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NOVARTIS

Clinical Development

FTY720D (Fingolimod)

CFTY720D2403 & CFTY720D2406 & CFTY720D2409

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

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

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

RAP Module 3 – Detailed Statistical Methodology

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Document History

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Draft 1.0	16-Aug-2019	First draft.
Draft 1.1	6-Dec-2019	Implementation of comments on draft 1.0 and decisions made during RAP discussion TCs.
Final 2.0	18-Mar-2020	Finalization of document. Few additional changes based on comments and input from programming. Additional analysis for incidence rate differences. Additional serious cardiovascular event table comparing pooled cardiac set to Other DMT patients stratified by Framingham risk score category.
Final 2.0 Amendment 1	21-Aug-2020	Implementation of dry-run 2 comments from Novartis: • Adjustment of the use of data cutoff date in programming changed due to missing study completion visits in several patients • Clarification of adverse event classification by time interval • Analyses of AEs excluding certain time intervals added back into RAP (erroneously deleted from previous versions) • Incidence rate ratios added for AE analyses by subgroups • Various outputs for substudy analyses of D2403 added • Notable criteria for liver function tests corrected • List of cardiovascular risk factor preferred terms extended

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1 Introduction

This analysis plan provides a description of the analyses needed for studies CFTY720D2403, CFTY720D2406, CFTY720D2409 and for a combined analysis of all three studies (in the following referred to as pooled analysis) as well as substudy analyses, where applicable, for the final analyses reporting. Data will be analyzed by [redacted], Germany according to the data analysis section of the study protocols (Section 9 of CFTY720D2403, Section 7 of CFTY720D2406 and Section 9 of CFTY720D2409) which are available in Appendix 16.1.1 of the respective CSRs. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSRs.

CFTY720D2403 (Study protocol Version 02):

CFTY720D2403, in the following referred to as D2403, is a multinational, long-term, prospective, parallel-cohort study to monitor and further describe the long-term safety of fingolimod (FTY720). It includes patients with relapsing forms of multiple sclerosis (MS) that have been newly prescribed FTY720 by their treating physician or patients that are treated within six months prior to study entry with other disease-modifying therapies as part of their MS treatment in accordance with the respective local prescribing information and routine clinical practice.

During the course of the study, patients will be allowed to switch MS DMT (i.e. FTY720 or other DMT) while remaining in the study except those switching to cytotoxic agents (e.g. mitoxantrone), natalizumab or an investigational DMT, in which case they are to discontinue from the study.

CFTY720D2406 (Study protocol Version 03):

CFTY720D2406, in the following referred to as D2406, is a multi-country, multi-center, long-term, prospective, non-interventional, parallel cohort study to monitor and further describe the long-term safety of FTY720. It includes patients with relapsing MS who either have been recently initiated with FTY720 by their treating physician or who are treated within six months prior to study entry or starting with other DMT as part of their MS treatment in accordance with the respective local prescribing information and routine clinical practice.

During the course of the study, patients will be allowed to switch MS DMT (i.e. FTY720 or other DMT) while remaining in the study unless they are converted to an investigational DMT.

CFTY720D2403 and CFTY720D2406 are similar studies and together called the PASSAGE study.

CFTY720D2409 (Study protocol Version 01):

CFTY720D2409, in the following referred to as D2409, is a multi-country, multi-center, long-term, prospective, interventional, study to estimate the long-term cardiovascular risk of fingolimod in patients who experienced a cardiovascular event during the first 24 hours of fingolimod treatment initiation or re-initiation in study D2406 which led to overnight monitoring or met seriousness criteria. Patients eligible and consenting to participation in

study D2409 will discontinue their study D2406 participation and be followed in study D2409. Study D2409 enrollment period will be open until 1-year before the end of study D2406 and the study will last until the end of study D2406 i.e. five years after the last patient has been enrolled in Study D2406. Within the summaries, patients will be reported under their original patient number from study D2406 and not be considered separate patients.

2 PASSAGE reports and use of the virtual data warehouse

The virtual data warehouse (VDW) is a collection of pooled datasets containing most of the FTY720 data in the MS indication. The VDW uses harmonized rules across all FTY720 trials. For now it is updated every 12 months (every 6 months until February 2017), with the main goal of preparing a periodic safety update report (PSUR) deliverable on a yearly basis. It does not pre-specify all possible analyses, but it contains rules and datasets to facilitate future analyses.

For reporting of PASSAGE studies, it has been decided to align the analysis concept with other Gilenya analyses, that is, to align it with the VDW (and thus the PSUR). PASSAGE analyses will be done as follows:

- Wherever possible, PASSAGE analyses will use the VDW analyses datasets, but filter on the appropriate studies (that is, D2403, D2406, D2409 or D2403/D2406/D2409). In that case, the VDW datasets (programmed by Novartis) will be made available to [redacted], who will program the analysis outputs.
- For specific data analyses where data are not analysis-ready in the VDW, the programming of the derived datasets as well as the programming of the analysis outputs will be performed by [redacted]. For these analyses too, the approach used will be consistent with the general approach used in the VDW, where applicable.

This document will clarify for each analysis whether VDW analysis datasets will be used, or whether there will be a need to derive the analysis datasets.

3 Pooling of data from patients who discontinue D2406 to enter D2409

Data for patients who discontinue study D2406 to enter D2409 will be appended for the pooled PASSAGE analysis, i.e., they will be reported under the identification number a patient was assigned to at the beginning of D2406 and will be analyzed as if collected under a single study. That means, e.g., adverse events for these patients will be reported for the entire duration of study participation within both studies and the reporting period will be the entire time from the first dose within D2406 until the end of D2409. Baseline data, demographic characteristics, medical history, disease characteristics and previous MS treatment etc. will be taken from the D2406 study. The study completion status, however, will be taken from D2409. Where specific rules for data pooling are needed for analysis these will be stated in the respective sections of this document.

4 Statistical and analytical plans

4.1 Terminology – MS DMT, permanent switch, initial cohort treatment, first DMT corresponding to cohort assignment

MS DMT is used to designate all MS disease modifying therapies: FTY720 and/or any other MS DMT.

A *permanent switch* is defined as a switch from FTY720 to non-FTY720 MS DMT, or a switch from a non-FTY720 MS DMT to FTY720.

Initial cohort treatment is used to designate:

- For patients assigned to the FTY720 cohort, the first sequence of FTY720 treatment (interruptions in FTY720 treatment are allowed) taken in the study, before first permanent switch to a non-FTY720 DMT.
- For patients assigned to the other DMT cohort, the first sequence of all non-FTY720 MS DMTs (not differentiating between the different non-FTY720 MS DMTs, interruptions are allowed) taken in the study, before first permanent switch to FTY720.

  Note: the initial cohort treatment is either 'FTY720' or 'other DMT'. To present initial cohort treatment data, VDW variable TRTN_CO will be used.

First DMT corresponding to cohort assignment is used to designate:

- For patients assigned to the FTY720 cohort, the first FTY720 treatment taken during the study, prior to any switch in DMT occurring after the initial cohort treatment date and prior to any interruption in FTY720 of more than 45 days.
- For patients assigned to the other DMT cohort, the first non-FTY720 DMT taken during the study, prior to any switch in DMT occurring after the initial cohort treatment date and prior to any interruption in first DMT of more than 45 days. This will be one single drug.

  Note: The first DMT corresponding to cohort assignment will be classified under 7 categories, based on the preferred term: FTY720, Interferon, Glatiramer Acetate, Dimethyl Fumarate, Teriflunomide, Natalizumab and other MS therapies. To present data by first DMT corresponding to cohort assignment, (i.e. by the 7 above categories), VDW variable TRTN_RI should be used. Mapping of medication preferred terms to these 7 categories is available in Appendix F.

For a patient with a permanent switch, *first dose of treatment at permanent switch* will be defined as follows:

- For patients assigned to the FTY720 cohort, it will be the first dose of non-FTY720 MS DMT taken during the study (after the first dose of FTY720 taken during the study)
- For patients assigned to the other DMT cohort, it will be the first dose of FTY720 taken during the study (after the first dose of non-FTY720 DMT taken during the study)

Link to VDW: the date of first dose of treatment at first permanent switch is available in FIRSMD9O.

Example

Patient 1 was assigned to the FTY720 cohort. He started FTY720 on the 3rd day in the study and switched to Avonex after 1.5 years. Patient 2 started Avonex 3 months prior to study entry, then switched to Glatiramer acetate after 1 year, and finally switched to FTY720 after 4 years.

For patient 1, both the *initial cohort treatment* and the *first DMT corresponding to cohort assignment* will be designated as FTY720. The *first dose of treatment at permanent switch* will be the first dose of Avonex.

For patient 2, while the *initial cohort treatment* will consist of Avonex followed by Glatiramer acetate the *first DMT corresponding to cohort assignment* will be Avonex alone. The *first dose of treatment at permanent switch* will be the first dose of FTY720.

4.2 General reporting approaches

One of the key features of the PASSAGE studies is that patients are allowed to switch DMT, while remaining in their original cohort (for example, a patient enrolled in the 'Other DMT' cohort can later decide to switch to FTY720). With this specific feature in mind, it has been decided to look at the PASSAGE data using different approaches are used:

1. "**All patients, by initial cohort treatment**" **(Group G) – providing rigorous data allowing meaningful comparisons:** Where all patients will contribute to the analyses and they will be grouped by original cohort assignment (i.e. the cohort they were assigned to at study entry). Unless otherwise specified, safety analyses in Group G will include data from first dose date in study of initial cohort treatment to the last dose date of initial cohort treatment + 45 days, day before the first dose date of the first permanent switch, or cut-off date, whichever is earliest. Unless otherwise specified, effectiveness analyses in Group G will only use data collected on the first DMT corresponding to cohort assignment (i.e. data from one single drug).

   Link to VDW: this approach corresponds to the Group G cohort approach.
2. **"All FTY720 treated patients" (Group F) - comprehensive view on long-term FTY720 data:** all patients who took at least one dose of FTY720 in the study will be included in the analyses. Unless otherwise specified, all data collected from first dose of FTY720 until the last dose of FTY720 +45 days or cut-off date, whichever is earlier will be considered, regardless of switch to other DMT. No analyses of effectiveness are planned for Group F.

   Link to VDW: this approach corresponds to the VDW Group F approach.

In this document and in statistical outputs, the wordings *Group G* and *Group F* will be used to refer to these two ways of looking at the data.

As a general rule, Group G outputs will be generated for each individual study (D2403 and D2406) as well as for the pooled D2403/2406 report. Group F analyses will be generated for the pooled analysis and each individual study.

4.3 Definitions

4.3.1 Cut-off date

The cut-off date will be set to the DB lock date for the individual studies in the VDW. If the DB lock dates differ the cut-off date will be set to the latest DB lock date.

4.3.2 Day 1 and other time definitions

An illustration of the key dates available in the VDW is provided in Appendix B.

Day 1 is defined as:

- In group G, Day 1 is the day of the first administration of initial cohort treatment in the study (VDW variable: Group G Day 1 is the day of FIRSMD1O).
- In group F, Day 1 is the day of the first administration of FTY720 in the study (VDW variable: Group F Day 1 is the day of FIRSMD3O).

  Note: Day 1 may be different from the baseline visit (Visit 1) day.

Date of last dose of initial cohort treatment (used in Group G safety analyses) is defined as the date of last dose of initial cohort treatment, prior to first permanent switch (see Section 4.1 for definitions). If the last dose date of initial cohort treatment is missing it will be imputed using the end of study participation date or the last visit date if the former is not available. (VDW variable: LSTSMD8O).

Date of last dose of FTY720 (used in Group F analyses) is defined as the date of last dose of FTY720 taken during the study. In the case where a patient took FTY720, then switched to another DMT then came back to FTY720, the date of the very last dose of FTY720 will be used (VDW variable: LSTSMD3O). If the dose date of FTY720 is missing it will be imputed using the end of study participation date or the last visit date if the former is not available.

Date of last dose of first DMT corresponding to cohort assignment (used in Group G effectiveness analyses) is defined as the date of last dose of first DMT corresponding to cohort assignment (as defined in Section 4.1) prior to any switch in DMT and prior to an interruption of more than 45 days. If the date of last dose of first DMT is missing it will be imputed using the end of study participation date or the last visit date if the former is not available. ([redacted] variable: LSTDMT1).

4.3.3 Time at risk

The *time at risk* matches the time generally considered in safety summaries. The time at risk will be used in the analysis of adverse events to derive the (exposure-adjusted) incidence rates and is defined as follows:

- In Group G, summaries by first DMT corresponding to cohort assignment: time at risk (days) is the number of days from first dose date of first DMT corresponding to cohort assignment (i.e. Day 1) to last dose date of first DMT corresponding to cohort assignment prior to any switch in DMT and prior to any interruption in the first DMT corresponding to cohort assignment of more than 45 days + 45 days. If this date lies after the cut-off date, the cut-off date will be used instead (Based on [redacted] derived variable TMATRSK2).

- In Group G, all other AE summaries: time at risk (days) is the number of days from first dose date of initial cohort treatment in the study (i.e. Day 1) up to the last dose date of initial cohort treatment + 45 days, day before first dose date of treatment after permanent switch, or cut-off date whichever is earliest. (Link to VDW: this will be derived as (CUTO_CO – FIRSMD1O +1)).
- In Group F: time at risk (days) is the number of days from first dose date of FTY720 in the study up to last dose date of FTY720 +45 days or cut-off date, whichever is earlier. (VDW variable: TMATRSK)

4.3.4 Definition of 'baseline'

In these observational studies, where patients were allowed to enter when already receiving study treatment (for details please refer to the study protocols), there is no classical definition of "baseline value". The following values will be used in the analyses :

- In group G, the *value prior to first dose of initial cohort treatment in study* refers to the last measurement prior to administration of the first dose of initial cohort treatment in the study. If there is no such measurement, the measurement taken on the day of administration of the first dose of initial cohort treatment in the study will be used. For patients who never received a dose of initial cohort treatment, data up to and including Visit 1 may be used.
- In group F, the *value prior to first dose of FTY720 in study* refers to the last measurement prior to the administration of the first dose of FTY720 in the study. If there is no such measurement, the measurement taken on the day of administration of the first dose of FTY720 in the study will be used if available.

Note about vital sign first dose monitoring assessments: on the day of first intake of FTY720, a pre-dose measurement and post dose measurements will be taken. Only the pre-dose measurement will be considered for the value prior to first dose of initial cohort or FTY720 in the study, if available.

4.3.5 Duration derivation

Unless otherwise specified for a specific panel or variable, duration variables will be derived according to the following rules:

- Duration (in days) = [End date – start date +1]
- Duration (in weeks) = [End date – start date +1]/ 7
- Duration (in months)= [End date – start date +1]/30
- Duration (in years) = [End date – start date +1]/365.25

Duration variables which are to be expressed in units greater than day (e.g. the duration of MS since first symptoms in years) will be rounded to 1 decimal place.

4.4 General rules

4.4.1 General rules on statistics to present

Categorical data will be presented as absolute and relative frequencies. Percentages will be rounded to 1 decimal place. For frequencies of categorical variables, a category of 'Missing' will be added if at least one patient has no response.

Summary statistics for continuous variables will include n, percentage of patients out of analysis set, mean, standard deviation, minimum, lower quartile (25^{th} percentile), median, upper quartile (75^{th} percentile), and maximum. The mean, median and percentiles will be rounded to 1 additional decimal place compared to the original data. Standard deviation will be rounded to 2 additional decimal places. Minimum and maximum will be displayed with the same accuracy as in the original data.

4.4.2 General rules for tables and listings

Unless otherwise stated, summary tables and listings will include all patients in their respective analysis sets. For more details on the analyses set and data considered in specific analyses, please refer to specific sections in this document.

Except for the listings presenting data related to participant's characteristics and unless otherwise stated, the following rules will apply to listings:

Group G listings

Group G listings will include all data collected in the study in the corresponding panel (even if collected prior to Group G Day 1).

Group F listings

Unless otherwise specified, Group F listings will include all data collected on or after first dose of FTY720 in the study in the corresponding panel.

Combined listings

The majority of the listings will include patients belonging to Group G and/or Group F, and will include all data mentioned in the above descriptions for Group G and Group F listings. Flags to identify the groups will be added, as necessary.

4.4.3 Partial dates (imputation rules)

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 (i.e. the 3 digits for month within the character date variable contain characters not belonging to a valid month

abbreviation) or missing (e.g. 17-XXX-2010), then the year-information 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. XX-FEB-2009), then the year and month will be kept, the 15th will be imputed (15-FEB-2009).

In the listing, when date variables from VDW are presented, the values in VDW data set will be presented. If VDW variables are not available and data from raw data set should be used, the original data without imputation will be presented.

4.5 Analysis sets

An analysis set is defined as a subset of patients who share common criteria. The analysis sets used in each of the 2 groups are defined below:

Group G - "all patients"

- **Enrolled set**: All patients who were enrolled into a study and were categorized to a cohort at the start of the study, excluding patients with a protocol deviation severity code of 8 (8=exclude from all analyses). (VDW variable: ENR)
- **Safety set:** All enrolled patients who received at least one dose of treatment corresponding to the cohort they were assigned to, excluding patients with a protocol deviation severity code of 5 (5=exclude from all safety analyses) or 8 (8=exclude from all analyses). (VDW variable: SAF_G)
- **Effectiveness set:** All patients who were treated with the first DMT corresponding to cohort assignment for a minimum of 180 days in the study, excluding interruptions. The determination of whether a patient completed a minimum of 180 days is based on the *duration on first DMT,* which is the time in study from first dose date of first DMT corresponding to cohort assignment to last dose date of first DMT corresponding to cohort assignment prior to any switch in DMT and prior to any interruption in the first DMT corresponding to cohort assignment of more than 45 days, excluding any interruptions. Patients with a protocol deviation severity of 0 (0=exclude from all efficacy analyses), 1 (1=exclude from all per protocol analyses), or 8 (8=exclude from all analyses) will be excluded ([redacted]-derived variable: EFF_G.)
- [redacted]

In Group G analyses on the enrolled set and on the safety set, patients will be grouped according to the cohort they were assigned to at study entry (VDW variable: TRTN_CO).

In Group G analyses on the effectiveness set, patients will be grouped according to the first DMT corresponding to cohort assignment. Specifically, the following DMTs will be presented: FTY720, Interferon, Glatiramer Acetate, Dimethyl Fumarate, Teriflunomide, Natalizumab, and other MS therapies (VDW variable: TRTN_RI).

Group F - "all FTY720 treated patients"

- **Safety set:** All enrolled patients who received at least one FTY720 dose in the study. (VDW variable: SAF_EF)

In Group F, there will be one single group, the FTY720 group.

Disposition, demographics, baseline characteristics, and medical history will use the enrolled set for Group G and safety set for Group F. Safety analyses (adverse events, vital signs, laboratory data, FTY720 first dose administration monitoring on ECG and vital signs) will be performed using the safety sets. Effectiveness analyses will be based on the effectiveness set.

The number and percentage of patients in each analysis set will be summarized for Group G. The enrolled population will be used as the denominator for percentages. The number of patients in the safety set will be summarized for Group F. Group F patients will be divided into patients who started in FTY720 cohort and patients who switched to FTY720. A listing will also be presented for the analysis sets.

4.5.1 Definition of subgroups/stratifications for analysis

Certain analyses, as specified in the corresponding sections of this document, will be performed on the following subgroups of patients:

- **Patients naïve to any prior MS DMT**: This subgroup will be defined as patients who do not have any prior DMTs (Day 1). It should be noted that prior DMTs in this definition include initial cohort treatments already ongoing at study start. Note: for some analyses in that subgroup, both cohorts will be presented, while for some other only the FTY720 cohort will be used.
- **Patients previously treated with any MS DMT**: This subgroup will be defined as all patients who have a history of any MS DMT (including FTY720) prior to study start (Day 1).
- **Patients never treated with FTY720**. This subgroup will be defined as patients who were never treated with FTY720 prior to study start (Day 1).
- **Patients in the FTY720 cohort split by subgroups based on the type of MS therapy previously used**: The last MS-DMT before switching to initial cohort treatment, as defined in Section 4.6.5., will be used to defined these subgroups. MS DMTs to be considered will be the following: interferon beta-1a, interferon beta-1b, glatiramer acetate, natalizumab, dimethyl fumarate and teriflunomide.
- **Patients who started their initial cohort treatment within the study.**
- **Patients who had an AE categorized as cancer:** This subgroup will be defined as all patients that have at least one adverse event categorized as cancer. The corresponding AEs are identified as all malignant forms of cancer in the system organ class "Neoplasms benign, malignant and unspecified (incl cysts and polyps)".
- **Patients stratified by duration of previous MS DMTs:** Patients will be split into subgroups according to duration of previous MS DMTs <= 3 years and > 3 years.
- **Patients stratified by age group:** Patients will be split into subgroups according to age (at first dose of initial cohort treatment) <= 40 years and > 40 years.
- **Patients stratified by gender:** Patients will be split into subgroups according to gender.
- **Patients stratified by ethnicity:** Patients will be split into subgroups according to ethnicity.

- **Patients stratified by geographic region:** For D2403 use North America, South America and APAC. For D2406 use Europe and APAC. For pooled analysis use North America, South America, Europe and APAC.
- **Patients stratified by Framingham risk score category:** Only done for pooled cardiac analysis. Patients will be split into subgroups according to the median Framingham risk score calculated over all patients in the pooled cardiac set who had FTY as initial cohort treatment.

The following table shows an overview of the usage of subgroups in the respective analyses:

Subgroup definition	**D2403**	**D2406**	**Pooled**
General subgroups			
Patients naïve to any prior MS DMT	X	X	X
Patients previously treated with any MS DMT	X	X	X
Patients who were never treated with FTY720	X	X	X
Patients in the FTY720 cohort split by subgroups based on the type of MS therapy previously used	X	X	X
Patients who started their initial cohort treatment within the study	X	X	X
Patients who had an AE categorized as cancer	X	X	X
Subgroups specific for AE analysis			
Patients stratified by duration of previous MS DMTs	X	X	X
Patients stratified by age group	X	X	X
Patients stratified by gender	X	X	X
Patients stratified by ethnicity	X	X	X
Patients stratified by geographic region	X	X	X
Patients stratified by Framingham risk score category*			
* Will only be done for pooled cardiac analysis.			

4.6 Characteristics of participants

4.6.1 Disposition

The number and percentage of patients who completed the study or discontinued the study prematurely along with the primary reason for discontinuation will be presented for Groups F and G.

For patients who discontinue from study D2406 and who continue in study D2409 the completion status from D2409 will be used in the pooled tables.

Patient disposition will also be provided for the following subgroups defined in Section 4.5.1 above:

- Patients naïve to any other DMT
- Patients previously treated with any MS DMT

- Patients never treated with FTY720.
- Patients who had an AE categorized as cancer

4.6.2 Protocol deviations

The number and percentage of patients with protocol deviations will be summarized for Group G. This will be done for individual studies and pooled analysis.

4.6.3 Cause of death from study completion form

4.6.4 The principal cause of death from the study completion page will be summarized by primary system organ class, preferred term for Group G, Enrolled set and Group F, safety set.Demographic variables

Demographic characteristics include age (derived), gender, race, and ethnicity collected on the demography CRF, height, and body weight recorded on the vital signs CRF, and the body mass index (BMI) calculated as (body weight in kilograms) / (height in meters)^2.

In Group G, age will be calculated at first dosing date of initial cohort treatment (VDW variable FIRSMD1O) and height and body weight values prior to first dose of initial cohort treatment in the study will be presented. If first dosing date is missing, then the Visit 1 date will be used for calculation. In Group F, age will be calculated at first dose of FTY720 during the study and height and body weight values *prior to first dose of FTY720 during the study* will be presented. See Section 4.3.4 for more details on derivation of baseline measurement.

Weight that is collected in pounds will be converted to kilograms using 1 kg=2.2 lb. Height that is collected in inches will be converted to cm using 1 in=2.54 cm.

For other variables, data as collected on the demography CRF will be presented.

The number of patients with any smoking history (i.e. who answered 'yes' to the question 'Has patient any smoking history?") and those who smoke at study entry will be presented for Group G. Alcohol history at study entry will be summarized by category (abstinent, less than 1 drink per day, 1-2 drinks per day, 3 or more drinks per day, unknown) for Group G.

The number of patients per geographic region and country will also be presented for Group G.

All demographic and baseline characteristic data described in this section will be summarized by presenting frequency and percentage (for categorical variables) and summary statistics (for continuous variables). Age group will also be summarized for the categories of <18, 18-40, 41-64, >=65 years of age.

Demographic characteristics will also be provided for the following subgroups defined in Section 4.5.1 above:

- Patients naïve to any other DMT
- Patients previously treated with any MS DMT
- Patients never treated with FTY720
- Patients who started their initial cohort treatment within the study.
- Patients who had an AE categorized as cancer

4.6.5 MS baseline characteristics and MS disease history variables

MS disease history and EDSS at study entry (Group G) and prior to first dose of FTY720 during the study (Group F) will be summarized.

Details of MS diagnosis (RRMS, SPMS, PPMS, other) will be summarized with the number and percentage of patients for Group G and Group F. Duration of MS since diagnosis and duration of MS since first symptom will be summarized as a continuous variable and as a categorical variable using the following categories: 0-<1, 1-<2, 2-<5, 5-<10, 10-<15, >=15 years. Number of relapses in the 12 months prior to study entry and between 12 and 24 months prior to study entry will be summarized as a continuous variable and as a categorical variable using the following categories: 0, 1, 2-3, 4-5, >5. The total number of relapses in the 12 months prior to study entry will be presented. The number and percentage of relapses that required steroid treatment will be presented. Time since the onset of the most recent relapse at study entry (months) will be derived for each patient using (date of Day 1 – the most recent relapse onset date + 1)/30.

The most recent EDSS score available at baseline will be summarized as a continuous variable. The subset of most recent EDSS scores that were not assessed in the course of a relapse will also be summarized.

For Group G, duration variables (duration of MS since diagnosis, duration of MS since first symptom, time since onset of the most recent relapse) will be calculated based on Group G Day 1 date (i.e. the date of first dose of initial cohort treatment taken during the study) and data collected on the MS history CRF page will be presented.

For Group F, duration will be calculated based on Group F Day 1 date (i.e. the date of first dose of FTY720 taken during the study). In this group, since a patient may start FTY720 at any time during the study (e.g. after switching from another MS DMT), any MS disease status (relapses and EDSS) collected prior to the first dose of FTY720 in the study will be considered an MS disease history. The EDSS data from both the MS history CRF page and the MS status page will be presented to represent Group F MS disease history. Only the number of relapses in the last 12 months and between the last 12 and 24 months before study entry as collected in the MS history CRF will be summarized for patients in Group F.

The patients' status of previous exposure to varicella zoster virus (VZV) combined with whether or not patient had VZV serology test prior to FTY720 initiation will be summarized by frequency for Group F using the safety set.

MS baseline characteristics and disease history variables will also be provided for the following subgroups defined in Section 4.5.1 above:

- Patients naïve to any other DMT
- Patients previously treated with any MS DMT
- Patients never treated with FTY720
- Patients who started their initial cohort treatment within the study
- Patients who had an AE categorized as cancer.

4.6.6 Prior MS DMT

To facilitate data summarization, the prior MS DMTs will be categorized into Fingolimod, Interferon, Glatiramer Acetate, Dimethyl Fumarate, Teriflunomide and Natalizumab, as defined in Appendix F. All other MS DMT will be summarized as recorded by the preferred term.

For Group G, MS DMTs that were taken prior to Group G - Day 1 will be classified into either one of the following mutually exclusive categories, and will be summarized by categorized preferred term:

- '*Prior MS DMT*': defined as MS DMT that started and ended before initial cohort treatment, or
- '*Initial cohort treatment ongoing at study entry*': defined as the initial cohort treatment that started before and was continuing at the study entry.

The number and percentage of patients for each prior MS DMT as well as each initial cohort treatment ongoing at study entry will be summarized.

The '*last MS DMT before switching to initial cohort treatment*' defined as the latest MS DMT that was taken before starting the initial cohort treatment, will also be summarized by categorized preferred term. Duration of exposure to prior MS DMTs, as well as duration of exposure to initial cohort treatment ongoing at study start will be summarized descriptively. A sample illustration for the calculation of durations for '*Prior MS DMT*' and '*Initial cohort treatment ongoing at study entry*' is provided in Appendix C.

Note: Duration of exposure to initial cohort treatment ongoing at study entry will be derived as [Study entry date (i.e. Visit 1 date) – first dose of initial cohort treatment prior to study entry]. These duration variables are not included in the VDW and will be derived for PASSAGE. The patient-years, defined as the sum of the number of days on initial cohort treatment ongoing at study entry for all patients in the cohort/365.25, will also be presented.

For Group G summaries, medications from both the *Previous MS treatment* CRF and the *MS disease modifying therapy record* CRF for D2403 and from the *MS disease modifying therapy record* CRF page for D2406 will be used.

For Group F, all MS DMT with a start date and end date prior to the first dose of FTY720 in the study will be considered as prior MS DMT and will be summarized by categorized preferred term. The '*last MS DMT before switching to FTY720*' defined as the latest MS DMT that was taken before the first FTY720 dose, will also be summarized by categorized preferred term. Duration of exposure to prior MS DMTs will be summarized descriptively. This duration variable will be derived for PASSAGE (not available in VDW).

For Group F summaries, medications from both the *Previous MS treatment* CRF and the *MS disease modifying therapy record* CRF for D2403 and from the *MS disease modifying therapy record* CRF for D2406 will be used.

All data will be listed. Note that the first version of the CRF page for D2403 did not collect start dates for the MS DMT so that some DMT records may have missing start dates.

Note about 'treatment naïve patients': in the prior MS medication table, all patients for whom a record of MS medication prior to study entry is available in the database will be presented. For the rest of the patients (i.e. the 'treatment naïve patients'), it will mean that no record was available in the database. It does not necessarily mean that they were all treatment naïve.

The percentage of patients by cohort treatment (Group G) or study (Group F) will be presented as bar chart for number of prior MS DMTs (0, 1, 2, etc.) and for each individual prior MS DMT. The duration of prior MS DMT will be presented in a box plot. The bar chart and box plot will be displayed in a multi-panel plot.

The specific imputation rule will be applied on dose start date of MS DMT.

- If start date of MS DMT (STTDOS1D in CRF) is incomplete then
  - If only year (yyyy) is available, then imputed date will be 1-Jan-yyyy.
  - If both year (yyyy) and month (mmm) are available, then impute date will be 01-mmm-yyyy.

The imputation of dose end date will follow the rule in Section 4.4.3.

4.6.7 Medical history

Relevant medical history and current medical conditions will be summarized as frequency and percentage of patients with relevant medical history/condition by primary system organ class (SOC) and preferred term using the MedDRA. All coded terms will be included in the summary regardless of whether the "Mark if no history" box was selected on the CRF. For Group F adverse events that occurred prior to the first dose of FTY720 in the study will be treated as medical history.

Data will be summarized by cohort treatment for Group G and for the FTY720 group in Group F. Additionally, medical history will also be summarized for Group G restricted to the subgroup of patients who had an AE categorized as cancer.

Relevant medical history and current medical conditions meeting the criteria for cardiovascular risk factors will also be summarized with frequency and percentage of patients. Additionally selected cardiovascular risk factors will be categorized into four categories (Cardiovascular disease, Diabetes mellitus, Hyperlipidaemia and Hypertension) and will be summarized by preferred and corresponding category. See Appendix I, Table I-1 for definition of cardiovascular risk factors and categorization into categories.

Relevant medical history and current medical conditions as well as only current medical conditions will also be provided for the following subgroups:

- Patients naïve to any other DMT
- Patients previously treated with any MS DMT
- Patients never treated with FTY720
- Patients who had an AE categorized as cancer.

4.7 Study medication duration of exposure

Duration of exposure will be presented as a continuous variable and as a categorical variable using the categories >=1, >=90, >=180, >=360, >=540, and >=720 etc. days. The patient-years, defined as the sum of the number of days on specified MS DMT for all patients in the cohort/365.25, will also be presented.

Group G

The following durations of exposure will be summarized for Group G:

- *Duration of exposure to initial cohort treatment* (as defined in Section 4.1) will be summarized by initial cohort treatment (FTY720 and other DMT) based on the safety set. Duration of exposure will be calculated as the number of days from the first dose of initial cohort treatment during the study to the last dose of initial cohort treatment prior to the first permanent switch, with all interruptions excluded.. Note: This exposure summary will be used to support the safety analyses. ([redacted] to derive this exposure variable)
- *Duration of overall exposure to FTY720 and duration of overall exposure to other DMT* will be summarized based on the safety set and presented by initial cohort treatment. Duration of exposure to FTY720 and duration of exposure to other DMT (non-FTY720 MS DMTs) are defined as the total number of days throughout the entire study that the patient took FTY720 or other DMT, respectively, excluding interruptions. If a patient is taking MS DMT on an ongoing basis (no study medication end date in DAR), then the end of study participation date or the last visit date if the former is not available will be used in place of the last dose date. Note: although this exposure does not support any specific analysis, it will provide an overview of the exposure for the whole study. (Exposure to FTY720: [redacted] derived variable EXPOFTY. Exposure to other MS treatment: [redacted] derived variable EXPOOTH)

Group F

In Group F, *duration of exposure to FTY720* will be summarized based on the safety set and presented by study. The duration of exposure will be calculated as the number of days from the first dose date of FTY720 during the study to the last dose date of FTY720, with all interruptions excluded. Note: This exposure summary will be used to support the safety analyses in Group F. ([redacted] derived variable: EXPOFTY.)

4.8 Time at risk

The time at risk, in years, (defined in Section 4.3.3 in days, divided by 365.25 to get time at risk in years) will be summarized as a continuous variable by initial cohort treatment for the Group G safety set and by study for the Group F safety set. The time at risk, in patient-years will also be summarized, and is calculated as the sum of the number of days at risk for all patients in the group or cohort, divided by 365.25.

4.9 Reasons for switch from treatment

Reasons for switches from first MS DMT corresponding to cohort assignment (FTY720 in FTY720 cohort, corresponding MS DMT in Other DMT cohort), as recorded on the drug

administration page, will be summarized. These switches consist of switches from FTY720 to non-FTY720 MS DMT as well as switches from first MS DMT corresponding to cohort assignment in Other DMT cohort to either FTY720 or another non-FTY720 MS DMT. The percentages are based on the total number of patients that had a switch.

Reasons for switch from FTY720 in the study will be summarized for Group F safety set, by study. Note that a patient can switch from FTY720 several times throughout the study. Therefore, percentages for reasons for switch of FTY720 are based on the total number of switches.

4.10 Switches from first DMT corresponding to cohort assignment and initial cohort treatment, and specified DMTs taken as the initial cohort treatment

The below summaries will be based on the Group G, safety set.

The number and percentage of patients on each first DMT corresponding to cohort assignment (FTY720, Interferon, Glatiramer Acetate, Dimethyl Fumarate, Teriflunomide, Natalizumab, and other MS therapies) will be presented. For each of these possible first DMTs corresponding to cohort assignment, the number and percentage of patients who switched from first DMT corresponding to cohort assignment and those who did not switch at time of database lock will be summarized. For patients in the 'Other DMT' initial cohort treatment, the number and percentage of patients who switched to FTY720 will also be summarized. All percentages will be calculated using the total number of patients in each initial cohort treatment as the denominator.

The number and percentage of patients on each MS DMT that was taken as 'initial cohort treatment', the number and percentage of patients who had a permanent switch, and the number of MS DMTs taken as the initial cohort treatment will be summarized by initial cohort treatment. Note that for patients in the FTY720 initial cohort treatment, the MS DMT taken as initial cohort treatment can only be FTY720, but for patients in the other DMT initial cohort treatment, the initial cohort treatment can consist of any MS DMTs prior to the first permanent switch and may consist of several non-FTY720 DMTs.

4.11 Concomitant medications

The number and percentage of patients taking concomitant medications and significant non-drug therapies will be summarized by preferred term for Group G safety set and for Group F safety set. A patient taking the same medication multiple times is counted only once under that preferred term.

For Group G, concomitant medications are medications taken at any time from first dose date of initial cohort treatment in the study to last dose date of initial cohort treatment prior to the first permanent switch + 45 days. If this date lies after the cut-off date, the cut-off date will be used instead.

For Group F, concomitant medications are medications taken at any time from first dose date of FTY720 in study to last dose date of FTY720 + 45 days. If this date lies after the cut-off date, the cut-off date will be used instead.

For imputation of concomitant medication start dates, in cases of missing or partial start dates, refer to the VDW Module 8 'Concomitant Medication Start Date Imputation (#IMPUTMED)' section.

4.12 Effectiveness evaluation

4.12.1 General effectiveness rules

Unless otherwise specified, all effectiveness analyses will be performed on the effectiveness set. Effectiveness analyses are not planned for Group F.

For Group G, results will be presented by the first DMT corresponding to cohort assignment. Specifically, the following DMTs will be presented: FTY720, Interferon, Glatiramer Acetate, Dimethyl Fumarate, Teriflunomide, Natalizumab and other MS therapies (VDW variable: TRTN_RI).

The ***time on first DMT*** is defined as the time in study from first dose date of first DMT corresponding to cohort assignment to last dose date of first DMT corresponding to cohort assignment prior to any switch in DMT and prior to any interruption in the first DMT corresponding to cohort assignment of more than 45 days. The time on first DMT will be used in the derivation of annualized relapse rate, and it matches the time considered in the effectiveness context. ([redacted] to calculate a flag for summarizing effectiveness data based on [redacted] derived variable LSTDMT1 and VDW variable FIRSMD1O)

4.12.2 Relapses

4.12.2.1 Annualized relapse rate (ARR)

Annualized relapse rate (ARR) is defined as the number of relapses with onset occurring during a specific period of time, adjusted to a one-year period. There are two types of ARR which will be reported:

- The raw group-level ARR is calculated by taking the total number of relapses with onset occurring during a specified time period for all patients in the group, divided by the total number of days in the specified time period for all patients in the group, and multiplied by 365.25. Estimates and 95% confidence intervals for the group-level ARR are derived from a negative binomial model with the number of relapses as dependent variable, the first DMT corresponding to cohort assignment as explanatory variable and the log of the exposure time in years as the time variable.
- The patient-level ARR is calculated for each individual by taking the number of relapses with onset occurring during a specified time period for that patient, divided by the total number of days in the specified time period for that patient, and multiplied by 365.25. 95% confidence intervals for the patient level ARR are calculated using normal approximation. If the lower limit of the CI becomes negative it will be set to 0.

The total number of relapses with onset occurring during the time on first DMT and the total time on first DMT (in days) will be reported for all patients in a group, by first DMT corresponding to cohort assignment, for the Group G, effectiveness set. Additionally, the

group-level ARR and the mean and standard deviation of the *patient-level ARR* will be reported.

Note that in the *MS status* CRF page, both the number of relapses since last visit and the individual relapses details are collected (start and end dates, recovery status, etc.). In the ARR calculation, the relapse start date will be used to derive the number of relapses (and not the summary information 'number of relapses since last visit'). The *MS Relapse details* CRF page will be used in conjunction with the *MS status* CRF page. When there is no relapse start date entered, the number of relapses since the patient's last visit will be assumed to be 0. (Variables needed for the analysis will be derived from the VDW relapse analysis dataset, AREL.)

ARR will also be summarized for the FTY720 cohort by the subgroups based on the type of MS therapy previously applied as defined in Section 4.5.1 Here, estimates and 95% confidence intervals for the group-level ARR are derived from a negative binomial model with the number of relapses as dependent variable, and the type of previous MS therapy as explanatory variable and the log of the exposure time in years as the time variable.

Further, ARR will be summarized for the subgroup of patients receiving the first dose of their initial cohort treatment within this study by first DMT corresponding to cohort assignment, as described above.

To account for a potential bias introduced by patients already receiving initial cohort treatment prior to entering the study for which exact number of relapses prior to study entry is hard to determine, an additional analysis of ARR will be done excluding each patient's first 180 days following their real first dose of initial cohort treatment. The denominator exposure time will be reduced by the same time of interest. It should be noted that a patient may have the real first dose of initial cohort treatment before or within this study. If a patient receives the real first dose of initial cohort treatment, e.g., 65 days before study start then 115 days from the start of study will be removed from these analyses. It should also be noted that relapses which occur after the real first dose but prior to the date of informed consent are not recorded on the eCRF. Both cohorts are impacted by the eCRF limitation; however, the impact of the early cohort start is greater for the other DMTs than for the FTY720 cohort.

4.12.2.2 MS relapse characteristics

The total number of relapses, the number and percentage of patients by recovery status of each relapse, whether or not the relapse was treated, and the duration of each relapse (days) will be summarized for the Group G, effectiveness set, by first DMT corresponding to cohort assignment. Duration of relapse is calculated based on imputed relapse start and end dates to restrict relapse duration to up to 90 days.

4.12.3 EDSS

Descriptive statistics on absolute EDSS scores and changes from baseline for Group G will be presented. The change from baseline ± SD will be displayed graphically over time by cohort. Time intervals are defined by visit windows which are defined in section 4.15.

4.13 Safety evaluation

4.13.1 General safety rules

Unless otherwise specified, all safety analyses will be performed on the safety set.

Group G general safety rules – analyses performed according to Group G general safety rules will include:

- All data from first dose date of initial cohort treatment in the study up to last dose of initial cohort treatment + 45 days, day before first dose of treatment at permanent switch, or data cut-off date, whichever is earliest.
- And SAEs from first dose date of initial cohort treatment in the study up to the day before first dose date of treatment at permanent switch, or data cut-off date whichever is earliest.

Results will be presented by initial cohort treatment (FTY720 and other DMT).

(VDW variable enabling corresponding data selection: FLGSAFCO (data selection flag) or CUTO_CO (date))

For results presented by first DMT corresponding to cohort assignment, analyses performed will include:

- All data from first dose date of first DMT corresponding to cohort assignment in the study up to last dose of first DMT corresponding to cohort assignment + 45 days, day before switch from first DMT, or cut-off date, whichever is earliest.
- And SAEs from first DMT corresponding to cohort assignment in the study up to the day before switch from first DMT, or cut-off date, whichever is earliest.

(Based on [redacted] derived variable FLGFDMT)

Group F general safety rules – analyses performed according to Group F general safety rules will include:

- All data from first dose of FTY720 in the study up to last dose date FTY720 + 45 days, or cut-off date whichever is earlier.
- And all SAEs after first dose of FTY720 in the study (i.e. all SAEs and deaths after the first intake of FTY720 in the study will be reported irrespective of when they happened)

And results will be presented for the FTY720 group, by study.

(VDW variable enabling corresponding data selection: FLGSAF_F (data selection flag) or CUTO_F (date))

4.13.2 Adverse events

Adverse events will be reported by primary system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) . Any other information collected (e.g., severity or relation to study drug) will be listed as appropriate.

Listings of deaths, AEs and SAEs will be provided for Group G and Group F together. Flags will show the analyses the events are counted for.

The MedDRA version used for reporting the study will be described in a footnote.

If a patient reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

The following summaries of adverse events will be provided for Group G and Group F:

- Incidence and incidence rate of *adverse events* per 100 patient-years, by primary system organ class and preferred term. Incidence rate ratio will be presented in Group G table. Another Group G table will be created presenting only the adverse events where the FTY cohort incidence rate is greater than zero while the Other DMT cohort incidence is equal to zero. For this table the incidence rate difference is presented instead of incidence rate ratio.
- Incidence and incidence rate of *serious adverse events* per 100 patient-years, by primary system organ class and preferred term. Incidence rate ratio will be presented in Group G table.
- Incidence and incidence rate of *death* per 100 patient-years, by primary system organ class and preferred term. Incidence rate ratio will be presented in Group G table.
- Incidence and incidence rate of *adverse events leading to permanent discontinuation* per 100 patient-years, by primary system organ class and preferred term (For Group G, only events leading to discontinuation of corresponding initial cohort treatment (FTY720 for the FTY720 cohort and other DMT in the other DMT cohort) will be summarized. For Group F only events leading to discontinuation of FTY720 will be summarized). Incidence rate ratio will be presented in Group G table.
- Incidence and incidence rate of *selected safety outcomes* per 100 patient-years. Incidence rate ratio will be presented in Group G table.
- Incidence and incidence rates of *adverse events*, by primary system organ class, preferred term, and maximum severity.
- Incidence and incidence rate of *adverse events with suspected relationship to study treatment* per 100 patient-years, by primary system organ class, preferred term, and initial cohort treatment, Group G, Safety set only. Incidence rate ratio will be presented in Group G table.
- Incidence rate of *adverse events* per 100 patient-years, by primary system organ class, preferred term, and first DMT corresponding to cohort assignment, Group G, Safety set only.
- Incidence rate of *serious adverse events* per 100 patient-years, by primary system organ class, preferred term, and first DMT corresponding to cohort assignment, Group G, Safety set only.
- Incidence and incidence rate of *adverse events* per 100 patient-years, by primary system organ class and preferred term – excluding AEs listed in Core Data Sheet (CDS). Incidence rate ratio will be presented in Group G table.
- Incidence and incidence rate of *serious adverse events* per 100 patient-years, by primary system organ class and preferred term – excluding AEs listed in CDS. Incidence rate ratio will be presented in Group G table.

- Incidence rate of *adverse events* per 100 patient-years, by preferred term and initial cohort treatment – Excluding AEs listed in Core Data Sheet (CDS). Incidence rate ratio will be presented in Group G table.
- Incidence rate of adverse events / SAEs per 100 patient-years, by primary system organ class and preferred term, excluding events which occurred in the first week (Days 1 to 7) / first 6 months (Days 1 to 180) following real first dose of initial cohort treatment. In these summaries all events which started during the excluded window will not be taken into account and the corresponding exposure time will be removed from the denominator. If, after removing the time interval of interest, a patient does not have any exposure within the study, the patient will be completely removed from this analysis. (This analysis is only done for Group G).
- Number and percentage of patients reporting adverse events and serious adverse events related to the primary system organ classes 'Cardiac disorders', 'Infections and infestations', and 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)', by time interval (Months 0-<3, Months 3-<6, Months 6-<9, Months 9-<12, Months 12-<24, Months 24-<36, Months 36-<48, >= Month 48), primary system organ class and preferred term for Group G, Safety set. Months will be defined using 30-day intervals, i.e., Day 1-90, Day 91-180, Day 181-Day 270, Day 271-Day 360, Day 361-720, Day 721-Day 1080, Day 1081- Day 1440, >= Day 1441, whereby the onset date of the first occurrence of such adverse events per patient will be used to classify them into the time intervals. The number of active patients, i.e., who did not discontinue from the initial cohort treatment and had at least 1 day of exposure during the interval, will be displayed. The date of first dose of initial cohort treatment in the study will be used as Day 1. This will be summarized separately for each of the selected system organ classes. When calculating percentages the denominator will be defined for each event as the total number of patients experiencing the specific event.
- An analysis as described above will be done for all AEs instead of only for a selection of AEs. The following time intervals will be used: Months 0 - <12, Months 12 - <24, Months 24 - < Months 36, Months 36 - <48, Months 48 - <50. The analysis will be done for Group G, safety set.
- Number and percentage of patients reporting bradycardia / serious bradycardia by time interval (Day 1-7, Day 8-30, Day 31-60 (Month 2), Day 60-91 (Month 3) etc. in 30 day intervals until Day 360 and then >= Day 361) for Group G, safety set. The onset date of the first occurrence of bradycardia / serious bradycardia per patient will be used to classify them into the time intervals. The number of active patients, i.e., who did not discontinue from the initial cohort treatment and had at least 1 day of exposure during the interval will be displayed. The date of first dose of initial cohort treatment in the study will be used as Day 1.
- The time to first onset of bradycardia / serious bradycardia will be analyzed using Kaplan-Meier curves for Group G, safety set. Patients not experiencing the event will be censored at their last dose date of initial cohort treatment + 45 days, day before first dose date of treatment after permanent switch, or cut-off date whichever is earliest (VDW variable CUTO_CO).

- Number and percentage of AEs/SAEs on selected safety outcomes by time interval (Months 0-<3, Months 3-<6, Months 6-<9, Months 9-<12, Months 12-<24, Months 24-<36, Months 36-<48, >= Month 48) for Group G, Safety set. Months will be defined using 30-day intervals, i.e., Day 1-90, Day 91-180, Day 181-Day 270, Day 271-Day 360, Day 361-720, Day 721-Day 1080, Day 1081- Day 1440, >= Day 1441, whereby the onset date of the first occurrence of such adverse events per patient will be used to classify them into the time intervals. The number of active patients, i.e., who did not discontinue from the initial cohort treatment and had at least 1 day of exposure during the interval, will be displayed. The date of first dose of initial cohort treatment in the study will be used as Day 1. This will be summarized separately for each of the selected system organ classes. When calculating percentages the denominator will be defined for each event as the total number of patients experiencing the specific event.
- The time to first onset of cancer will be analyzed using Kaplan-Meier curves for Group G, safety set. AEs will be identified as cancer by using the same excel sheet that is being used to define the subgroup of patients who had an AE categorized as cancer (see section 4.5.1). Patients not experiencing the event of interest will be censored at their last dose date of initial cohort treatment + 45 days, day before first dose date of treatment after permanent switch, or cut-off date whichever is earliest (VDW variable CUTO_CO).

[redacted]

Subgroup analyses of adverse events and selected safety outcomes

Incidence rates per 100 patient years of AEs/SAEs by primary SOC and preferred term will be provided for all subgroups as defined in Section 4.5.1 above.

Incidence rates per 100 patient years of selected safety outcomes (risks) will be provided for the following subgroups (see Section 4.5.1 for definition)

- Patients in naïve to any prior MS DMT
- Patients previously treated with any MS DMT
- Patients never treated with FTY720
- Patients in the FTY720 cohort split by subgroups based on the type of MS therapy previously used.

For the first three subgroups incidence rate ratio will also be presented.

Incidence rate, incidence rate ratio and incidence rate difference calculation

The incidence rate expressed per 100 patient-years of the at-risk population is calculated 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.

For patients who have that adverse event, the time at risk is the time from Day 1 (from Group G / Group F) to the first onset date of that adverse event. For patients who did not have that adverse event, the time at risk as defined in Section 4.3.3 is used.

The incidence rate ratio (IRR) is calculated by dividing the incidence rates of two cohorts for a particular AE term/category. It is only calculated if both incidence rates are >0.

In cases where the FTY720 incidence rate is >0 and the Other DMT Cohort incidence rate is equal to 0 an additional analysis will be carried out where the incidence rate difference will be calculated.

See Section 5 for details on incidence rate, incidence rate ratio, incidence rate difference and the corresponding 95% confidence intervals calculations.

About selected safety outcomes

One of the main objectives of the PASSAGE studies is to investigate the incidence of selected safety outcomes. Those selected safety outcomes contain Risk management plan (RMP) risks and some additional PASSAGE specific risks. All PASSAGE selected safety outcomes (RMP risks and additional ones) are defined in the program level Case Retrieval Sheet (CRS) which will be finalized prior to database lock.

Link to VDW: Adverse events risk data are available in the VDW Risk panel (AAEVRISK).

Pooled analyses of adverse events and medical history

Medical history records (i.e., all events reported on the medical history CRFs, which occurred on initial cohort treatment and within at most 180 days prior to FIRSMD1O reported as medical history) will be pooled with adverse event records and then the frequencies (total number and percentage of patients) and the incidence rates per 100 patient years for AEs will be generated for Group G Safety Set. Any partial condition start dates will be imputed using the rules of AE start date imputation.

The following summaries for Group G, safety set will be generated:

- Incidence rate by primary system organ class, preferred term and initial cohort treatment
- Incidence rate of selected safety outcomes (risks) by initial cohort treatment

Cox proportional hazard regression model

A comparative analysis to estimate adjusted Hazard Ratios (HR) using a Cox proportional hazards regression model will be performed. The analysis will be done for all selected safety outcomes of the RMP category, respectively, using exact method for handling ties in failure time.

The HRs and their associated confidence intervals will be estimated by means of a proportional-hazards model. The dependent variable is time-to-first occurrence of a particular selected safety outcome while initial cohort treatment, age at baseline, gender and study will be used as covariates in the model. This analysis will be provided for pooled analysis.

See section 5 for details on the calculations of the cox proportional hazard regression model.

Analysis of adverse events details for subgroup = Patients who had an AE categorized as cancer

For the subgroup of patients who had an AE categorized as cancer the adverse event details will be tabulated for Group G, safety set, by initial cohort treatment. The number and percentage of cancers by preferred term will be presented. Also the number and percentage of the action taken category and the relationship with MS therapy will be displayed. Each category for action taken category will be counted once per patient. For action taken multiple answers for one AE are possible. Relationship with MS therapy will be counted once per patient with worst category. Additionally the summary statistics of time to onset of first cancer (in years) will be shown.

Time to onset of AE of MS relapse

The time to onset of and adverse event of MS relapse will be presented in categories (< 1 month, >=1 month and <6 months, >=6 months and < 1 year, >=1 year and < 2 years, >= 2 years) by initial cohort treatment and by seriousness (AE or SAE) for Group G, safety set. Each category for time to onset of MS relapse is counted only once per patient. Multiple MS relapses from one patient that fall into different time categories are each counted in their respective category. The total number of patients with relapses will also be tabulated.

Summary of action taken for AE hypertension

The number and percentage of each action taken information from the eCRF AE page will be displayed by initial cohort treatment, for Group G, safety set. The number and percentage of preferred terms for hypertension AEs will be presented. Each action taken category is counted only once per patient. For action taken multiple categories for one AE of hypertension are possible. Additionally the total number of patients with hypertension AE will also displayed.

4.13.3 Laboratory data

4.13.3.1 Abnormal liver function tests

The number and percentage of patients with newly occurring abnormal liver function test values, as defined in Appendix D of this document, after Day 1 (from data per general safety rules) will be summarized for the Group G, safety set, by initial cohort treatment and Group F, safety set, by study. In order to present newly occurring events, the number and percentage of patients will be calculated based on the number of patients who have the specified liver function test(s) on or after first dose date of initial cohort treatment in study, the corresponding upper limit of normal(s), and either normal or missing result(s) for the specified liver function test(s) prior to first dose of initial cohort treatment in the study. The normal limit is set based on local lab criteria. This analysis includes Hy's Law cases.

Liver function tests include: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TBL).

The following rules will be applied for the summary tables:

For liver enzymes only those values where the SI value is available or can be calculated and the normal range is also available in SI units or can be calculated, and the SI upper normal limit is higher than the SI lower normal limit will be used.

All patients with newly occurring abnormal liver function tests will be listed.

4.13.3.2 Clinically notable laboratory abnormalities

The number and percentage of patients with newly occurring clinically notable laboratory results on or after Day 1 (from data per general safety rules) for leukocytes and lymphocytes will be presented by initial cohort treatment for the Group G, safety set and Group F, safety set, by study. Laboratory results will be converted to SI units for this summary. Criteria for notable laboratory abnormalities are provided in Appendix D of this document. Laboratory local reference normal ranges will not be used in the analysis instead clinical notable abnormality criteria are used.

In order to present newly occurring events, the number and percentage of patients will be calculated based on the number of patients who have at least one lab assessment on or after first dose date of initial cohort treatment in study for the specified lab test and either non-notable or missing lab assessment prior to first dose of initial cohort treatment in the study. If the baseline measurement is missing, all abnormal lab measurements after baseline should be reported.

For WBC and absolute lymphocytes count reported values which are outside the reported normal ranges and which can be converted to SI units will be used.

All patients with notable abnormalities will be listed.

4.13.3.3 Other laboratory data

Absolute values and changes from baseline of total cholesterol and HDL cholesterol will be summarized by visit for Group G, safety set. Values for corresponding visits will be derived by a visit windowing approach, detailed in Section 4.15.

4.13.4 Routine vital signs

For routine vital sign measurements (excluding first dose monitoring assessments), the number and percentage of patients with at least one value after Day 1 (from data per general safety rules) satisfying clinically notable criteria will be summarized for the Group G, safety set, by initial cohort treatment and Group F, safety set, by study. The criteria of notable vital signs are provided in Appendix E of this document.

All patients with notable abnormalities will be listed.

4.13.5 First dose monitoring (Group F only)

Note that only the first dose monitoring which starts on the first dose date of FTY720 in the study, but which may extend past the first dose date of FTY720 in the study, is considered data related to the first initiation of FTY720. Other first dose monitoring is conducted at re-initiation and summarized separately for patients with more than one first dose monitoring.

The hourly post-dose timepoints will be derived based on windowing the time of assessment – first dose administration time. In the case where either time is missing and the hours post-dose are labeled in the CRF (only labeled in D2403 vital signs CRF), the CRF post-dose label will be used to determine the timepoint.

Window	Timepoint
<1 minute	Pre-dose
1 minute to 1.5 hours	1 hour post-dose
>1.5 hours to 2.5 hours	2 hours post-dose
>2.5 hours to 3.5 hours	3 hours post-dose
>3.5 hours to 4.5 hours	4 hours post-dose
>4.5 hours to 5.5 hours	5 hours post-dose
>5.5 hours to 6.5 hours	6 hours post-dose

For example, an assessment taken 1 hour and 45 minutes after first dose administration will be classified as a 2 hours post-dose assessment. In the case where multiple assessments within a post-dose hour are available, the assessment closest to the expected time will be used for hourly summary by post dose hour. However, the lowest pulse should be based on all post dose observations no matter if the actual collection is closest to the expected time or not. All data will be presented in the listing.

4.13.5.1 First dose monitoring of vital signs

Hourly vital signs are collected on first dose administration monitoring pages for first dose of FTY720 in the study and re-initiation of FTY720 after interruption if applicable.

The Day 1 sitting pulse, sitting systolic, and sitting diastolic blood pressure will be summarized at hourly post-dose time points for up to 6 hours (1hour post-dose, 2 hours post-dose, ..., 6 hours post-dose), by study, for the Group F, safety set. Summary statistics will be provided for the pre-dose value, the post-dose value, and change (post-dose minus pre-dose).

The time in hours during first dose monitoring of the lowest pulse occurring post first dose of FTY720, and the lowest pulse (bpm) observed during first dose monitoring will be summarized for the Group F, safety set, by study. Only data from first FTY720 initiation are summarized.

A line plot of the mean pulse (bpm), along with corresponding standard deviation, during the 6 hours post-first dose administration monitoring will be presented for the Group F, safety set, by study. Only data from the first FTY720 initiation will be summarized.

4.13.5.2 First dose monitoring procedures

The FTY720 first dose monitoring procedures based on the first FTY720 initiation will be summarized on the Group F, safety set, by study. The number and percentage of patients with

first dose monitoring data will be reported out of the total number of patients in Group F, safety set. For all first-dose monitoring related frequencies, the percentage of patients reported will be calculated based on the number of patients with first dose monitoring data as the denominator. The same analysis will be repeated for first FTY720 re-initiation. There should be at least 45 days between the date of re-initiation of FTY and the last dose of FTY prior to re-initiation.

The following will be summarized:

- The number and percentage of patients with first dose monitoring data collected retrospectively and data collected prospectively will be reported. For patients with prior FTY720 that can be considered as 'Initial cohort treatment ongoing at study entry', first dose monitoring data is considered ***retrospective***. Otherwise, first dose monitoring data is considered ***prospective***. This will only be summarized for first FTY720 initiation.
- Whether a cardiologist consultation was conducted before starting FTY720. In study D2403, question was added during eCRF Amendment 1. So data are only available for second part of the patients enrolled post amendment implementation.
- Whether a patient required extended cardiac monitoring after the first 6 hours and whether a patient required >=12 hours and <=24 hours or >24 hours and <=48 hours post first dose monitoring time. In case the first dose time is missing the pre-dose ECG/vital sign measurement time + 5 minutes from the same day will be used, if available. This summary will be based on actual first dose monitoring times rather than responses to the CRF question on dose monitoring CRF pages. Even though the question of extended monitoring beyond 6 hours post dose was asked directly in CRF Amendment for 2403, the data should be derived for both studies. If patient has any first dose monitoring data collected after 6 hours post dose, it will be considered as extended monitoring.
- Whether a patient had symptomatic or treated bradycardia: In CRF for D2406 and previous CRF for D2403, the question "Did the patient have symptomatic or treated bradycardia?" exists in the CRF. For current eCRF of D2403, this corresponds to the cardiac event specified on CRF page of 'Fingolimod first dose extended/overnight monitoring procedure". In yet another CRF amendment, this question was split into two questions "Was the bradycardia symptomatic?" and "Was the bradycardia treated?". The responses from these three questions will be combined to determine whether a patient had symptomatic or treated bradycardia.
  The corresponding variable, for both studies, will be taken from the VDW. If no information about a symptomatic or treated bradycardia can be obtained then the question "Did the patient experience a cardiovascular event during the first dose observation period?" from the CRF will be used to determine the answer categories "No" or "Unknown". This approach will be used for D2403 and D2406.
- The number and percentage of patients with new or worsening ECG abnormalities reported over all post-dose hours related to the first FTY720 initiation: the data from old CRF for question 'Was any new or worsening ECG abnormalities recorded?' and from new CRF for post dose question 'Are new or worsening ECG abnormalities present?' are combined together on summarizing results. If subject has any answer of yes on the question, the overall evaluation is 'Yes'; else if there is any answer of 'No', then the

overall evaluation is 'No'. If all answers to this question is missing, and from new CRF data it's marked that post-dose evaluation was not done on any post-dose hours, the overall evaluation is 'Not done'. Otherwise, the overall evaluation is set as 'Unknown'.

- A listing of patients requiring extended cardiac monitoring >=12 hours after first dose administration of FTY 720 will be provided for the single study CSRs.

4.13.6 Ophthalmic and dermatological examination

For FTY720 treated patients, an ophthalmic examination could be performed before FTY720 initiation and 3 to 4 months later for the purpose of detecting macular edema. Examinations performed up to 45 days prior to fingolimod treatment initiation are also acceptable. In diabetic patients, additional ophthalmologic examinations are performed at the time they discontinued FTY720. Additionally, any patient having new visual symptoms should have an ophthalmic examination irrespective of the MS treatment the patient is taking.

The ophthalmic examination data will be summarized for Group F, safety set, separately for each study and combined. The visual acuity assessment result (normal, abnormal), as assessed by the Investigators, will be summarized with number of patients and percentages in shift tables comparing the status before FTY720 initiation to each evaluated time point and the worst post FY720 initiation result, separately for each eye. Presence of macular edema (no, yes, unknown, other abnormality) will be summarized by number and percentage of patients who develop a macular edema during the course of treatment with FTY720. The analyses will be presented for the right eye and left eye separately. Additionally they will be analyzed by an overall category which summarizes the results from left and right eye, using each patient's worst assessment.

A dermatological examination could be performed for a patient (irrespective of the MS therapy they are on) at baseline, at the time of change in MS therapy, and at the end of the study. This examination has to be conducted by a certified dermatologist or a physician experienced in dermatological evaluation for the purpose of detecting skin malignancies. The dermatological examination results will be summarized for Group G, safety set by number and percentage of patients per visit and category (normal, abnormal non-cancerous, abnormal pre-cancerous, abnormal cancerous lesion) in shift tables showing baseline results versus the results at each time interval.

Data will be taken from the single study databases, since they are not covered by the VDW.

4.14 Other assessments

4.14.1 D2403 Patient Reported Outcomes

Patients of this sub-study of study D2403 will be identified by having consented to participate in the Patient Reported Outcomes (PRO) sub-study.

The following will be summarized:

- Patient disposition will be summarized by cohort (Group G, enrolled set)

- Patient demographics, MS history and MS treatment(s) preceding fingolimod or comparator initiation will be summarized by cohort (Group G, safety set)
- Comparison of mean change in the patient-reported disability level by visit and cohort (Group G, safety set)
- MS Impact Scale (MSIS-29): Summary statistics of absolute values and change from baseline in summary scores (Physical impact, Psychological impact) will be presented by visit and cohort (Group G, safety set)
- Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH): Summary statistics of absolute values and change from baseline in summary scores (Absenteeism, Presentism, Work productivity loss, Activity impairment) will be presented by visit and cohort (Group G, safety set)
- Patient Reported Indices of Multiple Sclerosis (PRIMUS) – Activities: Summary statistics of absolute values and change from baseline in PRIMUS activity scale score will be presented by visit and cohort (Group G, safety set)
- Abbreviated Treatment Satisfaction Questionnaire for Medication (TSMQ-9): Summary statistics of absolute values and change from baseline in summary scores (Effectiveness, Convenience, Global Satisfaction) will be presented by visit and cohort (Group G, safety set)
- Treatment preference (for patients who are newly treated with fingolimod, yet have been on previous disease-modifying therapy) will be summarized with number and percentage at month 6 for Group F, safety set
- Annualized relapse rates for Group G, effectiveness set.

PRO manuals

MSIS-29

The MS IMPACT SCALE (MSIS) in this study contains 29 items with 5 possible outcomes for each item: 1 (Not at all), 2 (A little), 3 (Moderately), 4 (Quite a bit) and 5 (Extremely).

For the summary of MSIS data, two summary scales, physical impact score (20 items) and psychological impact score (9 items) will be calculated according to the scoring manual provided by Hobart et al. in Improving the evaluation of therapeutic interventions in multiple sclerosis (originally published in 1995, updated in 2007). Higher summary scores indicate worse health state. The detailed scoring algorithms are as following:

Physical impact score

The physical impact score is computed by summing items number 1-20 inclusive. This score can then be transformed to a score on a scale of 0 -100 using the formula below: transformed score = 100 x (observed score minus lowest possible score)/ (maximum possible score minus minimum possible score). For example, the MSIS-29 physical scale where min possible score = 20, max possible score = 100, range = (100 – 20) = 80 then physical impact score=100 x

(observed score - 20) /(100 – 20). Note that transforming scores to have a range of 0 – 100 is for ease of interpretation. It does not affect the properties of the scale.

Psychological impact score

The psychological score is computed by summing items number 21-29 inclusive. This score can then be transformed to a score on a scale of 0-100 using the formula below: 100 x (observed score - 9) / (45 – 9).

Missing data

For respondents with missing data, but where at least 50% of the items in a scale have been completed, a respondent–specific mean score computed from the completed items can be used for imputation. For example, consider person X who has completed 15 items in the physical scale. Sum the completed items and divide it by 15 to get person X's respondent–specific mean score. Then use this value as the score for each of the missing 5 items. Then generate a total score as usual by summing the values of the 15 completed items and the 5 imputed items. Note: respondents must have completed a minimum of 10 items in the physical scale, or 5 items in the psychological scale to use this imputing method.

If fewer answers are provided, the corresponding scores will not be calculated.

WPAI:GH

The WPAI questionnaire is an instrument that measures the impact of health problems on the ability to work and perform regular activities during the past 7 days. WPAI yields 4 types of scores: Absenteeism (work time missed), Presentism (impairment at work/reduced on-the-job effectiveness), work productivity loss (overall work impairment/absenteeism plus presentism) and Activity impairment. The WPAI consists of six questions:

Q1=currently employed (y/n)

Q2=hours missed from work due to health problems

Q3=hours missed from work due to other reasons

Q4=hours actually worked

Q5=degree health affected productivity while working (0 to 10)

Q6=degree health affected productivity in regular unpaid activities (0 to 10)

The recall period for questions 2 to 6 is seven days. The following scores will be calculated:

Absenteeism (percent work time missed due to health) = Q2/(Q2 + Q4)

Presentism (percent impairment while working due to health = Q5/10

Work productivity loss (percent overall work impairment due to health): Q2/(Q2 + Q4) + (1 – Q2/(Q2 + Q4)) x (Q5/10)

Activity impairment: Q6/10

Multiply scores by 100 to express percentages.

PRIMUS-Activities

The Subject Reported Indices of Multiple Sclerosis PRIMUS - activities scale will be calculated and analyzed according to the scoring manual provided by Galen Research Limited, 2007.

The activities scale in this study contains 15 items. Each of the 15 items will be given a score of 0 (able to do on own without difficulties) or 1 (able to do on own with difficulties) or 2 (unable to do on own). All 15 item scores will be summed to obtain a total score ranging from 0 (good) to 30 (poor), which is the PRIMUS activities scale score. Higher summary scores indicate worse health.

In case of missing item scores while calculating the scale score, the following rule applies: if more than 20% (i.e., three) of the item scores are missing, the scale score will not be calculated and set to missing. If no more than 20% of the item scores are missing, the scale score will be imputed as the average of the non-missing item scores multiplied by 15.

TSQM-9

The Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) is an abbreviated 9-item questionnaire derived from the TSQM without the five items of the side effects domain. The TSQM-9 domain scores range from 0 to 100 with higher scores representing higher satisfaction on that domain.

The scales of the TSQM-9 include the effectiveness scale (questions 1 to 3), the convenience scale (questions 4 to 6) and the global satisfaction scale (questions 7 to 9). The higher summary scores indicate better satisfaction with study drug.

TSQM-9 Scale scores will be computed by adding the items loading on each factor. The lowest possible score is subtracted from this composite score and divided by the greatest possible score minus the lowest possible score. This provided a transformed score between 0 and 1 that should be multiplied by 100 as described below.

Note that only one item may be missing from each scale before the subscale should be considered invalid for that respondent.

EFFECTIVENESS:

Score = {[(sum of items 1-3) – 3] / 18} * 100

If only one item is missing, Score = {[(sum of available items in 1-3) – 2] / 12} * 100

CONVENIENCE:

Score = {[(sum of items 4- 6) – 3] / 18} * 100

If only one item is missing, Score = {[(sum of available items in 4-6) – 2] / 12} * 100

GLOBAL SATISFACTION:

Score = {[(sum of items 7- 9) – 3] / 14} * 100

If only one item is missing:

Item 7 or 8 missing: Score = {[(sum of available items in 7 - 9) – 2] / 10} * 100

Item 9 missing: Score = {[(sum of items in 7 and 8) – 2] / 8} * 100

4.14.2 D2403 sub-studies

The number and percentage of patients in the respective sub-studies will be summarized for Group G, Enrolled set, for D2403.

Pulmonary sub-study

For all patients in the pulmonary sub-study the following analyses will be done:

- Patient disposition will be summarized by cohort (Group G, enrolled set)
- Demographics will be summarized by cohort (Group G, safety set)
- Medical history will be summarized by cohort (Group G, safety set)
- Exposure during initial cohort treatment by cohort (Group G, safety set)
- Summary statistics of absolute values and changes from baseline of pulmonary function test data (FEV_1, Percentage of predicted FEV_1, FVC and DLCO) will be presented by visit for each cohort (Group G, safety set)
    - Percentage of predicted FEV_1 is obtained as a percentage of FEV_1 relative to the predicted normal value. The predicted normal value is calculated as follows:
        - Male: (4.30 x Height in meters) – (0.029 x Age in years) – 2.49
        - Female: (3.95 x Height in meters) – (0.025 x Age in years) – 2.60
        - If Race = Black or Ethnicity = Indian then the predicted normal given by the formulae above will be multiplied by 0.9.

Patients of this sub-study will be identified by having consented to participate in the pulmonary sub-study.

Canadian sub-study

For all patients in the Canadian sub-study the following analyses will be done:

- Patient disposition will be summarized by cohort (Group G, enrolled set)
- Demographics (also education level, employment and occupation) will be summarized by cohort (Group G, safety set)
- Medical history will be summarized by cohort (Group G, safety set)
- Exposure during initial cohort treatment by cohort (Group G, safety set)
- Summary of MS relapse characteristics by cohort (Group G, Effectiveness set)
- Annualized relapse rates by first DMT corresponding to cohort assignment (Group G, Effectiveness set)
- Multiple sclerosis disease history at baseline (Group G, Safety set)
- Box-plot of change from baseline for EDSS score by visit (Group G, Effectiveness set)

- Summary statistics of absolute values and changes from baseline in serum levels of Vitamin D25 and LDL will be presented by visit and cohort (Group G, safety set)
- Summary of Resource Utilization Questionnaire (RUQ) presented by visit and cohort (Group G, safety set).
- MS-TAQ: The MS-TAQ questionnaire is a self-administered tool to identify barriers to adherence for MS patients taking DMTs. The MS-TAQ questionnaire contains 30 questions in three subscales, DMT-Barriers (Range: 0-39), DMT-Side Effects (Range: 0-40), DMT-Coping Strategies (Range: 0-7). Summary statistics of the subscales and n and percentage for the remaining questions will be presented by visit for Group G, safety set. The subscales are calculated as follows:
    - DMT-Barriers = sum of items 7 to 19. Answers are weighted as follows: "Not important at all" = 0, "A little important" = 1, "Moderately important" = 2, "Extremely important" = 3.
    - DMT-Side Effects = sum of items 20 to 29. Answers are weighted as follows: "Never" = 0, "A few times" = 1, "About half the time" = 2, "Most of the time" = 3, "All or nearly all the time" = 4.
    - DMT-Cope = sum of items 30 to 36. Answers are weighted as follows: "No" = 0, "Yes" = 1.
- Number and percentage of patients having received Vitamin-D supplementation at least once (yes/no) and summary of highest total daily dose (Group G, Safety set)

All patients from Canada will be taken into account in this sub-study analysis.

Cardiac sub-study

Patients in the cardiac-sub study will be identified by medical review of criteria relevant for cardiac sub-study before DB lock. The following summaries will be done for Group F, safety set:

- Patient disposition will be summarized (Group F, enrolled set)
- Demographics including Framingham risk score
- Medical history
- Incidence of serious cardiovascular events (see Appendix Table K-1 for definition) will be summarized with number and percentage by preferred term Corresponding exact 95% confidence interval (Clopper-Pearson, 1934) will be calculated.
- Summary statistics in absolute values and change from baseline in blood pressure and heart rate will be presented by visit
- Summary statistics in absolute values and change from baseline in total cholesterol and HDL will be presented by visit
- Incidence of any new abnormal ECGs will be summarized with number and percentage.

4.14.3 Pool of D2409 and D2403 cardiac sub-study data

In order to gain more information, data from the D2409 will be pooled with data from the cardiac sub-study of D2403 study in which patients will be followed similarly to the D2409 study.
The following summaries will be done for Group F, safety set, if not specified otherwise:

- Patient disposition will be summarized (Group F, enrolled set)
- Demographics including Framingham risk score and European CVD risk score
- Medical history
- Incidence of serious cardiovascular events (see Appendix Table K-1 for definition) will be summarized with number and percentage by preferred term. Corresponding exact 95% confidence interval (Clopper-Pearson, 1934) will be calculated.
- Incidence of serious cardiovascular events (as described above) will be summarized with number and percentage by preferred term for Group G, safety set, stratified by Framingham risk score category (<=median, >median). The median used for categorization will be calculated over the Framingham risk score of all pooled cardiac patients with FTY as initial cohort treatment. The comparison cohort (Other DMT) will contain all Other DMT patients from D2403 and D2406 from Group G, safety set.
- Summary statistics in absolute values and change from baseline in blood pressure and heart rate will be presented by visit
- Summary statistics in absolute values and change from baseline in total cholesterol and HDL will be presented by visit
- Incidence of any new abnormal ECGs will be summarized with number and percentage.

Framingham risk score calculation

The Framingham risk score will be derived based on the risk factors sex (m/f), age (years), (treated) systolic blood pressure (mmHg), smoking (yes/no), diabetes (yes/no), HDL (mg/dL) and total cholesterol (mg/dL) following the approach from D'Agostino et al., 2008. The tables G-1 and G-2 (see Appendix G) present the score sheets to estimate the risk of cardiovascular disease (CVD) events for women and men respectively. Depending on the category of each risk factor risk points are assigned. According to the total sum of all risk points of a patient the corresponding CVD risk (%) is determined (see tables G-3 and G-4, Appendix G).

In case of missing values for total cholesterol or HDL the following imputation rules will be used. Missing total cholesterol values with be imputed by 170 mg/dL and missing HDL cholesterol by 50 mg/dL. This approach follows Samuel Cykert et al. (2019).

The diabetes variable will be derived by using the medical history of the patient using the MedDRA High Level Term "Diabetes mellitus (incl subtypes)". To derive if systolic blood pressure was treated a patient must have a medical history of hypertension and the concomitant medications treating the hypertension (see Appendix table H-1 for list of corresponding ATC codes).

All risk factores will be assessed at baseline (last assessment before or on day of entering respective cardiac sub-study (for D2403 cardiac sub-study and D2409), last assessment before or on day of first Other DMT administration within the study for all D2403 and D2406 Other DMT cohort patients).

European CVD risk score calculation (SCORE - Systematic Coronary Risk Estimation)

The SCORE system estimates the 10 year risk of fatal CVD in Europe. Its applicability to non-Caucasian populations has not been examined (Piepoli MF, Hoes AW, Agewall S, et al. 2016). It will be derived based on the same risk factors and using the same time point as the Framingham risk score with the exception of diabetes and HDL. The score will be derived for Group F patients. The total cholesterol value will used using mmol/L as unit. Additionally to the risk factors mentioned previously patients are categorized into low and high risk countries and the respective low/high risk chart has to be used in derivation of the score. The following countries are defined as being in the low risk category: Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, The Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland and the United Kingdom. All other European countries are categorized as high risk countries. For patients from non-european countries are analyzed as if their country would be part of the high risk category. The low risk chart (see Appendix J-2) and the high risk chart (J-1) will be used to calculate the European CVD risk score.

4.14.4 D2409 study

For all patients in the D2409 study the following summary analysis will be done:

- Incidence of serious cardiovascular events (see Appendix Table K-1 for definition) will be summarized with number and percentage by preferred term. Corresponding exact 95% confidence intervals (Clopper-Pearson, 1934) will be calculated.

For this analysis D2409 patients will be compared to the population of D2406 patients in Group F who had no serious CV event during first dose monitoring (i.e. during Day 1 and Day 2 of first dose of FTY or re-initiation).

The following data will be listed for D2409 patients:

- Premature discontinuation from study
- Protocol deviations
- Demography including Framingham risk score and European CVD risk score
- Relevant medical history and co-morbidities
- Multiple sclerosis history
- Multiple sclerosis disease modifying therapy
- Study cohort treatment exposure
- Concomitant medications and significant non-drug therapies

- Multiple sclerosis relapses
- EDSS scores
- Laboratory assessments
- Fingolimod first dose monitoring procedures and observations
- ECG
- Ophthalmologic assessments

4.15 Visit windows

Visit windows will be used to present summary statistics by visit. If for a specific analysis the respective data is part of the data warehouse corresponding remapped visit data is used. If this is not the case or the visit windows defined in this document differ from the VDW the data will be remapped using an approach that is consistent with the general approach used in the data warehouse. Visit windows will only be used for post-baseline data.
The following table displays the visit windows that will be applied.

Table Visit-windows

For RUQ, MS-TAQ and EDSS				
Visit	**Start day (time)**	**Target Day (time)**	**End day (time)**	**VWINN**
Month 3	2	91	136	1
Month 6	137	182	273	2
Month 12	274	365	547	3
Month 24	548	730	912	4
Year 3 (M36)	913	1095	1278	5
Year 4 (M48)	1279	1461	1643	6
Year 5 (M60)	1644	1826	2008	7
For ophthalmologic examination[1], TSQM-9 and treatment preference				
Visit	**Start day (time)**	**Target Day (time)**	**End day (time)**	**VWINN**
Month 6	2	182	363	2
For dermatological examination[1]				
Month 6	2	182	273	2
Month 12	274	365	547	3
For pulmonary function test, total cholesterol, HDL cholesterol, Vitamin D, LDL, systolic blood pressure, diastolic blood pressure and heart rate				
Visit	**Start day (time)**	**Target Day (time)**	**End day (time)**	**VWINN**
Month 12	2	365	547	3
Month 24	548	730	912	4
Year 3 (M36)	913	1095	1278	5

Year 4 (M48)	1279	1461	1643	6
Year 5 (M60)	1644	1826	2008	7
For patient-reported disability, MSIS-29, WPAI-GH, PRIMUS				
Month 6	2	182	273	2
Month 12	274	365	547	3
Month 24	548	730	912	4
Year 3 (M36)	913	1095	1278	5
Year 4 (M48)	1279	1461	1643	6
Year 5 (M60)	1644	1826	2008	7
- For Group G Day 1 is defined as the first dose day of study medication within the study. - For Group F Day 1 defined as the first dose day of FTY within the study. - If a patient has multiple visits within the same visit window the one closest to the target day will be chosen. If both visits have the same distance from the target day the latter one will be chosen. - This visit windowing approach will only be used for summary statistics. - [1] If a patient has multiple values within the same visit window the worst value is used. - For Group G: Last assessment prior to or at first dose in study is used as baseline. - For Group F: Last assessment prior to or at first dose of FTY in the study is used as baseline.				

5 General statistical methodology

(Exposure adjusted) incidence rate and 100*(1-α)% confidence interval

It will be assumed that for each of n patients in the study, the time t_j (j=1,...,n) to the first occurrence of a certain event is observed, or if the event was not experienced, the (censored) time to the end of the observation period. The sequence of first occurrences of an event will be modeled to follow approximately a Poisson process with constant intensity θ. The rate parameter θ will be estimated as λ=D/T, where

$$T = \sum_{j=1}^{n} t_j$$

and D is the number of patients with at least one event. Conditionally on T, an exact 100*(1-α)% confidence interval for a Poisson variable with parameter θT and observed value D can be obtained based on (Garwood, 1936), from which an exact 100*(1-α)% confidence interval for D/T will be derived as follows (Sahai, 1993; Ulm, 1990):

Lower confidence limit $L = \frac{0.5c_{\alpha/2,2D}}{T}$ for D>0, 0 otherwise,

Upper confidence limit $U = \frac{0.5c_{1-\alpha/2,2D+2}}{T}$

Where $c_{\alpha,k}$ is the αth quantile of the Chi-square distribution with k degrees of freedom.

(Exposure adjusted) incidence rate ratio and 100*(1-α)% confidence interval

Assuming D_1 and D_0 denote the number of subjects with event in active and reference group, respectively, and T_1 and T_0 the corresponding total time at risk. The incidence rate ratio is then calculated as $IRR = IR_1 / IR_0$ where $IR_1 = D_1/T_1$ and $IR_0 = D_0/T_0$ following Sahai and Khurshid (1993).

An exact 95% CI (L_{IRR} ; U_{IRR}) for IRR will be obtained by conditioning on the total number of events observed in the two groups $d = D_1 + D_1$.

Lower confidence limit: $L_{IRR} = \frac{L_{Bin} T_0}{(1 - L_{Bin}) T_1}$

Upper confidence limit: $L_{IRR} = \frac{U_{Bin} T_0}{(1 - U_{Bin}) T_1}$

where L_{Bin} and U_{Bin} can be produced via the following formulae:

and $L_{Bin} = \left(1 + \frac{d - D_1 + 1}{D_1 F_{(\alpha/2, 2D_1, 2(d - D_1 + 1))}} \right)^{-1}$ and $U_{Bin} = \left(1 + \frac{d - D_1}{(D_1 + 1) F_{(1-\alpha/2, 2(D_1+1), 2(d-D_1))}} \right)^{-1}$.

(Exposure adjusted) incidence rate difference and 100*(1-α)% confidence interval

Using the same notation as above the difference between two exposure adjusted incidence rates can be estimated by $\hat{\theta} = \widehat{IR_1} - \widehat{IR_2}$. Using normal approximation the corresponding (1-α) confidence interval for $\hat{\theta}$ is defined by $\widehat{IR_1} - \widehat{IR_2} \pm Z_{\alpha/2}\hat{\sigma}$ where $\hat{\sigma} = \sqrt{\frac{D_1}{T_1^2} + \frac{D_2}{T_2^2}}$. This approach follows G. F. Liu et al., 2006.

Cox proportional hazard regression model

Time to first particular selected safety outcome will be analyzed with a Cox proportional hazards regression model. The null-hypothesis will be H_0: $\lambda_{FTY}(t) / \lambda_{Other\ DMT}(t) = 1$, where $\lambda(t)$ is the hazard function for the failure time of patients treated with FTY720 and other DMT, respectively.
The explanatory variables are age at baseline, gender, study and duration of disease since diagnose at study start (in years). The SAS procedure PHREG will be used with the following SAS code:

```
proc phreg data=aaa;
  class trt(order=internal) gender study;
  model aval*cnsr(1)=trt gender study age dur / rl ties=exact;
  contrast "FTY720 vs other DMT" trt 1 /estimate=exp;
```

```
run;
```

where aval = time to first particular selected safety outcome
cnsr = data are censored if cnsr = 1
trt = treatment (FTY720, other DMT)
gender = sex (male, female)
study = study patient is participating in (D2403, D2406)
age = age at screening, continuous
dur = duration of disease at study start

Results will be presented with the hazard ratio for FTY720/other DMT and associated 95% confidence interval and two-sided p-value. P-value will be obtained from the Wald chi-squared statistic testing the null-hypothesis that the parameter estimate for the respective treatment effect is 0 (then the hazard ratio is exp(0) = 1).

No check for the validity of proportional hazards assumptions will be done.

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Appendix A General principle on analysis sets and data selection in the virtual data warehouse

Any analysis based on the virtual data warehouse *must* make use of three mandatory data selection flags and a treatment option: only the combination of the three mandatory variables will allow a valid and meaningful data selection. The three mandatory flags are (1) the group flag, (2) the analysis set (3) the data selection flag. The following flags should be considered:

- **A group flag (study and timeframe selection, mandatory)**: The group flag will select all data (on an observation level) from patients in a predefined group of studies up to the cut-off date in pools that have a nominal cut-off date, and all data that are in scope of the respective pool in pools that have no nominal cut-off date. Group flags exist for F and G.
- **Analysis Set flag (patient selection, mandatory)**: An analysis set (i.e. an analysis population) is defined as a subset of patients who fulfill certain inclusion criteria. The analysis set flag will select patients within a predefined pool of studies that fulfill the inclusion criteria of the respective population (e.g. SAF).
- **Data selection flag (observation selection, mandatory):** The data selection flag will flag the relevant subset of observations to be included in an analysis from all the observations under consideration as defined by the group flag and the analysis set flag. The data selection criteria are uniquely defined by a combination of the pool definition (e.g. G), the analysis population (e.g. SAF), and the data domain (e.g. AE).
- **Subgroup flag (patient level, optional):** A subgroup flag is a flag that selects a subset of patients who share common (baseline) criteria from the overall analysis set. If no subgroup flag is selected all patients within the analysis set will be considered.
- **Visit (observation selection, optional):** Used for analyses by visit, or for an analysis at a specific visit. If a remapped “VISIT” variable exists in a specific panel then this should be used.
- **A treatment option (mandatory):** The treatment option will determine how patients are grouped in an analysis. This applies to statistical modeling and to the grouping of patients on outputs. For reports based on G this will usually be the initial cohort treatment option.

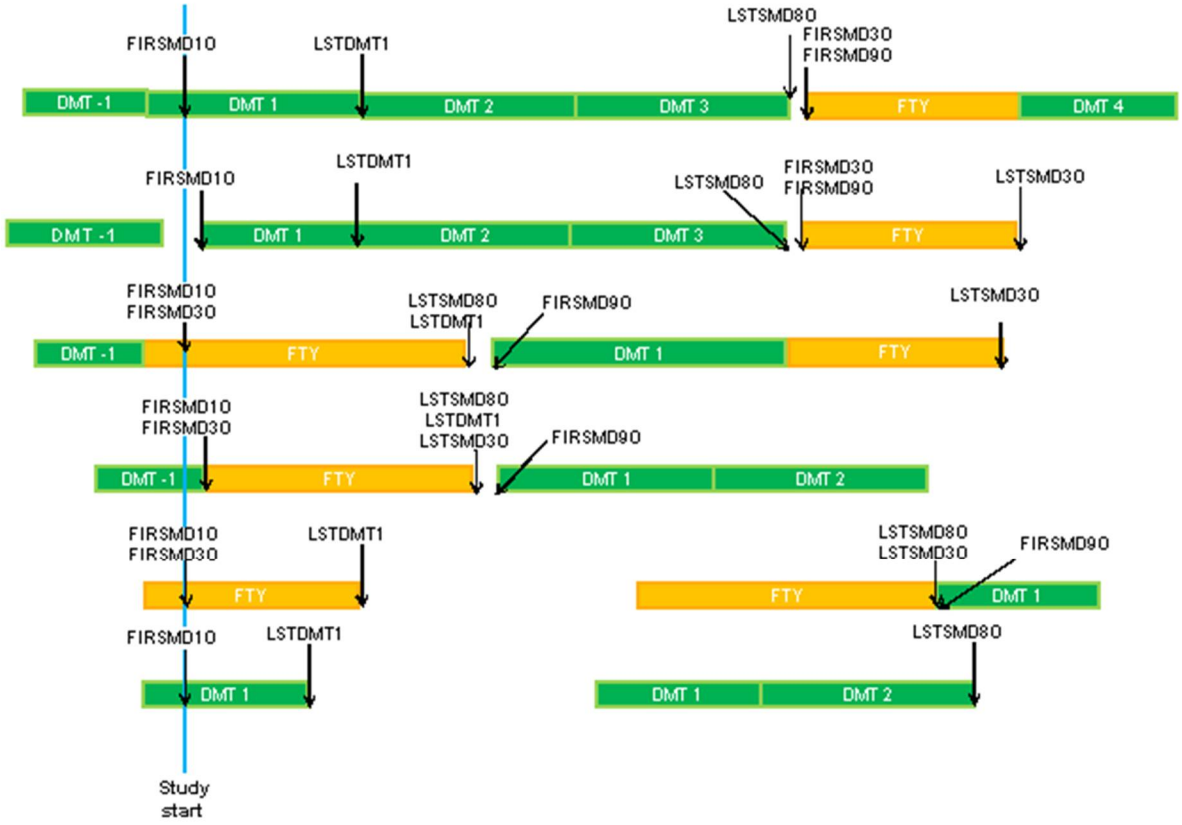
Rules for the derivation of "group flags" (Study and timeframe)

The group flag will select all observations from patients in a predefined group of studies from the baseline record up to the cut-off date in pools that have a nominal cut-off date, and all data that are in scope of the respective pool in pools that have no nominal cut-off date. For PASSAGE, only Group G and Group F flags will be used, and they will select all observations in PASSAGE. Unless otherwise specified, the mandatory flags used for PASSAGE analyses are summarized in table below:

Table A-1 Mandatory flags in PASSAGE main analysis

PASSAGE Analysis	Group flag (GRPFLG)	Analysis set flag	Data selection flag	Treatment option
Group G				
Effectiveness analyses	G	To be derived by [redacted]	To be derived by [redacted]	TRTN_RI
Safety analyses (based on Group G general safety rules)	G	SAF_G	FLGSAFCO	TRTN_CO
Group F				
Safety analyses (based on Group F general safety rules)	F	SAF_EF	FLGSAF_F	All patients in Group F

Appendix B Illustration of VDW key dates



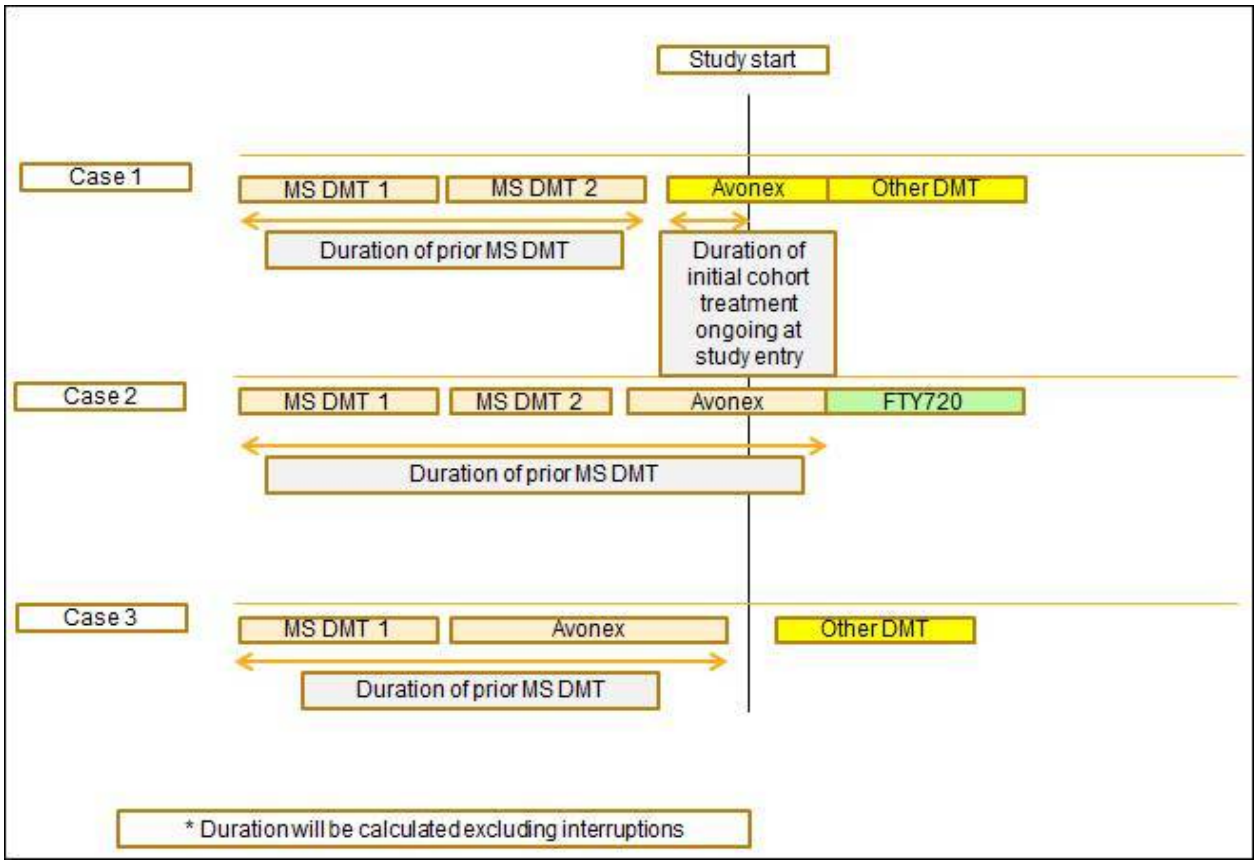
In Group G, dates of interest are:

- FIRSMD1O, defined as the date of first dose of initial cohort treatment in the study (Day 1 date)
- FIRSMD9O, defined as the date of first dose of DMT in the study after the first permanent switch.
- LSTSMD8O, defined as the date of last dose of initial cohort treatment prior to first permanent switch.
- LSTDMT1, derived by [redacted] and defined as the date of last dose of first DMT corresponding to cohort assignment prior to any switch in DMT and prior to an interruption in the first DMT corresponding to cohort assignment of more than 45 days.

In Group F, dates of interest are:

- FIRSMD3O, defined as the first dose of FTY720 during the study.
- LSTSMD3O, defined as the date of last dose of FTY720 in the study.

Appendix C Sample Illustration of Prior MS DMT and Initial cohort treatment ongoing at study entry duration calculations



Appendix D Criteria for notable laboratory abnormalities

Table D-1 Criteria for notable laboratory abnormalities

Notable Values		
Laboratory Variable	**Standard Units**	**SI Units**
HEMATOLOGY VARIABLES		
WBCs (Leukocytes)	≤2.0 k/mm^3 ≥15 k/mm^3	≤2.0 x 10^9/L ≥15 x 10^9/L
HEMATOLOGY VARIABLES: DIFFERENTIAL		
Absolute lymphocytes	<200/mm^3 ≥8000/mm^3	<0.2 x 10^9/L ≥8 x 10^9/L

Notable Values		
Laboratory Variable	**Criterion**	
LIVER FUNCTION AND RELATED VARIABLES		
SGOT (AST) or AGPT (ALT)	>3-<=5 x ULN >5-<=8 x ULN >8-<=10 x ULN >10-<=20 x ULN >20 x ULN	
Total bilirubin (TBL)	>1-<=1.5 x ULN >1.5-<=2 x ULN, >2 x ULN	
Alkaline Phosphatase (ALP)	>1.5-<=2 x ULN >2-<=5 x ULN >5 x ULN	
COMBINED CRITERIA		
ALP and TBL	ALP>3 x ULN and TBL>2 x ULN	
	ALP>5 x ULN and TBL>2 x ULN	
AST or ALT and TBL	AST or ALT >3 x ULN and TBL >1.5 x ULN	
	AST or ALT >3 x ULN and TBL >2 x ULN	
AST or ALT and TBL and ALP	AST or ALT >3 x ULN and TBL >2 x ULN and ALP <2 x ULN (Hy's Law)	

ULN = Upper Limit of Normal

Appendix E Notable vital signs criteria

Table E-1 Notable vital signs criteria

NOTABLE VITAL SIGNS	
Vital Sign Variable	**Notable Criteria**
Pulse (beats/min)	>120 bpm or Increase of ≥15 bpm Or < 50 bpm or Decrease of ≥15 bpm
Systolic BP (mmHg)	≥160 mmHg or Increase of ≥20 mmHg Or ≤ 90 mmHg or Decrease of ≥ 20 mmHg
Diastolic BP (mmHg)	≥ 100 mmHg or Increase of ≥ 15 mmHg Or ≤ 50 mmHg or Decrease of ≥ 15 mmHg
Body Weight (kg)	7% increase or decrease

Note that for Group G, an increase or decrease refers to a change from the value prior to first dose of initial cohort treatment in study. For Group F, an increase or decrease refers to a change from the value prior to first dose of FTY720 in study.

Appendix F Mapping of MS medications to the 7 categories of 1st DMT corresponding to cohort assignment

Table F-1 Mapping of MS medications

1st DMT categories	Original preferred term
FTY720	FINGOLIMOD
	FINGOLIMOD HYDROCHLORIDE
INTERFERON	BETASERON
	INTERFERON BETA
	INTERFERON BETA-1A
	INTERFERON BETA-1B
	INTERFERON
	PEGINTERFERON, PEGINTERFERON BETA-1A
GLATIRAMER ACETATE	GLATIRAMER
	GLATIRAMER ACETATE
DIMETHYL FUMARATE	DIMETHYL FUMARATE
	ETHYL FUMARATE
	FUMARIC ACID
	FUMARATE DISODIUM
TERIFLUNOMIDE	TERIFLUNOMIDE
NATALIZUMAB	NATALIZUMAB
Other MS therapies	All other DMTs

Note: First DMTs corresponding to initial cohort treatment within the "Other MS therapies" category will be displayed as separate category if there are 40 or more patients with this DMT.

Appendix G Framingham risk score calculation

Table G-1 CVD points for women

Points	Age, y	HDL	Total Cholesterol	SBP Not Treated	SBP Treated	Smoker	Diabetic
−3				<120			
−2		60+					
−1		50–59			<120		
0	30–34	45–49	<160	120–129		No	No
1		35–44	160–199	130–139			
2	35–39	<35		140–149	120–129		
3			200–239		130–139	Yes	
4	40–44		240–279	150–159			Yes
5	45–49		280+	160+	140–149		
6					150–159		
7	50–54				160+		
8	55–59						
9	60–64						
10	65–69						
11	70–74						
12	75+						
Points allotted							Total

SBP indicates systolic blood pressure.

Table G-2 CVD points for men

Points	Age, y	HDL	Total Cholesterol	SBP Not Treated	SBP Treated	Smoker	Diabetic
−2		60+		<120			
−1		50–59					
0	30–34	45–49	<160	120–129	<120	No	No
1		35–44	160–199	130–139			
2	35–39	<35	200–239	140–159	120–129		
3			240–279	160+	130–139		Yes
4			280+		140–159	Yes	
5	40–44				160+		
6	45–49						
7							
8	50–54						
9							
10	55–59						
11	60–64						
12	65–69						
13							
14	70–74						
15	75+						
Points allotted							Total

Table G-3 CVD risk for women

Points	Risk, %
≤−2	<1
−1	1.0
0	1.2
1	1.5
2	1.7
3	2.0
4	2.4
5	2.8
6	3.3
7	3.9
8	4.5
9	5.3
10	6.3
11	7.3
12	8.6
13	10.0
14	11.7
15	13.7
16	15.9
17	18.5
18	21.5
19	24.8
20	28.5
21+	>30

Table G-3 CVD risk for men

Points	Risk, %
≤−3 or less	<1
−2	1.1
−1	1.4
0	1.6
1	1.9
2	2.3
3	2.8
4	3.3
5	3.9
6	4.7
7	5.6
8	6.7
9	7.9
10	9.4
11	11.2
12	13.2
13	15.6
14	18.4
15	21.6
16	25.3
17	29.4
18+	>30

Appendix H Concomitant medications treating sBP

Table H-1 ATC codes to identify CMs to treat sBP

ATC code	Name
C02	Antihypertensiva
C03	Diuretika
C07	Beta Blocker
C08	Calcium Antagonisten
C09	ACE Hemmer / Angiotensinantagonisten

Appendix I Cardiovascular risk factors

Table I-1 Preferred terms for cardiovascular risk factors

Preferred term	Category
ALCHOL ABUSE	
ALCHOL USE	
ALCOHOLISM	
ANGINA PECTORIS	Cardiovascular disease
ANGIOPLASTY	Cardiovascular disease
ANTIPHOSPHOLIPID ANTIBODIES	
ARTERIAL OCCLUSIVE DISEASE	
ARTERIAL THROMBOSIS	
ARTERIOSCLEROSIS	Cardiovascular disease
ARTERIOSCLEROSIS CORONARY ARTERY	Cardiovascular disease
ATRIAL FIBRILLATION	
BLOOD CHOLESTEROL ABNORMAL	Hyperlipidaemia
BLOOD CHOLESTEROL INCREASED	Hyperlipidaemia
BLOOD GLUCOSE INCREASED	Diabetes mellitus
BLOOD PRESSURE DIASTOLIC INCREASED	Hypertension
BLOOD PRESSURE INCREASED	Hypertension
BLOOD TRIGLYCERIDES INCREASED	Hyperlipidaemia
BODY FAT DISORDER	
BODY MASS INDEX INCREASED	
BRAIN STEM HAEMORRHAGE	Cardiovascular disease
BRAIN STEM HAEMORRHAGE	Cardiovascular disease
BRAIN STEM ISCHAEMIA	Cardiovascular disease
CARDIAC ANEURYSM	
CARDIAC ARREST	Cardiovascular disease
CARDIAC DISORDER	Cardiovascular disease
CARDIAC FAILURE CHRONIC	Cardiovascular disease
CARDIAC FAILURE CONGESTIVE	Cardiovascular disease
CARDIOLIPIN ANTIBODY POSITIVE	
CARDIOMEGALY	Cardiovascular disease
CARDIOMYOPATHY	Cardiovascular disease
CARDIOVASCULAR DISORDER	Cardiovascular disease
CAROTID ARTERY DISEASE	Cardiovascular disease
CAROTID ARTERY STENOSIS	Cardiovascular disease
CAROTID ARTEY STENT INSERTION	
CEREBROVASCULAR ACCIDENT	Cardiovascular disease
CEREBROVASCULAR DISORDER	Cardiovascular disease
CEREBROVASCULAR INSUFFICIENCY	Cardiovascular disease
CIRCULATORY COLLAPSE	
COAGULOPATHY	
CORONARY ANGIOPLASTY	Cardiovascular disease
CORONARY ARTERIAL STENT INSERTION	Cardiovascular disease

CORONARY ARTERY BY-PASS	
CORONARY ARTERY DISEASE	Cardiovascular disease
DEEP VEIN THROMBOSIS	
DIABETES MELLITUS	Diabetes mellitus
DIABETIC DIET	Diabetes mellitus
DIABETIC HYPEROSMOLAR COMA	Diabetes mellitus
DIABETIC KETOACIDOSIS	Diabetes mellitus
DIABETIC METABOLIC DECOMPENSATION	Diabetes mellitus
DIABETIC NEUROPATHY	Diabetes mellitus
DIASTOLIC DYSFUNCTION	Cardiovascular disease
DIASTOLIC HYPERTENSION	Hypertension
DYSLIPIDAEMIA	Hyperlipidaemia
EMBOLISM VENOUS	
ESSENTIAL HYPERTENSION	Hypertension
EX-ALCHOLIC	
EX-TOBACCO USER	
FACTOR V LEIDEN MUTATION	
HAEMORRHAGIC STROKE	Cardiovascular disease
HIGH DENSITY LIPOPROTEIN DECREASED	Hyperlipidaemia
HYPERCHOLESTEROLAEMIA	Hyperlipidaemia
HYPERLIPIDAEMIA	Hyperlipidaemia
HYPERTENSION	Hypertension
HYPERTENSIVE CRISIS	Hypertension
HYPERTRIGLYCERIDAEMIA	Hyperlipidaemia
HYPERTROPHIC CARDIOMYOPATHY	Cardiovascular disease
INSULIN REQUIRING TYPE 2 DIABETES MELLITUS	
ISCHAEMIC CARDIOMYOPATHY	Cardiovascular disease
JUGULAR VEIN THROMBOSIS	
LABILE HYPERTENSION	Hypertension
LEFT VENTRICULAR HYPERTROPHY	Cardiovascular disease
LIPID METABOLISM DISORDER	Hyperlipidaemia
LIPIDS INCREASED	Hyperlipidaemia
LOW DENCITY LIPOPROTEIN INCREASED	
METABOLIC SYNDROME	
MYOCARDIAL INFARCTION	Cardiovascular disease
MYOCARDIAL ISCHAEMIA	Cardiovascular disease
NICOTINE DEPENDENCE	
OBESITY	
OVERWEIGHT	
PRE-ECLAMPSIA	
PRINZMETAL ANGINA	Cardiovascular disease
PROTEIN S DEFICIENCY	
SYSTOLIC HYPERTENSION	Hypertension
THROMBOSIS	
TOBACCO ABUSE	
TOBACCO USER	

TRIANSIENT ISCHAEMIC ATTACK	
TYPE 1 DIABETES MELLITUS	Diabetes mellitus
TYPE 2 DIABETES MELLITUS	Diabetes mellitus
TYPE IIA HYPERLIPIDAEMIA	Hyperlipidaemia
TYPE V HYPERLIPIDAEMIA	Hyperlipidaemia
VENOUS THROMBOSIS	
VENOUS THROMBOSIS LIMB	
WEIGHT INCREASED	
Aortic valve disease	Cardiovascular disease
Pulmonary valve incompetence	Cardiovascular disease
Left ventricular dysfunction	Cardiovascular disease
Heart valve incompetence	Cardiovascular disease
Cardiac valve disease	Cardiovascular disease
Cardiomegaly	Cardiovascular disease
Aortic valve incompetence	Cardiovascular disease
Ischaemic cardiomyopathy	Cardiovascular disease
Mitral valve incompetence	Cardiovascular disease
Mitral valve disease	Cardiovascular disease
Overweight	Cardiovascular disease
Carotid artery aneurysm	Cardiovascular disease
Carotid artery dissection	Cardiovascular disease
Carotid artery occlusion	Cardiovascular disease
Cerebral arteriosclerosis	Cardiovascular disease
Congenital mitral valve stenosis	Cardiovascular disease
Cardiac septal defect	Cardiovascular disease
Congenital heart valve disorder	Cardiovascular disease
Electrocardiogram PR prolongation	Cardiovascular disease
Antiphospholipid antibodies	Cardiovascular disease
Antiphospholipid antibodies positive	Cardiovascular disease
Electrocardiogram QRS complex prolonged	Cardiovascular disease
Echocardiogram abnormal	Cardiovascular disease
Cardiolipin antibody	Cardiovascular disease
Blood pressure increased	Cardiovascular disease
Electrocardiogram QT prolonged	Cardiovascular disease
Arterial occlusive disease	Cardiovascular disease
Pelvic venous thrombosis	Cardiovascular disease
Peripheral artery occlusion	Cardiovascular disease
Peripheral artery thrombosis	Cardiovascular disease
Aortic arteriosclerosis	Cardiovascular disease
Venous stenosis	Cardiovascular disease
Peripheral arterial occlusive disease	Cardiovascular disease
Intermittent claudication	Cardiovascular disease
Cardiac assistance device user	Cardiovascular disease
Aortic valve replacement	Cardiovascular disease
Peripheral artery angioplasty	Cardiovascular disease
Arterial stent insertion	Cardiovascular disease
Aortic valve repair	Cardiovascular disease

Cardiac operation	Cardiovascular disease
Cardiac septal defect repair	Cardiovascular disease
Impaired fasting glucose	Diabetes mellitus
Diabetic ketoacidosis	Diabetes mellitus
Diabetic metabolic decompensation	Diabetes mellitus
Insulin-requiring type 2 diabetes mellitus	Diabetes mellitus
Monogenic diabetes	Diabetes mellitus
Hyperglycaemia	Diabetes mellitus
Steroid diabetes	Diabetes mellitus
Blood glucose increased	Diabetes mellitus
Blood pressure diastolic increased	Hypertension
Blood triglycerides increased	Hyperlipidaemia
Lipids	Hyperlipidaemia
Endocrine hypertension	Hypertension

Appendix J Risk charts for European CVD risk score

Table J-1 SCORE – European High Risk Chart

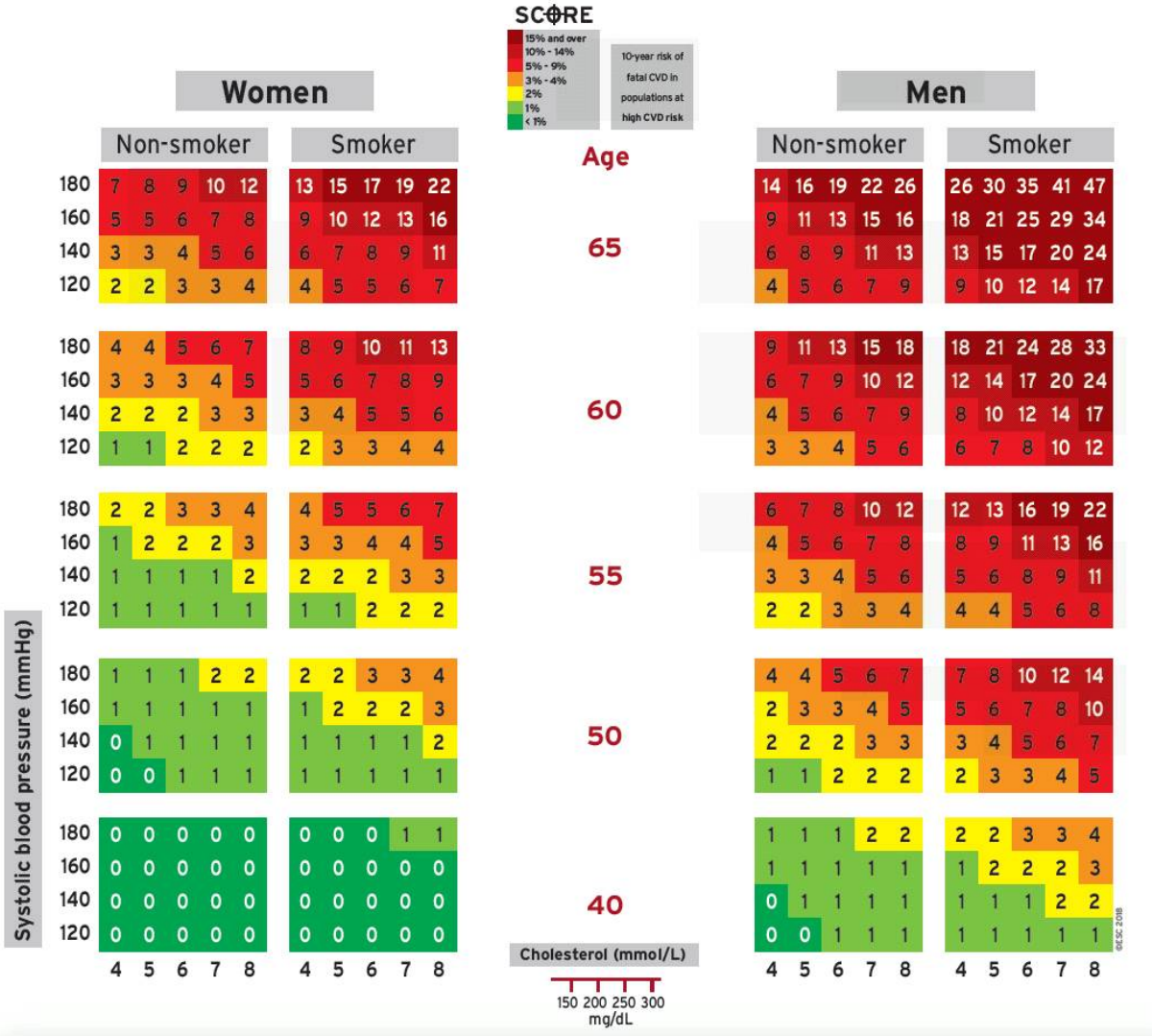
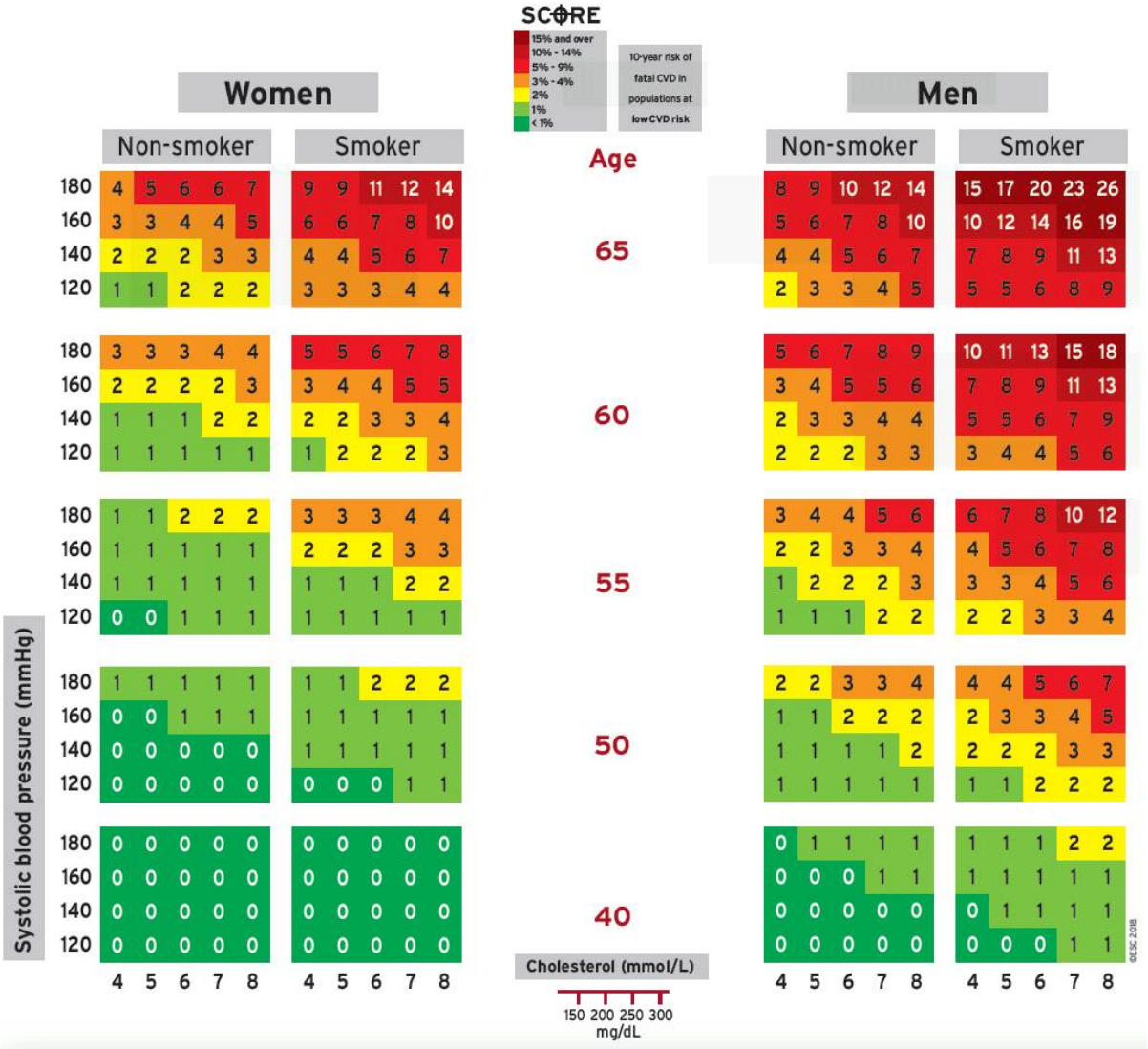


Table J-2 SCORE – European Low Risk Chart



Appendix K Serious cardiovascular event definition

Table K-1 List of SMQs, HLTs and PTs defining a cardiovascular event

Term category	Coded Term*
SMQ (narrow)	Ischaemic heart disease (SMQ)
SMQ (narrow)	Cardiac failure (SMQ)
SMQ (narrow)	Ischaemic central nervous system vascular conditions (SMQ)
SMQ (narrow)	Haemorrhagic central nervous system vascular conditions (SMQ)
SMQ (narrow)	Shock-associated circulatory or cardiac conditions (excl torsade de pointes) (SMQ)
HLT	Accelerated and malignant hypertension
HLT	Ventricular arrhythmias and cardiac arrest
PT	Atrioventricular block complete
Additionally all PTs from SOC=Cardiac Disorders that are flagged as leading to death. * Events fulfilling the definition must be serious.	