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Statistical Analysis Plan

A multi-center, single-arm, interventional Phase 4 study to evaluate a Treat and Extend regimen of intravitreal aflibercept for treatment of macular edema secondary to central retinal vein occlusion

CENTERA

Bayer study drug	BAY86-5321/ aflibercept / VEGF Trap-Eye (Eylea)		
Clinical study phase:	IV	**Date:**	14 Nov 2019
Study No.:	BAY86 5321/17514	**Version:**	3.0

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The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

AE	Adverse Event
APTC	Antiplatelet Trialists' Collaboration
ATC	Anatomical Therapeutic Chemical
ATE	Arterial Thrombotic Events
AUC	Area Under the Curve
BCVA	Best Corrected Visual Acuity
BMI	Body Mass Index
BRVO	Branch Retinal Vein Occlusion
CI	Confidence Interval
CRF	Case Report Form
CRT	Central Retinal Thickness
CRVO	Central Retinal Vein Occlusion
ERG	Electroretinogram
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
FAS	Full Analysis Set
FP	Fundus Photography
FPFV	First patient first visit
IOP	Intraocular Pressure
IVT	Intravitreal
LOCF	Last Observation Carried Forward
LR	Likelihood Ratio
MedDRA	Medical Dictionary For Regulatory Activities
MI	Multiple Imputation
OCT	Optical Coherence Tomography
PPS	Per-Protocol Set
PRP	Panretinal Photocoagulation
PT	Preferred Term
RAPD	Relative Afferent Pupillary Defect
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-emergent Adverse Events
T&E	Treat and Extend
VEGF	Vascular Endothelial Growth Factor
WHO-DD	World Health Organization Drug Dictionary

1 Introduction

1.1 Objective

This statistical analysis plan (SAP) describes the statistical methods and data presentations to be used in the summary and analyses of data from a multi-center, single-arm interventional Phase 4 study, to assess efficacy and durability of 2 mg aflibercept administered by intravitreal (IVT) injections in a Treat and Extend (T&E) regimen to subjects with macular edema secondary to central retinal vein occlusion.

SAP version 1.0 based on the Integrated Clinical Study Protocol No. BAY 86-5321 /17514, version 2.0 dated 20 April 2016, and was finalised before first patient first visit (FPFV).

SAP version 2.0, will be finalized before database-lock and contains some clarifications and updates. For details see section 7.

1.2 Background

Retinal venous occlusive disease is an important cause of vision loss, particularly in patients with associated chronic macular edema. The 2 major categories are central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO).

Central retinal vein occlusion results in impaired venous drainage from the eye, which may lead to increased venous pressure, reduced arterial perfusion, and retinal ischemia.

Aflibercept is a potent, specific inhibitor of vascular endothelial growth factor (VEGF) with a high affinity for all isoforms of VEGF and placental growth factor.

Further details are provided in the applicable Summary of Product Characteristics and the Clinical Study Protocol.

Further details are provided in the Clinical Study Protocol.

1.3 Treat and Extend

CENTERA is a Phase 4 study to investigate a proactive T&E regimen with IVT aflibercept for the treatment of macular edema secondary to CRVO.

Further details are provided in the Clinical Study Protocol.

2 Study Objectives

Primary objective

- To determine the efficacy and durability (treatment interval) of 2 mg IVT aflibercept in a T&E regimen over a treatment period of 76 weeks using protocol-defined visual and anatomic criteria in subjects with macular edema secondary to CRVO

Secondary objectives

- To assess the efficacy of IVT aflibercept as measured by visual acuity and anatomic outcomes using spectral domain optical coherence tomography (SD-OCT), and perfusion status using fluorescein angiography (FA) / fundus photography (FP).
- To assess T&E applied posology of IVT aflibercept (number of injections, length of injection interval)

Safety objective

- To assess the safety and tolerability of IVT aflibercept in this subject population

Exploratory objectives (only at those sites with equipment available)

- To evaluate wide-field (angle) FA for utility in assessing perfusion status in the periphery of the retina, which is currently not evaluable using traditional FA, and examination of morphological changes related to disease progression in CRVO
- To evaluate optical coherence tomography (OCT) angiography for dynamic assessment of retinal capillary perfusion status
- To evaluate full-field electroretinography (ERG) for functional assessment of retinal ischemia
- To evaluate relative afferent pupillary defect (RAPD) appearance or changes related to disease progression in CRVO

The number of available data for the exploratory endpoints from patients were much lower than expected as well as collected with different machines for which the pooling of the data is not ot not easily possible. Based on this and thus the very limited representativeness of the data it was decided to not statistically evaluate them but only provide the assessed parameters in the listings in the appendix of the CSR

3 Study Design

3.1 Design Overview

This is an international, multi-center, prospective, interventional, single-arm, cohort Phase 4 study in adult subjects with a diagnosis of macular edemea secondary to CRVO who have previously not been treated with any systemic or IVT anti-VEGF treatments.

3.2 Inclusion/Exclusion

Main inclusion/exclusion criteria are as follows:

Treatment-naïve subjects ≥ 18 years of age with center-involved macular edema secondary to CRVO for no longer than 3 months before the first administration of study drug. Subjects must have documented best-corrected visual acuity (BCVA) of Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 73 to 24 letters (Snellen equivalent of 20/40 to 20/320) in the study eye.

The inclusion and exclusion criteria will be assessed during the screening phase. Details are available in the Clinical Study Protocol, Sections 6.1 and 6.2.

3.3 Visit Overview

This study comprises a screening period of up to 21 days and a treatment period of 76 weeks, which begins with an initiation phase followed by the T&E phase. The treatment period is up to the last T&E visit before the final study visit at Week 76. There will be prescheduled visits at baseline, Weeks 24, 52, and 76 (end-of-study visit). Other visits between baseline and Week 76 will depend on the applied posology of IVT aflibercept and the monitoring schedule for each subject. A ± 7-day window will be allowed for all post-baseline visits.

Table 9-1 of the Clinical Study Protocol gives a description of the planned assessments and study procedures.

3.4 Efficacy and Safety variables

The co-primary efficacy variables will be as follows:

- The proportion of subjects who gain ≥ 15 letters in BCVA on the ETDRS chart compared with baseline at Week 76
- The proportion of subjects with a mean treatment interval between injections of ≥ 8 weeks from the last actual visit of the initiation phase to Week 76

A complete list of all efficacy variables is provided in Section 6.2.

The primary and secondary efficacy variables assessed at Weeks 24, 52, and 76 will use last observation carried forward (LOCF) method. The primary efficacy variable analysis will be conducted on the Full Analysis Set and Per-protocol Set as defined in Section 5.1.

Assessments of ocular safety will include tonometry, indirect ophthalmoscopy, slit lamp biomicroscopy, and gonioscopy.

Overall safety of the subjects will be assessed throughout the study by recording vital signs as well as by monitoring adverse events (AEs) and ophthalmological parameters.

Safety variables are provided in Section 6.4.

4 General Statistical Considerations

4.1 General Principles

The first version of the SAP of this open-label study was finalized before FPFV to avoid additional reporting bias. The current version takes recent changes in eCRF into account, clarifies and is finalized before database-lock.

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation (SD), minimum, quartiles, median, and maximum will be calculated for metric data.

Frequency tables will be generated for categorical data. For categorical variables, the number and percentage of patients with a specific level of the variable will be presented. These include the counts and percentages of each category including the category 'missing' as a separate category, if applicable. Percentages will be calculated using a denominator of all subjects in the specified population.

4.2 Handling of Dropouts

Subjects must or might be withdrawn from the study for different reasons, which are specified in the protocol in Section 6.3.1.

Depending on the time point of withdrawal, a withdrawn subject is referred to as either "screening failure" or "dropout" as specified below:

Screening failure

A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" (see below) is regarded a "screening failure".

Drop-out

A subject who discontinues study participation prematurely for any reason is defined as a "drop-out" if the subject has already received IVT aflibercept.

The number of screening failures and drop-outs as well as the respective reasons will be summarized. Data from subjects who drop-out of the study will be included in all summaries where possible.

4.3 Handling of Missing Data

All missing or incomplete data will be presented in the subject data listings as they are recorded on the Case Report Form (CRF). In general missing or incomplete data will not be substituted or replaced, except for the parameters described below and in Section 6.2 for efficacy analysis.

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

- **Safety variables**

  In general, data will not be imputed for safety analysis. If dates of adverse experiences (clinical or laboratory untoward events) are missing so that the determination of whether or not the event is treatment emergent is questionable, the event will be presumed to be treatment emergent.

- **Prior and concomitant medication**

  Completely missing start and stop dates of medication are considered missing and no replacement is generated. A medication with a complete missing start date will be assumed to start before first application of the study drug. A complete missing stop date will be handled as "ongoing".

  In addition, to flag the medications correctly, the worst-case scenario will be used:

  - for incomplete start dates: if only day is missing - first of month, if day and month missing - first day (1st January) of year.
  - for incomplete stop dates: if only day is missing - last of month, if day and month missing - last day (31st December) of year or "ongoing", when last day of year is after last study-day of the subject.

- **Efficacy variables**

  Efficacy analysis imputations will use LOCF for subjects in analysis populations. Multiple imputations (MIs) for missing values will additionally be performed on the primary and key secondary efficacy variables (see Section 6.2.1.4).

4.4 Interim Analyses and Data Monitoring

No interim analysis and no data safety monitoring are planned.

4.5 Data Rules

Determination of baseline values

Generally, pre-treatment values recorded at Visit 2 (Day 1) will be used as baseline values. This visit should take place within 3 weeks of the screening visit. However, according to the Clinical Study Protocol Section 9.2, screening and baseline visits can be combined. In case screening and baseline are combined or no baseline value is available, then last available screening values are used. Change

from baseline is calculated as the value at the post-baseline time point minus the baseline value, i.e. value at time point – value at baseline.

Handling of repeated measurements at the same visit

If measurements are repeated at the same scheduled visit, the value actually flagged as scheduled will be the

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

Generally, only scheduled measurements will be used for statistical summaries and analysis. Unscheduled measurements will not be used for analysis, but only listed.

Handling time-windows

The screening visit must occur within 3 weeks of the baseline visit (Day 1). Screening values collected more than 3 weeks before baseline will be flagged in the patient listings, however they will still be used for summary tables and analysis..

There will be prescheduled visits at baseline, Weeks 4, 24, 52, and 76 (end-of-study visit). Other visits between baseline and Week 76 will depend on the applied posology of IVT aflibercept and the monitoring schedule for each subject. A ± 7-day window will be allowed for all post-baseline visits.

The initiation phase of the treatment will extend from the first injection until the subject meets retreatment interval extension criteria as summarized in Section 7.1.3 in the Clinical Study Protocol.

Table 2: Time Windows

Analysis time point	Study days range
Screening	–21 to 1
Baseline (prescheduled)	1
Week 4 (prescheduled)	22 to 36
Week 5-8	37 to 59
Week 9-16	60 to 116
Week 17-23	117 to165
Week 24 (prescheduled)	166 to 172
Week 25-32	173 to 228
Week 33-40	229 to 284
Week 41-48	285 to 340
Week 49-51	341 to 361
Week 52 (prescheduled)	362 to 368
Week 53-60	369 to 424
Week 61-68	425 to 480
Week 69-75	481 to 529
Week 76 (prescheduled)	530 to 536
> Week 76	> 536

The screening and baseline visits can be combined. The necessary procedures can be performed on separate days. There will be a 7-day window allowed for all procedures to be completed in such a combined visit. If screening and baseline occur on the same visit, pregnancy test results and reading center evaluations need to be available prior to treatment with study drug.

In case of multiple scheduled visits in a specific time-window the following procedures will be performed to get only one value per subject in a window:

- Efficacy variables: the measurement of the last scheduled visit before or at the upper bound of the time interval will be displayed in each time interval.
- Safety variables:
    - Intra-ocular pressure (IOP): The highest values will be used.
    - Indirect ophthalmoscopy: “Abnormal” values and their descriptions will be used, if available, and the highest grading/numbers of vitreous cells.
    - Slit lamp biomicroscopy: “Abnormal” values and their descriptions will be used, if available, and the highest grading/numbers of anterior chamber flare or cells.
    - Vital signs: The highest values will be used.

Early termination

Visit-based information of the early termination visit will be mapped to the next (not unscheduled) visit if the visit was performed 2 weeks (± 1 week) after the last scheduled visit. This can result in data for visits at which this variable was not scheduled to be collected. This data will nevertheless be included into the (LOCF) analyses and be reported as observed value for the respective visit.

Early termination visits outside this window will not be used for analyses and will be handled in the same way as unscheduled assessments (see above) and the data will only be shown in the patient listings.

Pooling centers

Not applicable as no analysis by study center will be conducted. All centers will be combined for the purposes of the analysis.

Calculation of durations

Durations are calculated relative to baseline, if not specified otherwise. Durations will be presented and used (e.g. in summary tables) as days, weeks, months, or years.

The integer value of the durations will be listed and summarized, if not specified otherwise.

Coding

The verbatim of the following panels will be coded by the latest version of Medical Dictionary for Regulatory Activities (MedDRA) available before database lock

- Medical history
- Adverse events
- Surgeries after start of study

Prior and concomitant medications will be coded by the latest version of World Health Organization Drug classification Dictionary (WHO-DD) available before database lock.

Presentation

Listings will be sorted by unique subject identifier and analysis time point and/or date if applicable.

Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on CRFs.

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. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending 5-9 up will be employed.

Every table, listing, and figure will be produced with an electronic date stamp to document when it was produced.

4.6 Validity Review

Validity Review Meetings are performed according to Bayer Standard Operating Procedures (SOP) and will be led by the Syneos Health Lead Data Manager. Details are available in the Data Management Plan.

The results of the validity review meeting will be documented in the Validity Review Report and may comprise decisions and details relevant for statistical evaluation. Any changes to the statistical analysis prompted by the results of the validity review meeting will be documented in an amendment and, if applicable, in a supplement to this SAP.

5 Analysis Sets and Subgroups

5.1 Assignment of analysis sets

Final decisions regarding the assignment of subjects to analysis sets will be made during the Validity Review Meeting and documented in the Validity Review Report (see Section 4.6).

Populations for analysis will be defined as follows:

Full Analysis Set (FAS)

The FAS will include all enrolled subjects who receive any study drug, have a baseline BCVA assessment, and have at least 1 post-baseline BCVA assessment. With regard to the efficacy evaluation of this study, the FAS is considered the primary analysis.

Per-protocol Set (PPS)

The PPS will include all enrolled subjects who receive any study drug, have a BCVA assessment at study baseline, have at least 1 BCVA assessment at Week 24 or later, and do not have a major protocol deviation. The detailed definitions and the assignment of subjects to this analysis set will be based on the validity review meeting and the protocol deviations document.

Safety Analysis Set (SAF)

The SAF will include all subjects who receive any study drug.

5.2 Definition of subgroups

A subgroup analysis will be performed for each country contributing at least 5 patients to the FAS on both co-primary variables (see Section 6.2.1.1).

A subgroup analysis for subjects classified by mean treatment intervals (< 8 weeks, ≥ 8 weeks) between injections from the last actual visit of the initiation phase to Week 76 will be conducted in the FAS on the first co-primary variable (see Section 6.2.1.1).

6 Statistical Methodology

6.1 Population characteristics

Population characteristics will be summarized depending on the type of data as described in Section 4.1, if not specified otherwise.

For the Screening failures, the reason for the exclusion from study will be summarized and listed. Demographic and disposition data will be displayed in patient listings.

For screening failures with a serious AE (SAE), all information related to any AE or SAE will be listed.

Efficacy data from Screening failures will neither be summarized nor listed.

6.1.1 Study periods and sample sizes

Number of subjects enrolled and valid for the different analysis populations will be displayed in total and per trial unit.

Major protocol deviations will be summarized per category given in the latest available Protocol Deviation Document.

6.1.2 Subject validity status

An overview table will be given, displaying the number and percentages of subjects:

- Screening (failure/pass)
- Safety analysis set (SAF)
- SAF, but not FAS (by reason)
- Full analysis set (FAS)
- FAS, but not PPS (by reason)
- Per protocol set (PPS)

6.1.3 Subject Disposition

Subject disposition at the end of screening will be presented for all enrolled subjects, including number of subjects who completed screening period and entered treatment period or did not enter treatment period. The primary reason for withdrawal from treatment period will be summarized.

Another table will describe the subject disposition at end of treatment for SAF, including the number and percentages of subjects:

- Completed treatment
- Not completed treatment
- Reason for Withdrawal
    - Reason 1
    - Reason 2
    - …
- Time until Withdrawal

- Withdrawal until Week 24
- Withdrawal after Week 24 but before Week 52
- Withdrawal after Week 52

Similarily, a table with respect to the end of study will be created for SAF.

6.1.4 Demography

Demographic variables will be summarized for SAF, FAS and PPS and listed for all subjects, with screening failures on a separate page.

The following demographic parameters will be summarized:

- Sex
- Age
- Race
- Ethnicity
- Weight
- Height
- Body mass index (BMI)
- Study eye - left or right

6.1.5 Baseline Characteristics

The following baseline characteristics of the study eye are observed at screening and/or baseline. In case of repeated measures the last available value before first application of the study drug will be used for summary tables for SAF, FAS and PPS.

- BCVA letter scores
- BCVA letter scores - categorized (5 letters ranges)
- Central retinal thickness (CRT)
- Refraction sphere (dpt)
- Capillary nonperfusion from fluorescein angiography
- Gonioscopy

The number and percentages of the subgroups defined in Section 5.2 will be presented in a separate table for FAS.

6.1.6 Medical history

Medical history will be summarized for SAF and listed for all subjects, with screening failures on a separate page.

Overall medical history will be summarized based on the MedDRA version available before database lock. The number and percentages of subjects affected will be displayed. The following variables are of interest:

- Any medical history
- System Organ Classes (SOCs)
- Preferred Terms (PT)

The SOCs will be sorted by descending frequency of subjects, within each SOC the PT will be sorted by descending frequency of subjects affected.

The table will be presented overall, by ocular medical history (yes/no), by eye (study eye, fellow eye).

6.1.7 Prior and concomitant medication

Prior and concomitant medication will be summarized for SAF and listed for all subjects, with screening failures on a separate page.

Summaries of all prior and concomitant medications recorded will be presented in tabular form using 3-digit Anatomical Therapeutic Chemical Classification (ATC) classification codes and preferred drug name via the WHO-DD, latest version available before database lock.

The medications will be classified as.

- Concomitant: Medications that are ongoing at, began after the start of study drug, or medications that were started up to 30 days after end of study drug.
- New Concomitant: Medications that began after the start of study drug, and those that were started up to 30 days after end of study drug.
- Prior: Medications that started and stopped before the start of study drug.

Medication that is started more than 30 days after end of study will be listed as post-treatment medication.

Each of these categories will be summarized by medication class and preferred name and sorted by descending frequencies. The tables will be displayed overall, by ocular medication (yes/no) and eye (study eye/fellow eye).

6.1.8 Exposure

The number of injections per subject will be tabulated, classified (1-5, 6-10, >10), and presented as a metric variable, see Section 4.1. In addition, the total amount of study drug injected (mg), the number of injections per subject year and the duration of study drug exposure will be summarized.

The number of injections per subject year is calculated as 52*(Number of IVT injections) / (Number of weeks participating in the study). Study drug exposure in weeks is defined as (date of last injection – date of first injection + 28) / 7.

This table will be performed on SAF, FAS and PPS.

6.2 Efficacy

Assessments of efficacy will include BCVA, SD-OCT, and FA/FP procedures. At selected sites where instrumentation and technical competence is available, assessments will also include wide-field FA, OCT angiography, and full-field ERG.

The following co-primary, secondary and exploratory variables will be assessed:

Co-primary efficacy variables:

- The proportion of subjects who gain ≥ 15 letters in BCVA on the ETDRS chart compared with baseline at Week 76

- The proportion of subjects with a mean treatment interval between injections of ≥ 8 weeks from the last actual visit of the initiation phase to Week 76

Secondary efficacy variables:

- The change in BCVA as measured by the ETDRS letter score from baseline to Weeks 24, 52, and 76
- The change in CRT from baseline to Weeks 24, 52, and 76
- The number of injections from baseline to Week 76
- The mean treatment interval between injections from baseline to Week 76
- The proportion of subjects who gain ≥ 15 letters in BCVA on the ETDRS chart compared with baseline at Weeks 24 and 52
- The change in retinal perfusion (FA/FP) status from screening / baseline to Weeks 24, 52 and 76
- The proportion of subjects with absence of fluid at Weeks 24, 52, and 76

Exploratory efficacy variables as defined in the protocol:

- Perfusion status of the retina assessed by wide-field FA at screening/baseline, Weeks 24, 52, and 76
- OCT angiography measures for assessing perfusion status of the retina and examination of morphological changes related to disease progression in CRVO at baseline, Weeks 24, 52, and 76
- Full-field ERG assessments at baseline, Week 24, Week 52, and Week 76
- Status of RAPD at baseline, Weeks 24, 52, and 76

6.2.1 Co-Primary Efficacy Variables

6.2.1.1 The proportion of subjects who gain ≥ 15 letters in BCVA on the ETDRS chart compared with baseline at Week 76

The BCVA values range from 0 to 100.

Subjects will be considered to be fulfilling this criterion if they show a change from baseline to Week 76 in BCVA of greater than or equal to 15 letters.

All subjects who drop out of the study will be deemed to have not met the co-primary efficacy variable, except for the following:

If the investigator assesses in a subject who drops out after Week 24 resolution of macular edema secondary to CRVO with no need for further treatment with IVT aflibercept, the change from

baseline to the last measurement of BCVA for this subject will be categorized using the LOCF methodology[1].

Missing ETDRS BCVA letter scores will be replaced by LOCF using the last available scheduled post-baseline values. After the imputation the respective dataset will be filled and the data will be analyzed as if the missing values have been observed (as the last available value).

LOCF is considered to be conservative because subjects dropping out due to lack of efficacy might be stable and only a responder if having gained 15 letters before dropping out.

6.2.1.2 The proportion of subjects with a mean treatment interval between injections of ≥ 8 weeks from the last actual visit of the initiation phase to Week 76

The co-primary efficacy variable of the proportion of subjects with a mean treatment interval between injections of ≥ 8 weeks from the last actual visit of the initiation phase to Week 76 will be assessed as follows:

- For subjects completing the study to Week 76, the mean treatment interval between injections from the last actual visit of the initiation phase to Week 76 will be calculated as follows:

  (date of last injection up to and including Week 76 visit – date of last actual visit of initiation phase)/(number of injections taken from last visit of initiation phase until immediately prior to the Week 76 visit – 1)

- Should the mean treatment interval for a subject between injections from the last actual visit of the initiation phase to Week 76 be ≥ 56 days, then the mean treatment interval is deemed to be ≥ 8 weeks and the co-primary efficacy variable has been met, if the mean is < 56 days, then the co-primary efficacy variable has not been met for this subject.

- All subjects who drop out of the study will be deemed to have not met the co-primary efficacy variable, except for the following:

  - Subjects who drop out after Week 24 and who are defined by the investigator as having a permanent resolution of macular edema are considered to have met the co-primary efficacy variable. For subjects considered by the investigator to have a permanent resolution of macular edema, at least 1 additional confirmatory visit is required (after a minimum interval of 8 weeks from the visit when resolution was determined and up to the regular Week 76 visit).

The approach to handle discontinued subjects is considered sufficiently conservative with regard to assessing mean treatment interval. The number and percentage of subjects who gain ≥ 15 letters in BCVA on the ETDRS chart compared with baseline at the Week 76 variable and the subjects with a

[1] As proof of permanent resolution of macular edema, at least 1 additional, confirmatory monitoring visit is required (after a minimum of 8 weeks and no later than the Week 76 visit). Any additional CRT and BCVA measurements at subsequent visits need to be consistent with the permanent resolution of macular edema as well. In case these conditions are not fulfilled, the respective subject is considered to have not met the variable.

mean treatment interval between injections of ≥ 8 weeks from the last actual visit of initiation phase to Week 76 will be presented, and, in addition, the mean and median treatment interval and frequency from baseline to Week 76, and during the T&E phase, will be described based on 95% confidence intervals (CIs).

6.2.1.3 Primary analysis for the co-primary efficacy variables

By means of evaluating both co-primary variables, the exact 1-sample binomial test will be used for both co-primary variables using FAS.

Study success requires proof that both a gain of ≥ 15 letters in BCVA at Week 76 is reached by more than 40% of subjects and, additionally, 50% of subjects have a mean treatment interval of ≥ 8 weeks in the T&E phase.

In further explanations, the null hypothesis for evaluation of the co-primary variable 1 (proportion of subjects with gain of ≥ 15 letters in BCVA at Week 76) will be labeled as H_{01}, the alternative hypothesis as H_{11}.

Similarly, for evaluation of the co-primary variable 2 (proportion of subjects with a mean treatment interval of ≥ 8 weeks), the null hypothesis will be labeled as H_{02}, while the alternative hypothesis will be labeled as H_{12}.

Then, the primary hypothesis H_0 will be tested statistically[2], as:

- H_0: H_{01}: $p_1 \leq 40\%$ or H_{02}: $p_2 \leq 50\%$ versus
- H_1: H_{11}: $p_1 > 40\%$ and H_{12}: $p_2 > 50\%$

Where p_1 is the proportion of subjects with a ≥ 15-letter gain in BCVA at Week 76, p_2 is the proportion of subjects with a mean treatment interval of ≥ 8 weeks. The significance level α for this 2-sided test will be 5%.

Given the statistical paradigm of the intersection-union test, the test on H_0 can be performed as independent statistical tests on H_{01} and H_{02}.

For descriptive purposes, the co-primary efficacy variables will be summarized, including supportive 2-sided 95% CIs.

6.2.1.4 Sensitivity analysis for the co-primary efficacy variables

The primary efficacy variable analysis as described in Section 6.2.1.3 will be conducted based on the PPS, using LOCF for the first co-primary variable.

Additionally, the following sensitivity analyses will be performed on the FAS to support results of the primary analysis.

[2] In the study protocol the hypothesis was given by mistake as follows:
H_0: H_{01}: $p_1 < 40\%$ or H_{02}: $p_2 < 50\%$ versus
H_1: H_{11}: $p_1 \geq 40\%$ and H_{12}: $p_2 \geq 50\%$

In the correct mathematical notation the equality is part of the Null-hopthesis. This correction has no impact on the analysis-strategy, results and interpretation.

Subgroup analysis by length of treatment interval

The subgroup of subjects having a mean treatment interval of ≥ 8 weeks vs < 8 weeks will be analyzed with regard to gain of ≥ 15 letters in BCVA at Week 76 as a sensitivity analysis in FAS.

Subgroup analysis by country

A subgroup analysis of the primary variables will be performed for each country contributing at least 5 patients to the FAS.

Observed Cases (OC)

The primary method (LOCF) is considered to be conservative because subjects dropping out due to lack of efficacy are considered as stable.

Therefore, the primary analysis will be repeated on the observed values, i.e., only including patients that have a BCVA score result at Week 76 (+/- 7 days), i.e. without LOCF-imputation.

Multiple imputation (MI)

Multiple imputations (MI) for missing BCVA-values will be performed and used on the respective co-primary efficacy variable (see Section 6.2.1.1), as described below, `seed1=8357`, `seed2=99721`:

Multiple imputation methods involve three steps:

Imputation,
i.e., the generation of multiple copies of the original dataset by replacing missing values using an appropriate stochastic model.
First missing data will be imputed in order to achieve a monotone missing pattern using the Markov-Chain-Monte-Carlo method, using SAS-procedure proc MI similarly as below.

```
PROC MI DATA=<indata> SEED=<seed1> OUT=out1 NIMPUTE=20;
MCMC impute=monotone;
VAR base Week1 Week4 Week8 … ; RUN;
```

Subsequently missing data will be imputed by a regression model.

```
PROC MI DATA=out1 SEED=<seed2> OUT=full nimpute=1;
BY _Imputation_;
CLASS treatment;
MONOTONE method=reg;
VAR treatment base Week1 Week4 Week8 … ;
```

Analysis,
i.e., the analysis of the multiple imputed datasets as complete sets. The analysis step is performed for each of the multiply imputed datasets. Since all imputed datasets are complete there is no need to bother with any missing data. On each imputed dataset the primary and key secondary analysis will be performed. It should be clarified that classifications (gain of < 15 letters) will be performed after the imputation of the missing BCVA values.
Pooling,
i.e., the combination of the different parameter estimates across the multiple datasets based on Rubin's rules to produce a unique point estimate and standard error taking into account the uncertainty of the imputation process using SAS procedure proc MIANALYZE.

6.2.2 Secondary and Exploratory Efficacy Variables

The secondary and exploratory efficacy variable analysis will be conducted on the FAS.

6.2.2.1 Secondary efficacy variables

For the following change from baseline-based secondary efficacy variables, missing data will be imputed by means of the LOCF method. Sensitivity analyses for these variables will be provided based on MI as described for the primary variable. The respective seed numbers are pre-selected in brackets.

1. The change in BCVA as measured by the ETDRS letter score from baseline to
    a. Week 24,
    b. Week 52,
    c. Week 76 (MI: `seed1=61932, seed2=20056)`.
2. The change in CRT from baseline to
    a. Week 24,
    b. Week 52,
    c. Week 76 (MI: `seed1=1000, seed2=30864)`.
3. The proportion of subjects who gain ≥ 15 letters in BCVA on the ETDRS chart compared with baseline at Weeks 24 and 52. These will be calculated from using the values from 1.

These variables will be summarized descriptively as described in Section 4.1. The following two secondary efficacy variables will be summarized as described in Section 4.1 on the observed cases only:

4. The number of injections from baseline to Week 76
5. The mean treatment interval between injections from baseline to Week 76

For the following variables the exact 95%CI will be calculated:

6. The change in retinal perfusion (FA/FP) status, defined as a change from perfused (ischemia < 10 disc areas) to non-perfused (ischemia ≥ 10 disc area) or vice versa, from screening/baseline to Weeks 24, 52, and 76
7. The proportion of subjects with absence of fluid at Weeks 24, 52, and 76

For the change in retinal perfusion status, the number of subjects non-perfused at baseline will be compared with the number of subjects non-perfused at Week 24, Week 52, and Week 76 with shift tables. McNemar's test will be used, to describe the changes in the course of time.

6.2.2.2 Exploratory efficacy variables

Fluorescein Angiography (FA)/ Fundus Photography (FP) evaluations will be conducted in both eyes at screening/baseline, and in the study eye only at Weeks 24, 52, and 76, and the early termination visit (and in the fellow eye if there are signs of vein occlusion).

Wide-field FA, OCT angiography, and full-field ERG may be conducted, at selected study sites, in both eyes at baseline and in the study eye only at Weeks 24, 52, and 76, and the early termination visit (and in the fellow eye if there are signs of vein occlusion). The respective data will be collected for post-hoc analysis and will only be listed in the appendix of the CSR.

6.3 Pharmacokinetics/pharmacodynamics

Not applicable.

6.4 Safety

Safety parameters will be summarized as described in Section 4.1. The SAF will be used for the summary and listings of safety parameters.

The following safety variables are of special interest:

- Number and severity of systemic adverse events (AEs)
- Number and severity of ocular adverse events, which might all be detected by
  - tonometry,
  - indirect ophthalmoscopy,
  - slit lamp biomicroscopy, or
  - gonioscopy
- Percentage of subjects requiring panretinal photocoagulation (PRP) in the course of the study

6.4.1 Adverse Events (AEs)

The definitions of AEs and serious AEs (SAEs) are provided in the Clinical Study Protocol, Section 9.6.1.1. The classifications according to seriousness, intensity, causality, action taken, other specific treatment and outcome are provided in the Clinical Study Protocol, Section 9.6.1.2.

Treatment emergent adverse events (TEAEs) are AEs that start after the first application of aflibercept in the study. In addition, if it is clearly documented that the adverse event occurred more than 30 days after the last dose of study drug, it will be treated as not treatment emergent. The same rules apply due the surgeries.

A summary table will display the number and percentages of subjects with at least one

Any AE
Any AE causally related to study drug
Any AE causally related to intravitreal injection procedures
Any AE causally related to other protocol-required procedures
Maximun intensity for any AE
Maximum intensity for study drug-related AE
AE with outcome death
Any serious AE
Any serious AE causally related to study drug
Any serious AE causally related to intravitreal injection procedures
Any serious AE causally related to protocol-required procedures
Any APTC event
Discontinuation of study drug due to AE
Discontinuation of study drug due to serious TEAE

This overall summary will be repeated for

- Ocular AE in the study eye
- Ocular AE in the fellow eye
- Non-ocular AE
- TEAE
- Ocular TEAE in the study eye
- Ocular TEAE in the fellow eye
- Non-ocular TEAE

Number of subjects with TEAE will be presented by MedDRA PT within primary SOC for the following:

- All TEAE
  - Ocular TEAE in the study eye
  - Ocular TEAE in the fellow eye
  - Non-ocular TEAE
- All study drug-related TEAE
  - Ocular study drug-related TEAE in the study eye
  - Ocular study drug-related TEAE in the fellow eye
  - Non-ocular study drug-related TEAE
- All intravitreal procedure-related TEAE

- All serious TEAE
  - Ocular serious TEAE in the study eye
  - Ocular serious TEAE in the fellow eye
  - Non-ocular serious TEAE
- All serious study drug-related TEAE
  - Ocular serious study drug-related TEAE in the study eye
  - Ocular serious study drug-related TEAE in the fellow eye
  - Non-ocular serious study drug-related TEAE
- All serious intravitreal procedure-related TEAE
- All TEAE leading to discontinuation of study-drug
  - Ocular TEAE in the study eye leading to discontinuation of study-drug
  - Ocular TEAE in the fellow eye leading to discontinuation of study-drug
  - Non-ocular TEAE leading to discontinuation of study-drug
- All TEAE by maximum intensity
  - Ocular TEAE in the study eye by maximum intensity
  - Ocular TEAE in the fellow eye by maximum intensity
  - Non-ocular TEAE by maximum intensity
- All study-drug related TEAE by maximum intensity
  - Ocular study-drug related TEAE in the study eye by maximum intensity
  - Ocular study-drug related TEAE in the fellow eye by maximum intensity
  - Non-ocular study-drug related TEAE by maximum intensity
- All non-serious TEAE
  - Ocular non-serious TEAE in the study eye
  - Ocular non-serious TEAE in the fellow eye
  - Non-ocular non-serious TEAE
- All non-treatment emergent AE
  - Ocular non-treatment emergent AE in the study eye
  - Ocular non-treatment emergent AE in the fellow eye
  - Non-ocular non-treatment emergent AE
- All TEAE by worst outcome
  - Ocular TEAE in the study eye by worst outcome
  - Ocular TEAE in the fellow eye by worst outcome

- Non-ocular TEAE by worst outcome

Subjects may be counted under multiple SOCs and PTs, but for each SOC and PT, subjects are only counted once. SOCs will be sorted by descending frequency of subjects, within each SOC the PT will be sorted by descending frequency of subjects affected.

Potential arterial thrombotic events (ATEs) will be evaluated by an adjudication committee according to criteria formerly applied and published by the Anti-Platelet Trialists‘ Collaboration (APTC). The definition of ATEs as well as further details are described in the adjudication committee charter. They will be presented separately.

6.4.2 Indirect Ophthalmoscopy

At visits with study drug administration, pre-injection indirect ophthalmoscopy will be assessed for both the study eye and fellow eye. Post-injection assessments will be carried out in the study eye only.

Frequency tables for normal/abnormal findings for the study will be provided. The cup-to-disc ratio will presented by summary statistics.

6.4.3 Slit Lamp Biomicroscopy

The slit lamp examination is to be performed at all visits in both the study eye and the fellow eye irrespective of whether the fellow eye has signs of vein occlusion.

Frequency tables for normal/abnormal slit lamp biomicroscopy findings as well as for the grading of ‘anterior chamber flare’ and ‘anterior chamber cells’ will be provided for the study eye only.

6.4.3 Gonioscopy

The evaluation will be conducted at screening and at Week 76 and the early termination visit, and may be repeated if needed as determined by the investigator. Gonioscopy will be performed in the study eye only.

Frequency tables for normal/abnormal findings for the study will be provided.

6.4.4 Intraocular Pressure / Tonometry

Intraoculare pressure will be assessed for both the study eye and fellow eye at all scheduled visits.

At visits with study drug administration, pre-injection IOP will be assessed for both the study eye and fellow eye. Assessment of IOP 30-60 minutes following IVT injection will be carried out in the study eye only.

All IOP measurements will be classified as follows:

- > 25 mm Hg
- ≥ 30 mm Hg
- ≥ 35 mm Hg
- ≥ 40 mm Hg

Any increase from baseline of ≥ 10 mm Hg will be flagged.

The IOP summaries will include

- original measurements

- changes from baseline
- classified measurements
- flagged measurements

This analysis will be performed descriptively at all visits depending on the type of data as described in Section 4.1.

Additionally for the study eye, the changes of the measurements between pre- and post-injection will be analysed descriptively depending on the type of data as described in Section 4.1.

6.4.5 Subjects requiring panretinal photocoagulation in the course of the study

Panretinal photocoagulation (PRP) during the study will be captured in “Surgery after the study” page in CRF.

Number and percentages of subjects requiring PRP during the study will be presented in frequency tables.

6.4.6 Pregnancy test

Results of the pregnancy tests will be listed only.

6.4.7 Vital Signs and BMI

Vital signs (body temperature, blood pressure [diastolic and systolic] and heart rate),will be summarized as described in Section 4.1 during the course of the study.

7 Document history and changes in the planned statistical analysis

The main changes to Statistical Analysis Plan, version 1.0, 20th June 2016 are as follows:

a) Section 4.1: clarifications for displaying TFLs according to Bayer standards

b) Section 4.3: clarification of handling missing start- and stop-dates

c) Section 4.5: correction of time-windows and clarification of handling repeated measurements

d) Section 5.2: already defined subgroups in a separate section

e) Section 6.1: clarification of presentation of population characteristics, especially

- Section 6.1.5: drop of some baseline characteristics which are not applicable anymore
- Section 6.1.8: including “injections per subject year”

f) Section 6.2.1.1: clarification of LOCF main analysis.

g) Section 6.2.2.: exploratory variables will only be listed

h) Section 6.4.1:

- adaption of “treatment-emergent” to apply for a 30-day window
- adaption and calrification of presentation the Adverse Events summaries

i) Section 6.4.2: adaption and clarification of presentation

j) Section 6.4.3: adaption and clarification of presentation

k) Section 6.4.4: adaption and clarification of presentation

l) Section 6.4.6: adaption and clarification of presentation

The main changes to Statistical Analysis Plan, version 2.0, 31st January 2019 are as follows:

m) Section 6.1.6: number of events will not be displayed.

n) Section 6.2.1.3: Primary hypothesis corrected – typo in study protocol has been copied over in previous SAP versions.

o) Section 6.2.2.1:

- No separate seeds needed for the multiple imputations of Week 24 and Week 52 analysis.
- McNemar’s methodology, relative risk and CI are not applicable here and will be dropped.
- McNemar’s test can only be provided for the change in retinal perfusion status, to describe the changes in the course of time.

8 References

1. Integrated Clinical Study Protocol No. BAY86 5321/17514: A multi center, single arm, interventional Phase 4 study to evaluate a Treat and Extend regimen of intravitreal aflibercept for treatment of macular edema secondary to central retinal vein occlusion. Version 2.0, 20 Apr 2016, Bayer HealthCare AG, D 51368 Leverkusen, Germany.