NOVARTIS

Clinical Development

RTH258/brolucizumab

CRTH258ADE01 / NCT04679935

A 52-week, two-arm, randomized, open-label, multicenter study assessing the efficacy and safety of two different brolucizumab 6 mg dosing regimens for patients with suboptimal anatomically controlled neovascular age-related macular degeneration (FALCON)

Statistical Analysis Plan (SAP)

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26-APR-2022	*Prior to DB lock*	*Creation of final version*	*N/A – First version*	*NA*
22-MAR-2023	*Prior to DB lock*	*Update due to protocol amendment*	*Due to feasibility reasons (prematurely discontinuation of the study), purely descriptive analyses will be performed.*	*1.2, 2.5, 3* (objectives, sample size)
25-MAR-2024	*Prior to DB lock*	*Update on data from Reading Center*	*description of parameters collected by the reading center added in section 2.13*	*2.13*

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List of abbreviations

[redacted]	[redacted]
AE	Adverse event
AMD	Age-related Macular Degeneration
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
CFP	Color Fundus Photography
CNV	Choroidal Neovascularization
Covid-19	Coronavirus Disease 2019
CRC	Central Reading Center
CSP	Clinical Study Protocol
CSR	Clinical Study report
DAA	Disease Activity Assessment
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOS	End-of-Study
EOT	End-of-Treatment
ETDRS	Early Treatment Diabetic Retinophathy Study
FA	Fluorescein Angiography
FAS	Full Analysis Set
IOI	Intraocular Inflammation
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRF	Intraretinal Fluid
MedDRA	Medical Dictionary for Drug Regulatory Affairs
nAMD	Neovascular Age-related Macular Degeneration
OCT	Optical Coherence Tomography
PD	Protocol Deviation
PK	Pharmacokinetics
PPS	Per-Protocol Set
RAP	Report and Analysis Process
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SOC	System Organ Class
SRF	Subretinal Fluid
TFLs	Tables, Figures, Listings
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) describes how the statistical analyses of this study will be implemented. Based on the tables/listings/figures (TFL) resulting from this SAP the Clinical Study Report (CSR) will be written. The TFLs will be attached in section 14 of the CSR.

In addition this SAP describes which Patient Data Listings to be attached in section 16.2.1 of the CSR will be generated.

This SAP is not used for other analyses or other studies. It is based on the Study Protocol (CSP), Version 02 (Amendment 2) dated 30-Nov-2022.

1.1 Study design

This study is a 52-week, randomized, open-label, multi-center, two-arm study for pretreated patients with suboptimal anatomically controlled nAMD.

Consenting patients will participate in a screening period, lasting up to 14 days. Eligible patients will be randomized in a 1:1 ratio to one of the two treatment arms:

- Brolucizumab 6 mg “loading arm”: 3 x 4-weekly initial injections followed by an injection every 12 weeks
- Brolucizumab 6 mg “non-loading arm”: one initial injection followed by an injection every 12 weeks

There are three periods in this study (see Figure 1.1):

- Screening period: from day -14 to Baseline
- Open-label treatment period: from Baseline (day 1) to week 48
- Post-treatment follow-up period: from week 48 to week 52

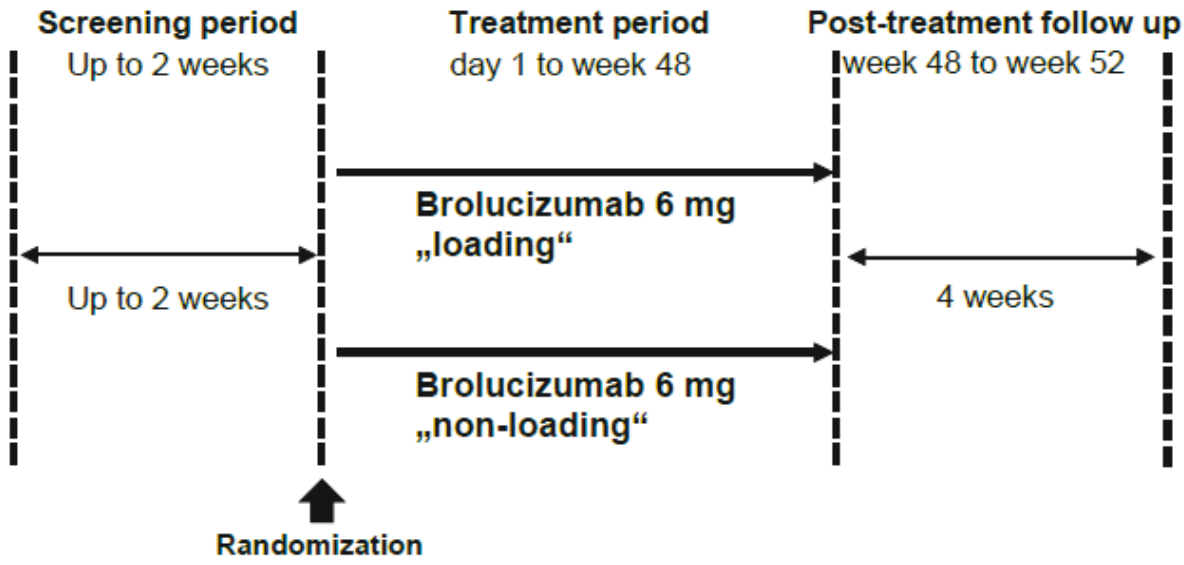

Figure 1.1 Study Design

1. Screening period: Day-14 to day -1

A screening period of up to 2 weeks will be used to assess eligibility.

One time rescreening of patients is allowed, except for the purpose of capturing new BCVA or imaging assessments that previously failed to qualify the patient. As long as testing can be repeated within 14 days of the first screening, the other screening assessments do not need to be repeated. If rescreening is to occur beyond 14 days from the original screening visit date, then all screening procedures must be repeated. Medical judgment should be exercised to ensure that treatment of nAMD is not withheld in order for a patient to participate in the study.

2. Open-label treatment period: Day 1 to Week 48

After confirmation of eligibility, patients will be randomized in a 1:1 ratio to one of the treatment arms.

Only one eye will be selected as study eye and treated with study medication.

The baseline visit is defined as Day 1/Visit 1, and end of treatment visit as Visit 13 (Week 48).

A study visit schedule will be established at the time of randomization for all patients with study visits scheduled every 4 weeks. All efforts should be made to adhere to this study visit schedule ±7 day window. Treatment is intended to be administered on the day of study visit, or if this is not possible, within 3 days after the study visit when the per-protocol assessments took place. In addition, for a given protocol visit, assessments can be performed on two consecutive days.

In the “loading arm”, patients will receive three consecutive injections every 4 weeks at baseline, weeks 4 and 8, which should be at least 21 days apart, followed by an injection every 12 weeks. In the “non-loading arm”, patients will receive one initial injection followed by an injection every 12 weeks. For both study arms the assessment of disease activity will be performed 8 and 12 weeks after the previous injection. If disease activity is identified by the investigator for the first time at any visit after / from week 8 respectively, patients should stay on a q12w dosing, if the decline in BCVA is clinically non-significant (BCVA loss < 4 ETDRS letters) compared to the previous visit. If after / from week 8 BCVA-loss of ≥ 5 ETDRS letters appears compared to the previous visit or disease activity is identified for a second time based on the investigator’s judgment of visual and / or anatomic outcomes and signs of disease activity, patients must be assigned to q8w dosing. One attempt of interval re-extension from q8w to q12w treatment will be allowed based on the investigator’s judgement if no disease activity (DA) is detected during the subsequent visit(s). If the patient shows significant DA at any visit after the re-extension attempt, injection intervals will be fixed to q8w until the end of the study.

Patients who require injections more frequently than every 8 weeks after the loading phase (week 8, loading arm) or baseline (non-loading arm) will be discontinued from further study treatment.

3. Post-treatment follow-up period: Week 48 to week 52

For all patients, the last study assessment will be performed at week 52.

Patients withdrawn from the study prior to study completion will be asked to return for an early discontinuation visit (EOS / Visit 14), four weeks (±7 days) following their last study visit.

1.2 Study objectives and endpoints

This study is designed as a randomized, open-label, multi-center, two-arm parallel study to assess the efficacy and safety of two different brolucizumab 6 mg regimen for pretreated patients with suboptimal anatomically controlled nAMD.

The primary objective of this study is to evaluate descriptively the difference of brolucizumab 6 mg with one (initial) injection followed by q12w maintenance as compared to brolucizumab 6 mg with 3x q4w loading injections followed by q12w maintenance with respect to the change in BCVA from baseline to mean of visits at week 40 to week 52.

Table 1.1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
To evaluate the difference of brolucizumab 6 mg with one (initial) injection followed by q12w maintenance as compared to brolucizumab 6 mg with 3x q4w loading injections followed by q12w maintenance	• Mean change in BCVA from baseline to mean of visits at week 40 to week 52
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
1. To evaluate treatment interval prolongation compared to previous treatment	• Mean treatment interval (overall as well as per study group comparing treatment intervals from week 8 to week 52 in the study vs. 24 weeks to baseline prior to enrollment) • Rate of patients (overall and per group) with prolonged interval compared to mean treatment interval in last 24 weeks prior to enrollment
2. To estimate the proportions of patients maintained at q12w treatment frequency in the two brolucizumab groups	• Comparison of proportions of patients maintained at a q12w interval from baseline / upload to week 52 between the two arms • Distributions of patients at q8w/q12w intervals from baseline to week 52
3. To evaluate the functional outcomes comparing the two brolucizumab groups	• Average change in BCVA from baseline to week 52 • Proportion of patients with BCVA improvements of ≥5, ≥ 10, and ≥ 15 letters from baseline to week 52 • Proportions of BCVA ≥ 69 letters at week 52 • Mean change in BCVA from baseline to mean of visits at week 16 to week 28
4. To evaluate the anatomical outcomes comparing the two brolucizumab groups	• Change from baseline in CST as assessed by SD-OCT per visit up to week 52 • Absence of IRF, SRF, and sub-RPE fluid as assessed by SD-OCT per visit up to week 52

Objective(s)	Endpoint(s)
5. To evaluate the safety and tolerability of brolucizumab	• Presence of active CNV leakage as assessed by fluorescein angiography at week 52 • Incidence of Ocular and Non-ocular AEs up to Week 52

[redacted]

2 Statistical methods

2.1 Data analysis general information

The primary safety and efficacy analysis will be based on all subject data at the time the trial ends. This analysis will be performed once all patients completed their final visits or terminated the study prematurely.

2.1.1 General definitions

The term study treatment is used for Brolucizumab 6 mg/0.05 mL.

The baseline visit is defined as day 1/visit 1.

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the last administration of study treatment (EOT) or EOS whichever is the latest.

Calculation of treatment interval:

- "Mean treatment interval from week 8 to week 52": (last injection – first injection from week 8 on*) divided by (number of injections from week 8 to week 52 -1)

  *the first injection from week 8 on could be at week 8 or later.

- "Mean treatment interval in last 24 weeks prior to first brolucizumab injection" will be calculated as: (date of first brolucizumab injection - date of first anti-VEGF pre-treatment within last 24 weeks) divided by number of injections within 24 weeks prior to first brolucizumab injection.

2.2 Analysis sets

The **Randomized Set** (RAS) consists of all randomized patients.

The **Full Analysis Set** (FAS) comprises all subjects who receive at least one IVT injection of the study treatment. The FAS will serve as the primary analysis set for all efficacy analyses. According to the intent to treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure.

The **Safety Set** includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the actual treatment regime. If the subject took only one dose of study treatment, the subject will be analysed according to the randomized treatment regime.

Relevant protocol deviations and their potential impact on the analysis will be assessed and adequately documented / processed before database lock.

2.2.1 Subgroup of interest

No subgroup analyses are planned.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Using all enrolled patients the number of patients screened, randomized, discontinued prematurely and completed treatment/ study by center and treatment will be displayed. For patients who discontinued/ completed treatment/ study percentages are computed using the number of randomized patients.

Furthermore, a listing will be provided for first patient first visit and last patient last visit by center.

In addition, the frequency of patients who completed/ discontinued is displayed separately for screening phase (all enrolled patients), for treatment completion (Randomized Set) and for study completion (Randomized Set) and the reason for discontinuation is analysed according to CRF-given categories.

2.3.2 Demographics and other baseline characteristics

Demographics and other baseline data including disease characteristics will be listed and summarized descriptively by treatment arm for the FAS and Safety set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical history (including underlying inflammation, autoimmune disease), nAMD history and current medical conditions at baseline will be summarized separately by system organ class (SOC) and preferred term of the MedDRA dictionary, by treatment arm for the FAS.

Prior Anti-VEGF medication will be listed and last pre-treatment medication (latest injection date) will be presented as frequencies and percentages.

In adition, the number of injections within the last 24 weeks and the mean injection interval in last 24 weeks prior to first brolucizumab injection will be summarized by sample statistics.

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

2.4.1 Study treatment / compliance

All collected injection data will be listed.

The duration of exposure to the investigational drug as number of injections from baseline to EOS/week 52 will be summarized by means of descriptive statistics using the safety set. Besides the total number of injections, the following treatment periods will be analysed separately:

- Baseline (day 1) to week 8: number of injections will be displayed by visit.

- Week 12 to week 48: average number of injections over this period will be displayed.

Switching from q12w to q8w dosing regime, including total number of switching patients and switching patients by visit, will be analysed by frequencies and percentages. The number of switching patients from q8w to q12w will be analysed in the same manner. The total number of switches per patient will be presented by sample statistics.

2.4.2 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system, by treatment arm, using the Safety Set.

There should be no rescue medication for nAMD in the study eye.

The number of patients who reported any laser treatment will be summarized by frequency table, using the Safety Set. Details on reported laser treatment will be listed.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary objective of this study is to evaluate descriptively the difference of brolucizumab 6mg with one (initial) injection followed by q12w maintenance and brolucizumab 6mg with 3x q4w loading injections followed by q12w maintenance with respect to the change in BCVA from baseline to mean of visits at week 40 to week 52. The analysis of the primary endpoint will be based on the following estimand:

Variable of interest: primary endpoint is the change in BCVA from baseline to mean of visits at week 40 to week 52; irrespective of adherence to treatment, i.e. the treatment policy.

Intervention effect: effect of brolucizumab “non-loading arm” versus “loading arm” after 52 weeks regardless of adherence to randomized treatment.

Summary measure: Difference in means.

The population will be male and female patients ≥50 years old diagnosed with active choroidal neovascularization (CNV) secondary to AMD and treated previously for this disease, who will be switched to brolucizumab at baseline.

2.5.2 Statistical hypothesis, model, and method of analysis

The analysis of the primary endpoint will be performed in a purely descriptive manner and non-inferiority testing will be omitted. To evaluate the outcome in terms of mean change in BCVA from baseline to mean of visits at week 40 through week 52, a two-sided 95% confidence interval for the treatment difference will be derived from a mixed model with repeated measures (MMRM) model with factors treatment arm, baseline BCVA and age. An unstructured

covariance structure shared across treatment arms was used to model the within-patient errors. Programming details are specified in section 5.4.

The FAS will be used to analyze the primary endpoint.

2.5.3 Handling of missing values/censoring/discontinuations

As a primary approach, retrieved data will be included, irrespective of intercurrent events such as prohibited medication or treatment interrupation or discontinuation (treatment policy, difference in all randomized patients). For statistical analyses of continuous parameters, missing data in case of lost to follow-up will be accounted for in a mixed model for repeated measures (MMRM) assuming data after loss to follow-up are missing at random (MAR), and assuming almost all data will be retrieved. Thus, every effort must be made to follow-up on patients after treatment discontinuation up to end of study.

2.5.4 Supportive analyses

2.6 No sensitivity analyses are planned. Analysis of the key secondary objective

There is no key secondary objective. Thus this section is not applicable.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

Secondary efficacy objectives and endpoints are listed in Table 1-1.

2.7.2 Statistical hypothesis, model, and method of analysis

Secondary endpoints will be analyzed using adequate descriptive statistics, if not otherwise specified. Details on planned analyses are listed in the table below.

Table 2 Endpoints and statistical method

Endpoints for secondary objectives	Statistical method
1.Treatment interval	
1.1. Mean treatment interval (overall as well as per study group comparing treatment intervals from week 8 to week 52 in the study vs. 24 weeks to baseline prior to enrollment)	Descriptive analysis of injection intervals (weeks): **Summary statistics** (n,mean, SD, min, median, max) for - Mean treatment interval from week 8 to week 52 - Mean treatment interval within 24 weeks prior to baseline. - Last treatment interval under observation **Box Plot** for “last treatment interval under observation”. **Stacked Bar Chart** for patients on q8w and q12w by visit (last documented DAA).

1.2. Rate of patients (overall and per group) with prolonged interval compared to mean treatment interval in last 24 weeks to baseline prior to enrollment	• **Frequencies and percentages** (n(%)) for total FAS and both treatment arms. • **Logistic regression model** Dependent variable: interval prolongation* (Y/N) Factors: - treatment arm - baseline BCVA - age Odds-ratio, 95% CI and p-value. Estimates for , non-loading arm, loading arm and difference (non-loading – loading). * Prolongation is calculated by comparing the "mean treatment interval in last 24 weeks prior to first brolucizumab injection" (defined in section 2.3.2) with the time interval between the last two brolucizumab injections. Patients with only one injection in treatment period are calculated as non-responders (no interval prolongation).
2. Maintenance of q12w intervals	
2.1. Comparison of proportions of patients maintained at a q12w interval at week 52 between the two arms	• **Frequencies and percentages** (n(%)) for total FAS and both treatment arms. • **Logistic regression model** Dependent variable: "q12w" (Yes/No): "DAA maintained at q12w from baseline / upload to week 52" Factors: - treatment arm - baseline BCVA - age Odds-ratio with 95% CI and p-value. Patients who discontinued treatment prior to week 52 are calculated as non-responders.
2.2. Distributions of patients at q8w/q12w intervals from baseline to week 52	Descriptive statistics for treatment regimens: **Frequencies and percentages** (n (%)) by visit
3. Functional Outcomes	
3.1. Average change in BCVA from baseline to week 52	Descriptive statistics for course and change in BCVA: **Summary statistics** (n,mean, SD, min, median, max) for BCVA in the study eye by visit.

3.2. Proportion of patients with BCVA improvements of ≥5, ≥ 10, and ≥ 15 letters from baseline to week 52 3.3. Proportions of BCVA ≥ 69 letters at week 52	Descriptive statistics (**rates and percentages**) for proportion of patients with: - Gain* in BCVA of ≥ 5 ETDRS letters - Gain* in BCVA of ≥ 10 ETDRS letters - Gain* in BCVA of ≥ 15 ETDRS letters *from baseline to week 52 - BCVA at week 52 ≥ 69 ETDRS letters
3.4. Mean change in BCVA from baseline to mean of visits week 16 to week 28	**Mixed model for repeated measures (MMRM)** Factors: - treatment arm - baseline BCVA - age Least square means with SE and 90% CI.
4. Anatomical outcomes	
4.1. Change from baseline in CST as assessed by SD-OCT per visit up to week 52 4.2. Absence of IRF, SRF, and sub-RPE fluid as assessed by SD-OCT per visit up to week 52 4.3. Presence of active CNV leakage as assessed by fluorescein angiography at week 52	Descriptive analysis of anatomical outcomes: Frequencies and percentages, **n (%)**, by visit

2.7.3 Handling of missing values/censoring/discontinuations

Missing values of secondary endpoints will not be replaced.

2.8 Safety analyses

The secondary safety objective and endpoint of this study is as follows:

To evaluate the safety and tolerability of brolucizumab

- Incidence of Ocular and Non-ocular AEs up to week 52

There are no formal safety hypotheses in this study. All safety analyses will be performed using the Safety Set. All listings and tables will be presented by treatment arm.

Safety endpoints are based on the variables from safety assessments which include:

- Extent of exposure
- Adverse events
- Ophthalmic examination and imaging
- Vital signs

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period

(treatment-emergent AEs). Separate summary tables will be provided for AEs of study eye, fellow eye and non-ocular AEs.

2.8.1 Adverse events (AEs)

A treatment-emergent adverse event is defined as any adverse event that develops after initiation of the study treatment or any event already present that worsens following exposure to the study treatment. Only treatment-emergent adverse events will be presented in the summary tables.

All information obtained on adverse events will be displayed by treatment arm and subject. The number (%) of subjects with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

Adverse events will be coded using the MedDRA dictionary and presented by system organ class (SOC) and preferred term (PT). Treatment-emergent AEs will be analyzed based on the number and percentage of patients with at least one AE in the category of interest.

Separate presentations will be provided related to ocular events in the study eye and fellow eye and non-ocular (systemic) events.

Additional summaries will be provided by severity and causality (separately assessed for the injection procedure and the drug). Serious adverse events, adverse events leading to discontinuation of study treatment and adverse events related to Covid-19 will also be summarized separately.

In addition, separate listings will be provided for AEs with a start date prior to on-treatment period and AEs after on-treatment period.

2.8.1.1 Adverse events of special interest / grouping of AEs

No adverse events of special interest are defined.

2.8.2 Deaths

Deaths and other serious or clinically significant non-fatal adverse events will be listed separately.

2.8.3 Laboratory data

No specific laboratory evaluations for safety assessment will be performed except serum pregnancy testing.

The serum pregnancy test will be conducted for all women of child-bearing potential to assess pregnancy before inclusion into the study at the screening visit. During the study, **urine** pregnancy testing will be performed at visits when serum pregnancy testing will not be

conducted. If a urine test is positive after inclusion in the study, a serum pregnancy test must be performed for confirmation. Results of pregnancy testing will be available as source documentation.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Not applicable.

2.8.4.2 Vital signs

All vital signs data will be listed by treatment arm, subject, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

2.8.4.3 Ophthalmic examinations

Pre-injection IOP measurements will be presented descriptively (absolute values and change from baseline). Post-injection IOP measurements will be listed.

Further ophthalmic parameters from slit lamp examination and posterior pole examination (anterior chamber cells/ flares and vitreous cells/ haze) will be presented by frequency tables by visit.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

Not applicable.

[redacted]

2.14 Interim analysis

There is no interim analysis planned.

3 Sample size calculation

Due to feasibility reasons, resulting in a substantial delay in recruitment, as described above, with Amendment 2 the recruitment will be prematurely discontinued. A final number of approximately 50 patients is expected to be recruited by the time of approval of the amendment.

As a consequence, all analyses will be performed and interpreted in a purely descriptive manner.

Based on an expected sample size of 25 patients per group, and an assumed common standard deviation of 13 letters, a precision in terms of the width of the respective 95% confidence interval for the difference in change from baseline of the visual acuity of +/- 7,21 can be achieved. Taking into account the current number of patients of (for 23 patients per group), the precision in terms of the half width of the 95% confidence interval would be 7,51.

4 Change to protocol specified analyses

The wording of secondary objective 2) was slightly changed to: “Comparison of proportions of patients maintained at a q12w interval **from baseline / upload to week 52**” instead of per protocol: “Comparison of proportions of patients maintained at a q12w interval **at week 52**”.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

If date of injection is missing, date of visit will be imputed.

5.1.2 AE date imputation

For start date:

- If day missing
    - if month/year(start) gt month/year(first injection)
      than impute max(date of first injection, mdy(month (start date),1,year(start date)))
      else impute mdy(month (start date),1,year(start date))

For end date:

- If complete missing than impute date of last injection+30.
- If day missing
    - if month/year(first injection) gt month/year(end date)
      than impute mdy(month(end date)+1,1,year(end date))-1)
    - if month/year(first injection) le month/year(end date) le month/year(last injection+30)
      than impute min(date of last injection+30, mdy(month(end date)+1,1,year(end date))-1)
    - if month/year(end date) gt month/year(last injection+30)
      than date of last injection+30

5.1.3 Concomitant medication date imputation

Like AE imputation

5.2 AEs coding/grading

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all adverse events (AE) to a system organ class (SOC) and a preferred term (PT). The current version at the time of database closing will be used.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

5.4.1 Primary analysis

1) SAS-Code for **mixed model for repeated measures** (MMRM):

Estimates for the primary objective ("Mean change in BCVA from baseline to mean of visits at week 40 to week 52 (Visit 11 to 14)") and the secondary objective ("Mean change in BCVA from baseline to mean of visits at week 16 to week 28 (Visit 5 to 8)") in one single model:

```
proc mixed alpha=0.1;
   where fasfl=Y and trteyen=1;
   where 2 le avisitn le 14;
   class subjid trtan avisitn;
   model chg = base age trtan avisitn trtan*avisitn /ddfm=kr;
   repeated avisitn /  sub = subjid type = un;
   lsmeans trtan*avisitn /slice = avisitn  cl ;
   estimate 'Treatment difference averaged over week 40 to week 52'
                     trtan -1 1
                     trtan * avisitn
                            0 0 0 0 0 0 0 0 0 -0.25 -0.25 -0.25 -0.25
                            0 0 0 0 0 0 0 0 0 0.25 0.25 0.25 0.25/cl;

   estimate 'Treatment difference averaged over week 16 to week 28'
                     trtan -1 1
                     trtan * avisitn
                            0 0 0 -0.25 -0.25 -0.25 -0.25 0 0 0 0 0 0
                            0 0 0 0.25 0.25 0.25 0.25 0 0 0 0 0 0/cl;
run;
```

3) SAS-Code for **logistic regression** model:

- Secondary endpoint: "rate of patients (overall and per treatment arm) with prolonged interval (*intlong*) compared to mean treatment interval in last 24 weeks prior to enrollment"

```
proc logistic descending alpha=0.05;
   where fasfl=Y;
   class trtan;
   model intlong = base age trtan;
run;
```

- Secondary endpoint: "proportions of patients maintained at a q12w interval from baseline / upload to week 52"

```
proc logistic descending alpha=0.05;
   where fasfl=Y;
   class trtan;
   model q12w = base age trtan;
run;
```

where 'maintained at a q12w interval' (q12w = Yes) is defined as DAA = q12w in all visits AND no treatment discontinuation.

5.4.2 Key secondary analysis

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

Table 1 Protocol deviations that cause subjects to be excluded

Deviation ID	**Description of Deviation**	**Exclusion from Analyses**
I_01	No written informed consent	Excluded from all analyses
D_00	Not treated with any study medication	Excluded from FAS and SAF
O_VI0	No Post-baseline visit performed	Excluded from FAS

Table 2 Subject Classification

Analysis Set	***PD ID that cause subjects to be excluded***	***Non-PD criteria that cause subjects to be excluded***
ENR	I_01	
RAN	I_01	*Not randomized*
FAS	I_01, D_00, O_VI0	*Not in RAN*
SAF	I_01, D_00	

6 Reference

Not applicable.

7 Declaration of sponsor and clinical research organisation

Declaration by client:

This statistical analysis plan has been approved after review by

Client:

[redacted]

Digitally signed by [redacted]
DN: dc=com, dc=novartis, ou=people, ou=PH, serialNumber=3168921, cn=[redacted]
Reason: I am approving this document
Date: 2024.04.03 21:12:12 +02'00'

Date [redacted]

[redacted]

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Date [redacted]

Declaration of clinical research organisation:

This statistical analysis was prepared based on the clinical study protocol (Amended Clinical Study Protocol, version 02 dated 03-NOV-2022) by

[redacted]**:**

[redacted]

Digital unterschrieben von [redacted]
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email=[redacted]
Grund: Authorship
Datum: 2024.03.28 16:22:57 +01'00'

Date [redacted] **(CRO Biometrician)**

[redacted]

Digitally signed by [redacted]
DN: dc=local, dc=wn, ou=[redacted], ou=Mitarbeiter, ou=Biometrie, cn=[redacted]
email=[redacted]
Reason: Review of document
Date: 2024.03.28 16:59:21 +01'00'

Date [redacted] **(CRO Biometrician)**