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Title page

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Protocol Number: 21912

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Short Title:

An Interventional Study to Investigate the Safety and Efficacy of IVT Aflibercept with Proactive Customized Treatment Intervals in Patients ≥50 Years of Age with No Fluid Due to CNV Lesions Secondary to nAMD Following Treatment Initiation with Aflibercept

Acronym: XPAND

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Version History

This Statistical Analysis Plan (SAP) for Study BAY 86-5321/21912 is based on the protocol Version 1.0 dated 25MAY2022.

SAP Version	Date	Change	Rationale
1.0	10MAR2023	Not applicable	Original version

List of Abbreviations

AE	Adverse Event
AMD	Age-Related Macular Degeneration
ANCOVA	Analysis of Covariance
anti-VEGF	Anti-Vascular Endothelial Growth Factor
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BCVA	Best-Corrected Visual Acuity
BMI	Body Mass Index
CI	Confidence Interval
CNV	Choroidal Neovascularization
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
CST	Central subfield retinal thickness
DB	Database
eCRF	Electronic Case Report Form
ED	Early Discontinuation
EOS	End of Study
ES	Enrolled Set
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
ICE	Intercurrent Event
IOP	Intraocular Pressure
IRF	Intraretinal Fluid
ISO	International Organization for Standardization
IVT	Intravitreal
IXRS	Interactive Response System
LOCF	Last Observation Carried Forward
LPLV	Last Patient Last Visit
LSmean	Least-square mean
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measurements
MSSO	Maintenance and Support Service Organization
nAMD	Neovascular (wet) Age-Related Macular Degeneration
OCT	Optical Coherence Tomography
OCT-A	Optical Coherence Tomography Angiography
PCV	Polypoidal Choroidal Vascularization
PD	Protocol Deviation
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation

SD-OCT	Spectral Domain Optical Coherence Tomography
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SRF	Subretinal Fluid
sub-RPE	Subretinal Pigment Epithelium
T&E	Treat and Extend
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TFLs	Tables, Figures and Listings
VA	Visual Acuity
WHO	World Health Organization

1. Introduction

Age-related macular degeneration (AMD) is a leading cause of adult blindness in the developed world. There are 2 forms of AMD, the dry and the wet (neovascular) form. Neovascular AMD (nAMD) is a major health issue in aging populations globally. Vision loss in nAMD results from the abnormal growth and leakage of blood vessels in the macula.

Intravitreal (IVT)-administered anti-vascular endothelial growth factor (anti-VEGF) therapies like aflibercept inhibit neovascular vessel growth and leakage in the retina, and they are currently the standard of care for patients with nAMD. Although the globally approved IVT anti-VEGF therapies are efficacious and well tolerated, the need for IVT aflibercept injections every 4 to 8 weeks, specifically in the initial phase and during maintenance of treatment, represents a significant burden to physicians, patients and caregivers. While the IVT procedure is straightforward and relatively easy to perform, capacity issues for ensuring an appropriate injection frequency in order to achieve patient outcomes similar to those seen in the pivotal studies represent an increasing challenge to individual practices and the healthcare system overall.

The use of anti-VEGF agents in an individualized, proactive treat and extend (T&E) for nAMD has become the standard of care. Utilization of proactive IVT aflibercept T&E regimens allows for a pragmatic approach to treatment and offers benefits to physicians and patients. With proactive, individualized T&E dosing regimens, the need for interim monitoring is minimized, as is the risk of disease recurrence. Reducing the number of appointments per patient and minimizing the need for monitoring visits could ease clinic flow and patient burden. Furthermore, planning the next injection helps minimize the possibility of treatment delays and facilitates clinic management.

This study will investigate the safety and efficacy of IVT aflibercept with proactive customized treatment intervals in patients ≥50 years of age with no fluid due to choroidal neovascularization (CNV) lesions secondary to nAMD following treatment initiation with aflibercept.

This statistical analysis plan (SAP) describes all details of the required statistical analyses to be conducted at Weeks 36 and 52 (end of study [EOS]). The summary tables, figures and listings (TFLs) to be included in the Clinical Study Report (CSR) will be defined in a separate document. This SAP is based on the integrated clinical study protocol version 1.0 (dated 25 MAY 2022). All references to study protocol hereafter refer to this version of the protocol. Changes to the protocol-planned analyses are described in Section 4.8.

1.1 Objectives, Endpoints and Estimands

Table 1-1: Objectives and Endpoints/Estimands

Objectives	Endpoints/Estimands
Primary	
To assess whether 2 mg intravitreal (IVT) aflibercept administered at a customized treatment interval (determined after the first extended treatment interval) is non-inferior to 2 mg IVT aflibercept administered according to a standard treat and extend (T&E) regimen (initiated after the first extended treatment interval) in patients with no fluid following treatment initiation for neovascular (wet) age-related macular degeneration (nAMD)	Primary Efficacy Endpoint • Change in best-corrected visual acuity (BCVA) (early treatment diabetic retinopathy study [ETDRS] letters) from baseline to Week 36
Secondary - Efficacy	
To assess treatment burden of 2 mg IVT aflibercept administered at a customized treatment interval compared with 2 mg IVT aflibercept administered according to a standard T&E regimen (initiated after the first extended treatment interval) in patients with no fluid following treatment initiation for nAMD	Key Secondary Efficacy Endpoint • Number of IVT aflibercept injections per patient up to Week 52 (descriptively) Additional Secondary Efficacy Endpoints • Number of IVT aflibercept injections per patient until Week 36 • Number of patients achieving pre-defined treatment intervals (≥4, ≥8, ≥10, ≥12¸ ≥14, and 16 weeks) at Weeks 36 and 52 • Change in BCVA (ETDRS letters) from baseline to Week 52
Secondary - Safety	
To evaluate the safety of aflibercept with proactive treatment intervals	Secondary Safety Endpoint • Treatment-emergent adverse events (TEAEs) and treatment-emergent serious AEs (TESAEs) through Weeks 36 and 52
Other Pre-Specified Exploratory	
To assess morphologic outcomes of 2 mg IVT aflibercept administered at a customized treatment interval compared with 2 mg IVT aflibercept administered according to a standard T&E regimen (initiated after the first extended treatment interval) in patients with no fluid following treatment initiation for nAMD	Other Pre-specified Exploratory Endpoints • Change in central subfield retinal thickness (CST) [µm] from baseline to Weeks 36 and 52 • Change in CST compared to treatment initiation (16 weeks before baseline) at Weeks 36 and 52 • Number of patients without any fluid at treatment initiation (16 weeks before baseline), baseline, Weeks 36, and 52 o without intraretinal fluid (IRF) o without subretinal fluid (SRF) o without sub-retinal pigment epithelium (sub-RPE) fluid Customized treatment interval arm only: • Change in retinal fluid volume and in volume by compartment (IRF and SRF) • Area under the curve (AUC) of fluid volumes • Agreement of home monitoring findings with spectral domain optical coherence tomography (SD-OCT) in-office monitoring performed at the same day

Table 1-1: Objectives and Endpoints/Estimands

Objectives	Endpoints/Estimands
Assess the change in choroidal neovascularization (CNV) size in both study arms with optical coherence tomography angiography (OCT-A) at study visits (optional for center)	• Assess change in CNV size using OCT-A (optional for center) in both study arms at study visits
To monitor the conversion rate from dry to wet form of AMD in fellow eye with OCT-A at study visits (optional for center)	• Number of patients with newly developed CNV in fellow eye in OCT-A at Weeks 36 and 52 in eyes with dry AMD signs at baseline for patients in both arms
To assess handling satisfaction with patient Home OCT user experience questionnaire	• Number of patients for agreement levels 1 to 5 assessed at Week 36 (Home OCT-customized treatment interval arm only)

1.2 Study Design

This is a multicenter, active-controlled, open-label, parallel-group treatment, 1:1 randomized Phase 4 study of male and/or female patients ≥50 years of age after treatment initiation with IVT aflibercept for active CNV lesions secondary to nAMD. The control arm is the widely adopted and approved T&E regimen.

In total, approximately 108 patients in Europe and Canada will be randomized. The study treatment phase will be 52 weeks plus the maximal length of the screening phase (up to 4 weeks) and the 30 days (phone) follow-up phase after the last injection which may be after the last patient last visit (LPLV).

Patients must give written informed consent before any data documentation and any study procedure. The study comprises a screening phase of up to 4 weeks (Visit 1; Week -4 until Day -1), a baseline visit (Visit 2; Week 0/Day 1), and a treatment phase (which starts at baseline) of 52 weeks.

Only patients with treatment naïve eyes which have received the 3 initial injections according to the label qualify for a screening visit of the study (between Weeks 12 and 16 when counting from the treatment start of nAMD).

The 3 initial injections will be administered as routine treatment outside of the study.

In the unlikely event that 2 eyes of a patient started treatment at the same time the eye with worse best-corrected visual acuity (BCVA) will be designated as the study eye. If a patient has similar BCVA in both eyes, the eye with the clearest media will be selected as the study eye. If the ocular media of both eyes are similar in clarity, the patient's non-dominant eye (if identifiable) will be selected as the study eye. Starting at baseline (Week 0/Day 1), aflibercept 2 mg IVT treatment will be administered to the study eye as detailed below in intervals maximum of 16 weeks and minimum of 4 weeks.

Patients will be stratified based on BCVA gains in the study eye from treatment initiation to study start (captured during screening - <8 or ≥8 letters gain in BCVA) and randomized 1:1 into one of the following parallel arms:

- Customized treatment interval arm

  In this treatment arm treatment interval will be extended in a single step from an extended treatment interval of 8 weeks to a 16 week interval (test arm, rapid treatment

individualization). After the initial study injection at baseline, patients will receive their next study injection at Week 16.

Patients in this study arm will also be issued a digital drug development tool, which allows an additional layer of assessments in an ongoing way (at least 5 times a week) at home. If no abnormal assessments between preplanned visits are seen, the patient will be evaluated at these study visits and the new treatment interval be determined.

If abnormal assessments during the treatment interval are reported by the digital drug development tool, the patient will be asked by the Investigator to return to the study site within 3 days at the latest to confirm the findings by spectral domain optical coherence tomography (SD-OCT). If fluid is verified and the treatment algorithm requires a change of treatment interval, the patient will be treated immediately, and the next treatment interval will be equal to the time between the last study injection and the SD-OCT-confirmed emergence of new fluid minus 7 days, unless fluid is verified 30 days after treatment (minimum treatment interval is once per month). After reduction of the treatment interval the following intervals will be extended in 4 weeks increments up to a maximum of 16 weeks, if all extension criteria are met. If the findings are not confirmed by SD-OCT or no change is required as per treatment algorithm, the patient will go on with the current treatment interval.

- T&E, 2 week-adjustment arm

  In this treatment arm, starting at baseline, patients will receive treatment in intervals maintained (8 weeks) or adjusted in 2 weeks increments each time (up to a maximum of 16 weeks and minimum of 4 weeks), depending on extension/shortening criteria.

After randomization, the treatment intervals will not be less than 4 weeks nor more than 16 weeks for both arms.

During the treatment phase, the next IVT aflibercept injection will be determined by Investigators at each treatment visit according to the following criteria:

- Shortening of subsequent treatment interval from the last interval

  When any of the following criteria are met for the study eye, subsequent treatment interval will be shortened by 1 week in the customized treatment arm and by 2 weeks in the standard T&E, 2-week adjustment arm.

  - Presence of intraretinal fluid

    Or

  - Subretinal fluid increasing to exceed 50 µm

    Or any of the following:

  - Loss of ≥5 early treatment diabetic retinopathy study (ETDRS) letters due to disease activity
  - New neovascularization
  - New macular hemorrhage

  Minimum interval must not be less than 4 weeks during entire period of the study.

- Maintenance of last treatment interval
  - No intraretinal fluid

And

- Subretinal fluid

  Increasing but not exceeding 50 µm in thickness
- No loss of ≥5 ETDRS letters
- No new neovascularization
- No new hemorrhage

- Extension of subsequent treatment interval from the last interval
  - No intraretinal fluid

    And
  - Subretinal fluid

    Unchanged or decreased compared to previous visit
  - No loss of ≥5 ETDRS letters
  - No new neovascularization
  - No new hemorrhage

  If all of the above criteria are met for the study eye, subsequent treatment interval will be extended by 2 weeks in the standard T&E, 2-week adjustment arm and by 4 weeks in the customized treatment interval arm until a maximum treatment interval of 16 weeks is reached (e.g., if prior T&E interval was 13 weeks then there will only be an extension of 3 weeks to reach the maximum of 16 weeks).

The study patients will have study visits in accordance with the treatment interval determined by the application of the treatment algorithm (as described above).

In addition, there are 2 mandatory study visits at Weeks 36 and 52 which may or may not coincide with a treatment visit but which have to be attended by every patient as examinations are performed from which the primary and secondary outcomes are determined.

After day of final visit (Week 52 ± 7 days or early termination), administration of study drug is not allowed. Any subsequent treatment of the underlying disease of a patient is not part of the study and is at the discretion of the patient's physician. Such treatment should only occur after all study relevant assessments have been performed.

The treating Investigator must follow-up by phone on any adverse events (AEs) that are ongoing or may occur within 30 days of the last administration of study drug. Information regarding such events is to be reported under the study protocol (i.e., not as spontaneous reports).

All ocular assessments are to be conducted in both eyes, unless indicated otherwise. Assessments of ocular efficacy and safety will include BCVA, SD-OCT, optical coherence tomography angiography (OCT-A), patient Home OCT user experience questionnaire (only applicable for patients in Home OCT arm), intraocular pressure (IOP), indirect ophthalmoscopy, slit lamp biomicroscopy, and AEs; these will be assessed at all study visits ("study visits" are all mandatory visits and injection visits, and "other visits" are unscheduled visits).

Patients will be centrally assigned to randomized study intervention using an Interactive Response System (IXRS). The treatment allocation will be done according to a generated randomization list specified by the Sponsor or delegate. Before the study is initiated, the directions for the IXRS will be provided to each site

The primary endpoint/estimand will be analyzed and the summaries up to Week 36 will be provided when all patients have completed Week 36 (or withdrew). The analysis will only use data collected up to Week 36 or premature discontinuation, whichever occurs first. All the secondary and exploratory endpoints/estimands will be analyzed and the summaries up to Week 52 will be provided when all patients have completed the study (i.e., completed Week 52 or prematurely withdrew, whichever occurs first). The analysis will use all data collected. This SAP covers all the planned analyses.

The databases (DBs) and analyses at Week 36 will only include study intervention information up to the visit prior to Week 36. For this visit (Week 36) only data assessed prior to the study intervention will be part of the DB/analyses. Further details are provided in Section 6.2.

2. Statistical Hypothesis

The test problem in relation to the primary objective and/or estimand will be conducted at a one-sided significance level of 2.5% after all patients completed Week 36 (or discontinued prematurely) using the following method:

Null hypothesis H_0: $\mu_1 \leq \mu_2 - D$ vs. alternative hypothesis H_1: $\mu_1 > \mu_2 - D$, where

- D = non-inferiority margin.
- μ_i = absolute mean change in BCVA as measured by the ETDRS letter score for the study eye from baseline to Week 36 in treatment arm i.
- i = 1: customized treatment interval arm; 2: standard T&E 2-week adjustment arm.

Note that a higher ETDRS letter score represents better vision. The aim is to show that the customized treatment interval arm is no less effective than the standard T&E 2-week adjustment arm, using a non-inferiority margin of 5 letters for the difference of the means of change from baseline in BCVA as measured by the ETDRS letter score for the study eye at Week 36.

The non-inferiority margin D is set to 5 letters and the rationale is that previous studies with anti-VEGF therapies in other indications regarded a difference of 5 letters as clinically relevant. The threshold of 5 letters has a clinical relevance and a direct meaning for the patients in terms of ETDRS chart, given that 5 letters are equal to 1 line in the chart. This choice of the non-inferiority margin is consistent with the margin used in the ARIES study.

Analyses on the key secondary, other secondary, and exploratory objectives/estimands will be conducted in an exploratory way and therefore no formal statistical hypothesis testing is planned.

2.1 Multiplicity Adjustment

The multiplicity control for the significance level is not relevant for the study, given that:

- There is only one test problem in relation to the primary objective to compare the 2 study arms (i.e., customized treatment interval arm vs. standard T&E 2-week adjustment arm)
- The analyses on the key secondary, other secondary and exploratory objectives will be conducted in an exploratory way, without any formal statistical hypothesis testing.

3. Analysis Sets

Primary, key secondary, other secondary, and exploratory efficacy variables will be evaluated on the Full Analysis Set (FAS). The primary and key secondary efficacy variables will be evaluated on the Per Protocol Set (PPS). Safety variables will be analyzed using the Safety Analysis Set (SAF).

Final decisions regarding the assignment of patients to analysis sets will be made during the Data Review Meetings prior to Weeks 36 and 52 and the list of important deviations and validity findings will be documented in the Data Review Meeting minutes (see Section 4.1.14).

Throughout this section the phrase “as randomized” is equivalent to the analysis being performed using the planned treatment arm.

All enrolled subjects (ES)

All ES will include all patients who signed the informed consent form.

All randomized subjects

This analysis set will include all randomized patients.

Full analysis set (FAS)

The FAS will include all randomized patients. The FAS will be analyzed “as randomized”, with subjects categorized into the customized treatment interval arm or the T&E 2 week-adjustment arm.

Safety analysis set (SAF)

The SAF will include all patients who receive any study treatment injection, excluding treatment initiation prior to screening. The SAF will be analyzed “as randomized”.

Per protocol set (PPS)

The PPS will include all participants in the FAS who did not have an important deviation from the protocol affecting the primary efficacy variable or a validity finding as listed below.

More concretely this means, the PPS will include all participants in the FAS that:

- did not have any violation of relevant inclusion / exclusion criteria
- had a baseline BCVA value available
- had at least one post-baseline BCVA value available
- received any study treatment
- were randomized and had study drug administered at the baseline visit.

Other relevant deviations from the protocol affecting efficacy will be considered as intercurrent events in the context of the Estimands strategy described in Appendix 8.2.

The final determination on the exclusion of participants from the PPS will be made during the Data Review Meetings held in accordance with ICH E9 prior to database freeze/lock on Week 36/52 data.

The PPS will be analyzed “as randomized”.

4. Statistical Analyses

4.1 General Considerations

4.1.1 General Principles

The below mentioned general principles will be followed throughout the study:

- Study day will be calculated as:
  - For event, assessment or visit prior to the first injection date: event/assessment/visit date – first injection date
  - For event, assessment or visit on the same day or after the first injection date: event/assessment/visit date – first injection date + 1 day.
- All p-values should have 4 decimal digits; in case of p-values less than 0.0001, they will be displayed as <.0001.
- Summary tables, in general, will be presented by treatment arm as follows:

Customized treatment interval N=xx	Standard T&E N=xx	Total N=xx

  "Total" column will be optional.
- All variables shown in summaries will also be included in patient data listings.
- Patient data listings will be presented and sorted by treatment arm, unique patient identifier, and relevant dates, if applicable.
- Dates will be formatted as <day> <month (first 3 letters in capitals)> <year> (e.g., 05JUL2008) or according to the International Organization for Standardization (ISO) 8601 standard (e.g., 2012-02-29).
- Rounding for all variables will occur only as the last step, immediately prior to presentation in listings and tables. No intermediate rounding will be performed on derived variables.
- Every table, listing and figure will be produced with an electronic date stamp to document when it was produced.

4.1.2 Descriptive Statistics

Continuous data will be summarized in terms of the number of observations, mean, standard deviation (SD), median, lower and upper quartiles, confidence intervals (CIs), minimum, and maximum.
The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the DB. All other statistics (mean, SD, median, quartiles, and CIs) will have one additional decimal place more than the raw data recorded in the DB.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts, and percentages.
Percentages will be presented to one decimal place.
Percentages will not be presented for zero counts.
Unless otherwise stated, percentages will be calculated using n (the number of observations

with non-missing values) as the denominator.
If applicable, the category 'missing' will be added as needed as a separate category.

4.1.3 Baseline Definition

For efficacy endpoints, the last valid non-missing assessment prior to or on the randomization date will be considered the baseline assessment. However, if an evaluable assessment is only available after randomization but before the date of first injection, then this assessment will be used as baseline.

For safety endpoints, the last valid-non missing assessment prior to the first injection of study treatment in the study eye (Visit 2; Week 0/Day 1) will be considered the baseline assessment. For assessments on the day of first injection:

- Where time is not captured but a nominal pre-injection indicator is available, the nominal pre-injection indicator will serve as sufficient evidence that the assessment occurred prior to first injection. For example, if the "Time taken" field is not completed at Visit 2 (Week 0/Day 1) on the "Intraocular pressure (Pre-Injection)" eCRF, then the information from this eCRF can still be considered the baseline assessment because the eCRF title indicates it must be completed pre-injection rather than the "Intraocular pressure (Post-Injection)" eCRF.
- Where neither time nor a nominal pre-injection indicator are captured, the assessment will be considered to be prior to the first injection if such procedures are required by the study protocol to be conducted before the first injection. For example, the "Vital Signs" eCRF does not have a time field and the name of the eCRF does not indicate when the assessment was performed. The protocol indicates that vital signs should be measured pre-injection so the information from the "Vital Signs" eCRF at Visit 2 (Week 0/Day 1) can be considered the baseline assessment.

Change from baseline will be calculated as the visit value of interest minus the baseline value.

4.1.4 Stratification Factors

A stratification by visual outcomes at screening is planned, to ensure equal allocation of subgroups, thereby making it easier to interpret the results. Visual outcomes will be determined at the screening visit, depending on whether the patients reached <8 or ≥8 letters gain in BCVA relative to aflibercept initiation prior to study enrollment (i.e., treatment initiation at 16 weeks before baseline).

4.1.4.1 Handling of Mis-stratifications

Patients will be randomly assigned in a 1:1 ratio to the two treatment arms by means of a stratified randomization based on visual outcomes at screening. The stratification variable aims to ensure equal allocation of subgroups, thereby making it easier to interpret the results. Visual outcomes will be determined at the screening visit, depending on whether the patients reached <8 or ≥8 letters gain in BCVA relative to aflibercept initiation prior to study enrollment (i.e., treatment initiation at 16 weeks before baseline). Randomization will be managed by means of an IXRS system and stratification will be based on the information entered into the IXRS system.

Possible mis-stratifications (i.e., stratification errors) will not exclude the respective patients from the analysis sets.

In general, whenever referring to the stratification variable for statistical models and subgroup analysis, the value entered in the IXRS system will be used instead of the potentially different, correct one recorded on the electronic Case Report Form (eCRF).

4.1.5 Handling of Dropouts

Dropouts will be defined as patients who prematurely discontinue from the study and study intervention at the same time for any reason. This also includes patients who are lost to follow-up. Possible reasons for premature discontinuation from the study can be found in the study protocol, Section 7.2. It may be also necessary for a patient to discontinue study intervention permanently, while remaining in the study to be evaluated for safety evaluation as described in the study protocol, Section 7.1.

In the case of such premature discontinuation of the study intervention, all assessments, as described in the study protocol for the EOS/early discontinuation (ED) visit, should be completed (ED assessments). Early discontinuation visit will be re-mapped to an injection visit window/week or relevant regular visit window, as described in Section 4.1.8.

Data assessed after the time period as described in Appendix 8.2, but prior to study completion or discontinuation will not be used in the efficacy analyses.

Handling of missing data due to dropouts is described in Section 4.2 for efficacy variables. No action for missing data due to dropouts is taken for other variables. Patients who dropped out will not be excluded from any summaries, except where clearly stated.

4.1.6 Missing Data Handling

All missing or partial data will be presented in the patient data listings as they are recorded on the eCRF.

4.1.6.1 Additional Descriptive Analyses in the Presence of Missing Data

The number of patients who prematurely discontinued from the study and/or study intervention for any reason, as well as the reasons for premature discontinuation from the study and/or study intervention, will be reported. Kaplan-Meier plots for “Time to end of study” and “Time to end of study intervention” will be provided.

4.1.6.2 General Rules

Where appropriate, the following rules will be implemented so as not to exclude patients from statistical analyses due to missing or incomplete data:

- **Efficacy variables**
  Statistical methods for missing data in efficacy variables are described in Section 4.2.
- **Safety variables**
  Missing data in safety variables will generally not be imputed.
  However, safety assessment values of the form of “<x” (i.e., below the lower limit of quantification) or “>x” (i.e., above the upper limit of quantification) will be imputed as “x” in the calculation of summary statistics but displayed as “<x” or “>x” in the listings.
  Additionally, AEs that have missing causality will be assumed to be related to study drug.
- **Dates for concomitant medications and adverse events**
  For AEs and medications the complete start and stop date must be available to

determine if the AE or the medication is occurring during the study intervention period.

When only partial dates are available, the following rules will be used.

Incomplete or missing start date:

- Missing day: Impute the 1st day of the month, unless the month/year is the same month/year of the first injection date. In this case, impute the first injection date.
- Missing day and month: Impute 1st January, unless the year is the same as the first injection date. In this case, impute the first injection date.
- Completely missing: Impute the first injection date, unless the end date suggests the missing date could have started prior to the first injection date. In this case, impute 1st January of the same year as the end date.
- Note: When imputing a start date, ensure that the new imputed date is sensible (i.e., prior to the end date of the AE or medication).

Incomplete or missing stop date:

- Missing day: Impute the last day of the month, unless the month/year is the same month/year of the last injection date. In this case, impute the last injection date.
- Missing day and month: Impute 31st December, unless the year is the same as the last injection date. In this case, impute the last injection date.
- Completely missing:
  - AE: Since there is no ongoing flag recorded in eCRF, then assume that the AE is still ongoing (i.e., do not impute a date).
  - Medication: If the ongoing flag is entered, then do not impute an end date and assume the medication is ongoing. If the ongoing flag is not entered, then impute a date that is after the last injection date (i.e., last injection date + 1 day).
- Note: When imputing a stop date, ensure that the new imputed date is sensible (i.e., after the start date of the AE or medication).

Imputed dates will only be used to determine whether the AE is treatment emergent or not and whether the medication is prior/concomitant/post-treatment.

Imputed dates will not be used for the derivation of the duration of AEs/medications.

Imputed dates will be used for summary tables only, while listings will contain the original (partial) entries.

4.1.7 Unscheduled Assessments

Handling of repeated measurements at the same visit

If measurements were repeated at the same scheduled visit or the same study injection visit, the value actually flagged as scheduled and potentially used in the data summaries and analysis, depending on the visit windowing described in Section 4.1.8, will be the:

- Last non-missing repeated measurement, if visit is before start of treatment
- First non-missing repeated measurement, if visit is after start of treatment.

All observations will be presented in the data listings.

Handling of measurements at unscheduled visits

Any measurements taken at unscheduled visits will be shown in patient data listings but will not be included in any summary tables, in general. If more than one measurement of a variable is taken at an unscheduled visit, all measurements will be shown in listings.

In case any injection data will be captured as an unscheduled assessment, information from that visit will still be included in all analyses after following the visit windowing described in Section 4.1.8.

4.1.8 Early Discontinuation Visit and Visit Windowing

If patients prematurely discontinue from the study intervention and/or from the study, they will be asked to come for an ED visit. At the ED visit all study procedures, including ocular efficacy and safety measurements as well as non-ocular safety measurements, will be performed. Visit-based information of the ED visit will be either re-mapped to an injection visit window/week or relevant regular visit window, where no other corresponding injection or regular study visit was recorded. This data will be reported as observed value for the respective visit.

All other visits will be mapped for analysis as shown in Table 4-1**Error! Reference source not found.**.

Mapping of Early Discontinuation visit to injection or regular study visits

Early discontinuation visit will be re-mapped to either an injection visit window/week or a relevant regular visit window as shown in Table 4-1, where no other corresponding injection or regular study visit was recorded, in order to ensure meaningful presentation of information on a visit level, e.g., in summary tables by visit.

Where more than one visit is mapped to one of the visits presented in Table 4-1, the non-missing measurement closest to the target day within the window will be used in data summaries and analysis. If two measurements are equally distant from the target day, then the first occurrence of the two will be selected.

If the visit windowing shown in Table 4-1 causes issues with any analysis, then wider visit windows may be considered.

Table 4-1: Re-mapping Rule for Early Discontinuation Visit and All Other Visits

Study day of Early Discontinuation visit or any other visits	Corresponding timing of injection or regular visit	Re-mapped visit
[1 - 43]	Week 4 ± 7 days	Week 4
57 ± 14 = (43 - 71]	Week 8 ± 7 days	Week 8
85 ± 14 = (71 - 99]	Week 12 ± 7 days	Week 12
113 ± 14 = (99 - 127]	Week 16 ± 7 days	Week 16
141 ± 14 = (127 - 155]	Week 20 ± 7 days	Week 20
169 ± 14 = (155 - 183]	Week 24 ± 7 days	Week 24
197 ± 14 = (183 - 211]	Week 28 ± 7 days	Week 28
225 ± 14 = (211 - 239]	Week 32 ± 7 days	Week 32
253 ± 14 = (239 - 267]	Week 36 ± 7 days	Week 36
281 ± 14 = (267 - 295]	Week 40 ± 7 days	Week 40
309 ± 14 = (295 - 323]	Week 44 ± 7 days	Week 44
337 ± 14 = (323 - 351]	Week 48 ± 7 days	Week 48
365 - 14/+ 7 = (351 - 372]*	Week 52 ± 7 days	Week 52

"[" and "]" mean lower and upper limits included, while "(" means lower limit not included.
Study day = assessment date – first injection date + 1 day.
* For the Early Discontinuation visit, the re-mapping to Week 52 would be for (351 – 357]. Any visit after that would already be classified as the Week 52 visit.

4.1.9 Statistical Software

The statistical evaluation will be performed by using the software package SAS release 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

4.1.10 Imaging data assessed by the reading center

In summary tables the following parameters from the reading center will be evaluated and classified as follows:

From SD-OCT assessment:

- Intraretinal fluid 3 mm
- Intraretinal fluid 6 mm
- Subretinal fluid 3 mm
- Subretinal fluid 6 mm
- Central subfield retinal thickness (CST) (note: it is recorded in µm)

From OCT-A assessment:

- CNV area (note: it is recorded in mm^2)

4.1.11 Definition of Fellow Eye Treatment

Fellow eye treatment will be identified from the concomitant medication page by

- Selecting for any of the following medications and corresponding biosimilars (available in the Biosimilars, Medical Histories and Definition of Grouped Adverse Event Terms document):
    - Aflibercept (trade name: Eylea)
    - Bevacizumab (trade name: Avastin)
    - Brolucizumab (trade name: Beovu)

  - Ranibizumab (trade name: Lucentis)
  - Faricimab (trade name: Vabysmo)
  - Conbercept (trade name Lumitin)
  - Pegaptanib sodium (trade name: Macugen)
- Selecting for the laterality of the fellow eye.

Medication that was administered prior to the first injection of study treatment will be considered prior fellow eye treatment, whereas medication that was administered at the first injection of study treatment or later will be considered concomitant fellow eye treatment (i.e. bilateral treatment).

4.1.12 Definition of Prohibited Medications

Prohibited medications as identified from the prior and concomitant medication page are

- Any of the following anti-VEGF medications and corresponding biosimilars (available in the Biosimilars, Medical Histories and Definition of Grouped Adverse Event Terms document) administered in the study eye:
  - Aflibercept (trade name: Eylea), unless administered as study intervention
  - Bevacizumab (trade name: Avastin)
  - Brolucizumab (trade name: Beovu)
  - Ranibizumab (trade name: Lucentis)
  - Faricimab (trade name: Vabysmo)
  - Conbercept (trade name Lumitin)
  - Pegaptanib sodium (trade name: Macugen)
- Medications and corresponding biosimilars (available in the Biosimilars, Medical Histories and Definition of Grouped Adverse Event Terms document) administered systemically with the intent of treating AMD in the study or fellow eye:
  - Verteporfin (trade name Visudyne)

Any medication considered necessary for the participant's welfare, and that is not expected to interfere with the evaluation of the study intervention, may be given at the discretion of the investigator.

4.1.13 Pooling of Data

All sites will be combined together for the purposes of the analysis.

4.1.14 Data Review

Upon each DB release (Weeks 36 and 52), listings of protocol deviations (PDs) and validity findings, as well as the analysis datasets will be produced after release of the final pre-freeze/pre-lock clinical eCRF DB and discussed in Data Review Meetings. At this time, a review of concomitant medications will take place in order to identify any prohibited medications as important protocol deviations. The results of these meetings may comprise decisions and details relevant for statistical evaluation. Any changes to the statistical analysis prompted by the results of the Data Review Meetings will be documented in an amendment to this SAP.

After the clinical eCRF DB is frozen/locked, the analysis datasets will be created again and will be compared with the pre-freeze/pre-lock analysis datasets to verify if there were changes to the clinical eCRF DB and/or to the relevant PDs.

4.1.15 Coronavirus Disease 2019 Related Outputs/Procedures

This study started after the onset of the coronavirus disease 2019 (COVID-19) pandemic. A listing will be provided that displays all patients affected by the COVID-19 related study disruption by unique patient identifier and by investigational site, and a description of how the patient's study participation was altered. Other listings will display all patients with PDs associated with the COVID-19 pandemic and with COVID-19 AEs. Furthermore, tables for patient validity status and disposition will contain COVID-19 pandemic associated findings and reasons.

Additionally, the following summary tables will be displayed:

- Study sample sizes by trial unit: Patients affected by COVID-19 pandemic related study disruption for all enrolled patients
- Number of patients by country/region for all patients affected by COVID-19 pandemic related study disruption
- Number of patients affected by COVID-19 pandemic related study disruption.

Additional analyses may be added due to regulatory requirements or requests.

4.2 Primary Endpoint/Estimand Analysis

All analyses described below for the primary efficacy variable will be analyzed on the FAS by randomized treatment arm, regardless of any changes to dose interval. As a supplementary analysis, the primary endpoint will also be evaluated based on the PPS.

All efficacy analyses will be based on the injection visits mapped to weeks as specified in Table 4-1 from Section 4.1.8. If the visit windowing causes issues with any statistical models, then wider visit windows may be considered.

4.2.1 Definition of Endpoint

ETDRS charts present a series of five letters of equal difficulty on each row, with standardized spacing between letters and rows; there is a total of 14 lines (70 letters). The ETDRS letter score can be calculated when 20 or more letters are read correctly at 4.0 m, the visual acuity (VA) letter score is equal to the total number of letters read correctly at 4.0 m plus 30. If fewer than 20 letters are read correctly at 4.0 m, the VA letter score is equal to the total number of letters read correctly at 4.0 m (the number recorded on line 1.0), plus the total number of letters read correctly at 1.0 m in the first six lines. The ETDRS letter score could therefore result in a maximum score of 100. BCVA is measured by the ETDRS letter score for the study eye.

The estimand of primary interest will be based on a hypothetical strategy. It describes the change in BCVA from baseline for all patients that started treatment assuming all patients have stayed on treatment until Week 36.

The estimand is specified through the following definitions of population, variable, treatment condition, intercurrent events (ICEs), and population-level summary:

Population:	Defined by the inclusion/exclusion criteria in the study protocol.
Variable:	Absolute change from baseline to Week 36 in BCVA as measured by the ETDRS letter score for the study eye.
Treatment condition:	Aflibercept customized treatment interval arm vs. aflibercept standard T&E 2-week adjustment arm.
Intercurrent events:	Premature discontinuation from treatment/study. Use of a prohibited medication / start of alternative anti-VEGF treatment, prior to treatment and/or study discontinuation. Shortening/extension of the dosing interval will not be considered an ICE, but as part of the randomized treatment regimen. Details for other potential ICEs and the handling of ICEs in the analysis are given in Appendix 8.2.
Population-level summary:	Difference in mean change from baseline to Week 36 in BCVA between the customized treatment interval arm and standard T&E 2-week adjustment arm.

The hypothesis described in Section 2 will be tested in the primary analysis to assess non-inferiority in the primary efficacy endpoint at a one-sided significance level of 2.5%.

4.2.2 Main Analytical Approach

For the analysis of the primary efficacy variable, a mixed-effect model repeated measure (MMRM) analysis making use of all observed BCVA data in the study eye from baseline up to Week 36 (after censoring for ICEs as defined in Appendix 8.2) will be used. Visit windows will be applied to the BCVA data as described in Section 4.1.8. The MMRM will include the fixed categorical effects of treatment, visit, treatment-by-visit interaction and stratification variable (BCVA gains in the study eye from treatment initiation to study start, captured during screening [<8 vs. ≥8 letters gain]); the fixed continuous covariate of baseline BCVA score in the study eye; and visit as a repeated measure. Restricted maximum likelihood estimation will be used. A Kenward-Roger approximation will be used for the denominator degrees of freedom. An unstructured covariance structure will be used to model the within-patient error, assuming different covariance parameters per group. If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached:

- Toeplitz with heterogeneity
- Autoregressive with heterogeneity
- Toeplitz
- Autoregressive
- Compound symmetry.

The model can be written as:

$$Y_{ij} = \beta_0 + x_i\beta_{base} + \beta_{strat}^{(l)} + \beta_{treat}^{(k)} + \beta_{visit}^{(j)} + \beta_{treat*visit}^{(k,j)} + b_i + \epsilon_{ij}$$

with

- Y_{ij} being the change in BCVA from baseline to visit j for the ith patient
- β_0 being the intercept
- x_i being the baseline BCVA measurement in the study eye of patient i
- β_{base} the fixed effect of the baseline BCVA measurement
- $\beta_{strat}^{(l)}$ the fixed effect of stratification variable (BCVA gains in the study eye from treatment initiation to study start, captured during screening [<8 vs. ≥8 letters gain]), as recorded on the IXRS system
- $\beta_{treat}^{(k)}$ the fixed effect of treatment arm k
- $\beta_{visit}^{(j)}$ the fixed effect of visit j
- $\beta_{treat*visit}^{(k,j)}$ the interaction between treatment arm k and visit j
- b_i the random effect of patient i
- ϵ_{ij} the residual error with $\epsilon_{ij} \sim N(0, \sigma^2)$ and $corr(\epsilon_{ij,}\epsilon_{i',j'}) = \rho_{ij}$ and ϵ_{ij} and b_i mutually independent.

In terms of the model parameters, the estimate of the population-level summary of the estimand (i.e., the treatment effect at Week 36) can then be expressed as

$$\widehat{diff}_{treat} = \left[\hat{\beta}_{treat}^{(Customized)} + \hat{\beta}_{treat*visit}^{(Customized,w36)}\right] - \left[\hat{\beta}_{treat}^{(T\&E\ 2week)} + \hat{\beta}_{treat*visit}^{(T\&E\ 2week,w36)}\right].$$

In line with the definition of estimands (see above), the primary analysis will be performed on the FAS and patient will be analyzed within their original randomized group (regardless of any changes to dose interval).

The analysis described above will be repeated on the PPS as a supplementary analysis.

The customized treatment interval arm will be considered to be non-inferior to the standard T&E 2-week adjustment arm if this analysis is statistically significant. Statistical significance will be achieved if the estimated lower limit of the one-sided 97.5% CI of the treatment difference lies entirely above the value of -5 letters, where a positive difference favors the customized treatment interval arm.

Summary tables will include number of patients, least-square mean (LSmean) change, (unadjusted) mean change and SD and baseline means of each treatment arm. For non-inferiority testing, the estimate expressed as LSmean change including the one-sided 97.5% CI, the test statistics, the degrees of freedom and corresponding p-value will be presented. The two-sided 95% CI will be provided as well.

The MMRM assumes missing at random (MAR) for patients who discontinue the study prematurely, i.e., missingness only depends on observed data.

Descriptive summary tables will be provided by treatment arm and visit for:

- All observed cases until the occurrence of an ICE (primary estimand strategy for continuous endpoints) in the FAS population
- All observed cases until the occurrence of an ICE (primary estimand strategy for continuous endpoints) in the PPS population
- All observed cases until the occurrence of an ICE with imputation of missing values with Last Observation Carried Forward (LOCF) in the FAS population.
- All observed cases until the occurrence of an ICE with imputation of missing values with LOCF in the PPS population.

4.2.3 Sensitivity Analyses

The following sensitivity analyses will be analyzed for the FAS with patient analyzed within their original randomized group (regardless of any changes to dose interval).

4.2.3.1 Analysis of Covariance with Last Observation Carried Forward

The sensitivity analysis of the primary efficacy endpoint using an analysis of covariance (ANCOVA) with LOCF follows the same estimand strategy as the primary analysis.

For this sensitivity analysis of the primary efficacy variable, an ANCOVA will be used, with the BCVA measure in the study eye at baseline as a covariate, and the treatment arm and the stratification variable (BCVA gains in the study eye from treatment initiation to study start, captured during screening [<8 vs. ≥8 letters gain]) as fixed effect factors. Missing data will be imputed using LOCF method. Observed values from both scheduled and unscheduled post-baseline visits will be used for the LOCF imputation. For patients who experience an ICE as defined in Appendix 8.2, the efficacy data will be censored at the time of the ICE as defined in Appendix 8.2, prior to implementation of the LOCF approach.

The observation at Week 36 of patient i in treatment arm t can be written as follows:

$$Y_{itb} = \beta_0 + \mu_t + \eta_b + x_i\beta_{base} + \epsilon_{itb}$$

with

- Y_{itb} being the change from baseline to Week 36 for the ith patient
- β_0 being the intercept
- μ_t being the treatment arm effect
- η_b being the categorical stratification variable (BCVA gains in the study eye from treatment initiation to study start, captured during screening [<8 vs. ≥8 letters gain]), as recorded on the IXRS system
- x_i being the baseline BCVA in the study eye of patient i
- β_{base} the fixed effect of the baseline BCVA measurement
- ϵ_{itb} the residual error with $\epsilon_{itb} \sim N(0, \sigma_t^2)$ being the residual error for treatment arm *t*.

In terms of the model parameters, the estimate of the population-level summary of the estimand (i.e., the treatment effect at Week 36) can then be expressed as

$$\widehat{diff}_{treat} = \hat{\beta}_{treat}^{(Customized)} - \hat{\beta}_{treat}^{(T\&E\ 2week)}.$$

Summary tables will include number of patients, LSmean change, (unadjusted) mean change and SD and baseline means of each treatment arm and the estimate of the treatment difference expressed as LSmean difference including the corresponding two-sided 95% CI.

The analysis described above will be repeated on the PPS as a supplementary analysis.

4.2.3.2 Complete Case (ANCOVA without imputation)

The same methodology of the first sensitivity analysis (i.e., ANCOVA) will be applied but without imputation of missing data and with censoring due to ICEs as defined in Appendix 8.2. Patients with missing BCVA assessment in the study eye at Week 36 will be excluded from the analysis. Analysis will be performed only on patients with available observed BCVA assessments in the study eye at both baseline and Week 36.

The complete case approach assumes missing completely at random for patients with missing data i.e., missingness does not depend on any observed or unobserved data.

For the model specification, please refer to Section 4.2.3.1.

Summary tables will include number of patients, LSmean change, (unadjusted) mean change and SD, baseline means of each treatment arm, and the estimate of the treatment difference expressed as LSmean difference including the corresponding two-sided 95% CI.

4.3 Secondary Endpoints/Estimands Analysis

4.3.1 Key Secondary Endpoint/Estimand

All analyses described below for the key secondary efficacy variable will be analyzed on the FAS by randomized treatment arm, regardless of any changes to dose interval. As a supplementary analysis, the key secondary efficacy variable will also be evaluated based on the PPS.

4.3.1.1 Definition of Endpoint

The estimand of key secondary endpoint interest will be based on a “while on treatment” strategy.

It describes the number of injections in the study eye per patient up to study Week 52, for all patients that started treatment until the timepoint when they had an ICE as defined in Appendix 8.2.

The estimand is specified through the following definitions of population, variable, treatment condition, ICEs, and population-level summary:

Population:	Defined by the inclusion/exclusion criteria.
Variable:	Number of IVT aflibercept injections in the study eye per patient in the time frame from baseline to Week 52.
Treatment condition:	Aflibercept customized treatment interval arm vs. aflibercept standard T&E 2-week adjustment arm.
Intercurrent events:	Premature discontinuation from treatment/study. Use of a prohibited medication / start of alternative anti-VEGF treatment, prior to treatment and/or study discontinuation. Shortening/extension of the dosing interval will not be considered an ICE, but as part of the randomized treatment regimen. Details for other potential ICEs and the handling of ICEs in the analysis are given in Appendix 8.2.
Population-level summary:	Difference in mean number of injections in the study eye per patient in the time frame from baseline to Week 52 between the customized treatment interval arm and T&E 2-week adjustment arm.

No hypothesis testing will be performed for the key secondary efficacy endpoint. Analyses will be performed in a descriptive manner, although 95% CI of the treatment difference will be estimated, as a reference.

4.3.1.2 Main Analytical Approach

For the main analysis of the key secondary efficacy variable, an ANCOVA will be used, with the treatment arm and the stratification variable (BCVA gains in the study eye from treatment initiation to study start, captured during screening [<8 vs. ≥8 letters gain]) as fixed factors.

No imputation of missing data will be performed, therefore the actual/observed number of injections in the study eye per patients from baseline to Week 52, performed prior to the occurrence of any ICE, will be analyzed.

The actual number of injections in the study eye at Week 52 of patient i receiving treatment t can be written as follows:

$$Y_{itb} = \beta_0 + \mu_t + \eta_b + \epsilon_{itb}$$

with

- Y_{itb} being the number of injections received in the study eye at Week 52 for the ith patient
- β_0 being the intercept
- μ_t being the treatment arm effect

- η_b being the categorical stratification variable (BCVA gains in the study eye from treatment initiation to study start, captured during screening [<8 vs. ≥8 letters gain]), as recorded on the IXRS system
- ϵ_{itb} the residual error with $\epsilon_{itb} \sim N(0, \sigma_t^2)$ being the residual error for treatment arm *t*.

In terms of the model parameters, the estimate of the population-level summary of the estimand (i.e., the treatment effect at Week 52) can then be expressed as

$$\widehat{diff}_{treat} = \hat{\beta}_{treat}^{(Customized)} - \hat{\beta}_{treat}^{(T\&E\ 2week)}.$$

Summary tables will include number of patients, LSmean, (unadjusted) mean and SD of each treatment arm, and the estimate of the treatment difference expressed as LSmean difference including the corresponding two-sided 95% CI.

A descriptive summary table, including the mean number of injections up to Week 52 as well as the frequencies for the number of injections up to Week 52, will be provided by treatment arm.

The analysis described above will be repeated on the PPS as a supplementary analysis.

4.3.1.3 Sensitivity Analysis

The same methodology of the main analysis for the key secondary efficacy endpoint (i.e., ANCOVA) will be applied but considering only data of patients who stay on treatment until Week 52. Patients who have an ICE that leads to exclusion of data as described in Appendix 8.2 will be excluded from the analysis.

The complete case approach assumes missing completely at random for patients with missing data i.e., missingness does not depend on any observed or unobserved data.

For the model specification and the corresponding summary tables, please refer to Section 4.3.1.2.

4.3.2 Supportive Secondary Endpoints

The other secondary efficacy endpoints are:

- Mean number of IVT aflibercept injections in the study eye per patient until study Week 36.
- Proportion of patients achieving pre-defined treatment intervals (≥4, ≥8, ≥10, ≥12, ≥14, and 16 weeks) at Weeks 36 and 52.
- Mean change in BCVA (ETDRS letters score in the study eye) from baseline to Week 52.

Analyses on the other secondary efficacy endpoints will be conducted on the FAS by randomized treatment arm, regardless of any changes to dose interval. As a supplementary analysis, the other secondary efficacy endpoints except fro the mean change in BCVA from baseline to Week 52, will also be evaluated based on the PPS. No hypothesis testing will be performed for the other secondary efficacy endpoints. Analyses will be performed in a descriptive manner, adjusting for the stratification factors as described in Sections 4.3.2.1, 4.3.2.2 and 4.3.2.3. This may include 95% CIs for treatment differences in an exploratory way, for reference.

4.3.2.1 Number of injections in the study eye per patient until Week 36

The same methodology of the main analysis for the key secondary efficacy endpoint (i.e., ANCOVA) will be applied.

No imputation of missing data will be performed, therefore the actual/observed number of injections in the study eye per patient from baseline to Week 36, performed prior to the occurrence of any ICE, will be analyzed.

For the model specification and the corresponding summary tables, please refer to Section 4.3.1.2 and Section 4.3.1.3.

4.3.2.2 Proportion of patients achieving pre-defined treatment intervals (≥4, ≥8, ≥10, ≥12, ≥14, and 16 weeks) for the study eye at Weeks 36 and 52

For the analysis of the proportion of patients achieving pre-defined treatment intervals (≥4, ≥8, ≥10, ≥12, ≥14, and 16 weeks) for the study eye at Weeks 36 and 52, a logistic regression with a binomial probability distribution and the identity link function will be used, with the treatment arm and the stratification variable (BCVA gains in the study eye from treatment initiation to study start, captured during screening [<8 vs. ≥8 letters gain]) as fixed factors.

No imputation of missing data will be performed. Only exposure data prior to the occurrence of any ICE will be considered for the analysis.

Achievement of the pre-defined treatment interval at the mandatory visit of Week 36 and at Week 52 will be based on the duration between the last 2 injections received prior to or on Week 36 and Week 52 respectively. This will be derived as follows:

- If last administration of study treatment occurs on the same date of (i.e., during) the mandatory visit, only if required per treatment schedule, difference in days between the date of the administration performed at the mandatory visit and the date of the previous administration of study treatment
- If last administration of study treatment occurs prior to the date of the mandatory visit, difference in days between the last administration date and the penultimate administration date.

Achievement of the pre-defined treatment interval at the mandatory visit of Week 36 and at Week 52 will be declared:

- ≥4 weeks flag achieved, if the length of the last injection interval prior to or on the mandatory visit is ≥28 - 7 days
- ≥8 weeks flag achieved, if the length of the last injection interval prior to or on the mandatory visit is ≥56 - 7 days
- ≥10 weeks flag achieved, if the length of the last injection interval prior to or on the mandatory visit is ≥70 - 7 days
- ≥12 weeks flag achieved, if the length of the last injection interval prior to or on the mandatory visit is ≥84 - 7 days
- ≥14 weeks flag achieved, if the length of the last injection interval prior to or on the mandatory visit is ≥98 - 7 days
- ≥16 weeks flag achieved, if the length of the last injection interval prior to or on the mandatory visit is ≥112 - 7 days.

The time window of 7 days is applied to allow for an early attendance of a mandatory visit. According to the study protocol, visit window for mandatory visits is +/-7 days.

The pre-defined treatment intervals flags will not be mutually exclusive, which means that a patient achieving (according to the definition above) a pre-defined treatment interval at a given mandatory visit, will be considered also achieving shorter intervals at the same given visit. For example, a patient achieving a pre-defined treatment interval of ≥10 weeks at Week 36 will be considered achievers for ≥4 weeks, ≥8 weeks and ≥10 weeks intervals at Week 36.

The model below applies for each of the pre-defined treatment interval at both timepoints of Weeks 36 and 52.
In the example, the proportion of patients achieving the pre-specified treatment interval ≥4 weeks at Week 36 can be written as follows:

$$Pr(Y_{\geq 4\ wk\ at\ wk\ 36} = 1) = \frac{e^{\beta_0+\beta_1 x_1+\beta_2 x_2}}{1 + e^{\beta_0+\beta_1 x_1+\beta_2 x_2}}$$

with

- Y being the response variable flag for patients achieving the pre-specified treatment interval (≥4 weeks) at Week 36 (i.e., 1 = achieved vs. 0 = not achieved)
- $Pr(Y_{\geq 4\ wk\ at\ wk\ 36} = 1)$ being the proportion of patients achieving the pre-specified treatment interval (≥4 weeks) at Week 36
- β_0 being the intercept
- β_1, β_2 being the coefficients of the explanatory variables/factors
- x_1 being the categorical stratification variable (BCVA gains in the study eye from treatment initiation to study start, captured during screening [<8 vs. ≥8 letters gain]), as recorded on the IXRS system
- x_2 being the treatment variable.

In terms of the model parameters, the estimate of the treatment effect can then be expressed as

$$\widehat{diff}_{treat} = \widehat{Pr}(Y_{\geq 4\ wk\ at\ wk\ 36} = 1)^{(Customized)} - \widehat{Pr}(Y_{\geq 4\ wk\ at\ wk\ 36} = 1)^{(T\&E\ 2week)}$$

The logistic model followed by use of the NLMeans macro allows the LSmean of proportions and difference in proportions to be calculated, rather than the default log odds and difference in the log odds.

Summary tables will include number of patients, observed proportion, LSmean estimated proportion of patients achieving the pre-defined treatment intervals for each treatment arm and the estimate of the treatment difference in proportions expressed as LSmean difference including the corresponding two-sided 95% CI.

The analysis described above will be repeated on the PPS as a supplementary analysis. The analysis will also be repeated on the FAS using the complete case approach.

4.3.2.3 Change in BCVA in the study eye from baseline to Week 52

The same methodology of the primary analysis for the primary efficacy endpoint (i.e., MMRM) will be applied.

Details for the management of data with regards to potential ICEs are given in Appendix 8.2.

For the model specification and the corresponding summary tables, please refer to Section 4.2.2.

The sensitivity analyses – ANCOVA with LOCF and complete case (ANCOVA without imputation) – specified in Section 4.2.3 will be performed and associated summary tables presented.

4.4 Exploratory Endpoints Analysis

The exploratory efficacy endpoints are:

For both treatment arms:

- Change in BCVA in the study eye from Week -16 to Week 52.
- Change in CST (µm) from baseline to Weeks 36 and 52 in the study eye.
- Change in CST compared to treatment initiation (i.e., 16 weeks before baseline) at Weeks 36 and 52 in the study eye.
- Proportion of patients without any fluid/without IRF/SRF at 8 weeks before baseline, baseline, Weeks 36 and 52 in the study eye.

For the customized treatment interval arm only:

- Change in retinal fluid volume and in volume by compartment (IRF and SRF) in the study eye.
- Area under the curve (AUC) of fluid volumes in the study eye.
- Agreement of home monitoring findings with SD-OCT in-office monitoring performed at the closest time prior to the office visit.

For both treatment arms:

- Change in CNV size using OCT-A (optional for center) in the study eye at study visits.
- Number of patients with newly developed CNV in fellow eye in OCT-A at Weeks 36 and 52 in eyes with dry AMD signs at baseline.

For the customized treatment interval arm only:

- Number of patients for agreement levels 1 to 5 assessed at Week 36.
  There is no scoring system/algorithm for the patient home OCT user experience questionnaire. Summary statistics will be presented for each of the 15 items of the questionnaire. See Section 8.1.1 for full details.

Analyses on the exploratory efficacy endpoints will be conducted on the FAS by randomized treatment arm, regardless of any changes to dose interval. No hypothesis testing will be performed for these endpoints. Analyses will be performed in a descriptive manner.

No imputation of missing data will be performed for the exploratory efficacy endpoints, with the exception of the change in BCVA in the study eye from Week -16 to Week 52 where summary statistics will include a table where LOCF is used if there is an ICE. For all other exploratory efficacy endpoints, available and observed data will be analyzed irrespective of the occurrence of ICEs.

The agreement of home monitoring findings with SD-OCT in-office monitoring will be evaluated by calculating the percentage of visits instigated by a home monitoring findings alert where a patient received an early injection, from all the clinic visits instigated by a home monitoring findings alert.

4.5 Safety Analyses

The analysis of safety variables will be conducted descriptively on the SAF population for the data up to Week 36 and up to Week 52/end of study, unless otherwise stated.

4.5.1 Extent of Exposure

Exposure to the study intervention will be analyzed for SAF, FAS and PPS. Descriptive statistics will be used for analysis. For the analyses at Week 36 only study intervention data prior to Week 36 will be used (as described in Section 6.2).

For each patient, the following variables for the study eye will be used to summarize exposure to study intervention (including scheduled and unscheduled study interventions):

Based on actual injections:

- Total number of injections
- Proportion of patients with at least one treatment interval reduction
- Number of treatment interval reductions per patient
- Proportion of patients with at least one treatment interval extension
- Number of treatment interval extensions per patient
- Proportion of patients achieving a last completed treatment interval of ≥4 weeks at Weeks 36 and 52 – secondary endpoint
- Proportion of patients achieving a last completed treatment interval of ≥8 weeks at Weeks 36 and 52 – secondary endpoint
- Proportion of patients achieving a last completed treatment interval of ≥10 weeks at Weeks 36 and 52 – secondary endpoint
- Proportion of patients achieving a last completed treatment interval of ≥12 weeks at Weeks 36 and 52 – secondary endpoint
- Proportion of patients achieving a last completed treatment interval of ≥14 weeks at Weeks 36 and 52 – secondary endpoint
- Proportion of patients achieving a last completed treatment interval of ≥16 weeks at Weeks 36 and 52 – secondary endpoint
- Duration of study intervention calculated in weeks as: [(date of last study intervention [prior to Week 36/up to and including Week 52]) – (date of first study intervention) +28]/7; 28 days are added because of the minimum 4-week dosing interval in the study

These exposure variables do not consider if the study intervention is temporarily interrupted.

Exposure to study intervention will be summarized for the following periods:

- From Baseline to Week 36 (excluding intervention data at Week 36) – summary to be displayed at Week 36 and final analysis
- From Baseline to end of study (Week 52).

For each patient who received concomitant fellow eye treatment (as defined in Section 4.1.11), the following variables will be shown for SAF only:

- Total number of injections in fellow eye

- Participants with concomitant fellow eye treatment and corresponding biosimilars (available in the Biosimilars, Medical Histories and Definition of Grouped Adverse Event Terms document)
    - Aflibercept (trade name: Eylea)
    - Bevacizumab (trade name: Avastin)
    - Brolucizumab (trade name: Beovu)
    - Ranibizumab (trade name: Lucentis)
    - Faricimab (trade name: Vabysmo)
    - Conbercept (trade name: Lumitin)
    - Pegaptanib sodium (trade name: Macugen)
- Duration of fellow eye treatment in weeks calculated as: [(date of last treatment of fellow eye) – (date of first treatment of fellow eye) +28]/7

Summaries for fellow eye treatment will be displayed for all patients with any fellow eye injection during the study.

Listings will show the patients' exposure duration and the number of injections.

A treatment interval pattern figure, showing the next treatment interval at each injection visit, will be created for the FAS at Week 36 and Week 52.

4.5.2 Adverse Events

An AE is any untoward medical occurrence in a clinical study patient, associated with the use of study intervention, whether or not considered related to the study intervention. All reported AEs will be coded using the currently available version of the MedDRA at time of analysis. Coding will be to lowest level terms according to Bayer global standards.

Adverse events will be collected from the time of informed consent signature and at each visit until the end of the study. If the patient withdraws from the study during the screening, AEs will be collected up until the patient withdraws. If the patient is withdrawn after receiving the first injection of study medication, AEs will be collected up until 30 days after the last dose of study intervention or the termination visit, whichever is later.

Adverse events will be summarized as:

- **Pre-treatment AE**: Pre-treatment AEs are defined as AEs that start after the patient has signed the informed consent, but prior to the first injection at baseline (i.e., date of informed consent ≤ AE onset date < date of the patient's first injection of study intervention).
- **Treatment-emergent adverse event (TEAE)**: TEAEs are defined as AEs that started in the time frame from first injection to the last injection in the study plus 30 days (i.e., date of the patient's first injection ≤ AE onset date ≤ date of the patient's last injection of study intervention + 30 days). For the patients who have not discontinued study treatment prematurely (i.e., are "ongoing") at the Week 36 analysis, all AEs that started at first injection or later will be considered treatment-emergent, even if they started more than 30 days after the latest injection.
- **Post-treatment AE**: Post-treatment AEs are defined as AEs that started more than 30 days after the last injection in the study (i.e., AE onset date > date of the patient's last dose of study intervention + 30 days). For the patients who have not discontinued study treatment prematurely (i.e., are "ongoing") at the Week 36 analysis, no AEs will

be considered post-treatment, even if they started more than 30 days after the latest injection.

The data cut-off rules for Week 36 AE reporting are described in Section 6.2.

The proportions of patients with AEs will be used as safety variables for AE summary.

Other variables for AE description and analysis will include AE Verbatim Term, AE start date/time and end date/time/ongoing and corresponding study day, AE duration, relationship of AE to study drug, relationship of AE to fellow eye treatment (as defined in Section 4.1.11), relationship of AE to intravitreal injection, relationship of AE to protocol required procedure, seriousness, intensity, action due to AE, treatment of AE, and outcome.

Summaries that include frequencies and proportions of patients reporting AEs will include the PTs and the SOCs. A patient who has multiple events in the same SOC and PT will be counted only once for each SOC and PT for the patient counts but all events will be included for the event counts.

Evaluations for TEAE will be mainly done for the following categories, which will be identified from the information of the CRF:

- Ocular TEAEs in the treated study eye
- Ocular TEAEs in the fellow eye
- Non-ocular TEAEs

AE summaries will be provided displaying AEs within each SOC in decreasing order of total percentage of patients reporting the AE.

For overall characterization of the AE profile for aflibercept in this study, an AE summary will include AEs within each SOC listed in decreasing order of total percentage of patients reporting the AE, with columns for treatment arm and a pooled arm.

TEAEs in the study eye assessed by the investigator as being related to the injection procedure, related to protocol required procedures and those related to the study medication will be summarized separately.

TEAEs in the fellow eye assessed by the investigator as being related to the injection procedure, related to protocol required procedures, related to the study medication and those related to fellow eye treatment (as defined in Section 4.1.11) will be summarized separately.

A listing will be constructed that includes the patient identification, the treatment arm, category of AE (ocular study eye, non-ocular), AE, MedDRA term, seriousness, severity, causality, elapsed time to onset, duration, and outcome.

Serious Adverse Events (SAEs) will be summarized in the same way as described for TEAEs.

A frequency table of TEAEs of **intraocular inflammation** terms, cross-tabulated with related MedDRA PT, will be displayed by treatment arm (see the Biosimilars, Medical Histories and Definition of Grouped Adverse Event Terms document for definition of terms).

A frequency table of TEAEs of **intraocular pressure increase** terms, cross-tabulated with related MedDRA PT, will be displayed by treatment arm (see the Biosimilars, Medical Histories and Definition of Grouped Adverse Event Terms document for definition of terms).

No AEs of special interest are defined.

4.5.3 Additional Safety Assessments

4.5.3.1 Surgeries

All surgeries after informed consent are collected on the eCRF. All surgeries and diagnostic procedures will be displayed in listings.

4.5.3.2 Clinical Laboratory Variables

No collection of chemistry, hematology, urinalysis and biomarker parameters is foreseen.

Only urine pregnancy testing is performed at each visit for women of childbearing potential. Results of pregnancy tests will be listed only.

4.5.3.3 Vital Signs

Vital signs will be collected pre-injection at each visit during the study. Variables for analysis of vital signs include body temperature, heart rate, systolic blood pressure, and diastolic blood pressure. Vital signs will be summarized by baseline and change from baseline to each visit by treatment arm for the SAF.

Heart rate and blood pressure assessments will also be displayed as figures with mean change from baseline for SAF.

4.5.3.4 Indirect Ophthalmoscopy

The number and proportion of patients with vitreous cells will be summarized by treatment arm for the SAF, according to the following categories:

- 0: clear (0-1 cells)
- Trace: few opacities (2-20 cells)
- 1+: scattered opacities (21-50 cells)
- 2+: moderate opacities (51-100 cells)
- 3+: many opacities (101-250 cells)
- 4+: dense opacities (>251 cells).

4.5.3.5 Slit Lamp Biomicroscopy

The number and proportion of patients with anterior chamber cells and anterior chamber flare will be summarized by treatment arm for the SAF, according to the following categories:

- Proportion of patients with anterior chamber cells
    - 0: no cells
    - Trace: less than 5 cells
    - 1+: 5 to 10 cells
    - 2+: 10 to 20 cells
    - 3+: 20 to 30 cells
    - 4+: cells too numerous to count.
- Proportion of patients with anterior chamber flare
    - 0: no protein

- Trace: trace amount of protein
- 1+: mild amount of protein
- 2+ and 3+: moderate amount of protein (continuum)
- 4+: severe amount of protein.

4.5.3.6 Intraocular Pressure

The number and proportion of patients with increased IOP will be summarized by treatment arm for the SAF, according to the following categories:

- ≥10 mmHg increase in IOP measurement from baseline to any (i.e., pre-dose or post-dose) measurement
- >21 mmHg for any (i.e., pre-dose or post-dose) measurement at any time during the study
- ≥25 mmHg for any (i.e., pre-dose or post-dose) measurement at any time during the study
- ≥35 mmHg for any (i.e., pre-dose or post-dose) measurement at any time during the study.

Summary statistics will also be displayed by visit and by treatment arm for the SAF for:

- change from baseline to pre-dose values
- change from pre-dose to post-dose values.

4.6 Other Analyses

4.6.1 Subgroup Analyses

4.6.1.1 Efficacy Analyses

The following subgroups will be considered for efficacy analyses:

- Age at enrollment: <65 years, ≥65 to <75 years, ≥75 years to <80 years, ≥80 years to <85 years, ≥85 years
- Sex: male, female
- Baseline BCVA: <35 letters, 35-69 letters, ≥70 letters
- Treatment start (Week -16, first pre-study treatment) BCVA: <35 letters, 35-69 letters, ≥70 letters
- Stratification factor – visual outcomes as determined at the screening visit by gain in BCVA relative to aflibercept initiation prior to study enrollment: <8 letters, ≥8 letters
- Actual gain in BCVA relative to aflibercept initiation prior to study enrollment as determined at screening visit (to address potential errors in the stratification factor): <8 letters, ≥8 letters

All subgroup analyses will be descriptive only, i.e., no statistical testing of treatment effects or treatment interactions will be performed.

All statistical analyses for primary and key secondary efficacy endpoints will be conducted for the FAS by each subgroup defined above for efficacy analyses. The number of IVT

aflibercept injections in the study eye from baseline to Week 36, a secondary efficacy endpoint, will be analysed using the FAS by each subgroup defined above.

The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic factors.

No adjustment to the significance level for testing will be made, since all these subgroup analyses will be considered exploratory and descriptive. For each subgroup, the estimate of the treatment difference and 95% CI will be presented in tables. These will be presented on a forest plot including the results of the overall analyses.

Analysis of subgroups for the primary endpoint will be done using the MMRM without imputation of missing values but with censoring for ICEs as described in Appendix 8.2, and the analyses of subgroups for the key secondary endpoint will be done using the ANCOVA without imputation of missing values but with censoring for ICEs as described in Appendix 8.2.

Summary statistics for the primary efficacy endpoint will be conducted for the FAS by each subgroup, both for the observed cases until the occurrence of an ICE, and for where there is imputation of missing values after occurrence of an ICE with LOCF.

Summary statistics for the key secondary efficacy endpoint will be conducted for the FAS, PPS and complete case FAS by each subgroup.

Summary statistics for the number of IVT aflibercept injections in the study eye from baseline to Week 36, a secondary efficacy endpoint, will be conducted for the FAS.

4.6.1.2 Safety Analyses

The following subgroups will be considered for safety analyses:

- Age at enrollment: <65 years, ≥65 to <75 years, ≥75 years to <80 years, ≥80 years to <85 years, ≥85 years
- Sex: male, female

Subgroup analyses for TEAEs will be performed for the safety analysis subgroups described above, for each of the following types of TEAE:

Number of patients with:

- Ocular TEAEs in the study eye
- Non-ocular TEAEs
- Serious ocular TEAEs in the study eye
- Serious non-ocular TEAEs

4.7 Interim Analyses

No formal statistical interim analyses are planned.

The primary endpoint/estimand will be analyzed and the summaries up to Week 36 will be provided when all patients have completed Week 36 (or withdrew). The analysis will only use data collected up to Week 36 or premature discontinuation, whichever occurs first.

No decisions on the outcome and/or study will be made (e.g., terminating the study or changing the design). Therefore, no α-adjustment is necessary.

All the secondary and exploratory endpoints/estimands will be analyzed and the summaries up to Week 52 will be provided when all patients have completed the study (i.e., completed Week 52 or prematurely withdrew, whichever occurs first). The analysis will use all data collected.

4.8 Changes to Protocol-planned Analyses

A clarification has been added in Section 4.1.7 of this document that for repeated measurements at a visit before the start of study treatment, the last non-missing repeated measurement would be used for data summarises and analysis. This does not match the unscheduled assessments paragraph of Section 9.3.1 of the study protocol.

The definition of FAS in Section 3 of this document has been amended to remove reference to the BCVA assessment, which is included in the definition provided in Section 9.2 of the study protocol. Section 3 of this document specifies that the SAF will be analyzed “as randomized” rather than “as treated”, which is what was specified in Section 9.2 of the study protocol. The PPS has been included in Section 3 of this document but was not included in Section 9.2 of the study protocol.

An additional exploratory analysis has been added in Section 4.4 for change in BCVA in the study eye from Week -16 to Week 52.

There is no exploratory analysis of sub-RPE, which is included as an exploratory endpoint in Section 9.3.4 of the study protocol and Table 1-1 of this document. There is no exploratory analysis for the proportion of patients without any fluid/without IRF/SRF at treatment initiation (16 weeks before baseline), which is included as an exploratory endpoint in Section 9.3.4 of the study protocol and Table 1-1 of this document.

5. Sample Size Determination

In ARIES study, patients which were dry (as no intraretinal fluid [IRF] and no subretinal fluid [SRF]) at Weeks 8 and 16 in the early T&E arm (N=59) had a mean BCVA change of -0.5 letters from Week 16 to Week 52 with a SD of 6.6 letters.

In ALTAIR study, patients which were dry (as no IRF and no SRF) at Weeks 8 and 16 in the 2-week adjustment arm (N=55) had a mean BCVA change of -0.7 letters from Week 16 to Week 52 with a SD of 7.2 and the 4-week adjustment arm (N=61) had a mean BCVA change of -0.5 letters from Week 16 to Week 52 with a SD of 6.1 letters.

Under the assumptions that:

- The customized treatment interval arm is similar to the 4-week adjustment arm from ALTAIR study (i.e., N=61 with a mean BCVA change of -0.5 letters from Week 16 to Week 52 with a SD of 6.1).
- The standard T&E 2-week adjustment arm is similar to the 2-week adjustment arm from ALTAIR study (i.e., N=55 with a mean BCVA change of -0.7 letters from Week 16 to Week 52 with a SD of 7.2).
- There is no true difference in mean BCVA change from baseline to Week 36 between both arms (which would be equal to the change from Week 16 to Week 52 in ALTAIR and ARIES studies).
- Both arms will have SD of 7 letters for the mean change in BCVA from baseline to Week 36.

A sample size of N=86 patients in total would be needed to show a non-inferiority of customized treatment interval arm compared to the standard T&E 2-week adjustment arm, using a non-inferiority margin of 5 letters, for the difference of the means change from baseline in BCVA at Week 36, achieving a power of 90% using a one-sided test with a significance level α of 2.5%. Assuming an expected dropout rate of 20%, a sample size of approximately N=108 patients in total (54 patients per arm) will be randomized.

The sample size was calculated using NCSS PASS 13 “Non-Inferiority Tests for Two Means using Differences”.

6. Supporting Documentation

6.1 Population characteristic

6.1.1 Participant disposition

The total number of patients who signed informed consent, were randomized, treated, completed study intervention and completed study for the respective analysis (Weeks 36 and 52) will be summarized for all ES. Patients prematurely discontinuing the study/study intervention will be summarized by reason for discontinuation for all ES.

The total number and percentage of patients who qualified as FAS and SAF (as defined in Section 3) including the reasons for exclusion from the respective analysis set will be summarized for all ES.

The disposition of patients who signed the informed consent will be summarized overall and by study site including the date of first consent, date of last visit and the number of patients with informed consent and in each analysis set for all ES.

The disposition of patients and the number of study sites in regions and countries will be presented for the FAS. Totals of all regions and within a country will be added.

The number of patients with important PDs by country and study site will be presented for all ES. Number of screen failures will be included. A second summary will show the number and percentage of patients in each PD category for all randomized subjects. Important PDs will be listed for all randomized subjects.

Additionally, a listing including all patients prematurely discontinuing from the study will be provided for all ES.

6.1.2 Demography and disease characteristics

Demographics and baseline assessments of vital signs to be summarized for FAS and PPS will include:

- Age (as entered in eCRF)
- Age categorized (<65 years, ≥65 to <75 years, ≥75 years to <80 years, ≥80 years to <85 years, ≥85years)
- Sex
- Race and ethnicity
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m²)
- BMI (≤25 kg/m², 25 kg/m² < BMI ≤30 kg/m², 30 kg/m² < BMI ≤35 kg/m², BMI >35 kg/m²)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (bpm)
- Body temperature (°C)
- Fellow eye with history of wet AMD (yes/no)

- Prior fellow eye treatment (as defined in Section 4.1.11) (yes/no)
- Medical history of hypertension (as defined in the Biosimilars, Medical Histories and Definition of Grouped Adverse Event Terms document) (yes/no)
- Medical history of cerebrovascular disease (as defined in the Biosimilars, Medical Histories and Definition of Grouped Adverse Event Terms document) (yes/no)
- Medical history of ischemic heart disease (as defined in the Biosimilars, Medical Histories and Definition of Grouped Adverse Event Terms document) (yes/no)
- Medical history of renal impairment (as defined in the Biosimilars, Medical Histories and Definition of Grouped Adverse Event Terms document) (yes/no)
- Medical history of hepatic impairment (as defined in the Biosimilars, Medical Histories and Definition of Grouped Adverse Event Terms document) (yes/no)

Baseline assessments of disease characteristics to be summarized for FAS and PPS will include:

- Baseline BCVA (ETDRS letters score)
- Categorized baseline BCVA (<35 letters, 35-69 letters, ≥70 letters)
- Baseline intraocular pressure (IOP in mmHg)
- Baseline CST (in µm as defined in Section 4.1.10)
- Baseline CNV area (in mm^2 as defined in Section 4.1.10)
- Presence of IRF or SRF at baseline

Demographic data and baseline characteristics variables will be summarized using descriptive statistics. Disease characteristics will be presented in a separate table. Only data of the study eye will be shown although most examinations are done bilaterally.

6.1.3 Medical history

Medical history will be coded according to the version of Medical Dictionary for Regulatory Activities (MedDRA) available at DB lock. Medical history is evaluated by a frequency table, showing number of patients with medical history findings by primary system organ class (SOC) and preferred term (PT). Patients will be summarized for all medical history findings, along with separate summaries for ocular medical or surgical history of the study eye, ocular medical or surgical history of the fellow eye and non-ocular medical or surgical history. All summaries will be presented for the SAF. A listing of the medical history records will be provided.

6.1.4 Prior and concomitant medication

Prior and concomitant medication or therapy will be coded to Anatomical Therapeutic Chemical (ATC) classification codes according to the version of the World Health Organization Drug Dictionary (WHO Drug Dictionary) available at DB lock.

Prior and concomitant medication will be presented for the number and percentage of patients who took at least one prior and (new) concomitant medication and by ATC class (level 1) and subclass (level 2) for the SAF. Patients with prior and concomitant medication will be summarized for all medications. All medication will be included in a listing that includes reason for use, start and end dates and dosage information for the SAF. The following definitions will be used:

- Concomitant medications are defined as medications that are ongoing at or began after the start and prior to the stop of study intervention.
- Prior medications are defined as medications that began before the start of study intervention regardless of when they ended.

Treatment of the fellow eye (as defined in Section 4.1.11) will be collected as concomitant medication.

All prior and concomitant medication will be listed.

6.2 Data Cut-Off Specifications

The aim of this section is to specify which data to include in the Week 36 and Week 52 evaluations and which data to remove. It follows the principles and rules described in the sponsor's best practice document "RD-SOP-1119 - Data cutting rules specification (for SDTM+)" (v2.0).

As described in Section 1.2, the evaluation of data will be performed at two different time points:

- After Week 36 (i.e. after all participants have prematurely discontinued or completed Week 36), the primary endpoint/estimand will be analyzed.
- After Week 52 (i.e. after all participants have prematurely discontinued or completed Week 52).

The database cut-off for this study will be based on the SDTM+ database (Study Data Tabulation Model provided by CDISC plus additional variables added by BAYER) and on the visit based cut-off approach.

For Week 36 evaluations, a strategy for performing the data cut-off for the clinical database was developed, i.e. to include cumulative data up to Week 36. For Week 52 evaluations, all available data will be included and no data will be removed.

6.2.1 Definitions

Screening Failures:

Participants who have recorded "Did the subject complete Screening?" as "No" on the latest "End of Screening" form and who have not been randomized, will be considered Screening Failures.

Participants considered as non-completer for Week 36:

Participants who have

- No Week 36 visit recorded (i.e. Week 36 "Subject Visit" form not available) and
- "Did the subject complete the study?" = "No" recorded on the "End of Study" form, with a premature "Date of study completion/discontinuation" prior to the date of Week 36 visit (i.e. "Date of study completion/discontinuation" ≤ date of randomization + 252 days (+ 7 days visit window permitted by protocol)),

will be considered non-completer for Week 36 in context of data cut-off logic.

Participants considered as completer for Week 36:

All participants who are neither screening failures nor discontinued study prior to Week 36 will be considered Completer for Week 36 in context of data cut-off logic, i.e.

- Week 36 visit recorded (i.e. Week 36 “Subject Visit” form recorded, no matter if “Visit date” or “Not done”), or
- Week 36 visit not recorded, but participant either discontinued study later than after 36 weeks or is still in the study (i.e. “Date of study completion/discontinuation” > date of randomization + 252 days (+ 7 days visit window permitted by protocol)).

Individual data cut-off date:

Each participant will be assigned an individual data cut-off date/time, using the last available visit/assessment of the following:

Screening Failures:

The participant’s individual data cut-off date/time will be the “Date of discontinuation”, as recorded in the “End of Screening” folder.

Non-completer for Week 36:

The participant’s individual data cut-off date/time will be the “Date of study completion/discontinuation”, as recorded in the “End of Study” folder.

Completer for Week 36:

The participant’s individual data cut-off date/time will be one of the following:

1. Date/time of study intervention at the Week 36 visit (if Week 36 visit performed, i.e. visit date available and study intervention was given)
2. Last date/time from the Week 36 visit (if Week 36 visit performed, i.e. visit date available and no study intervention was given)
3. Planned date/time of the Week 36 visit (if Week 36 visit was not performed, i.e. “Not done”; then planned date of Week 36 visit: date of randomisation + 252 days)

Study intervention data at Week 36 and “post-intervention” data at Week 36 needs to be removed as well, i.e. for the cases 1) and 2) all assessments which are (as per protocol) to be taken after the study intervention at Week 36 should be removed.

6.2.2 Data cut-off rules

6.2.2.1 General remarks and rules

- All variables which are calculated according to the timing guideline as well as the treatment emergent flag will be re-calculated after the cut-off is done.
- Usually authorities request a special listing of all subjects who died after cut-off date. For this purpose, the information related to “death” (cause of death, death date) should not be removed even if after the cut-off date. This covers related information from Disposition and Death domains only.
- If there is a domain, which depends on another, the parent domain is always cut first, the dependent domain will then be cut accordingly.
- If an observation has a partial date, the observation will be cut only if the partial date is without any doubt after the cut-off date.
- If an observation has a missing date and occurred up to the cut-off visit (based on the visit number), the observation will not be cut.

- If an observation is clearly related to a later visit (based on the visit number) it will also be removed.
- If an observation has a missing time, “00:00” will be used for the cut-off process.
- If for the data cut-off date/time no time is available, “23:59” (11:59pm) will be used for the cut-off process.
- Different time zones will not be considered for comparison of dates.
- Trial design domains are updated to reflect the content after cut-off.

Study specific rules (described in more detail in the following sections):

- At Week 36 visit only pre-intervention assessment data from that visit will be included (study intervention data, intraocular pressure [post-injection], indirect ophthalmoscopy [post-injection], will be removed)
- Unscheduled visit data collected until the participant’s individual data cut-off date/time will be included
- Further study specific rules will be defined throughout Section 6.2

6.2.2.2 Types of datasets to be considered for database cut-offs

There are four different types of datasets regarding dates:

A. Trial Design domains.
B. Datasets without dates.
C. Datasets with only start dates (xxSTDTC) but no end dates (xxENDTC) or collection/assessment dates (xxxxDTC)
D. Datasets with start dates and respective end dates (xxSTDTC – xxENDTC).

These four different types have different data handling rules with respect to cutting data.

Trial Design domains

Table 6-1 Comments for trial design domains

Domain	Comments (only datasets/variables listed where actions are expected)
TS	• DCUTDESC (Data Cut-off Description) and DCUTDTC (Data Cut-off Date) must be updated (see below) • SENDTC (Study End Date) will be re-calculated based on the definition of RFPENDTC but does not include time.
TV	To be changed if after cut-off not all planned visits were performed (e.g. for Week 36 analysis all visits after the Week 36 vist need to be removed, except the End of Study/Week 52 visit if early termination information is captured there)

Data Cut-off Description (DCUTDESC)

For the Week 36 evaluation the following description will be used: “Analysis of data up to Week 36 (including the primary efficacy analysis)”.

For the Week 52 evaluation the following description will be used: “Final analysis of data up to Week 52”.

Data Cut-off Date

The data cut-off date shall be the date when the database is locked.

Study End Date (SENDTC)

The study end date shall be the date when the last study treatment up to Week 52 was given. At the Week 36 analysis, if this information is not available, this variable will be left blank.

Datasets without dates

Table 6-2 Comments for datasets without dates

Domain	Comments
CO	Comments are related to information given in other domains. If the information is removed by the cut-off process, the respective comment must be removed as well.
RELREC	Information in RELREC is related to information given in other domains. If the information is removed by the cut-off process, the respective RELREC lines must be removed as well.

Single date variables (DTC – variables) and single start dates (SDTC – variables)

Single date variables (DTC – variables) and single start dates (SDTC – variables), i.e. all variables with corresponding start and end date (##STDTC – ##ENDTC) are excluded.

General rule:

If a visit is clearly prior to the visit of the individual cut-off date/time, it will be kept. Otherwise, if date/time is after the subject's individual cut-off date/time, the complete observation should be removed. Also visits that are clearly after the visit of the individual cut-off date/time should be removed.

Table 6-3 Comments for single date variables and single start dates

Domain	Variable	Comments (only datasets/variables listed where actions are expected)
DS	DSSTDTC	Keep all records where DSDECODN = 3 (Death) without any regard to date. For "Participants completed study intervention until Week 36", "Participants started follow-up phase prior to Week 36", "Participants completed follow-up phase until Week 36" and "Participants completed Week 36" records need to be created according to definition in Section 6.2.1.

Single end dates (ENDTC – variables) and variables with corresponding start and end dates (##STDTC – ##ENDTC)

General rules:

If a visit is clearly prior to the visit of the individual cut-off date/time, it will be kept. If a visit is clearly after the visit of the individual cut-off date/time, it should be removed. Furthermore:

a) If start date/time is after the subject's individual cut-off date/time, remove the complete observation.

b) If end date/time is before the subject's individual cut-off date/time, keep the complete observation as is.

c) If start date/time is before or on the subject's individual cut-off date/time and end date/time is after the subject's individual cut-off date/time, keep the observation and apply the rules in table below.

d) If start date/time is before or on the subject's individual cut-off date/time and end date/time is completely missing, keep the complete observation as is, except for CM/MH apply the rules in table below.

e) If end date is a partial date, the earliest plausible date should be taken and rules a) or c) in table below to be applied.

f) For domains EX/EC: If start date/time is equal to or after the subject's individual cut-off date/time, remove the complete observation.

The table below covers tasks to be done for rule c) and d).

Table 6-4 Comments for single end dates and variables with corresponding start and end date

Domain	Variable	Specific actions for general rule c) and d)
(all domains except EC, EX. PC, SV)	##ENDTC	End date ##ENDTC is set to "blank"
AE	AEOUT	AE outcome should be set to missing
CM	CMENTPT	Rule c) and d):
	CMENRTPT	If Last Visit Date contained in CMENTPT is after cut-off date, CMENTPT will be set to cut-off date and CMENRTPT will be set to "ongoing" and the flag variable (CUTFL) should be set to "Y" to identify imputed information. Otherwise no change to CMENTPT and CMENRTPT.
MH	MHENTPT MHENRTPT	RULE c) and d): Same as CMENTPT / CMENRTPT
SV	SVENDTC	SVENDTC should be set to cut-off date/time and flag variable (CUTFL) to identify cut-off records.

Dependent domains

The dependent datasets do not have a date but if the related record from the parent domain is removed because of the cut-off process specified above, the related record in the dependent domain has to be removed as well.

Dependent Domain	Parent Domain
PP	PC
CO	Some Domains (AE, ...)
RELREC	Some Domains (AE, ...)
TE	TA

6.2.2.3 Database cut-off process (Overview)

- Copy and zip the source data before cut-off to a pre-defined folder for traceability.
- Cut all subject level data as specified above.
- Add or update cut-off related information: Data Cut-off Date (DCUTDTC), Data Cut-off Description (DCUTDESC) and Study End Date (SENDTC) in TS domain. Note: There should be only one pair of DCUTDTC/DCUTDESC related to the current cut-off date and description.
- Re-calculate SE domain and other timing information as well as information about treatment emergency. The following algorithm is to be applied: Keep the original elements of the pre-cut SE, create a temp DS with death and Survival Assessment Contact Date blanked out if those dates are after cut-off date, apply the timing concept rules on the temp DS and other cut datasets to populate the dates in SE and DM, delete records with blank SESTDTC from the new SE. Note: For Bayer in-house trials this can be done running the timing and the treatment emergent macro again.

7. References

1. National Research Council (US) Panel on Handling Missing Data in Clinical Trials. The Prevention and Treatment of Missing Data in Clinical Trials. Washington (DC): National Academies Press (US); 2010.

8. Appendix

8.1 Handling of Questionnaires

8.1.1 Patient Home OCT User Experience Questionnaire

Patient user experience with Home OCT device will be assessed with Notal Vision questionnaire (only applicable for patients in Home OCT-customized treatment interval arm).

The purpose of the questionnaire is to get patients' feedback on the Notal Home OCT device used during the study, with regards to the tutorial, ease of use and comfortability.

The questionnaire, shown in Table 8-1, is made up of 15 self-administered questions with responses, assessing the patients' level of agreement, ranging from 1=Strongly agree to 5=Strongly disagree. Patients are required to check the box with the answer that best fits their level of agreement.

Table 8-1 Notal Vision Patient Home OCT User Experience Questionnaire

		1 - Strongly agree	2 - Agree	3 - Not sure/Irrelevant	4 - Disagree	5 - Strongly disagree
1	The setup material, demonstrating how to install the device, was clear, and after reading it I was able to setup the device.					
2	Getting the device out of the box and setting it up was simple.					
3	The video tutorial, demonstrating how to use the device, was clear, and after watching it I was able to operate the device without further assistance.					
4	I understood the tasks I had to perform in order to scan my eyes, by myself.					
5	The tasks I had to perform to scan my eyes were easy.					
6	The time to scan each eye was short.					
7	Daily use of the device was convenient (posture, head rest, etc.)					
8	I did not feel my eyes get tired or hurt during the scans.					
9	The face rest on the viewer was comfortable to use.					
10	The handles on the sides of the device helped me stabilize myself during the scans.					
11	Using the device on a daily basis was easy.					
12	After using the device for a few days, it got easier.					
13	The fact that I can check my eyes at home every day makes me feel like I am in good care.					
14	Based on the study I participated in, I would like to use the device to scan my eyes on a daily basis.					
15	If you used the service call assistance during the study (otherwise leave blank): The service call helped me to solve problems and questions I had during the study.					

8.2 Strategies for Occurrence of Intercurrent Events

Analysis Strategies for ICEs for Primary Endpoint (i.e., Mean Change in BCVA from Baseline to Week 36)

Table 8-2: Strategies for Occurrence of ICEs for Primary Endpoint (i.e., Mean Change in BCVA from Baseline to Week 36)

		Primary Estimand		Sensitivity Analysis (LOCF)	Sensitivity Analysis (Complete Case)
Potential post-randomization event	ICE	Strategy	Analysis	Analysis	Analysis
Premature discontinuation of study intervention for any reason (and discontinuation of study) before Week 36	Yes	Hypothetical	Non-observed data beyond discontinuation of study intervention will be covered implicitly in the MMRM	Non-observed data beyond discontinuation of study intervention will be imputed by LOCF	Patient excluded from analysis
Premature discontinuation of study intervention for any reason (but continuation of study) before Week 36	Yes	Hypothetical	Observed data beyond last injection + minimum treatment interval of 4 week +7 days will be excluded from analysis and resulting missing data will be covered implicitly in the MMRM	Observed data beyond last injection + minimum treatment interval of 4 week +7 days will be excluded from analysis and resulting missing data will be imputed by LOCF	Patient excluded from analysis data if the last observed data go beyond the last injection + minimum treatment interval of 4 week +7 days
Use of a prohibited medication / start of alternative anti-VEGF treatment, prior to treatment discontinuation before Week 36	Yes	Hypothetical	Observed data beyond first administration of the prohibited medication will be excluded from analysis and resulting missing data will be covered implicitly in the MMRM	Observed data beyond first administration of the prohibited medication will be excluded from analysis and resulting missing data will be imputed by LOCF	Patient excluded from the analysis
Shortening/extension of dosing interval before Week 36	No	Not applicable	Observed data beyond shortening/extension of dosing interval will be included in the analysis	Observed data beyond shortening/extension of dosing interval will be included in the analysis	Observed data beyond shortening/extension of dosing interval will be included in the analysis

Any missing assessment of BCVA is not considered an ICE per se but is considered missing at random and covered implicitly in the MMRM or LOCF as applicable (or considered missing in the complete case).
Any missed injections are not considered an ICE per se but are considered missing at random.

Analysis Strategies for ICEs for Key Secondary Endpoint (i.e., Number of Injections up to Week 52)

Table 8-3: Strategies for Occurrence of ICEs for Key Secondary Endpoint (i.e., Number of Injections up to Week 52)

Potential post-randomization event	ICE	Primary Estimand		Sensitivity Analysis (Complete Case)
		Strategy	Analysis	Analysis
Premature discontinuation of study intervention for any reason (and discontinuation of study) before Week 52	Yes	While on treatment	Non-observed data beyond discontinuation of study intervention will not be imputed	Patient excluded from the analysis
Use of a prohibited medication / start of alternative anti-VEGF treatment, prior to treatment discontinuation before Week 52	Yes	While on treatment without prohibited medication	Observed data beyond first administration of the prohibited medication will be excluded from analysis and resulting missing data will NOT be imputed	Patient excluded from the analysis
Shortening/extension of dosing interval before Week 52	No	Not applicable	Observed data beyond shortening/extension of dosing interval will be included in the analysis	Observed data beyond shortening/extension of dosing interval will be included in the analysis

Any missing assessment of BCVA is not considered an ICE per se but is considered missing at random and covered implicitly in the MMRM or LOCF as applicable (or considered missing in the complete case).
Any missed injections are not considered an ICE per se but are considered missing at random.

Analysis Strategies for ICEs for Secondary Endpoint (i.e., Number of Injections up to Week 36)

Intercurrent events for the analysis of this endpoint will be handled similarly to what is specified in the primary estimand columns in Table 8-3.

Analysis Strategies for ICEs for Secondary Endpoint (i.e., Patients Achieving Pre-defined Treatment Intervals at Week 36 and at Week 52)

Intercurrent events for the analysis of these endpoints will be handled similarly to what is specified in the primary estimand columns in Table 8-3.

Analysis Strategies for ICEs for Secondary Endpoint (i.e., Mean Change in BCVA from Baseline to Week 52)

Intercurrent events for the analysis of this endpoint will be handled similarly to what is specified in the primary estimand columns in Table 8-2.

8.3 Participating Regions and Countries

The following regions and countries are participating in this study and are shown in Table 8-4.

Table 8-4: Participating Regions and Countries

Region	Country
Europe	FRANCE
	GERMANY
	SPAIN
	UNITED KINGDOM
North America	CANADA

Approval Signatures

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