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RAINBOW study: a randomized, controlled study evaluating the efficacy and safety of RAnibizumb compared with laser therapy for the treatment of INfants BOrn prematurely With retinopathy of prematurity

RAP Module 3 – Detailed Statistical Methodology

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List of tables

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Document History – Changes compared to previous version of RAP module 3.

Version	Date	Changes
Amendment 1		1. PD table updated, and non-PD table added. 2. Sections of Determination of sample size updated, according to the plan of a reduced sample size. 3. Sections 2.5.1 and 4 updated to consider a sequential testing approach. 4. Efficacy analysis imputation rules updated according to protocol 5. Combined (ocular and non-ocular) AE tables excluded as these are redundant 6. RMP risk tables and listing included 7. Section 2.4.4 revised according to TFL shell, and the definition of number of days laser treatment received added 8. Output on rescue medication included 9. Data reporting rules of additional assessment visits updated 10. SAS code for 95% CI of proportions using Clopper-Pearson method included 11. ROP zone information for primary efficacy analysis changed to CRF source [redacted] 12. Data exclusion rules for certain PDs updated, resulted from alignment made at a meeting 13. AE outputs and safety observation period revised, by removing the separate sets of before/after switch 14. PK and anti-VEGF analyses removed, and will be included in a separate report 15. Lab summary tables removed due to heterogeneity of data collected at local labs. 16. Prohibited medication will not be displayed separately, as these will be identified manually. Instead, they will be shown as part of the PDs in the PD outputs. 17. CTSD required outputs added.
Amendment 2		1. Revised the definition of number of days laser treatment received, added the definition of duration of laser treatment 2. Imputation rules in Section 2.4.7.1 clarified 3. Definitions of PK set and VEGF population set added. Outputs of PKPD added in Sections 2.8.x [redacted] 6. One deviation text updated
Amendment 3		1. Sensitivity analysis to the primary analysis included, with a modified imputation rule – Imputation rule 2.

List of abbreviations

AE	Adverse event
AP-ROP	Aggressive posterior retinopathy of prematurity
ATC	Anatomical Therapeutic Chemical (classification system)
BEAT-ROP	Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (study)
BL	Baseline
CSR	Clinical study report
DAR	Drug Administration Record
DMC	Data Management Committee
eCRF	Electronic case report/record form
FAS	Full analysis set
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
PD	Protocol deviation
PK	Pharmacokinetic
PPS	Per-protocol set
PT	Preferred term
RAP	Reporting analysis plan
RMP	Risk management plan
ROP	Retinopathy of prematurity
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SI	International System of Units
SOC	System organ class
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

1 Statistical methods planned in the protocol and determination of sample size

This Report and Analysis Plan (RAP) 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.

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 Statistical and analytical plans

The planned analysis is described in Section 9 of the Study Protocol (Appendix 16.1.1).

This is an open-label study where the CTT team is not masked to the patient level clinical or PK data. However, to minimize the impact of assignment knowledge, aggregated statistical analysis done by treatment arm will be kept confidential from the CTT until DBL. Therefore, the CTT will not have access to the DMC closed session outputs.

Dry runs will be performed by assigning dummy variable to the three treatment groups so that each dummy group will have a randomly assigned mixture of patients from both dose groups.

2.1 Changes to the planned analyses in the protocol

[redacted]

Therefore, in the primary efficacy analysis, stratification [redacted] information recorded at the screening visit from the CRF page. In addition, a sensitivity analysis will be performed [redacted]

[redacted]

The population PK and VEGF analyses mentioned in Sections 9.5.4 and 9.5.6, respectively, of the protocol will be described in a separate report, other than in the CSR.

[redacted]

[redacted]

2.3 General considerations

All analyses will be based on the assessments according to the investigator. [redacted]

Study treatment refers to both study ranibizumab and laser therapy. In this document, patient and subject are used interchangeably in the document.

During the study, the patient can switch treatment (also called rescue treatment). A patient randomized to ranibizumab can receive switch/rescue laser therapy in either eye; a patient randomized to laser therapy can receive switch/rescue ranibizumab 0.2 mg in either eye.

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 values) will be presented for continuous variables. The number and percentage of patients in each category defined will be presented for categorical variables. If a confidence interval is presented for the proportion of a categorical variable, then the exact Clopper-Pearson method will be used to calculate the 2-sided 95% confidence interval.

All data will be listed/summarized by patient unless otherwise specified.

2.4 Analysis data sets

The following data sets are defined for the trial.

The **Screened Set** will consist of all patients whose parent(s) or legal guardian(s) has provided informed consent.

The data from patients whose parent(s) or legal guardian(s) has not provided informed consent prior to any study procedures will be listed only and will not be used in any analyses.

This is expected to occur extremely rarely and would be regarded as violation of good clinical practice.

The **Randomized Set** will consist of all randomized patients.

The **Full Analysis Set (FAS)** will comprise all patients from the Randomized Set to whom treatment regimen has been assigned. Following the intent-to-treat principle, patients will be analyzed for efficacy according to the treatment regimen they are assigned to at randomization.

The **Per Protocol Set (PPS)** will consist of all patients in the Full Analysis Set who follow the treatment regimen as randomized and complete the study period for the analysis of the primary and key secondary objectives without clinically important protocol deviations. Clinically important protocol deviations will be identified and documented prior to the database lock in the latest version of the Data Review Plan.

The **Safety Set (SAF)** will consist of all patients who receive at least one application of study treatment and have at least one post baseline safety assessment. The statement that a patient has no AEs also constitutes a safety assessment. Reports using safety set will be by initial treatment received at baseline.

[redacted]

The **VEGF Set** will consist of all patients who provide valid VEGF plasma samples. Reports using the VEGF Set will be by initial treatment received at baseline.

The **PK Set** will consist of all patients who provide valid pharmacokinetic serum samples. Report using the PK Set will be by initial treatment received.

Table 2-1 shows the analyses sets to be used for specific analyses.

Table 2-1 Analysis sets used for specific analyses

	Screened set	Rando-mized Set	FAS	PPS	SAF	PK Set	VEGF Set	[redacted]
Screen failures	x							
Demographics and baseline characteristics		x						
Patient disposition		x						
Protocol deviations		x						
Medical history		x						
Primary efficacy analysis			x					
Other efficacy analyses			x					
Subgroup analyses			x					
Sensitivity analyses			x	x				
Concomitant medication					x			
Safety analyses					x			
Exposure					x			
Prior medication					x			
Hospitalization					x			
PK						x		
VEGF							x	
[redacted]								

Table 2-2 and Table 2-3 defines the rules for subject classification in the analysis sets based on important CSR reportable protocol deviation IDs and non-protocol deviation classification criteria.

Table 2-2 Major Protocol Deviations

PD ID	Deviation Text	Data exclusion
INCL01	Informed consent is not obtained before study related assessment performed	Exclude from Randomized set, FAS, SAF, and PPS
INCL02	Patient did not satisfy protocol specified weight criteria	Exclude from PPS
INCL03	Absence of indication to be studied in either eye (as defined in the protocol)	Exclude from PPS
EXCL01	Presence of ROP disease characteristics which is exclusionary in either eye	Exclude from PPS
EXCL02	Prohibited medication or procedure indicated in protocol exclusion criteria (with potential impact on key efficacy assessments)	Exclude from PPS

PD ID	Deviation Text	Data exclusion
EXCL03	Medical/ocular history or conditions indicated in protocol exclusion criteria (with potential impact on key efficacy assessments)	Exclude from PPS
TRT01	Wrong dose/wrong treatment given	Exclude from PPS
TRT02	Non-adherence to dosing algorithm as per protocol, except for valid medical reasons (re-treated wrongly, switched wrongly)	Exclude from PPS
WITH01	Patient was not discontinued from the investigational treatment despite administration of prohibited concomitant medications and procedures	Exclude from PPS
WITH02	Patient was not withdrawn from the study despite withdrawal of consent	Exclude from Randomized set, FAS, SAF, and PPS
WITH03	Patient was not discontinued from study treatment despite PD with a significant risk to the patient's safety	Exclude from PPS
OTH1	Any other protocol deviation with impact on primary efficacy endpoint or key secondary efficacy endpoint	Exclude from PPS
COMD01	Prohibited concomitant medications and procedures taken during the study (with impact on efficacy)	Exclude from PPS

Table 2-3 Non-Protocol Deviation Classification Criteria

Analysis Set	Non-PD criteria that cause patients to be excluded
Randomized set	Not randomized
FAS	Not in the RAN
	Mis-randomized
PPS	Not in the FAS
	Did not complete the study
SAF	Did not receive at least one study treatment
	Did not record at least one post-Baseline safety assessment

In addition, it should be noted that the analysis data sets for this study are based on the Novartis Clinical Data Standards.

2.5 Assessment windows, baseline and post baseline definitions, missing data handling

2.5.1 Baseline definition and post-baseline definitions

Baseline (day 1) for treated patients is the date of the first study treatment in either eye.

The baseline value for efficacy and safety variables is the last available, non-missing value collected prior to baseline (i.e., prior to receiving the first study treatment for treated patients).

If a patient is randomized but not treated, then the baseline value for a variable is the last available non-missing value collected prior to or on the day of randomization.

Baseline assessments may be recorded on the day of the baseline visit or randomization. The assessments, according to the protocol, conducted before the first study treatment at the baseline visit will be used when deriving baseline values recorded at the baseline visit.

All data collected after day 1 are defined as post-baseline.

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

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

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

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

[redacted]

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).

[redacted]

2.5.2 The last scheduled study visit

The last scheduled study visit will be the latest of (premature withdrawal Visit 199, Visit 112, last additional assessment visit as per protocol).

The study day for the premature withdrawal Visit 199 will be allocated to the nearest planned main visit. If data for the nearest planned main visit already exist then the premature withdrawal visit will be assigned to the next main visit. In case the Visit 199 happens on the same day as a scheduled visit, then Visit 199 will be re-mapped to the next visit number of that scheduled visit. All applicable assessments will be captured by scheduled visit, while visit 199 only contains the assessments specific to premature withdrawal visits. [redacted]

[redacted]

2.5.3 Additional assessment visit schedule

The additional assessment visits are triggered by a post-baseline treatment (re-treatment with ranibizumab or switch treatment with ranibizumab or laser therapy) (see 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. E.g., analyses on outcomes at or before 24 weeks after the first study treatment will not consider data collected at additional assessment visits after the planned main visit of week 24, [redacted] All data collected at additional assessment visits will be listed.

2.5.4 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.

Efficacy collected at unscheduled visits will not be used except when imputing missing primary variable values as Section 2.5.7.

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

2.5.5 Missing dates

The general approach to handling missing dates is shown below for dates of AEs (Section 2.5.5.1 and Section 2.5.5.2), medical history diagnosis (Section 2.5.5.3), and concomitant treatment (Section 2.5.5.4 and Section 2.5.5.5). The imputation of missing dates for surgery or procedures will use the same rules as for concomitant treatment.

The detailed algorithms will appear in Programming Dataset Specifications.

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

2.5.5.1 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.

2.5.5.2 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 treatment start date (TRTSTD) as 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 the (imputed) AE end date < treatment start date then AE start reference date = min (informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date

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

The following matrix explains the logic behind the imputation.

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

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
Imputation Calculation	
NC / Blank Uncertain	No convention
(A) After Treatment Start or Uncertain	MAX(01MONYYYY, TRTSTD+1)
(B) Uncertain	AE start reference date+1
(C) Before Treatment Start	15MONYYYY
(D) Before Treatment Start	01JULYYYY
(E) After Treatment Start	01JANYYYY

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

2.5.5.3 Medical history date of diagnosis imputation

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

- If DIAG year < 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 = treatment start date year
  - and (DIAG month is missing OR DIAG month is equal to treatment start month), the imputed DIAG date is set to one day before treatment start date
  - else if DIAG month < treatment start month, the imputed DIAG date is set to the mid-month point (15MON YYYY)
  - else if DIAG month > treatment start month => data error
- If DIAG year > treatment start date year => data error

2.5.5.4 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.

2.5.5.5 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. Completely missing start dates will be set to one day prior to treatment start date. As a conservative approach, such treatments will be classified as prior and concomitant (and summarized for each output). 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 (TRTSTD) in accordance with the rules outlined below:

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

The following matrix explains the logic behind the imputation.

	MON MISSING	**MON < TRTM**	**MON = TRTM**	**MON > TRTM**
YYYY MISSING	(C) Uncertain	(C) Uncertain	(C) Uncertain	(C) Uncertain
YYYY < TRTY	(D) = 01JULYYYY Before Treatment Start	(A) = 15MONYYYY Before Treatment Start	(A) = 15MONYYYY Before Treatment Start	(A) = 15MONYYYY Before Treatment Start
YYYY = TRTY	(C) Uncertain	(A) = 15MONYYYY Before Treatment Start	(C) Uncertain	(B) = 01MONYYYY After Treatment Start
YYYY > TRTY	(E) = 01JANYYYY After Treatment Start	(B) = 01MONYYYY After Treatment Start	(B) = 01MONYYYY After Treatment Start	(B) = 01MONYYYY After Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Treatment Start	Partial date indicates CMD start date prior to Treatment Start Date
After Treatment Start	Partial date indicates CMD start date after Treatment Start Date
Uncertain	Partial date insufficient to determine relationship of CMD start date to Treatment Start Date
Imputation Calculation	
NC / Blank	No convention
(A) Before Treatment Start	15MONYYYY
(B) After Treatment Start	MAX(01MONYYYY, TRTSTD+1)
(C) Uncertain	TRTSTD-1
(D) Before Treatment Start	01JULYYYY
(E) After Treatment Start	01JANYYYY

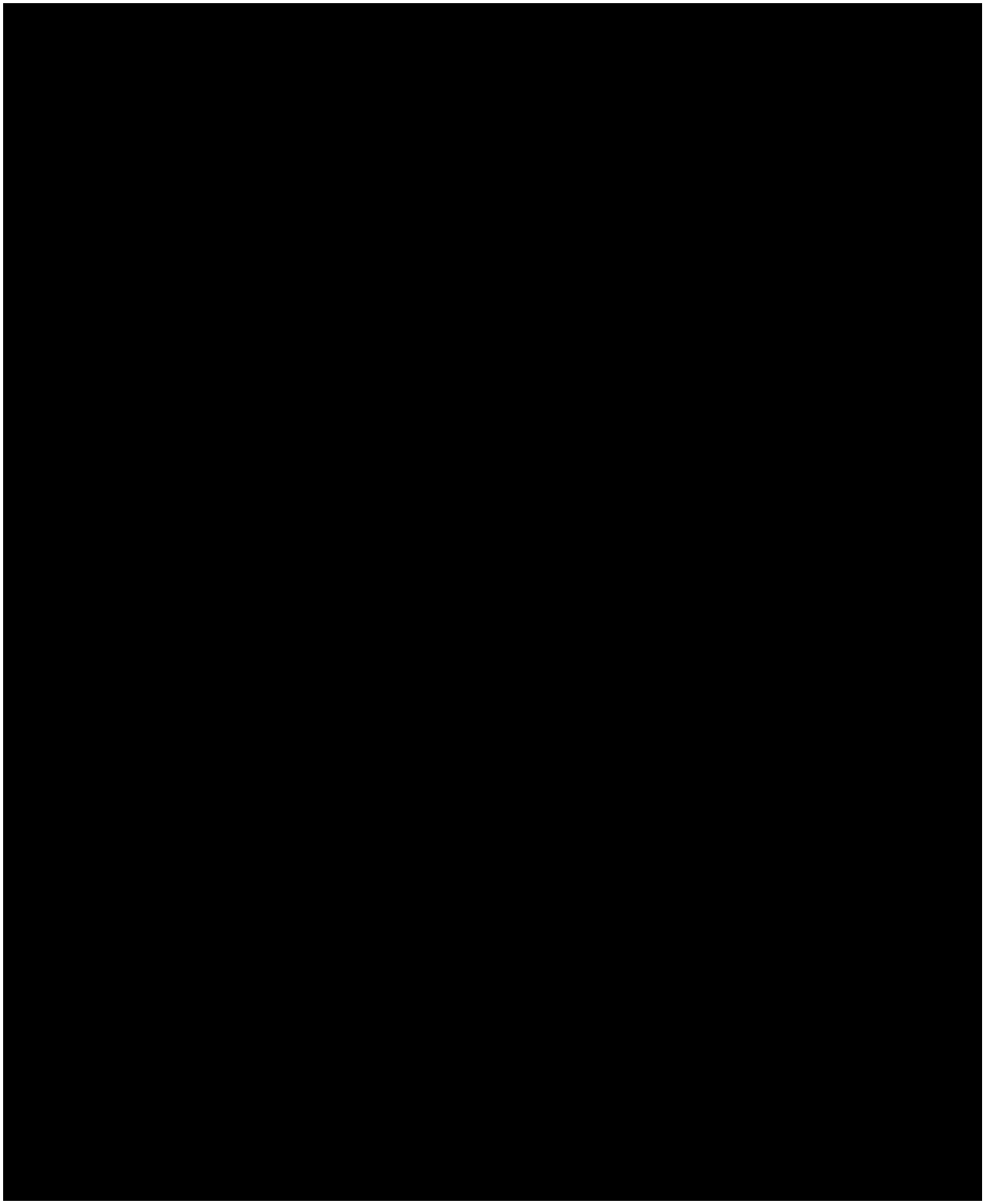
If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

2.5.6 Missing baseline data

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

2.5.7 Missing post-baseline data

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



2.5.7.2 Safety data

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

2.5.7.3 Other data

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

2.5.8 Data for permanent study treatment discontinuation

Patients that permanently discontinue study treatment will remain in the study and all planned assessments should be conducted. No change to the planned analyses will be made for such patients that do not receive a prohibited treatment (as defined in Section 5.5.8 of the protocol).

As specified in Table 2-2, patients that receive a prohibited treatment will be excluded from the PPS. In addition, the data for these patients will be censored in the FAS at the date of the first administration of such treatment. If there is a large (or disproportionate across treatment arms) number of patients that receive a prohibited treatment then a sensitivity analysis will be conducted without censoring the data.

2.6 Subject disposition, background and demographic characteristics

Outputs for subject disposition, background and demographic characteristics will be reported by the randomized set presented for each randomized treatment arm and total.

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

2.6.1 Subject disposition

The number and percentage (based on the number of patients within each randomized treatment arm) of patients who complete the study will be displayed by randomized treatment and overall. The primary reason for premature study discontinuation and permanent study treatment discontinuation will be displayed by randomized treatment and overall.

The total number of patients screened and the number of patients screened, but not randomized will be shown. The primary reason for screening failures will be summarized. The number of patients randomized but did not receive treatment will also be summarized by randomized treatment.

The number of patients with PDs and non-PDs according to the applicable SOP will be presented. The results of the PDs will be grouped using the broad categories defined in the applicable SOP, which currently are:

- Eligibility: Patient did not satisfy entry criteria
- Withdrawal: Patient developed study/treatment withdrawal criteria during the study, but was not withdrawn
- Study Drug: Patient received the wrong treatment or incorrect dose
- Concomitant Medication: Patient took an excluded concomitant medication
- Other reportable protocol deviation

The number of patients within each of the analysis sets used in the study will be given.

Patients with PDs and non-PDs leading to data exclusion from analysis sets will be listed.

Patients removed from the randomized set will not appear in the summary of protocol deviations. These patients will be documented in the output summarizing the patients excluded from analysis sets.

2.6.2 Background 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 2-6 shows the allocation of baseline parameters into groups and which are displayed as continuous and/or categorical variables. Thresholds to convert continuous to categorical variables will be given in RAP Module 7.1.

Table 2-6 Display of the 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 (week)	x		x	x
Chronological age at baseline (week)	x		x	
Postmenstrual age at baseline (week)	x		x	
Birth weight (g)		x	x	x
Birth length (cm)		x	x	x
Head circumference at birth (cm)		x	x	x
ROP disease status by patient		x		x
ROP disease status by eye (worst/best)		x		x
[redacted]				
Time from first diagnosis of ROP (weeks)		x	x	x

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

[redacted]

[redacted]

2.6.3 Medical history

Medical history outputs will be based on the randomized set displayed by treatment and overall. The reporting level will be by patient (not eye). Separate tables will be provided for ocular and non-ocular histories and conditions.

Relevant medical history and current medical conditions will be tabulated by system organ class (SOC) and preferred term (PT) of the latest Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The SOCs will be presented in alphabetical order. Preferred terms will be ordered within each SOC by decreasing proportion in the ranibizumab 0.2 mg treatment arm.

2.6.4 Study medication

Exposure will be calculated for patients in the SAF. Note that only study ranibizumab, and laser treatment 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.

Exposure to ranibizumab is defined as the number of injections of ranibizumab received by worst/best eye (as defined in Section 2.3) and by patient. For example, a patient who only receives ranibizumab treatment in both eyes at baseline will be recorded as having received two ranibizumab injections in total. If the patient additionally receives a single ranibizumab injection in only one eye at a later date then the total number of ranibizumab injections will be recorded as three in total.

The total number of ranibizumab injections will be summarized by worst/best eye and by patient by initial treatment received at baseline.

The number of days laser treatment was received will also be displayed. By considering only laser treatment recorded on the DAR page (not the ConMed page), count the number of days laser treatment received in the following way.

- Each laser treatment for either eye received not on the same day will be counted as 1 day (Laser treatment is considered to have been received if on the DAR laser page, ‘number of laser applications’ is not entered as 0 or NA);
- [redacted]

[redacted]

In addition, duration of the safety observation period will be summarized by treatment group (initial treatment received at baseline). Safety observation period (days) is defined as: date of last visit – date of first study treatment in either eye +1.

Moreover, number of patients requiring [redacted] ranibizumab treatments by ROP zone and combined, and number of days laser treatment received will be summarized by eye and by subject for SAF and FAS.

2.6.5 Concomitant medication

Separate listings and summaries will be produced for ocular and non-ocular for both prior and concomitant medication according to the investigator's response to the relevant CRF page.

Prior medications are defined as those taken and stopped prior to the date of first study treatment. Any medication given at least once on or after the first study treatment date will be defined as a concomitant medication including those which were started before first study treatment date and continued after first study treatment date. Prior or concomitant medication will be identified based on recorded or imputed start dates of medication taking. The rules for imputing incomplete start and end dates are described in Section 2.5.5.4 and Section 2.5.5.5 respectively. Medications with start date equal to that of first study treatment will be classified as concomitant.

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.

2.6.6 Surgery and procedures

Surgery and procedures will be displayed together and separately from concomitant medications.

The same approach will be taken to display surgeries and procedures as specified for concomitant medications in section 2.5.5.

2.6.7 Prohibited treatment

Analysis of concomitant medications that are prohibited as per protocol (shown in protocol Table 5-1) and given during the conduct of the study as well as significant non-drug therapies will be addressed by the currently planned outputs of the Protocol deviations. No separate outputs will be produced related specifically to prohibited medications, as stated in the protocol.

2.7 Efficacy evaluation

2.7.1 Analysis for the primary and key secondary objectives

2.7.1.1 Primary objective and key secondary objectives

The primary objective is to demonstrate that:

- Intravitreal ranibizumab 0.2 mg has superior efficacy to laser therapy in the treatment of ROP as measured by the absence of active ROP and absence of unfavorable structural outcomes in both eyes 24 weeks after starting study treatment, [redacted]

The key secondary objectives are to demonstrate that:

- The intravitreal ranibizumab 0.1 mg has superior efficacy to laser therapy in the treatment of ROP as measured by the absence of active ROP and absence of unfavorable structural outcomes in both eyes 24 weeks after starting study treatment, [redacted]
- The intravitreal ranibizumab 0.2 mg has superior efficacy to intravitreal ranibizumab 0.1 mg in the treatment of ROP as measured by the absence of active ROP and absence of unfavorable structural outcomes in both eyes 24 weeks after starting study treatment, [redacted]

2.7.1.2 Primary efficacy variable

The primary efficacy variable is the absence of active ROP and absence of unfavorable structural outcomes in both eyes 24 weeks after starting study treatment, [redacted] To achieve this outcome, patients cannot fulfill any of the following criteria:

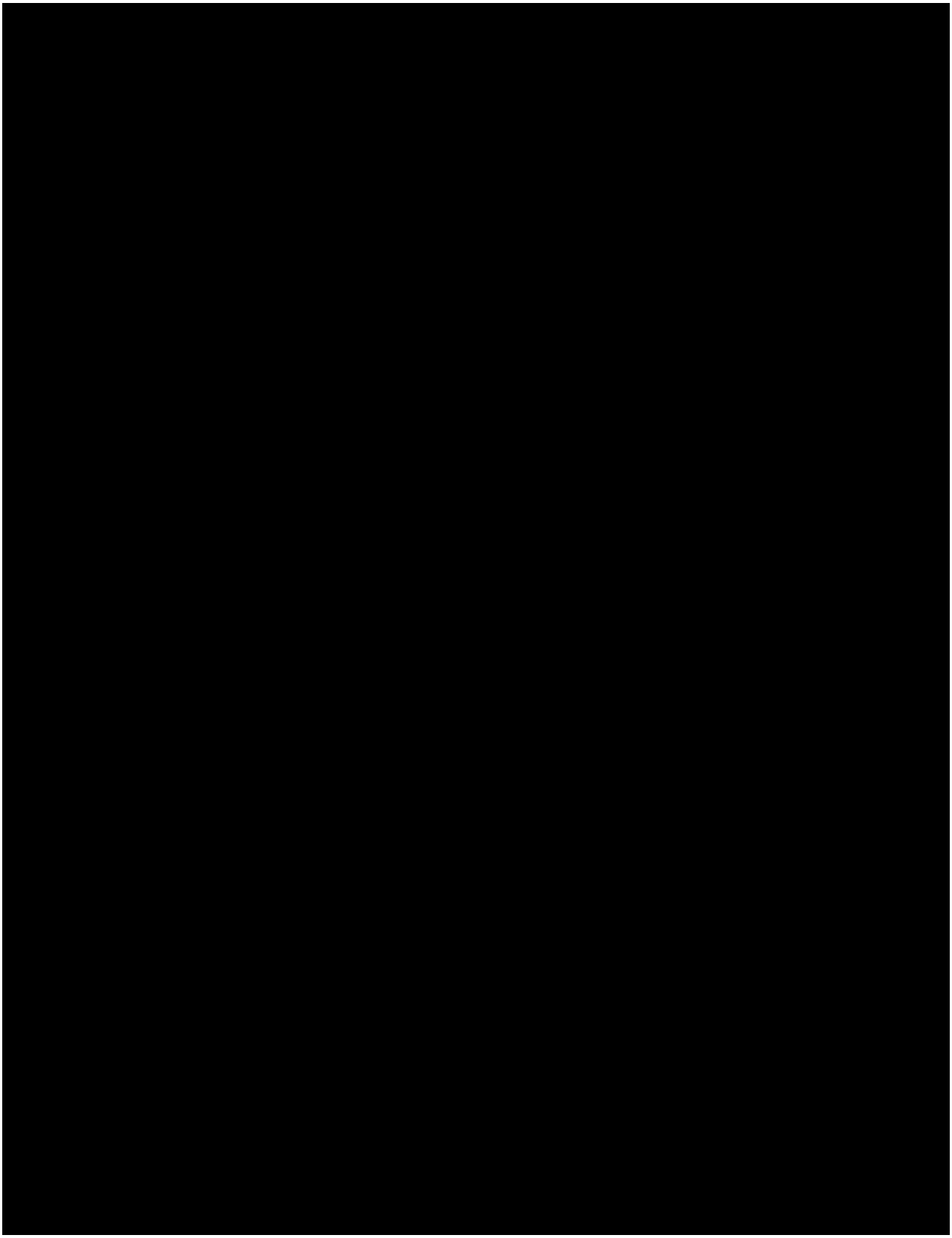
- Death at or before the 24-week assessment visit
- Requires intervention for ROP in either eye at or before the 24-week assessment visit with a treatment modality other than the modality of the first study treatment
- Have active ROP in either eye at the 24-week assessment visit [redacted]
- Have unfavorable structural outcomes in either eye at or before the 24-week assessment visit [redacted]

[redacted]

A patient may be defined as a "success" (favorable outcome) or "failure" (unfavorable outcome) for each of the criteria above. Patients will be defined as a "success" for the primary efficacy variable only if they are a "success" for each component. Consequently a patient will be defined as a "failure" for the primary efficacy variable if they are defined a "failure" for at least one of the criteria above.

A 2-sided family-wise type I error rate of 5% will be used. Two-sided exact 95% confidence intervals will be presented for the primary variable event rate within each treatment arm, overall and by zone (see Section 2.11).

[redacted]



[redacted]

2.7.1.4 Handling of missing primary efficacy variable

Please refer to Section 2.5.7.1.

2.7.1.5 Supportive analysis for primary efficacy

The robustness of the primary analysis (testing the hypotheses specified in Section 2.7.1.3) may be assessed by:

- Repeating the primary analyses using the Per Protocol Set
- Repeating the primary analyses without imputing missing data at Week 24
- Repeating the primary analyses imputing missing primary efficacy variable at Week 24 with ”success”
- Repeating the primary analyses imputing missing primary efficacy variable at Week 24 with “failure”
- Repeating the primary analyses with imputation rule 2

[redacted]

The primary efficacy variable will also be assessed by a binary logistic regression model by using treatment arm [redacted] as factors. The odds ratio of the primary variable will be displayed (with values greater than one in favor of ranibizumab) with its two-sided 95% confidence interval and one-sided p-value. If the number of events of some cells is very small (<5 for at least one cell), then exact logistic regression will be used to assess the primary efficacy variable (Please refer to Section 4.2 for SAS code).

[redacted]

The subgroup and its interaction with treatment will be added to the binary logistic regression model above and the p-value for the subgroup by treatment interaction term will be displayed.

The binary logistic model with treatment arm and ROP zone will be fitted to each subgroup level separately and the odds ratio of the primary variable with its two-sided 95% confidence interval will be presented.

[redacted]

2.7.2 Analysis of secondary variables

All secondary efficacy analyses will be performed on the FAS based on observed data unless otherwise specified. No imputation of missing data will be undertaken on secondary efficacy variables.

2.7.2.1 Binary variables

The following binary variables will be summarized giving the number and percentages (with Clopper-Pearson exact 2-sided 95% confidence interval) for each treatment arm overall and by zone

- Each of the components that constitute the definition of primary variable will be presented. Note that if a patient switches treatment then each of the other components will be defined as "failure".
- Each of the following unfavorable structural outcomes in either eye at or before 24 weeks after the first study treatment, [redacted]
- Recurrence of ROP receiving any post-baseline intervention at 24 weeks or before

2.7.2.2 Time-to-event variable

The time from the first study treatment to the first occurrence of one of the following event:

- Death
- Intervention for ROP with a treatment modality other than the modality of the first study treatment

- An unfavorable structural outcome [redacted]

will be evaluated using data collected at all visits from baseline until the last study visit inclusive. [redacted]
Please refer to Section 4.3 for SAS code.

[redacted]

2.8 Safety evaluation

Safety analyses will be conducted on data from SAF by initial treatment received. Adverse events, vital signs measurements, requirement for respiratory support and laboratory evaluations will be summarized and listed.

The safety observation period (days) for treated patients begins at the first administration of study treatment in either eye. It finishes at the last study visit.

Safety observation period (days) is defined as

date of last study visit–date of first study treatment in either eye + 1

The safety observation period [days] will be summarized by treatment for patients in the SAF.

2.8.1 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 separately for patients who receive monotherapy and those who receive both treatment modalities. 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.

2.8.2 Adverse Events

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 will be listed for patients in the randomized set using the randomized treatment.

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. When an AE's start date is equal to the date of first study treatment and either the start time of AE or the first treatment time is missing, AEs are defined as treatment emergent. As stated in Section 2.5.5, adverse events with completely missing start date will be defined as treatment emergent.

The number of patients with AE and the incidence rates will be tabulated by treatment using the latest MedDRA SOCs and PTs. 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. Patients who experienced multiple AEs for a preferred term will be counted once, similarly for patients with multiple AEs per system organ class. Separate In-text tables will display the frequency of AEs at the SOC and PT levels. 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 to the AE CRF form). All AE tables will be summarized separately by initial study treatment received at baseline, and by patients who switch/do not switch treatment modality after receiving the initial study treatment at baseline.

All AE tables will show the frequency and crude incidence rate by initial study treatment received at baseline 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
- Serious adverse event, regardless of study treatment or procedure relationship
- All adverse events suspected to be related with study treatment or procedure
- Serious adverse event suspected to be related with 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.

- Primary reasons for deaths
- Deaths, SAE, or AE leading to permanent study treatment discontinuation

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

In addition, CTSD required tables will be presented as part of the CSR, i.e.: deaths and serious adverse events by system organ class and preferred term, non-serious adverse events by system organ class and preferred term.

2.8.3 Vital signs

Vital signs (weight, body length, head circumference, lower 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) of values and change from baseline at days 85 and 169 [redacted] by treatment arm.

[redacted]

2.8.5 Laboratory data

Laboratory assessments (hematology, chemistry, urinalysis) are collected at local labs with heterogeneity across different labs. Therefore, only listings will be provided for each individual at baseline, days 85 and 169 by treatment arm.

2.9 Other analysis

[redacted]

2.9.1.1 Electrocardiogram (ECG)

Not applicable

2.9.2 Pharmacokinetic analysis

For patients who receive initial ranibizumab treatment and with an odd patient identification number, blood samples (Appendix 1) for the determination of ranibizumab concentrations will be collected at the following time points:

- Within 24 hours after the first administration of ranibizumab
- At Day 15, [redacted]
- At Day 29, [redacted]

All patients providing valid pharmacokinetic serum samples will be included in the PK analysis population. Individual ranibizumab concentrations versus time profiles, as well as mean and SD plot over time will be displayed graphically. Moreover, a summary table will be provided.

2.9.3 Pharmacogenetics/Pharmacogenomics

Not applicable.

2.9.4 Systemic vascular endothelial growth factor level

For patients who receive initial ranibizumab treatment and with an even patient identification number and for all patients who receive initial laser therapy, blood samples (Appendix 2) for the determination of systemic VEGF levels (i.e., pharmacodynamics) will be collected at the following time points:

- Before the first investigational treatment
- At Day 15, [redacted]
- At Day 29, [redacted]

All patients providing valid VEGF plasma samples will be included in the VEGF analysis population. Individual VEGF concentrations versus time profiles, as well as mean and SD plot over time will be displayed graphically. Summary statistics table will be presented for VEGF samples.

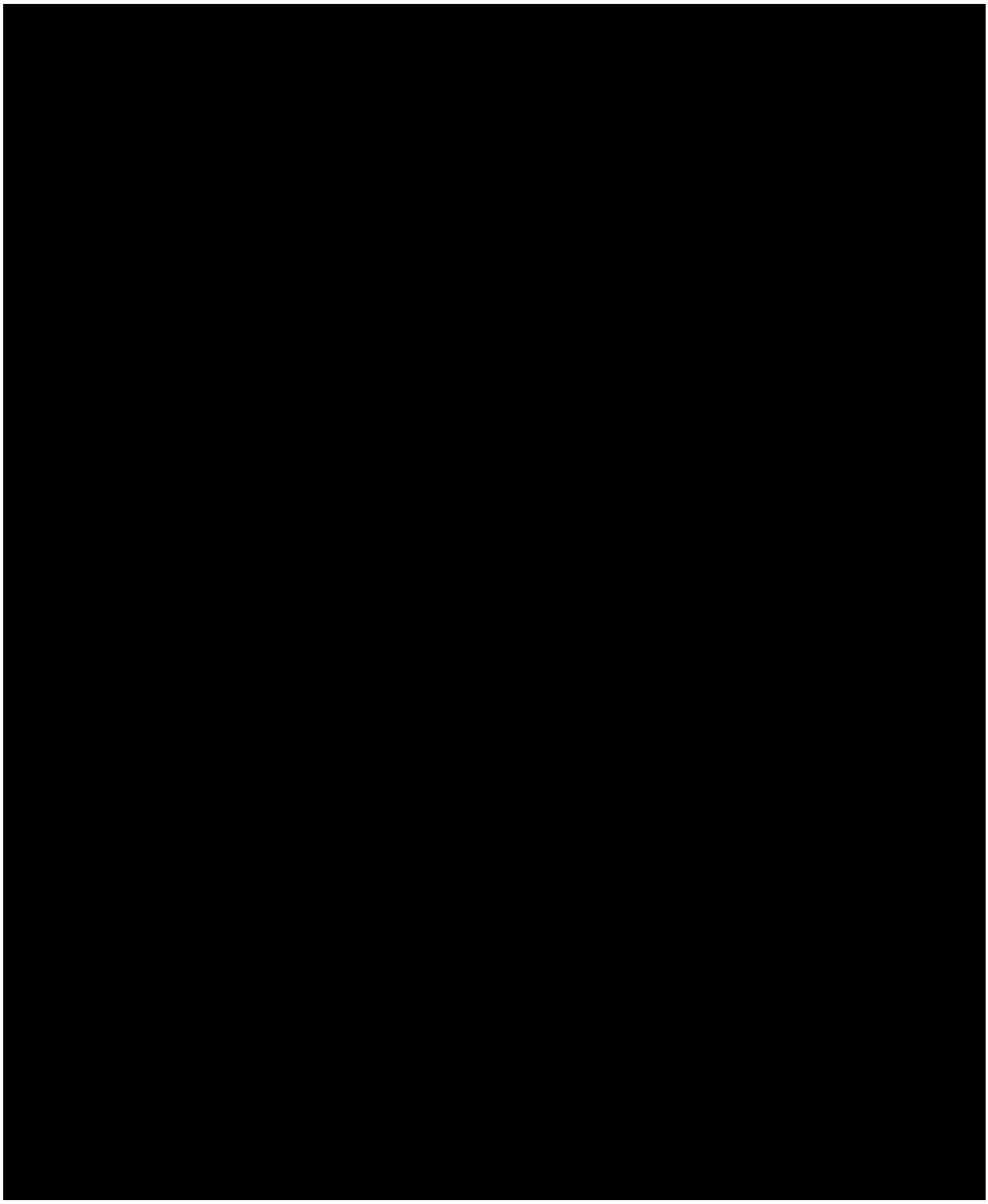
[redacted]

2.9.6 Hospitalization

The duration of hospitalization and the weight at hospital discharge will be summarized and tabulated by treatment.

2.10 Interim analysis

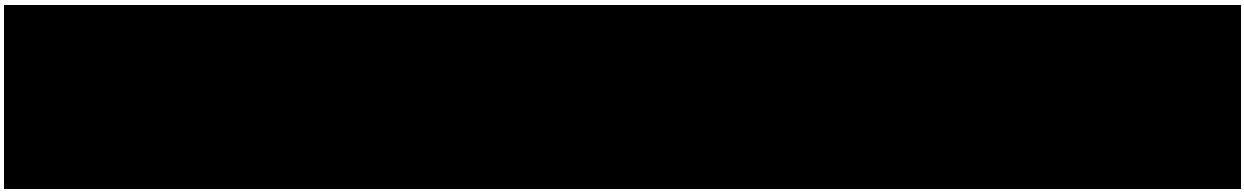
There will be no interim analyses during this trial.



2.12 Data monitoring committee (DMC)

An independent DMC will be established to monitor the safety of the trial participants to ensure that the trial is being conducted with the highest scientific and ethical standards and make appropriate recommendations based on the data seen.

Refer to the DMC charter which includes the DMC membership and responsibilities, the timing of DMC meetings, the content of the analysis report for the DMC meetings, and the communication with the Sponsor. The DMC will only make recommendations for changes in study conduct.



3 Reference

1. A note on the power of Fisher's least significant difference procedure, Meier U., Pharmaceutical Statistics, 2006; 5 (4): 253-63.