NOVARTIS

Clinical Development

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An Open-Label, Single-Arm, Multicenter, Phase IIIb Study in Patients With Neovascular Age-Related Macular Degeneration to Evaluate the Safety of Brolucizumab 6 mg in Prefilled Syringe

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 of update	Section and title impacted (Current)
9 Aug 2019	Prior to DBL	Data is coded with MedDRA V21.1	References to "most recent version at the time of DBL" changed to reflect Version 21.1 is used	S2.3.2 Subject demographics and baseline characteristics S2.4.2 Prior, concomitant and post therapies S2.8.1 Adverse events
9 Aug 2019	Prior to DBL	Sites have entered events prior to IFC on the eCRF	Text updated to reflect prior non-drug therapies and procedures are included in the listing	S2.4.2 Prior, concomitant and post therapies
9 Aug 2019	Prior to DBL	Criteria changed from increase ≥ 20 mmHg from pre-injection IOP to post-injection IOP within a visit to an increase ≥ 10 mmHg	Text stating the criteria is updated	Section 2.8.3.1 Intraocular pressure (IOP) (mmHg)
9 Aug 2019	Prior to DBL	Imputation of partial dates for medications is not required for any analyses	Section 5.1.2 removed	S5.1.2 Concomitant medication date imputation

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
CM	Concomitant medication
CSR	Clinical Study report
DBL	Database Lock
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
IOP	Intraocular pressure
MedDRA	Medical Dictionary for Drug Regulatory Affairs
nAMD	Neovascular Age-Related Macular Degeneration
PFS	Prefilled Syringe
PT	Preferred Term
SAP	Statistical Analysis Plan
SOC	System Organ Class
WHO	World Health Organization

1 Introduction

This document contains details of the statistical analyses planned in Section 12 of the protocol that will be presented in the clinical study report (CSR). It also contains details of the analyses to be performed for CT.gov which will not be presented in the CSR.

This statistical analysis plan (SAP) is based Protocol version number 01 (amended protocol) dated 11th April 2019

1.1 Study design

This study is an open-label, single arm, multicenter, phase IIIb study. Screening and Baseline visits may be performed on the same day. The Follow-up, which is End of Study is 7 days ± 2 days after Baseline.

Subjects who consent will undergo all screening activities to evaluate their eligibility based on the inclusion and exclusion criteria. Subjects who meet all inclusion criteria and none of the exclusion criteria will receive:

- Brolucizumab 6 mg prefilled syringe (PFS), one injection.

The study population will be male and female subjects ≥ 50 years old who are diagnosed with neovascular age-related macular degeneration (nAMD). Approximately 30 subjects are expected to be injected at approximately 3 sites in the United States of America.

Randomization is not applicable for this open-label study.

The primary analysis will be conducted after database lock (DBL).

No interim analyses are planned.

1.2 Study objectives and endpoints

The primary objective and endpoint is given in Table 1-1 below:

Table 1-1 Objectives and related endpoints

Objective	Endpoints
Primary objective	**Endpoints for primary objective**
• To evaluate the safety of brolucizumab 6 mg delivered in PFS in subjects with nAMD.	• Incidence of ocular and non-ocular Adverse Events (AEs).

There are no secondary endpoints.

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by Novartis using SAS Version 9.4.

Categorical variables will be presented as frequencies and percentages. For continuous data, the mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum will be presented.

2.1.1 General definitions

The term ‘study treatment’ refers to brolucizumab 6 mg (PFS).

2.1.1.1 Study day

Study day is defined as the number of days since the date of the injection of study treatment. The date of the injection of study treatment will be defined as Day 1 and the day before the injection of study treatment will be defined as Day −1.

Therefore, for a particular date, study day will be calculated as follows:

- For dates on or after the date of the injection of study treatment,
  Study day = Visit/Assessment date − date of injection of study treatment + 1
- For dates prior to the date of the injection of study treatment,
  Study day = Visit/Assessment date − date of injection of study treatment

2.1.1.2 Baseline definition

Baseline is defined as the last measurement/value before the injection of study treatment.

2.1.1.3 Post-baseline definition

Post-baseline measurements are defined as assessments after the injection of study treatment.

When change from baseline is of interest the following formula will be used for each scheduled visit where baseline and post-baseline values are both available:

Change from baseline = post-baseline value − baseline value

2.1.1.4 End of study/treatment

The end of study date for a subject is the date when a subject completes or discontinues the study.

2.1.1.5 Missing dates

Details on handling missing dates are shown in Section 5.

2.2 Analysis sets

The only analysis set defined is the Full Analysis Set (FAS) which will include all enrolled subjects who receive an injection of study treatment.

The FAS will be used for the analysis of all variables.

2.2.1 Subgroup of interest

No subgroup analyses will be conducted.

2.3 Subject disposition, demographics and other baseline characteristics

2.3.1 Subject disposition

The number of subjects screened and treated will be summarized.

The number and percentage of subjects who complete or discontinue from the study will be summarized including the reasons for discontinuation.

The number and percentage of subjects with protocol deviations will be summarized by deviation category (selection criteria not met, subject not withdrawn as per protocol, treatment deviation, prohibited concomitant medication, other).

2.3.2 Subject demographics and baseline characteristics

Age at study entry (as a continuous variable), gender, race and ethnicity will be summarized descriptively and listed.

The following baseline ocular characteristic will be summarized for the study eye:

- primary diagnosis of nAMD

This baseline ocular characteric will be listed for the study eye and fellow eye.

Medical histories and current medical conditions will be coded with the Medical Dictionary for Regulatory Activities terminology (MedDRA) Version 21.1. All medical histories and current medical conditions will be listed.

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

2.4.1 Study treatment / compliance

The total number of subjects who received an injection of study treatment will be presented.

2.4.2 Prior, concomitant and post therapies

Medications will be coded according to the Anatomical Therapeutic Chemical (ATC) classification system.

Non-drug therapies and procedures will be coded using MedDRA Version 21.1.

Prior and concomitant medications and non-drug therapies and procedures will be listed.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The incidence of ocular and non-ocular AEs are the primary endpoints. The primary endpoints will be analyzed for the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

No formal hypothesis testing will be performed in this study.

See Section 2.8.1 for details of the analyses to be performed for AEs.

2.5.3 Handling of missing values/censoring/discontinuations

This is a single dose, open-label study with 2 scheduled visits over the period of 1 week. Therefore, missing data will not be imputed.

2.5.4 Supportive analyses

Not applicable.

2.6 Analysis of the key secondary objective

No key secondary objectives are defined for this study.

2.7 Analysis of secondary efficacy objective(s)

No secondary objectives are defined for this study.

2.8 Safety analyses

All safety analyses will be performed for the FAS.

2.8.1 Adverse events

AEs will be coded using MedDRA Version 21.1.

All AEs will be listed.

Summaries will include all treatment emergent AEs which are defined as AEs which start on or after the date of the injection of study treatment up until the patient discontinues or completes the study.

Analyses will be performed for ocular AEs for the study eye only and non-ocular AEs. Ocular and non-ocular AEs will be presented separately. Ocular AEs for the fellow eye will be listed only.

The number and percentage of subjects who reported treatment emergent AEs will be summarized by primary SOC and PT for:

- all AEs
- all AEs by maximum severity
- all AEs by investigator causality assessment (relationship to study treatment and/or study treatment administration procedure)
- AEs leading to study discontinuation
- all serious adverse events (SAE)

If a subject reports more than one AE with the same PT, the AE will be counted only once for that PT. If a subject reports more than one AE within the same primary SOC, the subject will be counted only once for that SOC.

2.8.1.1 Adverse event reporting for CT.gov

For the legal requirements of clinicaltrials.gov, two required tables on treatment emergent AEs which are not SAEs with an incidence greater than or equal to x% (default is 5% but a lower cut off may be applied and this will be determined based on the final data) and on treatment emergent SAEs will be provided by SOC and PT for the FAS.

If for the same subject, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

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

2.8.2 Deaths

A summary of treatment emergent deaths will be presented by primary SOC and PT.

All deaths recorded in the clinical database will be listed.

2.8.3 Other safety data

2.8.3.1 Intraocular pressure (IOP) (mmHg)

All IOP measurements will be listed for subjects who fulfil at least one of the following criteria:

- IOP > 30 mmHg
- Increase ≥ 10 mmHg from pre-injection IOP to post-injection IOP within a visit

2.8.3.2 Vital signs

All vital signs measurements will be listed for subjects who fulfil at least one of the following clinically notable criteria:

Table 2-1 Clinically notable criteria for vital signs

Variable	Category	Critical Values
Systolic blood pressure (mmHg)	High	Either >180 with an increase from baseline >30 or >200 absolute
	Low	Either <90 with a decrease from baseline >30 or <75 absolute
Diastolic blood pressure (mmHg)	High	Either >105 with an increase from baseline >20 or >115 absolute

Variable	Category	Critical Values
	Low	Either <50 with a decrease from baseline > 20 or <40 absolute
Pulse rate (bpm)	High	Either >120 with an increase from baseline of >25 or >130 absolute
	Low	Either <50 with a decrease from baseline >30 or <40 absolute

2.9 Other Exploratory analyses

No exploratory objectives are defined for this study.

2.10 Interim analysis

No interim analysis is planned for this study.

3 Sample size calculation

No formal statistical power calculations to determine sample size were performed for this study.

4 Change to protocol specified analyses

Protocol section 12.2 states that relevant medical histories and current medical conditions at baseline will be summarized. Given the small sample size this data will be listed only.

Protocol section 12.3 states that descriptive statistics for exposure to study treatment and the cumulative number of injections will be presented. As subjects are only scheduled to receive a single injection of study treatment the total number of patients who received an injection will be presented.

Protocol section 12.3 states that concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized. Given the small sample size this data will be listed only.

Protocol section 12.4.2 states that treatment emergent AEs will be summarized by SMQ and PT. This summary will not be produced, treatment emergent AEs will be presented by SOC and PT only.

Protocol section 12.4.2 states that AE presentations will be presented for the fellow eye. Adverse events for the fellow eye will be listed only.

Protocol section 12.4.2 states that pre-injection and post-injection IOP measurements will be listed. Instead, IOP measurements will only be listed for subjects who have at least IOP measurement meeting the criteria defined in SAP Section 2.8.3.1.

Protocol section 12.4.2 states that all vital signs data will be listed. Instead, vital signs measurements will only be listed for subjects who have at least one vital signs measurement meeting the criteria defined in SAP Section 2.8.3.2.

5 Appendix

5.1 Imputation rules

5.1.1 AE date imputation

5.1.1.1 AE end date imputation

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.

If the imputed AE end date is less than the existing AE start date then use AE start date as AE end date.

5.1.1.2 AE start date imputation

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

	Day	**Month**	**Year**
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	**MON < TRTM**	**MON = TRTM**	**MON > TRTM**
YYYY MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.c) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min (informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date

Impute AE start date -

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.

2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:

a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).

b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).

3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:

a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).

b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

4. If the AE start date year value is equal to the treatment start date year value:

a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.

b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).

c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.2 Statistical models

No hypothesis testing will be performed for this study.

5.3 Rule of exclusion criteria of analysis sets

Only one analysis set is defined, the FAS. No protocol deviations are defined which lead to exclusion from the FAS.

6 Reference

Not applicable.