NOVARTIS

Clinical Development

CFTY720 / Fingolimod / Gilenya®

CFTY720DDE15TS (PASSOS) / NCT01705236

A 3-year multi-center study to describe the long term changes of optical coherence tomography (OCT) parameters in patients under treatment with Gilenya®

Statistical Analysis Plan (SAP)

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Document type: SAP Documentation

Document status: Final 1.0

Release date: 26-MRZ-2019

Number of pages: 17

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
29-Jan-2019	Prior to DB lock	Creation of first draft version	N/A - First version	NA
18-MRZ-2019	Prior to DB lock	After review by Novartis	Biomarkers are no longer applicable Relative change defined as M36/Baseline Normality investigated graphically not by Shapiro-Wilk test	several
26-MRZ-2019	Prior to DB lock	Finalization	Version change from draft to final 1.0	Version number only

Signature Page

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
CRF	Case report/record form
CSP	Clinical Study Protocol
CSR	Clinical Study report
[redacted]	[redacted]
FAS	Full Analysis Set
MedDRA	Medical Dictionary for Drug Regulatory Affairs
[redacted]	[redacted]
OCT	optic coherence tomography
[redacted]	[redacted]
[redacted]	[redacted]
PPS	Per-Protocol Set
[redacted]	[redacted]
[redacted]	[redacted]
RAP	Report and Analysis Process
RNFL(T)	retinal nerve fiber layer (thickness)
RRMS	relapsing remitting multiple sclerosis
SAF	Safety Set
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SOC	System Organ Class
TFLs	Tables, Figures, Listings
TMV	Total Macular volume

1 Introduction

This statistical analysis plan (SAP) describes the statistical methods for the final analysis of this study. The final statistical analysis serves as basis for the Clinical Study Report (CSR). This SAP displays the analysis of the PASSOS study and has the following reference documents:

- Study Protocol, Version 4.0 (Original protocol incl. Amendment 4), dated 26-JUL-2016

1.1 Study design

This is a multi-center, open-label study in RRMS patients treated with fingolimod. After signing the informed consent, patients will enter a Screening Phase (day -28 to day 0) before starting the study at Baseline (visit 2/day 0), followed by a 36-month longitudinal data collection phase. Visits are performed at month 3 (visit 3), month 6 (visit 4), month 12 (visit 5), month 24 (visit 6), and month 36 (visit 7). Eligibility will be determined at Screening. OCT and other assessments will be performed according to the schedule in Table 7-1 of the Clinical Study Protocol (CSP).

1.2 Study objectives and endpoints

The primary objective is to evaluate the change in average RNFL thickness (RNFLT) in RRMS patients treated with fingolimod over 36 months as assessed by OCT. The average RNFL thickness following OCT assessment will be calculated for the left and right eye per visit and per patient. The following table describe the objectives and endpoints:

	Objective	**Endpoint**
Primary	To evaluate the change in average RNFL thickness (RNFLT) in RRMS patients treated with fingolimod over 36 months as assessed by OCT	Absolute Difference in mean RNFLT from baseline (BL) to M36 (or last values in case of missing data) in the full analysis set (FAS). Mean RNFLT is the average of valid measurements of right and left eye. Sensitivity analyses are performed with the Per-Protocol Set (PPS) and for relative change (M36/BL)
Secondary	To compare changes in OCT parameters between eyes with and without history of optic neuritis	Absolute Difference in RNFLT from baseline (BL) to M36 (or last values in case of missing data) in the full analysis set (FAS) for: - eyes with versus without optic neuritis
Secondary	To evaluate the change in average RNFLT under fingolimod therapy from	Absolute Difference and ratios in average RNFLT from baseline (BL) to M12 respectively M24 (or last values in case of missing data) in the full analysis set (FAS).

	Objective	**Endpoint**
	baseline to months 12 and 24 as assessed by OCT	
Secondary	To evaluate change in quadrant RNFLT under fingolimod therapy from baseline to months 12, 24 and 36	Absolute Difference and ratios in average quadrant RNFLT from baseline (BL) to M12, resp. M24 resp. M36 (or last values in case of missing data) in the full analysis set (FAS). Quadrant RNFLT are: - Nasal-inferior - Nasal-superior - Temporal.inferior - Temporal-superior
Secondary	To evaluate changes in total macular volume (TMV) under fingolimod therapy from baseline to months 12, 24 and 36	Absolute Difference and ratios in average TMV from baseline (BL) to M12, resp. M24 resp. M36 (or last values in case of missing data) in the full analysis set (FAS).
Secondary	To evaluate changes in ganglion cell layer thickness (GCLT) under fingolimod therapy from baseline to months 12, 24 and 36	Absolute Difference and ratios in average GCLT from baseline (BL) to M12, resp. M24 resp. M36 (or last values in case of missing data) in the full analysis set (FAS).
Secondary	To evaluate safety and tolerability of fingolimod in MS patients followed for up to 36 months and specifically to determine the frequency of macular edema under treatment with oral fingolimod in this patient population	Incidence of adverse events, serious adverse events and (S)AEs at least possible related to fingolimod in the Safety Set (SAF) Incidence of macular edema (AE of special interest)
[redacted]		

2 Statistical methods

2.1 Data analysis general information

CRO [redacted] perform the final analysis. The software SAS, version 9.2 is used for analysis. The data base lock is done when all patient data are documented, entered into the clinical database, all data checks are completed, the data from reading center (OCT data) are received/checked and the data review meeting was compled.

Continuous variables are displayed by descriptive sample statistics which include: N, mean, standard deviation, minimum, median and maximum.

Categorical variables are displayed by frequencies and percentages.

No hypothesis is to be tested. Thus, the results – including p-values – have to be interpreted in an exploratory manner.

P-values are not adjusted for multiplicity.

2.1.1 General definitions

The following terms are defined for the rest of the document:

Baseline	Visit 2 at month 0 (labelled V2/M0/BL)

Last value until Visit x	The last (post-baseline) value documented until Visit x, i.e. missing or invalid data are replaced by the last available value. Baseline values are not carried forward.

2.2 Analysis sets

The analysis sets were defined in section 10 of the Clinical Study Protocol (CSP):

The Safety Set (SAF) consists of all patients treated with investigational drug (fingolimod) for whom safety information was collected. Of note, the statement that a patient has had no adverse events also constitutes a safety assessment.

The Full Analysis Set (FAS) consists of all patients treated with investigational drug (fingolimod) for whom data was collected and who have at least one post-baseline efficacy assessment. This is analogous to the ITT population.

The Per Protocol Population consists of all patients from the FAS population, for whom no major protocol violations are reported. All reported protocol violations will be classified as minor or major in a data review meeting prior to data base lock.

2.2.1 Subgroup of interest

No subgroup analyses are performed.

2.3 Patient disposition, demographics and other baseline characteristics

Background and demographic characteristics are presented using summary statistics for SAF, FAS and PPS.

2.3.1 Patient disposition

The disposition of all enrolled patients displays the number and reasons of screening failures.

The disposition of all patients in the treatment period (i.w. who received at least one dose of fingolimod) displays the number and reasons for premature discontinuation from the study.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The total exposure (i.e., last fingolimod administration from study completion CRF – date of V2/D0/BL + 1 day) is displayed by sample statistics. It should be noted that patients are allowed to be pre-treated for 1 to 4 month according to the inclusion criteria. The total drug exposure per 100 subject years is presented also.

The interruption in fingolimod treatment is displayed by incidences, reason, number of interruption and total duration per patient.

2.4.2 Prior, concomitant and post therapies

Prior and concomitant medication is coded by WHO-DD. Frequencies of Anatomic Therapeutical Classes (ATC) and preferred terms within ATCs are displayed. Here, each patient with multiple medications is counted only once in that class.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary endpoint is the change, i.e. difference, in mean RNFLT from baseline to month 36 (or last values in case of missing data) in the full analysis set. Mean RNFLT is the average of valid measurements of the right and left eye.

Sensitivity analyses are performed with the Per-Protocol Set (PPS) and for the relative change assessed by the M36/BL.

2.5.2 Statistical hypothesis, model, and method of analysis

No hypothesis is to be tested.

Descriptive pairwise comparisons are performed using a paired t-test in case of normality, In case of non-normality a Wilcoxon signed-rank test is applied instead. No adjustment for multiple comparisons are made. For each parameter the normality distribution is graphically proved for the change from BL to M36. Differences as well as pre-post ratios are displayed. When non-normality is detected for the change to M36 the changes to M12 respectively M36 are analysed also non-parametrically.

The primary efficacy variable is presented graphically by standard boxplots for each time point. Sample statistics are presented for each time point and changes (differences as well as ratios) to each time point.

2.5.3 Handling of missing values/censoring/discontinuations

Missing values are replaced by the last available value. Post-baseline values are carried forward but no baseline values.

An analysis without replacing the missing data is performed as sensitivity analysis.

2.5.4 Supportive analyses

A comparison for eyes with versus without optic neuritis is done by a mixed model including the subject as random factor. LSMeans for RNFLT in eyes with versus withour optic neuritis are displayed as well as the difference including p-value.

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

The following endpoints are defined as secondary:

- change from baseline to month 36 in quadrant RNTFT, i.e. nasal-superior, nasal-inferior, temporal-superior, and temporal-superior RNFLT

2.7.2 Statistical hypothesis, model, and method of analysis

No hypothesis is to be tested. P-values are displayed as descriptive measures.

Analysis is similar to the primary endpoint. All analyses are done with the FAS only.

Correlations in the change from baseline to month 12, month 24 and month 36 are presented by the Pearson correlation coefficient or Spearman Rank correlation coefficient, depending on distribution of data. Normality was graphically investigated..

Correleations are displayed graphically by scatter plots. Here, only changes from baseline to last value until Month 36 are displayed.

2.7.3 Handling of missing values/censoring/discontinuations

Missing values are replaced by the last available value. According to the definition of FAS (at least one post-baseline value of the primary parameter is required) all patients have a value after baseline.

In contrast to the primary parameter no sensitivity analysis without replacing the missing data is performed.

2.8 Safety analyses

All safety analyses were presented for the SAF population.

2.8.1 Adverse events (AEs)

Adverse events which started before BL/M0 were listed only. Analyses were performed on AEs which started at/after BL/M0.

The incidence of adverse events is displayed with n, percentage and 95% confidence interval for the SAF. Here, different types of AEs are presented:

(1) Any AE

(2) AE with suspected relationship to fingolimod

(3) AE leading to study drug dosage adjustment/temporary interruption

(4) AE leading to permanent study drug discontinuation

(5) Serious adverse event

(6) Non-Serious AE

(7) Death

For AEs of type (1) to (6) a two-level frequency table for MedDRA system organ classes (SOC) and Preferred Terms (PT) within SOC are presented. Here, a patient with multiple occurrences is counted only once on the respective class.

The maximum severity of (several) AEs occurring in a patient ist displayed for PTs within SOCs, SOCs and overall.

For AEs of type (7), (5), and (3) separate listings are generated.

2.8.1.1 Adverse events of special interest / grouping of AEs

Not applicable

2.8.2 Deaths

See above.

2.8.3 Laboratory data

Abnormal laboratory values or test results constituted adverse events only if they induce clinical signs or symptoms, were considered clinically significant, require medication discontinuation or required therapy. Then they should be documented as AEs. Therefore, no separate analysis of laboratory data applies.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Not applicable.

2.8.4.2 Vital signs

Sample statistics of vital signs were presented for V2/BL/M0 as well as the last value until V7/M36 and the change (i.e. difference) between these time points. The average of the three measurements of blood pressure war analysed.

Abnormal values for pulse, diastolic and systolic blood pressure was defined in the study protocol. A shift table for abnormal values at baseline versus post-baseline was presented. For the post-baseline period, an abnormality was counted if it occurred at any visit after V2/BL/M0.

2.9 Pharmacokinetic endpoints

No pharmacokinetic endpoints were defined.

2.10 PD and PK/PD analyses

No pharmacodynamics/pharmakokinetic endpoints were defined.

2.12 Biomarkers

2.13 Not applicable.Other Exploratory analyses

Not applicable.

2.14 Interim analysis

Not applicable.

3 Sample size calculation

Published data varies widely as to the average thinning of RNFL in MS patients and no data is available on patients treated with Fingolimod. As this is an explorative study to get a better understanding of RNFL thinning in RRMS treated with Fingolimod we will take a representative sample of approximately 100 patients with RRMS who are stable on Fingolimod

4 Change to protocol specified analyses

The change in ganglion cell layer thickness (GCLT) was defined as secondary endpoint, but OCT measured the ganglion cell inner plexiform layer (GCIP). This was done because both layers are not clearly separable by OCT. The volume of GCIP is declared as usual parmeter.

5 Appendix

5.1 Imputation rules

Missing dates are completed by 15th for missing days and 6th for missing months.

Imputation of primary and secondary parameters are described above.

5.3 Statistical models

5.3.1 Primary analysis

See 2.5 Analysis of the primary objective.

5.3.2 Key secondary analysis

The SAS syntax for mixed model to compare RNFLT in eyes with versus without optic neuritis is:

proc mixed data=test5;

```
class patno opt_neur ;
model rnflt = opt_neur;
random patno;
lsmeans krank / tdiff pdiff;
run;
```

RNTFL ist the difference from BL to last value until M36. Here no average over both eyes is calculated, but each measurement is included in the dataset and flagged in OPT_NEUR if the respective eye was affected by optic neuritis history.

5.4 Rule of exclusion criteria of analysis sets

Table 1 Protocol deviations that cause subjects to be excluded

Deviation ID	***Description of Deviation***	***Exclusion in Analyses***
I1	Informed consent not obtained	Excluded from all analyses
I3	Subject aged < 18	Excluded from PP analysis
I4	Subject not diagnosed with RRMS	Excluded from all efficacy analyses
I5	Subject with EDDS > 6.0 at baseline visit	Exclude from PP analysis
I6	Subject not stable on Fingolimod for at least 28 days and at most 4 months prior to screening	Excluded from PP analysis
I7	Evidence of acute relapse within 30 days prior to baseline visit	Excluded from PP analysis
E1	Forbidden concomitant medication	Case by case review: excluded from PP analysis
E3	Subject is suffering from a cardiovascular condition	Case by case review: excluded from PP analysis (if relevant for primary parameter)
E4	Subject suffering from severe respiratory disease	Case by case review: excluded from PP analysis
E5	Subjects with history of specific MRI findings	Excluded from PP analysis
E7	Subject with a history of a malignancy of any organ system within the past 5 years	Excluded from PP analysis (Exception: localized basal cell carcinoma of the skin)
E8	Use of other investigational drug/therapy within 90 days or 5 half-lives of screening	Case by case review: excluded from PP analysis
E9	Pregnant or nursing women	Excluded from PP analysis
E10	Subject with any ophthalmologic reason for RNFL pathology other than MS	Case by case review: excluded from PP analysis
E11	History or active severe myopia	Case by case review: excluded from PP analysis
E12	Acute optic neuritis within the last 6 months prior to screening	Excluded from PP analysis

Deviation ID	*Description of Deviation*	*Exclusion in Analyses*
E13	Evidence of advanced diabetic retinopathy	Excluded from PP analysis
E14	Presence of retinal conditions	Case by case review: excluded from PP analysis
E15	Concomitant use of drugs that may directly affect retinal structure and function	Case by case review: excluded from PP analysis
S1	Treatment regime changed	Excluded from PP analysis
O1	Baseline OCT measurements not performed	Excluded from PP analysis
O3	Difference between visit 7 and baseline ≤ 1035 days	Excluded from PP analysis

Table 2 Subject Classification

Analysis Set	**PD ID that cause subjects to be excluded**	**Non-PD criteria that cause subjects to be excluded**
ENR	NA	Not having informed consent; Not having screening epoch disposition page (i.e. date for Screening visit, vis1n=1)
SAF	NA	No dose of fingolimod taken
FAS	I1	Not in SAF No post-baseline efficacy data are collected
PPS	I1, I3, I4, I5, I6, I7 E1, E3 to E15 S1, O1, O3	

6 Reference

None