NOVARTIS

Clinical Development

RFB002/Ranibizumab

CRFB002H2301E1 / NCT02640664

Rainbow Extension study: an Extension study to evaluate the long term efficacy and safety of RAnibizumab compared with laser therapy for the treatment of INfants BOrn prematurely With retinopathy of prematurity

Statistical Analysis Plan (SAP)

Author: [redacted]

Document type: SAP Documentation

Document status: Final

Release date: 24-May-2022

Number of pages: 46

Document History – Changes compared to previous final version of SAP

Version	Date	Changes
Amendment 1	June 14, 2016	1. Combined (ocular and non-ocular) AE tables are excluded as these are redundant 2. RMP safety risk tables/listing included 3. Study day for Extension baseline modified 4. Rules of data mapping/reporting of last study visit and additional assessment visits updated 5. Definitions updated on: prior/concomitant medications, Extension safety set, 6. Section of baseline and demographic characteristics added 7. Data entry/reporting rules included for prior/concomitant medications, medical history, AEs, etc. 8. Text added in Section 1.2, as suggested by DMC member to emphasize that the study is not intended or powered for hypothesis testing. 9. Definitions of absence of active ROP, absence of structural abnormalities, etc. included in Section 2.7 10. Objectives of efficacy analyses of hypotheses tesing changed, as requested by DMC member [redacted] 12. SAS codes of inferential analyses included 13. Safety observation period and AE presentation updated 14. Japan specific outputs adeed to interim analysis I 15. Disposition and demographics added to interim analysis I
Amendment 2	Mar 13, 2018	1. Definitions of absence of ocular structural abnormalities and active ROP clarified in Section 2.8.1 2. Data cut-off date added
Amendment 3	Sept 6, 2018	1. Primary analysis changed to descriptive statistics, as defined in the protocol. 2. Imputation rule changed for primary, secondary [redacted] analyses by not exluding data after the use of the treatments prohibiting further use of investigational ranibizumab (protocol Table 5-2). 3. AEs presented by switch/no switch removed following the amendment of the protocol. 4. Additional analyses added to the interim analyses II in Sections 2.14 and 2.15. 5. Analysis of recurrence of ROP up to Week 52 removed, as it's not applicable. 6. Output of demographics and baseline characteristics at core baseline included in IA2 in Section 2.15 7. Definition of absence of ocular structural abnormalities updated in Section 2.8.1 8. Interim analysis II updated in Section 2.15 [redacted]

Version	Date	Changes
Amendment 4	December 16, 2019	1. Definition on the composite and individual components of ocular structural abnormality updated in Section 2.8.1, to align with the protocol.
Amendment 5	May 24, 2022	1. Align section numbers in Table 1.1 2. Update definition of study day relative to Core/Extension baseline. 3. Update mapping rules for end of study visit 4. Update definitions of better-seeing eye, worse-seeing eye, best eye, worst eye, best vision of the Low Visual Acuity Testing 5. Added several sensitivity analyses for the primary endpoint 6. Added analyses for the Low Visual Acuity Testing 7. Added outputs for AEs that start prior to / on or after the Extension baseline 8. Added reference SAS code for unstratified ANOVA

Table of contents

Table of contents 4
List of abbreviations 6
1 Introduction 7
1.1 Study design 7
1.2 Study objectives and endpoints 8
1.3 Cut-off dates 12
2 Statistical methods 12
2.1 Changes to the planned analyses in the protocol 12
2.2 Data analysis general information 13
2.2.1 General definitions 13
2.2.2 Data for permanent study treatment discontinuation 17
2.3 Analysis sets 17
2.4 Patient disposition, demographics and other baseline characteristics 17
2.4.1 Patient disposition 19
2.4.2 Baseline and demographic characteristics 19
2.5 Treatments (study treatment, rescue medication, concomitant therapies, compliance) 21
2.5.1 Study treatment / compliance 21
2.5.2 Prior and concomitant medications 21
2.5.3 Surgical and medical procedure 23
2.6 Analysis of the primary objective 23
2.6.1 Primary endpoint 23
2.6.2 Statistical hypothesis, model, and method of analysis 24
2.6.3 Handling of missing values/censoring/discontinuations 24
2.6.4 Supportive analyses 24
2.7 Analysis of the key secondary objective 25
2.8 Analysis of secondary efficacy objective(s) 25
2.8.1 Secondary endpoints 25
2.9 Safety analyses 27
2.9.1 Risk Management Plan (RMP) adverse events 28
2.9.2 Adverse events (AEs) 28
2.9.3 Laboratory data 30
2.9.4 Other safety data 30
2.10 Pharmacokinetic endpoints 31
2.11 PD and PK/PD analyses 31
2.12 Patient-reported outcomes 32

2.13 Biomarkers....32
[redacted] [redacted]....32
2.15 Interim analysis....33
3 Sample size calculation....35
4 Appendix....35
4.1 Imputation rules....35
4.1.1 Study drug....36
4.1.2 Adverse event date imputation....36
4.1.3 Medical history date of diagnosis imputation....38
4.1.4 Concomitant treatment date imputation....39
4.2 Laboratory parameters derivations....41
4.3 Statistical models and SAS codes....41
4.4 Rule of exclusion criteria of the analysis setset....43
[redacted] [redacted]....43
5 Reference....46

List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Classification
ANOVA	Analysis of Variance
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
CRF	Case Report Form
[redacted]	[redacted]
DMC	Data Monitoring Committee
DAR	Drug Administration Record
eCRF	Electronic Case Report Form
EMA	European Medicins Agency
[redacted]	[redacted]
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
PIP	Pediatric Investigational Plan
Q1	Lower Quartile
Q3	Upper Quartile
RMP	Risk Management Plan
ROP	Retinopathy of Prematurity
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
SOP	Standard Operating Standard
VA	Visual Acuity
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analysis according to Section 9 of the study protocol and along with any additional analyses, specifications or deviations from the protocol planned.

1.1 Study design

This is a multicenter open-label Extension study (Figure 1-1). Patients who have successfully completed the 24-week Core study (CRFB002H2301) are eligible for entry into the study. Visit 201/ baseline visit of the Extension study can occur on the same day as the last visit in the CRFB002H2301 study.

At Visit 201 (Extension baseline), the investigator or his/her delegate will contact the IRT after confirming the patient fulfills all the inclusion/exclusion criteria. Sample size estimation or formal power calculation was not done for this study. The number of patients is the actual enrollment in the Extension study (Section 4 of study protocol).
Treatment with study ranibizumab (either as re-treatment after ranibizumab has already been injected or as switch ranibizumab treatment from study laser therapy administered in the Core study) will be permitted for eligible eyes up to and including the study visit V203 (week 40 from the baseline visit in the Core study (CRFB002H2301) (equal to week 16 from the baseline visit in Extension study, when the baseline visit in Extension study coincides with the week 24 visit in the Core study) [Epoch 1]). During Epoch 1, the investigator or his/her delegate will contact the IRT upon decision to administer study treatment. IRT will specify a unique medication number for the package of study drug to be dispensed to the patient. The remainder of the Extension study (from the study visit V203, to patients' 5th birthday visit) [Epoch 2] is observational.

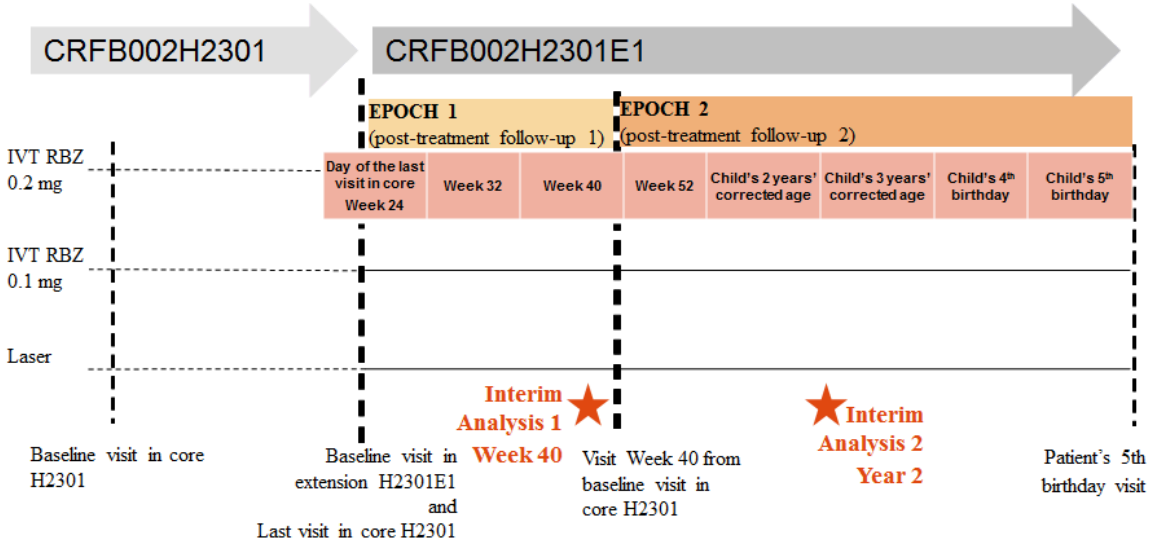
Assessment visits will be performed regularly throughout Epoch 1 and Epoch 2, with the last study visit to be as close as possible to the patient's fifth birthday. The assessments related to the primary objective will be performed at the study visit V399, corresponding to the approximate time of the patient's fifth birthday.

Two interim analyses are planned for the study. Additional interim analyses may be conducted on safety or efficacy data as required.

The first interim analysis will be conducted to comply with the plan for specific follow-up set out in the Pediatric Investigational Plan (PIP) with the EMA and to support the inclusion of information related to the treatment of ROP in the Lucentis product information. This will be performed when the last patient has completed the last visit in the Core study or when at least half of the patients who were enrolled in the Core study have completed the visit which corresponds to the visit occurring 40 weeks after the first study treatment (in the Core study), whichever is the latest.

The second interim analysis will be performed when the last patient has completed the visit which corresponds to the patient's 2 years' corrected age. A patient's corrected age is its chronological age corrected for its prematurity, i.e. calculated by subtracting the number of weeks of prematurity from the chronological age.

Figure 1-1 Study design



1.2 Study objectives and endpoints

All study objectives will be assessed by initial study treatment received at baseline of the Core study CRFB002H2301. The objectives, along with its endpoints and time point for analyses are presented in Table 1-1.

Table 1-1 Study objectives and endpoints

OBJECTIVE	Endpoint Title, Description and Reporting Time frame for analysis and Unit of measure
Primary	
To evaluate the visual function of patients, by assessing the visual acuity in the better-seeing eye at the patient's fifth birthday[a,e]	Title: visual acuity in the better-seeing eye at the patient's fifth birthday Unit of measure: visual acuity score (Lea symbols optotypes) Time frame: at the patient's fifth birthday[e]
Secondary	
To evaluate the safety outcomes by analyzing the type, frequency and severity of ocular and non-ocular Adverse Events[b]	Title: ocular and non-ocular Adverse Events Unit of measure: number and percentage of patients having e.g. any AE; number of hospitalization/ prolongation of hospitalization due to SAE Time frame: from the first study treatment in the Core study up to V203 (Week 40), V302 (the patient's 2 years' corrected age) and V399 (the patient's fifth birthday) in the Extension study

OBJECTIVE	Endpoint Title, Description and Reporting Time frame for analysis and Unit of measure
To evaluate the visual function by assessing the visual acuity in the worse-seeing eye at the patient's fifth birthday[a]	Title: visual acuity in the worse-seeing eye at the patient's fifth birthday Unit of measure: visual acuity score (Lea symbols optotypes) Time frame: at the patient's fifth birthday
To evaluate the absence of active ROP at 40 weeks and 52 weeks post baseline visit in the Core study	Title: absence of active ROP Unit of measure: number and percentage of patients Time frame: at V203 and V301 (40 weeks and 52 weeks post baseline visit in the Core study)
To evaluate the absence of ocular structural abnormalities at or before 40 weeks post baseline visit in the Core study, at the patient's 2 years' corrected age and fifth birthday	Title: absence of all ocular structural abnormalities as listed in Section 2.8.1 Unit of measure: number and percentage of patients Time frame: at or before V203 (Week 40) in the Core/ Extension study, at or before V302 (the patient's 2 years' corrected age), at or before V399 (the patient's fifth birthday) Title: absence of each ocular structural abnormality as listed in Section 2.8.1considered individually Unit of measure: number and percentage of patients Time frame: at or before week 40, at or before patient's 2 years' corrected age, at or before patient's fifth birthday
To evaluate the recurrence of ROP up to 40 weeks post baseline visit in the Core study	Title: recurrence of ROP Unit of measure: number and percentage of patients with recurrence of ROP Description: Recurrence of ROP is defined as ROP receiving any intervention after the 1st study treatment in the Core study[d]. Time frame: up to 40 weeks postbaseline visit in the Core study
To assess the number of ranibizumab injections received in the treatment of patients with ROP up to and including 40 weeks post baseline visit in the Core study	Title: number of ranibizumab injections Unit of measure: number of ranibizumab injections Description: as per title Time frame: up to and including 40 weeks post baseline visit in the Core study

OBJECTIVE	Endpoint Title, Description and Reporting Time frame for analysis and Unit of measure
To evaluate the refraction in each eye at the patient's 2 years' corrected age and fifth birthday[a]	Title: refraction in each eye Unit of measure: diopters Time frame: at patient's 2 years' corrected age, patient's fifth birthday
To evaluate the physical development at the patient's 2 years' corrected age and fifth birthday[b]	Title: standing/sitting height, leg length, weight Unit of measure: centimeter, gram (as appropriate) leg length will be derived from standing/sitting height difference Time frame: at the patient's 2 years' corrected age, at the patient's fifth birthday Title: head circumference Unit of measure: centimeter Time frame: at the patient's 2 years' corrected age
To evaluate the health status at the patient's 2 years' corrected age and fifth birthday[b,c]	Title: respiratory function[b] Unit of measure: number and percentage of patients with oxygen supplementation; with presence of wheezing symptoms Title: hearing function[c] Unit of measure: number and percentage of patients with presence of hearing impairment Title: duration of hospitalization after first hospital discharge home; weight at first hospital discharge home Unit of measure: days/months as appropriate; gram Time frame: at the patient's 2 years' corrected age, at the patient's fifth birthday
[redacted]	

OBJECTIVE	Endpoint Title, Description and Reporting Time frame for analysis and Unit of measure
[redacted]	

a - Variable corresponding to “ocular effects” in the plan for specific follow-up in the Pediatric Investigation Plan (EMA)

b - Variable corresponding to “clinical outcomes” in the plan for specific follow-up in the Pediatric Investigation Plan (EMA)

c - Variable corresponding to “neurodevelopmental outcomes” in the plan for specific follow-up in the Pediatric Investigation Plan (EMA)

d - Supplementary laser treatments (as per CRFB002H2301 study protocol) are considered part of the complete laser treatment

e - At the visit as close as possible to the patient’s fifth birthday

1.3 Cut-off dates

Interim Analysis I: only subjects who have completed Week 40 visit prior to or on December 31, 2017 will be included in Interim Analysis I. For all domains with visit numbers (e.g., DM, DS, ZX, EX), Week 40 visit number will be used for cut-off. For event data without visit number (e.g., AE), December 31, 2017 will be used as the cut-off date.

Interim Analysis II： all subjects from the extension safety set will be included in Interim Analysis II, with a cut-off date defined as the date when the last patient has completed the 2 years’ corrected age visit. For all domains with visit numbers (e.g., DM, DS, ZX, EX), the 2 years’ corrected age visit number will be used for cut-off. For event data without visit number (e.g., AE), all data up to the cut-off date will be reported.

2 Statistical methods

2.1 Changes to the planned analyses in the protocol

The Extension study is conducted to fulfill regulatory requirements independent of whether the Core study succeeds on its primary objective or not. As such, Type I error and power control is not a feature of the Extension study design, and the results cannot be viewed within a valid inferential context. Thus, statistical significance cannot be inferred from any analyses based upon reaching specific significance thresholds. As a result, all hypotheses testing is not aimed to claim statistical significance or superiority of one treatment group against another, but needs to be interpreted with caution.

Patients may receive study treatment up to Week 40 only, while the study is purely observational beyond this time point. Therefore, results from the analysis of “recurrence of ROP up to 52 weeks post baseline visit in the Core study” (stated in protocol Section 9.5.1) would be identical to the results performed for “recurrence of ROP up to week 40 post baseline visit in the Core study”, since recurrence (defined as intervention, i.e. study treatment, received after baseline of the Core study”) remains unchanged and such analysis at week 52 is considered not meaningful.

2.2 Data analysis general information

Three planned analyses will be performed in this study: two interim analyses and one final analysis at the completion of the study. The statistical analysis will be performed or directed by the Biostatistics & Pharmacometrics of Novartis.

Assessments documented in the database that occur as "bilateral" will be summarized and listed for each eye separately. To facilitate derivations and analysis based on eye, database records for bilateral will be split into two records containing identical information as the original record with the exception of the laterality which shall be recoded to "Right" and "Left", respectively.

Change from baseline will only be summarized for patients with both baseline and post-baseline values for the relevant visit and will be calculated as:

Change from baseline = post-baseline value – baseline value

Descriptive statistics (mean, median, standard deviation, lower quartile (Q1), upper quartile (Q3), minimum, and maximum) will be presented for continuous variables. The number and percentage of patients in each category will be presented for categorical variables. If a confidence interval is presented for a categorical variable, then the exact Clopper-Pearson method (Newcombe, R.G., 1998) will be used to calculate the 2-sided 95% confidence interval.

This document is written in the future tense. It will be reviewed and updated (including conversion to past tense) for entry into the clinical study report (CSR) after the analysis has taken place. The analyses described in this document will be conducted using SAS version 9.4 or later.

2.2.1 General definitions

Study treatment refers to study ranibizumab in both Core and Extension studies, and laser therapy in the Core study. (Please note that laser is a study treatment in the Core study but not a study treatment in the Extension study.) In this document, patient and subject are used interchangeably throughout the document.

A patient randomized to ranibizumab in the Core study can receive switch/rescue laser therapy in either eye; a patient randomized to laser therapy in the Core study can receive switch/rescue ranibizumab 0.2 mg in either eye. The change of treatment modality from laser to ranibizumab can occur at any time in the Core study and only in Epoch 1 of the Extension study, while the change of treatment modality from ranibizumab to laser can only occur in the Core study as only ranibizumab is available as study treatment in the Extension study. No further ranibizumab treatment can be administered to the eye after it has been switched to laser. The switch of study treatment occurs when the patient first receives a treatment modality other than the modality of the first study treatment in either eye, which can occur in the Core or Extension study period.

There are three treatment arms defined by the initial treatment received at baseline of the Core study:

- 0.2 mg Ranibizumab arm (same as Ranibizumab 0.2 mg arm)
- 0.1 mg Ranibizumab arm (same as Ranibizumab 0.1 mg arm)
- Laser treatment arm (same as Laser arm)

All results will be displayed by the initial treatment received at Core study baseline. If appropriate, within each of these three treatment arms, analyses may also be conducted separately for patients who received monotherapy or who switched treatment (by eye or by patient as applicable) during the Core study.

Two baselines are defined; Core baseline and Extension baseline. For statistical purposes, the last available non-missing values collected in study CRFB002H2301 or CRFB002H2301E1 prior to or on visit 201 will be considered to be the Extension baseline values. Core baseline will be used as baseline for both efficacy and safety analyses. The Extension baseline will be used for the demographic summary of the Extension study.

2.2.1.1 Baseline definition and post-baseline definitions

All data collected after Day 1 of the Core study are defined as post-Core baseline.

All data collected after the Extension baseline visit are defined as post-Extension baseline. The study day relative to Core baseline for a scheduled or unscheduled visit which is on or after the date of first study treatment (of the Core study) in either eye is defined as

Study day = (Date of visit) – (date of first study treatment in either eye in Core study) + 1

The study day relative to Core baseline for a scheduled or unscheduled visit which is before the date of first study treatment (of the Core study) in either eye is defined as

Study day = (Date of visit) – (date of first study treatment in either eye in Core study)

The study day relative to Extension baseline for a scheduled or unscheduled visit on or after Extension baseline is defined as

Study day = (Date of visit) – (date of Visit 201 in Extension study) + 1

For the purposes of classifying an eye by ROP disease status, the worst disease present in any clock hour of the eye, ranked in descending order from worse to best in Table 2-1, will be used to classify the eye at Core baseline and during the study.
Plus disease is defined as vascular tortuosity and dilatation in at least 2 quadrants of the eye (International Committee for the Classification of Retinopathy of Prematurity 2005).
For the purposes of classifying a patient by ROP disease status, the worst eye ranked in descending order from worse to best in Table 2-1 will be derived from the eCRF.
If both eyes have the same zone and stage, then the worst eye is the one with the greater total number of clock hours with the highest stage. If this is also the same for both eyes, then the left eye will be assigned as the worst eye.
The better-seeing eye and the worse-seeing eye at the 5th birthday visit are defined as the eye with a higher and lower ETDRS letter score, respectively. If both eyes have the same ETDRS letter score, then the left eye will be assigned as the worse-seeing eye.
The best vision of the Low Visual Acuity Testing is defined as the best assessment with an answer 'YES', in the order of 'Count fingers' > 'Hand movement' > 'Light perception'. If all assessments have answers 'No', the best vision of the Low Visual Acuity Testing is defined as 'None of the above'. If the eye had a Low Visual Acuity Testing and all assessments have missing answers, the best vision of the Low Visual Acuity Testing is defined as 'Missing'.

Table 2-1 Ranking of Retinopathy of Prematurity Disease

Zone	Stage
Any	5
Any	4
I	AP-ROP
II	AP-ROP
I	3+
I	3
I	2+
I	1+
II	3+
II	2+
I	2
I	1
II	3
II	2
II	1+
II	1
III	3+
III	3
III	2+
III	2
III	1+
III	1

Abbreviations: AP-ROP - aggressive posterior retinopathy of prematurity; ROP - retinopathy of prematurity

2.2.1.2 The last study visit

The last study visit is Visit 399 (including premature withdrawal). If the patient does not discontinue the study, Visit 399 will occur close to the patient's fifth birthday.

For the visual acuity at Visit 399, the study day will be allocated to the 5th birthday visit if the study day is before the 5th birthday and within 3 months of the 5th birthday, or if the study day is after the 5th birthday.

For all other variables except for the visual acuity, the study day for the premature withdrawal Visit 399 will be allocated to the nearest planned main visit if data for the nearest planned main visit does not already exist and if the study day is within the allocation windows of the planned main visit.

All applicable assessments will be captured by scheduled visit. Table 2-2 shows the allocation windows of premature withdrawal visit to a scheduled main visit of H2301E1.

Table 2-2 Allocation of premature withdrawal visit

Scheduled main visit number	Scheduled visit study week/year	Scheduled visit window in days
202	Week 32	197 – 253
203	Week 40	254 – 323
301	Week 52	324 – (Start date of mother's last menstrual period – Core study baseline visit date+766)
302	2-year corrected age	(Start date of mother's last menstrual period – Core study baseline visit date+891) – (Start date of mother's last menstrual period – Core study baseline visit date+1131)
303	3-year corrected age	(Start date of mother's last menstrual period – Core study baseline visit date+1257) – (Start date of mother's last menstrual period – Core study baseline visit date+1497)
304	4th birthday	(Start date of mother's last menstrual period + gestational age (in weeks) *7 – Core study baseline visit date +1341) – (Start date of mother's last menstrual period + gestational age (in weeks) *7 – Core study baseline visit date +1581)
	5th birthday	For visual acuity: (Start date of mother's last menstrual period + gestational age (in weeks) *7 – Core study baseline visit date +1736) – End of study For variables other than visual acuity: (Start date of mother's last menstrual period + gestational age (in weeks) *7 – Core study baseline visit date +1706) – (Start date of mother's last menstrual period + gestational age (in weeks) *7 – Core study baseline visit date +1946)

2.2.1.3 Additional assessment visit schedule

The additional assessment visits of Epoch 1 are triggered by a post-baseline treatment (re-treatment with ranibizumab or switch ranibizumab treatment from study laser therapy in the Core study) (Section 6 of Protocol). When a visit as per the additional assessment schedule coincides with a visit as per the main assessment schedule, assessments have to be performed as per the main assessment schedule.

For analyses by visit, only data of planned main visits will be reported. For analyses up to a certain time point, data of both planned main visits and additional assessment visits up to that time point will be considered. All data collected at additional assessment visits will be used for analysis and listed.

2.2.1.4 Unscheduled visits

All data collected at unscheduled visits will be listed.

All safety and exposure to treatment data collected at unscheduled visits will be considered. [redacted]

Other data collected at unscheduled visits will not be used for tables and graphs analyzing post-baseline data when reporting by scheduled visit.

2.2.1.5 Missing baseline data

Missing baseline data (both Core baseline and Extension baseline) will not be imputed. This includes variables which are not allowed to be collected according to local regulations (e.g. race in France).

2.2.1.6 Missing post-baseline data

Observations with values 'not done', 'not evaluable', 'not applicable' will be treated as missing values.

Missing efficacy data will not be imputed.

Apart from AE and concomitant medication dates, missing post-baseline safety data will not be imputed.

Missing data for other variables will not be imputed unless otherwise specified.

2.2.2 Data for permanent study treatment discontinuation

Patients that permanently discontinue study treatment will remain in the study and all planned assessments should be conducted (Section 5.6.2 of Protocol).

2.3 Analysis sets

The Extension Safety Set for this study is defined as the subset of the patients from the Safety Set of the Core study who enter this Extension study and comprises data from both the Core and Extension studies.

All analyses will be carried out on the Extension Safety Set and displayed by the initial study treatment received at the baseline of the Core study unless otherwise specified.

Table 4-1 shows the protocol deviations leading to data exclusion from the analysis data set.

2.4 Patient disposition, demographics and other baseline characteristics

Outputs for subject disposition, and demographic characteristics will be reported for each treatment arm and all patients (total). Demographic and baseline characteristics will be summarized for both Core baseline and Extension baseline.

No tests for differences in demographic characteristics among treatment arms will be performed.

Relevant medical history and current medical conditions using the Core baseline will be tabulated by system organ class (arranged alphabetically) and preferred term (arranged by decreasing frequency sequentially in the ranibizumab 0.2 mg treatment arm) according to the latest MedDRA version . Separate tables will be presented for ocular and non-ocular histories and conditions. The reporting will be by patient (not eye).

The same approach will be used for the relevant medical history and current medical conditions using the Extension baseline, which will include medical history/condition collected after the last visit in Core study and before the baseline visit in this Extension study, corresponding to segment b of Figure 2-1.

Partial dates of diagnosis will be imputed using imputation rules as stated in Section 4.1.3.

Guidance of Data Entry rules in the Extension study eCRF which provides details on handling of Medical History in the Extension study.

- Core Medical History which is still ongoing at the time of enrollment (Baseline Visit) into the Extension study will not be reported again as Extension Medical History.
- Core Medical History which resolved before enrollment into the Extension will not be reported as Extension Medical History.
- Core Medical History which resolved before the Core End of Study visit and which reoccurred after the Core End of Study visit but before enrollment into the Extension study, will be entered as Extension Medical History. For such cases, multiple episodes of the same Medical History will appear across the Core and Extension study but with different start dates.
- Adverse Events (AEs) and Serious Adverse Events (SAEs) continuing at the end of Core study which resolved prior to Extension informed consent form date will be reported as Extension medical history with medical history ongoing status as "No", further medical history term, preferred term (start date) should be an exact match to adverse event term, preferred term and adverse event start date. No plausible entries are accepted.
- Adverse Events (AEs) and Serious Adverse Events (SAEs) which started after end of Core study and resolved before the time of Extension study enrollment (Baseline Visit) will be reported as Extension medical history with medical history ongoing status as "No".
- Adverse Events (AEs) and Serious Adverse Events (SAEs) which started after end of Core study and are ongoing at the time of Extension study enrollment (Baseline Visit) will be reported as Extension medical history with medical history ongoing status as "Yes"..

Tabular format for Data Entry rules in the Extension study eCRF for Medical History

Item	Started	Ended	Action for ECRF
Med Hx	before Core	Ongoing end of Core and at beginning of Ext	Don't record as MHx in Ext (MHx of Core)
Med Hx	before Core	Ongoing end of Core and finished in Gap	Don't record as MHx in Ext (MHx of Core)
Med Hx	Gap	Gap	Record as MHx in Extension (not ongoing)
Med Hx	Gap	Ongoing at beginning of Ext	Record as MHx in Extension (ongoing)
(S)AEs	Core	ongoing end of Core and finish in gap (before Ext)	Record as MHx in Extension (not ongoing)
condition	Gap	Ongoing at beginning of Ext	Record as MHx in Extension (ongoing)
condition	Gap	Gap	Record as MHx in Extension (not ongoing)

2.4.1 Patient disposition

All disposition tables will be based on the Extension safety set. Subject disposition data is collected in specific eCRF disposition pages based on the epochs (time intervals in the course of the study) as defined in the protocol; reporting of disposition data will be presented by epoch.

The Extension study period starts from Extension baseline and includes 2 epochs: post-treatment follow-up 1 and post-treatment follow-up 2.

The number and proportion of patients who completed each epoch and who discontinued the study prior to completion of the epoch will be presented. Also the number and proportion of the primary reason for not completing each epoch will be presented.

The primary reason for premature study discontinuation and permanent study treatment discontinuation will be displayed by actual treatment and overall for this Extension study.

Baseline-Failure Subjects are patients with informed consent obtained from their parent(s) or legal guardian(s) but who were discontinued at the baseline visit because they did not meet all inclusion/exclusion criteria. The number of these patients and their reasons for inclusion/exclusion failure will be summarized.

The number of patients with CSR reportable PDs according to the applicable SOP will be presented for this Extension study. The results will be grouped using the broad categories defined in the applicable SOP, which currently are:

- Eligibility: Patients who entered the trial even though they did not satisfy the entry criteria
- Withdrawal: Patients who developed withdrawal criteria during the trial, but were not withdrawn
- Study Drug: Patients who received the wrong treatment or incorrect dose
- Concomitant Medication: Patients who received an prohibited concomitant medication
- Other reportable protocol deviation

The reasons for exclusion from efficacy or safety analysis will be listed.

2.4.2 Baseline and demographic characteristics

Descriptive statistics (mean, median, standard deviation, minimum and maximum, quartiles 1 and 3) will be presented for the continuous variables. The number and percentage of patients will be presented for categorical variables.

Table 2-3 shows the allocation of baseline parameters into groups and which are displayed as continuous and/or categorical variables.

Table 2-3 Display of baseline parameters:

	Demographic	ROP characteristics and relevant medical history	Continuous	Categorical
Race	x			x

Ethnicity (based on that of mother)	x			x
Sex	x			x
Gestational age at birth (by completed weeks)	x		x	x
Chronological age at Core baseline (by weeks)	x		x	
Chronological age at Extension baseline (by weeks)	x		x	
Post-menstrual age at Core baseline (by weeks)	x		x	
Post-menstrual age at Extension baseline (by weeks)	x		x	
Corrected age at Extension baseline (by weeks)	x		x	
Birth weight (g)		x	x	x
Body length at birth (cm)		x	x	x
Head circumference at birth (cm)		x	x	x
Lower leg length		x	x	x
ROP zone by patient		x		x
ROP zone by eye		x		x
AP-ROP status by patient		x		x
AP-ROP status by eye		x		x
ROP disease status by patient		x		x
ROP disease status by eye (worst/best)		x		x
APGAR sCore at 1 minute		x	x	
APGAR sCore at 5 minutes		x	x	
Intubation requirement before enrollment (y/n)		x		x
Multiple pregnancy (y/n)		x		x
Number in multiple infants born of a multiple pregnancy		x	x	
Born in study hospital (y/n)		x		x
Time from first diagnosis of ROP to screening visit (weeks)		x	x	x
Time from ROP fulfilling treatment criteria to screening visit (weeks)		x	x	x

Chronological age and Post-menstrual age will be calculated from Core study baseline as below:

Chronological age at Core/Extension baseline (weeks) = [Core/Extension baseline visit date - (start date of the mother's last normal menstrual period + gestational age at birth*7)+1]/7

Post menstrual age at baseline (weeks) = (Core/Extension baseline visit date - start date of the mother's last normal menstrual period+1)/7

Corrected age at Extension baseline (weeks) = [Extension baseline visit date - (start date of the mother's last normal menstrual period + 40*7)+1]/7

The time from a pre-screening event (e.g. diagnosis of a condition or taking a medication) in days will be derived using the formula:

Time since <event> [days] = date of screening– date of event

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

2.5.1 Study treatment / compliance

Exposure will be calculated for patients in the Extension safety set from Core baseline. Note that only study ranibizumab as collected in the Drug Administration Record (DAR) eCRF panel will be included. Treatments collected as a concomitant medication will not be included in the study medication analysis. Laser treatment is not a study treatment in the Extension study and therefore will not be collected in the DAR eCRF and will not be summarized here.

Exposure to ranibizumab is defined as the number of injections of ranibizumab received by worst/best eye (as defined in the Core study) and by patient.

The total number of ranibizumab injections will be summarized by worst/best eye and by patient by treatment arm. Summaries will be provided for the entire study period from Core baseline, and for Extension study period. (Note: summary will be summarized by initial treatment received at the baseline ofofof the Core.

The duration of the observation period will be displayed for each treatment arm, and in the Extension study, and overall from Core study baseline.

2.5.2 Prior and concomitant medications

Separate listings and summaries will be produced for ocular and non-ocular, for both prior and concomitant medication, in both Core baseline and Extension baseline based on the Extension safey set.

<u>For Core baseline:</u>

Prior medications are defined as those taken and stopped prior to the date of first study treatment in the Core study. Any medication given at least once on or after the first study treatment date of the Core study will be defined as a concomitant medication. Concomitant therapies taken after the first study treatment in the Core study, which prohibits further use of study treatment

(refers to ranibizumab or study laser in the Core study period and only refers to ranibizumab in the Extension study period) may be summarized separately.

For Extension baseline:

Prior medications are defined as those with an end date prior to the Extension baseline visit. Any medication given at least once on or after the Extension baseline visit will be defined as concomitant medication. Concomitant therapies taken after the extension baseline visit, which prohibits further use of ranibizumab (in the Extension study) may be summarized separately.

Guidance of Data Entry rules in the Extension study eCRF which provides details on handling of Concomitant Medication in Extension study.

- Concomitant Medications continuing at the Core End of Study visit which are ongoing at the time of enrollment into the Extension need to be reported as Extension Concomitant Medication with the same Medication term, Category, Location, Laterality, Is med used for ocular condition, Location of treated condition, Reason and Start date.

- Concomitant Medications continuing at the Core End of Study visit which stopped before enrollment into the Extension, need to be reported again as Extension Concomitant Medication with the same Medication term, Category, Location, Laterality, Is medication used for ocular condition, Location of treated condition, Reason and Start date. Note, that in such a case the Extension Concomitant record must have an end date.
- For subjects where the Core End of Study and Extension baseline visit are occurring on the same date; any ongoing concomitant medication with a start date at this combined Core End of Study and Extension baseline visit, should be recorded in both, the Core and Extension "Prior and Concomitant Medications" CRF pages.
- With regards to vaccinations, if the initial administration was performed in the Core study, this should not be again recorded in the Extension. Only booster doses administered during the Extension study, if any, should be recorded.

Tabular format for Data Entry rules in the Extension study eCRF for Concomitant Medication

Item	Started	Ended	Action for ECRF
Con Meds	Core	Ongoing at beginning of Ext	Record as Con Med in Extension
Con Meds	Core	Gap	Record as Con Med in Extension (=reported as prior medication)
Con Meds	Gap	Gap	Record as Con Med in Extension *(Only if this conmed is of relevance and in the context of a recorded medical history record or (S) AE. Not as a standalone.=reported as prior medication)
Con Meds	Gap	Ongoing beginning of Ext	Record as Con Med in Extension
Con Meds	Ext		Record as Con Med in Extension

Medications will be identified by preferred term (PT) according to the latest World Health Organization (WHO) Drug Reference List dictionary and ATC code. Tables will show the overall number and percentage of patients within the treatment arm receiving at least one dose of the medication ordered by decreasing frequency in the ranibizumab 0.2 mg treatment arm.

For missing medication date, please refer to Appendix 4 for imputation rule.

2.5.3 Surgical and medical procedure

Surgical and medical procedures will be displayed separately for Core and Extension studies, and separate from concomitant medications.

Guidance of Data Entry rules in the Extension study eCRF which provides details on handling of Surgeries and procedures in Extension study:

- It is not expected that records for surgery and procedures in the Core study must be re-entered in the Extension study, as they are usually not continuing over a long period of time. However, if any, records are expected to match (with the exceptions of end dates).
- Procedures which occurred after end of Core study and ended prior to enrollment in to the Extension study should be entered in Extension medical history.

The same approach will be taken to display surgeries and procedures as specified for concomitant medications in Section 2.5.2. Surgical and medical procedures will be identified by primary system organ class and preferred team according to the WHO Drug Reference List dictionary.

2.6 Analysis of the primary objective

2.6.1 Primary endpoint

The primary efficacy variable is the visual acuity (VA) in the better-seeing eye at the patient's fifth birthday as recorded by the investigator.

The primary efficacy analysis will be based on the Extension safety set.

Note that the ranibizumab 0.2 mg arm includes those patients that received ranibizumab 0.2 mg at baseline in the Core study. This includes patients that received laser treatment at a later date in either the Core or Extension study. Patients that permanently discontinue treatment with ranibizumab 0.2 mg are also included in primary efficacy analysis. However, patients for which the value of the primary variable is missing are excluded. A similar approach is taken for the ranibizumab 0.1 mg arm.

Similarly, the laser arm includes those patients that received laser at baseline in the Core study CRFB002H2301. This includes patients that received ranibizumab 0.2 mg treatment at a later date in either the Core or Extension study. Patients that permanently discontinue treatment with laser are also included in the primary efficacy analysis. However, patients for which the value of the primary variable is missing are excluded.

2.6.2 Statistical hypothesis, model, and method of analysis

If the primary hypothesis testing in the Core study shows statistical significance, the primary objective is to compare ranibizumab 0.2 mg versus laser with an informal testing as follows:

H_{01}: $\mu_{\text{ranibizumab 0.2 mg}} - \mu_{\text{Laser}} = 0$ versus H_{A1}: $\mu_{\text{ranibizumab 0.2 mg}} - \mu_{\text{Laser}} \neq 0$

where $\mu_{\text{Treatment}}$ arm is the unknown mean VA in the better-seeing eye at the fifth birthday of patients in the relevant treatment arm.

The hypothesis will be tested by using stratified analysis of variance (ANOVA) using the Cochran-Mantel-Haenszel (CMH) test with the observed VA values (letters) as the ordinal response variable and the treatment arm as the factor (with levels ranibizumab 0.2 mg and laser). The effect of ROP zone at the baseline of the Core study is expected to have an effect at 5 years of age. Hence this variable is used as stratification factor in the analysis.

If the primary hypothesis testing in the Core study does not show statistical significance, only descriptive statistics (i.e., point estimate, and the 95% confidence interval) will be provided for the comparison between ranibizumab 0.2 mg and laser.

In addition, an unstratified two-way ANOVA using VA as the response variable and treatment arm and ROP zone as factors will be performed. This is essentially a one-way ANOVA using VA as the response variable and treatment arm as the factor, without ROP zone as the stratification factor. Two-sided 95% confidence intervals, assuming normality, will be produced for the VA within each treatment arm and the difference in VA between a pair of treatment arms will be calculated from least squares means. No p-values will be displayed for this analysis.

2.6.3 Handling of missing values/censoring/discontinuations

Missing data will not be imputed for the primary efficacy analysis. Hence, the analysis of the primary variable is only conducted for patients with a non-missing value of VA at the patient's fifth birthday visit.

2.6.4 Supportive analyses

The primary variable will also be assessed by using the randomized rather than the initial treatment received at baseline of Core study.

If a sufficient number of patients switch treatment during either the Core or Extension studies then additional analyses may be considered. This includes providing summary statistics for patients that receive monotherapy and on those that switch treatment separately.

If a sufficient number of patients receive a medication which prohibits further use of ranibizumab or study laser then an additional analysis will be conducted by performing the primary analysis (CMH test of Section 2.6.2) on the total Extension safety set including patients who received prohibited medications.

As a sensitivity analysis, the primary variable was also assessed separately for patients who had positive visual acuity letter score (excluding patients who have a 0 or missing visual acuity letter score).

As a sensitivity analysis, the primary variable was also assessed separately by best/worst eye.

The primary endpoint was also summarized by frequency of its value falling into several categories: 0 letter, >= 1 letter to <= 34 letters, >=35 letters to <= 70 letters, and >= 71 letters.

2.7 Analysis of the key secondary objective

There is no key secondary objective.

2.8 Analysis of secondary efficacy objective(s)

The analyses for objectives which are assessed up to a particular time (e.g. up to the patient's fifth birthday) will include data collected in both the Core and Extension studies. The secondary efficacy analysis will be based on Extension safety set.

No multiplicity adjustment will be used for the analysis of secondary variables.

2.8.1 Secondary endpoints

Continuous variables:

The following objectives will be assessed for the continuous variables below by using the same CMH test approach as the primary analysis with ROP zone at Core baseline as stratification factor.

- The comparison between ranibizumab 0.1 mg and laser with regard to the VA of the better- seeing eye at the patient's fifth birthday
- The comparison of ranibizumab 0.2 mg versus ranibizumab 0.1 mg with regard to the VA of the better-seeing eye at the patient's fifth birthday
- The three pairwise comparisons of treatment arms will be repeated with regard to the VA of the worse-seeing eye at the patient's fifth birthday

Again, one needs to be cautious interpreting the p-values when they show statistical significance and the point estimates indicate ranibizumab treatment is better than laser.

Recurrence of ROP is defined as ROP receiving any study intervention after the first study treatment of the Core study.

Binary variables:

- The absence of all ocular structural abnormalities (see below for the definitions) at or before the patient's 2 years' corrected age and fifth birthday.
- The absence of active ROP at 52 weeks post Core baseline

The CMH test with ROP Zone as assessed at the baseline of the Core study as stratification factor will be used for inference concerning binary secondary efficacy variables. Mantel-Haenszel odds ratios and their two-sided 95% confidence intervals will be presented. The rejection of the null hypothesis (equality of proportions) and the Mantel-Haenszel odds ratio being in favor of the hypothesized superior treatment should be interpreted with caution.

The absence of active ROP in both eyes is defined by the absence of all of the following features:

- Vessel dilatation of plus disease in at least 2 quardrants (some persisting tortuosity is allowed)

- Extra-retinal vessels extending from the retina into the vitreous and judged to be a sign of active ROP disease.

The absence is defined as the absence of both of the above individual components at a particular time point, e.g., at week 40.

The absence of all ocular structural abnormalities is defined by the absence of all of the following fundus features in both eyes at or before a particular time point, e.g., week 40 after the first study treatment in the Core study:

- Substantial temporal retinal vessel dragging causing abnormal structural features/ macular ectopia
- Retrolental membrane obscuring the view of the posterior pole
- Posterior retinal fold involving the macula
- Retinal detachment involving the macula

The absence is defined as the absence of the above individual components at all visits prior to and at a particular time point. Therefore, at least one presence of the above individual components at any visit prior to or at that time point is considered presence of ocular structural abnormalities. If at all visits up to that time point, the entry of at least one of the individual components is missing and none of the others indicates the presence of the disease feature, the subject will be considered as having missing record for this outcome.

The absence of each ocular structural abnormality considered individually in both eyes at or before a particular time point:

- Substantial temporal retinal vessel dragging causing abnormal structural features/ macular ectopia
- Retrolental membrane obscuring the view of the posterior pole
- Posterior retinal fold involving the macula
- Retinal detachment involving the macula
- Retinal detachment not involving the macula
- Pre-retinal fibrosis
- Optic disc pallor (from Visit 301/week 52 included onwards)
- Optic disc swelling (from Visit 301/week 52 included onwards)
- Pigmentary disturbance in the macula (from Visit 301/week 52 included onwards)
- Atrophic changes in the macula (from Visit 301/week 52 included onwards)

- Low visual acuity testing:

  Descriptive statistics will be provided for the best vision of the Low Visual Acuity Testing by treatment arm for subjects who have 0 or missing ETDRS letter scores at the 5th birthday visit by best/worst eye.

Other efficacy variables:

Descriptive statistics with 95% Clopper-Pearson exact confidence interval will be provided for these efficacy variables by treatment arm:

- The absence of all ocular structural abnormalities (see Section 2.15 for the definitions) at or before 40 weeks post baseline visit in the Core study
- The recurrence of ROP up to 40 weeks post Core baseline
- The absence of active ROP at 40 weeks post Core baseline
- The absence of each ocular structural abnormality considered individually (see Section 2.14 for the definitions) at or before the patient's 2 years' corrected age and at or before the patient's fifth birthday
- At the patient's 2 years' corrected age and fifth birthday
  - The refraction in each eye: Refractive error will be categorized into myopia (spherical equivalent of equal to or less than -0.25 dioptres) and high myopia (spherical equivalent of equal to or less than -5.00 dioptres). The percentage of patients with and without myopia, and with high myopia will be displayed.

If the entry of one of the above individual components is missing and the other indicates absence of the disease feature, the subject will be considered as having missing record for this outcome.Handling of missing values/censoring/discontinuations

No imputation of missing data will be used for the analysis of secondary variables unless specified in a scoring manual or similar.

2.9 Safety analyses

Safety analyses will be conducted on data from the Extension Safety Set by initial treatment received in the Core study. Adverse events, vital signs, health status and laboratory evaluations will be summarized and listed.

The safety observation period (days) for treated patients comprises two segments:

(1) the first segment starts from first study treatment in the Core study and ends at the last visit in the Core study. This corresponds to period "a" in Figure 2-1.

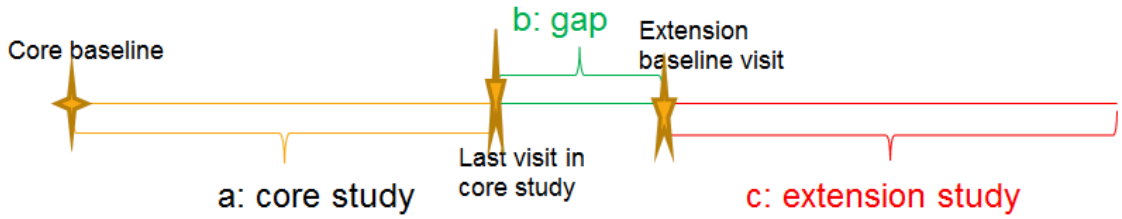
(2) the second segment starts from the Extension baseline visit to the last visit in the Extension study. This corresponds to period "c" in Figure 2-1.

This safety observation period for a patient can be seamless (when the last visit of Core study occurs on the same day as the Extension baseline visit) or non-seamless (when the last visit of Core study does not occur on the same day as the Extension baseline visit). Any safety signs occurring in the gap, segment "b", will be reported as medical history of Extension baseline as in Section 2.3. The resulted safety observation period (days) for the Extension study is defined as below:

- For seamless roll-over:
  - Safety observation period for the Extension: date of last visit in Extension study – date of baseline visit of Extension study
  - Safety observation period from Core baseline: date of last visit in Extension study – date of first study treatment in Core study + 1
- For non-seamless roll-over:

- Safety observation period for the Extension: date of last visit in Extension study (or cut-off date) – date of baseline visit of Extension study +1
- Safety observation period from Core baseline: (date of last visit in Extension study – date of baseline visit of Extension study +1) + (date of last visit in Core study – date of first study treatment in Core study +1)

Figure 2-1 Safety observation period



2.9.1 Risk Management Plan (RMP) adverse events

The number and percentage of patients who report adverse events (AEs) as safety risks (based on selected preferred terms) by the current version of the Risk Management Plan (RMP) at the time of database lock, will be summarized by risk categories for ocular and systemic safety risks for the entire study period. In addition, the analysis will include number and percentage of patients with each of the preferred terms that define each of the safety risk categories. Detailed specifications to identify which MedDRA preferred terms belong to which risk category will be added later – based on the valid RMP at that time-point.

A listing for AEs of safety risk by preferred term will also be produced.

2.9.2 Adverse events (AEs)

As a default, no summary tables for AEs that occur prior to the first study treatment in either eye will be produced.

Adverse events that occur prior to the first study treatment in either eye in Core study will be listed for patients.

Adverse events will be deemed treatment emergent if the AE start time is on or after the time of dose of the first study treatment in the Core study. When an AE's start date is equal to the date of first study treatment and either the start time of the AE or the first treatment time is missing, AEs are defined as treatment emergent. As stated in Appendix 4, adverse events with completely missing start date will be defined as treatment emergent.

The AE incidence rates will be tabulated using the latest MedDRA SOCs and PTs by initial study treatment received at Core baseline. The SOCs will be presented in alphabetical order and PTs will be ordered within the SOC by decreasing proportion in the ranibizumab 0.2 mg treatment arm (with/without laser).)). Patients who experienced multiple AEs for a preferred

term will be counted once, similarly for patients with multiple AEs per system organ class. In-text tables will display the frequency of AEs at the PT level. Post-text table will commonly display the frequency of AEs at the PT levels within the relevant SOC.

Only treatment-emergent AEs will be summarized, separately for ocular and non-ocular AEs (according to the investigator's response on the AE CRF form).

Guidance of Data Entry rules in the Extension study eCRF which provides details on handling of Adverse Events (AEs) and Serious Adverse Events (SAEs) in Extension study.

- Adverse Events (AEs) and Serious Adverse Events (SAEs) ongoing at the end of Core study visit which are ongoing at the Extension study informed consent form date needs to be reported as Adverse Event (AEs) or Serious Adverse Events (SAEs) for Extension study. Adverse event term, preferred term, category, does Adverse event meet definition of Serious Adverse events, Serios adverse event date, severity, location, laterality, Adverse Event start date and time must match between Core and Extension study.

  Note: there can be differences across seriousness criteria, action taken with study treatment, medication or therapies taken etc.
- AEs which resolved in the Core study should not be re-entered (duplicated) in the Extension.
- An Extension adverse event or serious adverse events with a start date prior to end of Core study must have a corresponding Core adverse event record.
- Any serious adverse events, regardless of causality, newly occurring or recurring after Informed Consent Form was obtained for the Extension study needs to be reported to Novartis Safety as part of the Extension study.
- Serious adverse events should never be reported to Novartis Safety in duplicate, i.e. for the Core and the Extension study. Any serious adverse events follow-ups sent to Novartis Safety should be sent as part of the study where the original SAE was reported.

Item	Started	Ended	Action for ECRF
(S)AEs	Core	Ongoing end of Core and ongoing at beginning of Ext (Signed ICF)	Record as (S)AE in Extension
(S)AEs	Ext		Record as (S)AE in Extension

All AE tables will show the frequency and crude incidence rate by initial study treatment received and total. The following AE tables will be produced for ocular and non-ocular AEs separately.

- All adverse events regardless of study treatment or procedure relationship
- Adverse events with start dates prior to the extension baseline
- Adverse events with start dates on or after the extension baseline
- Serious adverse event, regardless of study treatment or procedure relationship
- All adverse events suspected to be related to study treatment or procedure
- Serious adverse event suspected to be related to study treatment or procedure

- All adverse events causing permanent study treatment discontinuation
- All adverse events causing permanent study discontinuation
- All adverse events by maximum severity (mild, moderate, severe)

In addition, the following summaries will be produced.

- Deaths, SAE, or AE leading to permanent study treatment discontinuation

All deaths, SAEs, and AEs leading to permanent study drug discontinuation will be listed separately.

For missing dates for medication or AE, please refer to Appendix 4 for imputation rule.

2.9.2.1 Adverse events of special interest / grouping of AEs

The number of hospitalizations/prolongations of hospitalization due to an SAE will be summarized.

2.9.3 Laboratory data

Laboratory evaluations (hematology, chemistry, urinalysis) will be summarized by presenting summary statistics of values and change from Core baseline at applicable visits by treatment arm.

2.9.4 Other safety data

2.9.4.1 ECG and cardiac imaging data

Not applicable.

2.9.4.2 Vital signs

Vital signs (weight, head circumference, body length, standing height, knee to heel length, sitting height, leg length, and blood pressure (systolic/diastolic)) will be summarized by presenting summary statistics (n, mean, median, standard deviation, min, max, quartiles 1 and 3) for available visits by treatment group. Their changes from Core baseline values will also be summarized if applicable by treatment arm.

Leg length= standing height – sitting height

Table 2-2 Vital signs collection in Core and Extension study

Vital signs	Core study		Extension study	
Weight	x	Day 1, 85, 169	x	Year 2, 5th birthday
Head circumference	x	Day 1, 85, 169	x	Year 2
Body length*	x	Day 1, 85, 169		
Standing height*			x	Year 2, 5th birthday

Sitting height			x	Year 2, 5th birthday
Knee to heel length	x	Day 1, 85, 169		
Leg length*				
Blood pressure	x	Day 1, 85, 169	x	Year 2

Note: * body length is collected in the Core study while standing height is collected in the Extension study. These two variable are assessing whole body growth but are not fully comparable. Leg length will be derived from the standing/sitting height difference.

2.9.4.3 Health status

Respiratory function status:

The patient's respiratory function status will be summarized and listed for applicable visits by treatment arm.

For the Core study period, the requirement for respiratory support (other than oxygen therapy) and the requirement for oxygen therapy will be summarized. Positive end-expiratory pressure, fraction of inspired oxygen and percentage of oxygen saturation will be summarized by presenting summary statistics of values and change from Core baseline to day 169 by treatment arm.

For the Extension study period, the respiratory function status (wheezing/whistling status, number of attacks of wheezing, frequency of sleep disturbance, presence of wheezing limiting patient's speech ability, dry cough status and presence of smoker at home) will be summarized for the patients' 2 years' corrected age visit and 5th birthday visit.

Hearing function status:

The patient's hearing function status will be summarized and listed for the patients' 2 years' corrected age visit and 5th birthday visit.

Hospitalization:

Duration of hospitalization (from birth to first hospital discharge home) from the Core study and weight at the first discharge from hospital home will be summarized.

2.10 Pharmacokinetic endpoints

Not applicable.

2.11 PD and PK/PD analyses

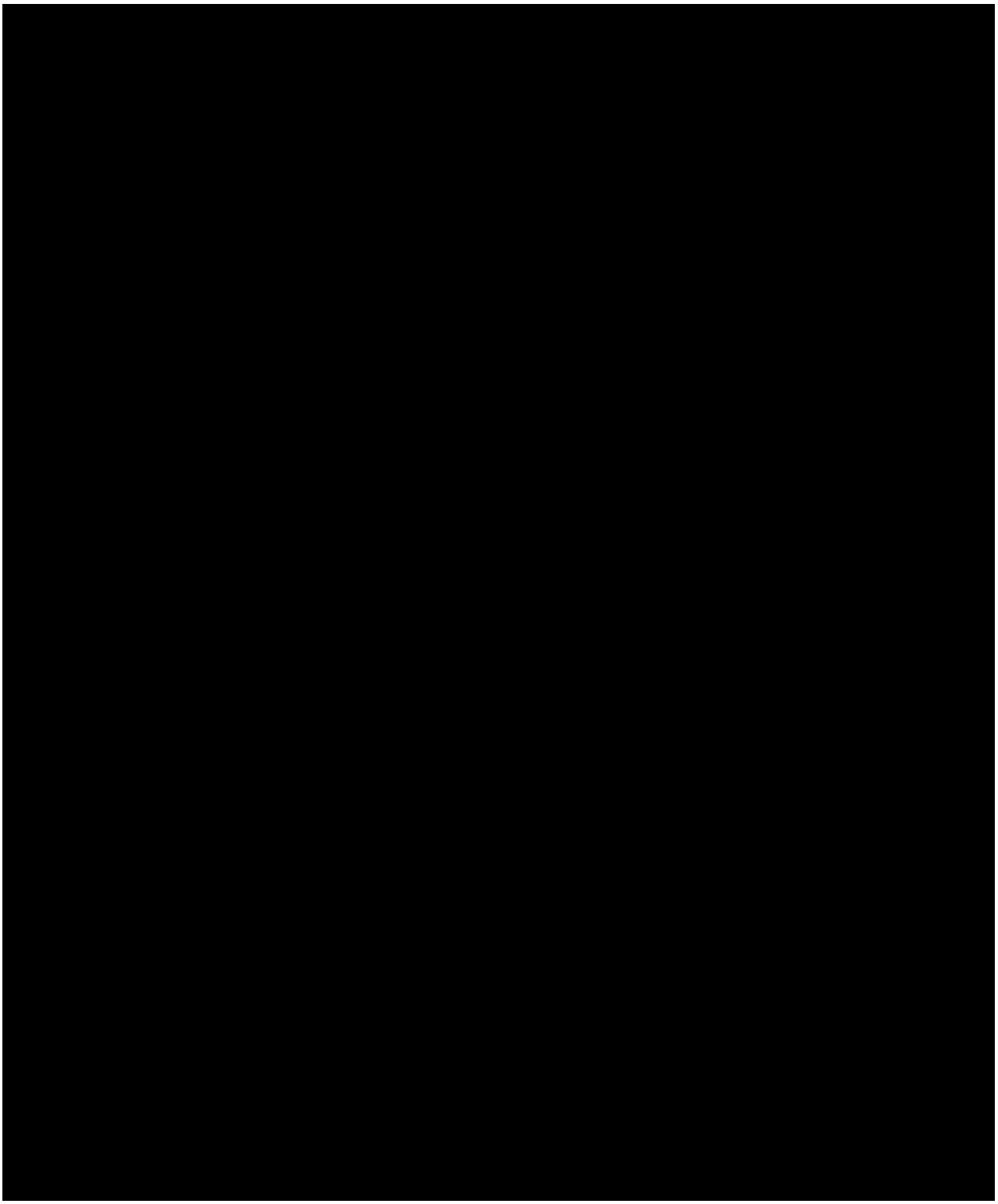
Not applicable.

2.12 Patient-reported outcomes

Not reported.

2.13 Biomarkers

Not applicable.



2.15 Interim analysis

Two interim analyses will be performed by the Novartis CTT.

Interim Analysis I:

The first interim analysis will be performed when the last patient has completed the last visit in Core study or when at least half of the patients enrolled in the Core study have completed the visit corresponding to 40 weeks after the first study treatment (in the Core study), whichever is later.

The purpose of the first interim analysis is to provide some longer term data on ocular structural abnormalities. This is to comply with the plan for specific follow-up in the Pediatric Investigation Plan (EMA). At the first interim analysis, descriptive statistics will be produced as appropriate and no inferential analyses will be conducted. The variables below will be summarized.

- Epoch 1 phase subject disposition
- Subject demographics
- The absence of all ocular structural abnormalities as defined in Section 2.8.1.
- The recurrence of ROP up to 40 weeks post baseline visit from the Core study
- The absence of active ROP at 40 weeks as defined in Section 2.8.1
- The number of ranibizumab injections received in the treatment of patients with ROP up to 40 weeks post baseline visit of the Core study by eye and overall
- The type, frequency, and severity of ocular and non-ocular adverse events

The above outputs will be repeated for the subgroup of Japan, to support the submission to the PMDA.

Interim analysis II:

The interim analysis II will be performed when the last patient has completed the visit which corresponds to the patient's 2 years' corrected age.

The purpose of the second interim analysis is to evaluate the absence of all ocular structural abnormalities as defined in Interim Analysis I at the patient's 2 years' corrected age.

At the second interim analysis, the variables below will be evaluated.

The appropriate CMH test (as specified in Section 2.6.2) with ROP Zone at Core baseline as stratification factor will be used to analyze secondary binary efficacy variables (Section 2.8.1) at interim analysis II. p-values and 95% confidence intervals will be provided. No adjustment for multiplicity will be conducted. For other variables, descriptive statistics will be provided by treatment arm.

Binary variables:

- The absence of all ocular structural abnormalities (as in Section 2.8.1)

Other variables:

- The absence of each of the ocular structural abnormalities defined in Section 2.8.1
- The absence of active ROP at 52 weeks from the baseline visit of the Core study as defined in Section 2.8.1
- The recurrence of ROP up to 40 weeks from the baselind visit of the Core study
- The absence of active ROP, and individual components of active ROP at 40 weeks from the baseline visit of the Core study

[redacted]

- Patient's physical development (standing/sitting height, leg length, weight and head circumference)
- The patient's health status (respiratory function, hearing function, duration of hospitalization from birth to first hospital discharge home, and weight at discharge)
- The type, frequency, and severity of ocular and non-ocular adverse events including AEs, SAEs, AEs by maximum severity
- The type, frequency, and severity of ocular and non-ocular adverse events with onset date on/after extension baseline, including AEs, SAEs, AEs by maximum severity

[redacted]

- Demographics (including sex, geographical region, gestational age at birth, gestational age at birth by category) and ROP disease status by subject at core baseline will be presented descriptively.
- Summary of the safety follow-up period since Core study baseline

- Summary of body height, body weight, and head circumference at Core study baseline, at the year 2 visit of the Extension study, and their change from Core study baseline to the year 2 visit
- Subject disposition
- Summary of reasons for permanent discontinuation from study treatment
- Deaths by preferred term
- Number (%) of subjects with deaths, SAEs or AEs leading to permanent discontinuation of study treatment
- Analysis sets by treatment
- Pre-retinal fibrosis and its relationship to laser therapy, ocular injection therapy, and study drug by eye

The safety follow up period (in months) is defined as: (The earlier date of the extension EOS data and snapshot date of the interim analysis – Core study baseline date +1)/30.

In addition, a selection of the above outputs will be repeated for the subgroup of Japan, to support the submission to the PMDA.

3 Sample size calculation

The sample size calculation is not based on a power calculation. The number of patients enrolled in this study depends on the number of patients that were enrolled and completed the Core study, are willing to participate in the Extension study and fulfill the eligibility criteria of the Extension study (Section 4 of Protocol).

4 Appendix

4.1 Imputation rules

The general approach to handling missing dates is shown below for dates of AEs, medical history diagnosis, and concomitant treatment. The imputation of missing dates for surgery or procedures will use the same rules as for concomitant treatment.

Imputation rules described here only apply to events, conditions and treatments

(1) That are ongoing at the end of the Core study and at the time the patient enters the Extension study

(2) That are not ongoing at the end of the Core study (start after last visit of Core study and are recorded in the Extension study for the first time).

For events, conditions and treatments that ended before/on last visit of the Core study, the imputation rules defined in the Core study are applicable.

The detailed algorithms will be described in the Programming Dataset Specifications.

For the purpose of date imputation, the treatment follow up period date is defined as the last available visit date.

4.1.1 Study drug

Missing date and time of study treatment will not be imputed for this study.

4.1.2 Adverse event date imputation

Adverse event end date imputation

If the AE end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death).

If the AE end date day is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, last day of the month, date of death).

If AE year is missing or AE is ongoing, the end date will not be imputed. If the imputed AE end date is before the corresponding AE start date then the AE end date will be set to the AE start date.

Adverse event start date imputation

Adverse events with partially missing onset dates will also be included as treatment emergent when the month (if it exists) and the year occur on or later than the month and year of the initial study treatment date.

Partial AE start dates are imputed with reference to the two reference dates depending on whether the AE is ongoing or not ongoing at the end of the Core study. If the AE is ongoing at the last visit of the Core study, treatment start date (TRTSTD) will be used as reference date for imputation, otherwise, if the AE is not ongoing at the last visit of the Core study, the Extension baseline visit date (EXTBL) will be used as the reference date for imputation. The reference dates are outlined in the imputation table below.

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

1. If the (imputed) AE end date is complete and AE is ongoing at the the end of Core study , AE start reference date = treatment start date
2. If the (imputed) AE end date is complete and AE is not ongoing at the the end of Core study
   (a) The (imputed) AE end date < Extension baseline visit date then AE start reference date = min (informed consent date of Extension study, earliest visit date).
   (b) Else AE start reference date = Extension baseline visit date

Completely missing start dates will not be imputed. As a conservative approach, such adverse events will be defined as treatment emergent.

The date value is split into day, month, year sections and referenced in the imputation table as outlined below	Day	Month	Year
Partial AE Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSTD)	Not used	TRTM	TRTY
Extension Baseline Visit Date (EXTBL)	Not used	EXTBLEXTBLEXTBL	EXTYEXEXTY

The following matrix explains the logic behind the imputation.

If the AE is ongoing at the end of the Core study:

Comparison of Month section	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	NC	NC	NC	NC
YYYY < TRTY	01JULYYYY Before Treatment Start	15MONYYYY Before Treatment Start	15MONYYYY Before Treatment Start	15MONYYYY Before Treatment Start
YYYY = TRTY	AE start reference date + 1 day Uncertain	15MONYYYY Before Treatment Start	TRTSTD +1 Uncertain	01MONYYYY After Treatment Start
YYYY > TRTY	01JANYYYY After Treatment Start	01MONYYYY After Treatment Start	01MONYYYY After Treatment Start	01MONYYYY After Treatment Start

If the AE is not ongoing at the end of the Core study:

Comparison of Month section	MON MISSING	MON < EXTBL	MON = EXTBL	MON > EXTBL
YYYY MISSING	Uncertain	Uncertain	Uncertain	Uncertain
YYYY < EXTBLY	Later of (01JULYYYY, date of last visit of Core study+1) Before Extension baseline visit	Later of (15MONYYYY, date of last visit of Core study+1) Before Extension baseline visit	Later of (15MONYYYY, date of last visit of Core study+1) Before Extension baseline visit	Later of (15MONYYYY, date of last visit of Core study+1) Before Extension baseline visit
YYYY = EXTBLY	EXTBL + 1 day Uncertain	Later of (15MONYYYY, date of last visit of Core study+1) Before Extension baseline visit	EXTBL +1 Uncertain	01MONYYYY After Extension baseline visit
YYYY > EXTBLY	01JANYYYY After Extension baseline visit	01MONYYYY After Extension baseline visit	01MONYYYY After Extension baseline visit	01MONYYYY After Extension baseline visit

The following table is the legend to the logic matrix.

Relationship

Before Treatment Start	Partial date indicates AE start date prior to Treatment Start Date
After Treatment Start	Partial date indicates AE start date after Treatment Start Date
Uncertain	Partial date insufficient to determine relationship of AE start date to Treatment Start Date
Before Extension Baseline Visit	Partial date indicates AE start date prior to Extension Baseline Visit Date
After Extension Baseline Visit	Partial date indicates AE start date after Extension Baseline Visit Date
Uncertain	Partial date insufficient to determine relationship of AE start date to Extension Baseline Visit Date

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

4.1.3 Medical history date of diagnosis imputation

Medical history date of diagnosis imputation for the Core study

Completely missing dates and partially missing diagnosis dates will not be imputed. Partial dates of diagnosis will be compared to the treatment start date.

- If DIAG year <= Core study treatment start date year and DIAG month is missing, the imputed DIAG date is set to the mid-year point (01JULYYYY)
  - else if DIAG month is not missing, the imputed DIAG date is set to the mid-month point (15MONYYYY)
- If DIAG year = Core study treatment start date year
  - and (DIAG month is missing OR DIAG month is equal to Core study treatment start month), the imputed DIAG date is set to one day before Core study treatment start date
  - else if DIAG month <= Core study treatment start month, the imputed DIAG date is set to the mid-month point (15MON YYYY)
  - else if DIAG month > Core study treatment start month => data error
- If DIAG year > Core study treatment start date year => data error

Medical history diagnose year imputation for the Extension study

Completely missing dates and partially missing end dates will not be imputed. Partial dates of diagnosis will be compared to the end of Core study date (if medical conditions is ongoing at the end of Core study but not onoing at Extension baseline) , the ExtensionICF signsignsign date (if medical conditions is ongoing at Extension baseline), .

<u>If medical condition is ongoing at the end of Core study but not ongoing at Extension baseline:</u>

Completely missing dates and partially missing end dates will not be imputed. Partial dates of diagnosis will be compared to end of Core study date.

- If diagnosis year <= end of Core study date year and diagnosis month is missing, the imputed diagnosis date is set to the mid-year point (01JULYYYY)
    - else if diagnosis month is not missing, the imputed diagnosis date is set to the mid-month point (15MONYYYY)
- If diagnosis year = end of Core study date year
    - and (diagnosis month is missing OR diagnosis month is equal to end of Core study date month), the imputed diagnosis date is set to one day before end of Core study date
    - else if diagnosis month < end of Core study date month, the imputed diagnosis date is set to the mid-month point (15MON YYYY)
    - else if diagnosis month > end of Core study date month => data error
- If diagnosis year > end of Core study date year => data error

If medical condition is ongoing at Extension baseline (CIF sign date):

- If diagnosis year <= Extension ICF sign date year and diagnosis month is missing, the imputed diagnosis date is set to the earlier of (mid-year point (01JULYYYY), Extension ICF sign date ---1)
    - else if diagnosis month is not missing and not equal to ICF sign date month, the imputed diagnosis date is set to the earlier of (mid-month point (15MONYYYY), Extension ICF sign date---1)
    - else ifdiagnosisififdiagnosis month equal to ExtensionICF sign date month,, the imputed diagnosis date is set to one day before Extension ICF sign date
    - ICF> Extension ICF sign date month => data error
- If diagnosis year > Extension ICF sign date year => data error

4.1.4 Concomitant treatment date imputation

Concomitant treatment end date imputation

If the concomitant treatment end date year value is missing, the date uncertainty is too high to impute a reliable date. Therefore, if the concomitant treatment end year value is missing or ongoing, the imputed concomitant treatment end date is set to NULL.

Else, if the concomitant treatment end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death).

If the concomitant treatment end date day is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, last day of the month, date of death).

If the imputed concomitant treatment end date is before the existing concomitant treatment start date, use the concomitant treatment start date as the imputed concomitant treatment end date.

Concomitant treatment start date imputation

In order to classify a medication as prior and prior/concomitant, it may be necessary to impute the start date.

If medication is ongoing at the last visit of Core study:

Completely missing start dates will be set to one day prior to start treatment date.... Concomitant treatments with partial start dates will have the date or dates imputed. Partial concomitant treatment start dates are imputed with reference to the treatment start date (TRTM) in accordance with the rules outlined below:

	Day	Month	Year
Partial CMD Start Date	Not used	MON	YYYY
Treatment Start Date (TRTM)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	**MON < TRTM**	**MON = TRTM**	**MON > TRTM**
YYYY MISSING	Uncertain	Uncertain	Uncertain	Uncertain
YYYY < TRTY	01JULYYYY Before treatment start	15MONYYYY Before treatment start	15MONYYYY Before treatment start	15MONYYYY Before treatment start
YYYY = TRTY	Uncertain	15MONYYYY Before treatment start	Uncertain	01MONYYYY After treatment start
YYYY > TRTY	01JANYYYY After treatment start	01MONYYYY After treatment start	01MONYYYY After treatment start	01MONYYYY After treatment start

<u>If medication is not ongoing at the last visit of Core study:</u>

Completely missing start dates will be set to one day prior to Extension baseline visit date. Concomitant treatments with partial start dates will have the date or dates imputed. Partial concomitant treatment start dates are imputed with reference to the Extension baseline visit date (EXTBL) in accordance with the rules outlined below:

	Day	Month	Year
Partial CMD Start Date	Not used	MON	YYYY
Extension Baseline Visit Date (EXTBL)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	**MON < EXTBL**	**MON = EXTBL**	**MON > EXTBL**
YYYY MISSING	Uncertain	Uncertain	Uncertain	Uncertain
YYYY < EXTBL	Later of (01JULYYYY, date of last visit of Core study +1) Before Extension baseline visit	Later of (15MONYYYY, date of last visit of Core study +1) Before Extension baseline visit	Later of (15MONYYYY, date of last visit of Core study +1) Before Extension baseline visit	Later of (15MONYYYY, date of last visit of Core study +1) Before Extension baseline visit

YYYY = EXTBL	Uncertain	Later of (15MONYYYY, date of last visit of Core study +1) Before Extension baseline visit	Uncertain	01MONYYYY After Extension baseline visit
YYYY > EXTBL	01JANYYYY After Extension baseline visit	01MONYYYY After Extension baseline visit	01MONYYYY After Extension baseline visit	01MONYYYY After Extension baseline visit

The following table is the legend to the logic matrix.

Relationship	
Before Extension baseline visit	Partial date indicates CMD start date prior to Extension baseline visit Date
After Extension baseline visit	Partial date indicates CMD start date after Extension baseline visit date
Uncertain	Partial date insufficient to determine relationship of CMD start date to Extension baseline visit date

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

4.2 Laboratory parameters derivations

Not applicable.

4.3 Statistical models and SAS codes

CMH test:

The primary efficacy variable is the visual acuity (VA) in the better-seeing eye at the patient's fifth birthday as recorded by the investigator.

The following primary hypothesis will be used to test the comparison of ranibizumab 0.2 mg versus laser as follows:

H_{01}: $\mu_{\text{ranibizumab 0.2 mg}} - \mu_{\text{Laser}} = 0$ versus H_{A1}: $\mu_{\text{ranibizumab 0.2 mg}} - \mu_{\text{Laser}} \neq 0$

where $\mu_{\text{Treatment}}$ arm is the unknown mean VA in the better-seeing eye at the fifth birthday of patients in the relevant treatment arm.

The hypothesis will be tested by using stratified analysis of varaiance (ANOVA) using the Cochran-Mantel-Haenszel (CMH) test with the observed VA values as the response variable and the treatment arm as the factor (with levels 0.2 mg and laser). Stratification will be based on the ROP zone at the Core study baseline.

The test statsitics can be written in the form (Lehmann, E. L. (1975) and Van Elteren, P.H. (1960)):

$$W^* = \frac{\sum_{j=1}^{J} a_j \sqrt{\frac{n_{0j} n_{1j}}{n_{0j} + n_{1j}}} \left(\frac{1}{n_{0j}} \sum_{k=1}^{n_{oj}} R_{0jk} - \frac{1}{n_{1j}} \sum_{k=1}^{n_{1j}} R_{1jk} \right)}{\sqrt{\sum_{j=1}^{J} a_j^2 \frac{1}{n_{0j} + n_{1j} - 1} \sum_{i=0}^{1} \sum_{k=1}^{n_{ij}} (R_{ijk} - \bar{R}_{\bullet j \bullet})^2}}$$

where R_{ijk} is the VA sCore of subject k within strata j of treatment i, i=0,1 denotes the treatment arm, j=1, 2 denotes the ROP zone, k=1,.., n_{ij} denotes the subjects within the i^{th} treatment arm in the j^{th} ROP zone and $\bar{R}_{\bullet j \bullet}$ is the average VA sCore of all subjects in Zone j.

For large sample sizes (within each strata) the test statistic has a standard normal distribution; therefore the two-sided test would reject the null hypothesis if $|W^*| > Z_{\alpha/2}$, where Z is the N(0, 1) distribution.

The option CMH with SCORESSCORES=TABLE in the OUTPUT statement requests the CMH row means sCore statistics and the corresponding two-sided p-value:

```
proc freq data = <input_dataset sorted> noprint;
tables <stratavar> * <treatmentvar> * <responsevar> / CMH
SCORESSCORES=TABLE ;
output out = <output_dataset> (keep =_CMHRMS_ P_CMHRMS) CMH;
run;
```

The two-sided p-value will then be converted to a one-sided p-value: For each comparison, if the direction of the observed difference supports the superiority outcome (e.g. mean ifference > 0), the two-sided p-value will be converted to a one-sided p-value by dividing by two. If mean difference < 0, the one-sided p-value will be calculated as 1 - (the two-sided p-value divided by two).

ANOVA model:

The ANOVA analysis will be performed using SAS procedure PROC MIXED.

Stratified ANOVA:

```
proc mixed data = <input_dataset sorted> noprint;
class <treatmentvar> <stratavar>;
model <responsevar> = <stratavar> <treatmentvar> ;
lsmeans <treatmentvar> / om;
estimate ""<treatmentvar>;
run;
```

Unstratified ANOVA:

```
proc mixed data = <input_dataset sorted> noprint;
class <treatmentvar>;
model <responsevar> = <treatmentvar> ;
lsmeans <treatmentvar> / om;
estimate ""<treatmentvar>;
run;
```

Calculating 95% confidence intervals for proportions using Clopper-Pearson method:

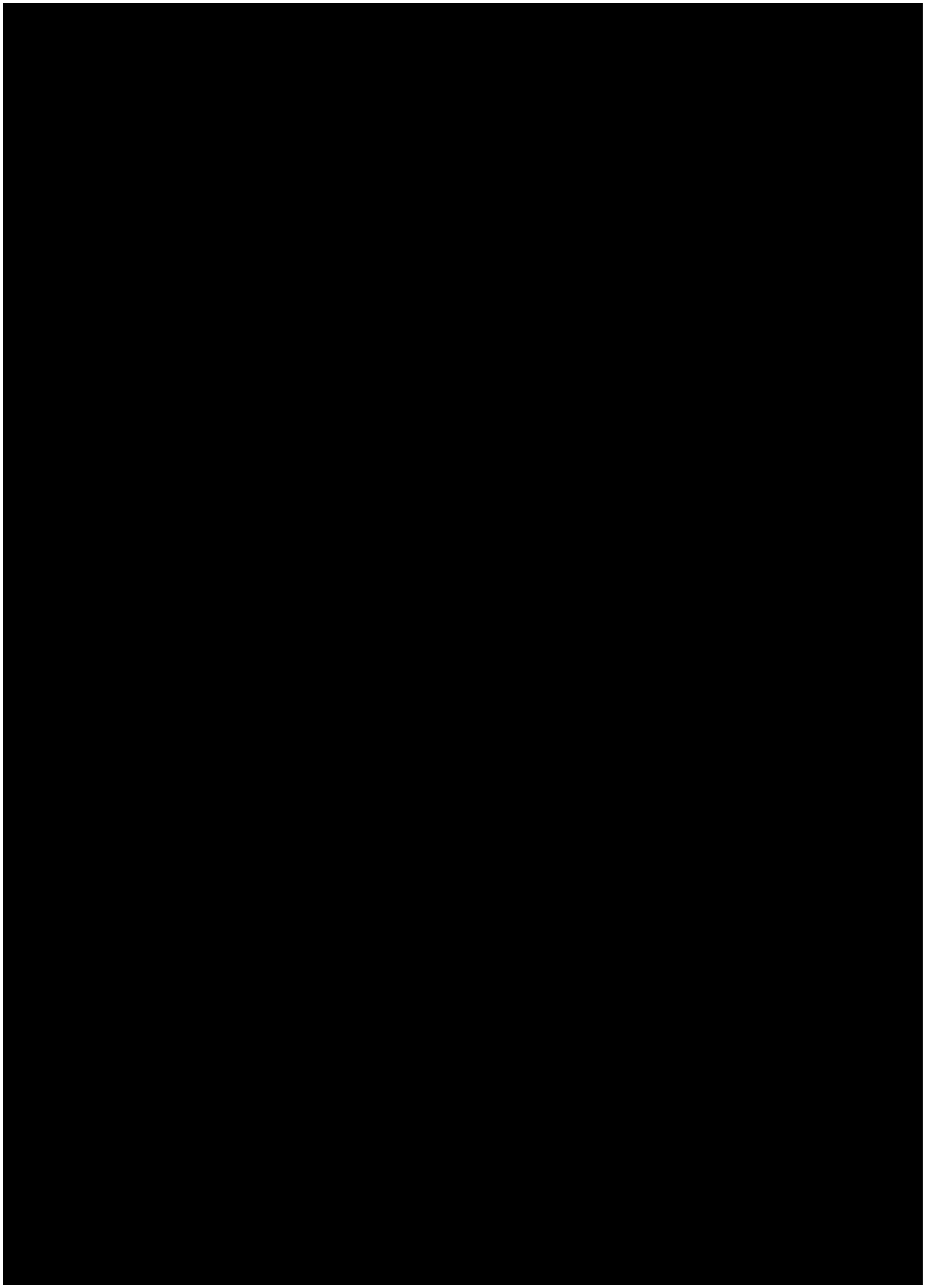
The confidence intervals for the proportions will be calculated using the Clopper-Pearson method. It will be performed using SAS procedure PROC FREQ with the BINOMIAL option in the TABLES and EXACT statements:

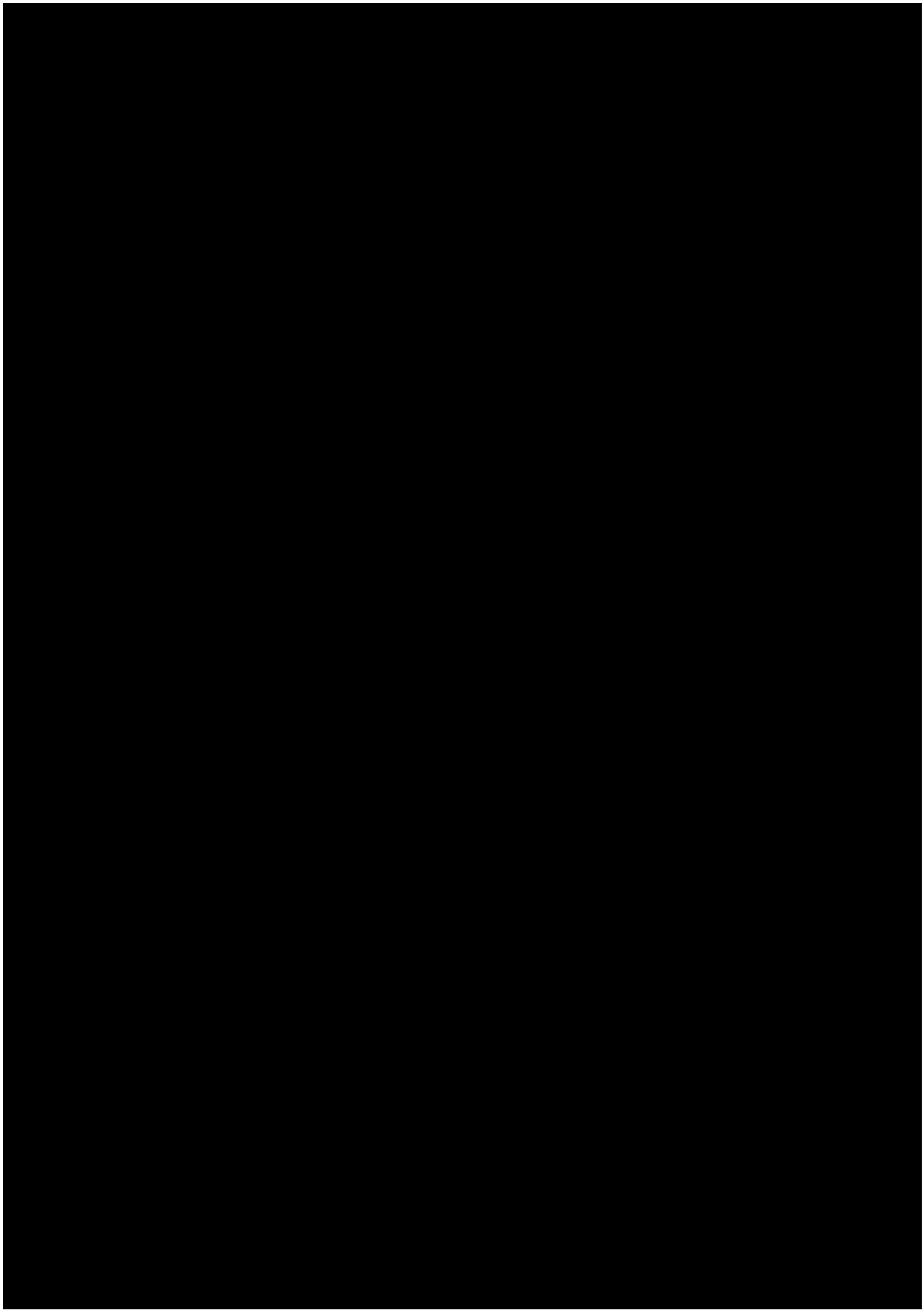
```
proc freq data = <input_dataset sorted> noprint;
by <treatmentvar>;
tables <responsevar> / binomial (cl=exact );
exact binomial;
run;
```

4.4 Rule of exclusion criteria of the analysis setset

Table 4-1 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses
INCL01	Informed consent was not obtained before study related assessment performed	Excluded from extension safety set: both safety and efficacy analysis
WITH02	Patient was not withdrawn from the study despite withdrawal of consent	Excluded from extension safety set: both safety and efficacy analysis





5 Reference

1. Lehmann, E. L. (1975). Nonparametrics: Statistical Methods Based on Ranks, San Francisco: Holden-Day, pp 132-137, 145.
2. Van Elteren, P. H. (1960). "On the combination of independent two-sample tests of Wilcoxon, Bulletin of the International Statistical Institute", 37, 351-361.
3. Newcombe R.G., Two-sided CIs for the single proportion: comparison of seven methods, Statistics in Medicine, (1998) 17, 857-872
4. Newcombe R.G., Interval Estimation for the Difference between Independent Proportions: Comparison of Eleven Methods. Statistics in Medicine 1998; 17: 873-890