NOVARTIS

Clinical Development

FTY720/Fingolimod/Gilenya®

CFTY720D2419 / NCT04667949

A 24-month, open-label, prospective, multicenter interventional, single-arm study assessing the efficacy and safety of fingolimod (Gilenya) 0.5mg in relapsing multiple sclerosis (RMS) patients in China

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
30-Jan-2022	Prior to interim DB lock	Creation of final version	N/A - First version	NA
25-May-2022	Prior to interim DB lock	Creation of amendment 1	Typo of “fingolimod”	Section 2.1
			Add abbreviation of “Functional score”	List of abbreviation
			Add rule of baseline for vital signs and ECG	Section 2.1.2.1
			Add time points for first dose monitoring ECG and Vital signs	Section 2.1.2.1.1
			Add the multiple assessment rules	Section 2.1.2.3
			TEAE will be reported	Section 2.8.1
			Modify the names of cholesterol, Neutrophils and Lymphocytes	Section 2.8.3
			Modify ECG parameters	Section 2.8.4.1
			Add rule of non by-visit summaries	Section 2.8.4.1
			Add the listings of clinical notable vital signs	Section 2.8.4.2
			Add dermatology evaluations	Section 2.8.4.4
			Add first dose (second dose/restart dose) monitoring	Section 2.8.5
			Add summary statistics for vital signs measurements and ECG parameters.	Section 2.8.6
			[redacted]	[redacted]
			Add the definition of Severity of MS relapses	Section 5.1.4.3
			Add one reference	Section 6
1-July-2022	Prior to interim DB lock	Creation of amendment 2	[redacted]	[redacted]
			Add sensitivity analyses on laboratory, ECG and vital sign data	Section 2.8.3 Section 2.8.4.1 Section 2.8.4.2
			[redacted]	[redacted]
29-December-2022	Prior to interim DB lock	Creation of amendment 3	Add the mapping rule to ECG	Section 2.1.2.1
			Refine multiple assessments	Section 2.1.2.3
			Refine analysis sets which are only for final analysis	Section 2.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Add approved MS disease-modifying drugs list	Section 2.3.3
			Delete the endpoint of the volume of new or enlarged T2 lesions, add the volume of T2 lesions	Section 2.7.1
			Refine MRI analysis period	Section 2.7
			Delete eosinophils from criteria for notable laboratory abnormalities	Section 2.8.3
			Modify the unit of creatinine	Section 2.8.3
			[redacted]	[redacted]
			[redacted]	[redacted]
13-November-2024	Prior to final DB lock	Creation of amendment 4	Update the list of abbreviations	List of abbreviations
			Update the protocol version	Section 1
			Change Gd-enhancing lesion into Gd-enhancing T1 lesion	Section 2.7
			[redacted]	[redacted]
			Add frequency distribution analysis of key hematological parameters	Section 2.8.3
			Change section number from Section 3.1.1 to Section 3.1	Section 3.1.1
2-April-2025	Prior to final DB lock	Creation of amendment 5	Change language in Table 1-1	Section 1.2 and Section 2.7.1
			Clarify the data handling for MRI parameters	Section 2.5.3
			Clarify the covariates	Section 2.7.2
			Delete MS medication history of DMT by PT	Section 2.3.3
			Add the summary of most common TEAEs	Section 2.8.1

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AE	Adverse event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase
ARR	Annualized Relapse Rate
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
bid	bis in diem/twice a day
BP	Blood Pressure
[redacted]	[redacted]
CI	Confidence Interval
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical Study report
DBL	Database Lock
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
(e)EDSS	(electronic) Expanded Disability Status Scale
EOS	End of Study
EOT	End of Treatment
[redacted]	[redacted]
eCRF	Electronic Case Report Form
eCRS	Electronic Case Retrieval Sheet
FAS	Full Analysis Set
FS	Functional score
Gd	Gadolinium
[redacted]	[redacted]
KM	Kaplan-Meier
LDD	Last Dose Date
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRI	Magnetic Resonance Image
MS	Multiple Sclerosis
NB	Negative binomial
[redacted]	[redacted]
NMPA	National Medical Products Administration
PDS	Programming Datasets Specifications
PK	Pharmacokinetics
PRO	Patient-reported Outcomes
PT	Preferred Term
RMS	Relapsing MS
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCR	All screened subjects
SOC	System Organ Class
TEAE	Treatment Emergent AE
TFLs	Tables, Figures, Listings

ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WBC	White blood cell
WHO	World Health Organization

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis planned in the protocol for study CFTY720D2419.

There will be one report resulting from this SAP: The clinical study report (CSR) of the D2419 study. [redacted]

The final CSR will be completed after the final database lock.

This document is consistent with the current study protocols (version 03 original protocol).

1.1 Study design

This is a 24-month, open-label, multicenter, interventional, single-arm study to collect efficacy, safety and health outcome data of fingolimod (Gilenya) 0.5 mg/day in approximately 100 relapsing multiple sclerosis (RMS) subjects in China.

The study will consist of three Phases (see Figure 1-1):

Screening (up to 1 month): After signing informed consent, subjects will enter a Screening Phase to determine eligibility according to inclusion and exclusion criteria.

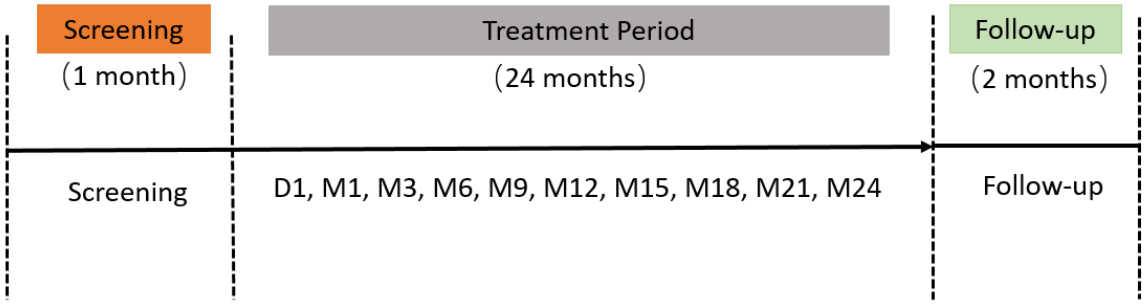
The investigator must ensure that all subjects meet the inclusion and exclusion criteria to be eligible to enter the study.

Treatment Period (24 months): On visit Day 1, all eligibility criteria will be confirmed, including a pre-dose ECG and vital signs. The first dose of study drug will be taken in the clinic on Day 1 and the subject will be monitored for at least 6 hours after the first dose administration before discharge. Refer to [Protocol Section 16.5] for Guidance for monitoring of subjects taking their first dose of the study drug.

Then the subjects should come to site and be evaluated at month 1 and then every three months till the end of treatment up to 24 months.

Follow Up (2 months): Subjects who completed Treatment Period will return for the Follow-up visit 2 months after the last dose of study drug.

Figure 1-1 Study design



[redacted]

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the efficacy of fingolimod 0.5mg on annualized relapse rate (ARR) in subjects with RMS treated for up to 24 months.	• Annualized relapse rate (ARR)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the safety and tolerability of fingolimod 0.5 mg in subjects with RMS treated for up to 24 months.	• Adverse events (AE) and serious adverse events (SAE) • Laboratory tests (hematology, biochemistry) • Vital signs • Electrocardiogram (ECG) • Ophthalmology
• To evaluate the efficacy of fingolimod 0.5 mg on MRI lesions.	• T1 hypo-intense lesion number and volume; T2 lesion volume, new/newly enlarged T2 lesion number; Gd-enhancing T1 lesion number and volume.

[redacted]

2 Statistical methods

2.1 Data analysis general information

Novartis statistical and programming team will be performing the CSR analysis as planned in this document unless otherwise specified. The Statistical Analysis System (SAS) 9.4 and/or R 3.6.1 or higher versions will be used.

Unless otherwise stated, summary tables/figures/listings will be on all subjects in the respective analysis sets. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviations, median, 25th and 75th percentiles (optional), minimum and maximum will be presented.

[redacted]

For efficacy analyses in the final CSR, all available data until EOT (i.e. excluding the data collected in the safety follow-up part) will be considered and no other cut-offs will be applied.

For safety analyses in the final CSR, only data up to and including the safety cutoff of 45 days (5 times the half-life of fingolimod, 9 days) after the last dose administration of study drug will be considered. For safety analyses on the follow-up period, all data (including assessments or events more than 45 days after the last dose of study drug) will be considered.

Presentation of p-values: p-values from statistical tests will be presented with 3 decimal places, or as <.001 where applicable. Statistically significant p-values will be flagged with an asterisk. In general, this is when p-values ≤0.05.

2.1.1 General definitions

The table below summarizes some general definitions to be used in the rest of the document.

Table 2-1 General Definitions

Study treatment/Study drug	The investigational drug (fingolimod) will be referred as study treatment or study drug.
Study Day 1 or Day 1	The date of first administration of study drug/first dose date.
Study Day	All other study days will be labeled relative to Day 1. For events with dates on or after Day 1, study day for the event is calculated as (event start date – first dose date + 1). For events with dates before Day 1, study day for the event is calculated as (event start date – first dose date). Day 0 will not be used.
Duration of an event	Duration of an event is calculated as (event end date – event start date +1).
1 month	30 days; to be used in determining target days of scheduled visits [redacted]
Day post-study drug discontinuation	Day post-study drug discontinuation for a particular event is calculated as (event start date – study drug discontinuation date).

Baseline	Baseline is the last assessment with non-missing value obtained prior to the first administration of study drug. No visit windows will be needed for the identification of baseline assessment. For pulse and blood pressure vital sign values, the baseline is the average of the non-missing values of the 3 measurements taken on the last visit prior to the first administration of study drug.
On-treatment period	On-treatment period includes days from the first dose date until the last dose date. This definition applies to efficacy analyses only. For calculation of compliance to study drug administration, same definition will be used.
Off-treatment period	Off-treatment period includes days after the last dose date. This definition applies to both efficacy and safety analyses.
Safety cutoff	Safety cutoff: Unless explicitly otherwise stated (e.g. SAEs and deaths), data up to and including the safety cutoff of 45 days after permanent study drug discontinuation will be included in the analysis and data beyond this time point for a given subject will be excluded from the safety analysis. The safety cutoff of 45 days (5x9 days) takes the half-life of the investigational drug into consideration. The safety cutoff applies to safety analyses only.
Nominal visits	Nominal visits are defined as all scheduled visits as per the clinical study protocol including the EOS and EOT visits. The definition of nominal visit excludes unscheduled visits.
End of Study (EOS)	EOS, used in the context of individual subjects, refers to EOS visit.
End of Treatment (EOT)	EOT refers to EOT visit. Only subjects who prematurely discontinue study drug but agree to continue to follow the schedule of assessments in the treatment period will have EOT visit.
End of treatment period date	This date is the date of discontinuation/study phase completion as recorded in the Treatment disposition CRF page.
Last assessment on drug	It is the last assessment with non-missing value taken before or on the date of last administration of study drug. No visit windows will be needed for the identification of the last assessment on drug evaluation.

2.1.2 Visit windows

2.1.2.1 Visit windows for treatment period

Visit-windows will be used for both efficacy and safety data summaries by visit. Visit windows define a time period “around” the targeted visit date as defined in the evaluation schedule of the clinical study protocol. Visit-windows are non-overlapping and defined without gaps between

consecutive visit windows. The width of visit windows may vary over the course of the study period.

Baseline assessments are defined in Section 2.1.1 and do not require a visit window.

The purpose of visit windows is to analyze data based on the actual study days (rather than "nominal" visits). E.g. if a subject's Month 1 visit is delayed; it is possible that the Month 1 data be re-aligned to visit-window Month 2 and be summarized under Month 2.

- For **efficacy analyses** all nominal visits (i.e. excluding unscheduled visits) will be mapped into one of the defined visit-windows. [redacted]

-For **safety analyses** all visits (scheduled and unscheduled) will be mapped to visit windows. Safety data from unscheduled visits may be reported separately if applicable.

It is possible that more than one assessment of a subject fall into a particular visit-window. Section 2.1.2.3 deals with the statistical approaches to handle multiple visits in a given visit-window.

Tables displaying summary statistics "by visit" will also use the term *visit-window* as column header; this is to remind the reviewer that multiple assessments of a subject might be summarized. Below tables provide visit-windows definitions for applicable parameters.

[redacted]

Table 2-3 Visit-windows for MRI

Visit-window	Start day	Target Day	End day
Month 12	1	360	540
Month 24	541	720	900

Table 2-4 Visit-windows for routine laboratory values

Visit-window	Start day	Target Day	End day
Month 1	1	30	60
Month 3	61	90	135
Month 6	136	180	225
Month 9	226	270	315
Month 12	316	360	450
Month 18	451	540	630
Month 24	631	720	810

Table 2-5 Visit-windows for vital signs*

Visit-window	Start day	Target Day	End day
Month 1	1	30	60
Month 3	61	90	135
Month 6	136	180	225
Month 9	226	270	315
Month 12	316	360	405
Month 15	406	450	495
Month 18	496	540	585
Month 21	586	630	675
Month 24	676	720	765

*Data collected from Day 1 protocol scheduled visit will not be mapped to the visit windows due to different data collection on those visits.

Table 2-6 Visit-windows for Electrocardiogram (ECG)

Visit-window	Start day	Target Day	End day
Month 1	1	30	60
Month 3	61	90	135
Month 6	136	180	270
Month 12	271	360	450
Month 18	451	540	630
Month 24	631	720	810

*Data collected from Day 1 protocol scheduled visit will not be mapped to the visit windows due to different data collection on those visits.

For vital signs, the mean of the FTY Day 1 pre-dose value will be used as FTY baseline. If unavailable, the last available (including unscheduled) value before the first dose will be used. Missing Day 2 pre-dose values are not imputed. Day 2 assessments are only collected in subjects that meet Day 1 protocol monitoring guidelines.

For ECG, the FTY Day 1 pre-dose value will be used as FTY baseline. If unavailable, the last available (including unscheduled) value before the first dose will be used. Missing Day 2 pre-dose values are not imputed. Day 2 assessments are only collected in subjects that meet Day 1 protocol monitoring guidelines.

2.1.2.1.1 Time points for first dose monitoring ECG and Vital signs

The first dose monitoring for Gilenya treatment will be analyzed.

The vital sign values at specified hours as recorded in the database will be used. For the second dose vital signs, data will be summarized similarly.

2.1.2.2 Visit windows after study drug discontinuation

For summaries of data collected after study drug discontinuation, data from both treatment period and safety follow-up period will be considered. All reporting will be done based on visit windows defined relative to the last administration of study drug.

The visit window definitions are provided in Table 2-7 where the Start day and End day are relative to the date of last administration of study drug. For the "Last assessment on drug", the last assessment with non-missing value taken before or on the date of last administration of study drug will be summarized (no visit window applies). For the "Month 3 after LDD (last dose date)" visit-window, assessments taken at least 1 day after but no more than 135 days after the date of last administration of study drug will be considered. LDD stands for last dose date and will be footnoted in applicable outputs.

Table 2-7 Visit-windows after study drug discontinuation

Visit-window	Start day	Target Day	End day
Last assessment on drug	NA	NA	NA (see above or section 2.1.1)
Month 3 after LDD	2	90	135
Month 6 after LDD	136	180	225
Month 9 after LDD	226	270	315
Month 12 after LDD	316	360	405
Month 15 after LDD	406	450	495
Month 18 after LDD	496	540	585
Month 21 after LDD	586	630	675
Month 24 after LDD	676	720	765
Month 27 after LDD	766	810	855

2.1.2.3 Multiple assessments within visit windows

It is possible that multiple assessments of a subject fall into the same visit-window (e.g. due to unscheduled visits). All results (scheduled and unscheduled) will be displayed in listings, but only one value (observed or derived) will be selected for summary statistics by visit-window. If multiple unscheduled visits within visit window are allocated to the same missed scheduled visit:

For **quantitative variables,** the unscheduled assessment closest to the target day will be selected. If more than one assessment is at the same distance to the target day, the later one will be selected. For tables displaying the worst case scenario, such as notable abnormalities, all assessments within a visit window will be used to identify the worst (e.g. the maximum or the minimum depending on parameter). Where applicable it will be defined for each parameter what the worst case is.

For **qualitative variables**, the worst record is selected; it is noted that in the relevant data subsection, worst case is always well defined.

Note that "Last assessment on study drug" is not like other visit-windows where multiple assessments could occur. The assessment to be summarized at that time point is the last on drug observation which is the last observation a subject has while he or she is on fingolimod. Therefore, the above multiple assessment rules do not apply.

In addition, the multiple assessment rules do not apply to the first dose/second dose / restart dose (if applicable) monitoring data.

2.2 Analysis sets

Full Analysis Set (FAS): The FAS comprises all subjects who have signed the Informed Consent and who have received at least one dose of study treatment. The FAS will be used for the summary of demography and baseline characteristics as well as for all efficacy analyses.

Safety Set (SAF): The SAF includes all subjects who have signed the Informed Consent and who have received at least one dose of study treatment. The Safety Set is identical to FAS in this study and will be used for all safety analyses in the final analysis.

All screened subjects (SCR): The SCR set comprises all subjects who have signed the Informed Consent and were screened.

2.2.1 Subgroup of interest

Subgroups for efficacy safety analyses:

- Age at baseline (Adult, Child): adult group is defined as subjects who have baseline age ≥18; child group is defined as subjects who have baseline age < 18. This subgroup is defined to assess the efficacy and safety of fingolimod on adult and pediatric subjects separately.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number and percentage of subjects who were screened but did not continue into the Treatment Period will be presented, along with the reason for discontinuation being "Screen Failure". Data collected on the Disposition CRF page will be used to summarize this information. The summary will be on the SCR set.

The number and percentage of subjects who completed the treatment period on treatment or prematurely discontinued the study treatment will be presented, along with the primary reason for discontinuation. Data collected on the Treatment disposition CRF page will be used to summarize this information. The summary will be on the FAS.

The number and percentage of subjects who completed the study (i.e. the Treatment Period) or prematurely discontinued the study prior to the end of the treatment period will be presented, along with the primary reason for discontinuation. Data collected on the Study disposition CRF page will be used to summarize this information. The summary will be on the FAS. Subjects who prematurely discontinue the study treatment will be listed along with the reason for discontinuation.

Protocol deviations will be summarized by deviation categories for the FAS. In addition, protocol deviations that led to exclusion from the analysis set will be listed.

All summaries in this section will be presented by age group and then overall.

2.3.2 Background and demographic characteristics

All analyses in this section will be presented by age group on FAS.

Background characteristics include subject demographic characteristics (sex, race and ethnicity collected on the Demography CRF), age at screening, height, body weight and BMI at baseline.

Age, baseline height, body weight and derived BMI will be presented. These variables will be summarized for the FAS using frequency distributions (for categorical variables) and descriptive statistics of mean, standard deviation, minimum, median and maximum (for continuous variables).

2.3.3 MS baseline disease characteristics

All analyses in this section will be presented by age group on FAS.

MS baseline characteristics, MS disease history and MS medication history will be summarized by age group and then overall for the FAS.

MS baseline characteristics include baseline EDSS and key MRI parameters (e.g. number of Gd-enhancing T1 lesions and T2 lesion volume).

MS disease history includes duration of MS since diagnosis (years), duration of MS since first symptom (years), number of relapses in the last 12 months prior to screening, number of relapses in the 12 to 24 months prior to screening, and time since onset of most recent relapse (months) prior to screening.

Duration of MS since diagnosis (years) will be derived as [(first dose date − MS diagnosis start date + 1) / 365.25]. Duration of MS since first symptom (years) will be derived as [(first dose date − first MS symptom date + 1) / 365.25]. Time since onset of most recent relapse (months) will be derived as [(first dose date − most recent relapse onset date + 1) / (365.25 / 12)]. In these calculations, partial dates (if any) will be imputed according to the rules specified in Section 5.1.4.1.

MS medication history of previous disease-modifying drugs (coded by World Health Organization (WHO) drug dictionary) will be summarized. The number and proportion of treatment-naïve subjects (i.e. subjects who have not been treated with any disease- modifying drug before study enrollment) will also be presented. Approved MS disease-modifying drugs list: interferon beta-1a, interferon beta-1b, peginterferon beta-1a, glatiramer acetate, natalizumab, mitoxantrone hydrochloride, mitoxantrone, dimethyl fumarate, fumaric acid, teriflunomide, fingolimod, daclizumab, siponimod, ozanimod, diroximel fumarate, monomethyl fumarate, cladribine, alemtuzumab, ocrelizumab, ofatumumab, ponesimod, etc.

2.3.4 Medical history

Medical history will be summarized by age group on the FAS (or listed for the Child group if more appropriate). Any condition entered on the Medical History CRF will be coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA) dictionary. The medical history will be summarized by primary system organ class (SOC) and preferred term.

2.4 Treatments (study treatment, concomitant therapies, compliance)

2.4.1 Exposure to study treatment / compliance

The Safety Set will be used for the analyses in this section. Summaries will be presented by age group and then overall.

Duration of exposure to study drug expressed in days is defined as the number of days spent on study treatment. Intermediate treatment interruptions will be subtracted from drug exposure, i.e. the duration of exposure to study treatment (in days) will be calculated as (last dose date − first dose date + 1 − Σ [days with temporary study treatment interruption]), where any day with no drug taken is considered a study treatment interruption.

Exposure to investigational study drug will be summarized with number and percentage of subjects by time category, and with summary statistics of the number of patient years of exposure.

Duration of exposure to study treatment will be summarized descriptively by duration category (i.e. ≥ 1 month, ≥ 2 months, ≥ 3 months, ≥ 6 months, ≥ 9 months, ≥ 12 months, ≥ 15 months, ≥ 18 months, ≥ 21 months). Descriptive statistics of duration in days will also be provided. The number of patient years is calculated as the sum of the duration of exposure for all subjects in the group.

Compliance to the study treatment administration schedule will be calculated as duration of exposure to study treatment in (days) / duration of on-treatment period (as defined in Table 2-1) (in days) × 100%. This rule means that compliance will be measured during the time interval the subject took study treatment, i.e. premature discontinuation from study treatment will not be considered non-compliance. Compliance to study treatment administration will be summarized descriptively on the SAF. In addition, compliance will be summarized with cumulative number and percentage of subjects in each compliance category (i.e. ≥ 20%, ≥ 30%, ≥ 40%, ≥ 50%, ≥ 60%, ≥ 70%, ≥ 80%, ≥ 90%, ≥ 95%, ≥ 98%, = 100%).

2.4.2 Prior, concomitant and post therapies

Analyses described in this section will be performed on the SAF. Summaries will be presented by age group (or listings for the Child group if more appropriate) and then overall.

2.4.2.1 Concomitant medication

Records on the Concomitant Medications CRF page will be coded using the WHO drug dictionary. All medications will be classified as prior, concomitant or post study treatment discontinuation medication as follows:

- Prior medications are defined as drugs taken and stopped prior to first dose of study medication.
- Concomitant medications are defined as drugs taken at least once between the first and last dose of study medication (including those which were started prior to first dose and continued into the treatment period).

- Post-study treatment discontinuation medications are defined as drugs started after the discontinuation of study medication.

Medications will be categorized into one (and only one) of the above classes based on recorded or imputed start and end dates. When incomplete or missing, dates will be imputed according to Novartis standards (details will be given in programming datasets specifications (PDS) document). If both the start date and the end date are completely missing and medication has not been collected on the "Previous MS Disease Modifying Treatment" page, the medication will be classified into concomitant medication category.

Medications in each of these three categories will be summarized by Anatomical Therapeutic Chemical (ATC) code and preferred term (and/or listed, if appropriate). ATC level 1 and level 3 (e.g. M [Musculo-skeletal system], M01A [anti-inflammatory and anti-rheumatic products, non-steroids], etc.) will be used.

Data collected from the Previous MS disease modifying treatment pages will not be included in this summary.

2.4.2.2 Surgical and medical procedures

Records on the Prior or Concomitant non-drug therapies/procedures CRF page will be coded using the MedDRA dictionary. All procedures will be classified as prior, concomitant or post-study treatment discontinuation procedure, in the same way as done for concomitant medications. Surgical and medical procedures in each of these three categories will be summarized separately by system organ class and preferred term (and/or listed, if appropriate).

Imputation rules for start and end dates will be the same as for the concomitant medications.

2.5 Analysis of the primary objective

All analyses for primary objective will be conducted using the FAS.

2.5.1 Primary endpoint

Two variables are required for the calculation of the ARR (excluding covariates):

- The cumulative number of confirmed MS relapses by subject is the response variable in the negative binomial model. All confirmed relapses with a start date on or after the date of first administration of study drug and prior to or on the end of treatment period date will be included in the analysis. Additional details are provided in Section 5.1.4.
    - The definition of a confirmed MS relapse is one accompanied by a clinically relevant change in the EDSS assessment, i.e. an increase of at least 0.5 points on the EDSS (total) score, or an increase of at least 1 point on at least two Functional scores (FSs), or an increase of at least 2 points on at least one FS, excluding changes involving bowel/bladder or cerebral FS, compared to the last EDSS assessment taken in the absence of (confirmed or unconfirmed) relapse and prior to the current relapse. EDSS obtained on the date as indicated on the Summary of MS Relapse eCRF page will be used. If such EDSS assessment is missing or not meeting the criteria to confirm the relapse, all other EDSS assessments taken within 30 days from the relapse start date (i.e. EDSS assessment date – relapse start date <=30) and before the relapse end date

(EDSS assessment date < relapse end date) will be checked. If at least one of such available EDSS assessments meets the criteria, the relapse is a confirmed relapse. Otherwise, the relapse is considered an unconfirmed relapse.

- The time in study by subject will be used as an offset variable to adjust for the various length subjects have been observed (due to premature study discontinuation) and at-risk of a confirmed MS relapse in the study. Time in study for ARR will be calculated as (end of treatment period date – first dose date+1)/365.25.

2.5.2 Statistical hypothesis, model, and method of analysis

In the primary analysis, the ARR will be estimated by a negative binomial regression model with log-link function, the cumulative number of confirmed MS relapses per subject as the response variable, number of relapses in the previous two years before enrollment and baseline EDSS as continuous covariates. Natural log of time on study in years will be used as the offset variable to account for the varying lengths of subjects' time in the study. The adjusted ARR (i.e. model-based estimate adjusted for covariates) and the corresponding 95% confidence interval will be obtained.

In case of non-convergence, continuous covariates may be removed from the regression model in the order of: baseline EDSS, number of relapses in the previous two years.

The primary analysis will only be performed for the Adult group.

2.5.3 Handling of missing values/censoring/discontinuations

According to the protocol, subjects who discontinue study treatment should remain in the study and follow the assessment schedule. The primary analysis will use all available data up to the end of treatment period date, irrespective of on or off study treatment.

For subjects who early withdraw from the study, the number of relapses up to the study discontinuation will be used for the primary analysis. No imputation will be applied to the incomplete study duration.

The primary negative binomial regression model with an offset for the time in study adjusts for missing information (drop-out) under the assumption of non-informative drop-out, information is missing at random, and constant relapse rate over time.

2.5.4 Supportive analyses

The primary analysis will be repeated to analyze all reported MS relapses (confirmed and unconfirmed) for Adult group.

ARR time-based and ARR patient-based by age group will be provided for confirmed relapses and then for all relapses (confirmed and unconfirmed). ARRs using a "time-based approach" are calculated by taking the total number of relapses observed for all subjects within an age group divided by the total number of days in study of all subjects within the group and multiplied by 365.25 days. "Patient-based approach" is calculated in the way where individual ARRs are computed and summarized over subjects within an age group.

Listings of relapses along with their confirmation status (confirmed or unconfirmed) will be presented by age group.

2.6 Analysis of the key secondary objective

Not applicable as there is no key secondary objective in this study.

2.7 Analysis of secondary efficacy objective(s)

All analyses for secondary efficacy objectives will be conducted using the FAS.

For MRI parameters, only assessments taken within 30 days from the last dose date will be included in the analysis.

2.7.1 Secondary endpoints

Secondary efficacy endpoints include:

- To estimate annualized rate of new or newly enlarged T2 lesions, below variables will be derived:
  - The total number of new or newly enlarged T2 lesions within 30 days from the last dose date will be derived by taking the sum of number of new or newly enlarged T2 lesions from all scheduled MRI scans (as compared to the previous scan) with a non-missing value within 30 days from the last dose date.
  - The time (in years) from screening scan will be calculated as (date of last scheduled MRI scan with a non-missing value for the number of new or enlarging T2 lesions within 30 days from the last dose date – date of screening scan +1)/365.25.
- Volume of T2 lesions.
- To estimate the number of Gd-enhancing T1 lesions per scan, below variables will be derived:
  - The total number of Gd-enhancing T1 lesions within 30 days from the last dose date will be derived by taking the sum of number of Gd-enhancing T1 lesions from the all scheduled MRI scan with a non-missing value within 30 days from the last dose date. Any Gd-enhanced T1 data obtained less than 30 days after the termination of steroid therapy which is used to treat MS relapses will not be included in analysis of Gd-enhancing T1 lesion related endpoint.
  - The number of MRI scans will be derived by counting the number of scheduled MRI scans with non-missing values for the number of Gd-enhancing T1 lesions within 30 days from the last dose date (i.e. the number of scans contributed to the derivation of the above variable: the total number of Gd-enhancing T1 lesions within 30 days from the last dose date).
- Volume of Gd-enhancing T1 lesions.
- Number of T1 hypo-intense lesions.
- Volume of T1 hypo-intense lesions.

Change and % change in volume of T2 lesions, Gd-enhancing T1 lesions and T1 hypo-intense lesions from baseline will only be defined for subjects with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline value – baseline value;

% change from baseline = change from baseline / baseline value*100.

2.7.2 Statistical hypothesis, model, and method of analysis

Methods of analyses for efficacy endpoints defined in Section 2.7.1 are described below.

- The annualized rate of new or newly enlarged T2 lesions for Adult group will be estimated by a negative binomial regression model with log-link function, the total number of new or newly enlarged T2 lesions within 30 days from the last dose date (per subject) as the response variable. Natural log of time from screening scan in years will be used as the offset. The model will include baseline age and baseline volume of T2 lesions as continuous covariates. The estimated number of new or newly enlarged T2 lesions will be obtained together with the corresponding 95% confidence interval.

  Supportive analyses: similar analyses may also be conducted to obtain the estimated annualized rate of new or newly enlarged T2 lesions at month 0 to month 12 and at month 12 to month 24 for Adult group.

  Descriptive summary statistics (mean, median, standard deviation, min, max) for the number of new or newly enlarged T2 lesions will be provided by age group and by visit. Number and percentage of subjects free of new or newly enlarged T2 lesions will also be provided by age group.
- The number of Gd-enhancing T1 lesions per scan for Adult group will be estimated by a negative binomial regression model with log-link function, the total number of Gd-enhancing T1 lesions within 30 days from the last dose date (per subject) as the response variable. Natural log of the number of MRI scans will be used as the offset. The model will include baseline age and number of Gd-enhancing T1 lesions at baseline as continuous covariates. The estimated number of Gd-enhancing T1 lesions per scan will be obtained together with the corresponding 95% confidence interval.

  Supportive analyses: descriptive summary statistics (mean, median, standard deviation, min, max) for the number of Gd-enhancing T1 lesions will be provided by age group and by visit. Number and percentage of subjects free of Gd-enhancing T1 lesions will also be provided by age group.
- Descriptive summary statistics (mean, median, standard deviation, min, max) will be provided by age group and by visit for the following: volume of T2 lesions, volume of Gd-enhancing T1 lesions, number of T1 hypo-intense lesions, volume of T1 hypo-intense lesions, change and % change in volume of T2 lesions, Gd-enhancing T1 lesions and T1 hypo-intense lesions from baseline.

2.7.3 Handling of missing values/censoring/discontinuations

As a general rule, missing data will not be imputed in any secondary endpoint analyses. For MRI parameters, only assessments taken within 30 days from the last dose date will be included in the analysis.

2.8 Safety analyses

All safety analyses will be conducted using the SAF. The safety cutoff is defined as 45 days (5 times the half-life of fingolimod, 9 days) after the last dose administration of study drug. Unless

explicitly otherwise stated, only data up to and including the safety cut-off will be included in the analysis and data beyond this time point for a given subject will be excluded from the safety analysis.

The assessment of safety will be primarily based on the frequency of adverse events (including death and non-fatal serious adverse events). Additional safety assessments include laboratory tests, vital sign measures, ECG evaluations, ophthalmic and dermatology. Clinically significant findings in these additional safety assessments and other will be reported as adverse events and analyzed as such.

2.8.1 Adverse events (AEs)

An adverse event (AE) is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation subject after providing written informed consent for participation in the study. That means that a subject can report AEs before having started study medication. For reporting purposes, the main focus will be on treatment emergent adverse event (TEAE), defined as any AE which started on or after the day of first dose of study medication or events present prior to the start of treatment but increased in severity based on preferred term.

Except for serious TEAEs and deaths, only TEAEs up to and including the safety cut-off will be included in the analyses. All serious TEAEs and deaths will be included, regardless of the safety cut-off.

TEAEs will be reported by primary system organ class (SOC) and preferred term (PT) according to the most recent Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA version used for reporting the study will be specified in a footnote of the tables, figures or listings (TFLs).

Overview of TEAE will be provided. The number and percentage of subjects reporting any TEAEs (referred to as incidence of any TEAEs in the following) will be summarized by age group, primary SOC and preferred term. Separate summaries will be provided for serious TEAEs, drug related TEAEs, TEAEs leading to permanent discontinuation of study treatment, TEAEs causing study treatment interruption, and most common TEAEs (≥10% in any of the age groups), which could be replaced by listings (for Child or even for both Adult and Child) if more appropriate. Additionally, the incidence of any TEAEs will also be summarized by age group, primary SOC, preferred term, and maximum severity (Mild, Moderate and Severe). Missing severity will not be imputed.

If a subject reported more than one AE within the same primary SOC, the subject will be counted only once with the maximum severity at the SOCs level, where applicable.

All AEs will be presented in listings.

2.8.1.1 Adverse events of special interest / grouping of AEs

Selected tables will be produced for Adverse Events of Special Interest (AESI) (i.e. risks), which will be defined in the electronic case retrieval sheet (eCRS) at the time of analysis implementation (i.e. study DBL). Specifically, incidence of TEAEs that fulfill the risk search terms as defined in eCRS will be summarized by age group, risk name and preferred term.

Similarly, separate summaries will be provided for serious TEAEs that fulfill the risk search terms as defined in the eCRS (could be replaced by listing for Child if more appropriate). Additionally, incidence of any TEAEs that fulfill the search terms as defined in the eCRS will also be summarized by age group, risk name, preferred term and maximum severity.

2.8.2 Deaths

Detailed listing for deaths will also be provided. All deaths as recorded in the final database (i.e. up to DBL) will be included.

2.8.3 Laboratory data

The summary of laboratory evaluations will be presented for two groups of laboratory tests: Hematology and Chemistry. On presenting summary statistics, laboratory data will be grouped and displayed in an alphabetical order within the Hematology and Chemistry groups and subgroups.

Descriptive summary statistics (mean, median, standard deviation, Min and Max) of the change from baseline in the laboratory result to each study visit-window by age group will be presented. Change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline value − baseline value

For continuous variables databased as <lower limit, these will be imputed as being half of the lower limit.

The number and percentage of subjects with notable laboratory abnormalities (as defined in Table 2-8 below) at any time post baseline will be presented by age group (or listing for the Child group if more appropriate). Frequency (%) distribution of key hematological parameters (absolute lymphocytes, absolute neutrophils, leukocytes, and platelet count), with categories defined by either upper limit of normal (ULN), actual values, or a ratio of actual value, will be presented by age group (or listing for the Child group if more appropriate).

Table 2-8 Criteria for notable laboratory abnormalities

Notable Values		
Laboratory Variable	**Standard Units**	**SI Units**
Serum glutamic oxaloacetic transaminase (SGOT) (AST)	>82 U/L	>82 U/L
Serum glutamic pyruvic transaminase (SGPT) (ALT)	>90 U/L	>90 U/L
Total bilirubin	≥ 2.0 mg/dL	≥ 34.2 µmol/L
RENAL FUNCTION / METABOLIC VARIABLES		
Creatinine	≥2.0 mg/dL	≥176 umol/L
Total cholesterol	≥ 240 mg/dL	≥ 6.21 mmol/L
Triglycerides	≥ 300 mg/dL	≥ 3.39 mmol/L
HEMATOLOGY VARIABLES		
Hemoglobin	≤ 10.0 g/dL	≤ 100g/L
Platelets (Thrombocytes)	≤ 100 k/mm^3	≤ 100 x 10^9/L
	≥ 600 k/mm^3	≥ 600 x 10^9/L

Leukocytes (WBCs)	≤ 2.0 k/mm^3	≤ 2.0 x 10^9/L
	≥ 15 k/mm^3	≥ 15x 10^9/L
HEMATOLOGY VARIABLES: DIFFERENTIAL		
Neutrophils(absolute)	≤ 1,000/mm^3	≤ 1 x 10^9/L
	≥12000/mm^3	≥ 12 x 10^9/L
Lymphocytes(absolute)	<200/mm^3	<0.2 x 10^9/L
	≥8000/mm^3	≥8 x 10^9/L
Red blood cells (RBCs)	<3,300,000/mm^3	<3.3 x 10^{12}/L
	>6,800,000/mm^3	>6.8 x 10^{12}/L
RBC and Triglycerides are not collected on the “Hematology - Local Lab Results” page.		

Number of subjects with newly occurring liver enzymes abnormalities at any time post-baseline will be summarized. Newly occurring liver enzymes abnormalities are defined in the table below.

Table 2-9 Criteria for newly occurring liver enzymes abnormalities

Laboratory Variable (unit)	**Criteria**
SGOT (AST) (U/L)	>ULN >=2xULN >=3xULN >=5xULN >=10xULN >=20xULN
SGPT (ALT) (U/L)	>ULN >=2xULN >=3xULN >=5xULN >=10xULN >=20xULN
Bilirubin (total) (umol/L))	>ULN >=2xULN >=34.2 umol/L
ULN=upper limit of normal; normal range in the local laboratory of each site will be applied to subjects in that site. The results are presented in cumulative form, i.e. the highest actual laboratory value/upper limit value was used. If the value is >= 20 x ULN, it is also included in the >= 10 x ULN category and all the above categories.	

For the patients who missed the visits, but took off-site laboratory evaluations due to COVID19 (lockdown, site issue, subject concern or other), the off-site laboratory data will be included to analyze. The sensitivity analysis will be conducted to assess laboratory data (WBC, neutrophils, lymphocytes, ALT, AST, total bilirubin and platelets), with the only change to exclude off-site laboratory data. For this sensitivity analysis, summary of patients with clinically notable laboratory abnormalities by age group and summary of patients meeting potentially clinically significant criteria based on laboratory data will be presented.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

ECG data will be collected at selected scheduled visits as specified in [Protocol Table 8-1]. Clinically significant findings from ECG evaluations will be reported as AEs and included in the analysis of AEs. ECG parameters include mean heart rate, mean PR interval, mean uncorrected QT interval, mean QRS duration, and QT corrected using Fridericia's correction formula (all as collected on the ECG CRF). Descriptive statistics of each ECG parameter will be provided for each baseline and post-baseline visit-window by age group. Similar summaries will also be provided for change from baseline ECG parameters for each post-baseline visit-window. Criteria in corrected QT interval as defined in Table 2-10 will be provided for each criterion by age group (or listing for the Child group if more appropriate).

Table 2-10 Abnormality criteria for corrected QT interval

	Male subjects	Female subjects
1	>450 msec	>470 msec
2	>500 msec	> 520 msec
3	30 - 60 msec increase from Baseline	
4	>60 msec increase from Baseline	

For first dose administration monitoring, ECG parameters and change from pre-dose in ECG parameters by timepoint during 1st and 2nd dose (if necessary) administration will be summarized by age group. The number and percentage of subjects meeting the criteria in corrected QT interval (at any timepoint post-dose during 1st and 2nd dose (if necessary) administration) will be presented by age group (or listing for the Child group if more appropriate).

For non by-visit summaries, visits defined by visit-windows will not be used. All available data from scheduled and unscheduled visits will be considered.

For the patients who missed the visits, but took off-site ECG evaluations due to COVID19 (lockdown, site issue, subject concern or other), the off-site ECG data will be included to analyze. The sensitivity analysis will be conducted to assess ECG data, with the only change to exclude off-site ECG data. For this sensitivity analysis, number and percentage of patients meeting the criteria in corrected QT interval and the corrected QT interval criteria (at any timepoint post-dose during first/second dose administration) by age group will be presented.

2.8.4.2 Vital signs

Vital sign measurements include sitting systolic and diastolic blood pressures, sitting pulse, body temperature, height and body weight.

Three sitting measurements of blood pressure (SBP and DBP) and pulse will be taken at each vital sign assessment.

For post-baseline assessments, the blood pressure and pulse values will be the average of the non-missing values of the 3 measurements. If more than one blood pressure/pulse assessment (scheduled or unscheduled) exists in a particular visit-window (as defined in Section 2.1.2.1),

derivation should follow the rules as defined in Section 2.1.2.3. Derivation of baselines for blood pressure and pulse are provided in Section 2.1.1.

Height will be collected at screening visit only and will only be summarized as demographics.

Analyses of vital sign measurements (excluding data collected on Day 1 protocol scheduled visit) using descriptive summary statistics (mean, median, standard deviation, min, max) for the change from baseline for each post-baseline visit-window will be performed. These descriptive summaries will be presented by vital sign parameter and age group. Change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline value − baseline value

The number and percentage of subjects with clinically notable vital signs (at any time post-baseline) will be presented by age group Listings of clinical notable vital signs during treatment period will be presented by age group.

Clinical notable vital signs values are defined in the table below.

Table 2-11 Vital signs clinically notable values

NOTABLE VITAL SIGNS AND BODY WEIGHT		
Vital Sign Variable	Age	**Notable Criteria**
Heart Rate (bpm)	< 12 years	>130bpm or Increase of ≥ 15bpm from baseline Or < 70bpm or Decrease of ≥ 15bpm from baseline
	≥ 12 years	>120bpm or Increase of ≥ 15bpm from baseline Or < 50bpm or Decrease of ≥ 15bpm from baseline
Systolic BP (mmHg)	< 12 years	≥ 125 mmHg or Increase of ≥ 20mmHg from baseline Or ≤ 70 mmHg or Decrease of ≥ 20mmHg from baseline
	≥ 12 to < 18 years	≥ 160 mmHg or Increase of ≥ 20mmHg from baseline Or ≤ 90 mmHg or Decrease of ≥ 20mmHg from baseline
	≥ 18 years	≥ 180 mmHg or Increase of ≥ 20mmHg from baseline Or ≤ 90 mmHg or Decrease of ≥ 20mmHg from baseline
Diastolic BP (mmHg)	< 12 years	≥ 85 mmHg or Increase of ≥ 15mmHg from baseline Or ≤ 50 mmHg or Decrease of ≥ 15mmHg from baseline
	≥ 12 to < 18 years	≥ 95 mmHg or Increase of ≥ 15mmHg from baseline Or ≤ 50 mmHg or Decrease of ≥ 15mmHg from baseline
	≥ 18 years	≥ 105 mmHg or Increase of ≥ 15mmHg from baseline Or ≤ 50 mmHg or Decrease of ≥ 15mmHg from baseline
Temperature (°C)	All	>38.3 °C/ 101°F
Body weight (kg)	All	± 7% from baseline weight

For first dose administration monitoring, pulse, sitting systolic, diastolic blood pressures and their change from pre-dose will be summarized by timepoint and age group during 1st and 2nd dose (if necessary) administration. Boxplots on these three parameters will also be provided as graphical presentation. The number and percentage of subjects with clinically notable values for these three parameters (at any timepoint post-dose during 1st and 2nd dose (if necessary) administration) will also be presented by age group (or listing for the Child group if more appropriate).

For the patients who missed the visits, but took off-site vital sign measurements due to COVID19 (lockdown, site issue, subject concern or other), the off-site vital sign data will be included to analyze. The sensitivity analysis will be conducted to assess vital sign data (heart rate, SBP and DBP), with the only change to exclude off-site vital sign data. For this sensitivity analysis, number and percentage of patients with clinically notable vital sign abnormalities and patients with clinically notable vital sign values at any timepoint post-dose during first/second dose administration by age group will be presented.

2.8.4.3 Ophthalmic evaluations

If any subject reports a TEAE of macular edema (occurs after first dose and before safety cutoff), a listing with assessments of optical coherence tomography (OCT) at the time of screening, diagnosis and resolution (if resolved) will be provided. This listing can be omitted if no such subject in the study.

2.8.4.4 Dermatology evaluations

If any subject reports a TEAE of skin lesions (occurs after first dose and before safety cutoff), a listing with skin lesions will be provided. This listing can be omitted if no such subject in the study.

2.8.5 First dose (second dose/restart dose) monitoring

Any cases where restarting first dose monitoring after study drug interruption was required but was not performed will be reported as a PD.

2.8.5.1 Vital signs

Hourly vital signs including pulse, SBP and DBP are collected for the first dose, second dose (if necessary), and restarting of dose after interruption (if applicable).

2.8.5.2 ECG

ECG will be performed at pre-dose, 6 hours post dose, and >6 hours post dose during the first dose, second dose (if necessary), and restarting of dose after interruption (if applicable).

2.8.5.3 Dose monitoring experience

The first dose/second dose (if necessary) /restart dose (if applicable) monitoring experience refers to the information collected on the dose administration monitoring eCRFs (e.g. whether subjects are discharged after 6 hours post-dose or extended monitoring is required after 6 hours

post-dose, whether subjects are hospitalized, whether subjects discontinue the study drug permanently, and whether SAE is reported, etc.).

All data with yes/no responses will be summarized.

2.8.5.4 Data summaries

Summaries on the FTY SAF set by treatment group include:

- Frequency (%) distribution of categorized sitting pulse or change (or percent change) from pre-dose sitting pulse during first dose administration (note that categories are given in table shells)
- Summary of the overall dose monitoring experience (1st dose, 2nd dose (if necessary), and restart dose (if applicable))
- Incidence of notable vital sign abnormalities based on the notable criteria in Table 2-8 (1st dose and 2nd dose (if necessary))
- Summary statistics and changes from pre-dose in ECG parameters by time point during 1st and 2nd dose (if necessary) administration
- Incidence of abnormal QTc interval as defined by the abnormality criteria in Table 2-10 during 1st and 2nd dose (if necessary) administration

2.8.6 Safety evaluation after last administration of study treatment

The SAF will be used for analyses in this section.

Safety data collected after last administration of study treatment includes adverse events, vital signs, routine laboratory parameters and ECG. No safety cutoff date will be applied in the analyses defined in this section. Safety data within the safety cutoff date but after last administration of study treatment will also be included. Only subjects who prematurely discontinue the study treatment will be included.

The number and percentage of subjects with at least one TEAEs that started after the date of last administration of study treatment will be reported by SOC, preferred term, and age group. The subset of subjects in the SAF who had data reported after the date of last administration of study treatment will be included in the analysis and the number of subjects in this subset will be the denominator in calculating the percentage.

Summary statistics for vital signs measurements and changes from baseline. These descriptive summaries will be presented by vital sign parameter, treatment group and visit-window.

Summary statistics for each ECG parameter and change from baseline. These descriptive summaries will be presented by vital sign parameter, treatment group and visit-window.

In addition, subjects with notable lab abnormalities or clinically notable vital signs will be listed.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

2.12 Biomarkers

Not applicable.

[redacted]

[redacted]

- [redacted]

[redacted]

Analysis sets:

Full Analysis Set (FAS): around fifty subjects (including early withdrawn subjects) who had signed the Informed Consent and who had received approximately one year of study treatment. The FAS will be used for the summary of demography and baseline characteristics as well as for all efficacy analyses.

Safety Set (SAF): all subjects who had signed the Informed Consent and who had received at least one dose of study treatment. The SAF will be used for the summary of demography and baseline characteristics as well as for all safety analyses.

All screened subjects (SCR): all subjects who had signed the Informed Consent and were screened.

[redacted]

3 Sample size calculation

3.1 Primary endpoint(s)

The assumption of true ARR is based on previous studies of fingolimod and literature review (see Table 3-1). ARR ranged from 0.16 to 0.21 in non-Chinese populations from three controlled studies for fingolimod 0.5 mg (FREEDOMS, FREEDOMS II, TRANSFORMS). The similar ARR was reported in Chinese population treated by teriflunomide 14 mg (ARR = 0.18, TOWER). Two observational studies reported ARR at 0.38 in Chinese population treated by interferon-β 250 μg, and ARR at 0.21 in non-Chinese population treated by teriflunomide 14 mg (Teri-RADAR). The ARR reported in Chinese population from placebo group was 0.63 (TOWER). The true ARR is assumed ranging from 0.20 to 0.38 for this Chinese interventional study.

Table 3-1 ARR data on RRMS from historical studies

Study/Reference	Study Population	ARR (FTY 0.5 mg)	ARR (placebo)	ARR (Interferon-β 250 µg)	ARR (Teriflunomide 14 mg)
Interventional studies					
FREEDOMS (non-Chinese)	RRMS	0.18 (0.15, 0.22)	0.40 (0.34, 0.47)	NA	NA
FREEDOMS II (non-Chinese)	RRMS	0.21 (0.17, 0.25)	0.40 (0.34, 0.48)	NA	NA
TRANSFORMS (non-Chinese)	RRMS	0.16 (0.12, 0.21)	NA	0.33 (0.26, 0.42)	NA
TOWER, NCT00751881 (Chinese)	RRMS	NA	0.63 (0.44, 0.92)	NA	0.18 (0.09, 0.36)
Observational studies					
NCT00370071, 2006 (Chinese)	RRMS	NA	NA	0.38 (-,-)	NA
Teri-RADAR, 2019 (non-Chinese)	RRMS	NA	NA	NA	0.21 (0.11, 0.39)

Assume ARR follows negative binomial distribution (~ NB(μ, k)). The dispersion parameter k is set as 1 based on the historical data. The 95% upper limit and lower limit of estimated ARR are calculated by normal approximation approach for sample size estimation. Assuming ARR at 0.25, sample size of 80 subjects will serve the 95% probability for estimated ARR within [0.13 to 0.37], which will be lower than the ARR observed in Chinese population treated by interferon-β 250 µg. Assuming ARR at 0.38, sample size of 80 is expected to show a lower ARR than placebo, with 95% probability within [0.22, 0.54]. So the sample size of 80 subjects is considered. Considering 20% drop-out rate, the total sample size will be around 100 subjects.

Sample size calculation was performed in nQuery.

4 Change to protocol specified analyses

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Missing or partial dates are not allowed in completing the study treatment CRF pages. The end date of study treatment will be the last end date.

5.1.2 AE date imputation

Incomplete or missing start and end dates of AE records will be imputed according to Novartis standards (details will be given in programming data sets specifications (PDS) document).

5.1.3 Concomitant medication date imputation

Incomplete or missing start and end dates of concomitant medication records will be imputed according to Novartis standards (details will be given in programming data sets specifications (PDS) document

5.1.3.1 Prior therapies date imputation

Same handling as for concomitant medications.

5.1.3.2 Post therapies date imputation

Same handling as for concomitant medications.

5.1.4 Other imputations

5.1.4.1 MS disease baseline characteristics

For the calculation of duration or time since relevant history events (MS disease baseline characteristics), partial dates will be imputed for the MS diagnosis start date, the first MS symptom date, and the most recent relapse onset date via below imputation rules:

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

- If the year and the month are not missing and possible, but the day is impossible or missing (e.g. 31-FEB-2009), then the year and month will be kept, and date will be imputed as 15th (e.g. 15-FEB-2009).
- The imputed dates should be prior to the screening visit date. That is, if imputed dates are on or after the screening visit date, the dates will be imputed to be one day before the screening visit date.
- To guarantee the first MS symptom date is earlier than the MS diagnosis start date, and most recent relapse onset date is not earlier than the first MS symptom date after the imputation. If, after imputation, MS diagnosis date is before first MS symptom date, then the imputed first MS symptom date will be set to MS diagnosis date; or if, after imputation, most recent relapse onset date is before the first MS symptom date, then the imputed relapsed onset date should be set to the first MS symptom date.

5.1.4.2 Relapse date imputation

Missing or partial dates are not expected for the start and end dates of relapses on the Summary of MS relapse CRF pages. In case partial dates (unknown day with month and year available) exist in the final database, the following rules will apply:

- The start date will be imputed as the first day of the month or the first dose date if it occurs in the same month as the first dose date.
- The end date will be imputed as the last day of the month or truncated to have a duration of maximally 90 days (whatever comes first).

5.1.4.3 Data handling for relapses within 30 days of onset of previous relapses or relapses with duration beyond 90 days

According to the protocol definition of MS relapses, the start date of a new relapse has to be at least 30 days after the start date of a previous relapse (i.e. start date of a new relapse – start date of a previous relapse ≥ 30). If a relapse is recorded with a start date < 30 days after the start date of a previous relapse, the below data manipulation will be done to combine them into a single relapse by creating a new relapse record with the following information:

- Start date: Take the earliest start date.
- End date: Take the latest end date. If one of the end dates is missing, set it to missing.
- Date of EDSS intended to confirm the relapse:
  - Take the date of EDSS by which the relapse can be confirmed.
  - If more than one EDSS assessments meet the above criterion, take the date of the EDSS from which the worst severity value is derived.
  - If no EDSS assessment meets the above criterion, take the earliest date of EDSS as captured on the Summary of MS Relapse CRF page.
- Severity: Take the value representing the worst case (severe > moderate > mild > missing) (as specified in Table 5-1)
- "Did the relapse affect daily activities?", "Hospitalization?", "Steroid used?", "Recovery status": For each of these characteristics, take the value representing the worst case (yes > no for the first 3 questions; no > partial > complete recovery for the last question).

Table 5-1 Severity of MS relapses

Mild relapse	Moderate relapse	Severe relapse
EDSS increase of 0.5 point	EDSS increase of 1 or 2 points	Exceeding moderate criteria
or	or	Or
1-point FS change in one to three systems	2-point FS change in one or two systems	Exceeding moderate criteria
	or	Or
	1-point change in four or more systems	Exceeding moderate criteria
Definition is based on the EDSS obtained to confirm the relapse as compared to the last EDSS (scheduled or unscheduled) taken in the absence of (confirmed or unconfirmed) relapse and prior to the current relapse. EDSS refers to total score; FS refers to functional score; all of the 7 functional scores are considered in this derivation.		

According to the protocol definition of MS relapses, the maximum duration of a relapse is furthermore limited to 90 days. If a relapse is recorded with a duration longer than 90 days, the end date will be truncated to have a duration of exactly 90 days. This applies also to the artificial records created by the above procedure. Missing end date of relapse is not allowed. In the rare cases that missing end date exists in the final database, it will be imputed so that the duration of relapse is exactly 90 days.

5.2 AEs coding/grading

AEs are coded using the Medical dictionary for regulatory activities (MedDRA) terminology. The latest MedDRA version will be used and will be described in the footnote of relevant outputs.

5.3 Laboratory parameters derivations

For each subject, the estimated creatinine clearance values (without collecting urine) will be calculated using the Cockcroft-Gault formula (as specified in Table 5-2). In these calculations, the body weight is the last measurement collected on or before the day when the subject takes the laboratory test and age should also be calculated based on the time when the subject takes the laboratory test.

If the creatinine value is collected in the unit *µmol/L* (SI unit), it will be converted to *mg/dL* in order to use the formulas. The conversion is via the equation below:

- mg/dL = 88.4 µmol/L (e.g. creatinine = 2.0 mg/dL = 176.8 µmol/L).

Table 5-2 Creatinine clearance calculation

Variable	Formula
Creatinine clearance [mL/min] using Cockcroft-Gault formula (Cockcroft and Gault 1976)	$= (140 - A) \times W / (72 \times C) \times G$ Where A is age [years] W is body weight [kg] C is the serum concentration of creatinine [mg/dL] G is a constant: G=1 for males and G=0.85 for females.

The estimated creatinine clearance will be included as one of the laboratory parameters.

5.4 Statistical models

5.4.1 Primary analysis

The SAS procedure GENMOD will be used to conduct the analysis on the negative binomial regression model. In GENMOD, the log of the dispersion parameter will be used (lognb) as an option in model statement. The natural log of time in year is used as an offset by specifying offset option in the model statement.

5.4.2 Key secondary analysis

Not applicable as there is no key secondary objective in this study.

5.5 Rule of exclusion criteria of analysis sets

Subject classification in the analysis sets is entirely based on protocol deviation and non-protocol deviation criteria. Details are provided in Table 5-3 and Table 5-4.

Table 5-3 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analysis sets
INCL01	Written informed consent was never obtained	Excluded from all analysis sets

Table 5-4 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
FAS	INCL01	No study treatment taken
SAF	INCL01	No study treatment taken

6 Reference

Cockcroft DW, Gault MJ (1976) Prediction of creatinine clearance from serum creatinine. Nephron; 16:31-41.

Panitch H, Goodin DS, Francis G, et al (2002) Randomized, comparative study of interferon beta-1a treatment regimens in MS. The EVIDENCE trial. Neurology. 2002;59:1496-506.