visit/evaluation date across all panels).

A Kaplan-Meier plot of time to first relapse from first dose of fingolimod to end of the long-term follow-up study part I will be presented.

## 8.2 Analysis of MRI

MRIs are required only for patients from phase II/III trials who had MRI assessments in prior fingolimod trials. MRI parameters analyzed in this study include: number of new/newly enlarging T2 lesions, volume of T2 lesions, T1 hypointense (black hole) volume, percent brain volume change, and annualized rate of brain volume change. MRI data will be analyzed for the fingolimod full analysis set.

### 8.2.1 Annualized rates of new-/newly enlarging T2 lesions

Annualized rate of new/newly enlarging T2 lesions is defined as the *number of new or newly enlarging T2 lesions* experienced during a specific period of time adjusted to a one-year period. The group level annualized rate of new/newly enlarging T2 lesions will be calculated as follows: (total number of new/newly enlarging T2 lesions) / (total number of days in the study for all patients for that specific period of time) x 365.25. The number of days in study will be calculated based on MRI scan date and first dose date of fingolimod. The annualized rate will be provided from first dose of fingolimod.

In addition to a group level annualized rate estimate, another annualized rate estimate and corresponding two-sided 95% confidence interval will be presented from a negative binomial (NB) regression model adjusted for total volume of T2 lesions at first dose of fingolimod baseline. Log (time in study) will be the offset variable.

These annualized rate summaries will be presented by cumulative yearly intervals: Month 0 to Month 3, Month 0 to Month 6, Month 0 to Month 12, Month 0 to Month 24, etc.

In general the number of new/newly enlarging T2 lesions is provided by the reading center. It is obtained by comparing two scans (e.g. the baseline scan to the Month 24 scan). If an assessment is provided by the reading center, then this should be used. Derived parameters should only be used when no assessment from the reading center is available. It is of note that any such derived number is an approximation. When an assessment is not provided by the reading center (i.e. 2399 results relative to FDF), derivation rules regarding number of new/newly enlarging T2 lesions relative to FDF baseline should be followed as below:

- Patients who were randomized to fingolimod in core: new/newly enlarging T2 lesions relative to FDF baseline = new/newly enlarging T2 lesions relative to core baseline.
- Patients who were randomized to another treatment (placebo or interferon) than fingolimod in core and switched to fingolimod in extension:
    - If the record of extension FDD was available in the extension database, new/newly enlarging T2 lesions relative to FDF baseline = new/newly enlarging T2 lesions relative to extension FDD.
    - If no records relative to extension FDD were available, new/newly enlarging T2 lesions relative to FDF baseline = max(result relative to FDD – end of core result relative to FDD, 0).

### 8.2.2 Total volume of T2 lesions and T1 hypointense lesion

Total volume of T2 lesions and T1 hypointense lesion (black hole) volume will be summarized separately by presenting descriptive statistics for change from FDF baseline values by visit.

### 8.2.3 Percent brain volume change (PBVC)

Descriptive statistics on normalized brain volume at core baseline and percent brain volume change from FDF baseline will be presented by visit. Additionally, a mixed effects model with repeated measures will be used with visit, normalized brain volume at core baseline, T2 lesion volume at first dose of fingolimod baseline and Gd-T1 lesion count at first dose of fingolimod baseline as fixed effects and individual patient as a random effect. Kenward and Rogers' adjustment for the degrees of freedom will be applied. Based on this model, least square mean, standard error, and a two-sided 95% CI will be displayed for each group.

When an assessment is not provided by the reading center (i.e. 2399 results relative to FDF), derivation rules regarding percent brain volume change from FDF baseline should be followed as below:

- Patients who were randomized to fingolimod in core: PBVC relative to FDF baseline = PBVC relative to FDD.
- Patients who were randomized to a treatment (placebo or interferon) other than fingolimod in core and switched to fingolimod in extension:
    - If the record of extension FDD was available in the extension database, PBVC relative to FDF baseline = PBVC relative to extension FDD.

- If no records relative to FDF baseline were available in the extension, the formula stated below was used to get the PBVC relative to FDF baseline:

  p2=100*[(p3-p1)/(p1+100)].

  where p1=PBVC relative to FDD at end of core, p2=PBVC relative to FDF, p3=PBVC relative to FDD, and p3 = [(1+p1/100)*(1+p2/100)-1]*100).

### 8.2.4 Annualized rate of brain volume change (ARBA)

The annualized rate of brain volume change is an "averaged annual percentage change" in brain volume. The logic of interest rates applies. The formula for ARBA is as below:

ARBA = [(SIENA/100+1) ^ (365.25/#days)-1]*100

SIENA=(Vk/V0-1)*100

k=days/365.25

where V0 is the brain volume at time 0, and Vk is the brain volume at time k (where k is the time in years).

The annualized rate of brain volume change relative to FDF baseline will be calculated from the SIENA estimate of the percentage brain volume change relative to FDF baseline and the number of days in study relative to FDF. For the calculation of k and V0, below rules should be followed:

- Patients who were randomized to fingolimod: k = MRI date – first dose date +1; V0 = brain volume at FDD
- Patients who were randomized to a treatment (placebo or interferon) other than fingolimod in core and switched to fingolimod in extension control treatment: k = MRI date – first dose date of extension +1; V0 = brain volume at extension FDD (if there is record), or at the end of core (if there is no record at extension FDD) .

Descriptive statistics on ARBA will be presented by visit. Additionally, a mixed effects model with repeated measures will be used with visit, normalized brain volume at core baseline, T2 lesion volume at first dose of fingolimod baseline and Gd-T1 lesion count at first dose of fingolimod baseline as fixed effects and individual patient as a random effect. Kenward and Rogers' adjustment for the degrees of freedom will be applied. Based on this model, least square mean, standard error, and a two-sided 95% CI will be displayed for each group.

## 8.3 Analysis of EDSS scores

The EDSS scores are used for the confirmation of MS relapse and the confirmation of disability progression. All EDSS summaries are based on the fingolimod full analysis set.

### 8.3.1 By-visit summaries

Overall EDSS score and EDSS functional system scores will be summarized by presenting descriptive statistics for baseline, post-baseline, and change from baseline values by visit. EDSS functional systems are: visual, sensory, brainstem, bowel and bladder, pyramidal, cerebral, and cerebellar.

The number and percentage of patients will be summarized based on EDSS (overall score) change categories: improvement, stable, and deterioration. If baseline EDSS score is <=5, improvement is indicated by an EDSS score change of <= -1, stable is indicated by an EDSS score change of > -1 and <= 0.5, deterioration is indicated by an EDSS score change of > 0.5; if baseline EDSS score is > 5, improvement is indicated by an EDSS score change of <= -0.5, stable is indicated by an EDSS score change of > -0.5 and <= 0, deterioration is indicated by an EDSS score change of > 0. Within each visit window, the record with worst category will be selected.

### 8.3.2 EDSS score of 4/6/7 or greater

The time to first EDSS score of 4/6/7 or greater from first dose of fingolimod among all studies will be analysed for patients with a baseline EDSS score of less than X, where X=4, 6, or 7 depending on the analysis being conducted. Specifically, the number of patients at risk, the cumulative number of patients with event, the Kaplan-Meier (KM) estimate of the percent of patients without event and corresponding standard error and two-sided 95% CI will be provided at each yearly time point (1 year = 360 days).

A Kaplan-Meier plot of 3 Kaplan-Meier curves showing time to first EDSS score of X or greater from first dose of fingolimod to the end of the long-term follow-up study Part will be provided, where X is 4, 6, and 7.

The time to event/censoring for Kaplan-Meier analyses will be calculated as follows:

For patients with EDSS score of 4/6/7 or greater:

Time to event = first assessment date (after first dose date of fingolimod among all studies) that patient has an EDSS score of X or greater – first dose date of fingolimod among all studies +1 day.

For patients who do not have EDSS score of 4/6/7 or greater (in other words, censored):

Time to censoring = last EDSS assessment date – first dose date of fingolimod +1 day. If the patient does not have post-baseline EDSS assessment, then that patient will be censored at Day 1 (Time to censoring =1).

A patient will be censored if the patient exits the study without receiving an EDSS score of 4/6/7 or greater after first dose of fingolimod among all studies.

### 8.3.3 Analysis of 6-month confirmed disability progression

Disability progression in this study is defined based on an increase in the EDSS score by 1.5 point for patients with a FDF baseline EDSS score of 0, 1 point for patients with FDF baseline EDSS of >=1 and <=5.5, and by 0.5 points for patients with an FDF baseline EDSS>5.5, confirmed after 6 months and all intermediate EDSS assessments. A 6-month confirmed disability progression is defined as a 6-month sustained increase from the reference (potential onset of progression) value in the EDSS scores. i.e., every EDSS score (scheduled or unscheduled) within a 6-month duration after the first progression should

meet the progression criteria as specified above. The confirmation can only happen at a scheduled visit.

To evaluate disability progression, all available scheduled and unscheduled EDSS assessments after the reference time point (e.g. Day 1) will be compared to the EDSS at the reference time point to assess if the change from the reference time point meets the disability progression criteria. The disability progression onset date will be the date of the first EDSS score meeting the disability progression criteria.

The disability progression confirmation can only happen at a scheduled visit and in the absence of a relapse. Note that the end of study or early discontinuation visit and the follow-up visit are protocol specified visits and will be treated as scheduled visits and thus can be used to confirm a disability progression if applicable. Specifically, the confirmation visit for 6-month confirmed disability progression will be the first scheduled visit meeting the following conditions:

- The confirmation visit needs to be ≥166 days from the potential onset date and the disability progression criterion needs to be met at that visit (and all visits in between the onset and the confirmation).
- The EDSS is not performed during a relapse (information collected as a flag in the CRF).
- All available EDSS scores (scheduled or unscheduled) between the disability progression onset and this visit meet the disability progression criteria.

If the first scheduled visit after ≥166 days for a "6-month confirmed disability progression" does not meet the conditions above, the subsequent scheduled visits will be checked until a confirmation visit is found. If a confirmation visit cannot be found, then above process will be repeated to look for the next disability progression onset and its confirmation visit or until it is certain that no confirmation visit can be found for the progression onset.

A patient is considered to have a 6-month confirmed disability progression if a progression onset with a confirmation visit is found. Otherwise, the patient is considered not to have a 6-month confirmed disability progression and will be referred to as a censored patient.

If a patient died due to MS (EDSS=10), he or she will be considered to have a 6-month confirmed disability progression, irrespective of the EDSS at the reference time point or the change in EDSS.

The time to first 6-month confirmed disability progression from first dose of fingolimod among all studies until the end of the long-term follow-up study part I will be summarized in a yearly interval for fingolimod full analysis set. Specifically, the number of patients at risk, the cumulative number of patients with event, the Kaplan-Meier (KM) estimate of the percent of patients without 6-month confirmed disability progression and corresponding standard error and two-sided 95% CI will be provided at each yearly time point (1 year = 360 days).

A Kaplan-Meier plot of time to first 6-month confirmed disability progression from first dose of fingolimod among all studies to the end of long-term follow-up study part I will be presented.

## 8.4 Analysis of Multiple Sclerosis Functional Composite (MSFC)

The MSFC assessment is done in patients who had previous assessments during their fingolimod period, including studies CFTY720D2201/E1, CFTY720D2301/E1, CFTY720D2302/E1, CFTY720D2309/E1, and the long-term follow-up study part I. There are 3 components (dimensions) to the MSFC: leg, arm, and cognitive function. The corresponding tests are 25-foot Timed Walking Test (T25FW), 9-Hole Peg Test (9HPT), and Paced Auditory Serial Addition Test 3 (PASAT3). First, the mean score is calculated for each component for each patient at a given time point:

- The average scores of two T25FW trials, i.e.

  $$\text{T25FW}_{\text{mean}} = \tfrac{1}{2}\left(\text{T25FW}_1 + T25\text{FW}_2\right)$$

  If one of the values is missing, the mean of the remaining values is taken.

- The average scores from the 4 trials on the 9-HPT. For computing 9-HPT subscale, the following will be used:

  $$9HPT_{mean} = \tfrac{1}{4}(9HPT_{left1} + 9HPT_{left\,2} + 9HPT_{right1} + 9HPT_{right\,2})$$

  Mean is only calculated if balanced (i.e., all 4 are available, or 1 from each hand is available).

  For the 9-HPT value that will be used in computing the z-score, the mean 9-HPT will be computed differently. The 2 trials for each hand are averaged, converted to the reciprocals of the mean times for each hand and then the 2 reciprocals are averaged, i.e.

  $$9HPT_{mean} = \tfrac{1}{2}\left(\frac{1}{\tfrac{1}{2}(9HPT_{left1} + 9HPT_{left2})} + \frac{1}{\tfrac{1}{2}(9HPT_{right1} + 9HPT_{right\,2})}\right)$$

  This mean is only calculated if all 4 values are available (ie. none are missing).

- The number of correct answers from the PASAT 3, i.e.

  $$PASAT3 = \#correct(PASAT3)$$

Further, a z-score is created for each component. In general, z-scores involve comparing each outcome with that found in a reference population, a process called standardizing each variable. This involves a decision about which population to use as the reference to derive the means and standard deviations to create the z-scores. The preferred method in clinical trials is to use test results from the analysis time-point visit from all patients, with reference population being the baseline population for this study:

- The z-scores for the T25FW

$$\mathrm{T25FW}_Z = \left(\mathrm{T25FW}_{\mathrm{mean}} - T25\mathrm{FW}_{\mathrm{baseline\text{ - }mean}}\right) / T25\mathrm{FW}_{\mathrm{baseline\text{ - }stdev}}$$

- The average scores from the 4 trials on the 9-Hole Peg Test (9HPT). The 2 trials for each hand are averaged, converted to the reciprocals of the mean times for each hand and then the 2 reciprocals are averaged, i.e.

$$9\mathrm{HPT}_Z = \left(9\mathrm{HPT}_{\mathrm{mean}} - 9\mathrm{HPT}_{\mathrm{baseline\text{- }mean}}\right) / 9\mathrm{HPT}_{\mathrm{baseline\text{- }stdev}}$$

- The number of correct answers from the PASAT 3, i.e.

$$PASAT3_z = \left(PASAT3_{mean} - PASAT3_{baseline\text{- }mean}\right) / PASAT3_{baseline\text{- }stdev}$$

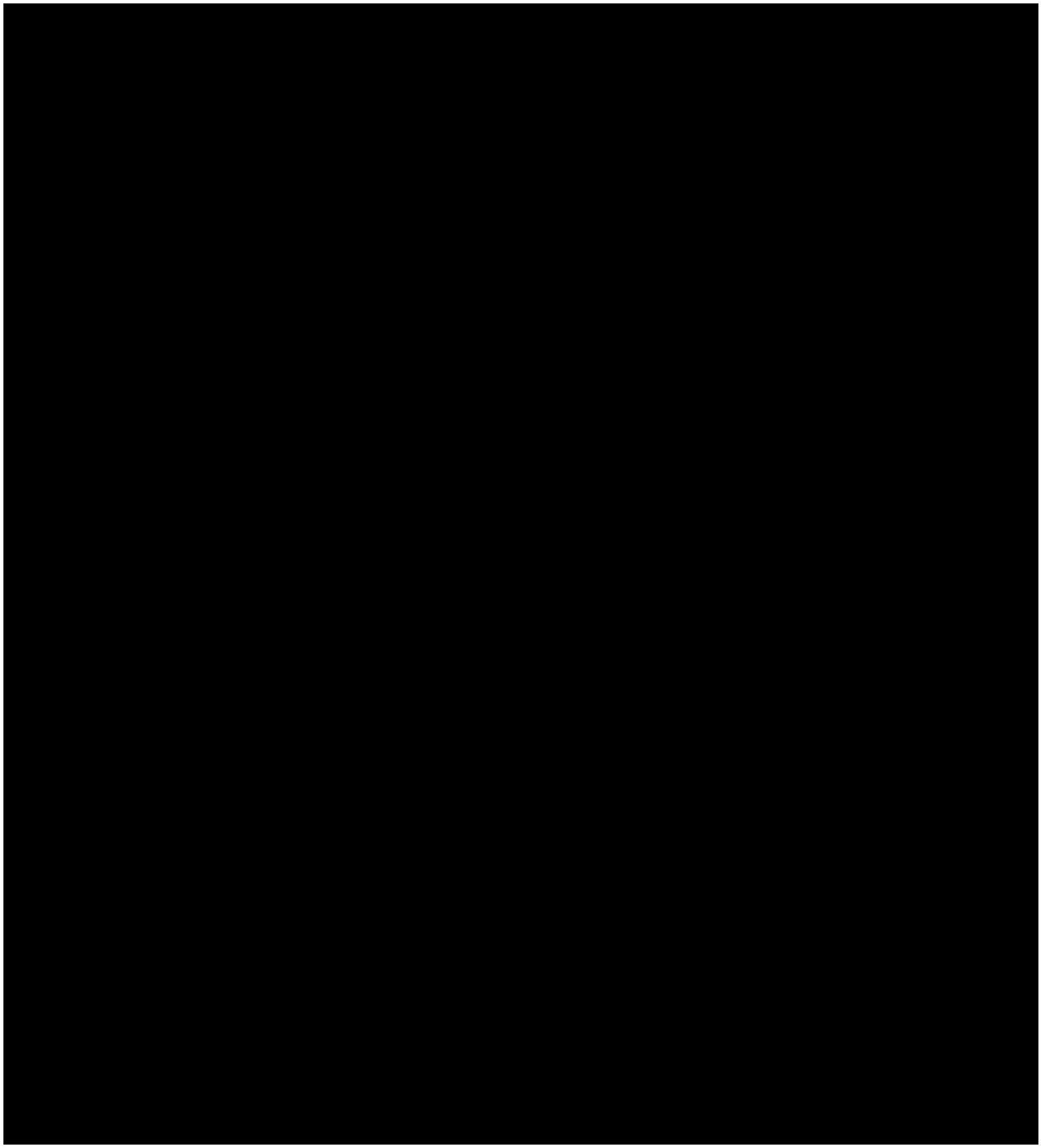
Finally, these individual z-scores are averaged to create an overall composite score:

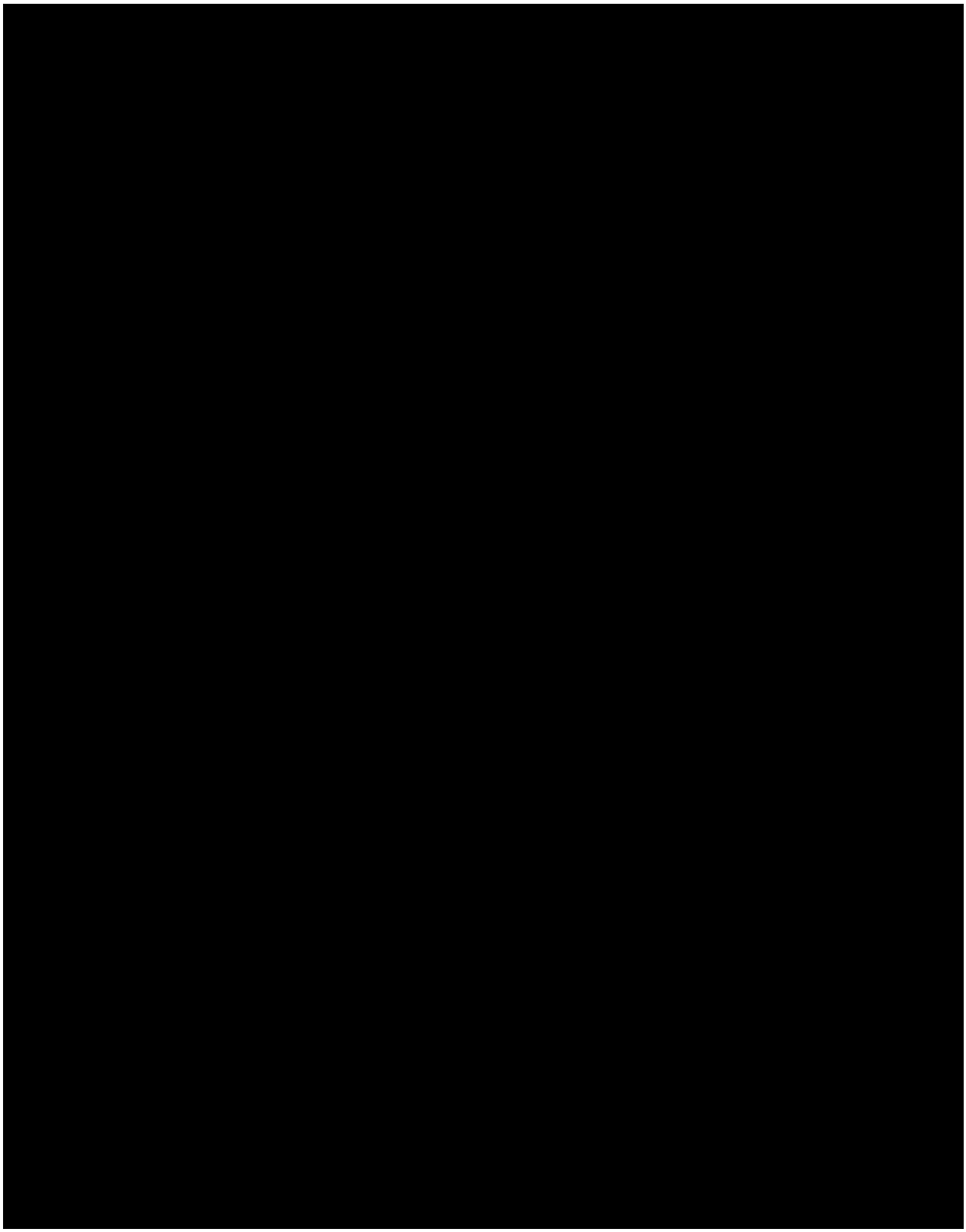
$$MSFC_Z = \frac{1}{3}\left\{9HPT_Z - T25FW_Z + PASAT3_Z\right\}$$

The negative value of the T25FT z-score is taken to make the direction of change the same as the other components. In computing $\mathrm{MSFC}_z$ for each patient, if any of the individual scores ($9\mathrm{HPT}_z$, $\mathrm{T25FW}_z$, or $\mathrm{PASAT3}_z$) are missing, then $\mathrm{MSFC}_z$ will be missing as well.

Descriptive statistics on baseline, post-baseline, and change from baseline will be presented for MSFC z-score and each subscale score by visit for the fingolimod full analysis set.

[redacted]





# 9 Safety evaluation

The primary objective of this study is to evaluate the long-term safety and tolerability of fingolimod 0.5 mg in patients with relapsing forms of MS.

Long-term safety will be assessed in terms of adverse events (AEs), laboratory, vital signs (including dose administration monitoring), electrocardiograms (ECG) dose administration monitoring, ophthalmic assessments, pulmonary function tests, and skin assessments. Except for summaries specifically for follow-up (e.g. summaries of Month 3 and Month 6 follow-up visits), serious adverse events, or adverse events after last dose date of fingolimod until end of follow-up, post-baseline safety summaries (not including listings) will limit reporting to only include assessments with dates from first dose date of fingolimod among all studies to last dose date of fingolimod + 45 days.

## 9.1 Adverse events

### 9.1.1 Imputation of adverse event start date

Missing or partial adverse event start dates are imputed following the VDW MAP Module 8 'Adverse Event Start Date Imputation (#IMPUTAEV)' section (displayed below):

**Adverse Event Start Date Imputation (#IMPUTAEV)**

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

Note, it may happen that the imputed AE start is after AE end date. Missing AE end date is not imputed by STL.

| | Day | Month | Year |
|---|---|---|---|
| **Partial Adverse Event Start Date** | Not used | MON | YYYY |
| **Treatment Start Date (TRTSTD)** | Not used | TRTM | TRTY |

The following matrix explains the logic behind the imputation.

| | MON MISSING | MON < TRTM | MON = TRTM | MON > TRTM |
|---|---|---|---|---|
| YYYY MISSING | NC | NC | NC | NC |
| YYYY < TRTY | ( D ) | ( C ) | ( C ) | ( C ) |
| YYYY = TRTY | (B) | ( C ) | (A) | (A) |
| YYYY > TRTY | (E) | (A) | (A) | (A) |

The following table is the legend to the logic matrix.

| Relationship | |
|---|---|
| Before Treatment Start | Partial date indicates AE start date **prior** to Treatment Start Date |
| After Treatment Start | Partial date indicates AE start date **after** Treatment Start Date |
| Uncertain | Partial date **insufficient to determine** relationship of AE start date to Treatment Start Date |
| **Imputation Calculation** | |
| NC / Blank Uncertain | No convention |
| (A) After Treatment Start or Uncertain | MAX( 01MONYYYY, TRTSTD+1 ) |
| (B) Uncertain | TRTSTD+1 |
| (C) Before Treatment Start | 15MONYYYY |
| (D) Before Treatment Start | 01JULYYYY |
| (E) After Treatment Start | 01JANYYYY |

### 9.1.2 Adverse events analyses

All adverse events (AEs) recorded on the adverse events CRF will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA). Note that adverse events that started or were ongoing during any gap between the completion of the prior study and enrollment into this CFTY720D2399 study, even if the adverse event was not ongoing at the time of CFTY720D2399 enrollment, can be recorded on the CFTY720D2399 adverse events CRF.

In AE summaries, primary system organ classes will be displayed in alphabetical order and preferred terms (within each system organ class) will be sorted by descending frequency in the fingolimod any dose column.

There are two categories of AE summaries in this study which are presented in the sections below.

#### 9.1.2.1 Adverse events during long-term follow-up study part I

Adverse events reported during the long-term follow-up study part I will be summarized for the safety set. Unless otherwise specified, all non-serious adverse events recorded in the CFTY720D2399 database with onset on or after first dose date of fingolimod among all studies to last dose date of fingolimod + 45 days are included. All serious adverse events

(SAEs) recorded in the CFTY720D2399 database with onset on or after the first dose date of fingolimod among all studies are also included in the summaries.

Adverse events reported during the long-term follow-up study part I will be summarized by primary system organ class (SOC) and preferred term (PT), and will show the number and percentage of patients with at least one adverse event in each SOC or PT category. Similarly, adverse events by study drug relationship (AEs suspected to be study drug related, AEs not suspected to be study drug related, and AEs regardless of study drug relationship), SAEs, SAEs by study drug relationship, suspected study drug related AEs, and AEs leading to study drug discontinuation will also be summarized by SOC and PT.

AEs and SAEs which are not considered to be known effects of fingolimod treatment (i.e., excluding those listed in the most recent version of Core Data Sheet), will be summarized by PT only.

To determine which AEs occur after discontinuation of fingolimod treatment, all AEs reported with onset date after the last dose of fingolimod until the end of the long-term follow-up study part I will be summarized by SOC and PT for the follow-up set.

Principal cause of death during the long-term follow-up study part I will be summarized by SOC and PT. All deaths recorded in the CFTY720D2399 database with onset on or after the first dose date of fingolimod (among all studies) will be included in the summary.

All information pertaining to any AE with severity information, SAEs, AEs leading to study drug discontinuation, deaths and neoplasms system organ class events that reported during the long-term follow-up study part I will be listed for the safety set. Additionally, adverse events, SAEs and all deaths recorded during the long-term follow-up study part I will be listed for the subgroup of patients from studies D2312 and D2402 in the enrolled set.

#### 9.1.2.2 Adverse events during the fingolimod treatment period

Unless otherwise specified, all non-serious adverse events with onset on or after first dose date of fingolimod among all studies to last dose date of fingolimod + 45 days are included. All serious adverse events (SAEs) with onset on or after the first dose date of fingolimod among all studies are also included in the summaries. Also, unless otherwise specified, adverse events will be summarized for the fingolimod safety set, by primary system organ class and preferred term, and will show the number of patients with at least one adverse event and the incidence rate of adverse events per 100 patient-years in each SOC or PT category.

The AE incidence rate (IR) is calculated per 100 patient-years. IR is defined as: the number of patients experiencing at least one event in a particular category, over the total patient-years of the “at risk” population for that event multiplied by 100. An underlying Poisson process for incidence rate within treatment group is assumed.

To calculate the total patient-years (time at risk) of the “at risk” population:

1. For patients who have a particular AE category, sum the number of days from first dose date of fingolimod among all studies to the first occurrence of that particular AE category

2. For patients who did not have a particular AE category, sum the number of days from first dose date of fingolimod among all studies to last dose date of fingolimod + 45 days.
3. Add the time at risk for patients who had a particular AE category with the time at risk for patients who did NOT have a particular AE category. This is the total time at risk of that AE category.
4. Divide the total time at risk by 365.25.

Incidence rate of adverse events will be presented for the fingolimod safety set and for the subgroup of fingolimod safety set patients from phase II/III studies, by SOC and PT. Incidence rate of AEs, excluding AE listed in the core data sheet, will be presented by PT. Incidence rate of AEs that fulfill the risk search term (defined in the case retrieval sheet) will be presented by risk name and lower level terms. Similarly, all above indicated AE IR summaries will be conducted for SAEs.

To further evaluate the long-term AE rate (based on patient count and percentage) within a particular fingolimod treatment duration, an analysis based on yearly intervals since first dose of fingolimod will be conducted. For summaries on this set of patients, all AEs and SAEs with onset on or after first dose date of fingolimod (among all studies) to last dose date of fingolimod are included. Each yearly interval will contain 360 days. For example: Year 1 will consist of Day 1 to Day 360, Year 2 will consist of Day 361 to Day 720, Year 3 will consist of Day 721 to Day 1080, Year 4 will consist of Day 1081 to Day 1440, Year 5 will consist of Day 1441 to Day 1800, and so on. Patients will be summarized within a particular yearly interval if they have been receiving study treatment for at least one day in that particular interval. The number and percentage of these patients who have adverse events with onset date occurring during the interval will be summarized. For example, for the Year 1 group, patients with at least one day exposure to fingolimod will be included, and AEs with onset date occurring between Day 1 and Day 360 will be summarized. For the Year 2 group, patients with at least 361 days exposure to fingolimod will be included, and AEs with onset date occurring between Day 361 and Day 720 will be summarized. The same will be done for other intervals.

Adverse events summarized by year will include the following:

- Adverse events, by yearly interval, primary system organ class, and preferred term
- Serious adverse events, by yearly interval, primary system organ class, and preferred term
- Adverse events that fulfill the risk search term, by yearly interval
- Serious adverse events that fulfill the risk search term, by yearly interval

Intervals will be included based on the length of fingolimod exposure. Risk search terms are defined in Novartis' case retrieval sheet. Associated summaries will be presented by risk name and lower level terms.

## 9.2 Laboratory

Hematology and blood chemistry data will be summarized separately by presenting descriptive statistics for baseline, post-baseline, and change from baseline values by lab parameter and visit. Shift tables (baseline to post-baseline values) based on normal range categories (low, normal, high, high & low) will be summarized separately for hematology and blood chemistry by lab parameter and visit.

Summaries of incidence of notable lab abnormalities for hematology and blood chemistry, reported from first dose of fingolimod among all studies, will present the number and percentage of patients with lab assessments satisfying notable criteria by visit. An overall study visit will be generated to indicate any notable abnormalities from post-baseline visits (including follow-up visits). Criteria for clinically notable laboratory values are specified in Appendix A. Percentages are based on the number of patients with non-missing lab result. A similar summary for patients with elevated liver function test values (elevation of 1, 2, 3, 5, 8 and 10 times the upper limit of normal) will be provided.

All summaries will be based on the fingolimod safety set.

Patients in the fingolimod safety set with notable post-baseline laboratory abnormalities will be listed separately for hematology and blood chemistry. All lab parameters with clinically notable criteria will be listed for a particular patient and visit if at least one of the parameters shows an abnormality. These listings will also indicate whether the lab result was above or below the normal range.

Patients with positive pregnancy test results during the long-term follow-up study part I will be listed for the safety set.

## 9.3 Routine vital signs

Vital signs include sitting pulse rate, sitting systolic and diastolic blood pressure, and oral temperature. Height and body weight were collected at the screening visit of the patient's previous fingolimod trial. First dose monitoring vital signs values will be excluded from routine vital signs summaries and listing.

Vital signs data will be summarized by presenting descriptive statistics for baseline, post-baseline, and change from baseline values by parameter and visit. The incidence of notable vital sign abnormalities reported from first dose of fingolimod among all studies will present the number and percentage of patients satisfying notable criteria by visit. An overall study visit will be generated to indicate any notable abnormalities from post-baseline visits (including follow-up visits). Criteria for clinically notable vital signs values are specified in Appendix B. Both summaries are based on the fingolimod safety set.

Patients in the fingolimod safety set with notable vital sign abnormalities will be listed. All vital sign parameters with clinically notable criteria will be listed for a particular patient and visit if at least one of the parameters shows an abnormality. The listing will also indicate whether the vital sign result was above or below the normal range.

## 9.4 Routine Electrocardiograms during the long-term follow-up study

Routine ECGs are only collected during the long-term follow-up study before protocol amendment 4 was approved. ECG parameters include QTc interval, QT interval, QTc interval (Fridericia), PR interval, RR interval, and QRS duration. The dose monitoring ECGs will be excluded from routine ECG summaries.

ECG data will be summarized by presenting descriptive statistics for baseline, post-baseline, and change from baseline values (relative to the first dose of fingolimod during the long-term follow-up study) by parameter and nominal visit. Incidence of abnormal ECGs will be presented by nominal visit.

A listing of ECG data for patients with abnormal findings will be provided for safety set.

## 9.5 Dose monitoring administration

First-dose monitoring should be done on any patient who enrolls into this long-term follow-up study part I from any blinded study which has comparator treatment arms (placebo or active comparator, e.g. study CFTY720D2309) or enrolls from the comparator arm of an open-label controlled study or for any patient who has been off fingolimod treatment for the following durations:

- The treatment lasted for 14 days or less and was interrupted for 1 day or more, or
- The treatment lasted for more than 14 days and less than 29 days and was interrupted for more than 7 consecutive days, or
- The treatment lasted for 4 weeks or more and was interrupted for more than 14 consecutive days.

Patients requiring first dose monitoring should receive the first dose of fingolimod at the study center at a time which will allow for the required 6-hour post-dose monitoring to occur as well as to allow for additional time for extended monitoring, if necessary. The patient may be discharged if specific discharge criteria (refer to Protocol Appendix 4) are met. Hourly monitoring will be extended until findings have resolved if the discharge criteria are not met, and should pharmacologic intervention be required during first-dose observation, overnight monitoring in a medical facility should be instituted and the first-dose monitoring procedures should be repeated upon the 2$^{nd}$ dose.

A dose administration monitoring summary will be provided for the safety set for first/second/restart of fingolimiod dose during the long-term follow-up study part I, and will include yes or no categorical summaries for the following: discharged at 6 hours, required extended monitoring after 6 hours, discharged but returned for monitoring, hospitalization, required Day 2 monitoring in the clinic (only recorded for first dose monitoring), study drug permanently discontinued, had symptomatic and/or treated bradycardia, and SAEs reported. The denominator for first/second dose monitoring data is based on the number of patients with assessment done; the denominator for restart monitoring data is based on the number of restarts.

### 9.5.1 Vital signs

During the long-term follow-up study part I, hourly vital signs, including sitting pulse rate and blood pressure will be monitored before the first dose of fingolimod and every hour for at least six-hours thereafter.

Hourly dose monitoring of vital signs will be summarized separately and will not be included in the by-visit summaries of routine vital signs. Descriptive statistics of pre-dose, post-dose, and change from pre-dose values will be summarized by parameter and time point for first dose monitoring, second dose monitoring, and dose monitoring after study drug restart. Summaries will be based on the safety set and include dose monitoring data during the long-term follow-up study part I only.

### 9.5.2 Electrocardiograms

During the long-term follow-up study part I, all patients requiring first dose monitoring will have an electrocardiogram (ECG) performed prior to dosing and at the end of the 6-hour monitoring period.

The hourly dose monitoring ECG will be summarized. Descriptive statistics of pre-dose, post-6 hour dose, and change from pre-dose values will be summarized by parameter and time point for first dose monitoring and second dose monitoring. The incidence of patients with abnormal ECG monitoring records will be summarized by time point, finding type, and finding.

Patients with abnormal dose monitoring ECG findings records will be listed. Summaries and listing will be based on the safety set and include dose monitoring data during the long-term follow-up study part I only.

## 9.6 Ophthalmic assessments

Ophthalmic assessments are done for patients who enter the long-term follow-up study from blinded studies with comparator treatments arms or patients who have been off fingolimod for 90 days or greater. Assessments are completed as needed.

The incidence of macular edema events during the long-term follow-up study part I will be summarized for the safety set. The number and percentage of patients with any macular edema events and particular event type (macular edema presence in left or right eye) will be provided based on either dilated assessment or OCT assessment (by olphthalmologist) if available. The number and percentage of patients with history of diabetes mellitus and the number and percentage of patients with history of diabetes mellitus and macular edema assessment done will also be provided to support data summary.

The patients with macular edema events during the long-term follow-up study part I will also be listed for the safety set. All records will be listed for a particular patient if there is at least one macular edema event. A separate listing for visual acuity assessment during the long-term follow-up study part I will be provided as support.

## 9.7 Pulmonary function tests

Pulmonary function tests are only done as needed during the study to monitor safety. It includes parameters: forced expiration volume in 1 second ($FEV_1$), forced vital capacity (FVC), diffusion capacity for carbon monoxide ($D_LCO$), and the derived FEV1/FVC ratio. Observed values, percentage of predicted values for these four parameters, respiratory infection status, and smoking status during the long-term follow-up study part I will be listed for the safety set.

## 9.8 Skin assessment

Skin assessment is only done as needed during this study to monitor safety. Patients with skin abnormalities (any dermatologic findings suspicious for being precancerous or cancerous, or if a skin disorder, for example abnormal cancerous lesion, is diagnosed) during the long-term follow-up study part I will be listed for the safety set.

# 10 Sample size and power considerations

Given that this is a long-term follow-up study with primary descriptive purpose, no formal sample size calculation will be used to determine enrollment in this study. The sample size is defined by the number of patients coming from ongoing/new core/extension trials that meet the inclusion and exclusion criteria. It is estimated that about 5000 patients will be enrolled in this trial.

# Appendices

## Appendix A: Clinically notable laboratory values

Only selected lab parameters identified as notable which have been shown to be sensitive to fingolimod exposure are included.

**CRITERIA FOR NOTABLE LABORATORY ABNORMALITIES**

| **Notable Values** | | |
|---|---|---|
| **Laboratory Variable** | **Standard Units** | **SI Units** |
| **LIVER FUNCTION AND RELATED VARIABLES** | | |
| SGOT (AST) | >82 U/L | >82 U/L |
| SGPT (ALT) | >90 U/L | >90 U/L |
| Total bilirubin | ≥ 2.0 mg/dL | ≥ 34.2 μmol/L |
| Alkaline Phosphatase | >280 U/L | >280 U/L |
| **RENAL FUNCTION / METABOLIC AND ELECTROLYTE VARIABLES** | | |
| Glucose ` | ≥200 mg/dL | ≥11.11 mmol/L |
| Creatinine | ≥2.0 mg/dL | ≥176 umol/L |
| Amylase | ≥ 300 U/L | ≥ 300 U/L |
| Cholesterol | ≥ 240 mg/dL | ≥ 6.21 mmol/L |
| Triglycerides | ≥300 mg/dL | ≥3.39 mmol/L |
| BUN | ≤ 2 mg/dL<br>≥ 30 mg/dL | ≤ 0.7 mmol/L<br>≥ 10.7 mmol/L |
| Sodium | < 125 mEq/L<br>>154 mEq/L | < 125 mmol/L<br>>154 mmol/L |
| Chloride | ≤85 mEq/L<br>≥119 mEq/L | ≤ 85 mmol/L<br>≥119 mmol/L |
| Potassium | ≤ 3.0 mEq/L<br>≥ 6.0 mEq/L | ≤ 3.0 mmol/L<br>≥ 6.0 mmol/L |
| Magnesium | ≤ 1.0 mg/dL<br>≥ 3.0 mg/dL | ≤ 0.40 mmol/L (in all other countries)<br>≤ 0.41 mmol/L (in Canada) |
| Calcium | ≤ 7.5 mg/dL<br>≥ 11.6 mg/dL | ≤ 1.87 mmol/L<br>≥ 2.89 mmol/L |
| Phosphate | ≤ 2.0 mg/dL<br>≥ 5.3 mg/dL | ≤ 0.65 mmol/L<br>≥ 1.71 mmol/L |

| **Notable Values** | | |
|---|---|---|
| **HEMATOLOGY VARIABLES** | | |
| Hemoglobin | ≤10.0 g/dL | ≤100 g/L |
| Platelets (Thrombocytes) | ≤100 k/mm$^3$<br>≥600 k/mm$^3$ | ≤100 x 10$^9$/L<br>≥600 x 10$^9$/L |
| Leukocytes (WBCs) | ≤2.0 k/mm$^3$<br>≥15 k/mm$^3$ | ≤2.0 x 10$^9$/L<br>≥15 x 10$^9$/L |
| **HEMATOLOGY VARIABLES: DIFFERENTIAL** | | |
| Granulocytes (Poly, Neutrophils) | ≤ 1,000 /mm$^3$<br>≥12000/mm$^3$ | ≤ 1 x 10$^9$/L<br>≥ 12 x 10$^9$/L |
| Lymphocytes | <200/mm$^3$<br>≥8000/mm$^3$ | <0.2 x 10$^9$/L<br>≥8 x 10$^9$/L |
| Red blood cells | <3,300,000/mm$^3$<br>>6,800,000/mm$^3$ | <3.3 x 10$^{12}$/L<br>>6.8 x 10$^{12}$/L |

# Appendix B: Clinically notable Vital sign values

**CRITERIA FOR NOTABLE VITAL SIGN ABNORMALITIES**

| **NOTABLE VITAL SIGNS** | |
|---|---|
| **Vital Sign Variable** | **Notable Criteria** |
| Pulse (beats/min) | >120bpm or Increase of ≥15 bpm from baseline<br>Or<br>< 50bpm or Decrease of ≥15 bpm from baseline |
| Systolic BP (mmHg) | ≥160 mm Hg or Increase of ≥20 mm Hg from baseline<br>Or<br>≤ 90 mm Hg or Decrease of ≥ 20 mm Hg from baseline |
| Diastolic BP (mmHg) | ≥ 100 mmHg or Increase of ≥ 15 mm Hg from baseline<br>Or<br>≤ 50 mmHg or Decrease of ≥ 15 mm Hg from baseline |
| Temperature (°C) | >38.3°C/ 101°F |
| Body Weight (kg) | ±7% from baseline weight |

NOVARTIS

Clinical Development

FTY720 (Fingolimod)

CFTY720D2399 / NCT01201356

# A single arm, open-label, multicenter study evaluating the long-term safety and tolerability of 0.5 mg fingolimod (FTY720) administered orally once daily in patients with relapsing forms of multiple sclerosis

## RAP Module 3 – Detailed Statistical Methodology for D2399 final CSR full analysis – study part 2

Author: [redacted] Trial Statistician; [redacted] Novartis Trial Statistician

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Release date: 26NOV2018

**Table of contents**

## List of abbreviations

| | |
|---|---|
| AE | adverse event |
| ARR | annual relapse rate |
| BPM | beats per minute |
| eCRF | electronic case report/record form |
| ECG | electrocardiogram |
| FDD | First dose of study drug (among all studies) |
| FDF | First dose of fingolimod |
| HR | heart rate |
| MS | multiple sclerosis |
| p.o. | by mouth |
| SAE | serious adverse event |
| s.c. | subcutaneously |

# 1 Overview

Study CFTY720D2399 is a single arm, open-label, multicenter study evaluating the long-term, safety, tolerability and efficacy of 0.5 mg fingolimod (FTY720) administered orally once daily in patients with relapsing forms of multiple sclerosis (MS). The term 'study part 2' is used to define the last extension phase of CFTY720D2399 study throughout this document, indicating that CFTY720D2399 is the extension of all historical fingolimod studies, and the term 'study part 2' means that this CFTY720D2399 study is the extension phase of CFTY720D2399 study part 1, which is completed in Jul2017. This study allows prior fingolimod study patients who are unable to obtain fingolimod outside a clinical trial to get access to the drug. These patients include a subset of patients participating in part 1, and other eligible patients from ongoing fingolimod trials (e.g.,CFTY720D2312). The purpose of study part 2 is to obtain additional long-term safety and tolerability data.

The end of the study treatment visit is planned for 30 June 2018. Individual patient's end of treatment visits should occur at their routine 6 monthly scheduled visit closest to 30 June 2018 to ensure all patients complete within the window for the end of the study.

# 2 General strategies of data presentation

Statistical Analysis System (SAS) version 9.3 or higher will be used to perform all analyses.

In general, variables will be summarized using frequency distributions for categorical variables and summary statistics for continuous variables. Summary statistics for continuous variables will include n, mean, standard deviation, minimum, first quartile (Q1), median, third quartile (Q3) and maximum.

Note that, the population sets are derived based on Virtual Data Warehouse, which does not include CFTY720D2312 and CFTY720D2402 studies, thus patients from the 2 studies are not included for any summary, and only information in the study part 2 (from part 2 raw data) is included for listing purposes.

## 2.1 Allocated treatment

All patients during the study part 2 are treated with fingolimod 0.5 mg per day, even though patients may have been assigned a different dose (5 mg, 1.25 mg) in their initial fingolimod trial. Unless otherwise specified, all summaries will only present the "fingolimod 0.5 mg" group, which indicates the dose level used during the study part 2. For adverse events by yearly interval, additional summaries will be provided by "highest fingolimod dose 0.5 mg" group, which indicates the subjects' highest fingolimod dose throughout all fingolimod trials.

## 2.2 Precision rules

Whenever possible, the minimum and maximum values of the data will be presented to the same precision as the raw data; the mean, median, quartile 1 (Q1), and quartile 3 (Q3) will

be presented to one more decimal place, and standard deviation will be presented to two more decimal places than the raw data.

## 2.3 Time frames, baseline, and visit windows

This section defines the study and data time frames, baseline, and rules for visit windows.

### 2.3.1 Database lock for Study part 2

The analyses specified in this document include data from study part 2 with a database lock planned around December 2018/January 2019. All qualified patients will participate until their scheduled visit closest to 30-Jun-2018 (+/- 3 months), which gives time for one follow-up study visit 3-months post last dose of fingolimod, for patients who discontinuing or completing the study after entering part 2 and who do not continue on commercial Gilenya.

### 2.3.2 Study day

The day of first administration of any dose of fingolimod study drug is defined as ***Day 1***. Day 1 does not need to occur in the study part 2.

All other study days will be labeled relative to Day 1. Thus, study day for a particular event date on or after Day 1 is calculated as: (*Date of event – Date of first dose of fingolimod study drug* + 1). An event that occurs prior to Day 1 is calculated as: (*Date of event – Date of first dose of fingolimod study drug*).

In addition to calculating study day with respect to the first dose date of fingolimod drug across all studies, study day will also be calculated relative to the first dose date of fingolimod during the study part 2.

The number of days after permanent study drug discontinuation will be calculated as (*Date of event – Date of last dose of fingolimod study drug*).

The duration of an event will be calculated as (*Event end date – Event start date* + 1). Day 0 will not be used.

### 2.3.3 Baseline and post-baseline

For the summary of change from baseline in vital signs, the baseline is defined as end of study visit from study part 1 or last assessment of that patient (excluding follow-up) in extension study part 1 if the subject's end of study visit is missing.

The baseline relative to first dose of fingolimod among all studies a subject has participated in, which is defined as the last available measurement made prior to administration of the first dose of fingolimod, will be used for efficacy summaries.

The baseline relative to first dose of study drug in the core study (e.g. demographic information, core baseline characteristics) is also used for mentioned sections.

Post-baseline assessments are assessments made after the baseline assessment.

### 2.3.4 Variables Summarized by Visits

Below are the visit windowing rules used for visits as defined in the Virtual Data Warehouse (VDW) RAP M4 draft version 4.3.

Visit windows will be widely used to align visits across studies. They are based on the assessment schedule of the pivotal studies and comprise a set of days around the nominal visits. The same visit windows will apply to all studies. Visit windows are non-overlapping; all together they cover the entire study period. Generally, visit-windows are not symmetrical around the nominal visit day. Among all the analysis, only efficacy summaries will use visit window. Safety summaries will be based on nominal visits.

Visit windows will be used to present summary statistics by visit. Efficacy data sets consider only scheduled visits. For efficacy analysis, if multiple assessments are available within a visit window, the record closest to the target day will be selected (if more than one assessment is equidistant to the target day, the later assessment will be used).

Unless otherwise specified, the following visit windows are derived with respect to the first dose date of fingolimod among all studies.

**Table 1 Visit-windows for efficacy data (MS relapse)**

| Visit | Start day (time) | Target Day (time) | End day (time) |
|---|---|---|---|
| ***Month 3*** | 1 | 91 | 136 |
| ***Month 6*** | 137 | 182 | 273 |
| ***Month 12*** | 274 | 365 | 547 |
| ***Month 24*** | 548 | 730 | 912 |
| ***Year 3 (M36)*** | 913 | 1095 | 1278 |
| ***Year 4 (M48)*** | 1279 | 1461 | 1643 |
| ***Year 5 M(60)*** | 1644 | 1826 | 2008 |
| ***Year 6 (M72)*** | 2009 | 2191 | 2373 |
| ***Year 7 (M84)*** | 2374 | 2556 | 2739 |
| ***Year8 (M96)*** | 2740 | 2922 | 3104 |
| ***Year 9*** | 3105 | 3287 | 3469 |
| ***Year 10*** | 3470 | 3652 | 3834 |
| ***Year 11*** | 3835 | 4017 | 4200 |
| … | | every 12 months | |
| ***Month X (row i)*** | $S_i$=Integerpart(($D_i$+$D_{i-1}$) /2)+1 | $D_i$ = Integerpart(X*365.25/12) | $E_i$=Integerpart(($D_{i+1}$+$D_i$) /2) |
| ... | ... | Every 12 months | ... |
| ***Month X (last row)*** | $S_{last}$ | $D_{last}$ | $E_{last}$=$D_{last}$+( $D_{last}$-$S_{last}$) |
| - Day 1 is defined as the first dose day of fingolimod among all studies.<br>- If multiple assessments are available within a visit window, the record closest to the target day will be selected (if more than one assessment is at the same distance to the target day, the later one will be used for summary statistics (after unscheduled visits are excluded). | | | |

**Table 2 Follow-up visit windows for efficacy data (MS relapse)**

| Visit label | Start day (time) | Target Day (time) | End day (time) |
|---|---|---|---|
| ***FU (Month 3)*** | Day 1 p.l.d | Day 90 p.l.d | |
| - Follow-up visit windows are defined relative to study drug discontinuation in the respective pool (unscheduled visits will be excluded).<br>- p.l.d = post last dose.<br>- Day 1 p.l.d is defined as the first day after the *last dose day of fingolimod*. | | | |

## 2.4 Imputation of Incomplete Dates

Incomplete or partial dates will be imputed (where appropriate, and will follow Virtual Data Warehouse (VDW) imputation rules – refer to VDW MAP M8) to decide on the inclusion or exclusion of related events in the summary tables. Each incomplete date will be split into its day, month, and year components, and an imputation rule will be applied. However in data listings, the dates as available in the database should be listed (without imputation).

General imputation rules from the VDW MAP M3, draft version 3.0 are given below.

Specific imputation rules may apply to certain panels (e.g. concomitant medications) and are described in the relevant sections. If no imputation rules are described then the general imputation rules apply to partially missing or impossible dates:

- If the year is missing or impossible (e.g. 12-Jan-1911), then the date will be imputed as missing.
- If the year is not missing and possible, but the month is impossible or missing (e.g. 17-XXX-2010), then the year will be kept and July 1st will be imputed (1-July-2010).
- If the year and the month are not missing and possible, but the Day is impossible or missing (e.g. 31-FEB-2009), then the year and month will be kept, the 15th will be imputed (15-FEB-2009).

## 2.5 Analysis sets

The following analysis sets will be defined. Analyses done on the fingolimod safety set and fingolimod full analysis set summarize all data starting from first dose of fingolimod among all studies, while other analysis sets generally summarize all data from the study part 2 only.

- **Enrolled set:** The enrolled set will include all patients who entered the study part 2 (excludes long-term extension study screen failures), but will exclude patients with protocol deviation severity code of 8 (8=exclude from all analyses) in the study part 2.
- **Safety set:** The safety set is a subset of the fingolimod safety set and will include all patients who entered the study part 2 and received at least one dose of fingolimod in any study, but will exclude patients with protocol deviation severity codes of 5 (5=exclude from all safety analyses) and 8 (8=exclude from all analyses) in the study part 2. Note that all data reported in the study part 2 will be analyzed, including assessments or events which started before the study part 2, unless otherwise specified. For example, adverse events which may have been continuing at the end of the long-term follow-up

study part 1 may be recorded in the study part 2 database with updated end date. These adverse events will be reported in listings and summarized if event occurs after first dose of fingolimod among all studies.

- **Fingolimod safety set**: The fingolimod safety set will include all patients who entered the study part 2 and received at least one dose of fingolimod in any study, but will exclude patients with protocol deviation severity codes of 5 (5=exclude from all safety analyses) and 8 (8=exclude from all analyses) during the core study prior to entry to the long-term follow-up study part 1. For patients with such protocol deviations after the core study, record level data associated with the protocol deviations will be excluded from the analysis.
- **Fingolimod full analysis set:** The fingolimod full analysis set will include all patients who entered the study part 2 and received at least one dose of fingolimod in any study but will exclude patients with protocol deviation severity codes of 0 (0=exclude from all efficacy analyses) and 8 (8=exclude from all analyses) during the core study prior to entry to the long-term extension study part 1. For patients with such protocol deviations after the core study, record level data associated with the protocol deviations will be excluded from the analysis.
- **Follow-up set:** The follow-up set will consist of all patients in the safety set who have any follow-up visit data or at least one safety record after the study drug discontinuation. It will be used for summary of adverse events and concomitant medications with occurrences after last dose of fingolimod only.

Patient disposition, core study, protocol deviations, analysis sets, demographics, and baseline and history information will be summarized based on the enrolled set. Efficacy analyses will be summarized based on the fingolimod full analysis set. Safety summaries that include only study part 2 data will be based on safety set or follow-up set as specified.

A summary of the number and percentage of patients in each analysis set will be summarized. Percentages will be based on the enrolled set. A listing of patient assignment into each analysis set will also be displayed.

### 2.5.1 Subgroups

The following subgroups are defined for subject disposition and AE analysis during fingolimod treatment period:

1. Duration of fingolimod treatment up to the end of the study part 2 (yearly interval):
    - Year 1 subgroup: patients on fingolimod treatment > 0 year (>= 1 day)
    - Year 2 subgroup: patients on fingolimod treatment > 1 year (>= 361 days)
    - Year 3 subgroup: patients on fingolimod treatment > 2 year (>= 721 days)
    - Year 4 subgroup: patients on fingolimod treatment > 3 year (>= 1081 days)
    - Year 5 subgroup: patients on fingolimod treatment > 4 year (>= 1441 days)

- Year N subgroup: patients on fingolimod treatment > N -1 year (>= (N -1) x 360+1 days)

# 3 Protocol Deviations

The number and percentage of patients in the enrolled set with each protocol deviation in the study part 2 will be displayed by protocol deviation category. Additionally, patients with at least one protocol deviation during the study part 2 and patients with at least one protocol deviation causing exclusion from any analysis set (deviation severity codes 0, 5, or 8) will be summarized.

The protocol deviation data will be listed as well.

Additionally, the investigator comments during the study part 2 will be listed.

# 4 Patient Disposition

All screen failures in the study part 2 will be listed along with their primary reason for failing screening.

The number and percentage of patients who completed the study part 2, and who discontinued the study part 2, along with the primary reason for discontinuation, will be summarized for the enrolled set. The number and percentage of patients who are expected to have month 3 follow-up visit and who returned will also be summarized. The number and percentage of patients who move to commercial fingolimod after study completion will also be included.

To further evaluate the disposition within a particular fingolimod treatment duration, study completion and discontinuation will be summarized in separate tables based on patients' fingolimod exposure by cumulative yearly interval. Patients will be summarized within a particular yearly interval if they have been receiving study treatment for at least one day in that particular interval. For example: year 1 will consist of subjects on fingolimod treatment for at least 1 day; year 2 will consist of subjects on fingolimod treatment for at least 361 days, year 3 will consist of subjects on fingolimod treatment for at least 721 days and so on. For study completion, the number and percentage of patients who completed the study part 2, and who move to commercial fingolimod after study completion will be provided by yearly exposure group as defined above. For study discontinuation, the number and percentage of patients who discontinued the study part 2, along with the reason for discontinuation, and who move to commercial fingolimod after study discontinuation will be provided by yearly exposure group as defined above.

The patients who discontinued from the study part 2 and corresponding reasons will be listed for the enrolled set. Additionally, a similar listing will be provided for the enrolled set of patients from D2312 and D2402 studies who discontinued early from the study part 2.

# 5 Background and demographic characteristics

## 5.1 Core study

The core study refers to the first fingolimod MS study the patient enrolled in. The number and percentage of patients in each core study prior to transfer into the long-term follow-up study will be provided.

## 5.2 Demographics

Using data collected from the patient's core study, the following demographic variables will be summarized for the enrolled set: sex, age (years), age groups [<18, 18-30, 31-40, 41-55, >55], race, ethnicity, baseline weight, baseline height, and baseline BMI. Baseline height and weight will be derived as the last non-missing assessment prior to first dose of any drug among all studies a patient has participated in. Baseline BMI will be derived based on baseline height and weight. Age will be calculated as the (core study's demographic screening or baseline visit date – patient's birth date +1) / 365.25.

Unless otherwise specified, age is presented in the listings in 3 ways: age 1 is the age at the visit where demographic data is collected (screening or baseline visit of core study); age 2 is the age at first dose of fingolimod among all studies; age 3 is the age at last dose of fingolimod.

## 5.3 MS disease history characteristics before enrollment in core study

Using data collected from the patient's core study, the following MS disease history characteristics will be summarized for the enrolled set: duration of MS since diagnosis in years, duration of MS since first symptoms in years, number of relapses in the last year prior to enrollment in the core study, number of relapses in the last 2 years prior to enrollment in the core study, time since the onset of the most recent relapse (in months) prior to enrollment in the core study, and duration from MS diagnosis date to last dose date of study drug (in years). The duration of exposure to fingolimod prior to first dose in the study part 2 will also be summarized for the enrolled set. Note that not all parameters are collected across all studies.

The following definitions will be used in calculations involving MS disease history characteristics: one year is defined as 365.25 days and one month is defined as 30 days.

For the MS disease history summary, the variable *Duration of MS since diagnosis* (years) will be derived for each patient as: (first dose date of any study drug among all studies a patient has participated in – the MS diagnosis date + 1)/365.25. *Duration of MS since first symptom* (years) is calculated as (first dose date of any study drug among all studies a patient has participated in – the first MS symptom date +1) / 365.25. The *time since the onset of the most recent relapse* (months) is computed as (first dose date of any study drug among all studies a patient has participated in – the most recent relapse onset date prior to enrollment in the core study + 1)/30. The duration from MS diagnosis date to last dose date of study drug (in years) is calculated as (last dose date of any study drug among all studies a patient has

participated in - the MS diagnosis date + 1)/365.25. Note that the first dose date of any study drug among all studies a patient has participated in may not be fingolimod.

### 5.4 MS medication history prior to enrollment in core study

For the MS medication history of disease-modifying drugs (DMDs), treatment-naïve patients are defined as those who never took MS disease-modifying medications prior to enrollment in core study. The number and percentage of treatment-naïve patients and patients who took categories of MS DMDs will be summarized for the enrolled set.

## 6 Study drug

### 6.1 Duration of exposure

The duration of exposure to fingolimod study drug during the study part 2, is defined as the number of days from first dose date of fingolimod in the study part 2 to the last dose date, excluding the days for which the patient did not take fingolimod (i.e., periods of temporary interruption). The number and percentage of patients being exposed for a minimum of ≥1 day, ≥90 days, ≥180 days, ≥360 days, etc. will be presented. Summary statistics of duration of exposure will also be provided. Patient-years of exposure will be reported and is calculated as the (sum of the total number of days on fingolimod study drug for all patients in the treatment group)/365.25. Duration of exposure to fingolimod study drug during the study part 2 will be presented for the safety set.

The fingolimod dose administration records during the study part 2 will be listed for the safety set.

## 7 Concomitant medication

### 7.1 Imputation of concomitant medication start date

Missing or partial concomitant medication start dates are imputed following the VDW MAP Module 8 ‘Concomitant Medication Start Date Imputation (#IMPUTMED)’ section (displayed below):

**Concomitant Medication Start Date Imputation (#IMPUTMED)**

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

| | Day | Month | Year |
|---|---|---|---|
| **Partial CMD Start Date** | Not used | MON | YYYY |
| **Treatment Start Date (TRTSTD)** | Not used | TRTM | TRTY |

The following matrix explains the logic behind the imputation.

| | MON MISSING | MON < TRTM | MON = TRTM | MON > TRTM |
|---|---|---|---|---|
| **YYYY MISSING** | **(C)** Uncertain | **(C)** Uncertain | **(C)** Uncertain | **(C)** Uncertain |
| **YYYY < TRTY** | **(D)** Before Treatment Start | **(A)** Before Treatment Start | **(A)** Before Treatment Start | **(A)** Before Treatment Start |
| **YYYY = TRTY** | **(C)** Uncertain | **(A)** Before Treatment Start | **(C)** Uncertain | **(B)** After Treatment Start |
| **YYYY > TRTY** | **(E)** After Treatment Start | **(B)** After Treatment Start | **(B)** After Treatment Start | **(B)** After Treatment Start |

The following table is the legend to the logic matrix.

| **Relationship** | |
|---|---|
| **Before Treatment Start** | Partial date indicates CMD start date **prior** to Treatment Start Date |
| **After Treatment Start** | Partial date indicates CMD start date **after** Treatment Start Date |
| **Uncertain** | Partial date **insufficient to determine** relationship of CMD start date to Treatment Start Date |
| **Imputation Calculation** | |
| **NC / Blank** | No convention |
| **(A)** | 15MONYYYY |
| **(B)** | MAX( 01MONYYYY, TRTSTD+1 ) |
| **(C)** | IF CMDTYP1C IN (1, 3) THEN TRTSTD-1<br>ELSE IF CMDTYP1C IN (., 2) THEN TRTSTD+1 |
| **(D)** | 01JULYYYY |
| **(E)** | 01JANYYYY |

## 7.2 Imputation of concomitant medication end date

Partial or missing concomitant end dates will be imputed such that the imputed end date is the latest possible date (i.e. last day of month if day is missing, last day of year if both month and day are missing). These imputation rules will tend to consider medications with an unknown start and/or end date to be "concomitant". See VDW MAP Module 8 variable CMDEND1O specifications for details.

## 7.3 Concomitant medication analyses

Concomitant medications are defined as medications, other than the study drug, that are reported during the study. All medications recorded on the CFTY720D2399 concomitant medications /significant non-drug therapies CRF will be coded using the current Hybrid DTD_DDE Dictionary. Concomitant medications and significant non-drug therapies, which are recorded in the CFTY720D2399 part 2 database and taken at any time from first dose date of fingolimod among all studies to last dose date of fingolimod + 45 days, will be summarized for the safety set by Anatomical Therapeutic Chemical (ATC) class and preferred term. The summary will show the number and percentage of patients receiving at least one drug of a particular ATC class and at least one drug in a particular preferred term (PT). To determine if any particular treatment is needed after discontinuation of fingolimod, concomitant medications and significant non-drug therapies, which are recorded in the CFTY720D2399 part 2 database and taken after last dose date of fingolimod, will be summarized in the same way as above for the follow-up set.

Note that concomitant medications which are recorded on the CFTY720D2399 part 2 concomitant medications / significant non-drug therapies CRF can include medications that may have been taken during any gap between the completion of the prior study (part 1) and enrollment into this study part 2, even if the medication is not ongoing at the time of enrollment.

All concomitant medications recorded during the study part 2 will be listed. The concomitant medications taken after study drug discontinuation but up to or after 45 days will be flagged. Records for steroid treatment of MS relapse during the study part 2 will be listed for the safety set.

# 8 Efficacy evaluation

The secondary objective of this study is to evaluate the long-term efficacy of fingolimod 0.5 mg in patients with relapsing forms of MS. Long-term efficacy will be assessed in MS relapse.

## 8.1 Analysis of MS Relapses

### 8.1.1 Relapse date imputations and handling of duplicate relapse records

The start date of a relapse should never be missing. However, missing or partial dates may be expected from some non-phase III trials where data checking may be less vigorous than in phase III trials. To avoid an artificial inflation of the number of relapses by low quality data, missing dates for relapses will only be imputed if the end date of the relapse is after the first dose of the initial study (i.e. if the relapse happened at least partially within the study). If partial or complete end dates are before the first dose date of the initial study, then no imputation will be done. If partial or complete relapse end dates are after the first dose of the initial study, the following algorithm will be applied:

**Firstly, drop blanks and impute missing or partially missing start dates**

1. Drop complete blanks: If the relapse onset date is invalid (e.g. “No”, “None”) or completely missing and there is no information recorded across all variables, the onset date will be set to missing.
2. Otherwise, if the record is not empty or the onset date is partially missing, check if another record may be available for the same relapse. Concretely:
    a. If a relapse onset date has a missing day-part (XX-MM-YYYY), where XX represents the missing or invalid part, the onset date will be imputed by the onset date of another treatment-emergent relapse record with a non-missing start date for the same patient within the same month and year, if such a relapse is available (choose the first one if more than one is available).
    b. If a relapse onset date has a missing day- and month part (XX-XX-YYYY, the onset date will be imputed by the onset date of another treatment-emergent relapse record for the same patient within the same year, if such a relapse is available (choose the first one if more than one is available).

3. Otherwise, if the onset date of a relapse is completely or partially missing, the onset will be imputed with the first possible day within the available non-missing date-part, or the first-dose date, or the relapse end-date minus 90, whatever occurs latest.

#### Secondly, impute the end date

The imputation of missing or partially missing end dates will be done after the imputation of start dates.

1. If the end date of a relapse is completely missing, it will be imputed as 90 days after the onset date.
2. If the end date of a relapse is partially missing, it will be imputed as the maximum of the relapse start day plus one or the minimum of either 90 days after the onset date, or as the last possible day based on the non-missing parts of the end-date (e.g. XXDEC2007 where XX indicated the missing end day would be imputed as 31-DEC-2007 if the onset date of the relapse was 26-NOV-2007).

#### Thirdly, handle duplicate relapse records:

After the imputation of start and end-dates is completed, records which refer to the same relapse (30-day rule) will be combined into a new artificial record. This step will help to consolidate core and extension databases where the same relapse may be recorded more than once, and it will help to ensure consistent relapse rules even for studies with a less vigorous date management.

1. For each patient relapses will be sorted by onset date (source or imputed).
2. **Combine relapses for which the distance between onset dates is <30 days:** Starting from the first relapse within each patient, the distance from each relapse to the next will be tested. If the onset date of a relapse is less than 30 days from the onset date of a previous one, an artificial record will be created using the "worst" or "most severe" information from both records (Conservative approach). The following rules apply:

    a. Onset date: use the *minimum* of the candidate dates with the highest degree of completeness. The degree of completeness is defined in descending order: 1. Original date, 2. Only day-part imputed, 3. Day and Month part imputed, 4. Day, Month and Year imputed.

    Example: an original date entered by the investigator has the higher degree of completeness compared to a partial/imputed date. An imputed date with just the day-part imputed has the higher degree of completeness compared to a completely imputed date. Rationale: amongst the candidate-dates with the highest reliability/completeness – choose the first/worst.

    b. End date: use the *maximum* of the candidate dates with the highest degree of completeness. The degree of completeness is defined in descending order: 1. Original date, 2. Only day-part imputed, 3. Day and Month part imputed, 4. Day, Month and Year imputed.

    Example: an original date entered by the investigator has the higher degree of completeness compared to a partial/imputed date. An imputed date with just the day-part imputed has the higher degree of completeness compared to a completely imputed date. Rationale: amongst the candidate-dates with the highest reliability/completeness – choose the last/worst.

c. When two records are combined from two consecutive phases (e.g. one from an initial study, the other one from an extension) the combined record will be considered as belonging to the first phase.

   Example: A relapse may have started at the end of an extension but ended in an Umbrella study. The same relapse may then be captured in the extension and also in the Umbrella study. When the two records are combined into one, the relapse – according to its start date – will be considered in the extension phase. Programmatically: Ext1n will take the minimum value of the two combined records.

d. Hospitalization: "yes" is worse than "no"

e. Severity: "severe" is worse than "moderate" is worse than "mild" is worse than "unknown"

f. Steroids: "yes" is worse than "no"

g. Relapse confirmed: "yes" is worse than "no"

h. Recovery: "none" is worse than "partial" is worse than "complete"

i. Daily activity: "affected" is worse than "not affected"

**Lastly, truncate the duration of all relapses to a maximum of 90 days**

1. For each relapse record, check whether the duration from onset to end date is less or equal to 90 days, if this is not the case do the following:
   a. Determine the degree of completeness of the start and end-date. The degree of completeness is defined in descending order: 1. Original date, 2. Only day-part imputed, 3. Day and Month part imputed, 4. Day, Month and Year imputed.

      Example: an original date entered by the investigator has the higher degree of completeness compared to a partial/imputed date. An imputed date with just the day-part imputed has the higher degree of completeness compared to a completely imputed date.

   b. Keep the date with the higher degree of completeness fixed and update the other date, so that the duration the relapse is maximized to 90 days

      Rationale: If one of the dates has to be replaced to keep truncate the duration of the relapse to 90 days, keep the date with the higher degree of completeness/reliability fixed (either the end- or the start date) and replace the other one.

   c. If the onset- and end-date have the same degree of completeness, keep the start date fixed and impute the end-date such that the duration of the relapse is maximized to 90 days.
2. If a relapse is recorded as ongoing at the final exam, impute an end date such that the duration is maximized to 90 days.

### 8.1.2 Annualized relapse rates

Annualized relapse rate (ARR) is defined as the *number of relapses* experienced during a specific period of time adjusted to a one-year period. The 'number of relapses' can refer to

either the number of *confirmed relapses* or the number of *all relapses* (including both confirmed and unconfirmed relapses).

Confirmation of relapses is not collected in the following studies: CFTY720D2316, CFTY720D2320, CTY720D2399E1, and the long-term follow-up study prior to protocol amendment 4. Therefore, the number of confirmed relapses during this time is not able to be reported. Additionally, confirmed relapses will not be reported for patients from the CFTY720D2324 study since it is a phase IIIb study and confirmation is not collected in the long-term follow-up study for patients coming from previous studies that are not phase II/III. The number of unconfirmed relapses is also not able to be reported for study CTY720D2399E1 since the study does not collect relapse start dates. However, note that the time during which number of relapses is not able to be counted and the time off study for patients who re-enrolled into the long-term follow-up study will still be included in the time in study, which can make the ARR appear lower than it actually is. If confirmation of a relapse is missing or not collected, the relapse will be treated as an unconfirmed relapse. Therefore, ARR based on all relapses (confirmed or unconfirmed) should be considered a more reliable estimation of relapse rate than ARR based on confirmed relapse.

The group level (aggregate) ARR will be calculated as follows: (total number of relapses) / (total number of days in the study for all patients for that specific period of time) x 365.25.

### 8.1.3 Time in study

For the analysis of ARR from first dose of fingolimod to end of study treatment, the time in study (days) is calculated as: last dose date of fingolimod – first dose date of fingolimod among all studies + 1 day. Similarly, the time in study from first dose of fingolimod among all studies to end of follow-up is calculated as: last available visit/evaluation date across all panels – first dose date of fingolimod among all studies + 1 day.

For the analysis of ARR from first dose of fingolimod among all studies to end of a particular month (i.e. “Month 6”, “Month 12”, “Month 24”, and every 12 months from then on), “Month 0 to X” time in study will be calculated as minimum of (first dose date of fingolimod + integerpart(X/12*365.25) where X denotes the month, last available visit/evaluation date across all panels) – first dose date of fingolimod + 1 day.

### 8.1.4 MS relapses analyses

MS relapses analyses will be conducted on the fingolimod full analysis set. All analyses will be done for all relapses (confirmed and unconfirmed) and for confirmed relapses.

A summary of ARRs will be presented by time period (cumulative time intervals: ‘Month 0 to Month 6’, ‘Month 0 to Month 12’, ‘Month 0 to Month 24’, ‘Month 0 to Month 36’, … incremented by 1 year for each successive interval, plus ‘Month 0 to end of study treatment’ and ‘Month 0 to end of follow-up’) from first dose of fingolimod among all studies. The summary will include number of patients summarized, number of relapses, time in study (days), and group level ARR. In addition, model based estimates of ARR and corresponding two-sided 95% confidence interval will be obtained by fitting a negative binomial regression model adjusted for the number of relapses in the last two years prior to enrolment in the core

study and EDSS score at first dose of fingolimod baseline, with the logarithm of the time in study as the offset variable.

A summary of relapse characteristics will be displayed by time period (consecutive yearly intervals: 'Month 0 to Month 12', 'Month 12 to Month 24', etc., plus 'End of study treatment to End of follow-up') from first dose of fingolimod among all studies. Relapse characteristics will be summarized at a patient level (the number and percent of patients with at least one relapse type) and at a relapse event level (the number and percent of a particular type of relapse out of the total number of relapses). The types of relapses being summarized include: relapses which affect daily activities, relapses which require steroids, and relapses which require hospitalization.

The time to first onset of relapse from first dose date of fingolimod among all studies will be analysed. Specifically, the number of patients at risk, the cumulative number of patients with relapse, the Kaplan-Meier (KM) estimate of the percent of patients without relapse and corresponding standard error and two-sided 95% CI will be provided at each yearly time point (1 year = 360 days). Patients with no relapse, patients for whom follow-up ends before a confirmed relapse occurs, and patients who drop out prior to the relapse will all be censored, i.e. the time to event for these patients will be the time in study (from first dose of fingolimod among all studies to last available visit/evaluation date across all panels).

A Kaplan-Meier plot of time to first relapse from first dose of fingolimod to end of the study part 2 will be presented.

# 9 Safety evaluation

The primary objective of this study is to evaluate the long-term safety and tolerability of fingolimod 0.5 mg in patients with relapsing forms of MS.

Long-term safety will be assessed in terms of adverse events (AEs), pregnancy tests, vital signs (including dose administration monitoring), and electrocardiograms (ECG) dose administration monitoring.

## 9.1 Adverse events

### 9.1.1 Imputation of adverse event start date

Missing or partial adverse event start dates are imputed following the VDW MAP Module 8 'Adverse Event Start Date Imputation (#IMPUTAEV)' section (displayed below):

**Adverse Event Start Date Imputation (#IMPUTAEV)**

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

Note, it may happen that the imputed AE start is after AE end date. Missing AE end date is not imputed by STL.

| | Day | Month | Year |
|---|---|---|---|
| **Partial Adverse Event Start Date** | Not used | MON | YYYY |

| | | | |
|---|---|---|---|
| **Treatment Start Date (TRTSTD)** | Not used | TRTM | TRTY |

The following matrix explains the logic behind the imputation.

| | **MON MISSING** | **MON < TRTM** | **MON = TRTM** | **MON > TRTM** |
|---|---|---|---|---|
| **YYYY MISSING** | **NC** | **NC** | **NC** | **NC** |
| **YYYY < TRTY** | **( D )** | **( C )** | **( C )** | **( C )** |
| **YYYY = TRTY** | **(B)** | **( C )** | **(A)** | **(A)** |
| **YYYY > TRTY** | **(E)** | **(A)** | **(A)** | **(A)** |

The following table is the legend to the logic matrix.

| **Relationship** | |
|---|---|
| **Before Treatment Start** | Partial date indicates AE start date **prior** to Treatment Start Date |
| **After Treatment Start** | Partial date indicates AE start date **after** Treatment Start Date |
| **Uncertain** | Partial date **insufficient to determine** relationship of AE start date to Treatment Start Date |
| **Imputation Calculation** | |
| **NC / Blank Uncertain** | No convention |
| **(A) After Treatment Start or Uncertain** | MAX( 01MONYYYY, TRTSTD+1 ) |
| **(B) Uncertain** | TRTSTD+1 |
| **(C) Before Treatment Start** | 15MONYYYY |
| **(D) Before Treatment Start** | 01JULYYYY |
| **(E) After Treatment Start** | 01JANYYYY |

### 9.1.2 Adverse events analyses

All adverse events (AEs) recorded on the adverse events CRF will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA). Note that adverse events that started or were ongoing during any gap between the completion of the prior study (part 1) and enrollment into this CFTY720D2399 study part 2 can be recorded on the CFTY720D2399 part 2 adverse events CRF.

In AE summaries, primary system organ classes will be displayed in alphabetical order and preferred terms (within each system organ class) will be sorted by descending frequency.

There are two categories of AE summaries in this study: AEs during the long-term follow-up study part 2 and AEs during the fingolimod treatment period.

#### 9.1.2.1 Adverse events during the study part 2

Only AEs captured in CFTY720D2399 study part 2 database will be summarized. Unless otherwise specified, all non-serious adverse events recorded in the CFTY720D2399 part 2 database with an onset at any time from first dose date of fingolimod among all studies to last dose date of fingolimod + 45 days are included. All serious adverse events (SAEs) recorded in the CFTY720D2399 part 2 database with an onset at any time from first dose date of fingolimod among all studies are also included in the summaries.

Adverse events reported during the study part 2 will be summarized for the safety set.

There are two subcategories of AE summaries during the study part 2 as below.

##### 9.1.2.1.1 Occurrence of adverse events

Adverse events reported during the study part 2 will be summarized by primary system organ class (SOC) and preferred term (PT), and will show the number and percentage of patients with at least one adverse event in each SOC or PT category. Similarly, adverse events by study drug relationship (AEs suspected to be study drug related, AEs not suspected to be study drug related, and AEs regardless of study drug relationship), AEs by severity (mild, moderate and severe), SAEs, SAEs by study drug relationship, SAEs by severity, suspected study drug related AEs, and AEs leading to study drug discontinuation will also be summarized by SOC and PT.

When subjects had AE occurrence on same PT for more than once, but with different relationship, the subject will be counted in each category of relationship. When severity are different, subject will only be counted once in maximum severity of that PT.

AEs and SAEs which are not considered to be known effects of fingolimod treatment (i.e., excluding those listed in the most recent version of Core Data Sheet), will be summarized by PT only. To determine which AEs occur after discontinuation of fingolimod treatment, all AEs reported with onset date after the last dose of fingolimod until the end of the study part 2 will be summarized by SOC and PT for the follow-up set.

To determine which AEs have occurrence after study part 2 enrollment, newly-occurring AEs will be summarized by SOC and PT for the safety set. A newly-occurring AE is defined as an AE which starts after part 2 informed consent date. A similar summary will be provided for SAEs.

Principal cause of death during the study part 2 will be summarized by SOC and PT. All deaths recorded in the CFTY720D2399 part 2 database with onset on or after the first dose date of fingolimod (among all studies) will be included in the summary.

All information pertaining to any AE with severity information, SAEs, AEs leading to study drug discontinuation, deaths and neoplasms system organ class events that reported during the study part 2 will be listed for the safety set. Additionally, adverse events, SAEs and all deaths recorded during the study part 2 will be listed for the subgroup of patients from studies D2312 and D2402 in the enrolled set.

#### 9.1.2.1.2 Incidence rate of adverse events

The AE incidence rate (IR) is calculated per 100 patient-years. IR is defined as: the number of patients experiencing at least one event in a particular category, over the total patient-years of the "at risk" population for that event multiplied by 100. An underlying Poisson process for incidence rate within treatment group is assumed. For the summary time period for extension part 2, only AEs with a start date between first dose date of fingolimod during the study part 2 and the last dose date of fingolimod + 45 days will be counted; or SAEs with a start date on or after first dose date of fingolimod during the study part 2 will be counted.

To calculate the total patient-years (time at risk) of the "at risk" population:

1. For patients who have a particular AE category, sum the number of days from first dose date of fingolimod during the study part 2 to the first occurrence of that particular AE category
2. For patients who did not have a particular AE category, sum the number of days from first dose date of fingolimod during the study part 2 to last dose date of fingolimod + 45 days.
3. Add the time at risk for patients who had a particular AE category with the time at risk for patients who did NOT have a particular AE category. This is the total time at risk of that AE category.
4. Divide the total time at risk by 365.25.

Incidence rate of adverse events will be presented for the safety set. Incidence rate of AEs, AEs by relationship, excluding AE listed in the core data sheet, will be presented by PT. Similarly, all above indicated AE IR summaries will be conducted for SAEs.

#### 9.1.2.1.3 Regulatory adverse events report

For the legal requirements of ClinicalTrials.gov and EudraCT, summary of on-treatment/treatment emergent non-serious AEs and SAEs and SAE suspected to be related to study treatment will be provided by system organ class and preferred term in separate tables. The number of subjects with indicated AEs and the occurrences of AEs will be provided. The summary will be based on the safety set. Specifically, for the SAE summary, the number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided at each PT level.

To count the AE occurrence, if for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

• A single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

• More than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

#### 9.1.2.2 Adverse events during the fingolimod treatment period

To further evaluate the long-term AE rate (based on patient count and percentage) within a particular fingolimod treatment duration, an analysis based on yearly intervals since first dose of fingolimod will be conducted. For summaries on this set of patients, all AEs and SAEs with onset on or after first dose date of fingolimod (among all studies) to last dose date of fingolimod are included. Each yearly interval will contain 360 days. For example: Year 1 will consist of Day 1 to Day 360, Year 2 will consist of Day 361 to Day 720, Year 3 will consist of Day 721 to Day 1080, Year 4 will consist of Day 1081 to Day 1440, Year 5 will consist of Day 1441 to Day 1800, and so on. Patients will be summarized within a particular yearly interval if they have been receiving study treatment for at least one day in that particular interval. The number and percentage of these patients who have adverse events with onset date occurring during the interval will be summarized. For example, for the Year 1 group, patients with at least one day exposure to fingolimod will be included, and AEs with onset date occurring between Day 1 and Day 360 will be summarized. For the Year 2 group, patients with at least 361 days exposure to fingolimod will be included, and AEs with onset date occurring between Day 361 and Day 720 will be summarized. The same will be done for other intervals.

Adverse events summarized by year will include the following:

- Adverse events, by yearly interval, primary system organ class, and preferred term
- Serious adverse events, by yearly interval, primary system organ class, and preferred term
- Adverse events that fulfill the risk search term, by yearly interval
- Serious adverse events that fulfill the risk search term, by yearly interval

Intervals will be included based on the length of fingolimod exposure. Risk search terms are defined in Novartis' case retrieval sheet (eCRS). Associated summaries will be presented by risk name and lower level terms.

## 9.2 Laboratory

Patients with positive pregnancy test results during the study part 2 will be listed for the safety set.

## 9.3 Routine vital signs

Vital signs include sitting pulse rate, sitting systolic and diastolic blood pressure, and body temperature. First dose monitoring vital signs values will be excluded from routine vital signs summaries and listing.

Vital signs data will be summarized by presenting descriptive statistics for baseline, post-baseline, and change from baseline values by parameter and nominal visit. The incidence of notable vital sign abnormalities reported during the study part 2 will present the number and

percentage of patients satisfying notable criteria by nominal visit. An overall study visit will be generated to indicate any notable abnormalities from post-baseline visits (including follow-up visits). Criteria for clinically notable vital signs values are specified in Appendix A. Both summaries are based on the safety set.

Patients in the safety set with notable vital sign abnormalities will be listed. All vital sign parameters with clinically notable criteria will be listed for a particular patient and visit if at least one of the parameters shows an abnormality. The listing will also indicate whether the vital sign result was above or below the normal range.

## 9.4 Dose monitoring administration

A dose administration monitoring summary will be provided for the safety set for first/second/restart of fingolimiod dose during the study part 2, and will include yes or no categorical summaries for the following: discharged at 6 hours, required extended monitoring after 6 hours, discharged but returned for monitoring, hospitalization, required Day 2 monitoring in the clinic (only recorded for first dose monitoring), study drug permanently discontinued, had symptomatic and/or treated bradycardia, and SAEs reported. The denominator for first/second dose monitoring data is based on the number of patients with assessment done; the denominator for restart monitoring data is based on the number of restarts.

### 9.4.1 Vital signs

During the study part 2, hourly vital signs, including sitting pulse rate and blood pressure will be monitored before the first dose of fingolimod and every hour for at least six-hours thereafter.

Hourly dose monitoring of vital signs will be summarized separately and will not be included in the by-visit summaries of routine vital signs. Descriptive statistics of pre-dose, post-dose, and change from pre-dose values will be summarized by parameter and time point for first dose monitoring, second dose monitoring, and dose monitoring after study drug restart. Summaries will be based on the safety set and include dose monitoring data during the study part 2 only.

### 9.4.2 Electrocardiograms

During the study part 2, all patients requiring first dose monitoring will have an electrocardiogram (ECG) performed prior to dosing and at the end of the 6-hour monitoring period.

ECG dose monitoring records will be listed for the safety set.

# 10 Sample size and power considerations

Given that this is a long-term follow-up study with primary descriptive purpose, no formal sample size calculation will be used to determine enrollment in this study. The sample size is defined by the number of patients coming from study part 1 and ongoing fingolimod trials.

# Appendices

## Appendix A: Clinically notable Vital sign values

**CRITERIA FOR NOTABLE VITAL SIGN ABNORMALITIES**

| NOTABLE VITAL SIGNS | |
|---|---|
| **Vital Sign Variable** | **Notable Criteria** |
| Pulse (beats/min) | >120bpm or Increase of ≥15 bpm from baseline<br>Or<br>< 50bpm or Decrease of ≥15 bpm from baseline |
| Systolic BP (mmHg) | ≥160 mm Hg or Increase of ≥20 mm Hg from baseline<br>Or<br>≤ 90 mm Hg or Decrease of ≥ 20 mm Hg from baseline |
| Diastolic BP (mmHg) | ≥ 100 mmHg or Increase of ≥ 15 mm Hg from baseline<br>Or<br>≤ 50 mmHg or Decrease of ≥ 15 mm Hg from baseline |
| Temperature (°C) | >38.3°C/ 101°F |