

A randomized, double-masked, sham-controlled phase 3b/4 study of the efficacy, safety, and tolerability of intravitreal aflibercept monotherapy and rescue aflibercept therapy with adjunctive photodynamic therapy as indicated in subjects with polypoidal choroidal vasculopathy

Short title: Aflibercept in polypoidal choroidal vasculopathy

BSP study drug BAY no. 86-5321 / Aflibercept / Eylea®

Study purpose: To compare the efficacy of intravitreally administered aflibercept monotherapy and rescue therapy with aflibercept plus photodynamic therapy as indicated on the best-corrected visual acuity in subjects with polypoidal choroidal vasculopathy

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Abbreviations

AE	Adverse event
AMD	Age-related macular degeneration
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical Classification
BCVA	Best-corrected visual acuity
CHMP	Committee for Medicinal Products for Human Use
CNV	Choroidal neovascularization
CRF	Case report form
CRT	Central retinal thickness
CST	Central subfield thickness
ECG	Electrocardiogram
EMA	European Medicines Agency
EOS	End of Study
ETDRS	Early treatment diabetic retinopathy study
FA	Fluorescein angiography
FAS	Full analysis set
FP	Fundus photography
GCP	Good Clinical Practice
GDM	Global Data Management
H ₀	Null hypothesis
IB	Investigator's Brochure
ICF	Informed consent form
ICGA	Indocyanine green angiography
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IOP	Intraocular pressure
IRB	Institutional Review Board
IVT	Intravitreal(ly)
K _d	Dissociation constant
LOCF	Last observation carried forward
LS	Least Squares
MedDRA	Medical dictionary for regulatory affairs
N.A.	Not Applicable
NEI VFQ-25	National eye institute 25-item visual function questionnaire
OAD	Operational Acquisition Dataset
OCT	Optical coherence tomography
PASS 11	Power Analysis and Sample Size Software 11
PCV	Polypoidal choroidal vasculopathy
PD	Protocol Deviation
PDT	Photodynamic therapy
PPS	Per Protocol Set
PT	Preferred Term



SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard Deviation
SOC	System organ class
TEAE	Treatment-Emergent Adverse Event
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WHO-DD	World Health Organization Drug Dictionary

1. Introduction

Polypoidal choroidal vasculopathy (PCV) is a subtype of neovascular age-related macular degeneration (AMD) characterized by polypoidal dilations of abnormal choroidal vessels. Retinal pigment epithelial detachment, serous exudation and hemorrhages are sequelae of PCV and lead to retinal dysfunction and loss of visual acuity. Polypoidal choroidal vasculopathy is particularly prevalent in Asians. Clinical studies suggest that 24.6% to 64.5% of Asian wet AMD patients suffer from this subtype. In Europe, prevalence is estimated to be 4.0% to 9.8% of the wet AMD population. One single study in South America suggests a prevalence of 10.6% of wet AMD patients.

The gold standard for diagnosis of PCV is indocyanine green angiography (ICGA).

Vascular endothelial growth factor (VEGF) Trap-Eye (generic name: aflibercept) is a recombinant protein consisting of human VEGF receptor (VEGFR) extracellular domains fused to the constant region (Fc) portion of human immunoglobulin (Ig) G1. It contains portions of the extracellular domains of 2 different VEGFRs. VEGFR1 binds to VEGF with a high affinity (picomolar range), while VEGFR2 binds VEGF much less tightly. The recombinant protein is expressed in Chinese Hamster Ovary K1 cells. Recovery and purification of the protein is accomplished via a combination of filtration and chromatographic techniques. The protein is then formulated for intravitreal (IVT) administration to produce aflibercept.

The recombinant protein aflibercept exhibits very potent binding activity to human VEGF, with an equilibrium dissociation constant (K_d) of approximately 0.5 pM. This binding activity was more potent relative to the activity of anti-VEGF agent ranibizumab (with a K_d in the order of 100 pM). The formulation, aflibercept is developed for intraocular use. Research using an animal ophthalmological disease model demonstrated that aflibercept could adequately inhibit the incidence of retinal neovascularization, choroidal neovascularization (CNV), and retinal edema. Further details can be found in the most recent version of the Investigator's Brochure (IB), which contains comprehensive information on the study drug.

Aflibercept is approved for wet AMD and central retinal vein occlusion in many countries. In particular, it has been investigated in a very large cohort of more than 2400 subjects in two pivotal clinical trials for wet AMD, VIEW 1 and VIEW 2.

Anti-VEGF therapies other than aflibercept

The standard treatment for wet AMD is IVT injection of anti-VEGF agents; however, concerns have been raised that closure of polyps may be an important therapeutic goal in treatment of PCV. Thus, attempts to optimize PCV therapy have been made, either by combining anti-VEGF treatment with photodynamic therapy (PDT), an established gold standard treatment before anti-VEGF therapy was approved, or by exploring PDT as an alternative to anti-VEGF agents.

The most comprehensive research in the treatment of PCV so far was performed with ranibizumab in a 6-month 3-arm controlled clinical pilot study in approximately 60 patients who received ranibizumab monotherapy, or PDT monotherapy, or a combination of the two. The primary endpoint was complete polyp regression, which was best achieved in the combination therapy group (77.8%), closely followed by PDT monotherapy (71.4%), whereas ranibizumab monotherapy achieved polyp regression in only 28.6% of the patients. However, polyp regression does not seem

to correlate well with visual acuity, and the outcome in best-corrected visual acuity (BCVA) was very similar in the three groups.

Aflibercept in polypoidal choroidal vasculopathy

In two large pivotal aflibercept studies (VIEW 1 and VIEW 2) in more than 2400 patients diagnosed with wet AMD, subjects with possible, probable or certain PCV were identified in a *post-hoc* analysis. (Data on file) Efficacy of aflibercept in PCV was not substantially different from the overall wet AMD population, however this result must be interpreted with caution as no ICGA was performed to confirm the diagnosis of PCV and the subgroup with PCV was comparably small.

Other

Steroids, thermal laser, and surgical approaches were used before the advent of anti-VEGF therapy. At this time, they no longer play a relevant role in the treatment of AMD of the PCV subtype.

Future therapy and rationale for the study

It remains unclear whether the enforced closure of polyps with PDT or PDT in combination with anti-VEGF offers any benefit over anti-VEGF alone as measured by visual acuity outcomes. Based upon these findings, many ophthalmologists have moved away from PDT and prefer anti-VEGF therapy only. To clarify whether aflibercept alone is efficacious, it is important to investigate the outcomes if PCV is treated with aflibercept monotherapy or aflibercept with optional adjunct PDT.

2. Study Objectives

Primary objectives:

- To collect data reflecting the efficacy and safety of aflibercept with and without PDT rescue treatment in subjects diagnosed with the PCV subtype of wet AMD
- To explore whether intravitreally administered aflibercept monotherapy is non-inferior to that of aflibercept plus PDT (as indicated) based upon BCVA in subjects diagnosed with the PCV subtype of AMD

Secondary objectives:

- To estimate the proportion of subjects diagnosed with the PCV subtype of wet AMD who require rescue therapy
- To estimate whether or not and to what extent rescue therapy is beneficial in subjects diagnosed with the PCV subtype of wet AMD who have suboptimal responses to aflibercept monotherapy

3. Study Design

3.1 Design Overview

This study is a phase 3b/4, randomized, double-masked, multi-center clinical trial that will be conducted at approximately 50 study sites in mainly Asian Pacific countries. After a run-in period

of 12 weeks, subjects will be randomized in a 1:1 ratio to receive aflibercept 2 mg monotherapy plus sham PDT, or to receive aflibercept 2 mg plus PDT (given only if criteria are met).

Subjects will be enrolled into the study after signing the informed consent form (ICF). After assessment of all screening procedures and confirmation of eligibility, all subjects will begin the run-in period and receive 3 injections of aflibercept in monthly intervals (Weeks 0, 4, and 8) then injections every other month through Week 52. After Week 52, subjects may receive aflibercept through Week 96 under a treat-and-extend regimen which will allow the extension of the treatment interval in increments of 1 or 2 weeks. Based on his or her judgment of the subject's visual and anatomic conditions, the investigator will inform the subject of when the next injection is due and will plan the next visit accordingly. When, or if, visual and anatomical outcomes indicate that the disease has re-activated, the aflibercept treatment interval will revert to the last treatment interval in which the disease was inactive (i.e., no signs of exudation were observed).

At Week 12, subjects will be randomized in a ratio of 1:1 into one of two treatment groups:

A Group 1 subject will receive aflibercept and, if he or she qualifies, this subject will also receive rescue treatment with monthly injections of aflibercept (until the medical condition allows extension of the treatment interval) plus sham treatment with PDT:

aflibercept + sham PDT

A Group 2 subject will receive aflibercept and, if he or she qualifies, this subject will also receive rescue treatment with monthly injections of aflibercept (until the medical condition allows extension of the treatment interval) plus active treatment with PDT:

aflibercept + active PDT

At the time of randomization, subjects will be stratified based upon the presence or absence of qualification for PDT as specified in the PDT treatment criteria and by ethnicity (Japanese or non-Japanese).

Evaluations for qualification for rescue will be conducted at each visit from Week 12 to Week 88 (Week 96 is optional). Intensified aflibercept treatment plus active or sham PDT treatments may be given at any of these visits if treatment criteria are met. Qualification for rescue will be based upon insufficient gain of BCVA, leakage, and presence of active polyps. All of the following three criteria must be met:

1. BCVA \leq 73 EDTRS letters
2. Evidence of new or persistent fluid on OCT
3. Evidence of active polyps on ICGA

Additionally, one of the following criteria must be fulfilled:

4. Deterioration, no change, or insufficient improvement in BCVA from baseline of < 5 letters,
or
5. Improvement in BCVA from baseline of \geq 5 letters, but < 10 letters, and the investigator determines based on the course of visual and anatomic outcomes over time that PDT might be of additional benefit to the subject.

Of note, BCVA and OCT will be performed at each visit. An assessment by ICGA will only be performed if Criteria 1 and 2 plus either Criteria 4 or 5 are met.

All subjects will return to the study clinic at Week 52 for the primary endpoint visit and for a final visit at Week 96 regardless of when the last actual aflibercept injection (or PDT) treatment was performed. If a treat-and-extend subject receives an injection at Week 96 or within 4 weeks of Week 96, it is the responsibility of the treating investigator to follow-up on any AEs (including ongoing events) that may occur within 4 weeks following this treatment. Information regarding such events is to be reported under this protocol (i.e., not as spontaneous reports).

For subjects who meet the need for rescue treatment and are randomized to the active PDT group, verteporfin (Visudyne[®]) will be given according to the label. Treatment with PDT may be delivered on the same visit day as aflibercept, preferably after the administration of aflibercept. If the administration of PDT is delayed, it should be administered within 2-3 days after ICGA/FA, but not later than 7 days.

Fluorescein angiography/fundus photography and ICGA will be performed at screening or baseline, and at Week 52 (primary endpoint visit) and Week 96 (EOT), and at all visits when BCVA and/or OCT results indicate that the subject may qualify for rescue treatment. In the second year (treat-and-extend visit schedule), these examinations will be mandatory only when BCVA and/or OCT results indicate that the subject may qualify for rescue, and at the final visit at Week 96. If deemed necessary by the investigator, FA and/or ICGA may be performed more often.

A central reading center will be used for reading of imaging data including OCT, FP, FA, and ICGA.

Assessment of adverse events (AEs) and vital signs will be performed at every visit.

Unscheduled visits may be planned at any time through the study if deemed necessary by the investigator. If necessary, an early termination visit that includes all EOT procedures may be scheduled.

Statistical analyses will be performed at Week 52 and Week 96. (See appendix 9.1 for process to derive Week 52 cut-off OAD data.)

3.2 Determination of Sample Size

Based on the assumptions of (i) a standard deviation of 12.5 for the mean change in BCVA from study baseline to Week 52, (ii) a non-inferiority margin of 5 letters, (iii) a mean change of 0.25 letters in BCVA of the difference between aflibercept plus PDT as indicated versus aflibercept monotherapy from study baseline to Week 52 in the two treatment groups, (iv) a power of 90%, and (v) a one-sided alpha of 2.5%, the sample size estimation resulted in 147 evaluable subjects per treatment group (calculated with PASS 11 [Power Analysis and Sample Size Software 11], non-inferiority of two means). With an expected drop-out rate of 5%, a total of 310 subjects should be randomized (155 per treatment group).

It is estimated that approximately 50 subjects will qualify for PDT in each treatment group of 155.

4. General Statistical Considerations

The present Statistical Analysis Plan (SAP) is based on the study protocol, version 1.0, dated 25 Nov, 2013.

4.1 General Principles

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, minimum, median, maximum, 25% and 75% quartiles will be calculated for metric data. Frequency tables will be generated for categorical data.

For statistical analysis by ethnicity, Japanese subjects will form one subgroup and all other randomized subjects will form a second subgroup. Data will also be analyzed by qualification or non-qualification for rescue therapy at any time during 52 weeks / 96 weeks.

The final statistical analysis of the Week 52 data will be performed as soon as the Week 52 data for all subjects is available and cleaned, although the study may be still ongoing. Investigators, subjects and monitors will remain masked. Although the conclusions from the analysis of the one year data may be made public, the identity of the study drug for a particular subject will not be known by the subject, the investigator, or the monitor.

The full report of the Week 52 data will be supplemented by a second full report of the Week 96 data for all subjects.

Due to the flexible nature of study visits, if applicable, the efficacy/safety endpoints will be summarized by time intervals as indicated below.

Run-in period (week)	After randomization (week)
0-4, >4-8, >8-12	>12-16, >16-24, >24-32, >32-40, >40-48, <u>>48-52</u> , >52-60, >60-68, >68-76, >76-84, >84-92, <u>>92-96</u>
Interval of 4 weeks	Interval of 8 weeks, except those with underline

4.2 Handling of Dropouts

A subject who discontinues study participation prematurely for any reason is defined as a “dropout” if the subject has already been administered at least one dose of study drug.

Once randomized (at Week 12), dropouts will not be replaced.

4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listing as they are recorded on the Case Report Form (CRF).

Missing replacement for efficacy data

If, for any given subject, the efficacy measurement at Week 52 and/or Week 96 is missing, the subject's corresponding last post-baseline measurement before that time will be carried forward (last observation carried forward; LOCF) for the assessment. For those visits prior to Week 52 and/or Week 96, the same rule will apply.

Missing replacement for safety data

Missing data will not be imputed for the safety analyses.

Missing replacement for dates

The replacement of missing date will only be used to determine the flag variable in the respective analysis dataset, which will be handled by the Global Data Management (GDM) group. The original date recorded in the CRF will be displayed in the listing.

4.4 Interim Analyses and Data Monitoring

Not applicable.

4.5 Data Rules***Baseline values of measurements***

The valid available measurement at Week 0 (Day 1) will be used as baseline. If no such measurement available, the latest value before Week 0 will be considered as baseline.

Unscheduled assessments

Unless otherwise specified, measurements from unscheduled visits, e.g. laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events (AE), will only be included in data listings, not in summary tables.

Repeated measurements at the same visit

If more than one measurement is available for a given visit, the first observation will be used in the data summaries if no special reason for the additional observation was provided by the investigator in the CRF, and all observations will be presented in the data listings.

If IOP > 22 mmHg on first measurement using non-contact tonometry, use confirmatory measurement. In case confirmatory measurement is missing, keep 1st measurement.

Disease duration

The disease duration will be calculated as date of first diagnosis of symptomatic macular PCV in the study eye established by ICGA until date of informed consent. The algorithm will be:

- As months: (informed consent date - first disease diagnosis date)/30.5

If the onset date of disease is not completely recorded, the date will be replaced using the following rule to calculate the duration of disease only. In data listing, the original entry will be displayed.

- Missing day, but month and year available: day is replaced by “15th” in the month;
- Missing month, but year available: day is replaced by “1st”, while month is replaced by “July”;
- Missing year: the date is considered as completely missing.

Category of adverse events

Generally, the flag variable of AE will be set by the GDM group in the dataset to be analyzed before unblinding. The following 3 types of AEs will be defined in database.

- Pre-treatment AE
 - AE onset date is earlier than date of first study drug injection;
 - AE onset date is equal to date of first study drug injection, and the investigator confirms in the CRF that the AE occurred before first dose of study drug.
- Treatment-emergent AE (TEAE)
 - AE onset date is later than date of first study drug injection and within 30 days after last study drug injection;
 - AE onset date is equal to date of first study drug injection, and the investigator confirms in the CRF that the AE DID NOT occur before first dose of study drug or no confirmation from investigator available.
- Post-treatment AE
 - AE onset date is later than date of last study drug injection and not within 30 days after last study drug injection

Prior/concomitant medication flag

A prior/concomitant medication flag will be set by the GDM group to indicate if therapy ended before (“prior”) or after the first study drug administration (“concomitant”). In case the flag variable is missing, it can be calculated by comparing the medication stop date with the first injection date.

Questionnaire (NEI-VFQ 25)

Details regarding the calculation of subscales and total scores for the NEI VFQ-25 questionnaire are provided in Appendix 9.2.

4.6 Validity Review

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

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).

Full analysis set (FAS)

The Full Analysis Set (FAS) will include all randomized subjects. The FAS will be analyzed as randomized.

Safety analysis set (SAF)

The safety analysis set will include all subjects who receive any study drug under this protocol. For active PDT or sham PDT as indicated, the SAF will be analyzed as treated.

Per protocol set (PPS)

A subject will be included in the PPS if he/she has no major protocol deviations, i.e. a patient must have a minimum of 24 week treatment after randomization to be included in PPS. The detailed definitions and the assignment of subjects to this analysis set will be based on the validity review meeting.

6. Statistical Methodology

As already mentioned in section 4.1, the statistical analysis of the Week 52 data will be performed as soon as the Week 52 data for all subjects is available and cleaned. After the Week 96 data for all subjects is available and cleaned, the analysis of the Week 96 data will be performed and used as a supplement to the Week 52 data.

The following subgroup analyses will be performed for both the Week 52 data and the Week 96 data:

- Japanese vs. non-Japanese
- Qualification for rescue therapy at any time during 52 weeks / 96 weeks.

6.1 Population characteristics

6.1.1 Patient disposition

The number of patients included in each of the analysis sets (i.e., FAS, PPS, and SAF) will be summarized by treatment group, and country. A table will summarize the reasons for exclusion from

each analysis set and a listing will be provided that indicates each patient’s in/exclusion from the analysis sets and the reason for exclusion from each analysis set.

The number and percentage (number of randomized is considered as 100%) of patients screened, entered run-in therapy, randomized, completed 52 weeks, and completed 96 weeks, will be summarized by treatment group and overall for FAS. Reasons for premature discontinuation of study drug and/or premature withdrawal from the study as recorded on the e-CRF will be summarized (number and percentage) by treatment group. A listing of all patients who prematurely discontinued from study drug or prematurely withdrew from the study will be presented, and the primary reason for discontinuation of study drug or withdrawal from the study will be provided.

A listing will be provided of randomized patients who did not meet all inclusion/exclusion criteria, and which criteria were not met. PD listing will be presented.

Table 6–1 Analysis strategy for patient disposition

Disposition items	Definition
Analysis set	FAS, PPS, SAF By treatment group and by country
Reasons for exclusion from each analysis set	Summary table and patient listing
Disposition	Number and percentage of patients: Screened, run-in, randomized, 52 week completed, 96 week completed
Discontinuation listing	
Major protocol deviation	Summary table and patient listing

6.1.2 Demographics and baseline characteristics

Demographics and baseline characteristics were recorded at Screening and Baseline. Demographic data and baseline characteristics will be presented by treatment group and overall for FAS.

Table 6–2 Analysis strategy for demographic and baseline characteristics

Variables	Definition	Descriptive statistics
Age (years)	Year of birth to informed consent date	N, Mean, SD, Min, Median, Max, 25% and 75% Quartiles. Frequencies: <55, 55-<65, 65-<75, ≥75
Gender		N (percentage)
Ethnicity		N (percentage)
Race		N (percentage)
Weight, Height, BMI		N, Mean, SD, Min, Median, Max, 25% and 75% Quartiles.
Duration of disease	To informed consent date, Unit: month	N, Mean, SD, Min, Median, Max, 25% and 75% Quartiles.
BCVA		N, Mean, SD, Min, Median, Max, 25% and 75% Quartiles.
NEI VFQ-25 total score		N, Mean, SD, Min, Median, Max, 25% and 75% Quartiles.
Retinal thickness	From central reading	N, Mean, SD, Min, Median, Max, 25% and 75%

Variables	Definition	Descriptive statistics
		Quartiles.
CNV type		N (percentage)
Total lesion size		N, Mean, SD, Min, Median, Max, 25% and 75% Quartiles
CNV lesion size	From central reading	N, Mean, SD, Min, Median, Max, 25% and 75% Quartiles

*ethnicity refers to Japanese vs. Non-Japanese

6.1.3 Medical history and surgeries

Medical history and surgeries (ocular and non-ocular) will be coded by the Medical Dictionary for Regulatory Affairs (MedDRA). Medical/ophthalmic history will be evaluated by a frequency table, showing the number of subjects with medical/ophthalmic history findings by primary system organ class (SOC), high level term, preferred term (PT), and treatment group and overall.

Medical history will be summarized for FAS and SAF.

For surgeries after start of study, a frequency table will be presented.

6.1.4 Prior and Concomitant Medications

All prior and concomitant medications recorded in eCRF will be coded by World Health Organisation drug dictionary (WHO-DD, Version September 2005) Anatomical Therapeutic Chemical Classification (ATC) level 3 (third level indicates the therapeutic/ pharmacologic subgroup) and generic medication name. Medications are considered prior if administered prior to the first administration of study drug. Patients will be counted only once for an ATC class and generic medication name. Concomitant medications taken during the study treatment period will be similarly summarized, and by run-in and after randomization, respectively. Medications are considered concomitant if taken on or after the first dose of study drug. If it is impossible to classify a medication into prior or concomitant medication due to missing date, such drug will be considered as concomitant medication.

Prior and concomitant medication will be summarized for FAS and SAF.

6.1.5 Study Drug Exposure

Study drug exposure will be presented for FAS and SAF, and for run-in and after randomization

Because treatment in this study is being given on an as needed basis, a complete listing of subject drug exposure data will be presented to show drug administration during the course of study.

For each subject, the following variables will be used to examine exposure to treatment:

- Number of total injections / administrations of aflibercept and PDT (sham or active, for after randomization)
- Duration of treatment exposure:
 - As days: randomization day (or last available treatment date if not randomized) - first treatment day +1 (or + 28 if not randomized) for run-in, last treatment day – randomization day + 56 for after randomization

- As weeks: exposure in days / 7

Table 6–3 Analysis strategy for study drug exposure

Exposure	Definition	Analysis set
Study drug exposure	<ul style="list-style-type: none"> - Total number of aflibercept injections - Total number of PDT administrations (sham or active) - Duration of aflibercept exposure (in weeks) 	FAS, SAF

6.2 Efficacy

6.2.1 Primary efficacy variable and analysis

The primary efficacy endpoint is the mean change in BCVA from baseline to Week 52.

Statistical testing will be conducted to prove the non-inferiority of aflibercept monotherapy (treatment group i=1) to aflibercept plus PDT as indicated (treatment group i=2). The corresponding null hypothesis is $H_0: \mu_1 \leq \mu_2 - D$ versus the alternative hypothesis $K: \mu_1 > \mu_2 - D$, where D is the non-inferiority margin and $\mu_i, i=1,2$, is the mean change in BCVA letter score for the study eye from study baseline at 52 weeks in treatment group i.

The non-inferiority margin is 5 letters. The methodological approach will be the calculation of two-sided 95% confidence intervals for the difference in the least squares (LS) means (aflibercept monotherapy treatment group minus aflibercept plus PDT as indicated treatment group) of the change in ETDRS letter score from study baseline to 52 weeks based on a 3-way analysis of covariance (ANCOVA, main effect model), with baseline measure as a covariate and treatment group, ethnicity, and qualification for rescue therapy at Week 12 as a fixed factors (last observation carried forward [LOCF] will be used for missing values at 52 weeks). Aflibercept monotherapy will be considered to be non-inferior to aflibercept plus PDT as indicated if the confidence interval of the difference lies entirely above -5 letters, where a positive difference favors aflibercept monotherapy. A non-inferiority margin of 5 letters is consistent with margin used in the CATT¹ Study.

Following sensitivity analyses will be used for handling missing Week 52 values, and will be compared to the LOCF method:

- Same analysis with PPS
- Multiple imputation method using a Markov chain Monte Carlo full data imputation

Table 6–4 Analysis strategy for primary efficacy variables

Primary variable	Method	Missing Data Handling	Analysis set
Primary analysis			
Change from baseline in BCVA at Week 52	ANCOVA: baseline BCVA as covariate, treatment, ethnicity, and qualification for rescue therapy at Week 12 as fixed factors	LOCF	FAS
Sensitivity analysis			

Primary variable	Method	Missing Data Handling	Analysis set
Change from baseline in BCVA at Week 52	ANCOVA: baseline BCVA as covariate, treatment, ethnicity, and qualification for rescue therapy at Week 12 as fixed factors	LOCF	PPS
Change from baseline in BCVA at Week 52	ANCOVA: baseline BCVA as covariate, treatment, ethnicity, and qualification for rescue therapy at Week 12 as fixed factors	Multiple imputation method using a Markov chain Monte Carlo	FAS
Change from randomization in BCVA at Week 52	ANCOVA: baseline BCVA as covariate, treatment, ethnicity, and qualification for rescue therapy at Week 12 as fixed factors	LOCF	FAS
Change from randomization in BCVA at Week 52	ANCOVA: baseline BCVA as covariate, treatment, ethnicity, and qualification for rescue therapy at Week 12 as fixed factors	LOCF	PPS
Change from randomization in BCVA at Week 52	ANCOVA: baseline BCVA as covariate, treatment, ethnicity, and qualification for rescue therapy at Week 12 as fixed factors	Multiple imputation method using a Markov chain Monte Carlo	FAS

6.2.2 Secondary efficacy variable and analysis

The secondary efficacy endpoint is the avoidance of at least a 15-letter loss (“maintenance of visual acuity”) from baseline to Week 52.

If aflibercept monotherapy is statistically proven to be non-inferior to aflibercept plus PDT as indicated in the primary efficacy analysis, then confirmatory non-inferiority testing will be continued for the secondary efficacy variable identifying the proportion of subjects maintaining visual acuity at Week 52 (with LOCF for missing 52-week ETDRS letter score). Otherwise, such analysis will be exploratory in nature. This conditional sequence of statistical hypotheses (*a priori* ordered hypotheses) will control for multiplicity in the confirmatory analyses.

This analysis will be performed in the FAS. The null hypothesis is $H_0: p_1 \leq p_2 - d$ versus the alternative hypothesis $K: p_1 > p_2 - d$, where p_i is the proportion of subjects maintaining visual acuity at 52 weeks of treatment group i and d is the pre-specified non-inferiority margin of 7%. The methodological approach will be the calculation of the two-sided 95% Cochran-Mantel-Haenszel intervals adjusted for the 4 strata (ethnicity [Japanese vs non-Japanese] and qualification for rescue therapy at Week 12 [yes vs no]) of the difference between the proportions (aflibercept monotherapy minus aflibercept plus PDT as indicated) of subjects maintaining visual acuity at Week 52. The aflibercept monotherapy will be considered to be non-inferior to the aflibercept plus PDT as indicated, if the confidence interval of the difference lies entirely above $-7%$, where a positive difference favors aflibercept monotherapy. The non-inferiority margin of 7% was proposed by the European Medicines Agency (EMA) in their scientific advice regarding the proposed 10% non-inferiority margin in the VIEW studies (EMA/CHMP/SAWP/ 310870/ 2007, pages 22 and 23; May 2007).

The two-sided Cochran-Mantel-Haenszel method at level $\alpha=5%$ weight-adjusted by strata is detailed below (Koch et al, 1990)²:

$$d = \left(\sum_h w_h (\hat{p}_{ht} - \hat{p}_{hc}) \right) / \sum_h w_h, \text{ where } w_h = n_{ht} n_{hc} / (n_{ht} + n_{hc}).$$

$$\text{Then } \hat{\text{var}}(\hat{d}) = \left(\sum_h w_h^2 (\hat{p}_{hc}(1 - \hat{p}_{hc}) / (n_{hc} - 1) + \hat{p}_{ht}(1 - \hat{p}_{ht}) / (n_{ht} - 1)) \right) / \left(\sum_h w_h \right)^2.$$

With this, the 95% CI can be given as: $\hat{d} \pm z_{\alpha/2} \sqrt{\hat{\text{var}}(\hat{d})}$ ($z_{\alpha/2}$ being the cut-off value for the $\alpha / 2$ upper percentile of the standard normal distribution).

In the formulae,

- h : number of strata
- p_{ht} : proportion of subjects who maintain visual acuity in BCVA compared with baseline at Week 52 in the VEGF Trap-Eye treatment arm (aflibercept monotherapy), in stratum h ,
- p_{hc} : proportion of subjects who maintain visual acuity in BCVA compared with baseline at Week 52 in the control arm (aflibercept plus PDT as indicated), in stratum h ,
- n_{ht} : number of subjects in the treatment arm in stratum h ,
- n_{hc} : number of subjects in the control arm in stratum h .

Based on the result from this model, the difference in the proportions of subjects (aflibercept monotherapy minus aflibercept plus PDT as indicated) and a corresponding two-sided 95% confidence interval will be established.

Following sensitivity analyses will be used for handling missing Week 52 values, and will be compared to the LOCF method:

- Same analysis with PPS
- Worst case imputation

Table 6–5 Analysis strategy of secondary efficacy variables

Secondary variable	Method	Missing Data Handling	Analysis set
Primary analysis of the secondary efficacy variable will be confirmatory only if the primary analysis is successful. Otherwise, such analysis will be exploratory by nature.			
Avoidance of at least a 15-letter loss from baseline to Week 52	Cochran-Mantel-Haenszel method weight-adjusted by strata: ethnicity [Japanese vs non-Japanese] and qualification for rescue therapy at Week 12 [yes vs no]	LOCF	FAS
Sensitivity analysis			
Avoidance of at least a 15-letter loss from baseline to Week 52	Cochran-Mantel-Haenszel method weight-adjusted by strata: ethnicity [Japanese vs non-Japanese] and qualification for rescue therapy at Week 12 [yes vs no]	LOCF	PPS
Avoidance of at least a 15-letter loss from baseline to Week 52	Cochran-Mantel-Haenszel method weight-adjusted by strata: ethnicity [Japanese vs non-Japanese] and qualification for rescue therapy at Week 12 [yes vs no]	Worst case imputation	FAS

6.2.3 Exploratory variables and analyses

All exploratory efficacy variables will be summarized descriptively at each visit/week prior to/at Week 52 and prior to/at Week 96 (as observed and LOCF) for the FAS. Additionally, for continuous variables, the absolute change from baseline will be calculated and presented by visit/week.

For the exploratory efficacy variables, the difference between treatment groups and a corresponding two-sided 95% confidence interval will be estimated for descriptive purposes. The continuous variables, including the mean change from baseline to Week 52 and to Week 96 will be assessed using an analysis of covariance (ANCOVA) model, including treatment groups, ethnicity, and qualification for rescue therapy at Week 12 as fixed effects, and baseline measurement as covariate. The categorical variables will be analyzed using the Cochran-Mantel-Haenszel method, weight-adjusted for strata, from which the difference in proportions of subjects between treatment groups and a corresponding two-sided 95% confidence interval will be estimated.

If applicable, all missing data will be handled using LOCF. And the analysis set will be FAS.

The following exploratory analyses will be performed.

Table 6-6 Analysis strategy of exploratory efficacy variables

Variable	Method	Missing Data Handling	Analysis set
The proportion of subjects who never need rescue therapy in the first year	Descriptive analysis: proportion and 95% C.I.	N.A.	FAS: both treatment groups combined
Number of PDT treatments in the study eye before Week 52 and before Week 96	ANOVA: treatment, ethnicity, and qualification for rescue therapy at Week 12 as fixed factors	N.A.	FAS
Number of aflibercept treatments in the study eye (after randomization) before Week 52 and before Week 96	ANOVA: treatment, ethnicity, and qualification for rescue therapy at Week 12 as fixed factors	N.A.	FAS
Time to first administration of PDT in the study eye before Week 52 and before Week 96	Kaplan-Meier plot	N.A.	FAS
Change of visual acuity (letters) from baseline over time (week) in the study eye	Figure: line plot by treatment	Actual observations only	FAS
The proportion of subjects who gain ≥ 5 , 10, or 15 letters at Week 52 and at Week 96	Cochran-Mantel-Haenszel method weight-adjusted by strata: ethnicity [Japanese vs non-Japanese] and qualification for rescue therapy at Week 12 [yes vs no]	LOCF	FAS

Variable	Method	Missing Data Handling	Analysis set
The proportion of subjects who lose ≥ 5 , 10, or 15 letters at Week 52 and at Week 96	Cochran-Mantel-Haenszel method weight-adjusted by strata: ethnicity [Japanese vs non-Japanese] and qualification for rescue therapy at Week 12 [yes vs no]	LOCF	FAS
The proportion of subjects with complete polyp regression (no visual polyps on ICGA) at Week 52 and at Week 96	Cochran-Mantel-Haenszel method weight-adjusted by strata: ethnicity [Japanese vs non-Japanese] and qualification for rescue therapy at Week 12 [yes vs no] Only subjects with polyps present at baseline are included. AND patients not assessable at W52 are excluded.	OC and Worst-Case-Imputation	FAS
Change of leakage area in FA in the study eye at Week 52 and at Week 96	ANCOVA: baseline leakage area as covariate, treatment, ethnicity, and qualification for rescue therapy at Week 12 as fixed factors	LOCF	FAS
Change of CST on OCT from baseline to Week 52 and to Week 96	ANCOVA: baseline CST as covariate, treatment, ethnicity, and qualification for rescue therapy at Week 12 as fixed factors	LOCF	FAS
Change in NEI VFQ-25 total score from baseline to Week 52 and to Week 96	ANCOVA: baseline NEI VFQ-25 as covariate, treatment, ethnicity, and qualification for rescue therapy at Week 12 as fixed factors	N.A.	FAS
Proportion of subjects for whom rescue therapy is indicated over the course till Week 52 and till Week 96	Cochran-Mantel-Haenszel method weight-adjusted by strata: ethnicity [Japanese vs non-Japanese] and qualification for rescue therapy at Week 12 [yes vs no]	LOCF	FAS

Subgroup analysis

The following subgroup analysis will be performed.

- Japan vs. non-Japan: Descriptive analysis on all efficacy variables will be conducted for Japan and non-Japan subgroups. Statistical tests mentioned in section 6.2 will be repeated, and nominal p-value / confidence interval will be provided if applicable. For statistical models, ethnicity will not be a fixed factor (ANCOVA/ANOVA) or stratification factor (Cochran-Mantel-Haenszel method).
 - All efficacy endpoints will be repeated within these subgroups
 - AE reporting, particular ophthalmic AE, will be repeated within these subgroups
- Qualification for rescue therapy vs. not qualified for rescue therapy at any time during 52 weeks / 96 weeks: If the sample size is reasonable large for statistical analysis, statistical tests mentioned in section 6.2, and nominal p-value / confidence interval will be provided if applicable. For statistical models, qualification for rescue therapy at week 12 will not be a fixed factor (ANCOVA/ANOVA) or stratification factor (Cochran-Mantel-Haenszel method).
 - All efficacy endpoints will be repeated within this subgroup

- AE reporting, particular ophthalmic AE, will be repeated within this subgroup

6.3 Pharmacokinetics / pharmacodynamics

N.A.

6.4 Safety

In general, a frequency table will be generated for categorical variables, while summary table for quantitative measurements. A shift table will be provided for ‘abnormal’ by visits/weeks.

Safety evaluation will be performed with the SAF population.

6.4.1 Adverse events

All adverse events occurring during the study (i.e. from signing of informed consent until last visit) will be reported. Adverse events (AEs) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA, latest version).

Evaluations of TEAEs will be done for four sets of TEAEs, which will be identified from the information in the case report form (CRF):

- Ocular TEAE in the study eye
- Ocular TEAE in the fellow eye
- Non-ocular TEAE
- All TEAE (i.e., all TEAEs mentioned above combined).

All AEs will be classified into pre-treatment, treatment-emergent AE during run-in and after randomization, and post-treatment AEs.

Pre-treatment adverse events

Pre-treatment AEs will be defined as AEs that started and either stopped before the first dose of study treatment or continued after and did not worsen in intensity through the end of the AE reporting period. For events with partial onset dates if the question of “Did the AE occur prior to the first dose of Study Treatment?” is marked as Yes then these will be classed as pretreatment AEs.

Treatment-emergent adverse events (TEAEs)

A Treatment-emergent adverse event is defined as any event arising or worsening after the start of study drug administration through the end of the AE reporting period:

- Events that started on or after the date and time of administration of the first dose of study drug and within 30 days after the last dose of study drug and are not a continuation of a pre-treatment event.
- Events that started before the first dose of study drug and worsened after the first injection or within 30 days after the last dose of study drug.

- AEs with partial onset dates that indicate that that the event could be treatment emergent, (for example, an AE with missing onset day but month and year recorded as May 2012 and study treatment started on 20 May 2012), where the question of “Did the AE occur prior to the first dose of Study Treatment?” is marked as No.
- AEs with completely missing onset dates, where the question of “Did the AE occur prior to the first dose of Study Treatment?” is marked as No.

Post-treatment adverse events

A post-treatment adverse event is defined as any event arising or worsening after 30 days of last dose of study drug administration.

Overall summary of the number and percentage of patients with pre-treatment AE, TEAE during run-in and after randomization, and post-treatment follow-up AEs will be presented. This summary will include the number and percentage of patients with study drug related AEs, AEs leading to dose modification, and AEs leading to treatment discontinuation.

TEAEs will be summarized by MedDRA system organ class and preferred term. Additional summary of TEAEs by system organ class, preferred term and severity, serious TEAEs (SAEs) by system organ class, preferred term, and TEAEs leading to treatment discontinuation by system organ class, preferred term.

Tables of any TEAE leading to study drug discontinuation, infusion-related TEAEs, and SAEs will be provided also.

Patient listings of all AEs, SAEs, AEs leading to death, premature discontinuation and serious adverse events, will be listed.

A frequency table of APTC (Anti-Platelet Trialists Collaboration) adjudication of AE terms, cross-tabulated with related MedDRA Preferred Term, will be displayed by treatment arms. The adjudication of AE is described in the “APTC adjudication committee charter”.

Table 6–7 Analysis Strategy for AEs

Safety Variables	Method
Pre-treatment AE	Summary table
TEAE: <ul style="list-style-type: none"> - TEAE during run-in - TEAE after randomization 	<ul style="list-style-type: none"> - Overall summary - By SOC and PT - By SOC, PT, and severity - By SOC, PT, and relationship to study drug - By SOC, PT, and relationship to injection/laser procedures - Lead to Discontinuation of study drug by SOC and PT
Post-treatment AE	Summary table
Death and SAE	- by SOC and PT
APTC	Summary table

6.4.2 Pregnancies

According to the protocol, any subject who becomes pregnant during the study should undergo EOS assessments and be discontinued from the study. A listing of pregnancy events will be provided if applicable. Therefore, no statistical evaluation of pregnancy data is planned.

6.4.3 Weight and Vital signs

Weight and vital signs will be summarized using descriptive statistics at each scheduled study visit/week by treatment group. Descriptive statistics of the change from baseline to each post-baseline visit will also be provided.

Table 6–8 Analysis Strategy for vital signs

Safety Variables	Method
- Weight - Vital signs	- Baseline, actual, change from baseline, by visit/week

6.4.4 Ophthalmic safety examinations

Unless otherwise specified, results for the study eye will be tabulated, and results for the fellow eye will be listed only.

6.4.4.1 Intraocular pressure

Descriptive statistics of IOP value (pre-injection and post-injection, respectively) at each visit/week as well as the absolute change from baseline will be displayed by treatment and visit.

As a general assessment of IOP across the study, the proportion of subjects with the following increased IOP categories will be evaluated by treatment :

- ≥ 10 mm Hg increase in IOP measurement from baseline at any pre-dose measurement
- absolute value > 21 mm Hg for any pre-dose measurement
- absolute value ≥ 35 mm Hg at any time during the study

Table 6–9 Analysis Strategy for IOP

Safety Variables	Method
IOP	- IOP value by time point - Absolute change from baseline - Proportion of subjects with increased IOP categories

6.4.4.2 Slit lamp biomicroscopy

A frequency table for each parameter of slit lamp biomicroscopy, including lids, conjunctiva, cornea, anterior chamber, iris, pupil, lens, and other, will be displayed by treatment and visit/week. In addition, a separate frequency table for those subjects with ‘abnormal’ in any parameter measured will be given.

Frequency tables by treatment and visit will be provided for grading of anterior chamber flare (0: no protein, Trace: trace amount of protein, 1+: mild amount of protein, 2+ and 3+: moderate amount of

protein (continuum), 4+: severe amount of protein) and cells (0: no cells, Trace: less than 5 cells, 1+: 5 to 10 cells, 2+: 10 to 20 cells, 3+: 20 to 30 cells, 4+: cells too numerous to count). Additionally, shift tables will be presented by visit.

Subject listings with any parameter marked as ‘abnormal’ in the slit lamp biomicroscopy evaluation will be generated and presented by treatment and visit/week.

Table 6–10 Analysis Strategy for slit lamp

Safety Variables	Method
Slit lamp biomicroscopy parameters	<ul style="list-style-type: none"> - Frequency table by time point - Frequency table of ‘abnormal’ parameters - ‘Abnormal’ subject listing

6.4.4.3 Indirect ophthalmoscopy

Pre-injection

A frequency table for each parameter of indirect ophthalmoscopy, will be displayed by treatment and visit. In addition, a separate frequency table for those subjects with ‘abnormal’ in any parameter measured will be given.

Frequency tables by treatment and visit will be provided for the grading of vitreous cells (categories: 0 / trace / 1+ / 2+ / 3+ / 4+). Additionally, shift tables will be presented by visit.

Table 6–11 Analysis Strategy for indirect ophthalmoscopy

Safety Variables	Method
Pre-injection parameters	<ul style="list-style-type: none"> - Frequency table by time point - Frequency table of ‘abnormal’ parameters - ‘Abnormal’ subject listing

6.4.4.4 Fluorescein angiography / Fundus photography

A frequency table for each parameter of FA/FP will be displayed by treatment and visit.

For quantitative measurements, values at each visit and the change from baseline will be summarized using descriptive statistics by treatment. The descriptive statistics will include n, mean, SD, median, minimum and maximum.

For Blood total area, population only includes subjects with Blood total present at baseline.

For Classic CNV area, population only includes subjects with Classic CNV present at baseline.

For Occult CNV area, population only includes subjects with Occult CNV present at baseline.

For Subretinal Fibrous Tissue area , population only includes subjects with PRESENCE OF FIBROSIS present at baseline.

For Non-Fibrous Scar area, population only includes subjects with Non-Fibrous Scar present at baseline.

For Serous PED area , population only includes subjects with ARE PEDS VISIBLE(Serous PED) present at baseline.

For RPE Rip/Tear area , population only includes subjects with RPE Rip/Tear present at baseline.

For SSR Detachment area , population only includes subjects with SSR(Sensory Serous Retina) Detachment present at baseline.

For Geographic Atrophy (AMD) area , population only includes subjects with IS GA VISIBLE present at baseline.

Table 6–12 Analysis Strategy for FA/FP

Safety Variables	Method
FA/FP parameters	- Frequency table by time point
Quantitative measurements	- Summary table by time point

6.4.4.5 Optical coherence tomography

Results from OCT will be analyzed in a descriptive manner. For continuous variables, descriptive statistics including number of observations, mean, standard deviation, median, min and max will be provided for measurement at each visit and change from baseline by treatment and visit. For category variables, frequency tables with number of observations and percentage will be displayed.

For SSRD thickness at center point, SSRD maximum thickness, population only includes subjects with SSRD (subretinal fluid) present at baseline.

For Neovascular LC thickness at center point, Neovascular LC maximum thickness, population only includes subjects with Neovascular LC (Lesion complex) present at baseline.

For PED thickness at center point, PED maximum thickness, population only includes subjects with ARE PEDS VISIBLE present at baseline.

The complete OCT results for each subject, will be listed by treatment and visit.

Table 6–13 Analysis Strategy for OCT

Safety Variables	Method
OCT variables (except CRT)	- Summary/frequency table by time point - Listing by time point

6.4.4.6 Indocyanine green angiography

Results from ICGA will be analyzed in a descriptive manner. For continuous variables, descriptive statistics including number of observations, mean, standard deviation, median, min and max will be provided for measurement at each visit and change from baseline by treatment and visit. For category variables, frequency tables with number of observations and percentage will be displayed.

For area of BVN, BVN total perimeter of the area, population only includes subjects with BVN (Branch Vessel Network) present at baseline.

For number of polyps, polyps total perimeter of the area and area of polyps, population only includes subjects with polyps present at baseline.

The complete ICGA results for each subject, will be listed by treatment and visit.

Table 6–14 Analysis Strategy for ICGA

Safety Variables	Method
ICGA variables (except polyp regression)	<ul style="list-style-type: none"> - Summary/frequency table by time point - Listing by time point

7. Document history and changes in the planned statistical analysis

Amendment 1 dated 29 August 2016,

- APTC analysis was added.
- Fluorescein angiography / Fundus photography analysis was combined due to data reading practice.
- Baseline comparability (sex, age, baseline BCVA letter score, baseline NEI VFQ-25 total score, and baseline retinal thickness) will be implemented as in protocol.
- AESI details added.
- Some typo and minor errors were revised.

Amendment 2 (supplement) dated 25 October 2016,

- AESI removed.
- Inconsistency of subgroup definition between section 4.1 and 6.2 revised. ‘Qualification for rescue therapy vs. not qualified for rescue therapy at any time during 52 weeks / 96 weeks’ is the correct definition.

Amendment 3 (supplement) dated 20 November 2016,

- Section 4.5: data handling rule for IOP added
- Section 6.1.5: treatment exposure for run-in is defined for both randomized and non-randomized patients.
- Section 6.2.3: analysis of complete polyps regression is revised; CRT analysis is changed to CST analysis.
- Section 6.4.1: AE with $\geq 5\%$ patients removed
- Section 6.4.4: analysis population for some parameters is re-defined for FAFP/OCT/ICGA.

8. References

1. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, Toth C, Redford M, Ferris FL 3rd. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012 Jul;119(7):1388-98
2. Koch GG, Carr GJ, Amara IA, Stokes ME, Uryniak TJ, 'Categorical Data Analysis' in *Statistical methodology in the pharmaceutical sciences* / edited by DA Berry, Marcel Dekker, 1990

9. Appendices

9.1 Process to derive the Week 52 cut-off OAD

1. Visit dependent data

All visit dependent data up to and including Visit Week 52 will be kept for the 52 weeks analysis. All visit dependent data greater than Visit Week 52 will be excluded. Unscheduled visits with a date earlier than week 52 visit date will be kept on the 52 weeks analysis data.

At Visit Week 52, only data obtained before the injection at this visit will be included into data analysis.

For dropouts, available data with a date earlier or equal to Visit Week 52, will be kept in the Week 52 analysis data.

2. Visit independent data

Generally, all event records with a start date earlier or equal to the date of Visit Week 52 will be kept, and records with a start date later than the date of Visit Week 52 will be excluded, including incomplete dates when the incomplete date is without any doubts later than the Visit Week 52 date.

For events occurred at the same date with Visit Week 52, if the event is considered as “injection procedure related”, or the event has an additional time being recorded, which is later than study drug injection, it will be excluded from analysis at Week 52.

For the event with the stop date is later than the date of Visit Week 52, in Week 52 cut-off datasets, the stop date will be set to missing and the status/outcome of the event will be set to ongoing/unknown.

For dropouts, all event records with a start date earlier or equal to the date of Visit Week 52, will be kept. However, if the stop date for a given event is later than the date of Visit Week 52, the stop date will be set to missing and the status/outcome of the given event will be set to ongoing/unknown.

9.2 NEI-VFQ-25 sub-scale scores and total score

The calculation for NEI-VFQ-25 sub-scale scores and total score will be performed according to The National Eye Institute (2000). The algorithm is then:

As a preparation of the VFQ-25 calculation, the items of the questionnaire will be recoded according to Table 9-1. In the further calculations, only the recoded item values will be used.

For the recoded values, they generally represent the best possible result as “100” and the worst possible result as “0”.

Table 9-1 Recoding of NEI VFQ 25 items

Item no.	Original response to item	Recoded item value
1, 3, 4, 15c ^(a)	1	100
	2	75
	3	50
	4	25
	5	0
2	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 16a	1	100
	2	75
	3	50
	4	25
	5	0
b	6	*
17, 18, 19, 20, 21, 22, 23, 24, 25	1	0
	2	25
	3	50
	4	75
	5	100

(a) Item 15c has four-response levels but is expanded to a five-levels using item 15b.

Note: If 15b=1, then 15c=0

Item no.	Original response to item	Recoded item value
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If 15b=2, then 15c is set as missing
 If 15b=3, then 15c is set as missing

* Here, response “6” indicates that the person does not perform the activity because of non-vision related problems. If this choice is selected, the item is coded as “missing”.

For the VFQ questionnaire, 12 sub-scales will be evaluated (see Table 9–2), and 11 of these sub-scales will be included in the total VFQ score.

Table 9–2 Sub-scales of the NEI VFQ 25 score

Sub-scale no.	Sub-scale	Number of items	(Recoded) items to be averaged	Sub-scale included in total scale
1	General Health	1	1	No
2	General Vision	1	2	Yes
3	Ocular Pain	2	4, 19	Yes
4	Near Activities	3	5, 6, 7	Yes
5	Distance Activities	3	8, 9, 14	Yes
	Vision specific:			Yes
6	Social Functioning	2	11, 13	Yes
7	Mental Health	4	3, 21, 22, 25	Yes
8	Role Difficulties	2	17, 18	Yes
9	Dependency	3	20, 23, 24	Yes
10	Driving	3	15c, 16, 16a	Yes
11	Color vision	1	12	Yes
12	Peripheral Vision	1	10	Yes

The total score is calculated as the arithmetic mean of all non-missing sub-scales (except General Health).

Due to this calculation approach, the total result will be non-missing as long as at least one sub-scale result is non-missing.

For a single sub-scale, the value will be determined as the average of the non-missing recoded item values assigned to this sub-scale. A sub-scale value will only be assessed as missing if all items for this sub-scale have “missing” as a result.

Title page

A randomized, double-masked, sham-controlled phase 3b/4 study of the efficacy, safety, and tolerability of intravitreal aflibercept monotherapy compared to aflibercept with adjunctive photodynamic therapy as indicated in subjects with polypoidal choroidal vasculopathy (PLANET)

Short title: Aflibercept in polypoidal choroidal vasculopathy

Test drug: BAY no. 86-5321 / Aflibercept / Eylea®

Study purpose: To compare the efficacy of intravitreally administered aflibercept monotherapy with aflibercept plus photodynamic therapy as indicated on the best-corrected visual acuity in subjects with polypoidal choroidal vasculopathy

Clinical study phase: 3b/4 Date: 25 NOV 2013

EudraCT no.: 2013-004464-54 Version no.: 1.0

Study no.: 16995

Sponsor: **Bayer HealthCare AG, D-51368 Leverkusen, Germany**

Sponsor's medical expert: Hui Wang (Cecilia), MD
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The study will be conducted in compliance with the protocol, International Conference on Harmonisation – Good Clinical Practice and any applicable regulatory requirements.

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Synopsis

Title	A randomized, double-masked, sham-controlled phase 3b/4 study of the efficacy, safety, and tolerability of intravitreal aflibercept monotherapy compared to aflibercept with adjunctive photodynamic therapy as indicated in subjects with polypoidal choroidal vasculopathy
Short title	Aflibercept in polypoidal choroidal vasculopathy
Clinical study phase	3b/4
Study objective(s)	<p>Primary objectives:</p> <ul style="list-style-type: none"> • To collect data reflecting the efficacy and safety of aflibercept with and without photodynamic therapy rescue treatment in subjects diagnosed with the polypoidal choroidal vasculopathy subtype of wet age-related macular degeneration • To explore whether intravitreally administered aflibercept monotherapy is non-inferior to that of aflibercept plus photodynamic therapy (as indicated) based upon best-corrected visual acuity in subjects diagnosed with the polypoidal choroidal vasculopathy subtype of age-related macular degeneration <p>Secondary objectives:</p> <ul style="list-style-type: none"> ▪ To estimate the proportion of subjects diagnosed with the polypoidal choroidal vasculopathy subtype of wet age-related macular degeneration who require rescue therapy ▪ To estimate whether or not and to what extent rescue therapy is beneficial in subjects diagnosed with the polypoidal choroidal vasculopathy subtype of wet age-related macular degeneration who have suboptimal responses to aflibercept monotherapy
Test drug(s)	Aflibercept (Eylea®)
Name of active ingredient	Aflibercept
Dose(s)	2 mg (0.05mL)
Route of administration	Intravitreal injection
Duration of treatment	<p>Maximum duration is 96 weeks. Subjects will receive 3 initial monthly doses, then injections every other month through Week 52. After Week 52, the treatment interval may be extended based on visual and anatomic outcomes (treat-and-extend period), if deemed appropriate by the treating investigator. Typically, the extension will be added in increments of 1 or 2 weeks, providing a more flexible scheme allowing fewer injections.</p> <p>Subjects with a suboptimal response at any time from Week 12 onward will receive rescue treatment (a monthly injection regimen) until their visual and anatomic outcomes allow extension of the treatment intervals.</p>

Reference drug(s) Name of active ingredient Dose(s) Route of administration Duration of treatment	Reference treatment is the adjunct administration of photodynamic therapy (as indicated) Verteporfin 6 mg/m ² Intravenously Subjects may receive photodynamic therapy according to the label
Indication	Polypoidal choroidal vasculopathy
Diagnosis and main criteria for inclusion	Active polypoidal choroidal vasculopathy confirmed by indocyanine green angiography
Study design	Randomized, controlled, double masked, multicenter study
Methodology	<p>This study comprises the following study phases:</p> <ul style="list-style-type: none"> • Screening • Run-in therapy (Week 0 to Week 8) • Randomization (Week 12) • Continued therapy (Week 12 to Week 52; and Week 52 to Week 96 [treat-and-extend period]) • End-of-treatment (Week 96) • Safety follow-up, if needed (30 days post-final treatment) <p>Subjects will be enrolled into the study after signing the informed consent form (ICF). After assessment of all screening procedures and confirmation of eligibility, all subjects will begin the run-in period and receive 3 injections of aflibercept in monthly intervals (Weeks 0, 4, and 8) then injections every other month through Week 52. After Week 52, subjects may receive aflibercept through Week 96 under a treat-and-extend regimen which will allow the extension of the treatment interval (typically in increments of 1 or 2 weeks) at the discretion of the investigator. Based on his or her judgment of the subject's visual and anatomic conditions, the investigator will inform the subject of when the next injection is due and will plan the next visit accordingly. When, or if, visual and anatomical outcomes indicate that the disease has re-activated, the aflibercept treatment interval will revert to the last treatment interval in which the disease was inactive (i.e., no signs of exudation were observed).</p> <p>At Week 12, subjects will be randomized in a ratio of 1:1 into one of two treatment groups:</p> <p style="padding-left: 40px;">A Group 1 subject will receive aflibercept and, if he or she qualifies, this subject will also receive rescue treatment with monthly injections of aflibercept (until visual and anatomical outcomes allow extension of the treatment interval) plus sham treatment with photodynamic therapy:</p> <p style="text-align: center;">aflibercept + <u>sham</u> photodynamic therapy</p>

	<p>A Group 2 subject will receive aflibercept and, if he or she qualifies, this subject will also receive rescue treatment with monthly injections of aflibercept (until visual and anatomical outcomes allow extension of the treatment interval) plus active treatment with photodynamic therapy:</p> <p style="text-align: center;">aflibercept + <u>active</u> photodynamic therapy</p> <p>Stratification at randomization will be based upon the presence or absence of qualification for rescue therapy as specified in the rescue therapy criteria at Week 12 and by ethnicity (Japanese or non-Japanese).</p> <p>Evaluations for qualification for rescue therapy will continue to be conducted at each visit from Week 12 to Week 88 (Week 96 is optional) and aflibercept plus active or sham PDT treatments may be given at any of these visits if rescue criteria are met. Qualification for rescue therapy will be based upon insufficient gain of best-corrected visual acuity, leakage, and presence of active polyps. <u>All of the following three criteria must be met:</u></p> <ol style="list-style-type: none"> 1. Best-corrected visual acuity of ≤ 73 Early Treatment Diabetic Retinopathy Study letters 2. Evidence of new or persistent fluid on optical coherence tomography 3. Evidence of active polyps on indocyanine green angiography <p>Additionally, <u>one of the following criteria must be fulfilled:</u></p> <ol style="list-style-type: none"> 4. Deterioration, no change, or insufficient improvement in best-corrected visual acuity from baseline of < 5 letters, or 5. Improvement in best-corrected visual acuity from baseline of ≥ 5 letters, but < 10 letters, and the investigator determines based on the course of visual and anatomic outcomes over time that photodynamic therapy might be of additional benefit to the subject. <p>Of note, best-corrected visual acuity and optical coherence tomography will be performed at each visit. An assessment by indocyanine green angiography will only be performed if Criteria 1 and 2 plus either Criteria 4 or 5 are met.</p> <p>For subjects who meet the need for rescue therapy and who were assigned to the active photodynamic therapy, verteporfin (Visudyne®) will be given according to the label. Treatment with photodynamic therapy may be delivered on the same visit day as aflibercept, preferably after the administration of aflibercept.</p> <p>Fundus photography and fluorescein indocyanine green angiography will be performed at Screening/Baseline, and at Week 52 and Week 96, and at all visits when assessment of rescue therapy treatment criteria (best-corrected visual acuity and optical coherence tomography) indicate that the subject may qualify for rescue therapy.</p> <p>A central reading center will be used for reading of imaging data including optical coherence tomography, fundus photography, and fluorescein indocyanine green angiography.</p> <p>Assessment of adverse events and vital signs will be performed at every visit.</p>
Type of control	Adjunctive photodynamic therapy as indicated
Number of subjects	Approximately 310

Primary variable	The primary efficacy variable is the change from study baseline in Early Treatment Diabetic Retinopathy Study best-corrected visual acuity letter score for the study eye at Week 52 of the study.
Plan for statistical analysis	<p>The primary efficacy variable analysis will be conducted on the full analysis set. Statistical testing will be conducted to prove the non-inferiority of aflibercept monotherapy (treatment group i=1) to aflibercept plus photodynamic therapy as indicated (treatment group i=2). The corresponding null hypothesis is $H_0: \mu_1 \leq \mu_2 - D$ versus the alternative hypothesis $K: \mu_1 > \mu_2 - D$, where D is the non-inferiority margin and μ_i, $i=1,2$, is the mean change in best-corrected visual acuity letter score for the study eye from study baseline at 52 weeks in treatment group i.</p> <p>The non-inferiority margin is 5 letters. The methodological approach will be the calculation of the two-sided 95% confidence intervals for the difference in the least squares means (aflibercept monotherapy treatment group minus aflibercept plus photodynamic therapy as indicated treatment group) of the change in Early Treatment Diabetic Retinopathy Study letter score from study baseline to 52 weeks based on a three-way analysis of covariance, with baseline measure as a covariate and treatment group, ethnicity, and qualification for rescue therapy at Week 12 as a fixed factors (last observation carried forward will be used for missing values at 52 weeks). Aflibercept monotherapy will be considered to be non-inferior to aflibercept plus photodynamic therapy as indicated if the confidence interval of the difference lies entirely above -5 letters, where a positive difference favors aflibercept monotherapy.</p>

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List of abbreviations

AE	Adverse event
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
aPTT	Activated partial thromboplastin time
AREDS	Age-related eye disease study
BCVA	Best-corrected visual acuity
CNV	Choroidal neovascularization
CRT	Central retinal thickness
CRO	Clinical research organization
eCRF	Electronic case report form
EOT	End of treatment
ETDRS	Early treatment diabetic retinopathy study
EU	European Union
FA	Fluorescein angiography
FAS	Full analysis set
Fc	Constant region
FP	Fundus photography
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
H ₀	Null hypothesis
IB	Investigator's Brochure
ICF	Informed consent form
ICGA	Indocyanine green angiography
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
INR	International normalized ratio
IOP	Intraocular pressure
IRB	Institutional Review Board
ISF	Investigator's Site File
IVT	Intravitreal(ly)
IxRS	Interactive voice/web response system
K _d	Dissociation constant
LOCF	Last observation carried forward
MedDRA	Medical dictionary for regulatory affairs
NEI VFQ-25	National eye institute 25-item visual function questionnaire
OCT	Optical coherence tomography
PASS 11	Power Analysis and Sample Size Software 11

PCV	Polypoidal choroidal vasculopathy
PDT	Photodynamic therapy
PID	Patient identification number
PT	Prothrombin time
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SC	Steering Committee
SID	Subject identification number
SMT	Safety Management Team
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
Tx	Treatment
UPCR	Urine protein:creatinine ratio
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
YAG	Yttrium aluminum garnet

1. Introduction

1.1 Polypoidal choroidal vasculopathy

Polypoidal choroidal vasculopathy (PCV) is a subtype of neovascular age-related macular degeneration (AMD) characterized by polypoidal dilations of abnormal choroidal vessels. Retinal pigment epithelial detachment, serous exudation and hemorrhages are sequelae of PCV and lead to retinal dysfunction and loss of visual acuity. Polypoidal choroidal vasculopathy is particularly prevalent in Asians. Clinical studies suggest that 24.6% to 64.5% of Asian wet AMD patients suffer from this subtype.^{1,2,3} In Europe, prevalence is estimated to be 4.0% to 9.8% of the wet AMD population.^{4,5,6} One single study in South America suggests a prevalence of 10.6% of wet AMD patients.⁷

The gold standard for diagnosis of PCV is indocyanine green angiography (ICGA).

1.2 Aflibercept, a vascular endothelial cell growth factor inhibitor

Vascular endothelial growth factor (VEGF) Trap-Eye (generic name: aflibercept) is a recombinant protein consisting of human VEGF receptor (VEGFR) extracellular domains fused to the constant region (Fc) portion of human immunoglobulin (Ig) G1. It contains portions of the extracellular domains of 2 different VEGFRs (Figure 1). VEGFR1 binds to VEGF with a high affinity (picomolar range), while VEGFR2 binds VEGF much less tightly. The recombinant protein is expressed in Chinese Hamster Ovary K1 cells. Recovery and purification of the protein is accomplished via a combination of filtration and chromatographic techniques. The protein is then formulated for intravitreal (IVT) administration to produce aflibercept.

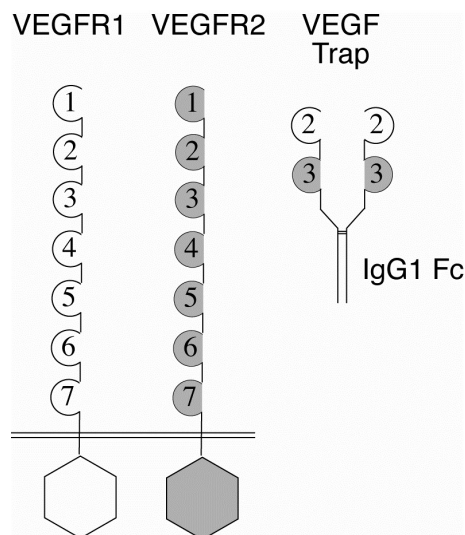


Figure 1: Structure of aflibercept (VEGF Trap)

The recombinant protein aflibercept exhibits very potent binding activity to human VEGF, with an equilibrium dissociation constant (K_d) of approximately 0.5 pM. This binding

activity was more potent relative to the activity of anti-VEGF agent ranibizumab (with a K_d in the order of 100 pM). The formulation, aflibercept is developed for intraocular use. Research using an animal ophthalmological disease model demonstrated that aflibercept could adequately inhibit the incidence of retinal neovascularization, choroidal neovascularization (CNV), and retinal edema. Further details can be found in the most recent version of the Investigator's Brochure (IB), which contains comprehensive information on the study drug.

Aflibercept is approved for wet AMD and central retinal vein occlusion in many countries. In particular, it has been investigated in a very large cohort of more than 2400 subjects in two pivotal clinical trials for wet AMD, VIEW 1 and VIEW 2.

1.3 Existing therapies for polypoidal choroidal vasculopathy

Anti-VEGF therapies other than aflibercept

The standard treatment for wet AMD is IVT injection of anti-VEGF agents; however, concerns have been raised that closure of polyps may be an important therapeutic goal in treatment of PCV. Thus, attempts to optimize PCV therapy have been made, either by combining anti-VEGF treatment with photodynamic therapy (PDT), an established gold standard treatment before anti-VEGF therapy was approved, or by exploring PDT as an alternative to anti-VEGF agents.

The most comprehensive research in the treatment of PCV so far was performed with ranibizumab in a 6-month 3-arm controlled clinical pilot study in approximately 60 patients who received ranibizumab monotherapy, or PDT monotherapy, or a combination of the two.⁸ The primary endpoint was complete polyp regression, which was best achieved in the combination therapy group (77.8%), closely followed by PDT monotherapy (71.4%), whereas ranibizumab monotherapy achieved polyp regression in only 28.6% of the patients. However, polyp regression does not seem to correlate well with visual acuity, and the outcome in best-corrected visual acuity (BCVA) was very similar in the three groups.

Aflibercept in polypoidal choroidal vasculopathy

In two large pivotal aflibercept studies (VIEW 1 and VIEW 2) in more than 2400 patients diagnosed with wet AMD, subjects with possible, probable or certain PCV were identified in a *post-hoc* analysis. (Data on file) Efficacy of aflibercept in PCV was not substantially different from the overall wet AMD population, however this result must be interpreted with caution as no ICGA was performed to confirm the diagnosis of PCV and the subgroup with PCV was comparably small.^{9,10}

Other

Steroids, thermal laser, and surgical approaches were used before the advent of anti-VEGF therapy. At this time, they no longer play a relevant role in the treatment of AMD of the PCV subtype.

Future therapy and rationale for the study

A number of reports have shown that subjects with sub-optimal responses to every other month dosing with anti-VEGF therapy may experience better outcomes following more

frequent dosing¹². Based upon these reports, the rescue regimen in the study described herein provides dosing of aflibercept in monthly intervals.

It remains unclear whether the enforced closure of polyps with PDT or PDT in combination with anti-VEGF offers any benefit over anti-VEGF alone as measured by visual acuity outcomes. Based upon these findings, many ophthalmologists have moved away from PDT and prefer anti-VEGF therapy only. To clarify whether aflibercept alone is efficacious, it is important to investigate the outcomes if PCV is treated with aflibercept monotherapy or aflibercept with optional adjunct PDT.

2. Study objectives

Primary objectives:

- To collect data reflecting the efficacy and safety of aflibercept with and without PDT rescue treatment in subjects diagnosed with the PCV subtype of wet AMD
- To explore whether intravitreally administered aflibercept monotherapy is non-inferior to that of aflibercept plus PDT (as indicated) based upon BCVA in subjects diagnosed with the PCV subtype of AMD

Secondary objectives:

- To estimate the proportion of subjects diagnosed with the PCV subtype of wet AMD who require rescue therapy
- To estimate whether or not and to what extent rescue therapy is beneficial in subjects diagnosed with the PCV subtype of wet AMD who have suboptimal responses to aflibercept monotherapy

3. Investigators and other study personnel

The Study Coordinating Investigator:

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All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature sheet before subject recruitment may start at the respective center. Likewise, all protocol amendments/integrated protocols must be signed and dated by the principal investigator before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

Safety evaluation bodies

A Steering Committee (SC), comprising Principal Investigators from the study sites and at least one Sponsor representative (e.g., the Global Clinical Leader) will guide the study in all aspects of safety and efficacy and will ensure that (i) all relevant information provided by investigators, the Sponsor's Global Pharmacovigilance department, and the central evaluation bodies (see below) is thoroughly reviewed, and (ii) all relevant decisions with regard to study conduct are made in a timely fashion. Activities of the SC will be governed by a charter, which describes the composition of the SC in more detail.

In addition, a Safety Management Team (SMT), led by the Sponsor's Global Safety Leader, will meet periodically to review safety data. Members of the SMT can include representatives from Global Pharmacovigilance, Pharmacoepidemiology, Clinical Development, Biostatistics, Data Management, Clinical Pharmacology, Preclinical Development, Regulatory Affairs, and Medical Affairs, as appropriate.

The SMT and Steering Committee will interact closely during the course of the study, and alert each other in order to assess thoroughly all relevant safety information.

Central evaluation bodies

Assessment of BCVA will be performed by site personnel who have been trained and certified by a qualified training center for assessment using the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. Only certified site personnel will be allowed to perform the examination. Documentation of this training and certification will be maintained on-site in the investigator site file (ISF).

Optical coherence tomography (OCT) images and ICGA performed for the purpose of evaluating subjects' eligibility for PDT will be read and evaluated locally for the purpose of decision-making with regard to PDT or sham PDT. Images will also be assessed by a central reading center for quantitative evaluation of pharmacodynamics parameters. Only qualified OCT and ICGA readers and technicians will be allowed to perform the examination and interpret the results. The results of fluorescein angiography (FA) including ICGA and fundus photography (FP) will also be evaluated centrally. The quality of FA and FP images will be controlled and maintained by training and certification of site personnel by the central reading center, and only qualified photographers/technicians will be allowed to perform FA and FP for the purposes of this study.

Blood and urine samples for laboratory safety determinations will be evaluated by a central laboratory.

4. Study design

This study is a phase 3b/4, randomized, double-masked, multi-center clinical trial that will be conducted at approximately 50 study sites in mainly Asian Pacific countries. After a run-in period of 12 weeks, subjects will be randomized in a 1:1 ratio to receive aflibercept 2 mg monotherapy plus sham PDT, or to receive aflibercept 2 mg plus PDT (given only if criteria are met).

4.1 Design overview

This study comprises the following study phases:

- Screening
- Run-in therapy (Week 0 to Week 8)
- Randomization (Week 12)
- Continued therapy (Week 12 to Week 52; and Week 52 to Week 96 [treat-and-extend period])
- End-of-treatment (EOT; Week 96)
- Safety follow-up, if needed (30 days post-final treatment)

Subjects will be enrolled into the study after signing the informed consent form (ICF). After assessment of all screening procedures and confirmation of eligibility, all subjects will begin the run-in period and receive 3 injections of aflibercept in monthly intervals (Weeks 0, 4, and 8) then injections every other month through Week 52. After Week 52, subjects may receive aflibercept through Week 96 under a treat-and-extend regimen which will allow the extension of the treatment interval at the discretion of the investigator (typically in increments of 1 or 2 weeks). Based on his or her judgment of the subject's visual and anatomic conditions, the investigator will inform the subject of when the next injection is due and will plan the next visit accordingly. When, or if, visual and anatomical outcomes indicate that the disease has re-activated, the aflibercept treatment interval will revert to the last treatment interval in which the disease was inactive (i.e., no signs of exudation were observed).

At Week 12, subjects will be randomized in a ratio of 1:1 into one of two treatment groups:

A **Group 1** subject will receive aflibercept and, if he or she qualifies, this subject will also receive rescue treatment with monthly injections of aflibercept (until the visual and anatomical outcomes allow extension of the treatment interval) plus sham treatment with PDT:

aflibercept + sham PDT

A **Group 2** subject will receive aflibercept and, if he or she qualifies, this subject will also receive rescue treatment with monthly injections of aflibercept (until the visual and anatomical outcomes allow extension of the treatment interval) plus active treatment with PDT:

aflibercept + active PDT

At the time of randomization, subjects will be stratified based upon the presence or absence of qualification for rescue therapy as specified in the rescue therapy criteria and by ethnicity (Japanese or non-Japanese).

Evaluations for qualification for rescue will be conducted at each visit from Week 12 to Week 88 (Week 96 is optional). Intensified aflibercept treatment plus active or sham PDT treatments may be given at any of these visits if treatment criteria are met. Qualification for rescue will be based upon insufficient gain of BCVA, leakage, and presence of active polyps.

All of the following three criteria must be met:

1. BCVA \leq 73 EDTRS letters
2. Evidence of new or persistent fluid on OCT
3. Evidence of active polyps on ICGA

Additionally, one of the following criteria must be fulfilled:

4. Deterioration, no change, or insufficient improvement in BCVA from baseline of < 5 letters, **or**
5. Improvement in BCVA from baseline of ≥ 5 letters, but < 10 letters, and the investigator determines based on the course of visual and anatomic outcomes over time that PDT might be of additional benefit to the subject.

Of note, BCVA and OCT will be performed at each visit (see Section 7.1 for details). An assessment by ICGA will only be performed if Criteria 1 and 2 plus either Criteria 4 or 5 are met.

All subjects will return to the study clinic at Weeks 24 and 40 for evaluations of safety and efficacy, at Week 52 for the primary endpoint visit, and at Week 96 for the end-of-treatment (EOT) visit regardless of when the last actual aflibercept injection (or PDT) treatment was performed. If a treat-and-extend subject receives an injection at Week 96 or within 4 weeks of Week 96, it is the responsibility of the treating investigator to follow-up on any AEs (including ongoing events) that may occur within 4 weeks following this treatment. Information regarding such events is to be reported under this protocol (i.e., not as spontaneous reports).

For subjects who meet the need for rescue treatment and are randomized to the active PDT group, verteporfin (Visudyne[®]) will be given according to the label. Treatment with PDT may be delivered on the same visit day as aflibercept, preferably after the administration of aflibercept. If the administration of PDT is delayed, it should be administered within 2-3 days after ICGA/FA, but not later than 7 days.

Fundus photography and ICGA will be performed at screening or baseline, and at Week 52 (primary endpoint visit) and Week 96 (EOT), and at all visits when BCVA and/or OCT results indicate that the subject may qualify for rescue treatment. In the second year (treat-and-extend visit schedule), these examinations will be mandatory only when BCVA and or OCT results indicate that the subject may qualify for rescue, and at the final visit at Week 96. If deemed necessary by the investigator, FA and/or ICGA may be performed more often.

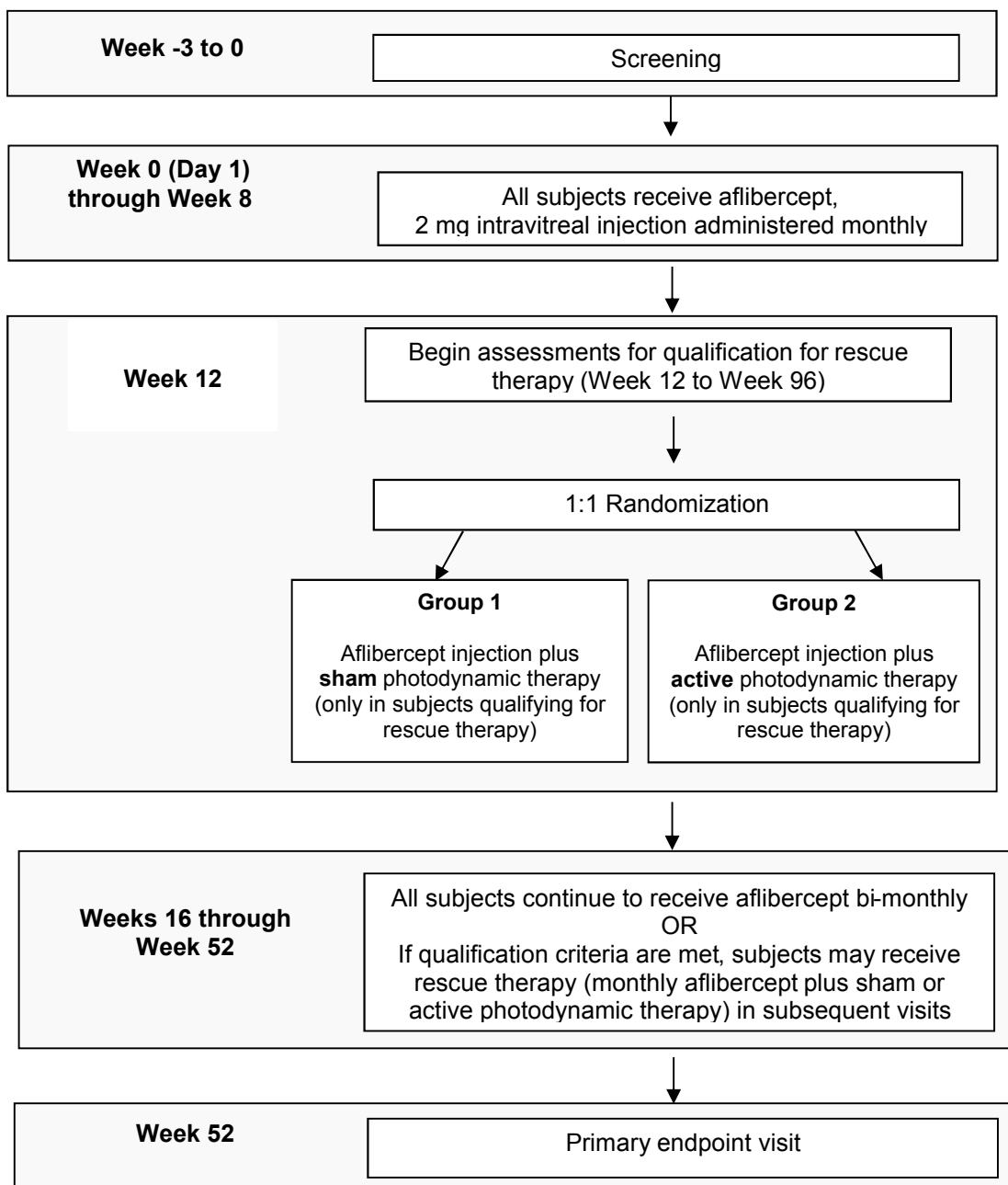
A central reading center will be used for reading of imaging data including OCT, FP, FA, and ICGA.

Assessment of adverse events (AEs) and vital signs will be performed at every visit.

Unscheduled visits may be planned at any time through the study if deemed necessary by the investigator. If necessary, an early termination visit that includes all EOT procedures may be scheduled.

Statistical analyses will be performed for two data cutoff points, Week 52 and Week 96.

The study design is presented in [Figure 2](#).



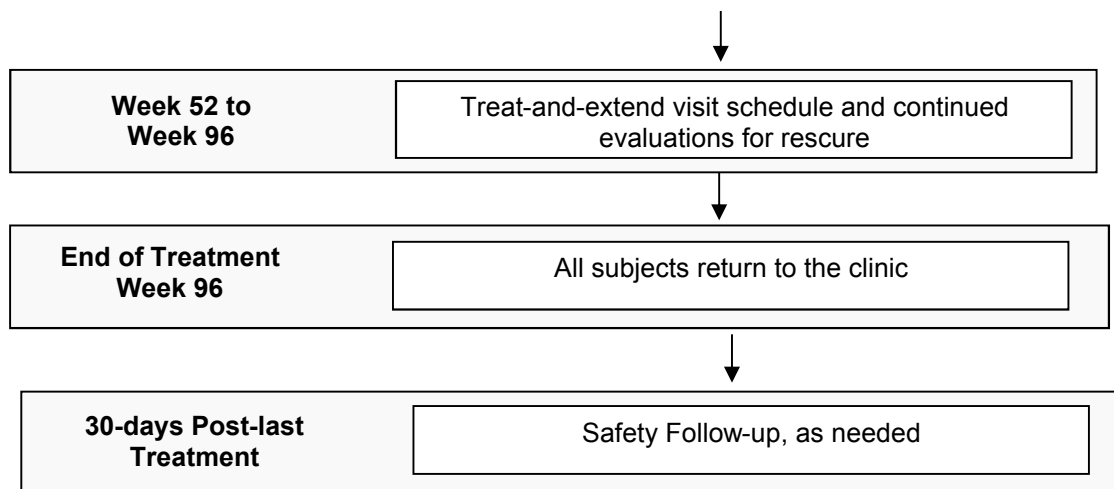


Figure 2: Study design

4.2 Selection of doses

The selection of the aflibercept dose and dosing interval is based on safety and efficacy data obtained from clinical studies in wet AMD, particularly in 2 large, pivotal Phase-3 studies in AMD in more than 2400 subjects. The dosing regimen reflects the aflibercept (EYLEA®) label. Aflibercept administration in this study is in accordance with the label for wet AMD, which describes 3 initial monthly doses followed by bi-monthly dosing as a standard regimen but does not exclude more frequent injections.

4.3 Justification of study design

Studies of aflibercept in wet AMD that included the enrollment of a subset of subjects suffering from the PCV subtype demonstrated that these subjects respond to anti-VEGF therapy in a similar way as other subjects with wet AMD. However, a definitive diagnosis of PCV by ICGA was not performed on these subjects.

The present study will provide responses to the following issues, which provide the justification for a sham-controlled study in subjects with diagnosed PCV:

- To date, there is no safety data for aflibercept in combination therapy with PDT
- From studies with anti-VEGF agents other than aflibercept,⁸ it is not clear whether or not and to what extent added PDT may improve the results in visual acuity
- The proportion of subjects in need of intensified aflibercept treatment or adjunctive PDT therapy is unknown
- No criteria exist that could predict which subjects would benefit from such additional treatment and which would not

The primary and secondary endpoints chosen for this study will demonstrate whether or not vision improvement or maintenance by aflibercept monotherapy is non-inferior to that

achieved by aflibercept/PDT combination therapy among subjects diagnosed with PCV. Additionally, the analysis of data obtained from those subjects who fulfill the criteria for suboptimal response (established in consensus with leading ophthalmologists in the field) will provide information for an estimate of whether or not and to what extent rescue therapy has added benefit. Finally, even if non-inferiority of aflibercept monotherapy cannot be established and even if the additional benefit of combination therapy must be acknowledged in subjects diagnosed with PCV, it will be of great interest to learn more about the proportion of patients who need rescue therapy.

The non-inferiority design is appropriate for the hypothesis. Testing for superiority would only be required for establishing the superiority of combination therapy over monotherapy, which is not the intention of this trial.

In the VIEW 1 and VIEW 2 studies, most subjects had reached significant improvement of their visual acuity after 3 initial monthly doses. It is therefore believed that the 12-week visit is the ideal time point for initiating assessment of subject eligibility for rescue therapy.

All drugs and procedures administered in this study have a well-defined safety profile.

For justification of the sample size and statistical methods, see Section 8.

4.4 End of Study

Planned study visits will continue until Week 96. All subjects are to return to the study site for this visit, irrespective of the timing of their last treatment visit. The final treatment may be administered at this visit, but for most subjects this visit will serve as an End-of-Study visit following their last treatment in the previous 8 weeks. Any subject who received their last treatment with either aflibercept or PDT within 4 weeks of Week 96 should return to the study site (or receive a follow-up telephone call) for an additional follow-up visit for safety 30 days following their last treatment. If a treat-and-extend subject receives an injection at Week 96 or within 4 weeks of Week 96, it is the responsibility of the treating investigator to follow-up on any AEs (including ongoing events) that may occur within 4 weeks following this treatment. Information regarding such events is to be reported under this protocol (i.e., not as spontaneous reports).

For each participating European Union (EU) country, the end of the study according to the EU Clinical Trial Directive will be reached when the last visit of the last subject for all centers in the respective country has occurred.

The end of the study as a whole will be reached as soon as the end of the study according to the above definition has been reached in all participating countries (EU and non-EU).

5. Study population

5.1 Eligibility

Subjects eligible for this study will have received a diagnosis of PCV as specified in the inclusion criteria below. Prior to administration of study drug, the site will confirm subject eligibility based on: medical history, ophthalmic examination, physical examination, laboratory testing, OCT, and imaging studies including ICGA.



Only one eye per subject may be enrolled in the study. For subjects who meet eligibility criteria in both eyes, the eye with the worst visual acuity will be selected as study eye. If both eyes have equal visual acuity, the eye with the greatest retinal thickness at the center point will be designated as the study eye.

If a subject's fellow (non-study) eye requires treatment for wet AMD including the PCV subtype at study entry, or during the subject's participation in the study, the fellow eye may receive any treatment for wet AMD including the PCV subtype within the framework of routine medical care deemed appropriate by the investigator, with the exception of PDT. Subjects who receive treatment for the fellow eye should remain in the study. Safety for the fellow eye will be monitored and AEs will be collected.

If a subject fails screening, i.e., does not meet all inclusion criteria or meets one or more of the exclusion criteria, the subject may be re-screened one time if the reason(s) for the screening failure is (are) resolved.

5.1.1 Inclusion criteria

1. Able to read and understand the ICF (or, if unable to read due to visual impairment, to be read to verbatim by the person administering the informed consent or a family member).
2. Signed informed consent.
3. Men and women ≥ 50 years of age.
4. Diagnosis of symptomatic macular PCV in the study eye established by ICGA at the study center
5. Greatest linear dimension of the lesion of < 5400 μm (approximately, 9 Macular Photocoagulation Study disk areas), assessed by ICGA
6. An ETDRS BCVA of 73 to 24 letters in the study eye.
7. Women of childbearing potential and men, when sexually active, must agree to use adequate contraception from the time point of signing the informed consent form until 3 months after the last study drug administration. Acceptable methods of contraception include (i) condoms (male or female) with or without a spermicidal agent; (ii) diaphragm or cervical cap with spermicide; (iii) intra-uterine device; (iv) hormone-based contraception.
8. Willing, committed, and able to return for all clinic visits and complete all study-related procedures.

5.1.2 Exclusion criteria

1. Prior use of intravitreal or sub-tenon corticosteroids in the study eye within 3 months prior to study entry.
2. Any prior use of intraocular anti-VEGF agents in the study eye, or systemic use of anti-VEGF products within 3 months prior to study entry
3. Prior macular laser treatment in the study eye including PDT.



4. Only one functional eye (a functional eye is defined as one that is not legally blind) even if that eye is otherwise eligible for the study. Furthermore, subjects with only one eligible eye should not have other ocular conditions with poorer prognosis in the fellow eye.
5. Any ocular disorders in the study eye that, in the opinion of the investigator, may confound interpretation of study results or interfere with subject safety, including, but not limited to:
 - a. Significant media opacities, including cataract, which can interfere with visual acuity, or fundus photography.
 - b. Significant scarring or atrophy in the macula that indicates substantial irreversible vision loss, or other conditions limiting capacity for visual acuity improvement.
 - c. Decrease in BCVA due to causes other than wet AMD/PCV.
 - d. History or presence of diabetic macular edema or diabetic retinopathy
 - e. Vitreomacular traction or epiretinal membrane in the study eye evident biomicroscopically or on OCT that is considered by the investigator to significantly affect central vision.
 - f. Ocular inflammation (including trace or above) or external ocular inflammation in the study eye. Evidence at examination of infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye or current treatment for serious systemic infection.
 - g. History of idiopathic or autoimmune uveitis in either eye.
 - h. Aphakia or absence of the posterior capsule; with the exception of pseudoaphakia or yttrium aluminum garnet (YAG) capsulotomy in the study eye.
6. Concomitant systemic disease which may affect the subject's regular visits or contraindicate use of PDT including, but not limited to
 - a. Uncontrolled hypertension defined as a single measurement of systolic >180 mm Hg, two consecutive measurements of systolic >160 mm Hg, or one measurement of diastolic >100 mmHg on optimal medical regimen
 - b. Uncontrolled diabetes mellitus, in the opinion of the investigator.
 - c. History of cerebrovascular disease or myocardial infarction within 6 months prior to entry into the study.
 - d. Renal failure requiring dialysis or renal transplant.
 - e. Clinically relevant impairment of liver function, in particular porphyria
7. Participation in an investigational study within 30 days prior to the initial screening visit that involved treatment with any drug (excluding vitamins and minerals) or device.

8. Pregnancy or lactation.
9. History of allergy to fluorescein used in fluorescein angiography, iodine and/or indocyanine green.
10. History of allergy to aflibercept, verteporfin, or their excipients.

5.2 Withdrawal of subjects from study

5.2.1 Withdrawal

Subjects *must* be withdrawn from the study for the following reasons:

- At their own request or at the request of their legally acceptable representative.
- At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Although it is the subject's right to withdraw without giving reasons, the investigator should document any particular reason for withdrawal if the subject is willing to disclose them.
- If, in the investigator's opinion, continuation of the study would be harmful to the subject's well-being.
- If during the course of the study, the fellow eye requires treatment with PDT
- If the subject becomes pregnant.

Subjects *may* be withdrawn from the study for the following reasons:

- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already been administered at least one dose of study drug.

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" is regarded a "screening failure".

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

In all cases, the reason for withdrawal must be recorded in the electronic case report form (eCRF) and in the subject's medical records.

Details for the premature termination of the study as a whole (or components thereof [e.g. centers, treatment arms, dose steps]) are provided in Section 10.

5.2.2 Replacement

Once randomized (at Week 12), subjects will not be replaced.

5.3 Subject identification

At screening, after signing the ICF, each subject will be assigned a unique multi-digit subject identification number (SID) for unambiguous identification (some electronic data systems may use PID [patient identification number] instead of SID). The SID will be constructed as follows:

- Digits 1 to 2: unique country code (International Organization of Standardization [ISO] code)
- Digits 3 to 5 center code (unique within each country)
- Digits 6 to 9: subject code (unique within each center)

Once allocated, the subject's SID number will identify the subject throughout the study, and will be entered into the eCRF.

6. Treatments

6.1 Treatments to be administered

6.1.1 Aflibercept

All subjects, regardless of assignment to treatment group A or B, will receive aflibercept treatment as per the label. They will be treated with 2 mg aflibercept (0.05 mL injected intravitreally) every month for the first 3 months. At Week 12, subjects will be randomized in a ratio of 1:1 to one of two groups (Group 1 or Group 2):

Group 1: aflibercept (2 mg) + sham PDT (if the defined criteria for rescue treatment are met; Section 6.1.2)

Group 2: aflibercept (2 mg) + active PDT (if the defined criteria for rescue treatment are met; Section 6.1.2)

In subjects without a need for rescue therapy, aflibercept will be given at Weeks 0, 4, 8, 16, 24, 32, 40, and 48. In the second study year, a more flexible schedule will apply, and treatment intervals may be extended beyond 8 weeks at the discretion of the investigator (typically in increments of 1 or 2 weeks) in a treat-and-extend paradigm. Based on his or her judgment of the subject's visual and anatomic conditions, the investigator will inform the subject of when the next injection is due and will plan the next visit accordingly. When, or if, visual and anatomical outcomes indicate that the disease has re-activated, the aflibercept treatment interval will revert to the last treatment interval in which the disease was inactive (i.e., no signs of exudation were observed).

In subjects with a need for rescue therapy at Week 12 or thereafter, aflibercept will initially be administered monthly. Once visual and anatomic outcomes allow, the treatment interval may be extended at the discretion of the investigator (typically in increments of 1 or 2 weeks). Thus, subjects who require rescue therapy will be on a flexible visit schedule which will allow more frequent treatments than the standard bi-monthly regimen; however, aflibercept may not be administered more frequently than once monthly. Subjects who receive rescue treatment must return to the clinic for mandatory visits at Weeks 24, 40, 52,

and 96 for assessment of safety and efficacy endpoints regardless of whether they require an injection at these visits. In the second study year, the treatment intervals may be extended beyond the regimen used in the first year using the treat-and-extend paradigm described above.

6.1.2 Verteporfin

Photodynamic therapy (or sham) will only be given to the subjects in each group that qualify for rescue at or after the Week 12 visit. Evaluations for qualification for rescue will be conducted at each visit from Week 12 to Week 88 (Week 96 is optional) and active or sham PDT treatments may be given at any of these visits if treatment criteria are met. Qualification for rescue will be based upon insufficient gain of BCVA, leakage, and presence of active polyps.

All of the following three criteria must be met:

1. BCVA \leq 73 EDTRS letters
2. Evidence of new or persistent fluid on OCT
3. Evidence of active polyps on ICGA

Additionally, one of the following criteria must be fulfilled:

4. Deterioration, no change, or insufficient improvement in BCVA from baseline of $<$ 5 letters, **or**
5. Improvement in BCVA from baseline of \geq 5 letters, but $<$ 10 letters, and the investigator determines based on the course of visual and anatomic outcomes over time that PDT might be of additional benefit to the subject.

For subjects who meet the need for rescue, verteporfin (Visudyne[®]) will be given according to the label. Treatment with PDT may be delivered on the same visit day as aflibercept, preferably after the administration of aflibercept. If the administration of PDT is delayed, it should be administered within 2-3 days after ICGA/FA, but not later than 7 days.

6.2 Identity of study treatment

Details of the study drug are given in [Table 6-1](#).

The study drug, aflibercept will be manufactured by Bayer Pharma AG, Berlin, Germany. The study drug, aflibercept will be supplied by the Sponsor in sealed, single-use, sterile 2-mL vials, each with a final extractable volume of 0.10 mL.

Table 6-1: Investigational test product

Name	Dose	Concentration	Volume	Formulation	Composition
BAY 86-5321 / aflibercept	2 mg	40 mg/mL	Injected: 0.05 mL	For intravitreal injection	40 mg aflibercept /mL, 5% sucrose, 10 mM sodium phosphate, pH 6.3, 0.03% polysorbate 20, 40 mM sodium chloride, water for injection

Study drug will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the label will be made available to the study site upon request.

For all study drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk ware of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies quality assurance group.

A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor study file.

6.3 Treatment assignment

At Week 12, before any injection, subjects will be randomized in a ratio of 1:1 to Group 1 or Group 2 (stratified by qualification/no qualification for rescue and by Japanese subject yes/no). The randomization list will be generated by the 'Randomization Management' department of the Bayer Pharma AG using the Bayer standard randomization tool 'RANDOM'. This randomization list will be uploaded into the interactive voice/web response system (IxRS) of the IxRS supplier to control the correct treatment assignment of each subject.

6.4 Dosage and administration

6.4.1 Storage

Aflibercept vial: Aflibercept is to be stored refrigerated (2°C to 8°C) and should not be frozen. An unopened vial of aflibercept may have an excursion to room temperature (below 25°C) for up to 24 hours. The vial should be stored protected from light in its outer carton.

Aflibercept prepared dose: Based on stability data and lack of bacteriostatic agents, a syringe containing a prepared dose of aflibercept may only be kept at room temperature (25°C) for up to 2 hours.

Verteporfin: Verteporfin is to be stored per commercial package instructions.

6.4.2 Dosage

The volume of aflibercept IVT injection will be 50 µL (0.05 mL) for the 2 mg aflibercept dose.

Photodynamic therapy will be administered according to the label for verteporfin (Visudyne®).

6.4.3 Administration

Please note: Aflibercept should be delivered before PDT treatment. If PDT administration is performed before aflibercept injection, strong light for the injection should be avoided. Photodynamic therapy or sham PDT may be administered on the same clinic day as

aflibercept. If administration of PDT is delayed, it should be administered within 2-3 days after ICGA/FA, but not later than 7 days.

6.4.3.1 Aflibercept

The IVT administration of aflibercept is to be completed within 2 hours of the start of dose preparation.

When aflibercept vials are taken out of the refrigerator, the solution should be visually inspected and should have no evidence of turbidity. If particulates, cloudiness, or discoloration is visible, the vial must not be used. Based on stability data and lack of bacteriostatic agents, aflibercept dosing solution may only be kept at room temperature (25°C) for up to 2 hours.

The study drug will be withdrawn using aseptic technique through an 18-gauge filter needle attached to a 1-mL syringe. The needle will be discarded after withdrawal of the vial contents and should not be used for IVT injection. The needle should be replaced with a sterile 30-gauge needle for the IVT injection. The contents in the syringe should be expelled until the plunger is aligned with the line that marks 0.05 mL on the syringe.

6.4.3.2 Photodynamic therapy

Verteporfin is a light-activated drug used in PDT. Visudyne (verteporfin for injection) is manufactured by Parkedale Pharmaceuticals Inc. USA, and will be packaged by Novartis Pharma S.A.S., France.

The finished drug product is a lyophilized dark-green cake.

Generic/Trade Name: Verteporfin / Visudyne

Specification: 15 mg

Composition: 2.0 mg/mL Verteporfin

Lactose

Egg phosphatidylglycerol

Dimyristoyl phosphatidylcholine

Ascorbyl palmitate

Butylated hydroxytoluene

Verteporfin will be administered and PDT performed according to the current Visudyne package labeling. The sham PDT procedure will consist of the IV administration of a 5% dextrose solution or physiological saline (provided by the study site) and a sham laser procedure (i.e., a true laser light will not be used) that will mimic the laser procedure of the active PDT treatment (standard fluence laser). The verteporfin infusion/sham infusion and laser/sham laser treatment will be performed by an unmasked physician.

6.5 Masking

All study-site personnel (except for those performing the unmasked roles as described below and in [Table 6-2](#)), must remain blinded or masked to treatment assignment of subjects in order to ensure an unbiased assessment of visual acuity, safety, and ancillary study measures. An independent monitor will be responsible for pharmacy site visits and will be unmasked to study treatment. Subjects, all other study personnel, and Steering Committee members must remain masked to treatment assignment.

Site personnel should not change between masked and unmasked roles. Under no circumstances may the unmasked physician administering PDT treatment make efficacy assessments or determine whether the subject meets the rescue criteria.

Active and sham verteporfin will be masked by delivery from a covered infusion line and will be administered by the unmasked investigator.

Masked roles

The masked principal investigator is responsible to (i) assess AEs, (ii) perform the masked assessment of efficacy, and (iii) assess qualification for rescue therapy at Weeks 12 through 88 (Week 96 assessment is optional). The masked principal investigator may also perform IVT injections of aflibercept.

Depending on their function, masked personnel are also responsible for assessing AEs as they occur, and performing the masked assessments of visual acuity, FA including ICGA and FP, and OCT, and other non-ophthalmic assessments (e.g., questionnaire, vital signs, medical history).

Unmasked roles

An unmasked physician, separate from the masked principal investigator, will perform verteporfin (Visudyne®) infusion for PDT and dextrose (or physiological saline) infusion for sham PDT, and will apply active laser or sham laser. The subject must remain unaware of the treatment assignment; thus, the infusion line and vial containing the infusion solution must be covered and remain unidentifiable to the subject. The unmasked physician will not have any role in the study beyond the receipt, tracking, preparation, destruction, and administration of verteporfin. An unmasked drug handler (e.g., pharmacist) may be assigned to handle receipt, storage, and preparation of verteporfin and sham infusion vials.

Every effort must be made to ensure that all study-site personnel other than those designated as unmasked remain masked to the treatment assignment. Independent study personnel responsible for drug supply and unmasked monitors who are not otherwise involved in the conduct of the study will be unmasked to study treatments.

All individuals performing unmasked roles must be trained for maintenance of the masking measures required in the context of this study.

An overview of the masked and unmasked study personnel is presented in [Table 6-2](#).

Table 6-2: Masked and unmasked personnel

Masked personnel
Principal investigator
Investigator
Study nurse
Monitor (clinical research associate)
Visual acuity examiner
Study staff for fluorescein angiography including fluorescein indocyanine green angiography
Study staff for fundus photography
Study staff for optical coherence tomography
Unmasked personnel
Investigator administering verteporfin, or sham, and performing active or sham laser
Drug handler/Pharmacist dispensing verteporfin or dextrose (or physiological saline) vials for infusion

Note: IVT injection of aflibercept may be performed by masked or unmasked personnel

Emergency unblinding / unmasking by the investigator

In compliance with applicable regulations, in the event of a suspected unexpected serious adverse reaction ([SUSAR]; Section 7.5.1.5), the subject's treatment code will usually be unblinded before reporting to the health authorities, ethic committees and investigators (see Section 7.5.1.4) if the SUSAR was related to the blinded treatment.

In the event of a medical emergency or other situation in which knowledge of a subject's assigned treatment is essential to the medical management of the subject, the investigator may unmask the treatment group to which the subject is assigned. The investigator must call the IxRS to request unmasking. Each unmasking event will be reported to the Sponsor and the reason for the unmasking must be documented in detail in the subject's hospital chart and eCRF.

Breaking the mask will automatically disqualify the subject from receiving any further study treatment with verteporfin. However, as described in Section 5.2, if a subject is prematurely discontinued from study treatment, every effort should be made not to terminate the subject from the study and to follow the subject for safety endpoints on the original visit schedule until the Week 96 Visit.

Although the unmasked physician at the study site (i.e., the physician performing the active/sham infusion for PDT) will be aware of a subject's treatment assignment, this information should not be provided to other site personnel, including the investigator, at any time during the conduct of the study, except in the case of an emergency in which the process for emergency unmasking (as described above) cannot be followed and in which time is essential to protecting the safety of the subject.

6.6 Drug logistics and accountability

All study drugs will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/clinical research organization [CRO]), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of

batch numbers and expiry dates can be found in the sponsor study file; the site-relevant elements of this information will be available in the investigator site file.

Aflibercept vials are to be stored at 2°C to 8°C. The drug may not be frozen. Exposure of the material to temperatures outside these limits, except for warming prior to administration, must be avoided as it may result in loss of activity. Records of actual storage conditions (i.e., temperature log) at the study site must be maintained. These must include a record of the dates on which the storage refrigerator was checked, the initials of the person checking the temperature, and the temperature at the time.

The responsible site personnel will confirm receipt of study drug via IxRS and will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

Written instructions on medication destruction will be made available to affected parties as applicable.

The unmasked physician or unmasked drug handler is responsible for the accountability of all used, partially used, and unused study drug for active and sham PDT. Drug accountability records must be kept current and should contain the dates, quantities, kit numbers, and batch numbers (or lot numbers) of study drug received by the investigator, dispensed or administered to specified subjects, disposed of at the site (disposal at the site may occur only with a Sponsor approval), or returned to the Sponsor or a specified designee for disposal. Drug accountability will be overseen by an unmasked monitor. All inventories, along with shipment receipts, shipment temperature recordings (if applicable), storage temperature logs, pharmacy dose preparation logs, and IxRS confirmation reports must be made available for inspection by the unmasked monitor. At the conclusion of the study, photocopies of all drug accountability records will be provided by each site to the Sponsor.

6.6.1 Packaging

All aflibercept study medication will be packaged with a kit number.

Aflibercept study drug will be supplied by the Sponsor in sealed, single-use, sterile 2-mL vials, each with a final extractable volume of 0.10 mL. Each aflibercept treatment kit will contain one vial of 40 mg/mL aflibercept. In accordance with local regulations, each kit may additionally contain 1 18-gauge filter needle.

6.6.2 Labeling

The study-drug label will generally contain the following information according to regulations applicable to the study countries. Additional information, as required, may be added to the study-drug label. In certain cases, local regulations may also require some of the following information to be removed.

- Name and address of Sponsor
- Protocol number
- Kit number

- Lot number
- Dosage form
- Quantity
- Storage conditions
- Expiration date
- Route of administration
- “To be Used as Instructed by the Clinical Study Documentation. For Clinical Trial Use Only.”

Each vial of aflibercept will be labeled. The SID number will be recorded on each vial and the SID number and investigator name (if locally required) will be recorded on the kit boxes for all the treatment kits. Each kit box will have a label with a tear-off section containing the study number, kit number, and a place to enter the SID number; this tear-off section will be completed and stored in the ISF. The kit number will be recorded in the subject’s source documentation and also entered into the eCRF.

6.6.3 Supply

6.6.3.1 Aflibercept

The treatment kits will be shipped to the investigator at regular intervals or as needed during the study. Study drug will be shipped to the site using appropriate methods to maintain transport conditions within those recommended by its stability profile. The investigator, or an approved representative (e.g., pharmacist), will ensure that all received study drugs are stored in a secured area on site, under recommended storage conditions and in accordance with applicable regulatory requirements.

6.6.3.2 Verteporfin

Verteporfin will be purchased by each study site and reimbursed by the sponsor. Sponsor-supplied study-specific labeling will be provided to each study site.

6.6.4 Return

At the end of the study and following reconciliation and documentation by the site unmasked monitor, all used, partially used, and unused vials of aflibercept will either be destroyed at the site or returned to a specified designee for disposal.

6.7 Treatment compliance

All study drug will be administered at the study site, therefore, compliance with study drug dosing will be monitored by review of clinic records (e.g., hospital charts) by the unmasked monitor.

6.8 Post-study therapy

After the end of this study, further treatment of PCV may be indicated. Subjects may receive any appropriate subsequent treatment in the context of routine clinical practice as judged necessary by the treating physician. Such further treatment will occur at the subject's expense and outside the purview of this study.

6.9 Prior and concomitant therapy

Subjects who received certain therapies for PCV within defined time frames are excluded from the study per exclusion criteria. Permissible prior treatments for PCV and time intervals to be observed are described in Section 5.1.1 and 5.1.2.

Once enrolled into the study (i.e., after signing the ICF), subjects may not receive any treatment for PCV other than the study drug and sham or active PDT in the study eye until completion of the Week 96 or early termination assessments. No PDT may be administered from the time of enrollment up to Week 12.

If the fellow eye has wet AMD including the PCV subtype, it may receive any approved treatment for this condition other than PDT. The fellow eye is not considered an additional study eye and any treatment of this eye should be scheduled to occur after formal visit procedures for the study eye have been completed at any given clinic visit. Data collected for the fellow eye in the context of routine evaluations will not be entered into the database; however, safety of the fellow eye will be monitored and AEs will be collected and recorded.

Any previous and/or concomitant treatments administered to the fellow eye will be recorded in the source documents and entered in the Previous and Concomitant Medications screen of the eCRF using the brand name.

Any other medications that are considered necessary for the subject's welfare, and that are not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator, with the exceptions noted above and in Sections 5.1.1 and 5.1.2. All concomitant medications are to be documented in the eCRF.

All previous and concomitant medications recorded in the eCRF will be coded by the Sponsor using an internationally recognized and accepted coding dictionary.

7. Procedures and variables

7.1 Schedule of procedures

This study comprises the following study phases:

- Screening
- Run-in therapy (Week 0 to Week 8)
- Randomization (Week 12)
- Continued therapy (Week 12 to Week 52; and Week 52 to Week 96 [treat-and-extend period])

- End-of-treatment (EOT; Week 96)
- Safety follow-up, if needed (30 days post-final treatment)

At screening, the purpose and the design of the study as well as the risks and benefits of the investigational program will be explained to the subject. Subjects will be given time and opportunity to ask questions and decide about participation. Signed and dated ICFs will be obtained by the investigator at screening, prior to the initiation of any study-related assessments or procedures. Assessments for eligibility will be performed.

After confirmation of eligibility, treatment will begin on Day 1 (Baseline); however, if screening data are available and eligibility is immediately confirmed, screening and baseline procedures may be combined into one study visit. Thereafter, study visits are to be scheduled within a window of ± 7 days of the specified study timing. In the event of schedule slippage between the real visit and the original schedule, every effort should be made to return the subject to the original schedule.

Randomization will occur at Week 12 after assessment of rescue criteria (Section 6.1.2).

After Week 12, in subjects with no need for rescue therapy, treatment will continue bi-monthly through Week 52, with an evaluation for the primary endpoint (mean change in BCVA from baseline) to be conducted at Week 52. Subjects with a need for rescue therapy may follow a more flexible regimen allowing injections more frequently than every 8 weeks through Week 52; however, these subjects must return to the clinic for mandatory visits at Weeks 24, 40, and 52. For all subjects, treatment may continue from Week 52 through Week 96 on a flexible treat-and-extend basis; however, only subjects with a need for rescue therapy may undergo injections more frequently than every 8 weeks. It is expected that the majority of subjects will likely receive their final treatment with aflibercept and/or PDT not later than Week 92. If a treat-and-extend subject receives an injection at Week 96 or within 4 weeks of Week 96, it is the responsibility of the treating investigator to follow-up on any AEs (including ongoing events) that may occur within 4 weeks following this treatment. Information regarding such events is to be reported under this protocol (i.e., not as spontaneous reports).

All subjects must return to the clinic for EOT evaluations at Week 96.

All activities and evaluations scheduled during the study are summarized in Section 7.1.1. A tabulated overview of the schedule of procedures and assessments at each visit is provided in Table 7-1.

Table 7-1: Table of procedures

Epoch	Screening	Treatment							EOT or Early Term	As needed Safety Follow-up ⁱ
		Wk -3 to 0 ^a	Wk 0 ^a	Wk 4, 8	Wk 12	Wk 16, 24, 32, 40, 48 ^b	Rescue ^b	Wk 52		
Study Visits	screening	Wk 0	Wk 4, 8	Wk 12	Wk 24, 40 ^b	Wk 24, 40 ^b	Wk 52		Wk 96 ^h	30 d post-last tx
Mandatory Study Visits	screening	Wk 0	Wk 4, 8	Wk 12	Wk 24, 40 ^b	Wk 24, 40 ^b	Wk 52		Wk 96 ^h	30 d post-last tx
Window	-	Day 1	± 7 d	± 7 d	± 7 d	± 7 d	± 7 d	± 7 d	± 7 d	± 2 d
Procedures										
Informed consent, eligibility criteria, demographic data	X	X								
Medical/ophthalmic history	X									
Interval history including AEs	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X
NEI VFQ-25 questionnaire		X					X		X	
Physical examination	X									
Weight	X						X		X	
Vital signs	X	X	X	X	X	X	X	X	X	
Intraocular pressure ^c	X	X	X	X	X	X	X	X	X	
Slit lamp	X	X	X	X	X	X	X	X	X	
Indirect ophthalmoscopy	X	X	X	X	X	X	X	X	X	
Optical coherence tomography	X	X	X	X	X	X	X	X	X	
Gonioscopy ^d	X						Optional		Optional	
BCVA using ETDRS chart	X	X	X	X	X	X	X	X	X	
FP and FA ^e and Indocyanine green angiography	X			X ^f	X ^f	X	X	X ^f	X	
Hematology and chemistry	X									
Serum pregnancy test	X									
PT/INR and aPTT	X									
Urinalysis ^e	X									
Assessment of rescue criteria				X	X	X	X	X	Optional	
Randomization				X						
Aflibercept injection		X	X	X ^g	X	X	X	Allowed	Optional	
PDT or sham PDT ^g				X	X	X	X	Allowed	Optional	

Abbreviations: Wk = week; V = visit; d = day; EOT = End-of-Treatment; AE = adverse event; NEI VFQ-25 = National Eye Institute 25-item Visual

Function Questionnaire; BCVA = best-corrected visual acuity; ETDRS = Early treatment diabetic retinopathy study; FP = fundus photography; FA = fluorescein angiography; PT = prothrombin time; aPTT = activated partial thromboplastin time; INR = international normalized ratio; PDT = photodynamic therapy; Term = termination; tx = treatment

- a. If screening eligibility is confirmed immediately and time permits, baseline procedures may be conducted at screening thus combining screening and Day 1 into one visit
- b. Study visits may occur more frequently if indicated based upon the implementation of rescue treatment. Additionally, visit frequency may be altered beyond Week 52 by the flexible “treat-and-extend” visit schedule. Clinic visits at Weeks 24, 40, 52, and 96 are mandatory for subjects undergoing rescue therapy regardless of whether a treatment is scheduled for that visit.
- c. To be performed prior to aflibercept injection and again at 30-60 minutes post injection. Non-contact tonometry is permitted, but if pathological measurements are obtained, a more accurate measurement should be performed with contact-tonometry.
- d. Both eyes at screening and Week 96 and the study eye alone at Week 52. Note: gonioscopy is required at screening, but is optional at the investigator’s discretion at Weeks 52 and 96.
- e. Urine should be collected prior to FA
- f. Except for required assessments at screening, Week 52, and Week 96, this assessment will be performed as needed for subjects meeting the criteria for visual acuity and OCT in the rescue criteria
- g. Only in subjects qualifying for rescue; i.e., respective criteria fulfilled
- h. All subjects must return for the Week 96 visit, irrespective of the timing of their last treatment with aflibercept or PDT
- i. An as needed follow-up visit (or telephone call) is required only for subjects who received their last treatment with aflibercept or PDT within 4 weeks of or at the Week 96 visit

7.1.1 Timing of assessments

7.1.1.1 Screening (Week -3 to Week 0)

At the screening visit, the following procedures and assessments will be performed:

- Signed informed consent
- Inclusion/exclusion criteria
- Demographics
- Medical history (including smoking history) and ophthalmic history
- Adverse events
- Prior and concomitant medications
- Weight (kg)
- Vital signs (pulse and blood pressure)
- Physical examination
- Laboratory assessment:
 - Hematology panel
 - Chemistry panel
 - Serum pregnancy (for women of childbearing potential)
 - Prothrombin time (PT) or International normalized ration (INR), and activated partial thromboplastin time (aPTT)
 - Urinalysis to be collected prior to FA
- Ocular assessments:
 - Gonioscopy
 - Slit lamp
 - Indirect ophthalmoscopy
 - Intraocular pressure (IOP)
 - OCT
 - FP and FA (bilateral), ICGA
 - BCVA using ETDRS chart

7.1.1.2 Run-in therapy

(Baseline; Week 0; Day 1)

This visit will serve as the baseline visit. It will include the first administration of the study drug. This visit should take place within 21 days after screening. If eligibility criteria are

met and time allows, screening and baseline procedures may be performed at the same clinic visit. The following assessments and procedures will be performed:

- Confirmation of eligibility criteria
- Interval history including recording of AEs
- Prior and concomitant medications
- National eye institute 25-item visual function questionnaire (NEI VFQ-25), in a quiet room (Section 14.1)
- Vital signs (pulse and blood pressure)
- Ocular assessments:
 - Slit lamp
 - Indirect ophthalmoscopy
 - IOP
 - OCT
 - BCVA using ETDRS chart
- IVT injection of 2 mg aflibercept will be performed in all subjects. Subjects will be observed for 30 to 60 minutes following injection
- Re-measuring of IOP 30 to 60 minutes after injection

Week 4 and Week 8

- Interval history including recording of AEs
- Prior and concomitant medications
- Vital signs (pulse and blood pressure)
- Ocular assessments:
 - Slit lamp
 - Indirect ophthalmoscopy
 - IOP
 - OCT
 - BCVA using ETDRS chart
- IVT injection of 2 mg aflibercept. Subjects will be observed for 30 to 60 minutes following injection
- Re-measuring of IOP 30 to 60 minutes after injection

7.1.1.3 Randomization

Week 12

Note: From Week 12 onwards, at each study visit, **all listed assessments are to be performed prior to the administration of any treatment.**

- Interval history including recording of AEs
- Prior and concomitant medications
- Vital signs (pulse and blood pressure)
- Ocular assessments:
 - Slit lamp
 - Indirect ophthalmoscopy
 - IOP
 - OCT
 - BCVA using ETDRS chart
 - FP and FA, including ICGA, for subjects meeting the criteria for BCVA and OCT in the rescue criteria
- Assessment of rescue criteria
- All subjects are randomized to Treatment Group 1 or 2, stratified by qualification or no qualification for rescue and by ethnicity (Japanese or non-Japanese)
- If rescue criteria are met:
 - Administer IVT injection of 2 mg aflibercept. Subjects will be observed for 30 to 60 minutes following injection
 - Re-measure IOP 30 to 60 minutes after injection
 - Administer sham or active PDT according to the randomization assignment. *Treatment with PDT may be delivered on the same visit day as aflibercept, preferably after the administration of aflibercept. If PDT administration is performed before aflibercept injection, strong light for the injection should be avoided. If the administration of PDT is delayed, it should be administered within 2-3 days after ICGA/FA, but not later than 7 days.*
 - Subjects qualifying for rescue and who are randomized to treatment Group 1 will receive sham PDT
 - Subjects qualifying for rescue and who are randomized to treatment Group 2 will receive active PDT
 - Subjects are asked to return for their next treatment visit in 4 weeks
- If rescue treatment is not needed, the subject will not receive their next treatment until Week 16

7.1.1.4 Continued therapy

After randomization and stratification at the Week 12 visit, the visit schedule of subjects with and without need for rescue therapy will differ:

- Subjects who were in need of rescue therapy at Week 12 will continue with a monthly treatment schedule unless the investigator feels that an improvement in their PCV warrants a return to aflibercept therapy without rescue. If some improvement is noted, a rescue interval of 6 weeks may be considered. Clinic visits for the collection of safety and efficacy data at Weeks 24, 40, 52, and 96 are mandatory for these subjects regardless of whether rescue treatment is scheduled at these time points.
- Subjects who were not in need of rescue therapy at Week 12 will follow a schedule of bi-monthly visits unless rescue therapy criteria are met in one of the visits.

Visits after Week 12 up to Week 52

- Interval history including recording of AEs
- Prior and concomitant medications
- Vital signs (pulse and blood pressure)
- Ocular assessments:
 - Slit lamp
 - Indirect ophthalmoscopy
 - IOP
 - OCT
 - BCVA using ETDRS chart
 - FP and FA, including ICGA, for subjects meeting the criteria for BCVA and OCT in the rescue therapy criteria
- Assessment of rescue criteria
- If rescue criteria are met:
 - Administer IVT injection of 2 mg aflibercept. Subjects will be observed for 30 to 60 minutes following injection
 - Re-measure IOP 30 to 60 minutes after injection
 - Administer sham or active PDT according to the randomization assignment. *Treatment with PDT may be delivered on the same visit day as aflibercept, preferably after the administration of aflibercept. If PDT administration is performed before aflibercept injection, strong light for the injection should be avoided. If the administration of PDT is delayed, it should be administered within 2-3 days after ICGA/FA, but not later than 7 days. **PDT may only be administered if at least 3 months have elapsed since the last PDT administration (per label use).***

- Subjects qualifying for rescue and who are randomized to treatment Group 1 will receive sham PDT
- Subjects qualifying for rescue and who are randomized to treatment Group 2 will receive active PDT
- Subjects are asked to return for their next treatment visit at an interval of 4 weeks or at a longer interval deemed appropriate by the investigator
- If rescue treatment is not needed:
 - Administer IVT injection of 2 mg aflibercept. Subjects will be observed for 30 to 60 minutes following injection
 - Re-measure IOP 30 to 60 minutes after injection
 - Subjects are asked to return for their next treatment visit in 8 weeks

Week 52 – additional evaluations

- NEI VFQ-25, in a quiet room (Section 14.1)
- Weight (kg)
- Gonioscopy (optional)
- FP and FA, including ICGA

After Week 52 through Week 88 (Treat-and-extend period)

- Interval history including recording of AEs
- Prior and concomitant medications
- Vital signs (pulse and blood pressure)
- Ocular assessments:
 - Slit lamp
 - Indirect ophthalmoscopy
 - IOP
 - OCT
 - BCVA using ETDRS chart
 - FP and FA, including ICGA, for subjects meeting the criteria for BCVA and OCT in the rescue criteria
- Assessment of rescue criteria
- If rescue criteria are met:
 - Administer IVT injection of 2 mg aflibercept. Subjects will be observed for 30 to 60 minutes following injection
 - Re-measure IOP 30 to 60 minutes after injection

- Administer sham or active PDT according to the randomization assignment. *Treatment with PDT may be delivered on the same visit day as aflibercept, preferably after the administration of aflibercept. If PDT administration is performed before aflibercept injection, strong light for the injection should be avoided. If the administration of PDT is delayed, it should be administered within 2-3 days after ICGA/FA, but not later than 7 days. **PDT may only be administered if at least 3 months have elapsed since the last PDT administration (per label use).***
 - Subjects qualifying for rescue and who are randomized to treatment Group 1 will receive sham PDT
 - Subjects qualifying for rescue and who are randomized to treatment Group 2 will receive active PDT
- Subjects are asked to return for their next treatment visit at an interval of 4 weeks or at a longer interval deemed appropriate by the investigator
- If rescue treatment is not needed:
 - Administer IVT injection of 2 mg aflibercept. Subjects will be observed for 30 to 60 minutes following injection
 - Re-measure IOP 30 to 60 minutes after injection
 - Based on his or her judgment of the subject's visual and anatomic conditions, the investigator will inform the subject of when the next injection is due and will plan the next visit accordingly

7.1.1.5 End-of-Treatment (Week 96) or early termination

All subjects are to return to the clinic for the Week 96 visit, irrespective of the timing of their last treatment. If needed, a final treatment may be administered at this visit.

- Interval history including recording of AEs
- Prior and concomitant medications
- NEI VFQ-25, in a quiet room (Section 14.1)
- Weight (kg)
- Vital signs (pulse and blood pressure)
- Ocular assessments:
 - Gonioscopy (optional)
 - Slit lamp
 - Indirect ophthalmoscopy
 - IOP
 - OCT

- FP and FA (bilateral), including ICGA
- BCVA using ETDRS chart

Note: If a treat-and-extend subject receives an injection at Week 96 or within 4 weeks of Week 96, it is the responsibility of the treating investigator to follow-up on any AEs [including ongoing events] that may occur within 4 weeks following this treatment [Section 7.1.1.6]. Information regarding such events is to be reported under this protocol (i.e., not as spontaneous reports).

The following procedures may be performed at the option of the investigator at Week 96:

- Assessment of rescue criteria
- If rescue criteria are met:
 - Administer IVT injection of 2 mg aflibercept. Subjects will be observed for 30 to 60 minutes following injection
 - Re-measure IOP 30 to 60 minutes after injection
 - Administer sham or active PDT according to the randomization assignment. *Treatment with PDT may be delivered on the same visit day as aflibercept, preferably after the administration of aflibercept. If PDT administration is performed before aflibercept injection, strong light for the injection should be avoided. If the administration of PDT is delayed, it should be administered within 2-3 days after ICGA/FA, but not later than 7 days. **PDT may only be administered if at least 3 months have elapsed since the last PDT administration (per label use).***
 - Subjects qualifying for rescue and who are randomized to treatment Group 1 will receive sham PDT
 - Subjects qualifying for rescue and who are randomized to treatment Group 2 will receive active PDT
 - Subjects are asked to return to the clinic or to participate in a follow-up telephone call for the collection of safety data in 4 weeks
- If rescue treatment is not needed:
 - Administer IVT injection of 2 mg aflibercept. Subjects will be observed for 30 to 60 minutes following injection
 - Re-measure IOP 30 to 60 minutes after injection
 - Subjects are asked to return to the clinic or to participate in a follow-up telephone call for the collection of safety data in 4 weeks

7.1.1.6 Safety follow-up (as needed)

The safety follow-up visit must be conducted for any subject who received a study injection within 4 weeks of or at the Week 96 visit. This safety visit may be conducted in the study clinic or by telephone call at the discretion of the investigator.

- Interval history including recording of AEs
- Prior and concomitant medications

7.2 Population characteristics

7.2.1 Demographic

Baseline subject demographic data, including the following, should be documented in the eCRF.

- Date of birth
- Sex
- Race/ethnicity
- Weight
- Height

7.2.2 Medical history

A complete medical history, including smoking history and ophthalmic history will be obtained at screening.

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

- Pertaining to and not pertaining to the study indication
- Start before signing of the ICF
- Considered relevant to the study.

Medical history must include the onset of PCV or wet AMD as defined by history of first symptoms, ophthalmic examinations, imaging, or other.

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section [7.5.1.1](#).

Previous and concomitant medication will also be recorded.

7.3 Efficacy

Variables to be analyzed for this study will be summarized in Section 8.3 and a complete list will be described in more detail in the Statistical Analysis Plan (SAP).

7.3.1 Best-corrected visual acuity

Visual function of the study eye and the fellow eye will be assessed at each study visit according to the standard procedures developed for the ETDRS adapted for Age Related Eye Disease Study (AREDS). Visual acuity examiners must be certified to ensure consistent measurement of BCVA. The visual acuity examiner **must** remain masked to treatment assignment throughout the study.

7.3.2 Fundus photography / Fluorescein angiography / Indocyanine green angiography

The anatomical state of the retinal vasculature of the study eye (e.g., CNV lesion size) will be evaluated by fundoscopic examination, FP and FA, including ICGA. Fundus photography and FA obtained at the screening visit, Week 12, Week 52, and Week 96 visits and any unscheduled FP or FA imaging will be assessed by the investigator and reviewed by the Central Reading Center. Confirmation of eligibility at baseline by the Central Reading Center is not required. In addition to the required FA evaluations at screening, and Weeks 12, 52, and 96, the investigator may perform additional FA evaluations at any time in accordance with his/her standard practice or if deemed necessary by subject status. Additional examinations may be performed when the results from BCVA indicates that the subject may qualify for rescue therapy. Fundus and angiographic images will be sent to an independent reading center where images will be evaluated by masked readers. All FA and FP images will be archived at the study site as part of the subject's source documentation. Photographers must be certified by the reading center to ensure consistency and quality in image acquisition. Every effort will be made to ensure that all photographers at the site remain masked to treatment assignment throughout the study.

Additional details regarding the FP, FA, and ICGA procedures will be provided in a separate Imaging Manual.

7.3.3 Optical coherence tomography

Retinal and lesion characteristics, such as central retinal thickness (CRT), will be evaluated by OCT in both eyes at every study visit. Images of the study eye will be captured and assessed by masked study-site personnel specifically trained and certified for this assessment in order to ensure consistency and quality in image acquisition. All OCTs will be electronically archived at the study site as part of the subject's source documentation.

Optical coherence tomography images will undergo central reading by the central reading center as part of this protocol.

Additional details regarding the OCT procedure will be provided in a separate OCT Manual.

7.3.4 Intraocular pressure

Intraocular pressure will be measured in both eyes at the screening visit. At other visits, IOP will be measured pre-dose in both eyes and again 30 to 60 minutes post-dose in the study eye. Any case of new-onset, clinically significant increase in IOP that does not respond to treatment (not including the transient pressure rise observed immediately after IVT injection)

must be recorded by the investigator as an AE. Intraocular pressure will be measured using applanation tonometry (Goldmann as standard technique or Tonopen). The same method of IOP measurement must be used in each subject throughout the study. Non-contact tonometry may be used, but re-examination with applanation tonometry is recommended in case of pathological IOP (>22 mmHg) is detected.

7.3.5 Gonioscopy

Subjects will be evaluated for the development of neovascularization and/or scarring of the iridocorneal angle by gonioscopy in conjunction with slit lamp biomicroscopy before the application of mydriatic agents. The examination should be performed on both eyes at screening. Thereafter, gonioscopy may be performed at the option of the investigator at Weeks 52 (study eye) and 96 (both eyes).

7.3.6 Patient reported outcomes

Vision-related quality of life will be assessed using the NEI VFQ-25 questionnaire (Section 14.1). This questionnaire will be presented in the local language and should be administered in a quiet room by a person certified to administer this type of questionnaire, preferably before other visit procedures are performed. For subjects unable to read the questionnaire due to vision impairment, a family member, other legal representative of the subject, study nurse, or study physician may assist the subject in completing the questionnaire.

7.4 Pharmacokinetics and Pharmacodynamics

Not applicable.

7.5 Safety

7.5.1 Adverse events

7.5.1.1 Definitions

Definition of adverse event

In a clinical study, an AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term “condition” may include abnormal findings (e.g., physical examination findings), symptoms, diseases, laboratory values.

- Conditions that started before signature of the ICF and for which no symptoms or treatment are present until signature of the ICF are recorded as medical history (i.e., seasonal allergy without acute complaints).
- Conditions that started before signature of the ICF and for which symptoms or treatment are present after signature of the ICF, at *unchanged intensity*, are recorded as medical history (e.g., allergic pollinosis).
- Conditions that started or deteriorated after signature of the ICF will be documented as adverse events.

Definition of serious adverse event

A serious adverse event (SAE) is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death

b. Is life-threatening

The term ‘life-threatening’ in the definition refers to an event in which the subject was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours

- The admission is pre-planned

(i.e., elective or scheduled surgery arranged prior to the start of the study. If investigational centers decide to hospitalize subjects solely for the purpose of infusion of verteporfin in the context of the study, this would also be regarded as pre-planned)

- The admission is not associated with an AE

(e.g. social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of ‘medically important’ and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity

Disability means a substantial disruption of a person’s ability to conduct normal life’s functions.

e. Is a congenital anomaly / birth defect

f. Is another medically important serious event as judged by the investigator

7.5.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

7.5.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 7.5.1.1.

7.5.1.2.2 Intensity

The intensity of an AE is classified according to the following categories:

- Mild
- Moderate
- Severe

7.5.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the eCRF.

The causality assessment will be performed separately for aflibercept and PDT, and for aflibercept injection and laser treatment as detailed in the eCRF.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question. Possible answers are “yes” or “no”.

An assessment of “no” would include:

1. The existence of a clear alternative explanation, e.g., mechanical bleeding at surgical site.
- or
2. Non-plausibility, e.g., the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of “yes” indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge):

- Subject's response after de-challenge or subjects response after re-challenge should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment:
The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the study treatment:
The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.

Causal relationship to protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s). Possible answers are "yes" or "no".

7.5.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

- Drug withdrawn
- Drug interrupted
- Not applicable
- Unknown

The study treatment action should be recorded separately for each study treatment as detailed in the eCRF.

7.5.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

7.5.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved

- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

7.5.1.3 Assessments and documentation of adverse events

All AEs occurring during the study that are volunteered, observed, or elicited will be recorded on the eCRF AE page. These include AEs that the subject reports spontaneously, those the investigator observes, and those the investigator elicits at each study visit, whether or not attributed to study drug. The observation phase for AEs will start with signature of the ICF and will end in general with the last study visit. New pathological findings observed and reported by the OCT and FA reading centers, and or central laboratory that are of clinical relevance will also be recorded as AEs.

The investigator is responsible for following those AEs related to study drug, injection procedure, or PDT until resolution or until the event is considered chronic and or stable by the investigator and or other physician who has the responsibility for the subject's medical care. This follow-up may extend after the end of the study. If a subject receives an injection at Week 96, 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 a spontaneous report).

Details for AE reporting and specific requirements in certain countries are specified in the Study Monitoring Plan.

7.5.1.4 Reporting of serious adverse events

The definition of SAEs is given in Section [7.5.1.1](#).

Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

All SAEs occurring during the observation period defined in Section [7.5.1.3](#) must immediately (within 24 hours of the investigator's awareness) be reported to the recipient detailed in the manual. An SAE form must also be completed within 24 hours of the investigator awareness and forwarded to the designated recipient. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

Notification of the Independent Ethics Committees / Institutional Review Boards

Notification of the Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) about all relevant events (e.g., SAEs, suspected, unexpected, SUSARs) will be performed by the sponsor and/or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g., SAEs, SUSARs) to the authorities will be performed by the sponsor according to all applicable regulations.

Sponsor's notification of the investigational site

The sponsor will inform all investigational sites about reported relevant events (e.g., SUSARs) according to all applicable regulations.

7.5.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the IB or summary of product characteristics.

Overview listings of frequent events that have occurred so far in clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

7.5.2 Pregnancies

Any subject who becomes pregnant during the course of the study should undergo EOS assessments and be discontinued from participation in the study.

The investigator must report to the sponsor any pregnancy occurring in a study subject during the subject's participation in this study, up to 3 months (12 weeks) following the last IVT dose. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For a study subject, the outcome of the pregnancy should be followed up carefully, and any outcome of the mother or the child should be reported.

Bayer does not routinely collect information of drug exposure of the father, however, if those cases are reported, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used.

7.5.3 Further safety

Safety assessments, in addition to AEs, will include laboratory measures and vital signs.

7.5.3.1 Laboratory evaluations

The safety laboratory variables to be assessed are summarized in [Table 7-2](#).

Laboratory testing will be performed at screening and will include:

- Blood samples for hematology, chemistry, and coagulation panels
- A serum pregnancy test (for women of child-bearing potential)
- Urinalysis

All blood samples will be drawn by direct venipuncture prior to administration of the study drug. The exact date and time (24-hour clock) of each blood sample obtained will be recorded in the eCRF. Instructions for phlebotomy and sample handling can be found in the laboratory manual.

Laboratory tests will be performed at a central laboratory and results will be electronically transferred to the Sponsor. In addition, a copy of the results will be provided to the study site for investigator assessment. These results are to be filed in the subject's source documentation. All abnormal laboratory values will require a judgment from the investigator as to their significance, if any. Clinically significant changes in laboratory values should be designated as AEs and should be reported on the AE eCRF.

Urine samples must be obtained before performing FA to avoid false elevations in urine protein values.

According to current International Conference on Harmonisation (ICH) guidelines, deviations from the reference range should be evaluated for clinical significance in each individual case. The reference ranges, reporting units, and methods for all variables will be provided by the central laboratory. Deviations of laboratory values from the laboratory reference ranges will be flagged on the laboratory results printouts.

Table 7-2: Safety laboratory variables to be assessed by the central laboratory

Laboratory variables		
Chemistry		
Albumin	Blood urea nitrogen	Glucose
Alkaline phosphatase	Calcium	Potassium
Alanine aminotransferase ^a	Chloride	Sodium
Aspartate aminotransferase ^b	Creatinine	Total bilirubin
		Total protein, serum
Hematology		
Hematocrit	Differential count	Red blood cells
Hemoglobin	Basophils	White blood cells
Mean corpuscular hemoglobin	Eosinophils	Platelet count
Mean corpuscular hemoglobin concentration	Lymphocytes	
	Monocytes	
Mean corpuscular volume	Neutrophils	
Coagulation		
Prothrombin time	International normalized ratio	Partial thromboplastin time
Other		
Serum pregnancy test ^c		
Urinalysis		
Blood	Glucose	Protein
Creatinine	Ketones	UPCR
	Specific gravity	

Abbreviations: UPCR = Urine protein:creatinine ratio

^a Also known as serum glutamate pyruvate transaminase (SGPT)

^b Also known as serum glutamate oxaloacetic transaminase (SGOT)

^c Women of child-bearing potential

7.5.3.2 Weight

The subject's weight (kg) is to be recorded at screening, Week 52, and Week 96.

7.5.3.3 Physical examinations

At screening, a complete physical examination will be performed. Any abnormal findings should be documented in the eCRF as medical history.

7.5.3.4 Vital signs

Blood pressure, and pulse rate will be measured at all study visits (screening through the Week 96 visit, or early termination). Vital signs should be assessed in a consistent, standardized way at each assessment.

7.6 Other procedures and variables

Not applicable.

7.7 Appropriateness of procedures / measurements

All efficacy and safety variables and the methods to measure them are standard variables and methods in clinical studies, and in ophthalmic practice. They are widely used and generally recognized as reliable, accurate, and relevant

8. Statistical methods and determination of sample size

8.1 General considerations

All variables will be analyzed descriptively with appropriate statistical methods: continuous variables by sample statistics (i.e., mean, standard deviation, median, quartiles, minimum and maximum) and categorical variables by frequency tables (absolute and relative frequencies). Statistical analyses will be performed using Statistical Analysis System (SAS), version 9.2 or higher.

For statistical analysis by ethnicity, Japanese subjects will form one subgroup and all other randomized subjects will form a second subgroup. Data will also be analyzed by qualification or non-qualification for rescue therapy at Week 12.

The final statistical analysis of the Week 52 data will be performed as soon as the Week 52 data for all subjects is available and cleaned, although the study may be still ongoing. Investigators, subjects and monitors will remain masked. Although the conclusions from the analysis of the one year data may be made public, the identity of the study drug for a particular subject will not be known by the subject, the investigator, or the monitor.

The full report of the Week 52 data will be supplemented by a second full report of the Week 96 data for all subjects.

8.2 Analysis sets

Populations for analysis will be defined as follows:

The Full Analysis Set (FAS) will include all randomized subjects. The FAS will be analyzed as randomized.

The safety analysis set will include all subjects who receive any study drug under this protocol.

8.3 Variables

8.3.1 Primary efficacy variable

The primary efficacy endpoint is the mean change in BCVA from baseline to Week 52.

8.3.2 Secondary efficacy variable

The secondary efficacy endpoint is:

- Avoidance of at least a 15-letter loss at Week 52 (“maintenance of visual acuity”) from baseline to Week 52.

8.3.3 Exploratory efficacy variables

In addition, the following efficacy variables may be explored, but are not limited to:

- Number of PDT treatments in the study eye
- Change of visual acuity from baseline over time (letters) in the study eye
- The proportion of subjects who gain ≥ 5 , 10, or 15 letters at Week 52 and at Week 96
- The proportion of subjects who lose ≥ 5 , 10, or 15 letters at Week 52 and at Week 96
- The proportion of subjects with complete polyp regression (no visual polyps on ICGA)
- Presence of leakage in FA in the study eye at Week 52 and Week 96
- Change of CRT on OCT over time
- The change in the NEI VFQ-25 total score from baseline to Week 52 and to Week 96
- The proportion of subjects for whom rescue therapy is indicated within the first year and over the course of the whole study

8.3.4 Safety variables

- Frequency and severity of ocular and non-ocular adverse events over time

Ongoing safety assessments will include ophthalmic examinations, the recording and evaluation of clinical AEs, and safety laboratory measurements.

8.4 Statistical and analytical plans

8.4.1 Demography and baseline characteristics

Demographic variables and baseline characteristics will be summarized by treatment group and all treatment groups combined for both analysis populations (FAS and safety analysis set), depending on the type of data as described in Section 8.3. Medical history and surgeries (ocular and non-ocular) will be coded by the Medical Dictionary for Regulatory Affairs (MedDRA) codes and prior and concomitant medications by ATC codes (World Health Organization Drug Dictionary). The total score and sub-scores of the NEI VFQ-25 will be calculated according to the NEI VFQ-25 scoring algorithm, August 2000 version.

The treatment group comparability will be checked for each of the analysis populations mentioned above. This comparison will be done with respect to age, baseline BCVA letter score, baseline NEI VFQ-25 total score, and baseline retinal thickness by a 3-way analysis of variance main effect model with treatment group, ethnicity, and qualification for rescue therapy at Week 12 as fixed factors. Furthermore, treatment groups will be compared with respect to sex by a Cochran-Mantel-Haenszel test (general association) adjusted for ethnicity and qualification for rescue therapy at Week 12.

The number of injections will be tabulated separately for aflibercept injections and PDT in both treatment groups.

8.4.2 Efficacy analyses

8.4.2.1 Primary efficacy analysis

The primary efficacy variable analysis will be conducted on the FAS. Statistical testing will be conducted to prove the non-inferiority of aflibercept monotherapy (treatment group $i=1$) to aflibercept plus PDT as indicated (treatment group $i=2$). The corresponding null hypothesis is $H_0: \mu_1 \leq \mu_2 - D$ versus the alternative hypothesis $K: \mu_1 > \mu_2 - D$, where D is the non-inferiority margin and μ_i , $i=1,2$, is the mean change in BCVA letter score for the study eye from study baseline at 52 weeks in treatment group i .

The non-inferiority margin is 5 letters. The methodological approach will be the calculation of two-sided 95% confidence intervals for the difference in the least squares (LS) means (aflibercept monotherapy treatment group minus aflibercept plus PDT as indicated treatment group) of the change in ETDRS letter score from study baseline to 52 weeks based on a 3-way analysis of covariance (ANCOVA, main effect model), with baseline measure as a covariate and treatment group, ethnicity, and qualification for rescue therapy at Week 12 as a fixed factors (last observation carried forward [LOCF] will be used for missing values at 52 weeks). Aflibercept monotherapy will be considered to be non-inferior to aflibercept plus PDT as indicated if the confidence interval of the difference lies entirely above -5 letters, where a positive difference favors aflibercept monotherapy. A non-inferiority margin of 5 letters is consistent with margin used in the CATT Study.¹¹ Sensitivity analyses using methods other than the LOCF method for handling missing Week 52 values will be described in the SAP.

The proportion of subjects who never need rescue therapy in the first year is also important information to assess aflibercept monotherapy in this population. Therefore, a 95% confidence interval for this proportion will be calculated based on all randomized subjects, i.e. both treatment groups combined.

8.4.2.2 Secondary efficacy analysis

If aflibercept monotherapy is statistically proven to be non-inferior to aflibercept plus PDT as indicated in the primary efficacy analysis, then confirmatory non-inferiority testing will be continued for the secondary efficacy variable identifying the proportion of subjects maintaining visual acuity at Week 52 (with LOCF for missing 52-week ETDRS letter score). This analysis will be performed in the FAS. The null hypothesis is $H_0: p_1 \leq p_2 - d$ versus the alternative hypothesis $K: p_1 > p_2 - d$, where p_i is the proportion of subjects maintaining visual acuity at 52 weeks of treatment group i and d is the pre-specified non-inferiority margin of 7%. The methodological approach will be the calculation of the two-sided 95% Cochran-Mantel-Haenszel intervals adjusted for the 4 strata (ethnicity [Japanese vs non-Japanese and qualification for rescue therapy at Week 12 [yes vs no]) of the difference between the proportions (aflibercept monotherapy minus aflibercept plus PDT as indicated) of subjects maintaining visual acuity at Week 52. The aflibercept monotherapy will be considered to be non-inferior to the aflibercept plus PDT as indicated, if the confidence

interval of the difference lies entirely above -7%, where a positive difference favors aflibercept monotherapy. The non-inferiority margin of 7% was proposed by the European Medicines Agency (EMA) in their scientific advice regarding the proposed 10% non-inferiority margin in the VIEW studies (EMA/CHMP/SAWP/ 310870/ 2007, pages 22 and 23; May 2007).

This conditional sequence of statistical hypotheses (*a priori* ordered hypotheses) will control for multiplicity in the confirmatory analyses.

Sensitivity analyses using methods other than the LOCF method for handling missing Week 52 values will be described in the SAP.

8.4.2.3 Other efficacy analysis

A subgroup analysis of subjects qualifying for rescue therapy in the first year will be conducted with regard to at least the primary and secondary efficacy variables. All other efficacy analyses variables including the second year efficacy variables will be summarized by treatment group in the FAS depending on the type of data as described in Section 8.3. Details regarding the statistical analysis of the other efficacy variables will be provided in the SAP. The posology of the therapies in the second year will be summarized in detail, e.g. number of injections of aflibercept as well as PDT and time between injections. More details will be provided in the SAP.

8.4.3 Safety variables

The safety analysis will be conducted in the safety analysis set. Treatment emergent AEs will be presented by MedDRA preferred term within primary system organ class (SOC). Intensity and causal relationship to the investigational product will be analyzed descriptively. Serious adverse events, including narratives, will be documented separately.

Other safety variables (e.g., IOP measurements, vital signs, and laboratory tests) will be analyzed descriptively including changes from baseline. The descriptive analysis of laboratory data will include a listing of laboratory data that fall outside of the normal range and the calculation of incidence rates for treatment emergent laboratory abnormalities.

Details of further analyses by type and time of treatment emergent AEs will be specified in the SAP.

8.5 Planned interim analyses

Not applicable.

8.6 Determination of sample size

Based on the assumptions of (i) a standard deviation of 12.5 for the mean change in BCVA from study baseline to Week 52, (ii) a non-inferiority margin of 5 letters, (iii) a mean change of 0.25 letters in BCVA of the difference between aflibercept plus PDT as indicated versus aflibercept monotherapy from study baseline to Week 52 in the two treatment groups, (iv) a power of 90%, and (v) a one-sided alpha of 2.5%, the sample size estimation resulted in 147 evaluable subjects per treatment group (calculated with PASS 11 [Power Analysis and

Sample Size Software 11], non-inferiority of two means). With an expected drop-out rate of 5%, a total of 310 subjects should be randomized (155 per treatment group).

It is estimated that approximately 50 subjects will qualify for PDT in each treatment group of 155.

9. Data handling and quality assurance

9.1 Data recording

It is the expectation of the sponsor that all data entered into the CRF has source documentation available at the site. A source document checklist will be used at the site to identify the source data for all data points collected and the monitor will work with the site to complete this.

Data recorded from “only screened subjects (screening failures)”

Data of 'only screened subjects' will be recorded at least as source data, as far as the reason for failure to continue is identifiable. At minimum, data to be recorded in the eCRF are demographic information (subject number, year of birth/age, sex, race, and ethnicity), date of informed consent, the reason for discontinuation, and date of last visit. These data will be source data verified and transferred to the respective database.

For screening failures with an SAE, the following additional data should be collected in the CRF, in addition to demographic information, primary reason for discontinuation and date of last visit:

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

9.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete
- Safety and rights of subjects are being protected

- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

9.3 Data processing

The data collection tool for this study will be a validated electronic system called RAVE™ eCRF system. Subject data necessary for analysis and reporting will be entered or transmitted into a validated database or data system (e.g., TOSCA; SAS). Clinical data management will be performed in accordance with applicable sponsor's standards and data cleaning procedures. This is applicable for data recorded on eCRF as well as for data from other sources (e.g. IxRS, laboratory, electronic patient-reported outcomes, adjudication committees).

For data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.

9.4 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

9.5 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study center.

10. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
 - Safety findings from this study (e.g. SAEs)
 - Results of any interim analysis
 - Results of parallel clinical studies
 - Results of parallel animal studies (e.g., toxicity, teratogenicity, carcinogenicity or reproduction toxicity)
- If the study conduct (e.g., recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction.
- In case of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section [5.2.1](#).

11. Ethical and legal aspects

11.1 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and

organizations. When necessary, an extension, amendment or renewal of the EC/IRB approval must be obtained and also forwarded to the Sponsor. The responsible unit (e.g., EC/IRB, head of the study center/medical institution) must supply to the Sponsor, upon request, a list of the EC/IRB members involved in the vote and a statement to confirm that the EC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 10.

11.2 Subject information and consent

All relevant information on the study will be summarized in an integrated subject information sheet and ICF provided by the sponsor or the study center. A sample subject information and ICF is provided as a document separate to this protocol.

Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject, prior to his/her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB/IEC has been obtained.

Each subject will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The subject / legal representative or proxy consentor will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the subject's note/file of the medical institution.

In the event that informed consent is obtained on the date that Screening study procedures are performed, the study record or subject's clinical record must clearly show that informed consent was obtained prior to these procedures.

If the subject is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the

investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

The ICF and any other written information provided to subjects or legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and or the written ICF. The investigator will inform the subject of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised ICF. Any revised written ICF and written information must receive the IEC/IRB's approval or favorable opinion in advance of use.

11.3 Publication policy

The sponsor is interested in the publication of the results of every study it performs.

All relevant aspects regarding publication will be part of the contract between the sponsor and the investigator/institution.

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

11.4 Compensation for health damage of subjects / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

11.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the eCRF, and if the subject name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects to be identified.

12. Reference list

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11. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, Toth C, Redford M, Ferris FL 3rd Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012 Jul;119(7):1388-98

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Lanzetta P, Mitchell P, Wolf S, et al. *Br J Ophthalmol* 2013;97: 1497–1507.

13. Protocol amendments

Not applicable.

14. Appendices

14.1 National eye institute 25-item visual function questionnaire

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Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is*:

(Circle One)

READ CATEGORIES:	Excellent	1
	Very Good	2
	Good.....	3
	Fair.....	4
	Poor	5

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

(Circle One)

READ CATEGORIES:	Excellent	1
	Good.....	2
	Fair.....	3
	Poor	4
	Very Poor	5
	Completely Blind.....	6

* Skip Question 1 when the VFQ-25 is administered at the same time as the SF-36 or RAND 36-Item Health Survey 1.0

3. How much of the time do you worry about your eyesight?

(Circle One)

- READ CATEGORIES:
- None of the time..... 1
 - A little of the time..... 2
 - Some of the time 3
 - Most of the time 4
 - All of the time? 5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

- READ CATEGORIES:
- None 1
 - Mild 2
 - Moderate 3
 - Severe, or 4
 - Very severe? 5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:

(READ CATEGORIES AS NEEDED)

(Circle One)

- No difficulty at all..... 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not
interested in doing this 6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not
interested in doing this 6

8. How much difficulty do you have reading street signs or the names of stores?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not
interested in doing this 6



9. **Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?**

(READ CATEGORIES AS NEEDED)

(Circle One)

- No difficulty at all..... 1
- A little difficulty..... 2
- Moderate difficulty..... 3
- Extreme difficulty..... 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

10. **Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?**

(READ CATEGORIES AS NEEDED)

(Circle One)

- No difficulty at all..... 1
- A little difficulty..... 2
- Moderate difficulty..... 3
- Extreme difficulty..... 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

11. **Because of your eyesight, how much difficulty do you have seeing how people react to things you say?**

(READ CATEGORIES AS NEEDED)

(Circle One)

- No difficulty at all..... 1
- A little difficulty..... 2
- Moderate difficulty..... 3
- Extreme difficulty..... 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6



12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

(READ CATEGORIES AS NEEDED)

(Circle One)

- No difficulty at all..... 1
- A little difficulty..... 2
- Moderate difficulty..... 3
- Extreme difficulty..... 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants?

(READ CATEGORIES AS NEEDED)

(Circle One)

- No difficulty at all..... 1
- A little difficulty..... 2
- Moderate difficulty..... 3
- Extreme difficulty..... 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?

(READ CATEGORIES AS NEEDED)

(Circle One)

- No difficulty at all..... 1
- A little difficulty..... 2
- Moderate difficulty..... 3
- Extreme difficulty..... 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6



15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?

(Circle One)

Yes 1 Skip To Q 15c

No 2

15a. IF NO, ASK: Have you never driven a car or have you given up driving?

(Circle One)

Never drove 1 Skip To Part 3, Q 17

Gave up..... 2

15b. IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight 1 Skip To Part 3, Q 17

Mainly other reasons 2 Skip To Part 3, Q 17

Both eyesight and other reasons ... 3 Skip To Part 3, Q 17

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all 1

A little difficulty 2

Moderate difficulty 3

Extreme difficulty 4

16. How much difficulty do you have driving at night? Would you say you have: (READ CATEGORIES AS NEEDED)

(Circle One)

- No difficulty at all..... 1
- A little difficulty..... 2
- Moderate difficulty..... 3
- Extreme difficulty..... 4
- Have you stopped doing this because of your eyesight..... 5
- Have you stopped doing this for other reasons or are you not interested in doing this 6

16a. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have: (READ CATEGORIES AS NEEDED)

(Circle One)

- No difficulty at all..... 1
- A little difficulty..... 2
- Moderate difficulty..... 3
- Extreme difficulty..... 4
- Have you stopped doing this because of your eyesight..... 5
- Have you stopped doing this for other reasons or are you not interested in doing this 6



PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.

(Circle One On Each Line)

READ CATEGORIES:

All of the time	Most of the time	Some of the time	A little of the time	None of the time
--------------------	---------------------	------------------------	----------------------------	---------------------

- | | | | | | |
|---|---|---|---|---|---|
| 17. <u>Do you accomplish less</u>
than you would like
because of your vision? | 1 | 2 | 3 | 4 | 5 |
| 18. <u>Are you limited</u> in how
long you can work or do
other activities because of
your vision? | 1 | 2 | 3 | 4 | 5 |
| 19. How much does pain or
discomfort <u>in or around</u>
<u>your eyes</u> , for example,
burning, itching, or
aching, keep you from
doing what you'd like to
be doing? Would you say: | 1 | 2 | 3 | 4 | 5 |



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For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I <u>stay home most of the time</u> because of my eyesight.....	1	2	3	4	5
21. I feel <u>frustrated</u> a lot of the time because of my eyesight.....	1	2	3	4	5
22. I have <u>much less control</u> over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to <u>rely too much on what other people tell me</u> ..	1	2	3	4	5
24. I <u>need a lot of help</u> from others because of my eyesight.....	1	2	3	4	5
25. I worry about <u>doing things that will embarrass myself or others</u> , because of my eyesight.....	1	2	3	4	5

That's the end of the interview. Thank you very much for your time and your help.