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Official Title:	A single-arm, non-randomized and open-label phase 3 study evaluating the efficacy, safety and tolerability of intravitreal aflibercept in Japanese patients with neovascular glaucoma (NVG)
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1. Title page

A single-arm, non-randomized and open-label phase 3 study evaluating the efficacy, safety and tolerability of intravitreal aflibercept in Japanese patients with neovascular glaucoma (NVG)

Japanese phase 3 study of aflibercept in NVG patients

VENERA

Test drug:	BAY 86-5321 / Aflibercept		
Study purpose:	Efficacy and Safety		
Clinical study phase:	3	Date:	18 May 2018
Registration:	EudraCT: N/A	Version no.:	Version 1.0
Sponsor's study no.:	19652		
Sponsor:	Bayer Yakuhin, Ltd. 4-9, Umeda 2-chome, Kita-ku, Osaka, 530-0001, Japan		
Sponsor's medical expert:	PPD Bayer Yakuhin, Ltd. PPD		

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Name: PPD Role: Global Clinical Leader

Date: 18 May, 2018 Signature: PPD

Signature of principal investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Affiliation:

Date: ..... Signature: .....

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

In the protocol document, this page may remain unsigned.

2. Synopsis

Title	A single-arm, non-randomized and open-label phase 3 study evaluating the efficacy, safety and tolerability of intravitreal aflibercept in Japanese patients with neovascular glaucoma (NVG)
Short title	Japanese phase 3 study of aflibercept in NVG patients
Acronym	VENERA
Clinical study phase	3
Study objective(s)	Primary objective: • To assess the efficacy of intravitreal (IVT) administration of aflibercept on the change in intraocular pressure (IOP) in patients with neovascular glaucoma (NVG). Secondary objective: • To assess the safety and tolerability of IVT administration of aflibercept in patients with NVG.
Test drug(s)	
Name of active ingredient	Aflibercept
Dose(s)	2 mg (0.05 mL)
Route of administration	Intravitreal injection (IVT)
Duration of treatment	1 day (single dose)
Reference drug(s)	
Name of active ingredient	N/A
Dose(s)	N/A
Route of administration	N/A
Duration of treatment	N/A
Background treatment	Topical IOP-lowering drugs
Indication	Neovascular glaucoma (NVG)

Diagnosis and main criteria for inclusion /exclusion	Key inclusion criteria: • Japanese men and women aged 20 years or older • Patients diagnosed as having NVG with neovascularization in the anterior segment (both iris and anterior chamber angle) • Patients with IOP higher than 25 mmHg in the study eye due to anterior segment (both iris and anterior chamber angle) neovascularization Key exclusion criteria: • Patients with angle-closure due to conditions other than NVG or complete angle-closure due to NVG • Patients with a known or suspected ocular or peri-ocular infection • Patients with severe intraocular inflammation in the study eye • Women who are pregnant, suspected of being pregnant or lactating • Patients with known allergy to aflibercept
Study design	The study is a single-arm, non-randomized and open label trial to evaluate the efficacy, safety and tolerability of intravitreal aflibercept
Methodology	Multicenter, single arm, non-randomized, and open label. **Efficacy** The efficacy of aflibercept 2 mg IVT will be assessed by the change in IOP from baseline (Day 1) to each visit. Other measures as efficacy variables will include change in neovascularization grades of iris and anterior chamber angle (NVI and NVA) as assessed by gonioscopy in conjunction with slit-lamp microscopy and the proportion of subjects who achieve IOP equal or lower than 21 mmHg. **Safety** Overall safety will be assessed by monitoring/evaluation of adverse events (AEs), physical examinations, vital signs (body temperature, blood pressure, and pulse rate), clinical safety laboratory tests (hematological test, blood biochemical examination and urine test),and ophthalmic examinations (indirect ophthalmoscopy, slit-lamp microscopy, gonioscopy, visual acuity test, and applanation tonometry) at pre-specified time points.
Type of control	N/A
Data Monitoring Committee	N/A
Number of subjects	The subjects' recruitment will be continued until 16 subjects are available as the per protocol set (PPS)
Primary variable(s)	Change in IOP from baseline to Week 1

Time point/frame of measurement for primary variable(s)	Week 1
Plan for statistical analysis	All variables will be analyzed with appropriate statistical methods: categorical variables by frequency tables and continuous variables by summary statistics (mean, standard deviation, minimum, median, and maximum). **Primary efficacy analysis** The change in IOP from baseline at Week 1 will be summarized descriptively. The point estimate and its two-sided 95% confidence interval using one-sample t-statistics will be calculated. The corresponding hypotheses for the efficacy analysis are the null hypothesis that μ equals to or greater than zero and the alternative hypothesis that μ is less than zero, where μ is the change in IOP from baseline at Week 1. If the upper limit of the two-sided 95% confidence interval in PPS is less than the threshold (i.e., 0), the null hypothesis will be rejected and the study will be regarded as success. **Secondary efficacy analysis** The proportion of subjects who have improved NVI grade from baseline at Week 1 will be summarized descriptively. The point estimate and its two-sided 95% confidence interval using Clopper-Pearson method will be calculated. Improvement by at least one grade from baseline will be categorized to “Improved”.

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List of abbreviations

AE	Adverse event
AMD	Age-related macular degeneration
APTC	Antiplatelet Trialists' Collaboration
ATC	Anatomical Therapeutic Chemical
ATE	Arterial thrombotic event
BCVA	Best corrective visual acuity
CAI	Carbonic anhydrase inhibitor
CRO	Contract research organization
CRVO	Central retinal vein occlusion
DME	Diabetic macular edema
eCRF	Electronic case report form
EDC	Electronic data capture
FAS	Full analysis set
GCP	Good clinical practice
GMP	Good manufacturing practice
IB	Investigator's Brochure
IgG1	Immune globulin G1
IOP	Intraocular pressure
IVT	Intravitreal
MedDRA	Medical Dictionary for Regulatory Activities
NVA	Neovascularization of the angle
NVG	Neovascular glaucoma
NVI	Neovascularization of the iris
OIS	Ocular ischemic syndrome
PAS	Peripheral anterior synechiae
PDR	Proliferative diabetic retinopathy
PG	Prostaglandin
PPS	Per protocol set
PRP	Panretinal photocoagulation
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SUSAR	Suspected, unexpected, serious adverse reaction
TEAE	Treatment-emergent adverse event
UPCR	Urine protein-to-creatinine ratio
VEGF	Vascular endothelial growth factor
WHO-DD	World Health Organization Drug Dictionary

3. Introduction

Background

Neovascular Glaucoma

Neovascular glaucoma (NVG) is a secondary glaucoma triggered by the formation of new blood vessels (neovascularization) on the iris and the anterior chamber angle. Neovascularization restricts aqueous outflow and consequently elevates intraocular pressure (IOP). NVG is a serious condition that may lead to permanent loss of vision, a persistently painful eye and, especially in the advanced stages, is unlikely to respond to treatment. NVG is caused by eye diseases leading to retinal ischemia, the major ones being central retinal vein occlusion (CRVO), proliferative diabetic retinopathy (PDR) and ocular ischemic syndrome (OIS)[1]. Although there have been no epidemiological reports for NVG, papers reported by Japanese medical institutions[2, 3, 4] indicated that PDR is the most common cause in Japan and estimated to be responsible for about 80% of NVG cases. The number of patients with diabetes mellitus in Japan is about 2,700,000 (summary of 2011 patient survey, Japanese Ministry of Health, Labour, and Welfare)[5] and 1.0% of patients with type-2 diabetes mellitus, which accounts for about 95% of all diabetes mellitus[6], are affected with NVG[7]. Approximately 27,000 Japanese diabetic patients are thus estimated to have NVG secondary to PDR. Given that PDR accounts for about 80% of the causes of NVG, the estimated number of NVG patients is therefore 30,000 to 40,000 in Japan.

Treatment of Neovascular Glaucoma

The clinical manifestations of NVG include elevated IOP and neovascularization in the anterior segment of the eye (iris and/or anterior chamber angle). Therefore, a combined approach is used to both reduce IOP and promote regression of neovessels. Panretinal photocoagulation (PRP) is commonly used to treat ischemic retina, induce regression of neovascularization in the anterior segment, and reduce IOP. The effects of PRP are not produced immediately, and during this period, further neovascularization may be seen and the anterior chamber angle may become progressively occluded worsening the prognosis. Moreover, it is often difficult to perform PRP in eyes with NVG, due to corneal edema secondary to high IOP or to other opacities of the optic media such as cataract or vitreous hemorrhage. If PRP is suboptimal, cryo-coagulation is conducted or endolaser coagulation may be combined with vitreous surgery. Despite such invasive treatments, progression of the neovascularization may continue because of persistent ischemia. The role of intravitreal anti-VEGF is to produce a fast regression of the anterior segment neovascularization, stabilizing disease progression and bridging the patient to a long-term solution after the effect of PRP is attained.

Open- and closed-angle NVG are associated with significantly high IOP, which leads rapidly to optic nerve atrophy and permanent vision loss. Even if PRP is successfully applied, regression of neovascularization requires time[8, 9], and IOP reduction is delayed. Additionally, in some cases neovascularization does not respond to PRP, or, in spite of responding (i.e. causing neovessel regression), an IOP decrease to the target level is not achieved. For this reason, PRP is routinely combined with conventional IOP-lowering agents. Nevertheless, these agents provide limited control of IOP[10, 11] and are thus considered adjunctive in the treatment of NVG. If the combination of PRP and medical treatment fails to

reduce IOP and there is a persistently high IOP, or if persistent neo-vascular membrane and synechiae lead to a closed-angle, the NVG becomes irreversible because of aqueous outflow. Invasive treatment is then necessary. The most frequently used surgical procedures are trabeculectomy (i.e. filtration surgery facilitating aqueous flow into the subconjunctival space through a fistula created under a scleral flap) and tube-shunt surgery (i.e. drainage-device surgery that promotes aqueous outflow to the subconjunctival space via an intraocular implant). Eyes with persistent neovascularization may have intra- and/or post-operative hemorrhage and often suboptimal control of IOP. As stated above, it was not uncommon for conventional NVG therapies to have persistent neovascularization in the anterior segment and continuously high IOP causing advanced optic nerve damage and permanent vision loss. NVG is therefore a disease of poor visual prognosis.

The potential of off-label administration of anti-VEGF drugs for the treatment of NVG was first reported in 2006[12, 13, 14]. Since then, several reports have been published on the use of anti-VEGF drugs to treat NVG with high IOP in addition to the conventional therapies previously described. The onset of neovascularization requires complex interactions between various inhibitory and promoting factors. VEGF stimulates the formation of new blood vessels by promoting proliferation of vascular endothelial cells. Activation of pro-angiogenic pathways by VEGF results in proliferation and migration of vascular endothelial cells and the formation of ectopic fragile and highly permeable blood vessels. These mechanisms of aberrant increase in VEGF-mediated neovascularization are the key elements in the pathology of NVG.

Intravitreally administered anti-VEGF drugs may be able to halt this process and even regress neovascularization by directly inhibiting VEGF. This process is also effective in causing regression of new blood vessels in the anterior segment of eyes with NVG. In eyes with open-angle NVG, anti-VEGF drugs may cause prompt regression of new vessels, IOP reduction, and prevention of the formation of a neo-vascular membrane and peripheral anterior synechiae (PAS). Moreover, the anti-VEGF agent is considered to be a useful time-buying treatment before the effect of PRP treatment for ischemic retina is exerted. In closed-angle NVG, permanent PAS have developed, and although anti-VEGF drugs are able to induce regression of neovascularization, they are not expected much to lower IOP. However, they are potentially able to enable a safer performance of glaucoma surgery, reducing intra- and/or post-operative hemorrhagic complications and improving post-operative outcomes[2, 15]. In recent years, intravitreal (IVT) administration of anti-VEGF drugs has been suggested to be an effective adjunctive treatment for NVG[16, 17, 18]. However, no anti-VEGF drugs have been currently approved for the treatment of NVG. In the Clinical Guideline for Glaucoma (Version 4; January 2018) issued by Japanese Glaucoma Society, the following text was added: “The efficacy of IVT injection of anti-VEGF drugs for NVG has been reported. Also it has been reported that the intraoperative or postoperative complications can be suppressed by IVT injection of anti-VEGF drugs preoperatively when conducting surgeries for NVG.”[19]

As stated above, being unlikely to respond to conventional treatments and often resulting in permanent vision loss, NVG is a refractory disease. Nevertheless, there are no approved drugs that cause regression of neovascularization and reduction of IOP by directly targeting VEGF, which is the primary cause of neovascularization in the anterior segment of eyes with NVG. For these reasons, there is a significant unmet medical need for new and efficacious treatment option for NVG, which will be potentially provided with aflibercept.

About BAY 86-5321 (aflibercept)

BAY 86-5321 [JAN: aflibercept (genetically recombinant)] 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 3-1). VEGFR1 binds to VEGF with a high affinity (picomolar range), while VEGFR2 binds to VEGF much less tightly. The recombinant protein is expressed in Chinese Hamster Ovary K1 cells. Recovery and purification of the protein are accomplished via a combination of filtration and chromatographic techniques. The protein is then formulated for intravitreal (IVT) administration to produce aflibercept.

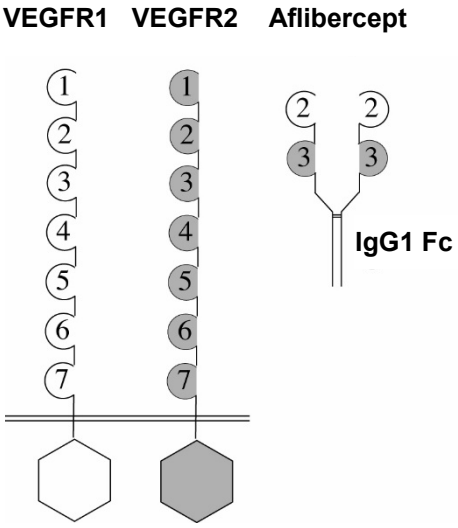

Figure 3-1: Structure of aflibercept

The recombinant protein aflibercept exhibits very potent binding activity to human VEGF, with an equilibrium dissociation constant (Kd) of approximately 0.5 pM. This binding activity is more potent relative to the activity of anti-VEGF agent ranibizumab (with a Kd in the order of 100 pM) [20]. The formulation, aflibercept, is developed for intraocular use. Research using an animal ophthalmological disease model demonstrated that aflibercept adequately inhibits 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.

Rationale for the study

NVG is a severe pathological condition with a risk for permanent vision loss, and anti-VEGF drugs have been suggested to have a positive influence on the outcome of patients with NVG. In expectation of aflibercept as an effective treatment for NVG, the sponsor have planned clinical development of aflibercept for this indication in Japan.

Prior clinical reports of anti-VEGF drugs[8, 12, 13, 16, 17, 18, 21] suggested drugs in this class were able to decrease high IOP caused by NVG with the same dose used to treat eyes with macular

edema secondary to CRVO, diabetic macular edema (DME), or wet age-related macular degeneration (AMD).

The 2 mg dose was chosen based on the finding that, to date, 2 mg has been shown to be an effective and safe dose in all clinical trials of aflibercept in other ophthalmologic indications.

Therefore, 2 mg, which is the currently-approved dose for the treatment of macular edema secondary to CRVO and DME in Japan, shall be recommended as a dose for testing the efficacy in Japanese patients with NVG. Given the well-established safety profile of aflibercept in various indications and the reports of anti-VEGF therapies successfully given to patients with NVG, a Japanese phase 3 study 17584 [VEGA] in NVG patients was conducted to expand the aflibercept labeling to include NVG. The results of all efficacy variables, including the primary endpoint "change in IOP," have consistently suggested the efficacy of aflibercept but did not show the statistical superiority of the aflibercept group to the control (sham) group in terms of the primary endpoint "change in IOP from baseline to pre-dose at Week 1" (two-sided 95%CI of treatment difference [aflibercept group minus sham group]: –10.2 to 0.3 mmHg, p=0.0644). It may have been mainly because systemic IOP-lowering drugs permitted to be used from baseline through Week 1 influenced efficacy assessment of aflibercept. Meanwhile, the proportion of subjects who have shown regression of NVI grade at Week 1 as a secondary endpoint was significantly higher in the aflibercept group when compared to the sham group (70.4% for the aflibercept group and 11.5% for the sham group showed regression of NVI by end of Week 1), strongly indicating the NVI-regressing disease modifying effect of aflibercept. In the generation of NVI and NVA secondary to retinal ischemic change, VEGF is the major factor in the development of anterior segment neovascularization, which impedes the aqueous outflow through the trabecular meshwork resulting in the possible rise of IOP. Anti-VEGF action regresses this anterior segment neovascularization (NVI and NVA in this case) and re-establishes the aqueous outflow through this channel, thereby resulting in lowering of IOP. Thus, it can be said that aflibercept used in VEGA exerted anti-VEGF effects by regressing anterior segment neovascularization with consequent IOP-lowering effects, although it cannot be ruled out that systemic medication may also have at least partly contributed to reduction of IOP among subjects in the aflibercept group.

The mean (± SD) IOP change from baseline to pre-dose at Week 1 in the subgroup comprising subjects without systemic IOP-lowering drugs in VEGA remained almost unchanged (–0.4 ± 7.7 mmHg) in the sham group versus markedly reduced (–8.8 ± 8.4 mmHg) in the aflibercept group. The applicant considered that a study design in the absence of the influence of systemic IOP-lowering drugs would be able to revisit aflibercept's IOP-lowering effect among NVG patients and consequently to complement efficacy evaluation in VEGA.

Thus, the applicant has set up the current study, No. 19652, with the mean change in IOP as the primary endpoint for the purpose of evaluating IOP-lowering effect and at the same time NVI-regressing effect as the secondary endpoint.

Benefit-risk assessment

Aflibercept has been administered to numerous patients, and the drug's safety and tolerability profile has been well established. Aflibercept IVT is not expected to have adverse effects other than those described in the IB. An already described important identified risk is the transient IOP increase. This IOP increase usually normalizes within one hour after the IVT

injection. Measures are implemented that ensure close monitoring of patients around injection procedure and emergency treatment. Other risks associated with the IVT administration of aflibercept are expected to be similar to those of other anti-VEGF therapies requiring IVT administration. Based on the efficacy of the drug in neovascular diseases other than NVG and existing reports on the use of anti-VEGF therapies in the NVG indication, it is expected that aflibercept will have a beneficial effect on a disease with a high medical need for effective treatment.

Therefore, IVT injection of aflibercept is justified in use for treatment of NVG and supported by the favorable benefit risk assessment in the indication NVG.

4. Study objectives

Primary objective:

- To assess the efficacy of IVT administration of aflibercept on the change in IOP in patients with NVG.

Secondary objective:

- To assess the safety and tolerability of IVT administration of aflibercept in patients with NVG.

5. Study design

Design overview

This study will enroll NVG patients. This is a multicenter, single-arm, non-randomized, and open-label phase 3 trial to evaluate the primary efficacy variable "change in IOP from baseline to Week 1" of IVT administration of aflibercept in NVG patients (Figure 5-1).

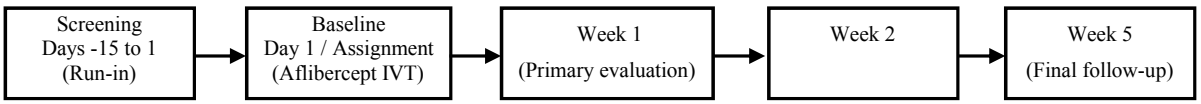

Figure 5-1: Study outline

After eligibility is confirmed, subjects will initiate treatment with at least 3 of the 5 allowed classes of topical IOP-lowering drugs. With application of the first eyedrop, the run-in-phase will start and IOP is monitored to determine whether the subject qualifies for assignment. If IOP is higher than 25 mmHg and all other criteria allow, the subject should be assigned (according to Section 7.3) and given aflibercept. Treatment with topical drug classes initiated during Run-in phase should be continued unchanged until Week 1 (see below).

If required, subjects can receive systemic IOP-lowering drugs, or undergo PRP or surgery intended to lower IOP, during study participation. Even if medically justifiable, any of these IOP-lowering interventions should not be performed before the primary endpoint visit. If IOP-lowering intervention is unavoidable or systemic IOP-lowering drugs are needed for the treatment of the study eye and/or fellow eye before the primary-endpoint visit, the evaluations of the Week-1 visit should be done before the intervention. The data obtained before the

intervention will be used for efficacy analysis according to the criteria established in Section 10.

Of note, since IOP may be transiently increased after aflibercept IVT injection, IOP will be carefully monitored.

Run-in phase

After the inclusion criterion 3 (IOP > 25 mmHg) is confirmed at the screening visit, subjects should initiate to receive topical IOP-lowering drug therapy as a run-in phase for a minimum of 1 to 2 hours. Subjects will receive a combination of at least 3 topical IOP-lowering drugs from the classes in the following list:

- Prostaglandin (PG) analog
- Sympatholytic agent
- Carbonic anhydrase inhibitor (CAI)
- Sympathomimetic agent
- Rho-kinase inhibitor

No more than 1 drug of each class should be used. Subjects who are intolerant to more than 2 drug classes should be treated with the highest number of drugs possible in light of their restrictions. The IOP will be re-evaluated 1 hour (± 10 minutes) after administration of the topical IOP-lowering drugs. If no decrease in IOP compared to screening is observed, this post-1-hour measurement can be considered the baseline measurement and the subject can immediately be assigned and treated with aflibercept. If a decrease in IOP compared to screening is detected, the subject will be kept under observation and re-evaluated 2 hours (± 10 minutes) after the start of the run-in phase. If the IOP is higher than 25 mmHg after 2 hours, this measurement can be considered the baseline measurement and the subject can be assigned and treated with aflibercept. If treatment with aflibercept cannot be performed on the day of screening, the baseline evaluation and assignment can be performed a maximum of 15 days after the diagnosis of NVG was made. If IOP drops to a value of 25 mmHg or lower between screening and planned assignment, the subject must not be assigned and will be excluded from the trial (see Sections 6 and 7.3). Intravitreal aflibercept injection should be administered as soon as the investigator considers either of them adequate after the baseline evaluation.

The number of topical drugs in the run-in phase combination may be reduced to less than 3 for subjects who have contraindications such as known allergies or potential suboptimal response to more than 2 of the drug classes. The topical drugs used during the run-in phase should be kept unchanged until the IOP measurement is performed at Week 1, after which they may be reduced according to the investigator's opinion.

A flow diagram for run-in phase is shown in Figure 5-2.

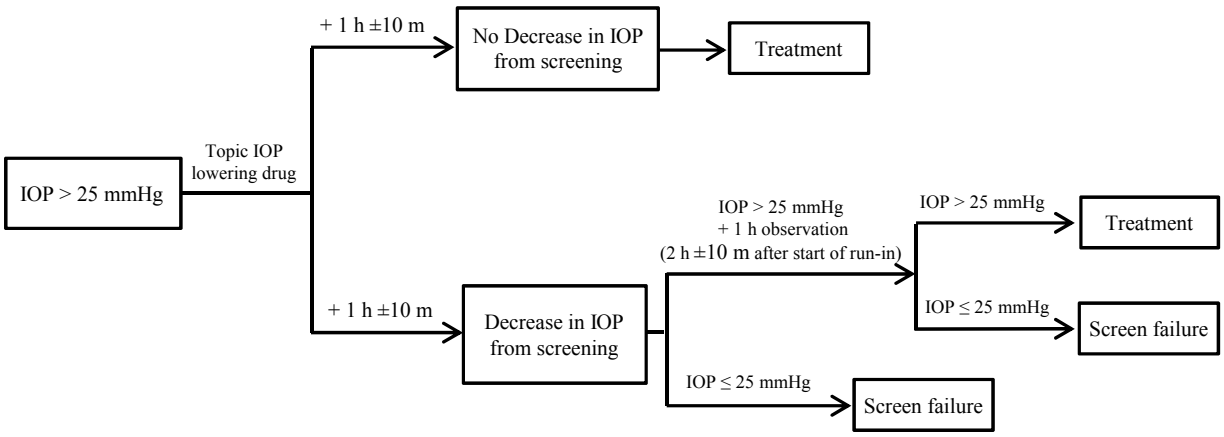

Figure 5-2: Run-in phase

Primary variable

- Change in IOP from baseline to Week 1

Justification for the design

The objective of NVG treatment is to control the consequences of retinal ischemia: neovascularization and the secondary IOP increase. Patients with very high IOP require acute therapy to achieve IOP decrease, but since IOP increase is dependent on the presence of neovascularization, IOP-lowering drugs have limited effect in lowering IOP. Also, PRP has a delayed effect in producing regression of neovascularization, and IOP decrease is not expected in the acute stage by performing this treatment. Since anti-VEGF drugs have been reported to produce a rapid regression of neovascularization in the anterior segment, un-blocking the angle and subsequently decreasing IOP, they present an ideal profile to treat patients in the acute stage, improving IOP control until full effect from PRP is obtained and long-term control is achieved. Therefore, the primary endpoint has been determined to be 'Change in IOP from baseline'.

In patients with NVG, anti-VEGF drugs are expected to rapidly decrease IOP and subsequently produce an early relief of high IOP and symptoms. Previous data reporting practical experience with anti-VEGF agents in small case series as well as general considerations about the disease suggest that an early endpoint is appropriate to detect whether the treatment with anti-VEGF is able to provide earlier control of the disease manifestations than standard treatment options. The evaluation timing was therefore determined to be at Week 1. Study 17584 (VEGA) has shown the efficacy and safety of aflibercept up to 3 months after its first injection in the aflibercept group, and in the sham group which include the subjects who received aflibercept from Week 2 if necessary. Since the primary objective of the present study 19652 is to verify the IOP-lowering effect of aflibercept at Week 1 in NVG patients without systemic-IOP lowering drugs or PRP and since VEGA has already shown the efficacy and safety of aflibercept at 3 months, the present study 19652 will focus on short-term efficacy at week 1 after a single dose of aflibercept and patients will be followed up to Week 5 for safety assessment.

NVG patients have a high probability of permanent vision loss if IOP is not properly controlled. To provide benefit to the patients in the study, the concomitant use of topical IOP-lowering drug therapy is required from screening, and only patients who do not achieve control of IOP before baseline with conventional therapy will be assigned.

Safety variables are similar to those of aflibercept clinical trials for other diseases, i.e. adverse events (AEs), physical examination, vital signs (body temperature, blood pressure and pulse rate), clinical laboratory findings (hematological test, blood biochemical examination and urine test), and ophthalmic examinations (indirect ophthalmoscopy, slit-lamp microscopy and gonioscopy). Visual acuity testing, which is used to evaluate visual functions in patients with glaucoma, and applanation tonometry, which is used to evaluate IOP after IVT injection, are also to be performed as a safety evaluation.

End of study

The end of the study as a whole will be reached as soon as the last visit of the last subject is completed in all centers.

Primary completion

The primary completion event for this study is the visit of the final subject at Week 1 or Early Termination before Week 1. This study will be continued up to Week 5.

6. Study population

Patients who meet all of the inclusion criteria and none of the exclusion criteria at both screening and baseline are eligible for assignment in the study.

Inclusion criterion 2 must be met within 15 days before baseline.

An individual subject may only be included in the study once and only one eye will be designated as the study eye; however, safety of the fellow eye will be monitored, and all systemic AEs will be collected. For subjects who meet eligibility criteria in both eyes, the study eye will be selected at the discretion of the investigators considering the interests of the patients.

6.1 Inclusion criteria

1. Japanese men and women aged 20 years or older
2. Patients diagnosed as having NVG with neovascularization in the anterior segment (both iris and anterior chamber angle)
3. Patients with IOP higher than 25 mmHg in the study eye due to anterior segment (both iris and anterior chamber angle) neovascularization
4. Patients who are willing and able to return for all planned visits and complete all study related procedures
5. Patients who are able to read and understand informed consent documents (if difficult for a patient to read because of visual impairment, the study staff or the patient's family member may read every word for the patient to help him/her understand the contents)
6. Written informed consent

7. Women and men of reproductive potential must agree to use adequate contraception when sexually active. This applies for the time period between signing of the informed consent form and at least three months after the last administration of study drug. The definition of adequate contraception will be based on the judgment of the investigator and on local requirements. Acceptable methods of contraception include (i) condoms (male or female) with or without a spermicidal agent; (ii) diaphragm or cervical cap with spermicide; (iii) intrauterine device; (iv) hormone-based contraception.

6.2 Exclusion criteria

1. Only one functional eye 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
2. Patients with angle-closure due to conditions other than NVG or complete angle-closure due to NVG
3. Patients with a known or suspected ocular or peri-ocular infection
4. Patients with severe intraocular inflammation in the study eye
5. Patients with any ocular disorder in the study eye that might contraindicate treatment with anti-VEGF drugs or confuse the interpretation of the results of the study
6. Patients who have received intraocular administration of anti-VEGF drugs (pegaptanib sodium, bevacizumab, ranibizumab, aflibercept, etc.) within 60 days before Day 1 in the study eye
7. Patients who have received intraocular or periocular injection of corticosteroids (solutions or suspensions) within 60 days before Day 1 in the study eye (topical corticosteroids are allowed)
8. Patients who have received intraocular injection of corticosteroids (depot formulations) within 120 days before Day 1 in the study eye
9. Patient who have received systemic anti-angiogenic agents within 180 days before Day 1
10. Patients who have received topical ophthalmic atropine sulfate hydrate within 30 days before Day 1 in the study eye
11. Patients who have received systemic IOP-lowering drugs in the past 3 days before Day 1
12. Patients with prior filtrating surgery and/or surgery involving posterior vitrectomy or resulting in aphakia or rupture of the posterior capsule in the study eye, with the exception of posterior capsulotomy performed with yttrium aluminum garnet (YAG) laser or pseudophakia
13. Patients who have received other intraocular surgeries including PRP in the study eye within 30 days before Day 1, and/or who are scheduled for surgery including PRP in 8 days following Day 1
14. Patients whose blood pressure is poorly controlled on optimal medical treatment: patients with systolic blood pressure of >180 mmHg in a single measurement; patients with systolic blood pressure of >160 mmHg in two consecutive measurements; or patients with diastolic blood pressure of >100 mmHg
15. Patients with a history of cerebrovascular disorder or myocardial infarction within 6 months before Day 1

16. Patients who are prohibited from use of the study drug because they have prior medical history, metabolic dysfunction, physical findings, or laboratory test findings (i.e. patients suspected to have conditions that may have influence the evaluation of the study results, or diseases or conditions that may render them at higher risk of a concomitant disease after study treatment)
17. Women who are pregnant, suspected of being pregnant or lactating
18. Patients with renal failure requiring dialysis or renal transplant
19. Previous assignment to treatment during this study
20. Previous (within 30 days or 5 half-lives of the investigational drug, whichever is longer) or concomitant participation in another clinical study with investigational medicinal product(s)
21. Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site)
22. Patients with known allergy to aflibercept

6.3 Justification of selection criteria

Inclusion and exclusion criteria for this study have been referenced as the criteria used in clinical research reports of anti-VEGF drugs[15, 16, 17)] and the previous aflibercept trials for other diseases, and tailored for the indication.

The present Study 19652 will include adult NVG patients who have high IOP. Although the upper limit of IOP in healthy adults is 21 mmHg, NVG is a disease condition usually associated with significantly higher IOP values. Therefore, the IOP for patient assignment was determined to be higher than 25 mmHg in order to exclude patients with slight increases in IOP for the diseases other than NVG. The criteria include requirements for selecting patients who are willing to complete the required treatments and examinations for this study, complying with Good Clinical Practice (GCP).

As exclusion criteria, patients whose underlying diseases can unreliably influence the efficacy and safety assessments, and from a view point of ensuring the safety of subjects, patients whose disease conditions may deteriorate because of participation in this study will be excluded.

Additionally, VEGA has left the possibility of concomitant use of systemic IOP-lowering drugs, in large part, influencing primary efficacy evaluation (IOP). The same can be said of concomitant use of PRP. Therefore, for the purpose of removing the influence of these treatments, the present study 19652 will exclude patients who have received systemic IOP-lowering drugs within 3 days and PRP within 30 days before baseline (Day 1) in the study eye. Additionally, in complete angle-closure NVG due to permanent PAS, IVT anti-VEGF drugs are not expected to lower IOP. Therefore, patients with complete angle-closure NVG will be excluded.

6.4 Withdrawal of subjects from study

6.4.1 Withdrawal

Once a subject receive study treatment, every effort should be made so as not to terminate him/her from the study, and to keep him/her on the original visit schedule until the Week 5 / End of Study Visit. It is preferred that each subject be followed for the scheduled study duration.

Withdrawal criteria

Subjects must be withdrawn from the study if any of the following occurs:

- 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.
- Systemic anti-angiogenic agents were taken by the subject during the study
- If the subject becomes pregnant

Subjects may be withdrawn from the study if any of the following occurs:

- If, in the investigator's opinion, continuation of the study would be harmful to the subject's well-being.
- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).
- Determination by the investigator that a subject requires alternate or additional treatment for NVG in the study eye.

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

Screening failure

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

Re-starting the defined set of screening procedures to enable the "screening failure" subject's participation at a later time point is allowed only once, and only if one of the following situations apply:

- The subject had successfully passed the screening procedures, but could not start subsequent treatment on schedule.
- The patient failed to meet inclusion criterion 3. A minimum of 24 hours must pass before the second screening can be performed.
- The patient met exclusion criteria 3, 6, 7, 8, 9, 10, 11, 13, 14, 15 or 20.

Rescreening is not allowed in any other situations. In any case, the investigator has to ensure that the repeated screening procedures do not expose the subject to an unjustifiable health risk. Also, for re-screening, the subject has to re-sign the informed consent form, even if it

was not changed after the subject's previous screening, and confirm that the patient meets all inclusion and no exclusion criteria.

Dropout

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already been assigned.

General procedures

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

The subject may object to the generation and processing of post-withdrawal data as specified in Section 13.4.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12 (Premature of termination of the study).

6.4.2 Replacement

Subjects who are withdrawn from the study after assignment, or who prematurely discontinue the study will not be replaced. For details for subject who deviated from PPS, see Section 10.4 (Determination of sample size).

6.5 Subject identification

The patient number is a 9 digit number consisting of:

Digits 1 to 5 = Unique center number

Digits 6 to 9 = Current patient number within the center

Subject registration

The registration center will be used for subject registration in this study. Detailed instruction for registration can be found in the manual provided to study sites. The study sites register the subject according to the manual

7. Treatments

7.1 Treatments to be administered

Subjects will receive one intravitreal injection of study drug (aflibercept) 2 mg.

7.2 Identity of study treatment

Details of the study drug are given in Table 7-1.

The study drug will be manufactured by Bayer AG, Berlin, Germany. The 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.

Table 7-1: 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/mL aflibercept, 5% sucrose, 10 mM sodium phosphate, pH 6.2, 0.03% polysorbate 20, 40 mM sodium chloride, water for injection

Each aflibercept treatment kit will contain one vial of 40 mg/mL aflibercept, one 1-mL syringe, one 18-gauge filter needle, and one 30-gauge injection needle.

All study drugs 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 labels 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 batch of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies QA 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's study file.

7.3 Treatment assignment

All eligible subjects will be assigned to aflibercept IVT injection.

7.4 Dosage and administration

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

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

When aflibercept vials are taken out of a refrigerator, the solution should be visually inspected for having no evidence of turbidity. If particulates, cloudiness, or discoloration is visible, the vial must not be used. Considering the stability of aflibercept and lack of bacteriostatic agents, aflibercept 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.

7.5 Blinding (Masking)

Not applicable for this open-label study.

7.6 Drug logistics and accountability

All study drugs will be stored at the investigational site in accordance with GCP and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/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's study file; the site-relevant elements of this information will be available in the investigator site file. On the day of receipt, the responsible site personnel will confirm receipt of study drug in writing. The personnel 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 study drugs are to be stored at 2°C to 8°C.

If performing drug accountability implies a potential risk of contamination, a safety process/ guidance for handling returned drug will be provided.

7.7 Treatment compliance

Study drug will be administered at the site; compliance with study treatments will be monitored by the monitor using the study site clinical records.

8. Non-study therapy

8.1 Prior and concomitant therapy

Prior therapy

See Section 6.2, exclusion criteria, for a description of prior therapies that exclude subjects from participation in this study. Treatment with systemic IOP-lowering drugs is prohibited for 3 days before Day 1.

Concomitant therapy

Systemic use of anti-VEGF drugs, topical ophthalmic atropine sulfate hydrate will be prohibited during the period of the study. Systemic IOP-lowering drugs, PRP or surgery intended to lower IOP are prohibited until IOP evaluation at Week 1 unless these treatments are inevitable at the discretion of the investigators.

Systemic IOP-lowering drugs are followings:

- Acetazolamide
- Isosorbide
- Glycerin
- Mannitol

If the fellow eye also has NVG, it may receive any locally approved treatment except for systemic IOP-lowering drugs. If the fellow eye has conditions such as, but not limited to, wAMD and CRVO for which anti-VEGF therapy is indicated, administrations should be

performed after the expected benefits and possible risks are carefully evaluated. Injecting both eyes in the same day is not recommended for safety reasons. The fellow eye will not be considered an additional study eye. 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.

Any previous and concomitant treatments given to the fellow eye for NVG will be recorded in the source documentation and then entered in the "Previous and Concomitant Medications/Therapies" eCRF using the brand names. Drugs used during the IVT injection procedure will not be recorded as concomitant medication/therapy.

All previous and concomitant medications/therapies will be coded using an internationally recognized and accepted coding dictionary.

8.2 Post-study therapy

After the observation period (through Week 5), subjects will not be restricted in taking available treatments for NVG.

9. Procedures and variables

9.1 Tabular schedule of evaluations

Table 9-1: Tabular schedule of assessments

Procedure	Screening [a]	Baseline	Observation		End of Study/Early Termination
Visit	**1**	**2**	**3**	**4**	**5**
Day/week	**-**	**Day 1**	**Week 1**	**Week 2**	**Week 5**
Day	**-15 to 1**	**1**	**8+3**	**15±3**	**36±7**
Informed consent	X				
Inclusion/Exclusion criteria	X	X			
Demographic data	X				
Medical/ophthalmic history	X				
AEs	X	X	X	X	X
Concomitant medications	X	X	X	X	X
Physical exam	X				X
Vital signs (temperature, blood pressure and pulse rate)	X	X	X	X	X
Assignment (eligibility check)		X			
Study drug injection [b]		X			
Telephone safety check [c]		X			
Ophthalmological assessment					
Visual acuity test	X	X	X	X	X
Slit-lamp microscopy	X	X	X	X	X
Gonioscopy	X	X	X	X	X
Evaluation of NVI and NVA grades	X	X	X	X	X
IOP [d]	X	X	X	X	X
Indirect ophthalmoscopy	X	X [e]	X	X	X
Topical IOP-lowering drug therapy [f]	X	X	X	X	X
Laboratory test (central)					
Hematology	X				X
Chemistry	X				X
Serum pregnancy test [g]	X				
Urinalysis (incl. UPCR)	X				X

Footnotes:

AEs = adverse events, NVI = neovascularization of the iris, NVA = neovascularization of the angle, IOP = Intraocular pressure, UPCR = Urine protein-to-creatinine ratio

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 Check of visual acuity (finger counting, hand movement and/or light perception) is to be performed in the study eye immediately after treatment, the presence or absence of the retinal perfusion should be verified by indirect ophthalmoscopy in the case the visual acuity is decreased, and an anterior chamber paracentesis should be performed in the case the IOP increases significantly after treatment.

c Telephone call to a subject to identify if there have been any signs or symptoms of retinal detachment, endophthalmitis, or other AEs at 3 ± 1 days post-treatment. Additionally, pay attention to the signs or symptoms of NVG and consider asking the patient to make an unscheduled visit if necessary.

d Assess pre-dose in both eyes, and again 15-60 minutes post-dose in the study eye at baseline. After baseline (Visit 2), IOP will be measured within ± 2 hours of the measurement time at baseline.

e Assess pre-dose in both eyes, and again post-dose in the study eye.

f A combination of at least 3 topical IOP-lowering drugs will be administered during a run-in phase before treatment and should be kept unchanged until IOP evaluation at Week 1, after which they may be reduced according to the investigator's opinion.

g In women of childbearing potential, a urine pregnancy test can be done at a study site, if the result from the central laboratory cannot be waited for.

9.2 Visit description

9.2.1 Visit 1, Screening (Day -15 to 1)

- Signed informed consent
- Inclusion / Exclusion criteria
- Demographic data
- Medical history (including smoking history) and ophthalmic history
- Interval history (AEs and concomitant medications)
- Physical examinations
- Vital signs (temperature, blood pressure and pulse)
- Visual acuity test
- Slit-lamp microscopy and gonioscopy
  - Evaluation of NVI and NVA grades
- IOP evaluation
- Indirect ophthalmoscopy
- Topical IOP-lowering drug therapy (run-in phase)
- Hematology and chemistry
- Serum pregnancy test (In women of childbearing potential, a urine pregnancy test can be done at a study site, if the result from the central laboratory cannot be waited for)
- Urinalysis/urine protein-to-creatinine ratio (UPCR)

9.2.2 Visit 2, Baseline (Day 1)

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.

The injection in the vitreous cavity can cause IOP increase by the addition of the liquid volume. Before administering an intravitreal injection, therefore, the investigator must evaluate IOP to confirm that it has decreased to a level considered safe for performing the injection. Immediately after the injection, and while still in the injection room, the investigator must make a visual acuity check by asking the subject to count fingers, detect hand movement or light perception depending on the pre-dose visual acuity. If a decrease in visual acuity is detected, indirect ophthalmoscopy should be performed to verify if the retinal perfusion has been compromised. If this is the case and this is considered to be caused by a significant increase in IOP due to the volume injection, an anterior chamber paracentesis should be performed to immediately reduce the IOP. If visual acuity is not decreased and retinal circulation not compromised, the subject may leave the injection room. The IOP will be reevaluated after a period ranging from 15 to 60 minutes, and the subject may be

discharged as soon as the IOP returns to the levels similar to or lower than those measured prior to the pre-injection IOP. If the IOP value is considered too high to discharge the subject, further therapy should be given within the choices available, and the subject should be kept under close observation until the IOP has decreased to the levels amenable to outpatient treatment.

- Inclusion / Exclusion criteria
- Topical IOP-lowering drug therapy (run-in phase)
- Interval history (AEs and concomitant medications)
- Vital signs (temperature, blood pressure and pulse rate)
- Visual acuity test
- Slit-lamp microscopy and gonioscopy
  - Evaluation of NVI and NVA grades
- IOP evaluation
- Indirect ophthalmoscopy
- Assignment (eligibility check)
- Study drug injection
- Check of visual acuity (finger counting, hand movement and/or light perception; immediately after injection, only study eye)
  - If visual acuity is reduced: check retinal perfusion study eye by an indirect ophthalmoscopy
  - If necessary: anterior chamber paracentesis
- Indirect ophthalmoscopy (post-treatment, only study eye)
- IOP evaluation (15 to 60 minutes following injection, only study eye)
  - If necessary: further IOP-lowering measures
- Topical IOP-lowering drug therapy (to be kept unchanged until IOP evaluation at Week 1)
- Telephone safety check (telephone call 3 ± 1 days post-treatment)

9.2.3 Visit 3, Week 1 (Day 8 + 3)

- Interval history (AEs and concomitant medications)
- Vital signs (temperature, blood pressure and pulse rate)
- Visual acuity test
- Slit-lamp microscopy and gonioscopy
  - Evaluation of NVI and NVA grades
- IOP evaluation (± 2 hours of the measurement time at baseline)
- Indirect ophthalmoscopy

- Topical IOP-lowering drug therapy (may be reduced according to the investigator's opinion)

9.2.4 Visit 4, Week 2 (Day 15 ± 3)

- Interval history (AEs and concomitant medications)
- Vital signs (temperature, blood pressure and pulse rate)
- Visual acuity test
- Slit-lamp microscopy and gonioscopy
  - Evaluation of NVI and NVA grades
- IOP evaluation (± 2 hours of the measurement time at baseline)
- Indirect ophthalmoscopy
- Topical IOP-lowering drug therapy (may be reduced according to the investigator's opinion)

9.2.5 Visit 5, Week 5 (Day 36 ± 7): End of Study (also Early Termination) visit

- Interval history (AEs and concomitant medications)
- Physical examinations
- Vital signs (temperature, blood pressure and pulse rate)
- Visual acuity test
- Slit-lamp microscopy and gonioscopy
  - Evaluation of NVI and NVA grades
- IOP evaluation (± 2 hours of the measurement time at baseline)
- Indirect ophthalmoscopy
- Topical IOP-lowering drug therapy (may be reduced according to the investigator's opinion)
- Hematology and chemistry
- Urinalysis/urine protein-to-creatinine ratio (UPCR)

9.3 Population characteristics

9.3.1 Demographic

The following demographic characteristics will be collected:

- Year of birth
- Age
- Sex
- Race/ethnicity
- Weight
- Height

9.3.2 Medical history

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

- Start before signing of the informed consent
- Considered relevant for the subject's study eligibility.

Detailed instructions on the differentiation between (i) medical history and (ii) AEs can be found in Section 9.6.1.1.

9.3.3 Other baseline characteristics

A complete ophthalmic history including NVG will be obtained at Screening.

9.4 Efficacy

9.4.1 Intraocular pressure (IOP)

IOP will be measured in both eyes at each visit. IOP will be measured using applanation tonometry with Goldmann as standard technique for all screening, baseline and other visit measurements. Other measuring methods are not allowed. After baseline, IOP will be measured within ± 2 hours of the measurement time at baseline. See Section 9.6.3.7 for the evaluation of post-dose IOP.

9.4.2 Neovascularization of iris and anterior chamber angle (NVI and NVA)

Subjects will be evaluated for the development of NVI and NVA by gonioscopy in conjunction with slit-lamp microscopy. NVI and NVA will be assessed in the study eye using the NVI and NVA grading systems[22)], as described in detail in Table 9-2, at each visit.

Table 9-2: Grading systems for NVI and NVA

Grade	Neovascularization of Iris	Neovascularization of Angle
0	No iris neovascularization	No angle neovascularization
1	Fine surface neovascularization of the pupillary zone of the iris involving less than two quadrants.	Fine neovascular twigs crossing the scleral spur and ramifying on the trabecular meshwork involving less than two quadrants.
2	Surface neovascularization of the pupillary zone of the iris involving more than two quadrants.	Neovascular twigs crossing the scleral spur and ramifying on the trabecular meshwork involving more than two quadrants.
3	In addition to neovascularization of the pupillary zone, neovascularization of the ciliary zone of the iris and/or ectropion uveae involving one to three quadrants.	In addition to neovascularization of the trabecular meshwork, peripheral anterior synechiae (PAS) involving one to three quadrants.
4	In addition to neovascularization of the pupillary zone, neovascularization of the ciliary zone of the iris and/or ectropion uveae involving more than three quadrants.	In addition to neovascularization of the trabecular meshwork, PAS involving more than three quadrants.

9.5 Pharmacokinetics / pharmacodynamics

Not applicable.

9.6 Safety

9.6.1 Adverse events

9.6.1.1 Definitions

Definition of adverse event (AE)

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 an 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 e.g. physical examination findings, symptoms, diseases, and laboratory.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at unchanged intensity, are recorded as medical history (e.g. allergic pollinosis).

- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events. This includes intercurrent illnesses.

Definition of serious adverse event (SAE)

A 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

(e.g. elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2)

– 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 serious or important medical event as judged by the investigator

9.6.1.2 Classifications for adverse event assessment

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

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Intensity

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

– Mild

- Moderate
- Severe

9.6.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the eCRF.

Causality should be assessed separately for each study treatment as detailed in the eCRF. If the investigator feels that the event cannot be firmly attributed to one of the study treatments (e.g. owing to a suspected underlying interaction), the same assessment will be documented for each study treatment.

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 highly likely 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 that the AE is reasonably 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 re-challenge should be considered in 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 might have caused the event in question.
- Known response pattern for this class of drug: Clinical/preclinical
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event

- 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.
- The assessment is not possible.

Causal relationship to protocol-required procedures

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"

9.6.1.2.4 Action taken with study treatment

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

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

- Drug withdrawn
- Drug interrupted
- Dose not changed
- Not applicable
- Unknown

9.6.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

9.6.1.2.6 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

9.6.1.3 Assessments and documentation of adverse events

The investigator has to record on the respective eCRF pages all AEs occurring in the period between the signing of the informed consent and the end of the follow-up phase; after the end

of the follow-up phase there is no requirement to actively collect AEs including deaths. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

"Death" should not be recorded as an AE on the AE page. Instead, "death" is the outcome of underlying AE(s).

For all SAEs the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to study drug.

9.6.1.4 Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

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.

The investigator must report immediately (within 24 hours of the investigator's awareness) all SAEs occurring during the observation period defined in Section 9.6.1.3 to the recipient detailed in the instructions for SAE reporting included in the Investigator File. For this, an AE page in the eCRF as well as the complementary pages provided in the Investigator File must be completed for each SAE.

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

Notification of the IECs / IRBs

Notification of the IECs / IRBs about all relevant events (e.g. SAEs, suspected, unexpected, serious adverse reactions [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 done 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.

9.6.1.5 Expected adverse events

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

Overview listings of frequent events that have occurred so far in the 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.

9.6.2 Pregnancies

The investigator must report to the sponsor any pregnancy occurring in a female study subject during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

For a pregnancy in the partner of a male study subject, all efforts will 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. The investigator should submit them within the same timelines as an SAE.

9.6.3 Further safety

Safety assessments, in addition to AEs, will include ophthalmic examinations and laboratory measures. Instructions for phlebotomy and sample handling can be found in each manual.

Reporting of medical device failures

The investigator must report immediately all non-approved medical device failures which could cause health damage, as well as any health damage that may be causally associated with a non-approved medical device failure. For this reporting, the forms provided are to be used and sent to the designated recipient.

9.6.3.1 Physical Examination

Abnormal physical examination findings are recorded as medical history or adverse event (see Section 9.6.1.1).

9.6.3.2 Vital Signs

Body temperature, blood pressure and pulse rate will be measured. Vital signs should be assessed in a consistent, standardized way at each assessment.

9.6.3.3 Visual acuity test

Best corrective visual acuity (BCVA) (decimal visual acuity) will be measured by using Landolt ring in both eyes. Check of visual acuity (finger counting, hand movement and/or light perception) will be performed in the study eye immediately after.

9.6.3.4 Slit-lamp microscopy

The condition of the anterior segment of the eye and annexes (lids, conjunctiva, cornea, anterior chamber, iris, pupil and lens) is assessed in both eyes.

9.6.3.5 Gonioscopy

The condition of the iris root and anterior chamber angle is assessed in both eyes.

9.6.3.6 Indirect ophthalmoscopy

The intraocular condition of the posterior segment of the eye (vitreous body, vitreous cells, optic nerve head, macula, peripheral retina) is assessed pre-dose in both eyes, and again post-

dose in the study eye. If a decrease in visual acuity is detected after treatment, additional indirect ophthalmoscopy should be performed immediately after treatment to verify if the retinal perfusion has been compromised. Mydriasis is usually needed to allow a comprehensive retinal exam. However, in patients with poor control of the IOP, the risk of additional IOP increase after mydriasis should be carefully considered before performing it.

9.6.3.7 Applanation tonometry

IOP will be measured 15 to 60 minutes post-dose in the study eye at baseline. IOP will be measured using applanation tonometry (e.g. Goldmann as the standard technique or Tonopen). In case of discrepancy, the final result will be evaluated by Goldman. Non-contact tonometry is not allowed. Since IOP is increased transiently after aflibercept injection, pre- and post-dose IOP will be monitored. If medically necessary, further IOP will be monitored.

9.6.3.8 Laboratory values

The laboratory tests will be performed at the 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 the investigator's assessment. These results are to be filed in the subject's source documentation. All abnormal laboratory values will require a comment in a timely manner from the investigator in terms of their significance, if any. Clinically significant changes in laboratory values should be designated as AEs and so reported. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the investigator should consult with the sponsor.

Samples for laboratory testing will be collected at the screening and Week 5/ End of Study or Early Termination visit. Laboratory test parameters are presented in Table 9-3, Table 9-4, and Table 9-5.

Table 9-3: Laboratory test — Chemistry panel

Sodium	Blood urea nitrogen (BUN)
Potassium	Creatine phosphokinase
Chloride	Creatine kinase MB
Carbon dioxide	Aspartate aminotransferase (AST)
Calcium	Alanine aminotransferase (ALT)
Amylase	Alkaline phosphatase (AP)
Glucose	Lactate dehydrogenase (LDH)
Albumin	Total bilirubin
Total protein, serum	Total cholesterol
Creatinine	Uric acid

Table 9-4: Laboratory test — Hematology panel

Hemoglobin
Hematocrit
White blood cells (WBCs)
Red blood cells (RBCs)
Red cell Indices
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Differential count
Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils
Platelet count
Hemoglobin A1c (HbA1c)

Table 9-5: Laboratory test — Urinalysis

Glucose	Yeast
Blood	Protein/creatinine ratio (UPCR)
Hyaline and other casts	Specific gravity
Crystals	RBC
Creatinine	Epithelial cells
Protein	WBC
Ketones	Cells
Bacteria	

9.6.3.9 Other laboratory tests

In women of childbearing potential, serum pregnancy test (beta HCG) will be performed at screening. A urine pregnancy test can be done at a study site, if the result from the central laboratory cannot be waited for.

9.7 Other procedures and variables

Not applicable.

9.8 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.

10. Statistical methods and determination of sample size

10.1 General considerations

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables and continuous variables by summary statistics (mean, standard deviation, minimum, median, and maximum).

Statistical analysis will be performed using SAS; the version used will be specified in the statistical analysis plan (SAP).

Medical history findings and AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA) codes and medications by Anatomical Therapeutic Chemical (ATC) codes (World Health Organization Drug Dictionary [WHO-DD]).

The analyses and data conventions are as follows:

- Definition of baseline: The baseline assessment will be the latest valid pre-injection assessment.
- Unscheduled assessments: Unless otherwise specified, extra assessments (e.g. vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in data listings, but not in data summaries. If more than one measurement is available for a given visit, the first observation will be used in the data summaries and all observations will be presented in the data listings.

The details of the statistical analyses will be specified in the SAP.

10.2 Analysis sets

Full Analysis Set (FAS)

The FAS will include all subjects who;

- are assigned,
- received at least one IVT administration of study drug on Day 1,
- have baseline valid IOP measurement, and
- have at least one post-baseline IOP measurement before or at Week 1.

The FAS will be used for supplemental analyses in efficacy.

Per Protocol Set (PPS)

The PPS will include the all subjects who;

- are assigned,
- received at least one IVT administration of study drug on Day 1,
- have baseline valid IOP measurement,
- have at least one valid (e.g. before prohibit treatment) post-baseline IOP measurement before or at Week 1, and
- show no validity findings that may affect efficacy.

The efficacy variables, which measured within four days from the dose (the day included), will be excluded from analyses in PPS. The PPS will be the primary analysis set for efficacy analyses.

Safety Analysis Set (SAF)

The SAF will include all subjects who are assigned and received at least one IVT administration of study drug.

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.

10.3 Variables and planned statistical analyses

10.3.1 Variables

10.3.1.1 Primary efficacy variable

Primary efficacy variable is

- Change in IOP from baseline to Week 1

10.3.1.2 Secondary efficacy variable

Secondary efficacy variable is

- Proportion of subjects who have improved NVI grade from baseline to Week 1.

10.3.1.3 Exploratory efficacy variables

Exploratory efficacy variables include, but not limited to, the followings:

- IOP and change from baseline to each visit,
- NVI and NVA and change from baseline to each visit, and
- Proportion of subjects who could control IOP (≤ 21 mmHg) at each visit.

10.3.1.4 Safety variables

The following are summarized descriptively for safety evaluations:

- AEs,
- Vital signs,
- Visual acuity, and
- Laboratory values.

10.3.2 Statistical and analytical plan

10.3.2.1 Demographic and other baseline characteristics

Study sample size and subject validity reasons for exclusion from analysis will be summarized using frequency tables. Subject disposition: end of treatment i.e., Week 1 and end of follow-up i.e., Week 5 will be summarized. Demographic and other baseline characteristics will be summarized descriptively.

10.3.2.2 Efficacy

The PPS is the primary analysis set for efficacy. The FAS is a set for supplemental analysis of the PPS analysis. No alpha adjustment for multiple comparisons is considered, therefore confidence interval of other analyses except the primary analysis in PPS will be interpreted in consideration of false positives due to multiple testing.

Primary efficacy analysis

Primary efficacy variable is

- Change in IOP from baseline to Week 1.

The imputation rule will be described in Sec 10.3.3.

The change in IOP from baseline at Week 1 will be summarized descriptively. The point estimate and its two-sided 95% confidence interval using one-sample t-statistics will be calculated. The corresponding hypotheses for the efficacy analysis are

$$H_0: \mu \geq 0,$$
$$H_a: \mu < 0,$$

where μ is the change in IOP from baseline at Week 1. If the upper limit of the two-sided 95% confidence interval in PPS is less than the threshold (i.e., 0), the null hypothesis will be rejected and the study will be regarded as success.

Secondary efficacy analysis

Secondary efficacy variable is

- Proportion of subjects who have improved NVI grade from baseline to Week 1.

The proportion of subjects who have improved NVI grade from baseline at Week 1 will be summarized descriptively. The point estimate and its two-sided 95% confidence interval using Clopper-Pearson method will be calculated. Improvement by at least one grade from baseline will be categorized to “Improved”.

Exploratory efficacy analysis

All exploratory efficacy variables will be summarized descriptively with appropriate statistical methods.

In addition, for the proportion of subjects who have improved NVA grade from baseline at Week 1, the point estimates and its two-sided 95% confidence interval using Clopper-Pearson method will be calculated.

The change in NVI and NVA grades categorized to “Improved” (improvement by at least one grade from baseline), “Worsened” (worsened by at least one grade from baseline) or “Stable” (no change in grade from baseline) will be also summarized by frequency tables.

In addition, the subgroup analyses will be performed in primary variable and secondary efficacy variables. The subgroups will include:

- Age (years): < 65, ≥ 65;
- Sex: Male, Female;

- Primary Diagnosis: CRVO, PDR, OIS, other;
- IOP at Baseline group (mmHg): ≤ median, > median;
- NVI grade at Baseline group: Grade 1 or 2, Grade 3 or 4;
- NVA grade at Baseline group: Grade 1 or 2, Grade 3 or 4.

Further details will be described in the SAP.

10.3.2.3 Safety

The safety analyses will be conducted in the SAF.

AEs that occurred or worsened after the first dose of study drug and no later than 30 days after the last dose of study drug will be considered as treatment-emergent AEs (TEAEs).

Treatment-emergent ocular AEs will be presented by MedDRA preferred term within the primary system organ class and summarized for the study eye and the fellow eye, separately. Treatment-emergent non-ocular AEs will be also summarized.

Intensity and causal relationship to the study drug / intravitreal injection will be analyzed descriptively.

Other safety variables will be analyzed descriptively including changes from baseline.

10.3.3 Missing data / drop outs

All missing or partial data will be presented in the subject data listing as recorded in the eCRF.

If no valid IOP is available at the Week 1, the last post-baseline before Week 1 will be utilized for imputation. If the prohibited treatment is received, the IOP after prohibited treatment will not be utilized for imputation in PPS analysis. On the other hand, the IOP after prohibited treatment will be utilized in FAS analysis. The same imputation rule will be conducted for NVI and NVA.

10.4 Determination of sample size

The target number of subjects to be treated with aflibercept was set at 16 as the PPS.

If left untreated, anterior segment neovascularization in NVG persists or becomes worse, which progresses chamber angle obstruction, leading eventually to elevated IOP. In the study design excluding influence of PRP on IOP to the extent possible, true change in IOP from baseline to at Week 1 is assumed not to fall below 0 mmHg in NVG patients who will receive neither anti-VEGF agents nor systemic IOP-lowering drugs, based on which the threshold for positive IOP-lowering effect was determined to be 0 mmHg.

A retrospective study[8)] compared mean change in IOP from baseline between bevacizumab IVT plus conventional treatment (e.g., IOP-lowering drugs, PRP) (11 eyes) and conventional treatment alone (12 eyes) in NVG patients. The combination therapy group had a mean change of –11.1 mmHg (at 9.2 [mean] days) while IOP remained unchanged without reduction (0 mmHg) in the monotherapy group (at 18.8 [mean] days). In VEGA, change (mean ± SD) in IOP from baseline to pre-dose at Week 1 in the sham group of the subgroup comprising subjects without systemic IOP-lowering drugs until pre-dose at Week 1 was -0.4 ± 7.7 (confidence interval –5.6 to 4.8).

Meanwhile, change (mean ± SD) in IOP from baseline to pre-dose at Week 1 in the aflibercept group of the subgroup comprising subjects without systemic IOP-lowering drugs until pre-dose at Week 1 in VEGA was –8.8 ± 8.4 mmHg. Therefore, change (mean ± SD) in IOP from baseline to pre-dose at Week 1 was assumed to be –8.0 ± 9.0 mmHg in the present study 19652 designed to prohibit the concomitant use of systemic IOP-lowering drugs until pre-dose at Week 1.

Based on the above assumption, 16 patients are required to achieve >90% power to detect "an upper limit of 2-sided 95% confidence interval (by 1-sample t-statistics) of mean change in IOP from baseline to pre-dose at Week 1 is less than the predetermined threshold of 0 mmHg (assumed change in IOP if untreated)."

The subjects' recruitment will be continued until 16 subjects as the PPS is assured. Finally, approximately 20 subjects will be assigned in case deviations of PPS (See Section 10.2) occurred during ongoing data review and cleaning.

10.5 Planned interim analyses

No formal interim analysis is planned.

11. Data handling and quality assurance

11.1 Data recording

The data collection tool for this study will be a validated EDC system called RAVE. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system (TOSCA; SAS).

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet based EDC software system RAVE, which Bayer has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigator site personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

The RAVE System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made. This information is available both at the investigator's site and at Bayer. Data

entries made in the RAVE EDC screens are supported by source documents maintained for all subjects enrolled in this study.

Source documentation

It is the expectation of the sponsor that all data entered into the eCRF has source documentation available at the site.

The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.

Data recorded from screening failures

Data of 'only screened subjects' will be recorded at least as source data, as far as the reason for the premature discontinuation is identifiable. At minimum, the following data should be recorded in the eCRF:

- Demographic information (subject number; year of birth / age; sex; if applicable race / ethnicity)
- Date of informed consent
- Relevant inclusion/exclusion criteria
- Reason for premature discontinuation
- Date of last visit.

These data will be transferred to the respective database.

For screening failures with an SAE, the following data should be collected in the eCRF in addition to the data specified above:

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

11.2 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.
  Supporting data may be requested (example: blood glucose readings to support a

diagnosis of diabetes).

- 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.

11.3 Data processing

Data will be collected as described in Section 11.1. Clinical data management will be performed in accordance with applicable sponsor's/CRO's standards and data cleaning procedures. This is applicable for data recorded on eCRF as well as for data from other sources (e.g. laboratory, adjudication committees).

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

11.4 Missing data

In principle, in order to achieve the goal of a well conducted clinical trial according to Good Clinical Practice (GCP), all efforts will be made to collect complete data for all subjects who receive study treatment in this study, and all subjects will be followed to the study end and will complete all required data collection.

11.5 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.

11.6 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.

12. 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 (on 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 is given by the sponsor for destruction.
- In the event 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 6.4.1.

13. Ethical and legal aspects

13.1 Investigator(s) and other study personnel

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 page and must receive all required external approvals (e.g. health authority, ethics committee, sponsor) before subject recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals 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's study file.

External data evaluation bodies

An Adjudication Committee will perform an additional analysis on possible arterial thrombotic events (ATEs) using criteria as proposed by the Antiplatelet Trialists' Collaboration (APTC). The members of the committee, the functional roles, and responsibilities are specified in its charter.

13.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

Each investigator (including principal and/or any sub investigators) who is directly involved in the treatment or evaluation of research subjects has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

13.3 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 Good Clinical Practice (GCP) guidelines and 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 IEC/IRB approval must be obtained and also forwarded to the sponsor. The responsible unit (e.g. IEC/IRB, head of the study center/medical institution) must supply to the sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/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 12.

13.4 Subject information and consent

All relevant information on the study will be summarized in an integrated subject information sheet and informed consent form provided by the sponsor or the study center. A sample subject information and informed consent form 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 be informed about the following aspects of premature withdrawal:

- Each subject has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The subject's consent covers end-of-study examinations as specified in the visit description described in Section 9.2 to be conducted after withdrawal of consent.
- The subject's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan.
- Subject-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The subject has the right to object to the generation and processing of this post-withdrawal data. The subject's oral objection may be documented in the subject's source data.

Each subject / legal representative or proxy consenter will have ample time and opportunity to ask questions.

Only if the subject / legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator will personally sign and date the form. The subject / legal representative or proxy consenter 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 patient's note/file of the medical institution.

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

The informed consent form and any other written information provided to subjects / 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 informed consent form. The investigator will inform the subject / legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB's approval / favorable opinion in advance of use.

13.5 Publication policy and use of data

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

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

13.6 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.

13.7 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.

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15. Protocol amendments

Not applicable.

16. Appendices

Not applicable.