Clinical Study Synopsis

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Date of report:	05 MAR 2018
Study 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 (PLANET)
Sponsor's study number:	16995
NCT number:	NCT02120950
EudraCT number:	2013-004464-54
Sponsor:	Bayer Collaborator: Regeneron
Clinical phase:	3b/4
Study objectives:	The primary objectives of the study were to: • collect data reflecting the efficacy and safety of aflibercept with and without photodynamic therapy (PDT) rescue treatment in subjects diagnosed with the polypoidal choroidal vasculopathy (PCV) subtype of wet age-related macular degeneration (AMD) • explore whether intravitreally administered aflibercept monotherapy is non-inferior to that of aflibercept plus PDT (as indicated) based upon best-corrected visual acuity (BCVA) in subjects diagnosed with the PCV subtype of wet AMD The secondary objectives were to: • estimate the proportion of subjects diagnosed with the PCV subtype of wet AMD who require rescue therapy • 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 response to aflibercept monotherapy

Test drug / Batch number(s):	Aflibercept (Eylea, BAY 86-5321) / KM500FG, KM500K9, KM500X6, 42097D, KM501DV, KM501VZ, 41070, 43145, 54268 KM501RS, KM501YV with sham PDT
Name of active ingredient(s):	Aflibercept
Dose:	2 mg Aflibercept
Route of administration:	Aflibercept was administered by intravitreal (IVT) injection. The sham PDT procedure consisted of the intravenous 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 was not used) that mimicked the laser procedure of the active PDT treatment (standard fluence laser).
Duration of treatment:	All subjects were treated with 2 mg aflibercept every month for the first 3 months. At Week 12, subjects were randomized in a ratio of 1:1 to one of two groups: **Group 1:** aflibercept (2 mg) + sham PDT **Group 2:** aflibercept (2 mg) + active PDT After randomization, subjects **without** a need for rescue therapy were treated with 2 mg aflibercept once every 2 months through Week 52. Between Week 52 and Week 96, the treatment interval could have been extended (typically in increments of 1 or 2 weeks) at the discretion of the investigator when the visual and anatomic outcomes allowed. In subjects **with** a need for rescue therapy at Week 12 or thereafter, aflibercept was initially administered monthly. Thus, subjects who required rescue therapy were on a flexible visit schedule which allowed more frequent treatments than the standard bi-monthly regimen. However, aflibercept was not allowed to be administered more frequently than once monthly. Sham PDT treatments were given at any of these visits if treatment criteria were met.
Reference drug:	Aflibercept (Eylea, BAY 86-5321) with active PDT
Dose:	2 mg aflibercept + **15 mg verteporfin**
Route of administration:	Aflibercept was delivered before PDT treatment as an IVT injection. PDT was administered according to the label for verteporfin (Visudyne®).

Duration of treatment:	All subjects were treated with 2 mg aflibercept every month for the first 3 months. At Week 12, subjects were randomized in a ratio of 1:1 to one of two groups: **Group 1:** aflibercept (2 mg) + sham PDT **Group 2:** aflibercept (2 mg) + active PDT After randomization, subjects **without** a need for rescue therapy were treated with 2 mg aflibercept once every 2 months through Week 52. Between Week 52 and Week 96, the treatment interval could have been extended (typically in increments of 1 or 2 weeks) at the discretion of the investigator when the visual and anatomic outcomes allowed. In subjects **with** a need for rescue therapy at Week 12 or thereafter, aflibercept was initially administered monthly. Thus, subjects who required rescue therapy were on a flexible visit schedule which allowed more frequent treatments than the standard bi-monthly regimen. However, aflibercept was not allowed to be administered more frequently than once monthly. Active PDT treatments were given at any of these visits if treatment criteria were met.
Indication:	The PCV sub-type of wet AMD

Diagnosis and main criteria for inclusion:	Main inclusion criteria • Men and women ≥ 50 years of age. • Diagnosis of symptomatic macular PCV in the study eye established by indocyanine green angiography (ICGA) at the study center. • Greatest linear dimension of the lesion of < 5400 mm (approximately, 9 Macular Photocoagulation Study disk areas), assessed by ICGA. • An Early treatment diabetic retinopathy study (ETDRS) BCVA of 73 to 24 letters in the study eye. Main exclusion criteria • Prior use of intravitreal or sub-tenon corticosteroids in the study eye within 3 months prior to study entry. • Any prior use of intraocular anti Vascular Endothelial Growth Factor (anti-VEGF) agents in the study eye, or systemic use of anti VEGF products within 3 months prior to study entry. • Prior macular laser treatment in the study eye including PDT. • History of allergy to fluorescein used in fluorescein angiography, iodine and/or indocyanine green. • History of allergy to aflibercept, verteporfin, or their excipients.
Study design:	This study was a phase 3b/4, randomized, double-masked, multi-center clinical trial.

Methodology

Only one eye per subject was enrolled in the study. For subjects who met the eligibility criteria in both eyes, the eye with the worst visual acuity was selected as the study eye. Safety for the fellow eye was monitored and adverse events (AEs) were collected.

At the time of randomization, subjects were 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 were conducted at each visit from Week 12 to Week 88 (Week 96 was optional). Intensified aflibercept treatment plus active or sham PDT treatments were given at any of these visits if treatment criteria were met. Qualification for rescue was based upon insufficient gain of BCVA, leakage, and presence of active polyps.

All of the following three criteria had to be met:

1. BCVA ≤ 73 ETDRS letters
2. Evidence of new or persistent fluid on OCT
3. Evidence of active polyps on ICGA

Additionally, either one of the following two criteria had to 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 determined based on the course of visual and anatomic outcomes over time that PDT might be of additional benefit to the subject.

BCVA and optical coherence tomography (OCT) were performed at each visit. An assessment by ICGA was performed if Criteria 1 and 2 plus either Criteria 4 or 5 were met. Fundus photography (FP) and ICGA were performed at screening or baseline, at Week 52 (primary endpoint visit), at Week 96 (end-of-treatment visit), and at all visits when BCVA and/or OCT results indicated that the subject had qualified for rescue treatment. A central reading center was used for reading of imaging data including OCT, FP, fluorescein angiography (FA), and ICGA. Assessment of AEs and vital signs was performed at every visit.

All subjects returned 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 visit.

Statistical analyses were performed for the first data cutoff point at Week 52 and for the final data cutoff point at Week 96.

Study center(s):	62 investigational sites screened subjects in 8 countries: 1 center in Germany, 36 centers in Japan, 5 centers in Australia, 4 centers in Hungary, 6 centers in the Republic of Korea (South Korea), 6 centers in Taiwan, 2 centers in Hong Kong, and 2 centers in Singapore	
Publication(s) based on the study (references):	None	
Study period:	Study Start Date:	29 MAY 2014
	Study Completion Date:	07 JUL 2017
Early termination	No	
Number of subjects:	Planned:	A total of 310 subjects were planned to be randomized (155 per treatment group).
	Analyzed:	333 subjects (157 subjects in the aflibercept plus sham PDT group, 161 subjects in the aflibercept plus active PDT group, and 15 subjects who were treated but not randomized)
Criteria for evaluation Efficacy:	The primary variable was the mean change in BCVA as measured by ETDRS from baseline to Week 52. The confirmatory secondary variable was the proportion of subjects who avoided at least a 15-letter loss (“maintenance of visual acuity”) from baseline to Week 52. The primary and secondary variables were also analyzed from baseline to Week 96 as exploratory variables.	
Safety:	Safety assessments included ophthalmic examinations, the recording and evaluation of clinical adverse events, and safety laboratory and vital signs measurements.	

Other:	The following efficacy variables were also explored: • Number of PDT treatments in the study eye • Change of visual acuity from baseline over time (letters) in the study eye • Proportion of subjects who gained or lost ≥ 5, 10, or 15 letters at Week 52 and Week 96 • 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 central subfield thickness (CST) on OCT over time • Change in the National eye institute 25-item visual function (NEI VFQ-25) questionnaire total score from baseline to Week 52 and Week 96 • Proportion of subjects for whom rescue therapy was indicated within the first year and over the course of the whole study

Statistical methods:	The primary efficacy endpoint was the mean change in BCVA from baseline to Week 52. Analysis of the primary efficacy variable was conducted on the full analysis set (FAS), which was defined as all randomized subjects. Statistical testing was conducted to prove the non-inferiority of aflibercept monotherapy to aflibercept plus PDT. The non-inferiority margin was 5 letters. The methodological approach was the calculation of two-sided 95% confidence intervals (CI) 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) was used for missing values at 52 weeks. Aflibercept monotherapy was considered to be non-inferior to aflibercept plus active PDT if the confidence interval of the difference was entirely above -5 letters, where a positive difference favors aflibercept monotherapy. The proportion of subjects who never needed rescue therapy in the first year was also important information to assess with regard to aflibercept monotherapy in this population. Therefore, a 95% confidence interval for this proportion was calculated based on all randomized subjects, i.e. both treatment groups combined.
Substantial protocol changes:	Not applicable

Subject disposition and baseline

A total of 428 subjects were enrolled in this study by signing the informed consent form (424 subjects were screened, and 4 subjects were re-screened, signed the informed consent form a second time, and received a new subject number). There were 95 subjects who did not complete screening. All 333 subjects who passed screening entered a run-in period (from Week 0 up to Week 12) and received at least one dose of aflibercept. All of these subjects were included in the safety analysis set (SAF). At Week 12 of the study, 318 of the 333 subjects were randomized in a 1:1 ratio (aflibercept plus sham PDT [AFL-sham]:aflibercept plus active PDT [AFL-PDT]), stratified by the presence or absence of qualification for rescue therapy as specified in the rescue therapy criteria, and by ethnicity (Japanese or non-Japanese). All of these subjects were included in the FAS. A total of 15 subjects were treated but not randomized, and were excluded from the FAS. The per protocol set (PPS) included subjects who had no major protocol deviations and had a minimum of 24 weeks of

treatment. Nearly all of the subjects from both randomized treatment groups (297 subjects) were included in the PPS.

Analysis of efficacy variables was based on the data of the FAS, and analysis of safety parameters was performed on the SAF. The PPS was used for sensitivity analyses of the primary and secondary efficacy variables.

Sub-group analyses were performed for the efficacy variables and safety parameters for ethnicity sub-groups (Japanese vs. non-Japanese) and qualification for rescue therapy at any time up to Week 96 sub-groups (qualified vs. did not qualify).

The FAS consisted of 222 (69.8%) male subjects and 96 (30.2%) female subjects aged between 50 and 90 years (median: 71.0 years). Most subjects (296, 93.1%) were Asian, with 152 (47.8%) Japanese subjects. The mean baseline visual acuity score as determined with the ETDRS letter chart was 58.4 ± 11.4 letters.

Among the SAF, 295 subjects (88.6%) had polyps present at baseline. The mean area of polyps for those subjects was 0.222 ± 0.443 mm^2. Branch vessel network (BVN) was found to be present with the central subfield involved in 234 subjects (70.3%) and without the central subfield involved (outside the central subfield) in 38 subjects (11.4%). The mean BVN area was 4.106 ± 3.398 mm^2. The mean area of fluorescein leakage observed in fluorescein angiography was 6.707 ± 6.104 mm^2. Overall, the treatment groups were well-balanced with regard to demographic and disease characteristics.

Of the 333 subjects treated with at least one dose of aflibercept, 284 (85.3%) completed 96 weeks of treatment.

Efficacy evaluation

The primary efficacy endpoint was the change in BCVA in ETDRS letters from baseline to Week 52. The non-inferiority margin was set at 5 letters, and non-inferiority of AFL-sham was indicated if the confidence interval of the difference was entirely above -5 letters. The mean change in BCVA from baseline to Week 52 was 10.7 ± 11.3 letters in the AFL-sham group and 10.8 ± 10.7 letters in the AFL-PDT group. Results from the ANCOVA showed that the 95% CI of the differences was entirely above -5 (-2.9, 1.6), demonstrating non-inferiority of AFL-sham compared to AFL-PDT. This variable was also analyzed from baseline to Week 96 as an exploratory efficacy variable. The Week 96 results were largely consistent with and supportive of the results in the primary analysis, with 10.7 ± 12.2 letters improvement observed in the AFL-sham group and 9.1 ± 13.2 letters improvement observed in the AFL-PDT group, and the 95% CI entirely above -5 (-1.7, 3.6). These data are summarized in Table 1. The robustness of these results was confirmed in sensitivity analyses in the PPS (LOCF), the FAS (multiple imputation), the FAS (LOCF) from randomization to Week 52 and Week 96, the PPS (LOCF) from randomization to Week 52 and Week 96, and the FAS (multiple imputation) from randomization to Week 52 and Week 96.

Table 1: Change in BCVA in ETDRS letter score from baseline to Week 52 and Week 96 - LOCF (full analysis set)

Treatment group	Number of subjects	Baseline mean (SD)	Mean change (SD)	LS mean change (SE)	LS mean difference (95% CI) [a]	p-value [a]
Week 52 Interim Analysis (primary efficacy)						
AFL-sham	157	57.7 (11.3)	10.7 (11.3)	6.4 (1.4)	-0.7 (-2.9,1.6)	0.5480
AFL-PDT	161	59.0 (11.5)	10.8 (10.7)	7.1 (1.3)		
Week 96 Final Analysis (exploratory efficacy)						
AFL-sham	157	57.7 (11.3)	10.7(12.2)	5.3(1.6)	0.9 (-1.7,3.6)	0.4826
AFL-PDT	161	59.0 (11.5)	-9.1(13.2)	4.3(1.5)		

AFL-PDT = aflibercept plus active photodynamic therapy; AFL-sham = aflibercept plus sham photodynamic therapy; ANCOVA = Analysis of covariance; BCVA = Best-corrected visual acuity; CI = Confidence interval; ETDRS = Early treatment diabetic retinopathy study; LOCF = Last observation carried forward; LS = Least squares; SD = Standard deviation; SE = Standard error

a → Point estimate, 95% CI and p-value are based on treatment difference (AFL-sham – AFL-PDT) of the LS mean changes using an ANCOVA model with the treatment group and ethnicity and qualification for rescue therapy at Week 12 as fixed effects, and the baseline value as covariate.

Results from the rescue subgroup analyses were generally in line with the outcomes of the overall population and supported those of the primary analysis. Few subjects (25 subjects [15.9%] in the AFL-sham group, 29 subjects [18.0%] in the AFL-PDT group) were indicated for rescue therapy between Week 12 and Week 96. In subjects who qualified for rescue treatment, the addition of active PDT failed to provide any meaningful functional benefit. There was no significant difference in the change in BCVA from baseline in this subgroup, and non-inferiority of AFL-sham vs. AFL-PDT was demonstrated at Week 96. Changes from baseline in BCVA in the FAS (LOCF) by rescue qualification sub-group are summarized in Table 2.

Table 2 Qualification for rescue therapy sub-group analysis: Change in BCVA in ETDRS letter score from baseline to Week 52 and Week 96– LOCF (full analysis set)

Sub-group Treatment group	Number of subjects	Baseline mean (SD)	Mean change (SD)	LS mean change (SE)	LS mean difference (95% CI) [a]	p-value [a]
Week 52 interim analysis (primary efficacy)						
Did not qualify for rescue therapy						
AFL-sham	138	57.4 (11.5)	12.0 (11.1)	11.7 (0.8)	-0.5 (-2.8,1.8)	0.6524
AFL-PDT	138	59.1 (11.6)	11.9 (9.7)	12.2 (0.8)		
Qualified for rescue therapy						
AFL-sham	19	59.8 (9.8)	1.9 (8.6)	2.9 (2.7)	-0.5 (-7.8,6.8)	0.8916
AFL-PDT	23	58.7 (11.0)	4.2 (13.8)	3.4 (2.4)		
Week 96 final analysis (exploratory efficacy)						
Did not qualify for rescue therapy						
AFL-sham	132	57.1 (11.6)	12.3 (12.2)	11.9 (1.0)	0.4 (-2.3,3.2)	0.7530
AFL-PDT	132	59.1 (11.6)	11.1 (12.0)	11.5 (1.0)		
Qualified for rescue therapy						
AFL-sham	25	61.0 (9.0)	2.6 (7.9)	2.7 (2.5)	2.9 (-3.9,9.7)	0.3952
AFL-PDT	29	58.7 (10.9)	0.0 (14.6)	-0.2 (2.3)		

AFL-PDT = aflibercept plus active photodynamic therapy; AFL-sham = aflibercept plus sham photodynamic therapy; ANCOVA = Analysis of covariance; BCVA = Best-corrected visual acuity; CI = Confidence interval; ETDRS = Early treatment diabetic retinopathy study; LOCF = Last observation carried forward; LS = Least squares; SD = Standard deviation; SE = Standard error

a Point estimate, 95% CI and p-value are based on treatment difference (AFL-sham – AFL-PDT) of the LS mean changes using an ANCOVA model with the treatment group and ethnicity as fixed effects, and the baseline value as covariate.

The confirmatory secondary efficacy endpoint was the proportion of subjects who avoided at least 15 letters loss in BCVA at Week 52, and the non-inferiority margin was set at 7%. The proportion of subjects who avoided at least 15 letters loss in BCVA at Week 52 was 97.5% in the AFL-sham group and 96.9% in the AFL-PDT group, and the two-sided 95% CI of the difference was entirely greater than -7% (-3.1, 4.3), supporting non-inferiority of AFL-sham compared to AFL-PDT. This variable was also analyzed from baseline to Week 96 in an exploratory analysis. The Week 96 results were largely consistent with and supportive of the results in the Week 52 analysis, with a proportion of subjects who avoided a loss of at least 15 letters of 96.8% observed in the AFL-sham group and 94.4% observed in the AFL-PDT group, and the 95% CI entirely above -7% (-2.5, 6.7). These data are summarized in Table 3.

Table 3: Proportion of subjects who avoided at least 15 ETDRS letters loss from baseline to Week 52 and Week 96- LOCF (full analysis set)

Treatment group	Subjects who avoided at least 15 ETDRS letters loss at Week 52 or Week 96 (%)	Difference % (95% CI) [a]	p-value [b]
Week 52 interim analysis (secondary efficacy)			
AFL-sham	153/157 (97.5%)	0.6 (-3.1, 4.3)	0.7402
AFL-PDT	156/161 (96.9%)		
Week 96 final analysis (exploratory efficacy)			
AFL-sham	152/157 (96.8%)	2.1 (-2.5, 6.7)	0.3732
AFL-PDT	152/161 (94.4%)		

AFL-PDT = aflibercept plus active photodynamic therapy; AFL-sham = aflibercept plus sham photodynamic therapy; CI = Confidence interval; ETDRS = Early treatment diabetic retinopathy study; LOCF= Last observation carried forward

a CI is based on the treatment difference in % (AFL-sham – AFL-PDT) using the Mantel-Haenszel weighting scheme adjusted by ethnicity and qualification for rescue therapy at Week 12

b The p-value is calculated using the 2-sided Cochran-Mantel-Haenszel test adjusted by ethnicity and qualification for rescue therapy at Week 12

The exploratory efficacy analyses supported the findings of the primary and confirmatory secondary analyses. In both treatment groups there was a steady improvement in BCVA from baseline to Week 52, with the highest mean gains (> 8 letters) occurring during the run-in period (the first 12 weeks of the study). After Week 52, improvements from baseline were consistently lower for the AFL-PDT group compared to the AFL-sham group, but no statistically significant differences between the treatment groups were evident. A corresponding steady decrease in mean retinal thickness was observed in both treatment groups, with most improvements also occurring during the run-in period. Overall gains in BCVA of > 10 letters occurred in more than half of the subjects, while gains in > 15 letters were also relatively frequent, occurring in roughly one third of the subjects. A small subset of subjects (8.3 to 9.3%) did not respond positively to the treatment and lost visual acuity (≥ 5 letters) by Week 96. There were small improvements in the NEI VFQ-25 questionnaire mean score in both treatment groups, and also improvements in the fluorescein leakage area in both groups.

Complete polyp regression by Week 96 in subjects who presented with polyps at baseline occurred in 33.1% of subjects in the AFL-sham group and in 29.1% of subjects in the AFL-PDT group, with no evidence of a significant difference between the groups. This is not consistent with the high proportion of subjects who showed gains in visual function in BCVA at Week 96 (71.3% in the AFL-sham group and 72.7% in the AFL-PDT group), which indicates that rates of complete polyp regression do not seem to be associated with better functional outcomes and should not be used to drive treatment decisions. In contrast, evaluation of polyp activity may be valuable in driving decisions about treatment intensification. By Week 96, approximately 82% of all subjects showed no evidence of active polyps, which corresponds with the high proportion of subjects who showed gains in visual function.

At Week 52, the mean number of PDT(sham or active) treatments in subjects in the FAS was equivalent in the AFL-sham group (0.2 ± 0.7) and the AFL-PDT group (0.2 ± 0.4). The LS mean difference was 0.1 (AFL-sham – AFL-PDT), with a 95% CI that contained 0 (0.0, 0.2) and a p-value of 0.0682. At Week 96, the mean number of PDT (sham or active) treatments was similar in the AFL-sham group (0.4 ± 1.1) and the AFL-PDT group (0.2 ± 0.6), with a LS mean difference of 0.2, a 95% CI that contained 0 (0.0, 0.3), and a p-value of 0.0574. Calculations were made using an

ANOVA model with the treatment group, ethnicity, and qualification for rescue therapy at Week 12 as fixed effects.

The proportion of subjects indicated for rescue therapy was relatively low, but similar between the treatment groups at both Week 52 and Week 96.

At Week 52, 19 subjects (12.1%) in AFL-sham group and 23 subjects (14.3%) in the AFL-PDT group qualified for rescue therapy. The difference between treatment groups was -0.6% (calculated using Mantel-Haenszel weighting scheme adjusted by ethnicity and qualification for rescue therapy at Week 12), and the 95% CI included 0 (-6.3, 5.1) with a p-value of 0.8423.

At Week 96, 25 subjects (15.9%) in AFL-sham group and 29 subjects (18.0%) in the AFL-PDT group qualified for rescue therapy. The difference between treatment groups was -0.6%, and the 95% CI included 0 (-7.5, 6.4) with a p-value of 0.8728.

Safety evaluation

During the course of the study, 24.8% of subjects (39 subjects) in the AFL-sham group and 30.4% of subjects (49 subjects) in the AFL-PDT received the 13 aflibercept injections expected for the standard, bi-monthly dosing regimen. Almost all subjects who received > 13 aflibercept injections had met the criteria for rescue therapy and were on a flexible visit schedule that allowed more frequent aflibercept treatments than the standard regimen. Subjects who received <13 aflibercept injections were either following the treat-and-extend dosing paradigm or did not complete 96 weeks. All subjects who were treated but not randomized received 1, 2, or 3 aflibercept injections, during the run-in period.

Randomized subjects were to be given rescue treatment at any visit after the run-in period but only if they met the rescue criteria, which was dependent on insufficient gain of BCVA, leakage, and presence of active polyps. A high proportion of randomized subjects (83.0%) did not receive PDT (sham or active) rescue therapy during the course of the study, as they did not meet the pre-defined criteria for rescue treatment. By Week 96, 54 subjects qualified for rescue therapy, and the number of PDT administrations in these subjects ranged from 1to 7. A summary of adverse events (AEs) is presented in Table 4.

Table 4: Adverse events (safety analysis set)

Number (%) of subjects with adverse events	AFL-sham N=157 (100%)	AFL-PDT N=161 (100%)	Treated but not Randomized N=15 (100%)	Total N=333 (100%)
Any AE	114 (72.6%)	110 (68.3%)	6 (40.0%)	230 (69.1%)
Any pre-treatment AE	16 (10.2%)	11 (6.8%)	1 (6.7%)	28 (8.4%)
Any post-treatment AE[a]	7 (4.5%)	12 (7.5%)	0	19 (5.7%)
Any TEAE	111 (70.7%)	105 (65.2%)	6 (40.0%)	222 (66.7%)
Any Aflibercept drug related TEAE	15 (9.6%)	5 (3.1%)	3 (20.0%)	23 (6.9%)
Any Aflibercept drug related ocular TEAE	11 (7.0%)	4 (2.5%)	2 (13.3%)	17 (5.1%)
Study eye	11 (7.0%)	4 (2.5%)	2 (13.3%)	17 (5.1%)
Fellow eye	1 (0.6%)	0	0	1 (0.3%)
Any Aflibercept drug related non-ocular TEAE	7 (4.5%)	2 (1.2%)	1 (6.7%)	10 (3.0%)
Any SAE	30 (19.1%)	27 (16.8%)	4 (26.7%)	61 (18.3%)
Any treatment-emergent SAE	27 (17.2%)	25 (15.5%)	4 (26.7%)	56 (16.8%)
Any Aflibercept drug related SAEs	4 (2.5%)	1 (0.6%)	1 (6.7%)	6 (1.8%)
Any Verteporfin drug related SAEs	0	1 (0.6%)	0	1 (0.3%)
Any injection related SAEs	1 (0.6%)	2 (1.2%)	1 (6.7%)	4 (1.2%)
Any laser related SAEs	0	1 (0.6%)	0	1 (0.3%)
Any AEs leading to discontinuation from study drug	5 (3.2%)	4 (2.5%)	2 (13.3%)	11 (3.3%)
Any AEs leading to interruption from study drug	5 (3.2%)	4 (2.5%)	0	9 (2.7%)
Any deaths	3 (1.9%)	0	1 (6.7%)	4 (1.2%)
Any APTC-classified events	2 (1.3%)	0	1 (6.7%)	3 (0.9%)

AE = Adverse event; AFL-PDT = aflibercept plus active photodynamic therapy; AFL-sham = aflibercept plus sham photodynamic therapy; APTC = Anti-Platelet Trialists Collaboration; SAE = Serious adverse event; TEAE = Treatment-emergent adverse event

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

SAEs (ocular and non-ocular) occurred in 18.3% of subjects overall (61 subjects; 19.1% among AFL-sham, 16.8% among AFL-PDT, 26.7% among treated but not randomized). Treatment-emergent SAEs occurred with a frequency of 16.8% overall (17.2% among AFL-sham, 15.5% among AFL-PDT, 26.7% among treated but not randomized).

The safety profile of AFL-sham treatment was similar to that of AFL-PDT treatment. The overall rates of both ocular and non-ocular treatment-emergent AEs reported during the study were similar between the randomized treatment groups as well as the treated but not randomized group, with some slight imbalances. Ocular injection-related treatment-emergent AEs (TEAEs) in the study eye were slightly more frequent in the AFL-sham group (13.4% of subjects) compared to the AFL-PDT group (11.2% of subjects). Similarly, non-ocular aflibercept-related TEAEs were also slightly more frequent in the AFL-sham group (4.5% of subjects) compared to the AFL-PDT group (1.2% of subjects).

Most of the TEAEs of subjects in the SAF were reported as mild in maximum intensity, and few AEs led to interruption of the study treatment. A total of 10 subjects (3.0%) experienced TEAEs

leading to discontinuation of the study drug, with 4 subjects in each randomized treatment group and 2 subjects in the treated but not randomized group. Four subjects experienced ocular TEAEs that resulted in discontinuation of the study drug. Overall, 6 subjects (1.8%) experienced an aflibercept-related Serious AE (SAE) and 1 subject (0.3%) experienced a verteporfin-related SAE. There were 4 subjects (1.2%) with an injection-related SAE and 1 subject (0.3%) with a laser-related SAE.

There were 4 deaths reported in the study, 1 due to sudden cardiac death in the treated but not randomized group and 3 in the AFL-sham group due to arrhythmia, pneumonia, and unknown causes, respectively. Two of the deaths (due to arrhythmia and sudden cardiac death) were considered by the investigator to be aflibercept-related. Three of the deaths were classified as APTC events.

The evaluation of laboratory data and vital signs at screening showed mean values to be within the normal range for the study subjects. The analyses of vital signs did not show any remarkable changes in mean values during the course of the study. There were also no relevant differences among the treatment groups.

No relevant differences between treatment groups were seen in the ophthalmic safety examinations in the study eye. Intraocular pressure, slit lamp, indirect ophthalmoscopy, FA/FP, OCT, and ICGA measurements did not reveal any unexpected results.

Safety analyses were also performed for the two sub-groups (ethnicity and qualification for rescue therapy). The evaluations revealed some numerical differences within the sub-groups, but these sub-group differences did not indicate any trends or lead to any conclusions about safety concerns or vulnerable subject groups.

Overall, the safety outcomes in all treatment groups in this study were in line with the results of previous studies with aflibercept.

Overall conclusions

- Overall, aflibercept monotherapy was demonstrated to be an effective treatment option for patients with the PCV subtype of wet AMD.
- Similar outcomes related to the efficacy variables were observed in the two treatment groups. The study met its primary endpoint.
- Efficacy of aflibercept monotherapy administered in 3 monthly doses followed by dosing every other month was further demonstrated by the low proportion of subjects qualifying for rescue therapy.
- While complete polyp regression does not seem to be associated with improvement in visual acuity, similar proportions of subjects showed improvement in BCVA and no evidence of active polyps at Week 96.
- In the sub-group of subjects who received rescue treatment, non-inferiority of AFL-sham vs. AFL-PDT was demonstrated at Week 96. In this sub-group, the rates of complete polyp regression also showed no association with changes in BCVA, and the addition of PDT does not seem to provide any functional benefits.

- The safety outcomes in all treatment groups in this study were in line with the results of previous studies with aflibercept.

Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Vital GmbH
Postal Address	D-51368 Leverkusen Germany
Sponsor in Germany (if applicable)	
Legal Entity Name	Bayer AG
Postal Address	D-51368 Leverkusen Germany

List of Investigational Sites

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
1	Prof. Paul Mitchell	Westmead Eye Clinic - Westmead Hospital	166-174 Hawkesbury Road Level 4 a, Block B	2145	Westmead	Australia
2	Dr Sanjeewa Wickremasinghe	Centre for Eye Research	32 Gisborne Street	3002	East Melbourne	Australia
3	Dr. Jennifer Arnold	Marsden Eye Surgery Center	152 Marsden Street	2150	Parramatta	Australia
4	Prof. I-Van Ho	Retina Associates	57 Memorial Ave	2170	Liverpool	Australia
5	Dr. James Wong	Strathfield Retina Clinic	9 Redmyre Road Suite 3A	2135	Strathfield	Australia
6	Hr. PD Dr. med. Armin Wolf	Klinikum der Universität München Grosshadern	Klinik für Augenheilkunde Mathildenstr. 8	80336	München	Germany
7	Professor Timothy Lai	Hong Kong Eye Hospital	147K Argyle Street		Kowloon	Hong Kong
8	Dr Ian Wong	Grantham Hospital	125 Wong Chuk Hang Road, Aberdeen,		Hong Kong	Hong Kong
9	Prof. Andras Berta	Debreceni Egyetem Klinikai Kozpont	Nagyerdei krt. 98.	4032	Debrecen	Hungary
10	Dr. Andras Seres	Budapest Retina Associates	Karpat u. 62-64. Hotel Helia	1133	Budapest	Hungary
11	Mr. Dr. Andras Papp	Semmelweis Egyetem	Ulloi ut 26.	1085	Budapest	Hungary
12	Ms. Dr. Agnes Kerenyi	Bajcsy Zsilinszky Korhaz-Rendelointezet	Maglodi u. 89-91.	1106	Budapest	Hungary
13	Dr. Hiroko Imaizumi	Sapporo City General Hospital	Department of Ophthalmology 1-1 Nishi-13, Kita-11, Chuo-ku	060-8604	Sapporo	Japan
14	Prof. Mineo Kondo	Mie University Hospital	Ophthalmology 2-174, Edobashi	514-8507	Tsu	Japan
15	Dr. Tetsuo Ueda	Nara Medical University Hospital	Department of Ophthalmology	634-8522	Kashihara	Japan

			840 Shijo-machi			
16	Dr. Masayuki Hata	Kyoto University Hospital	Department of Ophthalmology 54, Shogoin-kawahara-cho, Sakyo-ku	606-8507	Kyoto	Japan
17	Prof. Chie Sotozono	Kyoto Prefectural University of Medicine	Ophthalmology 465, Kajii-cho, Kawaramachidori Hirokoji-agaru , Kamigyo-ku	602-8566	Kyoto	Japan
18	Dr. Hirokazu Sakaguchi	Osaka University Hospital	Department of Ophthalmology 2-15, Yamadaoka	565-0871	Suita	Japan
19	Dr. Kunihiko Shiraki	Osaka City University Hospital	Department of Ophthalmology 1-5-7, Asahi-cho, Abeno-ku	545-8586	Osaka	Japan
20	Prof. Kanji Takahashi	Kansai Medical University Hospital	Department of Ophthalmology 2-3-1 Shinmachi	573-1191	Hirakata	Japan
21	Dr. Mio Hosokawa	Okayama University Hospital	Ophthalmology 2-5-1, Shikata-machi Kita-ku	700-8558	Okayama	Japan
22	Prof. Kohei Sonoda	Kyushu University Hospital	Department of Ophthalmology 3-1-1, Maidashi, Higashi-ku	812-8582	Fukuoka	Japan
23	Dr. Harumi Wakiyama	The Japanese Red Cross Nagasaki Genbaku Hospital	Department of Ophthalmology 3-15 Mori-machi	852-8511	Nagasaki	Japan
24	Dr. Daisuke Jin	Akita University Hospital	Department of Ophthalmology 44-2 Hasunumaaza Hiroomote	010-8543	Akita	Japan
25	Dr. Tetsuju Sekiryu	Fukushima Medical University Hospital	Department of Ophthalmology 1 Hikarigaoka	960-1295	Fukushima	Japan
26	Dr. Hidenori Takahashi	Jichi Medical University Hospital	Department of Ophthalmology 3311-1 Yakushiji	329-0498	Shimotsuke	Japan
27	Dr. Yoko Ozawa	Keio University Hospital	Department of Ophthalmology 35, Shinano-machi	160-8582	Shinjuku-ku	Japan
28	Dr. Miki Honda	Juntendo University Urayasu Hospital	Department of Ophthalmology 2-1-1 Tomioka	279-0021	Urayasu	Japan
29	Prof. Tomohiro Iida	Tokyo Women s Medical University Hospital	Ophthalmology 8-1, Kawada-cho	162-8666	Shinjuku-ku	Japan
30	Dr. Masahiro Morimoto	Gunma University Hospital	Department of Ophthalmology 3-39-15, Showa-machi	371-8511	Maebashi	Japan
31	Dr. Akira Obana	Seirei Hamamatsu	Ophthalmology	430-	Hamamatsu	Japan

		General Hospital	2-12-12 Sumiyoshi Naka-ku	8558		
32	Dr. Satoshi Kato	The University of Tokyo Hospital	Ophthalmology and Vision Correction 7-3-1, Hongo	113-8655	Bunkyo-ku	Japan
33	Prof. Ayame Okada	Kyorin University Hospital	Department of Ophthalmology 6-20-2 Shinkawa	181-8611	Mitaka	Japan
34	Dr. Akira Hirata	Hayashi Eye Hospital	Ophthalmology 4-23-35 Hakataekimae Hakata-ku	812-0011	Fukuoka	Japan
35	Prof. Hiroko Terasaki	Nagoya University Hospital	Department of Ophthalmology 65 Tsurumai-cho Showa-ku	466-8560	Nagoya	Japan
36	Dr. Akihiro Ishibazawa	Asahikawa Medical University Hospital	Ophthalmology 1-1-1 Higashinijyo, Midorigaoka	078-8510	Asahikwa	Japan
37	Dr. Hideyasu Oh	Hyogo Prefectural Amagasaki General Medical Center	Ophthalmology 2-17-77 Higashinaniwa-cho	660-8550	Amagasaki	Japan
38	Dr. Tsutomu Kawasaki	Ideta Eye Hospital	Department of Ophtalmology 39 Nishitoujin-machi Chuo-ku	860-0027	Kumamoto	Japan
39	Dr. Takashi Katome	Tokushima University Hospital	Department of Ophtalmology 2-50-1, Kuramoto-cho	770-8503	Tokushima	Japan
40	Dr. Masayasu Kitahashi	Chiba University Hospital	Department of Ophthalmology 1-8-1, Inohana, Chuo-ku	260-8677	Chiba	Japan
41	Dr. Masahito Ohji	Shiga University of Medical Science Hospital	Department of Ophthalmology Setatsukinowa-cho	520-2192	Otsu	Japan
42	Dr. Aoi Ono	Kagawa University Hospital	Department of Ophthalmology 1750-1, Ikenobe, Miki-cho	761-0793	Kita	Japan
43	Dr. Kunihiko Akiyama	National Hospital Organization Tokyo Medical Center	Department of Ophthalmology 2-5-1 Higashigaoka	152-8902	Meguro-ku	Japan
44	Dr. Tomoki Sakuraba	Aomori Prefectural Central Hospital	Department of Ophthalmology 2-1-1 Higashitsukurimichi	030-8553	Aomori	Japan
45	Dr. Takayoshi Sumioka	Wakayama Medical University Hospital	Department of Ophthalmology 811-1, Kimiidera	641-8510	Wakayama	Japan
46	Dr. Takatomo Miyake	Ogaki Tokushukai Hospital	Ophthalmology 6-85-1 Hayashimachi	503-0015	Ogaki	Japan
47	Dr. Ryusaburo	Nihon University	Department of	101-	Chiyoda-ku	Japan

	Mori	Hospital	Ophthalmology 1-6 Surugadai, Kanda	8309		
48	Dr. Shigeru Honda	Kobe University Hospital	Department of Ophthalmology 7-5-2 Kusunoki-cho, Chuo-ku	650-0017	Kobe	Japan
49	Dr Won Ki Lee	Seoul St. Mary s Hospital	222 BANPO-DAERO, SEOCHO-GU	137-701	Seoul	Korea, Republic of
50	Dr Kyu Hyung Park	Seoul National University Bundang Hospital	82, Gumi-ro 173beon-gil, Bundang-gu	463-707	Seongnam-si	Korea, Republic of
51	Prof Se Woong Kang	Samsung Medical Center	81 Irwon-Ro Gangnam-gu	135-710	Seoul	Korea, Republic of
52	Dr Hyeong Gon Yu	Seoul National University Hospital	101 DAEHAK-RO JONGNO-GU	03080	Seoul	Korea, Republic of
53	Dr Young-Hee Yoon	Asan Medical Center	88, OLYMPIC-RO 43-GIL, SONGPA-GU	05505	Seoul	Korea, Republic of
54	Dr. Ha Kyoung Kim	Kangnam Sacred Heart Hospital	Hallym University - Kangnam Sacred Heart Hospital Department of Ophthalmology 1 ShinGil-ro Yeongdeungpo-gu	153-950	Seoul	Korea, Republic of
55	Dr. Chui Ming Cheung	Singapore National Eye Centre	11 Third Hospital Ave	168751	Singapore	Singapore
56	Prof. Ka Lin Chee	National University Hospital	5, Lower Kent Ridge Road	119074	Singapore	Singapore
57	Dr. Lee-Jen Chen	Mackay Memorial Hospital	No. 92, Section 2, Chung shan North Road	10449	Taipei	Taiwan
58	Dr San-Ni Chen	Changhua Christian Hospital	Changhua Chrisitian Hospital 彰化基督教醫院 Department of Ophthalmology 135 Nanxiao St. 彰化市南校街135號	500	Changhua City	Taiwan
59	Shwu-Jiuan Sheu	Veterans General Hospital	Veterans General Hospital-Kaohsiung 高雄榮民總醫院 Department of Ophthalmology 386 Ta-Chung 1st Rd, 高雄市左營區大中一路386號	81362	Kaohsiung	Taiwan
60	Dr. Chang-Hao Yang	National Taiwan University Hospital	National Taiwan University Hospital No 7 Chung-Shan	10002	Taipei	Taiwan

			South Road, Zhongzheng Dist.			
61	Dr. Shih-Jen Chen	Taipei Veterans General Hospital	Department of Ophthalmology No 201, Shih-Pai Road, Section 2	11217	Taipei	Taiwan
62	Mr. Dr. Cheng-Kuo Cheng	Shing-Kong Wu Ho-Su Memorial Hospital	95 Wen-Chang Rd, Shih Lin District		Taipei City	Taiwan

Product Identification Information

Product Type	Biological Product
US Brand/Trade Name(s)	EYLEA
Brand/Trade Name(s) ex-US	EYLEA, EYLIA, Wetlia
Generic Name	Aflibercept
Main Product Company Code	BAY86-5321
Other Company Code(s)	N/A
Chemical Description	VEGF Trap belongs to the pharmacological class of VEGF inhibitors: it is a recombinant protein created by fusing the second Ig domain of human VEGFR1 with the third Ig domain of human VEGFR2, which is in turn fused to the constant region of human IgG1. Aflibercept is a potent, specific inhibitor of VEGF that is active in animal models of ocular neovascularisation after systemic and IVT administration. Aflibercept interferes with the biological actions of VEGF-A by binding to VEGF-A, preventing it from interacting with its receptors. It also binds to other VEGFR1 ligands, notably PlGF.
Other Product Aliases	VEGF Trap-Eye

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