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Managing neovascular age-related macular degeneration (nAMD) over 2 years with a Treat and Extend (T&E) regimen of 2 mg intravitreal aflibercept - a randomized, open-label, active-controlled, parallel-group phase IV/IIIb study (ARIES)

Managing nAMD with a T&E aflibercept regimen

Bayer study drug	BAY86-5321/aflibercept / VEGF Trap-Eye (Eylea)		
Study purpose:	To assess whether 2 mg IVT aflibercept administered in an early-start T&E regimen (initiated after the first 8-weekly treatment interval) is non-inferior to 2 mg IVT aflibercept administered in a late-start T&E regimen (initiated at the end of Year 1, per label) in subjects with nAMD		
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The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

2Q8	2 mg aflibercept administered every 8 weeks
AE	Adverse event
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
APTC	Antiplatelet Trialists' Collaboration
ATC	Anatomical Therapeutic Chemical
ATE	Arterial thromboembolic event
BCVA	Best-corrected visual acuity
CI	Confidence interval
CNV	Choroidal neovascularization
CRT	Central retinal thickness
eCRF	Electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	Fluorescein angiography
FAS	Full Analysis Set
FP	Fundus photography
IOP	Intraocular pressure
IRF	Intraretinal fluid
IVT	Intravitreal
LOCF	Last observation carried forward
LS	Least squares
MI	Multiple imputations
MedDRA	Medical Dictionary for Regulatory Activities
nAMD	Neovascular age-related macular degeneration
OCT	Optical coherence tomography
PPS	Per-protocol Set
PRN	As needed (pro re nata)
PT	Preferred term
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SF	Screening Failure
SOC	System organ class
SRF	Subretinal fluid
T&E	Treat and extend

TEAE	Treatment-emergent adverse event
US	United States
V	Visit
VEGF	Vascular endothelial growth factor
VRM	Validity Review Meeting
WHO-DD	World Health Organization Drug classification Dictionary
Wk	Week

1. Introduction

This SAP describes both the analyses described for final analysis after all patients have completed the study (Year 2), which is the time point of the primary and secondary endpoints, as well as the analyses planned for the exploratory interim analyses after the first year of treatment. Wherever appropriate, analyses that had been planned for the final analysis after year two will be performed analogously for the interim analysis. All analyses at the interim time point are purely exploratory.

1.1 Background

Age-related macular degeneration (AMD) is a leading cause of adult blindness in the developed world. Age-related macular degeneration has a dry and a wet form, the latter of which accounts for most AMD-related cases of blindness and is referred to as neovascular AMD (nAMD). Severe vision loss from nAMD is caused by a combination of retinal edema and neovascular proliferation. Vascular endothelial growth factor (VEGF), a protein growth factor that both stimulates angiogenesis and increases vascular permeability, is a major pathogenic factor in AMD. Anti-VEGF therapy has been shown to provide significant therapeutic benefit to patients suffering from nAMD.

Aflibercept is a potent, specific inhibitor of VEGF with a high affinity for all isoforms of VEGF and placental growth factor. To date, aflibercept has been approved as a treatment for nAMD, diabetic macular edema, and macular edema secondary to branch or central retinal vein occlusion in the United States (US), European Union (EU), Japan and many other countries; as well as for myopic choroidal neovascularization in the EU, Japan and several other countries; and for diabetic retinopathy in patients with diabetic macular edema in the US.

Further details can be found in the latest available version of the investigator's brochure, which contains comprehensive information on the study drug.

The approved European Union (EU) labeling for Eylea (aflibercept) states:

> The recommended dose for Eylea is 2 mg aflibercept, equivalent to 50 microliters.
>
> Eylea treatment is initiated with one injection per month for three consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections.
>
> After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections.

1.2 Rationale of the study

The use of anti-VEGF agents for nAMD has become the standard of care. The frequency of dosing for monthly anti-VEGFs has introduced a burden of illness on patients and caregivers as well as capability constraints on physicians in practice.

Physicians have developed a practicing trend towards individualizing treatment to reduce the burden and minimize reimbursement issues and healthcare costs. The current individualized treatment gaining momentum with practicing physicians is referred to as treat and extend (T&E). In the T&E dosing paradigm, the subject is injected at every visit and the follow-up examination intervals are incrementally extended according to the response to treatment.

This study has been designed to assess whether intravitreal (IVT) aflibercept administered in an early-start T&E regimen (initiated after the first 8-weekly treatment interval) is non-inferior to IVT aflibercept administered in a late-start T&E regimen (initiated at the end of Year 1, per the approved EU label for Eylea) in subjects with nAMD. In addition, the percentage of subjects requiring retreatment with IVT aflibercept less frequently than every 8 weeks (2Q8), as well as safety and tolerability, will be assessed.

1.3 Benefit-risk assessment

The risks of the local IVT application are limited to ocular adverse events (AEs).

Due to the low systemic level of aflibercept after IVT injection, systemic pharmacodynamic effects such as blood pressure changes are unlikely.

Proteinuria and hypertension are potential systemic effects from intravenous or subcutaneous administration of this class of drug; however, the low systemic blood levels observed in previous IVT studies suggest that direct IVT injection, at the dose levels proposed for this study, are not expected to have clinically significant systemic effects.

In addition, arterial thromboembolic events (ATEs) are AEs potentially related to systemic VEGF inhibition. The risks associated with IVT administration of aflibercept observed in the Phase 3 studies are thought to be similar to those of IVT administration of pegaptanib sodium and ranibizumab.

This study will generate evidence regarding the benefits of early T&E regimen initiation (i.e. initiation in the first year compared to initiation in the second year per the label) in order to provide optimal management of the patient without compromising visual outcomes. Strict extension criteria ensure that the benefit-risk ratio in this study is favorable.

1.4 List of documents used

- Clinical Study Protocol No. BAY86-5321/17508, version 2.0, 02 February 2016

2. Study Objectives

Primary objective

To assess whether 2 mg IVT aflibercept administered in an early-start T&E regimen (initiated after the first 8-weekly treatment interval) is non-inferior to 2 mg IVT aflibercept administered in a late-start T&E regimen (initiated at the end of Year 1, per label) in subjects with nAMD

Secondary objectives

- To assess the percentage of subjects requiring retreatment with aflibercept less frequently than every 8 weeks (2Q8)
- To assess the safety and tolerability of aflibercept

3. Study Design

3.1 Design overview

This is a multicenter, randomized, open-label, active-controlled, parallel-group, Phase IV/IIIb study in subjects with nAMD to assess the non-inferiority of a 2-mg IVT aflibercept T&E dosing regimen initiated after the first 8-weekly treatment interval (2Q8) to a 2-mg IVT aflibercept T&E dosing regimen per label (treatment individualization after Year 1).

In total, approximately 268 subjects in Europe, Canada, and Australia will be treated at baseline. The study duration will be 104 weeks plus the recruitment period.

3.2 Visit overview

The study comprises a screening phase of up to 3 weeks (Visit 1; -3 weeks to baseline), a baseline visit (Visit 2, Week 0/Day 1), and a treatment phase of 104 weeks.

Only 1 eye will be designated as the study eye. Starting at baseline (Week 0/Day 1), aflibercept 2 mg IVT treatment will be administered to the study eye every 4 weeks during the initiation phase (3 initial monthly doses at Weeks 0, 4, and 8). At Week 8, the treatment interval will be extended by 4 weeks (i.e. the next injection will take place at Week 16). If subjects require injections at shorter intervals before or at Week 16 than defined per protocol, the subjects will not be randomized at Week 16 but withdrawn from the study.

At Week 16, subjects will be stratified based on visual outcomes from baseline to Week 16 (either <8 or ≥8 letters gain in best-corrected visual acuity [BCVA]) and randomized 1:1 into 1 of the following 2 arms:

- In the **early-start T&E arm** (test group, early treatment individualization), starting at Week 16, subjects will receive treatment in intervals extended by 2 weeks each time

(up to a maximum of 16 weeks), as long as all anatomical criteria are met. For subjects who have no intraretinal fluid (IRF) and no subretinal fluid (SRF) at Week 16 ("completely dry at Week 16"), confirmed by the Central Reading Center, the treatment interval will be extended by 4 weeks for a total of 12 weeks (i.e. schedule next visit at Week 28). From Week 28 onwards, the normal extension algorithm will be applied.

- In the **late-start T&E arm** (per label, control group, treatment individualization after Year 1), subjects will receive treatment every 8 weeks to the end of Year 1 (4 x 2Q8 injections at Weeks 24, 32, 40, and 48). Then in Year 2 (starting from Week 48) the treatment intervals will be extended by 2 weeks each time (up to a maximum of 16 weeks), as long as all anatomical criteria are met.

The anatomical criteria for extending the treatment intervals for the study eye, based on optical coherence tomography (OCT), are as follows for both study arms:

- Absence of intraretinal fluid (IRF) and
- Absence of new neovascularization or hemorrhage and
- Subretinal fluid (SRF) not exceeding 50 µm in thickness

The investigator assesses whether the subject fulfills the anatomical criteria for treatment interval extension and determines the next treatment interval. If the anatomical criteria are not met, the retreatment interval will revert to the last treatment interval in which the disease was inactive. The subject will have all assessments during the proactive extension phase as described in Section 3.3.

After Week 16 (randomization), the treatment intervals will not be less than 8 weeks nor more than 16 weeks with the following exception:

- if, at any visit after Week 16, the subject has lost 15 or more letters from the best previous BCVA and the actual BCVA is not better than at baseline; or,

- if the investigator determines and documents that the subject's condition necessitates more frequent injections than 2Q8.

Such subjects will be considered "injection-intensive", remain in the study, and be treated according to the investigator's best clinical judgment (i.e. the frequency of IVT aflibercept injections is determined by the investigator who is free to subsequently adopt a T&E regimen similar to the per-protocol one, if deemed appropriate for the subject; however, the treatment intervals should not be less than 4 weeks).

Due to the per-protocol variability of treatment intervals, subjects may receive their last Year 1 and Year 2 injections at any time between Weeks 42 and 52 (for Year 1) and Weeks 90 and 104 (for Year 2). In case these visits do not occur at Weeks 52 and 104

(±1 week), subjects will return at Weeks 52 and/or 104 for mandatory visits, where no study drug is administered, but where examinations are performed from which the primary and secondary outcomes are determined.

If a subject receives an injection at Week 104, it is the responsibility of the treating investigator to follow-up on any AEs (including ongoing events) that may occur within 30 days following this treatment.

The end of the study as a whole will be reached as soon as the last visit of the last subject has been reached in all centers in all participating countries (European Union [EU] and non-EU).

The primary completion event for this study is the final study visit at Week 104.

3.3 Assessments overview

Overall safety of the subjects will be assessed throughout the study by monitoring ocular and non-ocular adverse events (AEs). All potential ATEs will be adjudicated according to the Antiplatelet Trialists' Collaboration (APTC) endpoints of non-fatal myocardial infarction, non-fatal stroke, and fatal vascular events. For the interim analysis APTC-adjudication will not be performed.

Vital signs will be assessed at all study visits.

All ocular assessments are to be conducted in both eyes, unless indicated otherwise.

Assessments of ocular safety will include

- intraocular pressure (IOP),
- indirect ophthalmoscopy, and
- slit lamp biomicroscopy;

these will be assessed at all study visits.

Assessments of efficacy are

- BCVA
- OCT
- Fluorescein angiography (FA)/fundus photography (FP)

BCVA and OCT will be performed at every visit, whereas mandatory FA-/FP-examinations will only be conducted at screening and at Weeks 52 and 104/early termination. However, the treating investigator may perform FA/FP at other times of the study based on his/her medical judgment and standard of care.

Table 1: Schedule of Evaluations and Study Procedures

Study Phase		**Initiation phase**		**Random.**	**Proactive extension phase**		
Treatment Arms	**All Subjects**				**Early-start T&E Arm[a]**	**Late-start T&E Arm[a]**	**All Subjects**
Visit[b]/Wk[c]	**Screening V1 Wk -3 to 0**	**Baseline V2 Wk 0 (Day 1)**	**V3, 4 Wk 4, 8**	**V5 Wk 16**	**Visits extended by anatomical criteria[d]**	**Year 1: Wk 24, 32, 40, 48 Year 2: Visits extended by anatomical criteria[d]**	**End of study/ Wk 104 or Early termination**
Mandatory visits	**Wk -3 to 0**	**Wk 0**	**Wk 4, 8**	**Wk 16**	**Wk 52[e]**	**Wk 52[e]**	**Wk 104[e]**
Informed consent	X						
Inclusion/exclusion criteria	X	X					
Demographic data	X						
Medical/ophthalmic history	X						
Physical examination	X						
Pregnancy test[f]	X	X	(X)[g]	(X)[g]	(X)[g]	(X)[g]	(X)[g]
BCVA using ETDRS chart[h]	X	X	X	X	X	X	X
OCT	X	X	X	X	X	X	X
FA/FP[i]	X				X (Wk 52 only)	X (Wk 52 only)	X
AEs[jk]	X	X	X	X	X	X	X
Indirect ophthalmoscopy[k]	X	X	X	X	X	X	X
Slit lamp biomicroscopy	X	X	X	X	X	X	X
IOP[k]	X	X	X	X	X	X	X
Vital signs[l]	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X
Randomization				X			
Administration of study treatment[m]		X	X	X	X	X	X[n]
Determination of next treatment interval[o]				X[p]	X	X[q]	
Telephone safety check[r]		X	X	X	X	X	X

2Q8 = 2 mg aflibercept administered every 8 weeks; AE = adverse event; BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluorescein angiography; FP = fundus photography; IOP = intraocular pressure; IVT = intravitreal; OCT = optical coherence tomography; random. = randomization; T&E = treat and extend; V = visit; Wk = week.

Note: All ocular assessments are to be conducted in both eyes, unless indicated otherwise.

a: Three initial monthly IVT aflibercept injections (initiation phase) followed either by one 8-weekly dose (2Q8) in the early-start T&E arm or by five 8-weekly doses (2Q8) in the late-start T&E arm. The treatment interval may then be extended by 2 weeks each time (individualized treatment intervals of between 8 to16 weeks) based on anatomical outcomes. When/if anatomical outcomes indicate that the disease has re-activated, the treatment interval will revert to the last treatment interval in which the disease was inactive (i.e. no signs of exudation). For details on treatment intervals see Section 5 of study protocol version 2.0, 02 Feb 2016.
b: Visit numbers refer to the mandatory visits for treatment administration to subjects for the 3 initial monthly doses at Weeks 0, 4, and 8, followed by one 8-weekly dose (2Q8) at the randomization visit.
c: Visit schedules may deviate by ±7 days. Scheduled visits should not be altered due to the deviation of the previous visit. The procedures required at each visit have to be complete within 3 days, i.e. split visits are allowed. Additionally, all procedures have to be complete within the 7-day window. Slit lamp (anterior segment), IOP measurement, and indirect ophthalmoscopy are recommended to take place on the same day as the IVT injection.
d: Anatomical criteria: No intraretinal fluid (IRF), no new neovascularization or hemorrhage, and subretinal fluid (SRF) not exceeding 50 µm in thickness. Even if all anatomical criteria are met, including the presence of SRF not exceeding 50 µm in thickness, the investigator has the option not to extend if, based on best clinical judgment the disease is considered active. This decision has to be justified and documented in the electronic case report form (eCRF). For further details on determining treatment intervals see Section 5 of study protocol version 2.0, 02 Feb 2016.
e: All subjects will have mandatory visits at Weeks 52 and 104. In case the scheduled retreatment visit does not occur at Weeks 52 and 104 (±1 week), subjects in both treatment arms will still have mandatory visits without treatment at Weeks 52 and 104.
f: Urine test, for women of child-bearing potential only; a positive result should be confirmed by a serum pregnancy test. Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential.
g: After the first treatment, a urine pregnancy test is mandatory at every treatment visit (prior to injection) in all countries where it is required by local regulations. If required by national /institutional regulations, a pregnancy test should be performed for women of childbearing potential at the end of study visit.
h: Refraction and BCVA using the ETDRS chart is to be performed at each visit.
i: Mandatory at screening, Week 52, and Week 104/early termination, but may be performed at other times based on the investigator's medical judgment and standard of care.
j: Any AE occurring up to 30 days after the last IVT injection of aflibercept has to be documented, regardless of the relationship to the study drug or the seriousness of the event and reported in accordance with this protocol (i.e. not as a spontaneous report). For any drug-related AE occurring after 30 days after the last IVT application of aflibercept, the standard procedures that are in place for spontaneous reporting will be followed. If a subject prematurely withdraws from the study, AEs should be recorded until withdrawal or 30 days after the last dose of study drug, whichever is later.
k: Pre- and post-dose, as applicable. If a subject receives a study injection, indirect ophthalmoscopy should be conducted post-dose and IOP should be assessed in the study eye 30 to 60 minutes post-dosing.
l: Temperature, blood pressure, and heart rate
m: See Appendix 16.1 of study protocol version 2.0, 02 Feb 2016. for an example study drug injection procedure.
n: IVT injection of study drug if the visit coincides with a scheduled treatment visit (±1 week) at Week 104, but only after all assessment have been performed. If a subject receives an injection at Week 104, it is the responsibility of the treating investigator to follow-up on any AEs (including ongoing events) that may occur within 30 days following this treatment. Information regarding such events is to be reported under this protocol (i.e. not as spontaneous reports).
o: Investigator assessment of whether the subject fulfills the anatomical criteria based on OCT for treatment interval extension (see Section 5 of study protocol version 2.0, 02 Feb 2016. for details) and determination of next treatment interval.
p: For subjects in the early-start T&E arm only.
q: In Year 2 only (starting from Week 48).
r: A mandatory safety telephone call will be made approximately 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred.

4. General Statistical Considerations

The Statistical Analysis Plan (SAP) version 1.0 of this open-label study was finalized and signed before the first subject received any study drug, to avoid additional reporting bias.

A summary of the updates of the SAP is given in Section 7.

The statistical evaluation will be performed by using the software package Statistical Analysis System (SAS) release 9.3 or higher (SAS Institute Inc., Cary, NC, USA).

4.1 General Principles

All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum will be calculated for metric data. Mean and standard deviation will be reported to one decimal place greater than the data were collected. Quartiles, median, minimum and maximum values will be reported with the same precision as they were collected.

Frequency tables will be generated for categorical data. 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 and treatment arm, and the percentage values will be reported to one decimal place.

If not stated otherwise, ANCOVA tables will include the least squares (LS) means and the LS mean changes relative to Week 16 for both treatment arms, and the difference in the LS means (early-start T&E arm minus late-start T&E arm) as point estimate and as 95% CI.

In general and if applicable, all analysis that had been planned for the final analysis time point after two years of treatment will be conducted analogously for the interim time point at Week 52, if appropriate. All analyses at the interim time point are to be considered exploratory.

4.2 Handling of Dropouts

Subjects must or might be withdrawn from the study for different reasons, which are specified in the study protocol in Section 6.3.1. Subjects who withdraw from the study will not be replaced. Premature permanent discontinuation from study medication implies premature discontinuation from study participation.

Depending on the time point of withdrawal, a withdrawn subject is referred to as either "Screening Failure" or "Drop-Out" as specified below.

Screening failure (SF)

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 "drop-out" (see below) is considered a "screening failure". Re-screening is only allowed under special conditions, specified in the study protocol, Section 6.3.1.

The number of Screening Failures will be summarized and the reasons will be listed.

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. Drop-outs before Week 16 are treated but not randomized.

The number of subjects who withdrew, as well as the reasons for drop-out of study treatment will be summarized.

4.3 Handling of Mis-Stratification

Subjects are randomized at Week 16, stratified by visual outcome at Week 16 into "< 8 letters BCVA gain from baseline" and "≥ 8 letters BCVA gain from baseline". Possible mis-stratifications will not exclude the respective patients from the PPS.

In general in the statistical models and in the subgroup analyses the true change from baseline to Week 16 will be used. In order to assess a potential impact of mis-stratifications on the primary efficacy endpoint a sensitivity analysis will be conducted using the stratification variable as collected in the IxRS instead of the potentially different correct one recorded on the eCRF.

4.4 Handling of Missing Data

4.4.1 General rules

Data from subjects who drop out of the study will be included in all summaries where possible.

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

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

4.4.2 Adverse events

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. If it is clearly stated, that the Adverse Event occurs prior to first dose of study drug then it will be treated as not treatment emergent.

Adverse Events starting later than 30 days after last study-drug injection will be considered as non-treatment emergent.

4.4.3 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".

4.4.4 Efficacy analysis

The primary method for replacing missing values will be "last observation carried forward" (LOCF), see Section 4.4.4.1. Sensitivity analyses (observed cases and multiple imputations (MI), see Section 4.4.4.2), will be performed to investigate the influence of the missing values.

4.4.4.1 Last Observation Carried Forward

Missing values regarding the primary and key-secondary efficacy variable will be replaced by LOCF using the last available post-baseline values. Last observation carried forward is considered an appropriate method especially in the late phase of the study (i.e. after Week 52), even though untreated nAMD is a progressive disease.

4.4.4.2 Multiple Imputation (MI)

Multiple imputation methods involve three steps:

I. Imputation
i.e., the generation of multiple copies of the original dataset by replacing missing values using an appropriate stochastic model.

a. First missing data will be imputed in order to achieve a monotone missing pattern using the MCMC (Markov Chain Monte Carlo) method, using SAS-procedure proc MI similarly as below.

```
PROC MI DATA=<indata> SEED=2345 OUT=out1 NIMPUTE=20;
MCMC impute=monotone;
VAR base Week4 Week8 Week 16 <time-windows>;
RUN;
```

b. Subsequently missing data will be imputed by a regression model.

```
PROC MI DATA=out1 SEED=6789 OUT=full NIMPUTE=1;
BY _Imputation_;
```

```
CLASS treatment;
MONOTONE method=reg;
VAR treatment base Week4 Week8 Week 16 <time-windows>;
RUN;
```

II. 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 are no issues with missing data. On each imputed dataset the primary and key-secondary analysis will be performed as described in Sections 6.2.1 and 6.2.2. It should be clarified that classifications (e.g. loss of < 15 letters / 3 lines) will be performed after the imputation of the missing BCVA-values.

III. 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.

4.5 Interim Analyses and Data Monitoring

4.5.1 Data Monitoring

Data monitoring procedures are described in the data management plan and in Section 11.2 of the study protocol.

4.5.2 Interim Analyses

An interim analysis is planned after all subjects have finished the 52-Week visit (or withdrew prior to Week 52). No data after the date of visit at Week 52 will be used in the interim analysis.

Primary and key secondary efficacy variables cannot be calculated, as no values from Week 104 will be analyzed. The analysis is only descriptive, no inferential tests will be performed, no decisions on the outcome will be made (e.g. terminating the study or changing the design) and it is planned to publish the descriptive results of this interim analysis. Therefore, no α-adjustment is necessary.

In general all analyses described below for the final analysis time point will be analogously conducted for the Week 52 time point, if applicable. Any analyses are to be regarded exploratory. For subjects who received a planned injection at their 52-Week visit, the injection time point represents a hard cut, i.e. no post-injection measurements and assessments contribute to the interim analysis.

The process of cut-off will follow the general specifications as decribed in the guideline "Database Cutoff Specification v1.0, 15Sept2017" and the ARIES-specific given in Section 9.1.

The efficacy endpoints will be analyzed in the Full Analysis Set (FAS) – LOCF and observed cases, where applicable –, safety endpoints in the Safety Analysis Set (SAF), and the description of the study population (including disposition, demography, baseline characteristics, medical history, concomitant medication, study exposure) in FAS and SAF, if not stated otherwise. Details can be found in the specifications of Tables, Listings and Figures for the interim analysis.

For definitions of the populations see Section 5.

4.6 Data Rules

Generally, pre-treatment values recorded at Visit 2 (Week 0/Day 1), will be used as baseline values. This visit should take place within 3 weeks of the screening visit. If no baseline value is available then last available scheduled 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, change from Week 16 (=randomization) is calculated similarly.

Handling of repeated measurements at the same visit

If measurements were 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; however, they will be listed.

Handling of time-windows

Visit schedules may deviate by ±7 days. Scheduled visits should not be altered due to the deviation of the previous visit.

The procedures required at each visit have to be complete within 3 days, i.e. split visits are allowed. Additionally, all procedures have to be complete within the 7-day window.

Screening

Screening visit must occur within 3 weeks of the baseline visit (Visit 2, Week 0/Day 1).

Initiation Phase and Randomization

Three initial monthly doses at baseline visit (Visit 2, Week 0/Day 1), Visit 3 (Week 4) and Visit 4 (Week 8) will be administered.

At the randomization visit (Visit 5, Week 16) the subjects will be stratified based on visual outcomes (either <8 or ≥8 letters gain in BCVA) and randomized in the early-start or the late-start T&E arm. Afterwards the subjects will receive their IVT injection of the study drug.

Proactive Extension Phase

In the early-start T&E arm, starting at Week 16, subjects will receive treatment in intervals extended by 2 weeks each time (up to a maximum of 16 weeks), as long as all anatomical criteria are met. For subjects who have no IRF and no SRF at Week 16 ("completely dry at Week 16") confirmed by the Central Reading Center, the treatment interval will be extended by 4 weeks for a total of 12 weeks (i.e. schedule next visit at Week 28). From Week 28 onward, the normal extension algorithm will be applied.

In the late-start T&E arm, subjects will receive treatment per label, every 8 weeks to the end of Year 1 (2Q8 injections at Weeks 24, 32, 40, 48). Baseline will be used for calculation of fixed visits. Then in Year 2 (starting from Week 48) the treatment intervals will be extended by 2 weeks each time (up to a maximum of 16 weeks), as long as all anatomical criteria are met. Date of the next visit during Year 2 will be calculated based on the actual visit date.

In both arms, the treatment intervals will not be less than 8 weeks nor more than 16 weeks.

All subjects will have mandatory visits at Week 52 and Week 104. In case a scheduled treatment visit does not occur at Week 52 (±1 week), subjects in both treatment arms will still have a mandatory visit without treatment at Week 52.

With the exception of these mandatory Week 52 and 104 visits, subjects MUST receive a treatment when they attend a scheduled study visit (based on their individualized treatment schedule/treatment interval).

Extended Visits

In the early-start T&E arm, starting at Week 16, and the second year of the late-start T&E arm, starting from Week 48, visits might be extended by anatomical criteria. A deviation of ± 1 week relative to baseline is acceptable.

Visit-wise summaries

The following visits are displayed in the summaries:

Screening, Baseline, Week 4, Week 8, Week 16, Week 52 and Week 104.

In general, the efficacy variables (Section 6.2.1 to 6.2.4) will be summarized according to these mandatory visits, if applicable.

Defining time-windows for the summaries

Study days will be calculated relative to baseline. Study days prior to first injection date are calculated as (actual date – first injection date), after first injection date as (actual date – first injection date)+1.

The following time-windows will be used for summaries of the efficacy (Section 6.2.1 to 6.2.4) and the safety variables from Section 6.4.1 to 6.4.2, except for the Adverse Events:

Pre-randomisation: Screening, Baseline, Week 4, Week 8, Week 16,

Interim Analysis:

Week 17-24 (days 117-172)

Week 25-32 (days 173-228)

Week 33-40 (days 229-284)

Week 41-48 (days 285-340)

Week 49-51 (days 341-361)

Week 52

Main Analysis - second year (both treatment arms):

Week 53-60 (days 368-423)

Week 61-68 (days 424-479)

Week 69-76 (days 480-535)

Week 77-84 (days 536-591)

Week 85-92 (days 592-647)

Week 93-100 (days 648-703)

Week 101-103 (days 704-724)

Week 104

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 stage/numbers of vitreous cells.
  - Slit lamp biomicroscopy: "Abnormal" values and their descriptions will be used, if available, and the highest stage/numbers of anterior chamber flare or cells.
  - Vital signs: The highest values will be used.

<u>Telephone Calls</u>

Mandatory safety telephone call will be made approximately 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred. Up to 2 days delay will be accepted.

Early termination

If a patient is terminated early, data from the early termination visit will be mapped to the next mandatory visit, if the visit falls in the respective time-window.

In addition, efficacy-data from the early termination visit will be mapped to the time-windows defined above.

Pooling centers

All centers will be combined for the purposes of the analysis.

Calculation of durations

Durations are calculated relative to baseline, 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 (interim) database lock.

Presentation

Listings will be sorted by treatment arm, unique subject identifier and 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.

4.7 Validity Review

Validity Review Meetings (VRMs) are performed according to Bayer AG Standard Operating Procedures and will be led by the INC Research Lead Data Manager. Details are available in the data management plan.

The results of the VRM 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 VRM will be documented in an amendment and, if applicable, in a supplement to this SAP.

5. Analysis Sets

Populations for analysis are defined as follows:

Full Analysis Set (FAS)

The FAS will include all randomized subjects who received any study drug and have a BCVA assessment at Week 16 and at least 1 additional post-Week 16 BCVA assessment.

The FAS will be analyzed “as randomized”.

Per-protocol Set (PPS)

The PPS will include all subjects in the FAS without any major protocol deviation.

Major protocol deviations are

- any violation of in- or exclusion criteria,
- a treatment duration shorter than 52 weeks,
- no BCVA assessment at Week 52 or later.

Additionally, injection-intensive subjects who need injections at shorter intervals than 2Q8 between Week 16 and Week 52 will be excluded from the PPS.

Additional reasons for exclusion from the PPS are defined in the final Study Protocol Deviation Document and includes

- Subject received medication expected to interfere with the evaluation of the study drug.
- Subjects received investigational pharmacological agents (not specified) to treat AMD in the study eye
- Subject received injection of study drug solution showing evidence of turbidity (particulates, cloudiness, or discoloration) after visual inspection of aflibercept solution.

Safety Analysis Set (SAF)

The SAF will include all subjects who received any study drug under this protocol. In the safety analysis subjects who dropped out after start of treatment before randomization will be described only in "total", since no allocation of such subjects to a treatment arm is possible.

6. Statistical Methodology

If not specified otherwise, all tables will be summarized by treatment arms and stratified by visual outcomes from baseline to Week 16 (either <8 or ≥8 letters gain in BCVA). Important efficacy and safety tables, as well as demographics and baseline characteristics and exposure data is in addition displayed broken down by the dryness status of the study eye at Week 16 ("completely dry at Week 16" versus "not completely dry at Week 16").

Tables for the safety population will account for the treated, but not randomized subjects supplementary to the two treatment arms.

6.1 Population characteristics

Population characteristics (except Screening Failures and Disposition) will be summarized by treatment arm and all treatment arms combined for all 3 analysis populations (overall and stratified by visual outcome at Week 16 as well as by the dryness status of the study eye at randomization), depending on the type of data as described in Section 4.1.

6.1.1 Screening Failures

All available data from Screening Failures (SF) will be listed. At minimum, the following data from SF should be displayed:

- demographic information,
- date of informed consent,
- reason for premature discontinuation,
- date of last visit

For SF with an SAE, the following data will be listed in addition to the data specified above:

- All information related to the SAE such as:
- Concomitant medication
- Medical history
- Other information needed for SAE complementary page

6.1.2 Disposition

The screened but not treated subjects (screening failures) will be summarized together with the reason(s) for non-treatment. Possible reasons are:

- Adverse Event

- Death
- Informed consent withdrawn
- Lost to follow-up
- Not met inclusion criteria
- Met exclusion criteria

The treated but not randomized subjects (drop-outs) will be summarized together with the reason(s) for non-randomization. Possible reasons are:

- Adverse Event
- Death
- Informed consent withdrawn
- Lost to follow-up
- Not met inclusion criteria
- Met exclusion criteria
- Determination of the treating physician/investigator/sponsor
- Less than 3 injections
- Injection-intensive (subjects require injections at shorter intervals than defined per protocol)

An overview table for all randomized subjects will be given, displaying in each treatment arm and overall the number and percentages of subjects:

- Completed
- Not completed
    - withdrawn after Week 16 up/including to Week 52
    - withdrawn after Week 52 up/including to Week 104
    - withdrawn during study (by primary reason)

Another overview table for all screened subjects will be given, displaying in each treatment arm and overall the number and percentages of subjects:

- Enrolled
- Screening failures
- Safety analysis set (SAF)
- Randomized
- FAS
- PPS
- SAF, but not randomized
- Randomized, but not FAS
    - missing BCVA-assessment at Week 16
    - baseline, but no post- randomization BCVA-assessment
- FAS, but not PPS
    - any violation of in- or exclusion criteria
    - treatment duration shorter than 52 weeks

- no BCVA assessment at Week 52 or later
- prohibited medication.
- pharmacological agents to treat AMD in the study eye
- injection of turbid solution
- injection-intensive (shorter intervals than 2Q8 between Week 16 and Week 52)

6.1.3 Demography

The following demographic variables are recorded at screening. In case of repeated measures the last available value before baseline will be used for summary tables. This table will also be presented by dryness status at Week 16.

- Gender
- Age
- Race
- Ethnicity
- Height
- Weight
- Body Mass Index
- Study eye - left or right

The treatment arm comparability will be checked for each of the analysis populations (FAS, PPS, SAF). This comparison will be done for age by a 2-tailed student's t-test comparing both treatment arms. The test statistics are reliable for variables not normally distributed as well, given the large sample sizes available here.

Furthermore, treatment arms will be compared with respect to gender by Fisher's exact test.

6.1.4 Baseline Characteristics

The following baseline characteristics are observed at screening, during the initiation phase and at randomization (Week 16). In case of repeated measures the last available value at the respective visit will be used for summary tables. This table will also be presented by dryness status at Week 16.

- BCVA letter scores (study eye)
- Categorized BCVA (5-letter intervals) (study eye)
- Central retinal thickness (CRT) (study eye)
- CNV size (study eye)
- Lesion size (study eye)

The treatment arm comparability will be checked for each of the analysis populations (FAS, PPS, SAF). This comparison will be done for baseline and Week 16 values of BCVA letter score and of CRT by a 2-tailed student's t-test comparing both treatment arms. The test statistics are reliable for variables not normally distributed as well, given the large sample sizes available here.

Furthermore, treatment arms will be compared with respect to gender by Fisher's exact test.

Additionally, the BCVA gain (<8 or ≥8 letters) from baseline at Week 16 will be presented as actual and as stratified via IVRS. A Fisher's exact test will be added to evaluate the treatment arm comparability (early T&E versus late T&E).

The dryness proportion will also be shown per treatment arm.

6.1.5 Medical/ophthalmic history

Medical history findings (i.e. previous diagnoses, diseases, or surgeries) meeting all criteria listed below will be collected:

- Not pertaining to the study indication
- Start date before signing of the informed consent
- Considered relevant for the subject's study eligibility

Detailed instructions on the differentiation between medical history and AEs can be found in Section 9.6.1.1 of the study protocol.

The number and percentages of subjects affected as well as the number of events will be displayed for the safety and the full analysis population by BCVA gain and dryness status. 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 PTs will be sorted by descending frequency of subjects affected.

The tables will be repeated for ocular medical history (i.e. ocular medical history ticked as Yes) by eye (study eye, fellow eye and both eyes).

6.1.6 Medical History of neovascular age-related macular degeneration (nAMD)

The medical history of nAMD will be collected for both eyes and presented per study eye and per fellow eye. The duration of nAMD (years) will be calculated as described in Section 4.6.

The following parameter will be summarized:

- Duration of nAMD (years)
- Typical age-related macular degeneration (yes/no)
- Polypoidal Choroidal Vasculopathy (yes/no)
- Retinal Angiomatous Proliferation (yes/no)

In addition, a complete ophthalmic history will be obtained to check the selection criteria. Inconsistencies will be flagged in the respective patient listings.

6.1.7 Prior and Concomitant Medications

Summaries of all prior and concomitant medications recorded will be presented in tabular form using 3-digit Anatomical Therapeutic Chemical (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 after end of study drug.
- New Concomitant: Medications that began after the start of study drug, and those that were started after end of study drug.
- Prior: Medications that started and stopped before the start of study drug.

For each of these categories a table will be created for each of the analysis populations (FAS, PPS, SAF), stratified by

- ocular medication (yes/no) and
- eye (study eye vs. fellow eye)

consisting of medication class and preferred name, sorted by descending frequencies.

6.1.8 Compliance, drug concentration data and/or related data

Treatment duration is calculated as (date of 'end of treatment' - date of first injection at/after baseline +1).

Treatment duration after randomization is calculated as (date of 'end of treatment' - date of first injection after randomization +1).

The total number of intravitreal injections in the study eye is defined as the number of administered injections per subject, computed at Week 52 and Week 104, respectively.

This will be accompanied by the proportion of subjects with at least one extension and, thereof, the maximum extension per subject.

Compliance (%) is calculated as the number of intravitreal injections in the study eye at the scheduled injection visits (+/- 10 days) divided by number of scheduled injection visits (multiplied by 100).

Treatment duration, treatment duration after randomization, number of injections, proportion of subjects with at least one extension, maximum number of extensions and compliance (%) will be summarized for all 3 analysis populations.

The proportions of subjects with last treatment interval of 8, 10, 12, 14, and 16 weeks up to Week 52 and up to Week 104 are presented together with summary statistics for the length of the last treatment interval up to Week 52 and up to Week 104 for the different treatment arms. An analogous analysis comprises the intended treatment interval after the last injection at the visit up to Week 52 and Week 104.

6.2 Efficacy

Generally, in non-inferiority studies the most interesting population for efficacy analysis is the PPS, and the FAS should support the results for a valid interpretation. Therefore, the primary efficacy variable will be analyzed for both analysis sets with the PPS as the primary population and the FAS as the supportive one. The key-secondary variable will also be analyzed for both analysis sets in the same order.

The other efficacy variables will be analyzed descriptively.

Efficacy analysis will use LOCF-imputed datasets as the datasets of first choice. To support these results, "Observed Cases" and MI for missing values will be performed on the primary and key-secondary efficacy variables (see Section 4.4).

An additional sensitivity analysis addresses the influence of mis-stratification with subsequent mis-randomization on the primary endpoint. This will be performed on the LOCF-imputed PPS with subjects stratified as actual and stratified as via IVRS.

Efficacy data for the treated but non-randomized subjects will be listed only.

6.2.1 Primary efficacy variable

The primary efficacy variable is the change in BCVA as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score from Week 16 to Week 104.

Statistical testing will be conducted to prove the non-inferiority of the early-start T&E regimen to the late-start T&E regimen.

Null hypothesis	H_0: $\mu_1 \leq \mu_2$-D versus
Alternative hypothesis	H_1: $\mu_1 > \mu_2$-D, where

D = non-inferiority margin

μ_i = mean change in BCVA as measured by the ETDRS letter score for the study eye from Week 16 to Week 104 in treatment arm i.

i = 1: early-start T&E regimen
2: late-start T&E regimen

The non-inferiority margin D is set to 5 letters.

The methodological approach will be the calculation of 2-sided 95% confidence intervals (CI) for the difference in the LS means (early-start T&E regimen minus late-start T&E regimen) of the change in ETDRS letter score from Week 16 to Week 104 based on a two-way analysis of

covariance (ANCOVA) with the BCVA measure at Week 16 as a covariate and treatment arm and the stratification variable "visual outcomes" (actual values) as fixed factors.

The primary statistical analysis will be performed on the PPS. The early-start T&E regimen will be considered to be non-inferior to the late-start T&E regimen if this analysis is statistically significant, i.e. if the CI of the difference lies entirely above -5 letters, where a positive difference favors the early-start T&E regimen.

Additionally, the analysis will be performed on the Full Analysis Set (FAS), and without the factor "visual outcomes" to support the results.

LOCF is the main analysis with observed cases and MI as supportive.

6.2.2 Key-secondary efficacy variable

The key-secondary efficacy variable denotes the proportion of subjects maintaining vision (<3 lines loss[1]) at Week 104 compared with baseline.

If, and only if, the early-start T&E regimen is statistically proven to be non-inferior to the late-start T&E regimen in the primary efficacy analysis, confirmatory testing will be continued on the PPS to assess the non-inferiority of the early-start T&E regimen to the late start T&E regimen with regard to the key-secondary efficacy variable (maintenance of vision).

Null hypothesis	H_0: $p_1 \leq p_2 - \Delta$ versus
Alternative hypothesis	H_1: $p_1 > p_2 - \Delta$ where

p_i = proportion of subjects maintaining vision at Week 104 of treatment arm i
Δ = pre-specified non-inferiority margin of 7%.
i = 1: early-start T&E regimen
2: late-start T&E regimen

The methodological approach will be the calculation of 2-sided 95% CIs of the difference between the proportions (early-start T&E regimen minus late-start T&E regimen) of subjects maintaining vision at Week 104, taking the actual stratification variable "visual outcomes" into account (CMH). The early-start T&E regimen will be considered to be non-inferior to the late-start T&E regimen if the CI of the difference lies entirely above -7%, where a positive difference favors the early-start T&E regimen. Additionally, the analysis will be performed on the FAS to support the results, and without "visual outcomes" as additional factor.

LOCF is the main analysis with observed cases and MI as supportive.

This hierarchical procedure (a-priori ordered hypotheses) will control for multiplicity in the confirmatory analyses on the PPS.

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[1] As each line on the ETDRS chart has 5 letters, subjects maintaining vision (<3 lines loss) are subjects who gain any number of letters, subjects without gain or loss of letters, and subjects who lose less than 15 letters in BCVA

6.2.3 Other secondary efficacy variables

Analyses on other secondary efficacy variables will be conducted on the PPS and FAS in a descriptive manner, with and without stratified by "visual outcomes", depending on the type of data as described in Section 4.1. This may include 95% CIs for treatment differences in an exploratory way.

The following variables are identified to be other secondary:

- Change in BCVA as measured by the ETDRS letter score from baseline to Weeks 52 and 104 and from Week 16 to Week 52 by mandatory visit and by time-window
- Change in central retinal thickness (CRT) from baseline to Weeks 52 and 104 and from Week 16 to Weeks 52 and 104 by mandatory visit and by time-window
- Number of study drug injections from baseline to Weeks 52 and 104
- Duration of last treatment interval
- Proportion of subjects requiring retreatment at 8, 10, 12, 14, and 16 weeks as the last treatment interval
- Proportion of 3-line gainers at Weeks 52 and 104 compared with baseline
- Proportion of subjects maintaining vision (<3 lines loss) at Week 52 compared with baseline

6.2.4 Exploratory efficacy variables

Analyses on other efficacy variables will be conducted on the PPS and FAS in a descriptive manner, with and without stratified by "visual outcomes", depending on the type of data as described in Section 4.1. This may include 95% CIs for treatment differences in an exploratory way.

- Change in CNV size and total lesion size from baseline to Weeks 52 and 104
- Proportion of subjects with non-deteriorating OCT morphology (as assessed by the central reading center) at Weeks 52 and 104 compared with baseline
- Proportion of subjects showing no IRF and no SRF at Weeks 8, 16, 52 and 104
- Proportion of subjects showing no intraretinal cysts, no IRF and no SRF at Weeks 8, 16, 52 and 104
- Proportion of subjects showing no IRF and no SRF exceeding 50 µm in thickness at Weeks 52 and 104
- Proportion of subjects showing no intraretinal cysts, no IRF and no SRF exceeding 50 µm in thickness at Weeks 52 and 104
- Percentage of subjects requiring retreatment with IVT aflibercept less frequently than every 8 weeks (2Q8)

6.2.5 Fluorescein Angiography (FA)/ Fundus Photography (FP)

For all visits where FP and FA procedures are scheduled, they will be performed on both eyes, but only the study eye will be evaluated by the independent reading center.

FA/FP measurements (except CNV and total lesion size) of the study eye will be listed only.

6.3 Pharmacokinetics / pharmacodynamics

Not applicable.

6.4 Safety

The safety analysis will be conducted on the SAF (as defined in Section 5).

6.4.1 Ocular Safety

6.4.1.1 Intra-ocular Pressure (IOP)

IOP will be assessed for both the study eye and fellow eye at all 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 the IVT injection will be carried out in the study eye only.

All IOP measurements will be classified as follows:

- > 25 mmHg
- ≥ 30 mmHg
- ≥ 35 mmHg
- ≥ 40 mmHg

Any increase from pre-injection/baseline/Week 16 of ≥ 10 mmHg will be flagged.

The IOP analysis will include

- original measurements
- changes from pre-injection/baseline/Week 16
- classified measurements
- flagged measurements

This analysis will be performed descriptively at all visits, stratified by study eye vs. fellow eye, 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 analyzed descriptively depending on the type of data as described in Section 4.1.

6.4.1.2 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 30-60 minutes following the IVT injection.

All indirect ophthalmoscopy variables from the respective eCRF-pages (i.e., Indirect ophthalmoscopy: posterior segment examination, Indirect ophthalmoscopy: study eye - post injection) will only be listed.

6.4.1.3 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 AMD.

Slit lamp biomicroscopy measurements form the respective eCRF-pages (Slit lamp biomicroscopy) will only be listed, except for the assessments of the anterior chamber and the lens in the study eye.

6.4.2 Overall Safety

6.4.2.1 Adverse Events (AEs)

The definitions of AEs and serious AEs (SAEs) are provided in the 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 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.

Potential ATEs will be evaluated by a masked adjudication committee according to criteria formerly applied and published by the APTC. Further details are described in the adjudication committee charter.

If not specified otherwise the following tables will be prepared for

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

Summary tables by treatment and overall will be produced for the following categories for AEs, treatment-emergent AEs and non-treatment AEs:

- Subjects with at least one AE
- Subjects with at least one AE causally related to study drug
- Subjects with at least one AE causally related to intravitreal injection procedures

- Subjects with at least one AE causally related to other procedures required by the protocol
- Maximum intensity for any AE
- Maximum intensity for study drug-related AEs
- AE with outcome death
- Subjects with any serious AE
- Subjects with any serious AE causally related to study drug
- Subjects with any serious AE causally related to intravitreal injection procedure
- Subjects with any serious AE causally related to other procedures required by the protocol
- Subjects with at least one APTC event[2]
- Discontinuation of study drug due to AEs
- Discontinuation of study drug due to serious AEs

The following tables will present the respective AEs by MedDRA preferred term (PT) within primary system organ class (SOC) and summarized by treatment arms. Subjects may be counted under multiple system organ classes and preferred terms, but for each system organ class and preferred term, subjects are only counted once.

- TEAEs
- TEAEs causally related to study drug or iv injection procedure
- TEAEs causally related to study drug
- TEAEs causally related to iv injection procedure[3]
- Serious TEAEs
- Serious TEAEs causally related to study-drug or iv injection procedure
- Serious TEAEs causally related to study-drug
- TEAEs resulting in discontinuation of study drug
- TEAEs by maximum severity
- Study drug-related TEAEs by maximum severity
- Non-serious AEs
- TEAEs by worst outcome
- Treatment-emergent APTCs[4]

The number and percentages of subjects affected as well as the number of events will be displayed. SOCs will be sorted by descending frequency of subjects, within each SOC the PT will be sorted by descending number of events.

[2] not applicable for the interim analysis
[3] Only for "All AE"
[4] not applicable for the interim analysis

6.4.2.2 Vital Signs

Vital signs (body temperature, blood pressure, heart-rate including changes from baseline will be displayed for each treatment arm and overall.

6.4.2.3 Laboratory Evaluations / Pregnancy Tests

A urine pregnancy test for women of childbearing potential will be performed at screening and baseline. After the first treatment, a urine pregnancy test is mandatory at every treatment visit (prior to injection) in all countries where it is required by local regulations.

A positive result should be confirmed by a serum pregnancy test. If required by national /institutional regulations, a pregnancy test should be performed for women of childbearing potential at the end of study visit.

Results of the pregnancy tests for women of childbearing potential will be listed only.

7. Document history and changes in the planned statistical analysis

7.1 Changes with respect to SAP version 1.0, 2. November 2015

1) Adopted the changes from the study protocol amendment v2.0.

2) Added introductory paragraph in Section 1 to underline validity of the SAP for interim as well as final analysis.

3) Added Section 4.3 on handling of mis-stratifications. Related consequences and sensitivity analyses are mentioned in the respective sections.

4) Interim analysis section (now Section 4.5): Described the interim analysis more concisely; added comment on the data cut-off date specification including the reference to the generic document. Replaced subsections on listings, tables and figures to be conducted for the interim analysis with an instructive reference to the final analysis to avoid redundancy.

5) Statistical Methodology section (Section 6) extended for subgroup analyses (completely dry vs. not completely dry) and the consideration of treated but not randomized subjects in the safety analyses.

6) Demography and baseline characteristics (Sections 6.1.3 and 6.1.4): updated the descriptive analyses to 2-tailed student's t-test and Fisher's exact test for consistency with the study protocol. Categorized BCVA and gain in BCVA with respect to mis-stratification is added.

7) Section 6.1.8 on compliance and exposure added

8) Intraocular pressure and slit lamp biomicroscopy (Sections 6.4.1.2 and 6.4.1.3): Planned descriptive analyses replaced by listings.

9) Safety analyses (Section 6.4.2.1): Added five tables on TEAEs by SOC and PT.

10) Appendix 9.1 Cut-Off Specification Clarifications added

Formal changes comprise the update of the header with the new company logo and name, the update of reference documents and the correction of minor mistakes, such as the abbreviation of PT as prothrombin time (SAP v1.0) instead of preferred term (SAP v2.0).

7.2 Changes with respect to SAP version 2.0, 24. November 2017

Beside some editorial changes and minor clarifications the following updates were implemented in ths vesion

1. Definition of "treatment emergent AE":
   Adverse Events starting later than 30 days after last study-drug injection will be considered as non-treatment emergent.

2. Definition of "Compliance" adapted, enlarging the interval to +/- 10 days.

3. Two exploratory endpoints were added

4. Tables for Adverse Events are updated to be consistent with other Bayer studies.

8. References

- Clinical Study Protocol No. BAY86-5321/17508, version 2.0, 02 February 2016
- Study Protocol Deviation Document, version 1.0, 21 October 2015
- Database Cutoff Specification v1.0, 15Sept2017

9. Appendix

9.1 Cut-Off Specification Clarifications

General rules from the guidelines "Database Cutoff Specification v1.0, 15Sept2017" will be followed:

- All variables which are set by the timing concept, e. g., relative days, as well as the treatment emergent flag will be re-calculated after the cutoff is done.
- If there is a domain, which depends on another, the parent domain is always cut first, the dependent domain will then be cut accordingly[5].
- If an observation has a partial date, the observation will be cut only if the partial date is without any doubt after the cutoff date.

There are some exceptions with regard to the guideline mentioned above.:

Section 5.1: Cutoff Visit: The visit which indicates any data collected by this visit will be used for analysis

As described in Section 6, the interim data release will be based on a planned observation time for each patients, i.e., a visit-based cut-off will be used. In addition to the definitions given above, study drug injections given at the cut-off visit as well as data of any assessments scheduled post-injection at this visit will not be included.

Section 7.1; Date based cutoff: Specification for different OAD Domains

Usually authorities request a special listing of all subjects who died after cutoff date. For this purpose the information related to "death" (primary cause of death, death date, etc.) should not be removed even if after the cutoff date.

This rule is applicable for oncological studies and will not be used here. Therefore, in this study fatal AEs are not treated different to other serious AEs.

[5] For example, after removal of an AE after cut-off, the respective concomitant medication for this AE shall also be removed