Clinical Study Synopsis

This Clinical Study Synopsis is provided for patients and healthcare professionals to increase the transparency of Bayer's clinical research. This document is not intended to replace the advice of a healthcare professional and should not be considered as a recommendation. Patients should always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document or on the related website should not be considered as prescribing advice.
The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare AG	
Study Number:	14130	NCT01012973; EudraCT No. 2009-010973-19
Study Phase	III	
Official Study Title:	A Randomized, Double-masked, Sham-controlled Phase-3 Study of the Efficacy, Safety, and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects with Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)	
Therapeutic Area:	Ophthalmology	
Test Product		
Name of Test Product	VEGF Trap-Eye / EYLEA / BAY 86-5321	
Name of Active Ingredient:	BAY 86-5321 / Aflibercept	
Dose and Mode of Administration:	2 mg intravitreal (IVT) injection	
Reference Therapy/Placebo		
Reference Therapy:	Not applicable (sham treatment to maintain masking)	
Dose and Mode of Administration:	Not applicable	
Duration of Treatment:	Up to 76 Weeks	
Studied period:	Date of first subjects' first visit:	28 October 2009
	Date of last subjects' last visit:	01 February 2012
Premature Study Suspension / Termination:	Not applicable	
Substantial Study Protocol Amendments:	There were three amendments to the study protocol. Amendment 1: In September 2009, Amendment 1 was instituted in Japan to specify that an approximate 10% of the total study population (or at least 16 subjects) would comprise Japanese citizens. At the time of this amendment, no subjects had been enrolled or treated in the study. Amendment 2: In December 2009, Amendment 2 was instituted in France to broaden the exclusion criteria for subjects with a history of vitreoretinal surgery in the study eye within 3 months of Day 1 (ie, initiation of treatment) such that, in France, subjects with <u>any</u> history of such treatment would be excluded. Additionally, the amendment allowed pan-retinal photocoagulation (PRP) rescue treatment to be administered at the discretion of the investigator. At the time of Amendment 2, three subjects had been randomized in the study (none in France). Amendment 3: Amendment 3 was a global amendment and became effective in June 2010. The original protocol stated that quarterly follow-up safety visits were to be conducted from Week 52 through and including Week 100. In addition, the protocol stated that "treatment details for the second year of the study will be specified prior to the first follow-up safety visit by the sponsor in consultation with the Independent Data Monitoring Committee (IDMC)" and "an amendment to this protocol describing possible drug treatment in the second study year will be submitted to the health authorities and the Institutional Review Boards (IRBs) for their approval prior to the first follow-up safety visit in the second year." Protocol Amendment 3, which was developed primarily to address the post-Week 52 follow-up phase of the study, affected all study sites worldwide. At the time of Amendment 3, 140 subjects	

had been randomized in the study. The two changes made to the protocol under Amendment 2 became global changes under this amendment. Other substantial changes made to the protocol under Amendment 3 are summarized below:

Removal of Quarterly Follow-up Safety Visits and Addition of a Follow-up Treatment Phase:

The original protocol specified that quarterly safety follow-up visits would be conducted from Week 52 to Week 100. This was replaced by a follow-up treatment phase such that, after the Week-52 assessment of the tertiary endpoints, the study would continue for an additional 6 months during which subjects would undergo safety assessments every 8 weeks or at Weeks 60, 68, and 76. At Weeks 52, 60, and 68, all subjects were to be assessed against the study retreatment criteria and would receive active EYLEA treatment as appropriate.

Retreatment at Week 52 and During the Follow-up Phase:

Visit 15 (Week 52): The protocol was amended to specify that a masked physician was to assess all subjects against the study retreatment criteria at Visit 15. An unmasked physician was to treat subjects as follows:

- Subjects in the VTE2Q4 group who met any of the retreatment criteria for deterioration were to receive EYLEA 2 mg
- Subjects in the VTE2Q4 group who met the retreatment criteria for improvement were to receive the same treatment (EYLEA or sham) as the one preceding the observed rapid and substantial improvement.
- Subjects in the VTE2Q4 group who did not meet any criteria for retreatment were to receive a sham treatment.
- The unmasked physician administering the retreatment must have been made aware of whether retreatment was being performed for deterioration or for improvement.
- Subjects in the sham-control group were to receive EYLEA 2 mg
- For both groups, if the masked investigator decided, for medical reasons, that study treatment was not in the best interest of the subject and EYLEA should not be administered, the subject was to receive a sham treatment.

Visit 16 (Week 60) and Visit 17 (Week 68): The protocol was amended to specify that the masked physician was to assess all subjects against the study retreatment criteria at Visit 16 and Visit 17. The unmasked physician was to treat the subject as follows:

- Subjects in either group who met any of the retreatment criteria for deterioration were to receive EYLEA 2 mg
- Subjects in either group who met the retreatment criteria for improvement were to receive the same treatment (ELYEA or sham) as the one preceding the observed rapid and substantial improvement. The unmasked physician administering the retreatment must have been made aware of whether retreatment was being performed for deterioration or for improvement.
- Subjects in either group who did not meet any criteria for retreatment were to receive a sham treatment

Early Termination:

The protocol was modified to clarify that subjects who discontinued study treatment (EYLEA or sham injection) for an adverse event (AE; including conditions requiring PRP rescue treatment) prior to Week 68 should be offered safety follow-up through Week 76. If the subject continued safety follow-up through Week 76, all scheduled visit procedures and assessments were to be conducted, except study drug administration and the post-injection safety assessment.

On the other hand, subjects who discontinued treatment with study drug for reasons other than an AE were to return to the study site for two early-termination visits, one at 30 days and one at 60 days following discontinuation of study treatment.

Extension of the Pharmacokinetics Sub-study:

The protocol was amended to allow for the recruitment of additional subjects into an abbreviated pharmacokinetics (PK) sub-study between Weeks 20 and 24 if fewer than 24 subjects had agreed to the sub-study by Visit 7. Similarly, if fewer than 24 subjects had agreed to the sub-study by Visit 15, subjects were to be asked to participate in an abbreviated PK study between Weeks 52 and 56. In both cases, subjects agreeing to participation were required to sign and date a PK informed

	consent form. Measurement of Intraocular pressure (IOP): The protocol was changed to specify that post-injection assessment of IOP should occur approximately 30 minutes after the injection rather than within 30 minutes after the injection.
Study Centre(s):	74 study sites screened patients for the study. Patients were treated at 63 study sites in 10 countries in Europe (Austria 3; France 5; Germany 21; Hungary 5; Italy 7; Latvia 2) and Asia/Pacific (Australia 6; Japan 6; Singapore 2; South Korea 6)
Methodology:	This study was reported in three parts: Week-24 results, Week-52 results, and Week-76 results. Primary and secondary endpoints were assessed at Week 24 and were reported in the Week-24 Clinical Study Report. During the first 20 weeks of the study, subjects received either VTE2Q4 as an IVT injection in the study eye or underwent a sham IVT injection. All primary and secondary efficacy endpoints were assessed at Week 24 prior to administration of study treatment. From Week 24 to Week 48, subjects in the VTE2Q4 group received either VTE2Q4 as an IVT injection or sham in the study eye, depending on the study retreatment criteria. Subjects in the sham group underwent a sham IVT injection. All subjects were evaluated every 4 weeks from Week 0 to Week 52 for safety and best corrected visual acuity (BCVA). Beginning at Week 52, all subjects were eligible to received active as needed (ie, PRN) injections based on the study retreatment criteria (in order to maintain masking, sham injections were given if the retreatment criteria were not met) and were evaluated for safety and BCVA every 8 weeks (Week 60 and Week 68). Optical coherence tomography (OCT) was conducted at each visit, and fundus photography (FP) and fluorescein angiography (FA) were conducted at Screening and Weeks 12, 24, 36, 52, and 76. Quality of Life (QOL) was evaluated using the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25 questionnaire). Overall state of health was assessed using the EQ-5D Health Questionnaire. Only one eye per subject was enrolled in the study. IVT injections into the fellow eye were not permitted; medications administered via other routes of administration (eg, topical, juxtascleral, subconjunctival, or periorbital routes) in the fellow eye were allowed. However, subjects could not receive any investigational treatment for CRVO in the fellow eye. The fellow eye was not considered an additional study eye and was not eligible to receive VEGF Trap-Eye. Subjects who received treatments for the fellow eye other than systemic medications, IVT injections, or investigational drugs were not required to be withdrawn from further study treatment. Safety of the fellow eye was monitored and systemic adverse events (AEs) were collected.
Indication/ Main Inclusion Criteria:	Indication: • Central Retinal Vein Occlusion Main inclusion criteria: • Center-involved macular edema secondary to CRVO for no longer than 9 months, with a mean central subfield thickness ≥ 250 µm on OCT • Adults ≥ 18 years of age • BCVA, as assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, of 20/40 to 20/320 (73 to 24 letters) in the study eye • For men and women of childbearing potential, willingness to use adequate contraception and not become pregnant (or have their partner[s] become pregnant) during the full course of the study. • Willing, committed, and able to return for all clinic visits and complete all study-related procedures • Willingness to provide written informed consent

Study Objectives:	Primary: To determine the efficacy of IVT administered EYLEA on BCVA as assessed by the ETDRS chart in subjects with macular edema secondary to CRVO Secondary: To assess the safety and tolerability of IVT administered EYLEA in subjects with macular edema secondary to CRVO. To assess the effects of IVT administered EYLEA on central retinal thickness (CRT) in subjects with macular edema secondary to CRVO.
Evaluation Criteria:	Efficacy (Primary): The primary efficacy variable was the proportion of subjects who gained at least 15 letters in BCVA on the ETDRS chart at Week 24 compared to baseline, with discontinued subjects judged as failures (ie, subjects who discontinued the study before Week 24 were included in the calculation as subjects who had not gained at least 15 letters by Week 24). Efficacy (Secondary): Secondary efficacy variables included change from baseline in BCVA at Week 24, change from baseline in CRT at Week 24, the proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization elsewhere in the fundus (NVE) at Week 24, change in the NEI VFQ-25 total score from baseline at Week 24, and change in the EQ-5D score from baseline at Week 24. Safety: Ongoing safety assessments (through Week 76) included ophthalmic examinations (including pre- and post-dose IOP), the recording and evaluation of clinical AEs, safety laboratory measurements, and vital signs.
Statistical Methods:	The full analysis set (FAS) included all randomized subjects who received any study treatment (VTE2Q4 or sham injection) and had a baseline ETDRS score and at least one post-baseline ETDRS score. The FAS was the primary efficacy analysis set and was analyzed as randomized. The safety analysis set (SAF) included all subjects who received any study treatment. The SAF was analyzed as treated. Efficacy (Primary): With respect to the primary efficacy endpoint, the proportion of subjects who gained at least 15 letters at Week 24 with discontinued subjects judged as failures, the two treatment groups were compared using a Cochran-Mantel-Haenszel (CMH) test with stratification adjustment for geographic region (Europe vs Asia/Pacific) and baseline visual acuity (BCVA > 20/200 vs BCVA ≤ 20/200) at a two-sided test level of 5%. Efficacy (Secondary): If the primary efficacy endpoint was statistically significant, secondary efficacy endpoints were to be tested by means of a pre-specified hierarchical sequence of statistical hypotheses testing in order to control for multiplicity (sequence: change in BCVA letter score at Week 24, change in CRT at Week 24, proportion of subjects progressing to any neovascularization at Week 24, change in total NEI VFQ-25 score at Week 24, and change in EQ-5D score at Week 24). For secondary endpoints, analysis of covariance (change in CRT, change in NEI VFQ-25 total scores, and change in EQ-5D scores), analysis of variance (change in BCVA) or CMH procedures (proportion of subjects progressing to any neovascularization) were used. Safety: For safety variables, three observation periods were defined: • The pretreatment period was defined as the time from signing the informed consent form to before the first dose of study drug. • The treatment period was defined as the day from first dose of study drug to 30 days after the last dose of study drug. • The post-treatment period was defined as later than 30 days after the last injection Treatment-emergent AEs (TEAEs) were defined as those that were not present at baseline or represented an exacerbation of a pre-existing condition during the treatment period. Treatment-emergent AEs were categorized as follows:

	• Ocular TEAEs in the study eye • Ocular TEAEs in the fellow eye • Non-ocular TEAEs Summaries of AEs, including frequencies and proportions of subjects reporting AEs, included the MedDRA system/organ class (SOC) and preferred terms (PTs). Summaries of all TEAEs by treatment group included: • The number and percentage of subjects with at least one TEAE by SOC and PT • TEAEs by intensity (severe, moderate, mild), presented by SOC and PT • TEAEs by relationship to treatment (related, not related; including categories of study drug, injection, and other protocol-specified procedures), presented by SOC and PT Deaths and other serious adverse events (SAEs) were listed and summarized by treatment group. Treatment-emergent AEs leading to permanent treatment discontinuation were listed and summarized by treatment group.
Number of Subjects:	Planned: 165 total, 66 sham and 99 VTE2Q4 Randomized: 177 total, 71 sham and 106 VTE2Q4 Analyzed: Full analysis set (FAS): 171 total; 68 sham and 103 VTE2Q4 Safety analysis set (SAF): 172 total; 68 sham and 104 VTE2Q4

Study Results

Results Summary — Subject Disposition and Baseline

Baseline:

The FAS comprised 95 (55.6%) male and 76 (44.4%) female subjects aged between 29 and 88 years (median: 64 years). Overall, the two treatment groups were well balanced with regard to demographic and disease characteristics at baseline. The majority of subjects (71.9%) were of White race and 24.0% were Asian (race was not reported for 4.1% of subjects); five subjects were of Hispanic or Latino ethnicity.

Subjects had a mean±standard deviation (SD) baseline BCVA (as measured with the ETDRS letter chart; FAS) of 52.5 ± 15.7 letters, with a range of 14 to 82 letters (median: 55 letters). Groups were similar in mean baseline BCVA; mean baseline BCVA was 50.9 ± 15.4 letters in the sham group and 53.6 ± 15.8 letters in the VTE2Q4 group. Similarly, treatment groups were similar in mean baseline CRT (sham 638.66 ± 224.69 microns; VTE2Q4 683.20 ± 234.46 microns). Baseline pre-injection IOP was similar and considered normal in both treatment groups (sham: 14.4 ± 2.7 mm Hg; VTE2Q4: 15.1 ± 2.8 mm Hg).

Mean baseline NEI VFQ-25 total scores were not different between treatment groups (sham 78.94 ± 14.00; VTE2Q4: 79.80 ± 13.05), although individual baseline scores were variable and ranged from 43.7 to 99.2 overall. Mean baseline EQ-5D score was similarly high in both treatment groups at baseline (sham 0.86 ± 0.16; VTE2Q4 0.87 ± 0.15).

All subjects had at least one finding on medical history. As expected, the most frequent medical history findings were in the MedDRA SOC Eye Disorders (100% of subjects in both treatment groups). Vascular Disorders, Surgical and Medical Procedures, and Metabolism and Nutrition Disorders were self-reported by 61.0%, 52.9%, and 41.3% of the subjects, respectively. The most common prior therapy reported was ophthalmologicals (17.6% of sham subjects and 16.3% of VTE2Q4 subjects). All subjects took at least one new additional therapy following initiation of study treatment. The most common new therapies were ophthalmologicals, throat preparations, and antibacterials for systemic use, all of which were used at a similar frequency in the two treatment groups.

Subject disposition:

The majority of subjects in both treatment groups completed the first 24 weeks of the study (ie, to the primary endpoint of the study); 57 (80.3%) in the sham group and 97 (91.5%) in the VTE2Q4 group. The most common reason for premature discontinuation of the study treatment before Week 24 was adverse event (7.0%) in the sham group and protocol violation (4.7%) in the VTE2Q4 group. Lack of efficacy was reported as the reason for premature discontinuation of study treatment by four (5.6%) subjects in the sham group and no subjects in the VTE2Q4 group.

Results Summary — Efficacy

Primary:

The primary efficacy endpoint, the proportion of subjects who gained at least 15 letters in BCVA at Week 24, with discontinued subjects before Week 24 judged as failures, was assessed using the FAS. In the VTE2Q4 group, 60.2% of subjects gained at least 15 letters compared with 22.1% of subjects in the sham group, for a difference (VTE2Q4 minus sham) of 38.1%. When adjusted for region and baseline BCVA, the difference between treatment groups was 38.3% (95% confidence interval [CI]=24.4 to

52.1%; p<0.0001; based on the CMH test) and demonstrated the superiority of VTE2Q4 over sham.

Gains of 15 letters or more were observed in 32.0% of the subjects in the VTE2Q4 group as early as Week 4 (ie, after only one treatment) and in 47.6% of the VTE2Q4 subjects at Week 8 (ie, after two treatments). In the sham group, gains of 15 letters or more were observed in 5.9% and 10.3% of the subjects at these time points, respectively.

Secondary:

The secondary efficacy endpoint analyses were performed at Week 24 with the FAS and also tested for the superiority of EYLEA over sham. A pre-specified hierarchical sequence of statistical hypotheses testing was used to control for multiplicity (sequence: change in BCVA letter score at Week 24, change in CRT at Week 24, proportion of subjects progressing to any neovascularization at Week 24, change in total NEI VFQ-25 score at Week 24, and change in EQ-5D score at Week 24).

At Week 24, the VTE2Q4 group mean ETDRS letter score increased by 18 letters compared with a mean increase of 3.3 letters in the sham group. The difference in least squares (LS) mean change in ETDRS letter score (adjusted for region and baseline BCVA) between treatment groups at Week 24 was highly statistically significant (p<0.0001) and supported the superiority of VTE2Q4 over sham. Mean BCVA improved by 12 letters at Week 4 compared to baseline in the VTE2Q4 group (FAS; LOCF) and continued to improve such that, by Week 16, this group had gained a mean of 18 letters over baseline. The improvements achieved at Week 16 were maintained through Week 24. In the sham group, however, mean BCVA increased by only about 3 letters over the full 24 weeks.

Changes in BCVA were categorized to provide a summary of vision gain (ie, at least 10, 15, or 30 letters) and loss (ie, less than 0, 10, or 15 letters) at Week 24. As seen in the primary efficacy analysis (ie, considering discontinued subjects as failures), over half of the subjects in the VTE2Q4 group (60.2%; FAS) gained at least 15 letters of vision at Week 24 compared to 22.1% of subjects in the sham group. Similarly, a higher proportion of subjects treated with VTE2Q4 than those treated with sham gained at least 10 letters (71.8% and 30.9%, respectively) or at least 30 letters (16.5% and 2.9%, respectively) by Week 24. Similarly, in all categories of vision loss, more subjects in the sham group experienced losses than did subjects treated with VTE2Q4.

At Week 24, the LS mean change in CRT (adjusted for region and baseline BCVA) between treatment groups was highly statistically significant (p<0.0001) and also supported the superiority of VTE2Q4 over sham. Mean change in CRT was greater in the VTE2Q4 group (-448.58 microns) compared to the sham group (-169.27 microns). The VTE2Q4 group showed a substantial reduction in CRT at the first post-baseline measurement (Week 4; mean change of -403.15 ± 248.32 microns) and CRT continued to decrease to Week 24 in this group. At Week 4, the sham group experienced a mean change from baseline of only -18.41 ± 202.26 microns.

In the FAS, general incidence of development of any neovascularizations was low. Three subjects in each treatment group developed any neovascularization (4.4% in the sham group and 2.9% in the VTE2Q4 group) in the first 24 weeks of the study. This did not result in a statistically significant difference between treatment groups. Of the three subjects treated with VTE2Q4 who developed any neovascularization, one developed NVE and two developed anterior segment neovascularization; in the sham group, two subjects developed NVE and one developed anterior segment neovascularization. No subject in either group developed NVD. Overall, four subjects underwent PRP, three in the sham group and one in the VTE2Q4 group.

Because the hierarchical testing of secondary efficacy variables stopped after the testing of the proportion of subjects progressing to any neovascularization, the changes in NEI VFQ-25 and EQ-5D scores at Week 24 were evaluated for descriptive purposes only.

Mean total NEI VFQ-25 scores were similar between treatment groups at baseline. At Week 24, a greater improvement in mean scores was seen in the VTE2Q4 group (LS mean change of 4.5 points; FAS; LOCF) compared to the sham group (LS mean change of 0.3 points). Only the change in the VTE2Q4 group was considered clinically relevant (ie, increase in score of at least 4 points). Mean EQ-5D scores were relatively high and similar between treatment groups at baseline. Mean EQ-5D scores remained relatively unchanged from baseline at Week 24 in both groups.

Results Summary — Safety

Safety results are presented for the full 76-weeks of the study. Please recall that subjects in the VTE2Q4 group received active drug on a PRN basis according to the study retreatment criteria from Week 24 to Week 68 and sham subjects were eligible to receive active drug (on a PRN basis according to the study retreatment criteria) beginning at Week 52.

In the safety analysis, AEs may have been classified as drug related, injection related, procedure related, or not related. Drug related meant that there was a reasonable possibility that the event was caused by the study drug (eg, a hypersensitivity reaction); Injection related meant that there was a reasonable possibility that the event occurred as a result of the IVT injection or sham procedure (eg, eye pain at the site of the injection) and procedure related meant that there was a reasonable possibility that the event occurred as a result of participation in the study but was not associated with the injection (ie, EYLEA/sham) procedure (eg, bruising at the site of a blood draw).

Approximately one-quarter of the subjects in both treatment groups experienced pretreatment AEs (23.5% sham; 28.8% VTE2Q4) and the majority of subjects in both treatment groups experienced at least one TEAE during the study (92.6% sham and 89.4% VTE2Q4).

Ocular TEAEs: In both treatment groups, the incidence of ocular TEAEs was higher in the study eye (77.3%) than the fellow eye

(22.7%).

The incidence of ocular TEAEs in the study eye was not appreciably different between the VTE2Q4 (78.8%) and sham (75.0%) groups. In both treatment groups, the ocular TEAEs in the study eye were more often considered related to the injection procedure than the study drug. The incidence of injection-related ocular TEAEs in the study eye was 39.7% and 42.3% in the sham and VTE2Q4 groups, respectively. Most ocular TEAEs in both treatment groups were considered to be mild (27.9%) or moderate (41.3%) in maximum intensity. In both treatment groups, the incidence of severe ocular TEAEs was low (7.4% and 9.6% in the sham and VTE2Q4 groups, respectively).

The most commonly reported ocular TEAE in the study eye was macular edema, which, overall, was reported more often in the VTE2Q4 group than the sham group (sham 25.0%; VTE2Q4 39.4%). Most events of macular edema in the VTE2Q4 group occurred following the switch to PRN dosing (3.8% at Week 24, 33.7% at Week 52, and 39.4% at Week 76). Conversely, with the initiation of active treatment in the sham group, the incidence of two important disease-related events dropped; the incidence of macular edema dropped to 3.8% from 22.1% at Week 52 and the incidence of visual acuity reduced dropped to 1.9% from 11.8% at Week 52 in these subjects.

Non-ocular TEAEs: Over half of the subjects in both treatment groups experienced a non-ocular TEAE during the course of the study. The incidence of non-ocular TEAEs was 73.5% in the sham group and 68.3% in the VTE2Q4 group. Only two subjects overall, one in each treatment group, experienced a non-ocular TEAE considered to be related to the study drug, and no non-ocular TEAEs were considered to be related to the injection procedure.

In general, individual non-ocular TEAEs occurred in only a small number of subjects. The most commonly reported non-ocular TEAEs were nasopharyngitis (sham 25.0%; VTE2Q4 15.4%), headache (sham 8.8%; VTE2Q4 11.5%), and hypertension (sham 10.3%; VTE2Q4 9.6%).

SAEs: A total of 37 (21.5%) subjects experienced treatment-emergent SAEs during the 76 weeks of the study. The incidence of such events was similar in the two treatment groups (sham 22.1%; VTE2Q4 21.2%).

A total of 17 (9.9%) subjects experienced ocular treatment-emergent SAEs in the study eye. The incidence of such events was similar in the two treatment groups (sham 8.8%; VTE2Q4 10.6%). Most ocular treatment-emergent SAEs in the study eye were reported in only one of the two treatment groups and appeared to be related to the disease state (eg, macular edema and visual acuity reduced). There were no clinically relevant differences between treatment groups in terms of frequency or pattern of the reported events. The most commonly reported ocular treatment-emergent SAE was macular edema, which occurred at a similar incidence in the two treatment groups (sham, 2.9%; VTE 3.8%).

The incidence of non-ocular treatment-emergent SAEs was low overall (12.8%) and similar in the two treatment groups (sham 14.7%; VTE2Q4 11.5%). Pneumonia, humerus fracture, and syncope were the only non-ocular treatment-emergent SAEs reported for more than one subject.

No deaths were reported in the 76 weeks of the study.

TEAEs Leading to Withdrawal: A total of 14 (8.1%) subjects permanently discontinued the study drug because of an adverse event (sham 10.3%; VTE2Q4 6.7%). Most of these subjects discontinued for a TEAE in the Eye Disorders SOC. All subjects in the sham group who discontinued for a TEAE did so before the initiation of active treatment (ie, discontinued before Week 52).

AEs of Interest: Adverse events of safety interest were specified in the study protocol and additional ocular and non-ocular events of interest were identified in the study Statistical Analysis Plan.

The overall incidence of ocular TEAEs of interest in the study eye was similar in the two treatment groups (sham 42.6%; VTE2Q4 43.3%). The most common ocular TEAEs of interest in the study eye were adverse events due to the intravitreal injection procedure (sham 23.5%; VTE2Q4 35.6%). Visual acuity reduced, an event in the category of other ophthalmic adverse events of interest, was reported for 13.2% of subjects in the sham group and 14.4% of subjects in the VTE2Q4 group.

The most common non-ocular event of interest was hypertension, which was reported for 7 (10.3%) subjects in the sham group and 10 (9.6%) subjects in the VTE2Q4 group. Hypertension was reported at a similar incidence in the two treatment groups throughout the study (Week 24: sham 4.4%; VTE2Q4 3.8% / Week 52: sham 8.8%; VTE2Q4 6.7% / Week 76: sham 10.3%; VTE2Q4 9.6%).

At Week 76, the TEAE of visual acuity reduced was reported at a similar incidence in the VTE2Q4 group (14.4%) and in the sham group (13.2%). At Week 24 (the end of the consistent 2Q4 dosing regimen) there were no subjects in the VTE2Q4 group and 10.3% in the sham group who experience this TEAE. By Week 52 the incidence of this TEAE increased in the VTE2Q4 group such that the two groups were similar with 10.6% subjects in the VTE2Q4 group and 11.8% subjects in the sham group experiencing reduced visual acuity. These data support the conclusion that better efficacy is maintained with a consistent, proactive fixed dosing regimen than is achieved with a reactive, less frequent PRN dosing regimen as measured by stable or increased visual acuity.

Arterial thromboembolic events based on the Anti-Platelet Trialists' Collaboration (APTC) endpoint: An APTC Adjudication Committee, comprising two masked Sponsor physicians with expertise in cardiology and two masked external cardiologists (ie, not Sponsor personnel), classified all potential treatment-emergent vascular events in a masked manner based on classification for arterial thromboembolic events (ie, non-fatal MI, non-fatal stroke, fatal [vascular] events or deaths of unknown cause) as proposed by the APTC. There were no arterial thromboembolic events based on the APTC endpoint reported in either treatment group.

Conclusions			
VTE2Q4 was shown to be statistically significantly superior to sham in the proportion of subjects who gained at least 15 letters of vision from baseline to Week 24 in the primary analysis. Similarly, VTE2Q4 was also shown to be statistically significantly superior to sham in the increase in BCVA (as assessed by ETDRS letter score) at Week 24 and in the decrease in CRT at Week 24. EYLEA 2 mg was well tolerated and displayed a favorable safety profile over the 76 weeks of treatment in this population of subjects with CRVO.			
Publication(s):	None		
Date Created or Date Last Updated:	5 Feb 2013	Date of Clinical Study Report:	24-week results (amended): 15 Aug 2012 52-week results (amended): 15 Aug 2012 76-week results: 08 Oct 2012

Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer HealthCare AG
Postal Address	D-51368 Leverkusen Germany
Sponsor in Germany	
Legal Entity Name	Bayer HealthCare AG
Postal Address	D-51368 Leverkusen Germany

List of Investigational Sites

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
1	Frank G.Holz	Universitaets-Augenklinik Bonn	Ernst-Abbe Str.2	D-53127	Bonn	Germany
2	Sabine Aisenbrey	Eberhard-Karls-Universitaet Tuebingen Universitaets-Augenklinik	Schleichstr.12-16	D-72076	Tuebingen	Germany
3	Lutz Lothar Hansen	Universitaets-Augenklinik Freiburg	Killianstr. 5	D-79106	Freiburg	Germany
4	Johann Roider	Universitaetsklinikum Kiel Klinik fuer Augenheilkunde	Hegewisch-strasse 2	D-24105	Kiel	Germany
5	Peter Wiedemann	Universitaetsklinikum Leipzig AoeR Klinik und Poliklinik fuer Augenheilkunde	Liebigstr. 10-14	D-04103	Leipzig	Germany
6	Chris Patrick Lohmann	Klinikum rechts der Isar Augenklinik	Ismaninger Str. 22	D-81675	Muenchen	Germany
7	Norbert Pfeiffer	Universitaetsmedizin der Johannes Gutenberg-Universitaet; Augenklinik und Poliklinik	Langenbeckstr. 1	D- 55131	Mainz	Germany
8	Stefan Dithmar	Universitaetsklinikum Heidelberg Augenklinik	Im Neuenheimer Feld 400	D- 69120	Heidelberg	Germany
9	Dirk Sandner	Klinik und Poliklinik fuer Augenheilkunde am Universitaets- klinikum Carl Gustav Carus	Fetscherstrabe 74	01307	Dresden	Germany
10	Bernd Kirchhof	Klinikum der Universitaet zu Koeln Zentrum fuer Augenheilkunde	Kerpener Str 62	50924	Koeln-Lindenthal	Germany

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
11	Helmut G. Sachs	Krankenhaus Dresden Friedrichstadt Staedtisches Klinikum - Augenklinik Akademisches Lehrkrankenhaus der TU Dresden	Friedrichstr. 41	01067	Dresde	Germany
12	Salvatore Grisanti	Universitaetsklinikum Luebeck	Ratzeburger Allee 160	23538	Lubeck	Germany
13	Nicolas Feltgen	Universitaets-Augenklinik	Robert-Koch-Strasse 40	37075	Goettingen	Germany
14	Karl-Heinz Emmerich	Augenklinik, Klinikum Darmstadt Heidelberger	Landstrasse 379	64297	Darmstadt	Germany
15	Lars-Olof Hattenbach	Klinikum Ludwigshafen, Augenklinik	Bremserstr. 79	D-67063	Ludwigshafen	Germany
16	Peter Walter	Augenklinik Universitaetsklinikum Aachen	Pauwelsstr. 30	D-52074	Aachen	Germany
17	Katrin Engelmann	Augenklinik Chemnitz Klinikum Chemnitz GmbH	Flemmingstr. 2	09116	Chemnitz	Germany
18	Norbert Bornfeld	Universitaetsklinikum Essen Zentrum fuer Augenheilkunde	Hufelandstr. 55	D-45122	Essen	Germany
19	Andreea Gamulescu	Universitaetsklinikum Regensburg Klinik und Poliklinik fuer Augenheilkunde	Franz-Josef-Strauss-Allee 11	93053	Regensburg	Germany
20	Gisbert Richard	Universitaetsklinikum Hamburg-Eppendorf Klinik und Poliklinik fuer Augenheilkunde	Martinistrasse 52	D-20246	Hamburg	Germany
21	Berthold Seitz	Augenklinik Universitatsklinikum Saarland	Kirrberg Str.1 Haus 22	66421	Homburg	Germany
22	Stefan Mennel	Universitaetsklinikum Gieben und Marburg GmbH, Standort Marburg, Klinik fuer Augenheilkunde	Robert-Koch-Strabe 4	D-35037	Marburg	Germany
23	Daniel Pauleikhoff	Augenabteilung am St. Franziskus Hospital	Hohenzollernring 74	48145	Muenster	Germany
24	Frank Koch	Klinikum der Johann-Wolfgang Goethe-Universitaet Klinik fuer Allgemeine Augenheilkunde	Theodor-Stern-Kai 7	60590	Frankfurt	Germany
25	Jean François Korobelnik	CHU de Bordeaux Hôpital Pellegrin- Département d'Ophtalmologie	Place Amélie Raba Léon	33000	Bordeaux	France
26	François Devin	Centre d'Ophtalmologie Paradis-Monticelli	433 Rue Paradis	13008	Marseille	France
27	Michel Paques	Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts - Service Pharmacie	28, Rue de Charenton	75012	Paris	France
28	Gabriel Quentel	Centre Ophtalmologique d'Imagerie et de Laser	11 Rue Antoine Bourdelle	75015	Paris	France
29	Michel Weber	CHU de Nantes Hôpital Hôtel-Dieu - service d'ophtalmologie	1 Place Alexis Ricordeau	44093	Nantes cedex 1	France

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
30	Catherine Creuzot-Garcher	CHU de Dijon Hôpital Général service d'ophtalmologie	3 rue Faubourg Raines	21000	Dijon	France
31	Yuichiro Ogura	Nagoya City University Hospital	1 Azakawasumi Mizuho-cho, Mizuho-ku.	467-8601	Nagoya	Japan
32	Miki Honda	Juntendo University Urayasu Hospital	2-1-1 Tomioka Urayasu-shi	279-0021	Chiba	Japan
33	Hiroko Terasaki	Nagoya University Hospital	65 Tsurumai-cho Showa-ku	466-8560	Nagoya	Japan
34	Nagahisa Yoshimura	Kyoto University Hospital	52 Shogo-in Sakyo-ku	606-8507	Kyoto	Japan
35	Mitsuko Yuzawa	Surugadai Nihon University Hospital	1-8-13 Surugadai, Kanda Chiyoda-ku	101-8309	Tokyo	Japan
36	Motohiro Kamei	Osaka University Hospital	2-2 Yamadaoka Suita	565-0871	Osaka	Japan
37	Francesco Boscia	Azienda Ospedaliera Ospedale Consorziale e Policlinico, Università degli Studi Dipartimento di Oftalmologia	Piazza Giulio Cesare, 11	70124	Bari (BA)	Italy
38	Alfonso Giovannini	Ospedali Riuniti Umberto I-GM. Lancisi-G. Salesi Università di Ancona U.O. Clinica	Oculistica Via Conca, 71	60020	Torrette di Ancona (AN)	Italy
39	Ugo Menchini	Azienda Ospedaliera Careggi Università degli Studi-Policlinico Universitario Dipartimento di Scienze Chirurgiche, Oto-Neuro-Oftalmologiche	Viale G.B, Morgagni, 85	50134	Firenze (Fi)	Italy
40	Federico Ricci	Policlinico tor Vergata Centro di Riferimento Regionale per la Diagnosi e la Terapia delle Degenerazione Maculare senile e delle Patologie Retiniche Cecitanti	Viale Oxford, 81	00133	Roma	Italy
41	Monica Varano	Fondazione G.B. Bietti-IRCCS Divisione di Retina Medica	Via Livenza, 3	00198	Roma (RM)	Italy
42	Francesco Viola	Ospedale Maggiore Policlinico, Mangiagalli, Regina Elena-IRCCS U.O. di Oculistica	Via M fandi	20122	Millano (MI)	Italy
43	Rosangela Lattanzio	Ospedale San Raffaele IRCCS- Unità Operativa di Oculistica	Via Olgettina, 60	20132	Milano (MI)	Italy
44	Alfredo Reibaldi	Azienda Ospedaliero-Universitaria Policlinico "G. Rodolico" U.O. di Oculistica	Via S.Sofia, 78	95123	Catania	Italy
45	Federico Grignolo	Ospedale Oftalmico Clinica Oculistica-Università degli Studi	Via Juvarra, 19	10122	Torino (TO)	Italy
46	Mark Gillies	Save Sight Institute, University of Sydney Eye Hospital	8, Maquarie Street	NSW 2001	Sydney	Australia
47	Jennifer Arnold	Marsden Eye Surgery Centre	152, Marsden Street	2150	Parramatta	Australia

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
48	Ian McAllister	Lion eye institute, Charles Gardner Hospital	2, Verdun Street	WA 6009	Nedlands	Australia
49	Simon Chen	Vision Eye Institute Level 4	270 Victoria Avenue	NSW 2067	Chatswood	Australia
50	Paul Mitchell	Eye Clinic, Westmead Hospital, Level 4a	Block B	NSW 2145	Westmead	Australia
51	Lyndell Lim	Centre for Eye Research	32 Gisborne Street	Vic 3002	East Melbourne	Australia
52	Ursula Schmidt-Erfurth	Universitaetsklinik fuer Augenheilkunde und Optomerie Wien Medizinische Universitaet Wien	Waehringer Guertel 18-20	A-1090	Vienna	Austria
53	Ulrich Schoenherr	Konventhospital Barmherzige Brueder Linz - Augenabteilung	Seilerstaette 2	A-4021	Linz	Austria
54	Siegfried Priglinger	AKh Linz, Abteilung fuer Augenheilkunde	Krankenhausstr. 9	A-4021	Linz	Austria
55	András Papp	Semmelweis Egyetem, Szemészeti Klinika	Toemő u. 25-29	H-1083	Budapest	Hungary
56	József Ferenc Győry	Veszprém Megyei Csolnoky Ferenc Kórház Non-Profit ZRT	Szemészet, Kórház u. 1	H-8200	Veszprém	Hungary
57	Ágnes Kerényi	Bajcsy-Zsilinszky Kórház, Szemészet	Maglódi u. 89-91	1106	Budapest	Hungary
58	András Seres	Budapest Retina Associates	Kárpát u. 62-64	1133	Budapest	Hungary
59	Andras Berta	University of Debrecen Medical and Health Science Center, Department of Ophthalmology	Nagyerdei blv.98	4032	Debrecen	Hungary
60	Lajos Szalczer	Zala megyei kórház, Szemészeti Osztály.	Zrínyi M. u. 1	H – 8900	Zalaegerszeg	Hungary
61	Dong-Heun Nam	Gachon University Gil Medical Center Department of Ophthalmology	1198 Guwol-dong, Namdong-gu	405-760	Incheon	Korea
62	Se-Joon Woo	Seoul National University Bundang Hospital, Department of Ophthalmology	166 Gumi-ro, Bundang-gu	463-707	Seongnam	Korea
63	Young-Hee Yoon	Asan Medical Center Department of Ophthalmology	3881-1 Pungnap 2-dong, Songpagu	138-736	Seoul	Korea
64	Won Ki Lee	Kangnam St.Mary's Hospital Department of Ophthalmology	505 Banpo-Dong, Seocho-Gu	137-701	Seoul	Korea
65	Hyeong-Gon Yu	Seoul National University Hospital, Department of Ophthalmology	101 Daehangno, Chongno-gu	110-744	Seoul	Korea
66	Hyoung Jun Koh	Severance Hospital, Yeonsei University College of Medicine	250 Seongsanno (134 Sinchon-dong), Seodaemun-gu	120-752	Seoul	Korea
67	Ranjana Mathur	Singapore National Eye Centre (SNEC)	11 Third Hospital Ave	168751	Singapore	Singapore

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
68	Caroline Chee	National University Hospital (NUH) Department of Ophthalmology	5 Lower Kent Ridge Road	119074	Singapore	Singapore
69	Ilze Zarinova	Latvijas-Amerikas acu centrs	Tallinas iela 93	LV-1009	Rīga	Latvia
70	Guna Laganovska	Paula Stradiņa Klīniskās Universitātes slimnīca, Oftalmoloģijas nodaļa	Pilsoņu iela 13	LV-1002	Rīga	Latvia
71	Antonia Joussen	Charité Campus Virchow-Klinikum (CVK) Augenheilkunde	Augustenburger Platz 1	13353	Berlin	Germany
72	Giovanni Staurenghi	Clinica Oculistica - Dip. Scienze Cliniche A.O. Sacco Polo Universitario	Via G.B. Grassi, 74	20157	Milano	Italy
73	Edoardo Midena	Oculistica A.O. di Padova	Via Giustiniani, 2	35128	Padova	Italy
74	Gerhard Kieselbach	Universitätsklinikum Innsbruck Universitätsklinikum fuer Augenheilkunde und Optometrie	Anichstrasse 35	6020	Innsbruck	Austria