STATISTICAL ANALYSIS PLAN
VERSION: FINAL 1.0

Clinical Study Protocol Title:	A Phase 3b Single-Arm Study of Aflibercept 8 mg in Participants With Neovascular Age-Related Macular Degeneration (nAMD) or Diabetic Macular Edema (DME)
Compound:	Aflibercept 8 mg
Protocol Number:	VGFTe-HD-OD-2444
Study Name:	ELARA
Clinical Phase:	Phase 3b
Sponsor:	Regeneron Pharmaceuticals, Inc.
Versions/Dates:	Original Statistical Analysis Plan / 05DEC2024

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP), and agreed on the planned analysis defined in this document for reporting.

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Study Biostatistician [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

8q4	Aflibercept 8 mg every 4 weeks
AE	Adverse event
AOBP	Automated office blood pressure
ATC	Anatomical Therapeutic Chemical
BCVA	Best-corrected visual acuity
BP	Blood pressure
CRF	Case report form (electronic or paper)
CST	Central subfield thickness
DME	Diabetic macular edema
DRM	Dose regimen modification
DRM-E	Dose regimen modification criteria for extension
DRM-S	Dose regimen modification criteria for shortening
EDC	Electronic data capture
EOS	End of study
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FP	Fundus photography
HR	Heart rate
ICF	Informed consent form
IOP	Intraocular pressure
IRF	Intraretinal fluid
IVT	Intravitreal
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
nAMD	Neovascular age-related macular degeneration
OCT	Optical coherence tomography
PCSV	Potentially clinically significant values
PT	Preferred term
q4	Every 4 weeks
Regeneron	Regeneron Pharmaceuticals, Inc.
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD-OCT	Spectral domain optical coherence tomography
SOC	System organ class

SRF	Subretinal fluid
TEAE	Treatment-emergent adverse event
VEGF	Vascular endothelial growth factor
WHODD	World Health Organization Drug Dictionary
WOCBP	Women of childbearing potential

1. OVERVIEW

This statistical analysis plan (SAP) is intended to be a comprehensive and detailed description of the statistical methods, timing of analyses, and analysis presentation to be used for the study specified in protocol VGFTe-HD-OD-2444, amendment 2 dated October 31, 2024.

1.1. Study Description and Objectives

This is a phase 3b, multicenter, single-arm study to assess the safety and measures of efficacy of treatment with aflibercept 8 mg dosed every 4 weeks (8q4) in participants with neovascular age-related macular degeneration (nAMD) or diabetic macular edema (DME) previously treated with intravitreal (IVT) anti-vascular endothelial growth factor (VEGF) injections.

1.1.1. Primary Objective(s)

The primary objective of this study is to evaluate the safety of aflibercept 8 mg.

1.1.2. Secondary Objective(s)

There is no secondary objective in this study.

1.1.3. Exploratory Objective(s)

[redacted]

1.2. Statistical Hypothesis

No formal hypothesis testing is planned.

1.3. Interim Analysis

No interim analysis is planned.

1.4. Modifications from the Statistical Section in the Final Protocol

[redacted] The data up to a cutoff date will be included in one or more analyses for participants who enrolled or screen failed by a certain date. The applicable analyses will follow the same analysis methods in this SAP.

1.5. Revision History for SAP Amendments

Not applicable

2. INVESTIGATION PLAN

2.1. Study Design

This is a phase 3b, multicenter, single-arm study to assess the safety and measures of efficacy of treatment with aflibercept 8q4 in participants with nAMD or DME previously treated with IVT anti-VEGF injections. This study consists of a screening/enrollment visit, a treatment period, and an end of study (EOS) visit at week 96.

Eligibility will be assessed at the screening visit on day 1. Participants with nAMD or DME are eligible for screening if they have been previously treated with ≥3 anti-VEGF injections over the prior 5 months (~150 days). Up to 1000 participants (~500 participants with nAMD and ~500 participants with DME) who meet all eligibility criteria will be enrolled.

The screening visit should be held approximately 4 to 7 weeks (25 to 49 days) after the most recent anti-VEGF injection and, for eligible participants, the initial study treatment will occur on the same day. Participants will receive a total of 7 injections of aflibercept 8q4, from baseline through week 24.

To assess the ability to extend dosing intervals with aflibercept 8 mg in this population, Dose Regimen Modification (DRM) criteria will be used to assess potential dose interval extensions, as well as subsequent dose interval shortening at each visit beginning at week 24. The minimum interval between injections is 4 weeks (28 days).

Dose Regimen Modification Criteria for Extension (DRM-E):

Beginning at week 24, if DRM criteria for extension (DRM-E) are met, the interval between consecutive injections will be extended following a "treat-and-extend" paradigm. Dose intervals will be extended by 2 weeks when DRM-E criteria are met at any dosing visit as long as the dose interval has not been shortened previously. For participants who have had their dose interval shortened previously, the dose interval will only be extended by 1 week increments and only after a minimum of 12 weeks (84 days) has passed.

Participants will be eligible for interval extension if the following criteria are met at **any dosing visit**:

nAMD

- No retinal fluid in central subfield

  AND

- No new onset foveal neovascularization or foveal hemorrhage

  AND

- No interval shortening within the last 12 weeks (84 days)

DME

- Central subfield thickness (CST) <300 µm [redacted]

  AND

- ≤10 µm increase (worsening) from lowest (best) previous CST value

AND

- No interval shortening within the last 12 weeks (84 days)

Dose Regimen Modification Criteria for Shortening (DRM-S)

If a participant's interval has been extended, then the dose interval may be shortened by 1 week if the DRM-S criteria are met. If the DRM-S criteria are met at either a dosing or a non-dosing visit, the participant will be dosed, and the subsequent interval will be shortened to the time from the most recent dose minus 1 week. The minimum interval between injections will be 4 weeks (q4).

Participants will be eligible for interval shortening (by 1-week increments), if one of the following criteria are met at **any scheduled visit**:

nAMD

- Any new retinal fluid in central subfield

OR

- New onset foveal neovascularization or foveal hemorrhage

OR

- >5 letter loss in best-corrected visual acuity (BCVA) from best previous attributable to recurrent or persistent disease

DME

- >25 µm increase in CST from previous visit

OR

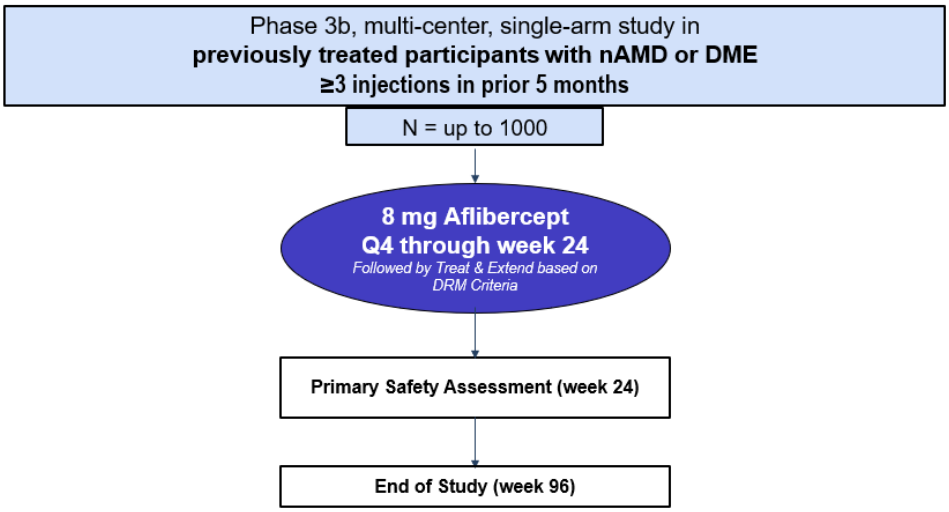
- >10 letter loss in BCVA from best previous attributable to recurrent or persistent disease

DRM-E and DRM-S criteria will be assessed by the investigator. Participants who do not meet the above criteria for interval extension or shortening at a given visit will continue treatment at the current interval.

The primary analysis will occur once all participants have completed week 24 (or prematurely discontinued), with the final analysis occurring after all participants have completed the study at week 96 (or prematurely discontinued). Additional analyses may be performed at other timepoints, e.g., week 48.

The study flow diagram and dosing schedules are presented in Figure 1 and Figure 2.

Figure 1: Study Flow Diagram



Q4=once every 4 weeks, DME=diabetic macular edema, DRM=dose regimen modification, nAMD=neovascular age-related macular degeneration

Figure 2: Dosing Schedule

	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24 ↓	Dosing Wks 28 to 35	Mand Wk 36	Dosing Wks 37 to 47	Mand Wk 48	Dosing Wks 49 to 59	Mand Wk 60	Dosing Wks 61 to 71	Mand Wk 72	Dosing Wks 73 to 83	Mand Wk 84	Dosing Wks 85 to 95	Mand Wk 96 EOS
8mg	X	X	X	X	X	X	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	

*Participants will be evaluated for interval modification based on DRM criteria beginning at week 24.
EOS=end of study, Mand=mandatory, ↓= primary safety assessment, wk(s)=weeks

2.2. Sample Size and Power Considerations

The sample size of up to 1000 participants (~500 participants with nAMD and ~500 participants with DME) will provide information on safety in these populations.

3. ANALYSIS SETS

The following defines the set of participants whose data will be used for statistical analysis.

3.1. Safety Analysis Set (SAF)

The SAF includes all enrolled participants who received at least 1 injection of aflibercept 8 mg during the study. The SAF will be used for analyzing all variables including treatment compliance, administration/exposure, efficacy endpoints, and clinical safety variables.

4. GENERAL STATISTICAL ANALYSIS CONSIDERATIONS

Unless otherwise stated, the following conventions will be applied when presenting summary level statistics for data.

Continuous variables will be summarized, presenting the following summary statistics: sample size (i.e., number of observations with an available value of the variable), average, sample standard deviation, median, minimum, maximum, 1st quartile and 3rd quartile.

Categorical data will be summarized by frequency (i.e., total number of observations within each level of the categorical variable). All levels of the categorical variable will be included. If there are observations where the level of the categorical variable is missing, a separate category titled "Missing" will be created. For categorical variables that are ordinal in nature, the order in which the levels of the categories are displayed will be consistent with the natural ordering of the category levels. Percentages will also be calculated for each level of the categorical variables with respect to the total sample size.

5. PARTICIPANT DISPOSITION

Disposition will be summarized by indication (nAMD, DME) and overall.

5.1. Screening Dispositions

The number of screened participants (i.e., participants who signed the ICF), treated participants and participants who discontinue prior to first treatment will be summarized, along with their primary reason for discontinuation. The corresponding percentages with respect to the total number of screened participants will also be presented.

5.2. Participant Dispositions

The following summaries will be provided for the disposition of participants during the study using the SAF:

- The total number of participants who completed week 24
- The total number of participants who completed the study
- The total number of participants who did not complete week 24 with the reason for not completing
- The total number of participants who did not complete the study with reasons for not completing

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics, baseline disease characteristics, and medical history will be summarized by indication (nAMD, DME) and overall using the SAF.

6.1. Demographics

The following demographic variables will be summarized:

- Age at screening (year)
- Age categories (<55 years, ≥55 years to <65 years, ≥65 years to <75 years, ≥75 years-<85 years, ≥85 years)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White, Not Reported, and Other)
- Ethnicity (Hispanic/Latino, Not Hispanic or Latino, and Not Reported)

6.2. Baseline Disease Characteristics

The following disease characteristics will be summarized:

- Best-corrected visual acuity (BCVA) (measured by Early Treatment Diabetic Retinopathy Study [ETDRS] letters) in the study eye
- BCVA category in the study eye (≤38 letters, >38 letters to ≤73 letters, >73 letters)
- Central subfield thickness (CST) in the study eye
- Baseline systolic and diastolic blood pressure (BP)
- Intraocular pressure (IOP) in the study eye
- Medical history: hypertension (Yes, No), cerebrovascular disease (Yes, No), and ischaemic heart disease (Yes, No). Detailed definitions are provided in Section 14.2.

6.3. Medical History

Participant medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Medical history will be separated into ocular medical history in the study eye, ocular medical history in the fellow eye, and non-ocular medical history. The frequency and percentage of each medical history will be summarized by primary system organ class (SOC) and preferred term (PT). The tables will be sorted by decreasing frequency of primary SOC. Within each primary SOC, PTs will be sorted by decreasing frequency.

7. EFFICACY DATA

7.1. Description of Efficacy Data

7.1.1. Primary Efficacy Variable

There is no primary efficacy endpoint in this study.

7.1.2. Exploratory Efficacy Variables

7.2. Analysis of Efficacy Data

All efficacy analyses will be conducted by indication (nAMD, DME) and overall using the SAF.

7.2.1. Analysis of Primary Endpoint

There is no primary efficacy endpoint in this study

7.2.2. Exploratory Efficacy Analyses

8. HYPOTHESIS TESTING METHODS AND MULTIPLICITY CONTROL

There is no formal statistical hypothesis in this study. No multiplicity adjustments are required for this study.

9. SUMMARY OF EXPOSURE DATA

9.1. Investigation Study Drug Exposure and Compliance

Study treatment exposure and compliance will be summarized using the SAF.

Exposure

The following variables will be used to examine exposure to study treatment for the study eye:

- Total number of injections through week 24
- Duration of treatment (weeks) calculated as: [(last study treatment date) - (first study treatment date) + 28]/7 (28 days are added because of the minimum 4-week dosing interval in the study) through week 24
- Total number of injections through week 96
- Duration of treatment (weeks) calculated as: [(last study treatment date) - (first study treatment date) + 28]/7 (28 days are added because of the minimum 4-week dosing interval in the study) through week 96
- Number of participants who remained on a q4 interval (ie. never extended).
- Number of participants who had their dosing interval extended at least once after week 24.
- Number of participants who had 6 weeks, 8 weeks, etc. as their longest dosing interval
- Number of participants who had 4 weeks as their last intended dosing interval
- Number of participants who had 6 weeks or longer, 8 weeks or longer, etc. as their last intended dosing interval
- Number of participants who had 4 weeks as their last completed dosing interval
- Number of participants who had 6 weeks or longer, 8 weeks or longer, etc. as their last completed dosing interval
- Number of participants whose dosing interval was extended and subsequently shortened at anytime

The following variables will be used to evaluate the fellow eye treatment, if applicable:

- Total number of participants with at least one fellow eye treatment through week 24
- Total number of injections through week 24
- Duration of fellow eye treatment calculated (weeks) as: [(last fellow eye treatment date) - (first fellow eye treatment date) + 28]/7 (28 days are added because of the minimum 4-week dosing interval in the fellow eye in the study) through week 24
- Total number of participants with at least one fellow eye treatment through week 96
- Total number of injections through week 96

- Duration of fellow eye treatment calculated (weeks) as: [(last fellow eye treatment date) - (first fellow eye treatment date) + 28]/7 (28 days are added because of the minimum 4-week dosing interval in the fellow eye in the study) through week 96

Compliance

Because participant dosing intervals will vary after week 24, only the compliance with protocol-defined study treatments from baseline through week 24 will be assessed per participant and calculated as follows:

- Treatment Compliance = (Number of received injections through a given week)/(Number of planned injections through a given week) x 100%

9.2. Prior and Concomitant Medications

Medications taken during the study will be recorded and coded using the World Health Organization Drug Dictionary (WHODD).

Medications will be summarized as follows in the SAF:

- Prior medication is defined as medication that starts before a participant received first study treatment regardless of when it was stopped.
- Concomitant medication is defined as medication that is ongoing at, or began after, the start of study treatment.

Summaries will present number and percentage of participants by decreasing frequency of Anatomical Therapeutic Chemical (ATC) class (ATC level 2), subclass (ATC level 4), and standardized medication name. In case of equal frequency across categories, alphabetical order will be used. Participants will be counted once in each category linked to the medication.

Concomitant medications will be summarized through week 24 and through end of study (EOS, week 96).

9.3. Concurrent Procedures

Procedures performed during the study will be coded using MedDRA. Treatment-emergent procedures, defined as having been performed on or after the start of study treatment, will be summarized in the SAF by SOC and PT in the following categories:

- Treatment-emergent ocular procedures in the study eye
- Treatment-emergent ocular procedures in the fellow eye
- Treatment-emergent non-ocular procedures

The following study periods will be used for treatment-emergent procedure summaries:

- Day 1 to week 24
- Day 1 to EOS (week 96)

For the week 24 primary analysis period, the treatment-emergent procedures will be summarized to the last dose of study drug plus 30 days or the week 24 visit, whichever is later. For the entire study period, the treatment-emergent procedure will be summarized to the last dose of study drug plus 30 days or the end of study, whichever is later.

10. ANALYSIS OF SAFETY DATA

The safety analyses will be conducted by indication (nAMD, DME) and overall using the SAF. No formal statistical testing of safety endpoints will be conducted.

10.1. Adverse Events

All adverse events (AEs) will be coded according to MedDRA.

Adverse events will be summarized with incidence tables. Adverse event incidence tables will present the number (n) and percentage (%) of participants experiencing an AE, sorted by decreasing frequency of SOC and PT. Multiple occurrences of the same event in a participant will only be counted once in the summary. For tables showing AE severity, if a participant has multiple occurrences of the same PT or SOC, only the worst severity will be counted in the summary.

AE summaries will be presented for treatment-emergent adverse events (TEAEs), which are defined as those AEs with either initial onset after the first dose of study treatment or that worsen after the first dose of study treatment.

The following study periods will be used for TEAE summaries:

- Day 1 to week 24
- Day 1 to EOS (week 96)

For the week 24 primary analysis period, the TEAEs will be summarized to the last dose of study drug plus 30 days or the week 24 visit, whichever is later. For the entire study period, the TEAEs will be summarized to the last dose of study drug plus 30 days or the end of study, whichever is later.

The following summaries for TEAEs will be presented:

- Ocular TEAEs of the study eye by primary SOC and PT
- Ocular TEAEs of the fellow eye by primary SOC and PT
- Non-ocular TEAEs by primary SOC and PT
- Ocular TEAEs of the study eye related to study treatment by primary SOC and PT
- Ocular TEAEs of the fellow eye related to study treatment by primary SOC and PT
- Non-ocular TEAEs related to study treatment by primary SOC and PT
- Ocular TEAEs of the study eye related to the injection procedure by primary SOC and PT
- Ocular TEAEs of the fellow eye related to the injection procedure by primary SOC and PT
- Non-ocular TEAEs related to the injection procedure by primary SOC and PT
- Ocular TEAEs of the study eye related to study conduct by primary SOC and PT
- Ocular TEAEs of the fellow eye related to study conduct by primary SOC and PT

- Non-ocular TEAEs related to study conduct by primary SOC and PT
- Ocular TEAEs of the study eye leading to study treatment discontinuation by primary SOC and PT
- Ocular TEAEs of the fellow eye leading to study treatment discontinuation by primary SOC and PT
- Non-ocular TEAEs leading to study treatment discontinuation by primary SOC and PT
- Ocular TEAEs of the study eye by primary SOC, PT, and maximum severity
- Ocular TEAEs of the fellow eye by primary SOC, PT, and maximum severity
- Non-ocular TEAEs by primary SOC, PT, and maximum severity
- Ocular serious TEAEs of the study eye by primary SOC and PT
- Ocular serious TEAEs of the fellow eye by primary SOC and PT
- Non-ocular serious TEAEs by primary SOC and PT
- Ocular serious TEAEs of the study eye related to study treatment by primary SOC and PT
- Ocular serious TEAEs of the fellow eye related to study treatment by primary SOC and PT
- Non-ocular serious TEAEs related to study treatment by primary SOC and PT
- Ocular serious TEAEs of the study eye related to the injection procedure by primary SOC and PT
- Ocular serious TEAEs of the fellow eye related to the injection procedure by primary SOC and PT
- Non-ocular serious TEAEs related to the injection procedure by primary SOC and PT
- Ocular serious TEAEs of the study eye related to study conduct by primary SOC and PT
- Ocular serious TEAEs of the fellow eye related to study conduct by primary SOC and PT
- Non-ocular serious TEAEs related to study conduct by primary SOC and PT
- TEAEs leading to death by primary SOC and PT

Death, treatment-emergent hypertension and treatment-emergent intraocular inflammation of the study eye will be tabulated. Detailed definitions for hypertension and intraocular inflammation are provided in Section 14.2.

Subgroup analyses in TEAE reporting will be performed for the following subgroups:

- Sex: male, female

- Age at enrollment: <55 years, ≥55 years to <65 years, ≥65 years to <75 years, ≥75 years-<85 years, ≥85 years
- Race (only subgroups with sufficient sample size): White, Black or African American, Asian
- Ethnicity: Not Hispanic or Latino, Hispanic or Latino
- Medical history of hypertension
- Medical history of cerebrovascular disease
- Medical history of ischaemic heart disease

The medical history subgroups are defined in more detail in Section 14.2..

The following summary of TEAEs will be provided for the above subgroups:

- Ocular TEAEs of the study eye by primary SOC and PT
- Non-ocular TEAEs by primary SOC and PT
- Serious ocular TEAEs of the study eye by primary SOC and PT
- Serious non-ocular TEAEs by primary SOC and PT

10.2. Vital Signs

Vital signs (heart rate [HR] and systolic/diastolic BP) and their changes from the baseline will be summarized by visit (or mandatory visit if after week 24). The baseline for vital signs endpoints will be the latest available valid measurement taken prior to the administration of study drug, as specified in Section 11.1 .

Systolic/diastolic BP measurements will be evaluated by potentially clinically significant values (PCSV) criteria (Section 14.3), specifically identifying participants with at least one valid post-baseline blood pressure value and with a valid baseline value. Participants meeting the PCSV criteria will be summarized in terms of participant count (and percent).

10.3. Other Safety Data

Pre-dose IOP measurements and their changes from baseline will be summarized by visit (or mandatory visit if after week 24) using descriptive statistics for the study eye and the fellow eye. Post-dose IOP measurements and their changes from pre-dose will be summarized for study eye. The proportion of participants who meet the following criteria will be summarized descriptively:

- ≥ 10 mmHg increase in IOP measurement from baseline to pre-dose measurement in the study eye (by visit (or mandatory visit if after week 24) and at any time)
- ≥ 10 mmHg increase in IOP measurement from baseline to pre-dose measurement in the fellow eye (by visit (or mandatory visit if after week 24) and at any time)
- ≥ 25 mmHg for any pre-dose measurement in the study eye (by visit (or mandatory visit if after week 24) and at any time)

- ≥ 25 mmHg for any pre-dose measurement in the fellow eye (by visit (or mandatory visit if after week 24) and at any time)
- ≥ 35 mmHg at any time (pre- or post-dose) in the study eye (by visit (or mandatory visit if after week 24) and at any time)
- ≥ 35 mmHg at any time (pre- or post-dose) in the fellow eye (by visit (or mandatory visit if after week 24) and at any time)

11. DATA CONVENTIONS

11.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment for all measurements will be the last available measurement prior to the administration of investigational product.

11.2. Data Convention

- For categorical variables, participants with missing data will not be included in calculations of percentages unless otherwise specified. When relevant, the number of participants with missing data will be presented.
- If the date of interest occurs on or after the first dose date, the study day will be calculated as (date of interest – date of the first dose) + 1.
- If the date of interest occurs prior to the first dose date, the study day will be calculated as (date of interest – date of the first dose).
- Percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form xx (xx.x%).
- Change from baseline will be calculated as a post-baseline value minus the baseline value.
- All analysis and summary tables will include the analysis population sample size in the column headings.

11.3. Data for Non-Efficacy Endpoints

Adverse event

AEs with partial start dates will be imputed based on the following rules:

1. If AE partial start date indicates it is before the first dose of study drug, then it will be imputed as the latest possible date.
2. If AE partial start date has the same partial date as the first dose of study drug, then it will be imputed as the date of the first dose of study drug.
3. If AE partial start date indicates it is after the first dose of study drug, then it will be imputed as the earliest possible date.
4. If imputed AE start date is later than AE end date, then the AE start date will be imputed as the AE end date.

If the severity of a TEAE is missing, it will be classified as “severe” in the frequency tables by severity of TEAEs. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as related to the investigational product.

Procedures

For the tabulation of procedures, partially missing start dates of the procedure will be imputed using the same rules as for AEs.

Medication missing/partial dates

For the tabulation of prior and concomitant medications, partially missing start dates of medications will be imputed by the earliest possible time point; partially missing stop dates will be imputed by the latest possible time point.

Date of first / last injection

Date of first injection will be the first non-missing start date of dosing filled in the CRF "Investigational Product" module.

If a participant's date of the last dose is totally missing or unknown, his/her last visit date will be substituted.

11.4. Assignment of Data to Visit Windows and Unscheduled Assessments

Visit Windows

The visits used for the analysis will be based on the nominal visits, i.e., according to the CRF assessment recorded by the investigator. No visit windows will be further defined.

Unscheduled Assessments

Unscheduled assessments will not be included in the summaries unless specified.

If more than one value is available for a given visit, the visit value actually used for statistical summaries and analyses will be as follows:

- The last non-missing repeated measurement, if respective visit is before start of treatment
- The first non-missing repeated measurement, if respective visit is after start of treatment

If an early termination visit is performed within the protocol-defined window of the next scheduled visit after the last previous visit, the visit-dependent assessments will be re-slotted to the next scheduled visit.

12. TECHNICAL DETAILS PERTAINING TO INTERIM ANALYSIS/(ES)

No formal interim analyses will be performed.

13. REFERENCES

Not applicable

14. APPENDIX

14.1. Schedule of Events

Study Procedure	Visit 1 Screening/Baseline Treatment[1]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7[2]	Dosing Visits[2] (Based on DRM)	Mandatory Visit 8	Dosing Visits[2] (Based on DRM)	Mandatory Visit 9	Dosing Visits[2] (Based on DRM)	Mandatory Visit 10	Dosing Visits[2] (Based on DRM)	Mandatory Visit 11	Dosing Visits[2] (Based on DRM)	Mandatory Visit 12	Dosing Visits[2] (Based on DRM)	EOS Mandatory Visit 13[12]
Week(s)	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28-35**	**36[3]**	**37-47**	**48[3]**	**49-59**	**60[3]**	**61-71**	**72[3]**	**73-83**	**84[3]**	**85-95**	**96**
Study Day	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197-239**	**253**	**267-323**	**337**	**351-407**	**421**	**435-491**	**505**	**519-575**	**589**	**603-659**	**673**
Window (days)		**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±2**	**±16**	**±2**	**±16**	**±2**	**±16**	**±2**	**±16**	**±2**	**±16**	**±2**	**±5**
Informed Consent (ICF)	X																		
Inclusion/ Exclusion	X																		
Medical History	X																		
Demographics	X																		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DRM Assessment[2]							X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Administration[4]	X	X	X	X	X	X	X	X[2]	X[2, 3]	X[2]	X[2,3]	X[2]	X[2,3]	X[2]	X[2,3]	X[2]	X[2,3]	X[2]	
BCVA/ refraction[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit-lamp exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedure	Visit 1 Screening/Baseline Treatment[1]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7[2]	Dosing Visits[2] (Based on DRM)	Mandatory Visit 8	Dosing Visits[2] (Based on DRM)	Mandatory Visit 9	Dosing Visits[2] (Based on DRM)	Mandatory Visit 10	Dosing Visits[2] (Based on DRM)	Mandatory Visit 11	Dosing Visits[2] (Based on DRM)	Mandatory Visit 12	Dosing Visits[2] (Based on DRM)	EOS Mandatory Visit 13[12]
Week(s)	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28-35**	**36[3]**	**37-47**	**48[3]**	**49-59**	**60[3]**	**61-71**	**72[3]**	**73-83**	**84[3]**	**85-95**	**96**
Study Day	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197-239**	**253**	**267-323**	**337**	**351-407**	**421**	**435-491**	**505**	**519-575**	**589**	**603-659**	**673**
Window (days)		**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±2**	**±16**	**±2**	**±16**	**±2**	**±16**	**±2**	**±16**	**±2**	**±16**	**±2**	**±5**
FA, FP[8]	X			X			X				X								X
SD-OCT[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[11] (Urine only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

BCVA=best-corrected visual acuity, DRM=dose regimen modification, FA=fluorescein angiography, FP=fundus photography, ICF=informed consent form, IOP=intraocular pressure, SD-OCT=spectral domain optical coherence tomography

14.1.1. Footnotes for the Schedule of Events Table

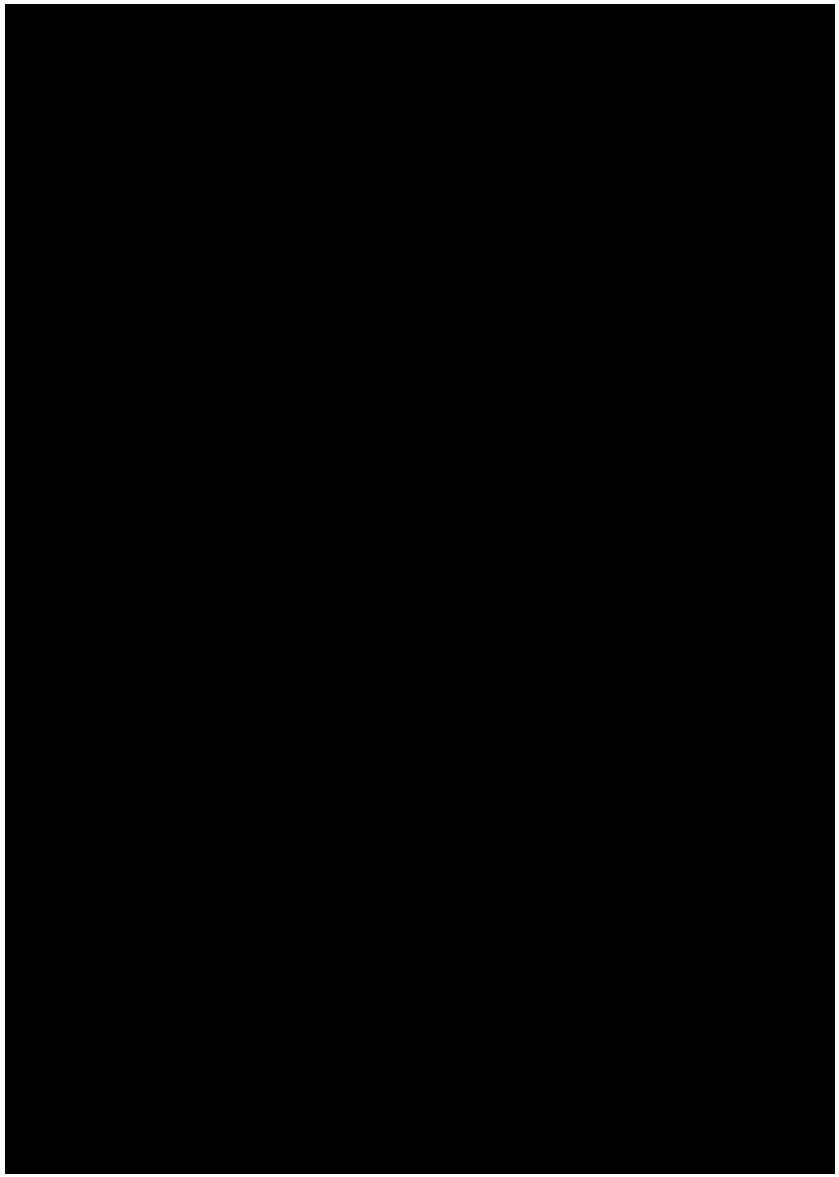
1. Participants who meet all eligibility criteria will be treated on the same day. Screening should take place approximately 4 to 7 weeks (25 to 49 days) after the last treatment.
2. Participants' study eye will be assessed based on DRM criteria starting at week 24. If DRM criteria are met, the participant will be dosed at that visit and the next dose will be given at the updated interval (see Section 5.1 of the protocol amendment 2). Subsequently, dosing visits will be scheduled as needed based on an individual participant's dosing interval, as determined by DRM assessments. Dosing visits should be scheduled as close to the planned dosing date as possible and will be combined with Mandatory visits as appropriate; it is expected that participants only complete the visits that coincide with their dosing schedule and the mandatory visits (see footnote #3).
3. Participants will return at least every 12 weeks for mandatory visits, regardless of whether a dose is required at that visit. However, whenever possible, the Mandatory visits (except visit 13, week 96) should be moved to be combined with a dosing visit if the dosing visit is scheduled 1) at the same time point, 2) 1 or 2 weeks before, or 3) 1 or 2 weeks after, given that the visit window for the Mandatory visit is +/-16 days. If a participant is scheduled for both a dosing visit 2 weeks before AND 2 weeks after a Mandatory visit, the Mandatory visit should be conducted with the earlier dosing visit, when possible.
4. Refer to pharmacy manual for study drug injection guidelines. Following study drug injection, participants will be observed for approximately 30 minutes.
5. [redacted]
6. IOP will be measured at all study visits (bilaterally). On days when the study drug is administered, IOP should be measured pre-dose (bilaterally) and approximately 30 minutes after administration of study drug (study eye only). IOP will be measured using applanation tonometry (e.g., Goldmann applanation tonometry, Perkins tonometer), combined applanation and indentation (e.g., Tono-pen®), or rebound tonometry (e.g., Icare), and the same method of measurement must be used in each participant throughout the study.
7. Indirect ophthalmoscopy will be performed pre-dose bilaterally at all visits. On days when study drug is administered, it should also be performed immediately after administration of study drug (study eye only).
8. FA and FP should be performed prior to administration of study drug, when applicable. For FA, the study eye will be the transit eye and images should be collected using the widest field available. If available, sites should also submit an optional ultra-widefield color photograph for DME participants.

9. Wherever possible, the same SD-OCT imaging system should be used at all study visits in each participant. Images will be taken in both eyes before dosing at each required visit.
10. Vital signs (HR and BP) should be measured pre-injection. When possible, BP assessments will be taken using automated office blood pressure (AOBP) with the Microlife WatchBP Office AFIB BP device (or comparable). BP assessments will be taken by the device in triplicate and a mean measure as displayed will be recorded in the electronic data capture (EDC).
11. For women of childbearing potential (WOCBP), a negative urine pregnancy test at screening is required for eligibility and before treatment is administered in either eye at subsequent visits.
12. The EOS visit (visit 13, week 96) cannot be combined with a dosing visit. This visit will also represent the early termination visit.

14.2. Detailed Definitions of Special AE Categories and Medical History Subgroups

Prior to database lock these preferred terms will be updated as necessary based on the current MedDRA version.

14.2.1. Medical history and AE grouping of hypertension



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14.2.2. Medical history of cerebrovascular disease

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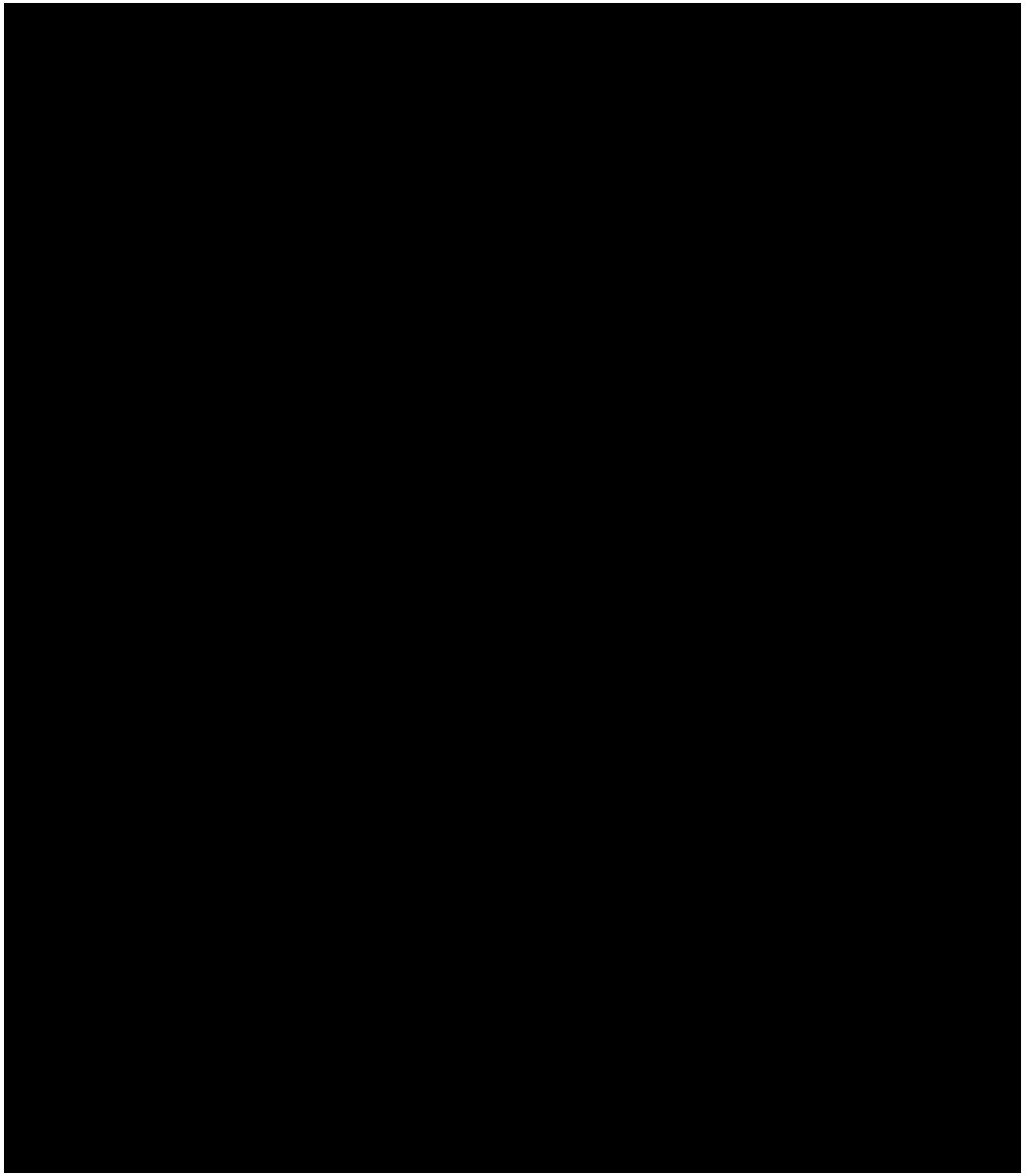
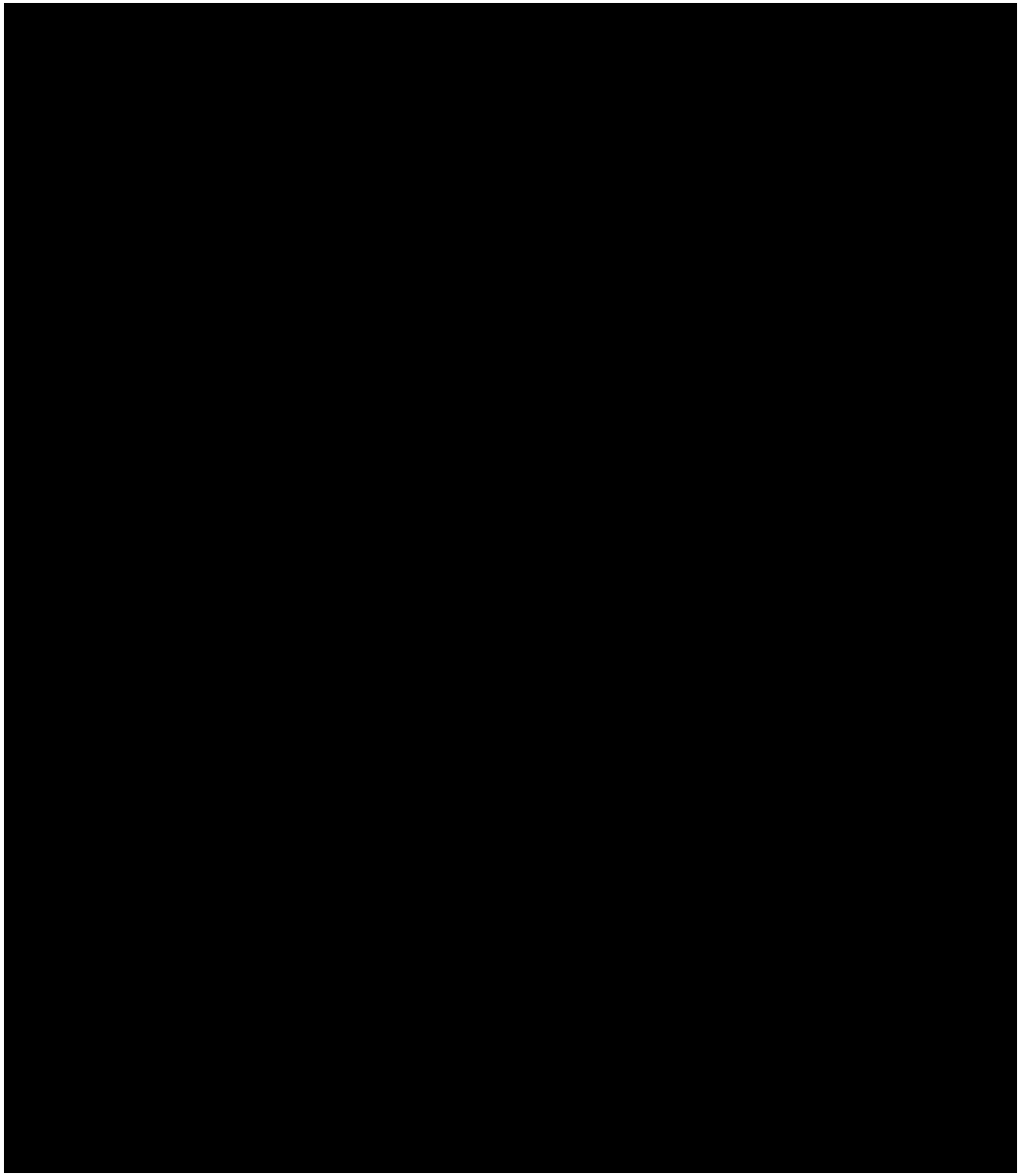
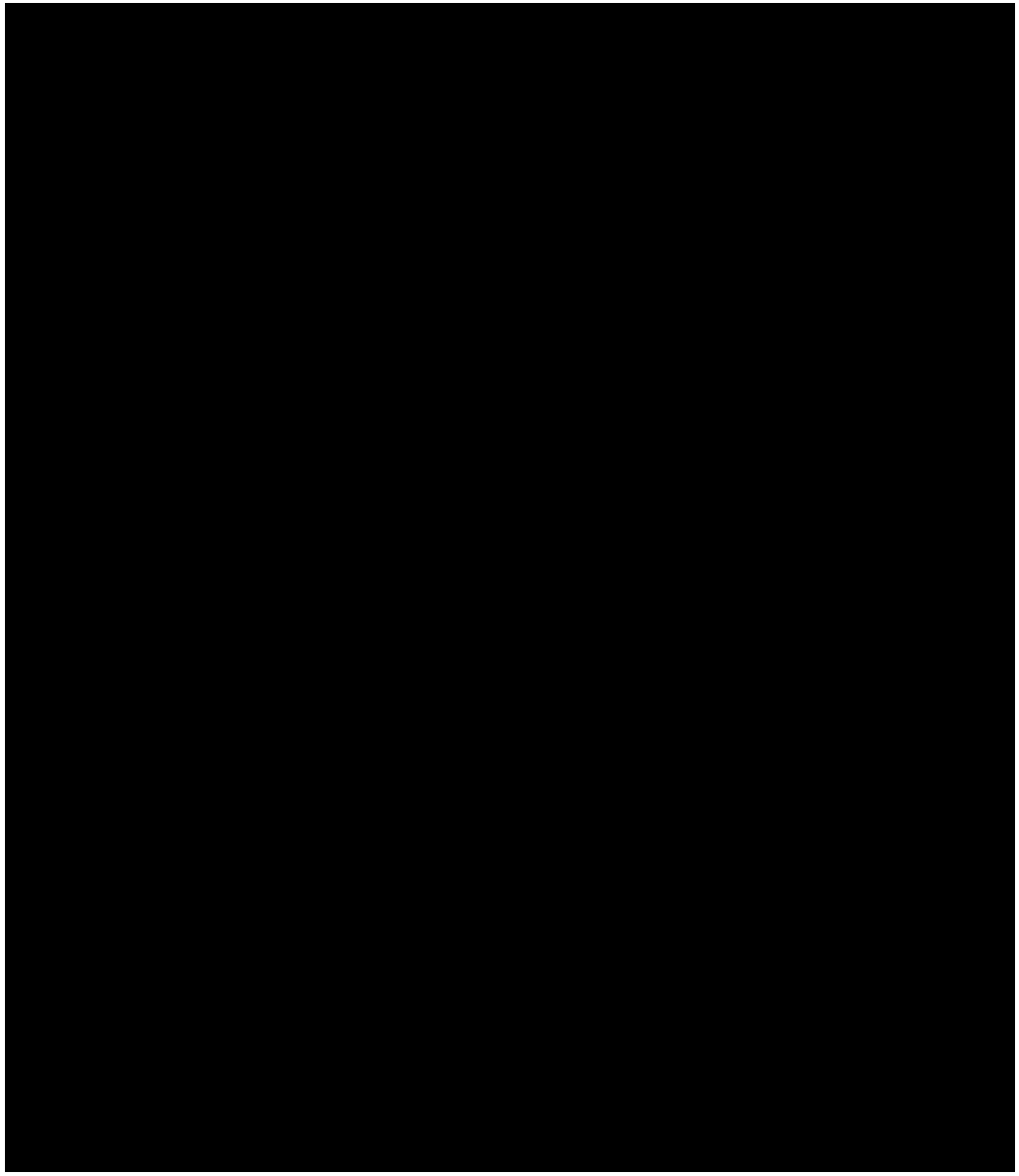
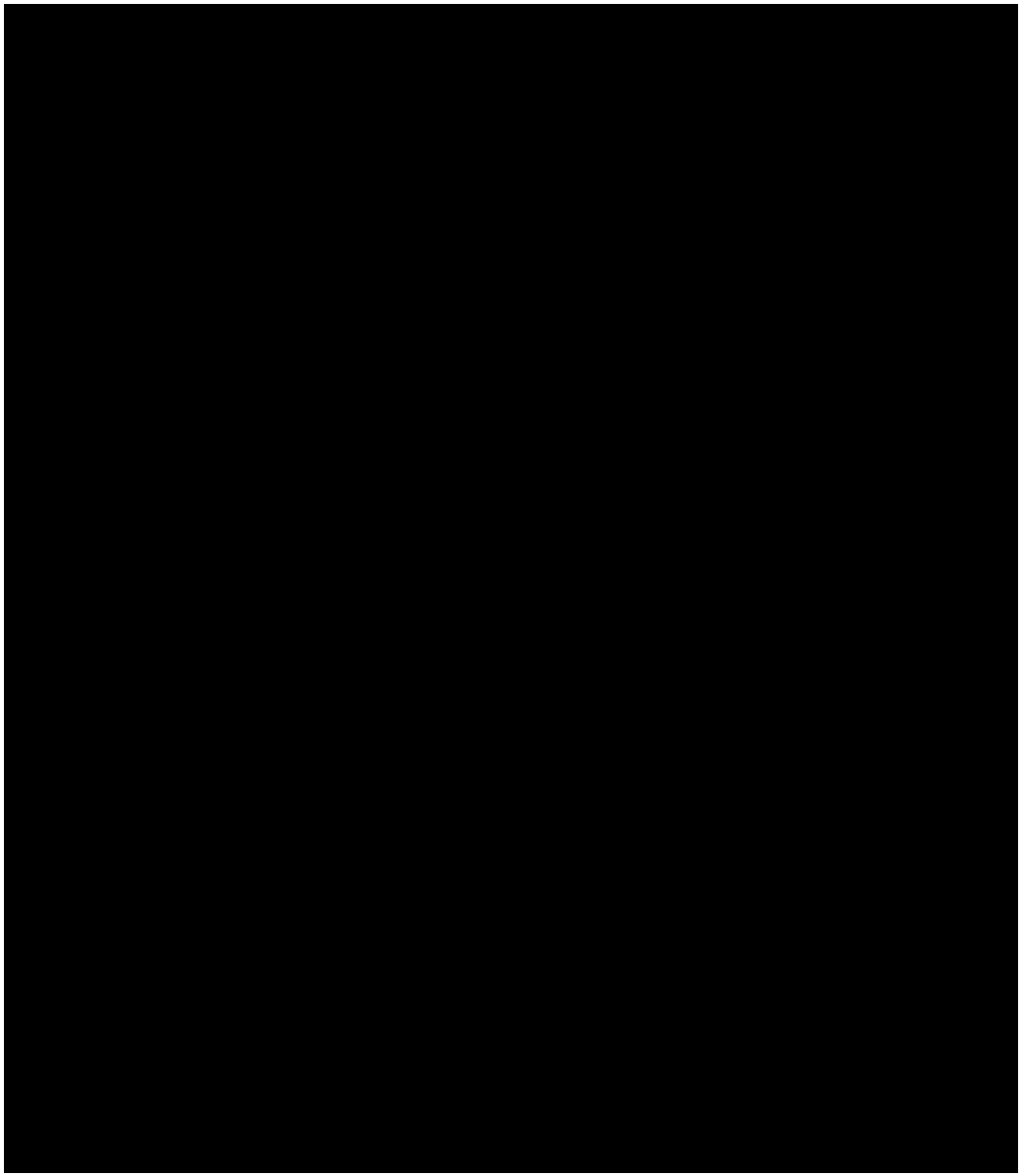
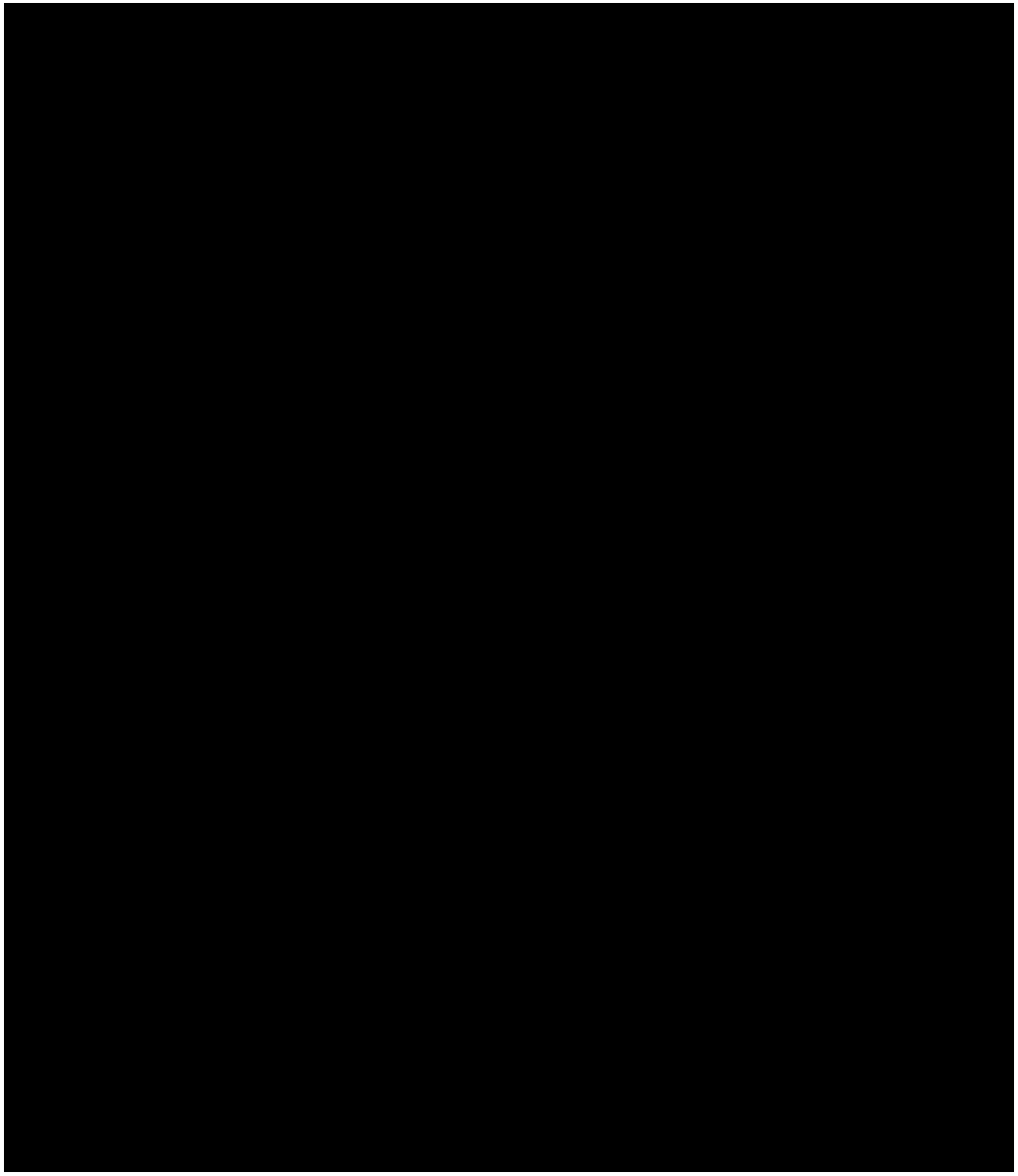
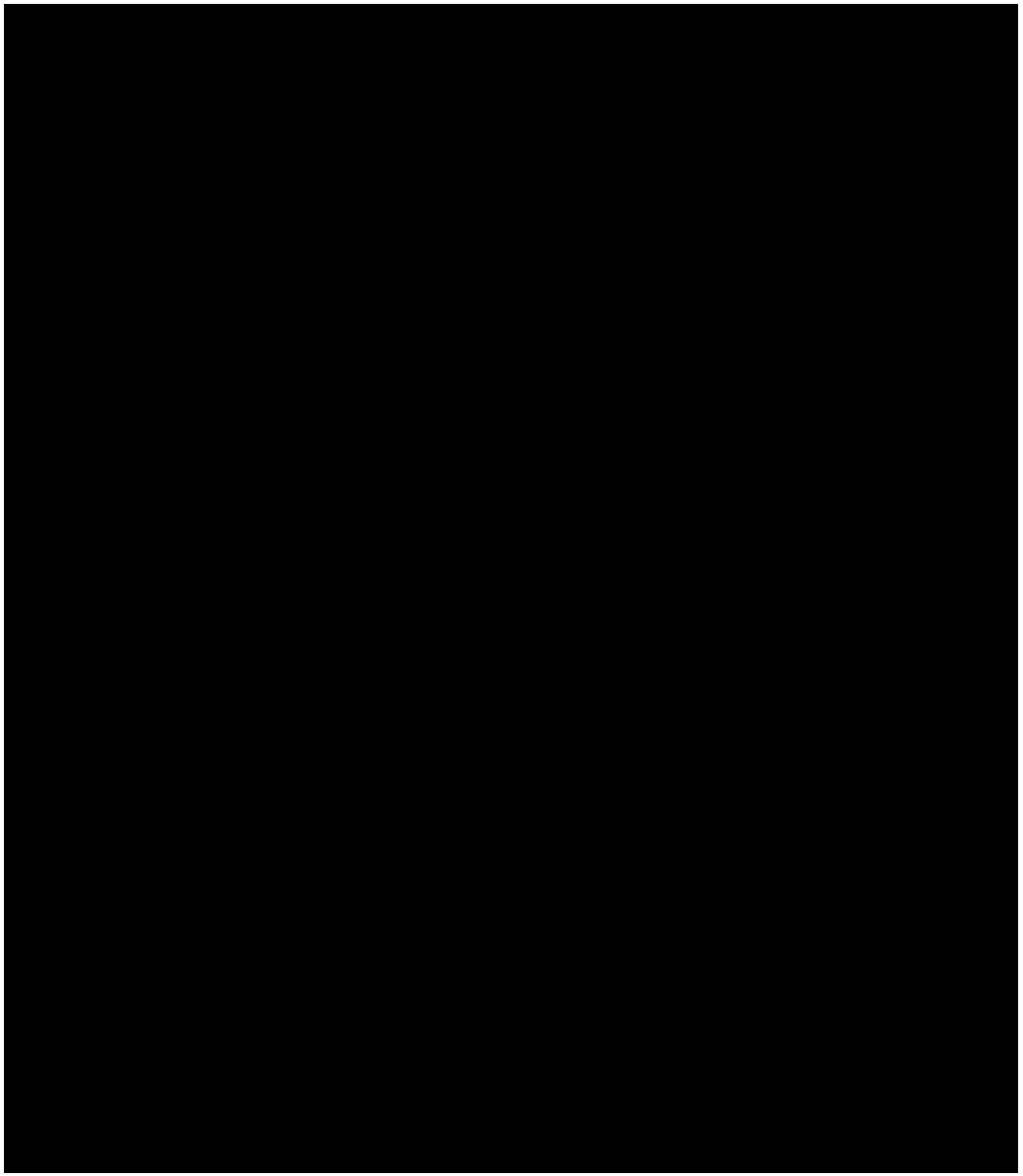


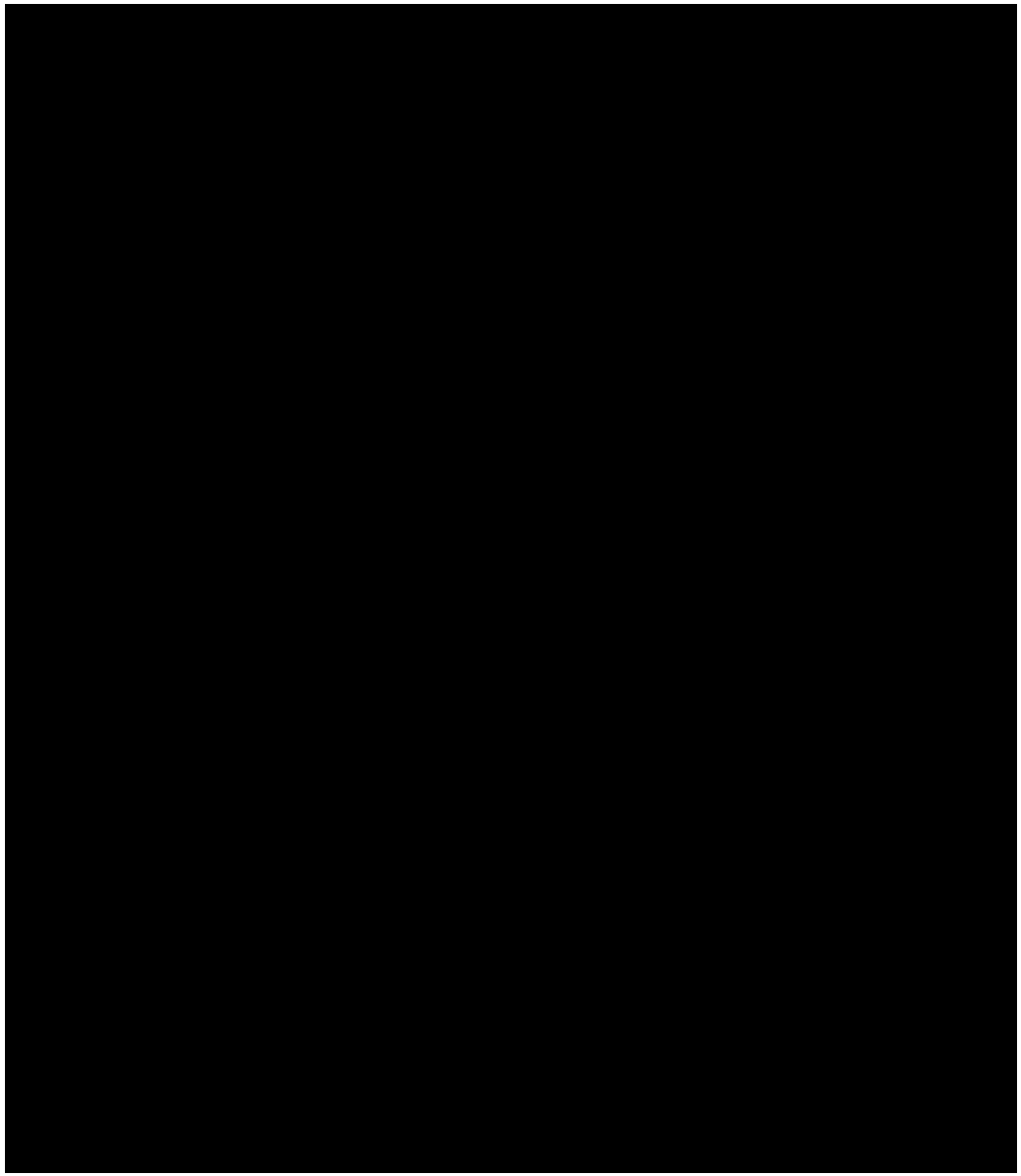


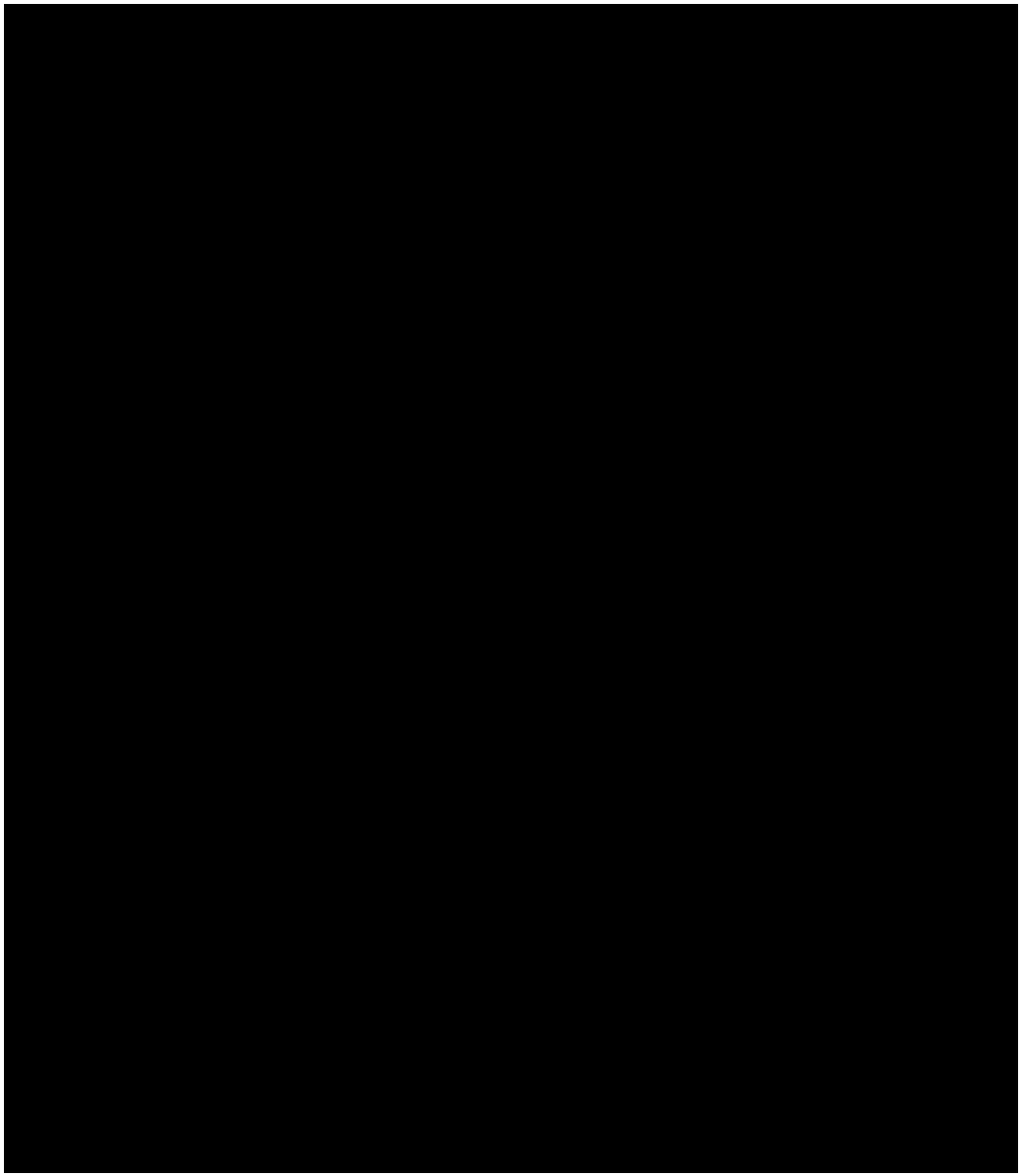








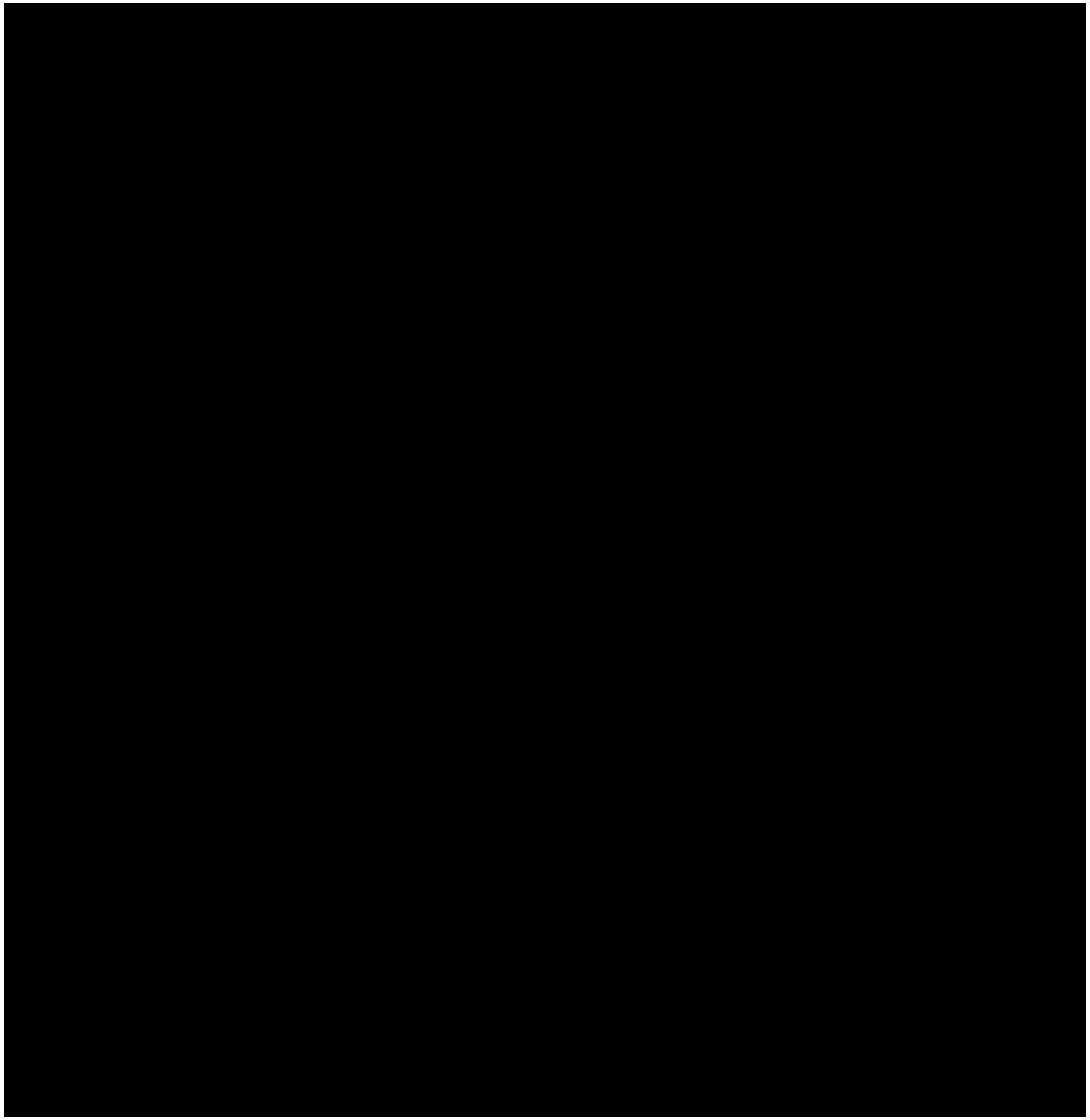


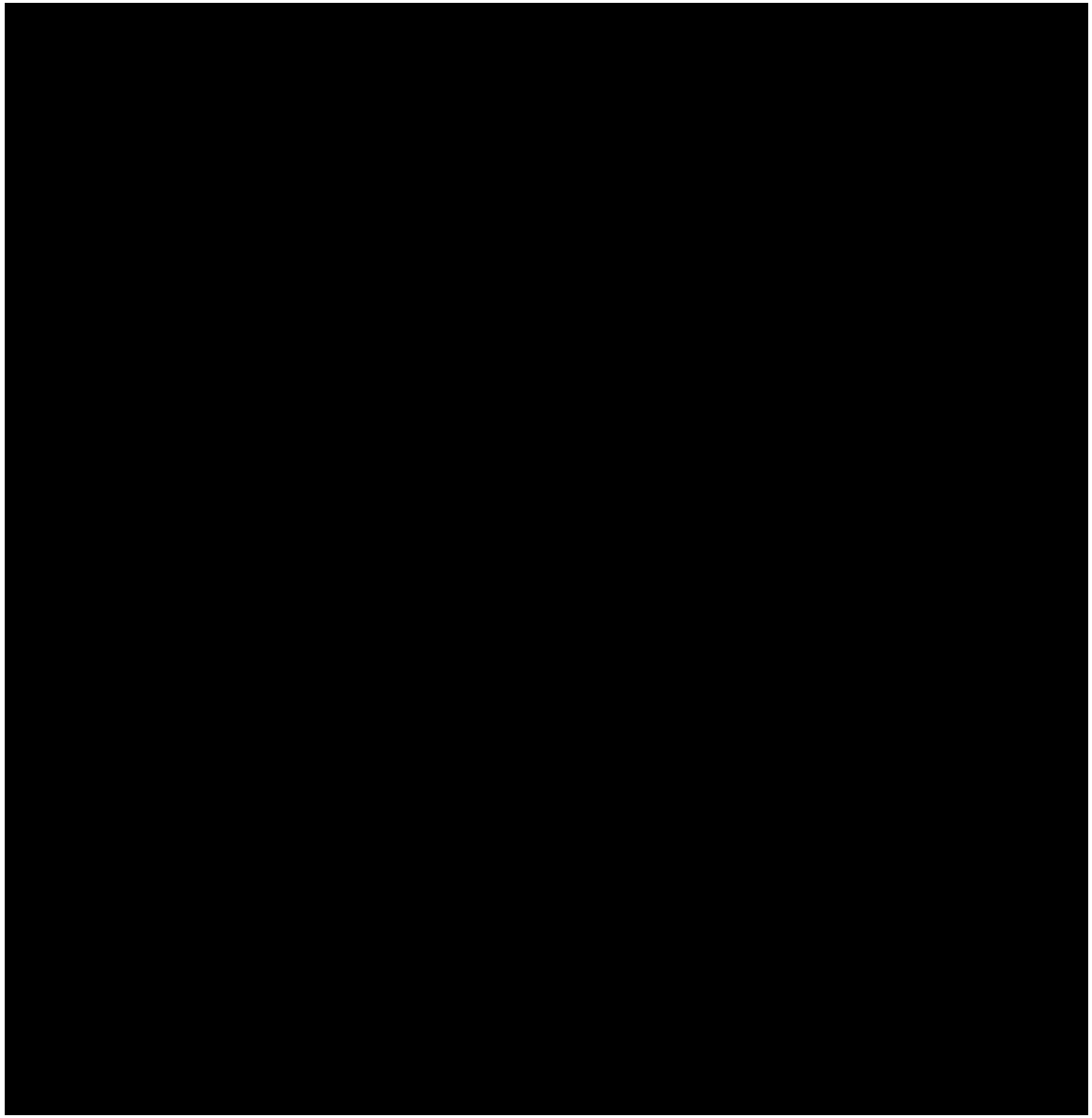


[redacted]

14.2.3. Medical history of ischemic heart disease

[redacted]

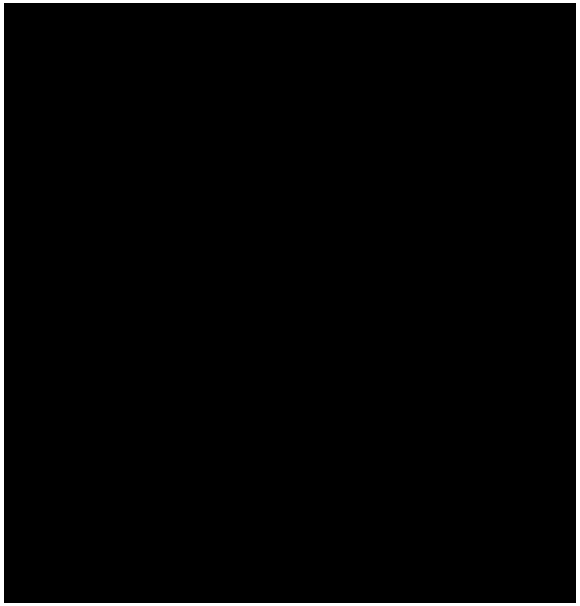




[redacted]

14.2.4. AE grouping of intraocular inflammation

[redacted]



14.3. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV
Blood pressure	
Systolic BP	≤ 95 mmHg and decrease from baseline ≥ 20 mmHg ≥160 mmHg and increase from baseline ≥ 20 mmHg
Diastolic BP	≤ 45 mmHg and decrease from baseline ≥ 10 mmHg ≥110 mmHg and increase from baseline ≥ 10 mmHg

14.4. Process to Derive Week 24 Data Cut-off

For week 24 evaluations, a strategy for performing the data cut-off for the clinical database was developed based on the week 24 visit date, as described in the following:

14.4.1. Visit Independent Data

Visit independent data (or event-based data) include adverse events, concomitant/prior medication, and surgeries.

Participants that discontinued study prematurely before or at week 24 (Visit 7)

These participants will be defined as having their end of study CRF page filled, and have either:

- a dropout date earlier or equal to date of first injection + 168 days + 5 days (to account for the visit window) or
- a dropout date equal to week 24 visit date

For such participants, all event-based records will be kept in the clinical database for week 24 analysis without any change.

Participants who stayed longer than week 24 (visit 7) in the study

These participants will be the participants who did not discontinue study prematurely at/before week 24 (visit 7). Therefore, these participants will be either:

- still ongoing after week 24 (visit 7)
- discontinued the study prematurely, but were in the study for longer than week 24 (visit 7)

For such participants, the following will be applied:

All event records with a start date later than the date of the week 24 (visit 7) will be censored. This includes the case where the incomplete date is without any doubt later than the week 24 visit date, e.g., week 24 (visit 7) is 10 April 2024 and the incomplete date is May 2024 or only 2025. If the week 24 visit date is missing, then the date of first injection + 168 days will be used instead.

Records with a start date earlier or equal to the date of week 24 (first injection + 168 days if date of week 24 visit is missing) will be kept. This includes records with incomplete dates when the incomplete date is earlier than the week 24 date or in cases where it is not clear if the record occurred before or after week 24 (e.g., week 24 [visit 7] is 10 April 2024 and the incomplete date is March 2024, April 2024 or only 2024 or even a missing date). If the date is incomplete, the following adaptions to the data will be made.

Concomitant medication:

If a stop date is reported which is earlier than the date of week 24 (visit 7) (first injection + 168 days if date of week 24 is missing), the record will not be changed.

If a stop date is reported which is later than the date of week 24 (visit 7) (first injection + 168 days if date of week 24 is missing), the stop date will be set to missing and the variable CMONG will be set to 1 (yes).

Adverse Events:

AEs with a start date on or after the date of the week 24 (visit 7) will be censored. Cut-off date will be first injection + 168 days if date of week 24 is missing.

If the stop date of AE is specified and earlier or equal to date of week 24 (visit 7) (first injection + 168 days if date of week 24 missing), then the record will not be changed.

If the stop date of AE is specified and later than the date of week 24 (visit 7) (first injection + 168 days if date of week 24 is missing), then the stop date will be set to missing and the outcome of the AE (Statistical Analysis System [SAS] variable AEOUT) will be set to missing.

If the stop date of AE is missing and the outcome is not missing, then the outcome will be set to missing (AEOUT is blank).

Procedures:

All procedures with a date of procedure later than week 24 (visit 7) date will not be included in the analysis. Cut-off date will be first injection + 168 days if date of week 24 is missing.

14.4.2. Study Medication Data

Study medication data in the study eye up to week 20 (visit 6) will be kept for the week 24 analysis. Study medication data in the fellow eye prior to week 24 (week 7) will be included for the week 24 analysis.

14.4.3. Visit Dependent Data

All visit dependent data up to week 24 (visit 7) will be kept for the week 24 analysis except for post-dose IOP at the week 24 visit. All visit dependent data later than week 24 (visit 7) will not be included for the week 24 analysis. Unscheduled visits with a date prior to the week 24 (visit 7) visit date will be kept for the week 24 analysis. If a participant did not have a week 24 (visit 7) visit, unscheduled visits will be kept up to date of first injection + 168 days for the week 24 analysis.

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Approval/eSignature	[redacted] 08-Dec-2024 03:02:27 GMT+0000

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