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Title Page

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Protocol Number: 21912

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Compound Number: BAY 86-5321/IVT aflibercept/Eylea®

Short Title:

An Interventional Study to Investigate the Safety and Efficacy of IVT Aflibercept with Proactive Customized Treatment Intervals in Patients ≥50 Years of Age with No Fluid Due to CNV Lesions Secondary to nAMD Following Treatment Initiation with Aflibercept

Study Phase: 4

Acronym: XPAND

Sponsor Name: Bayer AG

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Medical Monitor name and contact information will be provided separately.

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Parallel-group Phase 4, Open-label, Two-arm Study to Assess the Safety and Efficacy of Intravitreal (IVT) Aflibercept with Proactive Customized Treatment Intervals in Patients ≥50 Years of Age with No Fluid Due to Choroidal Neovascularization (CNV) Lesions Secondary to Neovascular (wet) Age-related-Macular Degeneration (nAMD) Following Treatment Initiation with Aflibercept

Short Title: An interventional Study to Investigate the Safety and Efficacy of IVT Aflibercept with Proactive Customized Treatment Intervals in Patient ≥50 Years of Age with No Fluid Due to CNV Lesions Secondary to nAMD Following Treatment Initiation with Aflibercept

Rationale:

The use of anti-vascular endothelial growth factor (anti-VEGF) agents for the treatment of neovascular "wet" age-related macular degeneration (nAMD) has become the standard of care. The frequency of dosing monthly anti-VEGFs has introduced a burden of illness on patients and caregivers as well as capability constraints on physicians in practice. Physicians have developed a practicing trend towards individualizing treatment to reduce the burden of patients and minimize reimbursement issues and healthcare costs. The current individualized treatment gaining momentum with practicing physicians is referred to as treat and extend (T&E), where the patient is injected at every visit and the follow-up examination intervals are incrementally extended or shortened according to the response to treatment.

After 3 monthly initial doses, the treatment interval may be maintained at 2 months or further extended using a T&E dosing regimen, where injection intervals are adjusted in 2- or 4-weekly increments to maintain stable visual and/or anatomic outcomes according to the approved European Union (EU) label for Eylea® (also known as aflibercept 2 mg). Optical coherence tomography (OCT) has been used in clinical practice to guide the detection of macular fluid in order to direct T&E increase, maintenance, or decrease of follow-up intervals and injections. This imaging modality readily permits visualization of anatomic changes consistent with choroidal neovascularization (CNV) in nAMD and allows assessment of the treatment response. However, until recently, OCT imaging was only possible in-office and was rarely conducted more frequently than every 4 weeks.

In spite of the encouraging results of Phase 4 T&E study (ALTAIR) and the supporting Phase 3b/4 study (ARIES) results, and the resulting label update for Eylea®, allowing for rapid, 4-week extension of treatment intervals up to 16 weeks, both are rarely done in everyday clinical practice, due to fear of catastrophic disease recurrence.

Artificial intelligence (AI) and new digital technologies are expected to transform medicine and especially ophthalmology fundamentally in the near future. Home monitoring is one potential mass application for such approaches and as of yet, there is no data on how home monitoring that can support treatment with Eylea®. In this study we investigate the rapid extension of a preselected patient population to a 16 week treatment interval. A digital drug development tool (home OCT) will provide an additional layer of assessments between 2 injection visits and therefore may have the potential to increase confidence of physicians and patients in applying long treatment intervals. The coronavirus disease 2019 (COVID-19)

pandemic has strongly impacted on ophthalmology. Reignited interest in home monitoring for exudative retinal disease is expected to persist as we transition to the "new normal".

Objectives and Endpoints/Estimands:

Objectives	Endpoints/Estimands
Primary	
• To assess whether 2 mg intravitreal (IVT) aflibercept administered at a customized treatment interval (determined after the first extended treatment interval) is non-inferior to 2 mg IVT aflibercept administered according to a standard treat and extend (T&E) regimen (initiated after the first extended treatment interval) in patients with no fluid following treatment initiation for neovascular (wet) age-related macular degeneration (nAMD)	Primary Endpoint: • Change in best-corrected visual acuity (BCVA) (early treatment diabetic retinopathy study [ETDRS] letters) from baseline to Week 36
Secondary	
• To assess treatment burden of 2 mg IVT aflibercept administered at a customized treatment interval compared with 2 mg IVT aflibercept administered according to a standard T&E regimen (initiated after the first extended treatment interval) in patients with no fluid following treatment initiation for nAMD • To evaluate the safety of aflibercept with proactive treatment intervals	Key Secondary Endpoint: • Number of IVT aflibercept injections per patient up to Week 52 (descriptively) Secondary Endpoints: • Number of IVT aflibercept injections per patient until Week 36 • Number of patients achieving pre-defined treatment intervals (≥4, ≥8, ≥10, ≥12¸ ≥14, and 16 weeks) at Weeks 36 and 52 • Change in BCVA (ETDRS letters) from baseline to Week 52 • Treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) through Weeks 36 and 52
Other pre-specified exploratory	
• To assess morphologic outcomes of 2 mg IVT aflibercept administered at a customized treatment interval compared with 2 mg IVT aflibercept administered according to a standard T&E regimen (initiated after the first extended treatment interval) in patients with no fluid following treatment initiation for nAMD	Other Pre-specified Exploratory Endpoints: • Change in central subfield retinal thickness (CST) [μm] from baseline to Weeks 36 and 52 • Change in CST compared to treatment initiation (16 weeks before baseline) at Weeks 36 and 52 • Number of patients without any fluid at treatment initiation (16 weeks before baseline), baseline, Weeks 36, and 52 ➢ without intraretinal fluid (IRF) ➢ without subretinal fluid (SRF) ➢ without sub-retinal pigment epithelium (sub-RPE) fluid Customized treatment interval arm only: • Change in retinal fluid volume and in volume by compartment (IRF and SRF) • Area under the curve (AUC) of fluid volumes • Agreement of home monitoring findings with spectral domain optical coherence tomography (SD-OCT) in-office monitoring performed at the same day

Objectives	Endpoints/Estimands
• Assess the change in choroidal neovascularization (CNV) size in both study arms with optical coherence tomography angiography (OCT-A) at study visits (optional for center)	• Assess change in CNV size using OCT-A (optional for center) in both study arms at study visits
• To monitor the conversion rate from dry to wet form of AMD in fellow eye with OCT-A at study visits (optional for center)	• Number of patients with newly developed CNV in fellow eye in OCT-A at Weeks 36 and 52 in eyes with dry AMD signs at baseline for patients in both arms
• To assess handling satisfaction with patient Home OCT user experience questionnaire	• Number of patients for agreement levels 1 to 5 assessed at Week 36

Overall Design:

This is a multicenter, active-controlled, open-label, parallel-group treatment, 1:1 randomized Phase 4 study of male and/or female patients ≥50 years of age after treatment initiation with intravitreal (IVT) aflibercept for active CNV lesions secondary to nAMD. Control arm is widely adopted and approved T&E regimen.

In total, approximately 108 patients in Europe and Canada will be randomized. The study treatment phase will be 52 weeks plus the maximal length of the screening phase (up to 4 weeks) and the 30 days (phone) follow-up phase after the last injection which may be after the last patient last visit (LPLV).

Patients must give written informed consent before any data documentation and any study procedure. The study comprises a screening phase of up to 4 weeks (Visit 1; Week -4 until Day -1), a baseline visit (Visit 2; Week 0/Day 1), and a treatment phase (which starts at baseline) of 52 weeks.

Only patients with treatment naïve eyes which have received the 3 initial injections according to the label qualify for a screening visit of the study (between Weeks 12 and 16 when counting from the treatment start of nAMD).

The 3 initial injections will be administered as routine treatment outside of the study.

In the unlikely event that 2 eyes of a patient started treatment at the same time the eye with worse BCVA will be designated as the study eye. If a patient has similar BCVA in both eyes, the eye with the clearest media will be selected as the study eye. If the ocular media of both eyes are similar in clarity, the patient's non-dominant eye (if identifiable) will be selected as the study eye. Starting at baseline (Week 0/Day 1), aflibercept 2 mg IVT treatment will be administered to the study eye as detailed below in intervals maximum of 16 weeks and minimum of 4 weeks.

Patients will be stratified based on BCVA gains from treatment initiation to study start (captured during screening) and randomized 1:1 into 1 of the following 2 arms:

- Customized Treatment interval arm
- T&E, 2-week adjustment arm

After randomization, the treatment intervals will not be less than 4 weeks nor more than 16 weeks for both arms.

During the treatment phase, the next IVT aflibercept injection will be determined by Investigators at each treatment visit according to the following criteria:

- Shortening of subsequent treatment interval from the last interval

  When any of the following criteria are met for the study eye, subsequent treatment interval will be shortened by 1 week in the customized treatment interval arm and by 2 weeks in the standard T&E, 2-week adjustment arm.

  - Presence of intraretinal fluid

    Or
  - Subretinal fluid increasing to exceed 50 µm

    Or any of the following:
  - Loss of ≥5 early treatment diabetic retinopathy study (ETDRS) letters due to disease activity
  - New neovascularization
  - New macular hemorrhage

  Minimum interval must not be less than 4 weeks during entire period of the study.
- Maintenance of last treatment interval
  - No intraretinal fluid

    And
  - Subretinal fluid

    Increasing but

    Not exceeding 50 µm in thickness
  - No loss of ≥5 ETDRS letters
  - No new neovascularization
  - No new hemorrhage
- Extension of subsequent treatment interval from the last interval
  - No intraretinal fluid

    And
  - Subretinal fluid

    Unchanged or decreased compared to previous visit
  - No loss of ≥5 ETDRS letters
  - No new neovascularization
  - No new hemorrhage

  If all of the above criteria are met for the study eye, subsequent treatment interval will be extended by 2 weeks in the standard T&E, 2-week adjustment arm and by 4 weeks in the customized treatment interval arm until a maximum treatment interval of 16 weeks is reached (e.g., if prior T&E interval was 13 weeks then there will only be an extension of 3 weeks to reach the maximum of 16 weeks).

The study patients will have study visits in accordance with the treatment interval determined by the application of the treatment algorithm (as described above).

In addition, there are 2 mandatory study visits at Weeks 36 and 52 which may or may not coincide with a treatment visit but which have to be attended by every patient as examinations are performed from which the primary and secondary outcomes are determined.

After day of final visit (Week 52 ± 7 days or early termination), administration of study drug is not allowed. Any subsequent treatment of the underlying disease of a patient is not part of the study and is at the discretion of the patient's physician. Such treatment should only occur after all study relevant assessments have been performed.

The treating Investigator must follow-up by phone on any adverse events (AEs) that are ongoing or may occur within 30 days of the last administration of study drug. Information regarding such events is to be reported under this protocol (i.e., not as spontaneous reports).

All ocular assessments are to be conducted in both eyes, unless indicated otherwise. Assessments of ocular efficacy and safety will include BCVA, spectral domain optical coherence tomography (SD-OCT), optical coherence tomography angiography (OCT-A), patient Home OCT user experience questionnaire (only applicable for patients in the customized treatment interval arm), intraocular pressure (IOP), indirect ophthalmoscopy, slit lamp biomicroscopy, and AEs; these will be assessed at all study visits ("study visits" are all mandatory visits and injection visits and "other visits" are unscheduled visits).

Short Summary:

The purpose of this study is to investigate the safety and efficacy of IVT aflibercept with proactive customized treatment intervals in patients ≥50 years of age with no fluid due to CNV lesions secondary to nAMD following treatment initiation with aflibercept.

Study details include the following:

- Study duration per patient:
  - Screening phase: Up to 4 weeks
  - Treatment phase: Up to 52 weeks
  - Telephone follow-up phase: Up to 30 days
- Visit frequency: Screening visit, Weeks 0 (baseline), 36, and 52. Following discontinuation of study treatment, patients will be followed unless they withdraw their informed consent for study participation or are lost to follow-up.

Number of Patients:

Approximately 108 patients will be randomized in 1:1 ratio to achieve 54 patients in each arm.

Intervention Groups and Duration:

- Customized treatment interval arm:

  In this treatment arm treatment interval will be extended in a single step from an extended treatment interval of 8 weeks to an 16 weeks interval (test arm, rapid treatment individualization). After the initial study injection at baseline, patients will receive their next study injection at Week 16. Patients in this study arm will also be issued a home monitoring device, which will allow for regular OCT monitoring (at least 5 times a week) at home. If no fluid exceeding patient threshold emerges between the treatment intervals, the patient will stay at a 16 weeks treatment interval until the end of the study.

If, before completing the planned treatment interval, recurrent fluid is detected by the home monitoring device the patient will be asked by the Investigator to return to the study site within 3 days at the latest to confirm the findings by SD-OCT. If fluid is verified, the patient will be treated immediately, and the next treatment interval will be equal to the time between the last study injection and the SD-OCT confirmed emergence of new fluid minus 7 days, unless fluid is verified 30 days after treatment. After reduction of the treatment interval the following intervals will be extended in 4 weeks increments up to a maximum of 16 weeks, if all extension criteria are met.

The monitoring flow of the customized treatment interval arm is depicted in Appendix 10.5.

- T&E, 2-week adjustment arm:

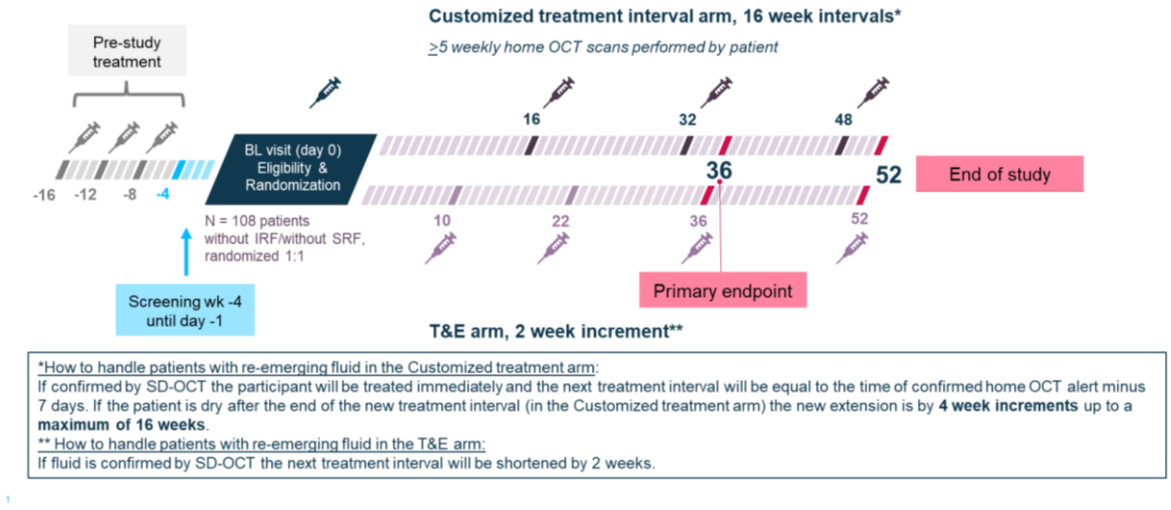
  In this treatment arm, starting at baseline, patients will receive treatment in intervals maintained (8 weeks) or adjusted in 2 weeks increments each time (up to a maximum of 16 weeks and minimum of 4 weeks), depending on extension/shortening criteria.

Data Monitoring/Other Committee: No

Steering Committee: Yes

1.2 Schema

Figure 1-1: Study Design



The end of the study will be achieved as soon as the last patient has undergone their last study visit (plus AE follow-up for recently injected patients) in all centers in all participating countries.

IRF=intraretinal fluid, OCT=optical coherence tomography, SD-OCT=spectral domain optical coherence tomography, SRF=subretinal fluid, T&E=treat and extend, wk = week.

1.3 Schedule of Activities

Table 1–1: Schedule of Activities

Study Phase	**Screening[a]**	**Baseline**	**Treatment**		
Treatment Arms	**All Patients**		**T&E, 2-Week Adjustment Arm**	**Customized Treatment Interval Arm**	**All Patients**
Visit/Wk	**V1 Wk -4 (Day -28) until Day -1**	**V2 Wk 0 (Day 1)**	**Visits determined by extension criteria**	**Wk 16 unless earlier visit required. Additional visits determined by extension criteria**	**End of study/ Wk 52 or early termination**
Study Visits	**Wk -4 until Day -1**	**Wk 0**	**Injection visits + Wk 36[b]**	**Injection visits + Wk 36[b]**	**Wk 52[b]**
Administrative					
Informed consent	X				
Inclusion/exclusion criteria	X	X			
Demographic data[c]	X				
Medical/ophthalmic history	X				
Prior/concomitant medications	X	X	X	X	X
Randomization		X			
Study Intervention					
Administration of study treatment		X	X[d]	X[d]	(X)[e]
Determination of next treatment interval		X	X	X	
Ocular Evaluation[f]					
BCVA using ETDRS chart	X	X	X	X	X
SD-OCT	X	X	X	X	X
OCT-A (optional)		(X)	(X)	(X)	(X)
Patient Home OCT user experience questionnaire				X	
Indirect ophthalmoscopy	X	X	X	X	X
Slit lamp biomicroscopy	X	X	X	X	X
IOP[g]	X	X	X	X	X
Safety					
Physical examination[h]	X				

Study Phase	Screening[a]	Baseline	Treatment		
Treatment Arms	**All Patients**		**T&E, 2-Week Adjustment Arm**	**Customized Treatment Interval Arm**	**All Patients**
Visit/Wk	**V1 Wk -4 (Day -28) until Day -1**	**V2 Wk 0 (Day 1)**	**Visits determined by extension criteria**	**Wk 16 unless earlier visit required. Additional visits determined by extension criteria**	**End of study/ Wk 52 or early termination**
Study Visits	**Wk -4 until Day -1**	**Wk 0**	**Injection visits + Wk 36[b]**	**Injection visits + Wk 36[b]**	**Wk 52[b]**
Vital signs[i]	X	X	X	X	X
Ocular and non-ocular AEs[j]	X	X	X	X	X[k]
Telephone safety check[l]		(X)	(X)	(X)	X
Laboratory Testing					
Pregnancy test[m]	X	(X)[m]	(X)[m]	(X)[m]	(X)[m]

AE=adverse event, BCVA=best-corrected visual acuity, BMI=body mass index, eCRF=electronic case report form, ETDRS=early treatment diabetic retinopathy study, IOP=intraocular pressure, IVT=intravitreal, OCT=optical coherence tomography, OCT-A=optical coherence tomography angiography, PRO=patient-reported outcome, SD-OCT=spectral domain optical coherence tomography, T&E=treat and extend, Wk=week, WOCBP=women of childbearing potential.

The end of the study will be achieved as soon as the last patient has undergone their last study visit (plus AE follow-up for recently injected patients) in all centers in all participating countries.

a) The screening visit and baseline visit can be combined in case screening is planned within 1 week before the scheduled baseline visit.
b) Visit window for injection visits and mandatory visits is +/-7 days.
c) Patient demographic data including the following, should be documented in the eCRF: year of birth, age, sex, race, and smoking status.
d) Administration of study treatment only if required per treatment schedule.
e) Treatment of underlying disease (intravitreal injection) on the day of the final if it coincides with a regular injection visit. Such treatment should only occur after all study relevant assessments have been performed.
f) All ocular assessments are to be conducted in both eyes, unless indicated otherwise. Assessments of ocular efficacy and safety will include BCVA, SD-OCT, OCT-A, PRO questionnaire, indirect ophthalmoscopy, slit lamp biomicroscopy, IOP, and AEs; these will be assessed at all study visits.
g) Pre- and post-dose, as applicable. If a patient receives a study injection, indirect ophthalmoscopy should be conducted post-dose per local practice and IOP should be assessed in the study eye 30 to 60 minutes post-dosing.
h) Weight, height, and BMI.
i) Temperature, heart rate, and blood pressure.
j) Any AE occurring up to 30 days after the last IVT aflibercept injection has to be documented, regardless of the relationship to the study drug or the seriousness of the event and reported in accordance with this protocol (i.e. not as a spontaneous report). For any drug-related AE occurring after 30 days after the last IVT application of aflibercept, the standard procedures that are in place for spontaneous reporting will be followed. If a patient prematurely withdraws from the study, AEs should be recorded until withdrawal or 30 days after the last dose of study drug, whichever is later.

k) The treating Investigator must follow-up by phone on any AEs that are ongoing or may occur within 30 days of the last administration of study drug. Information regarding such events is to be reported under this protocol (i.e., not as spontaneous reports).
l) If a patient has received an injection of study medication 30 days or less before the end of study visit a mandatory safety telephone needs to be made approximately 30 days after that last treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred. This telephone call will occur after the end of study visit. An optional safety telephone call will be made approximately 3 days after treatment at all other visits as per local standard.
m) For WOCBP only. Urine pregnancy test for WOCBP.

2. Introduction

2.1 Study Rationale

The use of anti-vascular endothelial growth factor (anti-VEGF) agents for the treatment of neovascular "wet" age-related macular degeneration (nAMD) has become the standard of care. The frequency of dosing for monthly anti-VEGFs has introduced a burden of illness on patients and caregivers as well as capability constraints on physicians in practice. Physicians have developed a practicing trend towards individualizing treatment to reduce the burden of patients and minimize reimbursement issues and healthcare costs. The current individualized treatment gaining momentum with practicing physicians is referred to as treat and extend (T&E), where the patient is injected at every visit and the follow-up examination intervals are incrementally extended or shortened according to the response to treatment.

After 3 monthly initial doses, the treatment interval may be maintained at 2 months or further extended using a T&E dosing regimen, where injection intervals are adjusted in 2- or 4-weekly increments to maintain stable visual and/or anatomic outcomes, according to the approved European Union (EU) label for Eylea® (also known as aflibercept 2 mg). Optical coherence tomography (OCT) has been used in clinical practice to guide the detection of macular fluid in order to direct T&E increase, maintenance, or decrease of follow-up intervals and injections. This imaging modality readily permits visualization of anatomic changes consistent with choroidal neovascularization (CNV) in nAMD, and allows assessment of the treatment response. However, until recently, OCT imaging was only possible in-office and was rarely conducted more frequently than every 4 weeks.

In spite of the encouraging results of Phase 4 T&E study (ALTAIR) and the supporting Phase 3b/4 study (ARIES) results, and the resulting label update for Eylea®, allowing for rapid, 4-week extension of treatment intervals up to 16 weeks, both are rarely done in everyday clinical practice, due to fear of catastrophic disease recurrence.

Artificial intelligence (AI) and new digital technologies are expected to transform medicine and especially ophthalmology fundamentally in the near future. Home monitoring is one potential mass application for such approaches and as of yet, there is no data on how home monitoring that can support treatment with Eylea®. In this study we try to understand whether an additional layer of assessments during the whole treatment interval by a digital drug development tool can increase the confidence of physicians and patients to increase treatment to longer intervals (maximum 16 weeks). The coronavirus disease 2019 (COVID-19) pandemic has strongly impacted on ophthalmology. Reignited interest in home monitoring for exudative retinal disease is expected to persist as we transition to the "new normal".

2.2 Background

Age-related macular degeneration (AMD) is a leading cause of adult blindness in the developed world (Rahmani et al,1996). There are 2 forms of AMD, the dry and the wet (neovascular) form. Neovascular AMD is a major health issue in aging populations globally (Ladas et al. 2004, Scassellati-Sforzolini et al. 2001, Lafaut et al. 2000). Vision loss in nAMD results from the abnormal growth and leakage of blood vessels in the macula.

The inhibition of VEGF activity by pharmacological intervention has proven to be a viable approach for the treatment of neovascular AMD (Maruko et al. 2007). Intravitreal (IVT)-administered anti-VEGF therapies like aflibercept inhibit neovascular vessel growth and leakage in the retina, and they are currently the standard of care for patients with nAMD.

They not only maintain visual function but also provide clinically meaningful visual gains. Treatment of nAMD is chronic and long-term in most patients to suppress retinal edema and recurrences of CNV. Although the globally approved IVT anti-VEGF therapies are efficacious and well tolerated, the need for IVT aflibercept injections every 4 to 8 weeks, specifically in the initial phase and during maintenance of treatment, represents a significant burden to physicians, patients and caregivers. While the IVT procedure is straightforward and relatively easy to perform, capacity issues for ensuring an appropriate injection frequency in order to achieve patient outcomes similar to those seen in the pivotal studies represent an increasing challenge to individual practices and the healthcare system overall.

The use of anti-VEGF agents in an individualized, proactive T&E for nAMD has become the standard of care. Utilization of proactive IVT aflibercept T&E regimens allows for a pragmatic approach to treatment and offers benefits to physicians and patients. With proactive, individualized T&E dosing regimens, the need for interim monitoring is minimized, as is the risk of disease recurrence. Reducing the number of appointments per patient and minimizing the need for monitoring visits could ease clinic flow and patient burden. Furthermore, planning the next injection helps minimize the possibility of treatment delays and facilitates clinic management (Mitchell et al. 2021).

This study will investigate the safety and efficacy of IVT aflibercept with proactive customized treatment intervals in patients ≥50 years of age with no fluid due to CNV lesions secondary to nAMD following treatment initiation with aflibercept.

Refer to Section 4.2 for a discussion on the rationale for study design and Section 4.3 for dose justification.

2.3 Benefit/Risk Assessment

Aflibercept is marketed for the treatment of adult patients with several retinal diseases that are characterized by up-regulation of VEGF, are related to pathological neo-vascularization and/or vascular leakage, and can result in retinal thickening and edema, which is thought to contribute to vision loss. The efficacy and safety of aflibercept 2 mg used in adult patients with retinal diseases are well established; and its benefit-risk profile is considered favorable.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of aflibercept may be found in the Investigator's Brochure (IB).

2.3.1 Risk Assessment

Based on current available data, it is anticipated that the safety profile of aflibercept in a customized treatment interval arm applied to preselected nAMD patients with a dry retina before study start, will be similar to that of the approved T&E regimen, and includes identified risks of aflibercept, such as hypersensitivity, and identified risks of the injection procedure, such as intraocular inflammation/infection, retinal tear, retinal detachment, transient increase in intraocular pressure (IOP), and traumatic cataract. Therefore, the same contraindications, precautions and warnings for Eylea® will also apply to this study.

The adverse reactions associated with Eylea® are shown in Table 2–1 (Company Core Data Sheet [CCDS]). The adverse reactions are listed by system organ class and frequency using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000). Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Table 2–1: All Treatment-emergent Adverse Drug Reactions Reported in Patients in Phase 3 Studies

System Organ Class	Very Common	Common	Uncommon	Rare
Immune system disorders			Hypersensitivity***	
Eye disorders	Conjunctival hemorrhage, Eye pain	Retinal pigment epithelial tear*, Detachment of the retinal pigment epithelium, Cataract, Cataract cortical, Cataract nuclear, Cataract subcapsular, Corneal erosion, Corneal abrasion, Intraocular pressure increased, Vision blurred, Vitreous floaters, Vitreous detachment, Injection site pain, Foreign body sensation in eyes, Lacrimation increased, Eyelid edema, Injection site hemorrhage, Punctate keratitis, Conjunctival hyperemia, Ocular hyperemia	Endophthalmitis**, Retinal detachment, Retinal tear, Uveitis, Iritis, Iridocyclitis, Lenticular opacities, Corneal epithelium defect, Anterior chamber flare, Corneal edema	Cataract traumatic, Vitritis, Hypopyon

AMD=age-related macular degeneration.
*Conditions known to be associated with wet AMD. Observed in the wet AMD studies only.
**Culture positive and culture negative endophthalmitis.
***During the post-marketing period, reports of hypersensitivity included rash, pruritus, urticaria, and isolated cases of severe anaphylactic/anaphylactoid reactions.

A detailed description of adverse reactions is provided in the CCDS of Eylea®.

The protocol has been designed to minimize the risk to the study patients. Special warnings and precautions for the use of aflibercept are reflected in strict inclusion and exclusion criteria for this study.

Patients will be monitored to detect AEs during the study and followed appropriately to ensure the resolution of AEs. Safety assessments will consist of the regular measurements of vital signs and physical examinations as well as monitoring and recording of AEs and serious adverse events (SAEs).

Risk Assessment for COVID-19 Pandemic:

There is currently an outbreak of respiratory disease (COVID-19) caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Appropriate medical measures have been implemented into this protocol to detect COVID-19 disease to confirm eligibility of patients and to safely conduct the study.

Aflibercept is a soluble decoy receptor fusion protein that has been shown to bind to VEGF-A, placental growth factor (PlGF) and VEGF-B, with subsequent blockade of activity demonstrated for VEGF-A and PlGF and is believed not to cause immune suppression.

Measures to mitigate the additional risks caused by COVID-19 are:

This study is going to start enrolling only when the Sponsor and contract research organization (CRO) in collaboration deem it is safe to start the study.

Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.

Once clinical signs of infection are reported by patients, the Investigator needs to determine whether samples can be collected, and safety data can be recorded on site. If not, AEs and concomitant medications will be obtained via phone calls. Daily body temperature measurement is recommended.

The study drug will not be administered to patients upon identification of any signs of COVID-19 infection.

Confirmation of COVID-19 infection by optional laboratory assessment will be conducted based on availability (test capacity and turnaround time) of approved tests and on the Investigator's discretion. This would include serology testing at screening and virus testing prior to any admission.

The probability of virus transmission will be controlled as much as possible by:

- Advice for patient to adhere to local requirements for reduction of the public exposure while ambulatory.
- Patients are asked for any contact with a person who has tested positive for SARS-CoV-2. If applicable, patients will be referred to the local health care system for further -follow-up- and treatment.
- Physical distancing and person to person contact restrictions will be applied during site visits and in-house confinement.
- Where physical distancing is not possible, personal protective equipment will be used by study patient (face mask, gloves) and staff (for example but not limited to masks, gloves, protectors, medical suits) if deemed appropriate by the Investigators and site staff and guided by local requirements.
- Logistical improvements of the site and structural measures of the study site building will be implemented to further improve physical distancing.

2.3.2 Benefit Assessment

Marketing authorizations have been granted for aflibercept (Eylea®, [aflibercept] IVT injection) for a 2 mg dose (delivered as a 50 µL [0.05 mL] injection of 40 mg/mL) in more than 110 countries for the treatment of patients with nAMD including the United States (US), countries in the EU (European Commission), Japan, Australia, and Canada.

The T&E treatment schedule allows a controlled prolongation of treatment intervals without interim visits needed between injections.

Going beyond the currently approved treatment intervals in a preselected population may further reduce treatment intensity burden for patients and their care givers.

The additional use of a a digital drug development tool which provides an additional layer of assessments during the treatment period will allow ongoing surveillance of patient disease status and increase confidence in fast prolongation to maximal treatment intervals.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to patients in this study, the potential risks identified in association with aflibercept are justified by the anticipated benefits that may be afforded to patients with nAMD.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of aflibercept may be found in the IB.

With proactive, individualized T&E dosing regimens, the need for interim monitoring is minimized, as is the risk of disease recurrence. In preselected patients who respond fast to the treatment with anti-VEGFs and experience complete dryness of the retina for 8 weeks preceding the start of the study, an even faster prolongation of treatment intervals is appropriate , which would further reduce the number of appointments per patient. By minimizing the need for monitoring visits patient flow within the clinic can be optimized and patient burden could be decreased. Furthermore, this study will use Home monitoring in one study arm which allows the patient to provide OCT scans in short time intervals (several times per week up to daily) to the treating physician who can surveille at an ongoing basis treatment success and patient safety and as such decrease risk of disease recurrence. Home OCT assessments may further minimize the risk of treatment delays and improve use of clinic resources.

3. Objectives and Endpoints/Estimands

Objectives	Endpoints/Estimands
Primary	
• To assess whether 2 mg intravitreal (IVT) aflibercept administered at a customized treatment interval (determined after the first extended treatment interval) is non-inferior to 2 mg IVT aflibercept administered according to a standard treat and extend (T&E) regimen (initiated after the first extended treatment interval) in patients with no fluid following treatment initiation for neovascular (wet) age-related macular degeneration (nAMD)	Primary Endpoint: • Change in best-corrected visual acuity (BCVA) (early treatment diabetic retinopathy study [ETDRS] letters) from baseline to Week 36
Secondary	
• To assess treatment burden of 2 mg IVT aflibercept administered at a customized treatment interval compared with 2 mg IVT aflibercept administered according to a standard T&E regimen (initiated after the first extended treatment interval) in patients with no fluid following treatment initiation for nAMD • To evaluate the safety of aflibercept with proactive treatment intervals	Key Secondary Endpoint: • Number of IVT aflibercept injections per patient up to Week 52 (descriptively) Secondary Endpoints: • Number of IVT aflibercept injections per patient until Week 36 • Number of patients achieving pre-defined treatment intervals (≥4, ≥8, ≥10, ≥12¸ ≥14, and 16 weeks) at Weeks 36 and 52 • Change in BCVA (ETDRS letters) from baseline to Week 52 • Treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) through Weeks 36 and 52

Objectives	Endpoints/Estimands
Other pre-specified exploratory	
• To assess morphologic outcomes of 2 mg IVT aflibercept administered at a customized treatment interval compared with 2 mg IVT aflibercept administered according to a standard T&E regimen (initiated after the first extended treatment interval) in patients with no fluid following treatment initiation for nAMD	Other Pre-specified Exploratory Endpoints: • Change in central subfield retinal thickness (CST) [μm] from baseline to Weeks 36 and 52 • Change in CST compared to treatment initiation (16 weeks before baseline) at Weeks 36 and 52 • Number of patients without any fluid at treatment initiation (16 weeks before baseline), baseline, Weeks 36, and 52 ➢ without intraretinal fluid (IRF) ➢ without subretinal fluid (SRF) ➢ without sub-retinal pigment epithelium (sub-RPE) fluid Customized treatment interval arm only: • Change in retinal fluid volume and in volume by compartment (IRF and SRF) • Area under the curve (AUC) of fluid volumes • Agreement of home monitoring findings with spectral domain optical coherence tomography (SD-OCT) in-office monitoring performed at the same day
• Assess the change in choroidal neovascularization (CNV) size in both study arms with optical coherence tomography angiography (OCT-A) at study visits (optional for center)	• Assess change in CNV size using OCT-A (optional for center) in both study arms at study visits
• To monitor the conversion rate from dry to wet form of AMD in fellow eye with OCT-A at study visits (optional for center)	• Number of patients with newly developed CNV in fellow eye in OCT-A at Weeks 36 and 52 in eyes with dry AMD signs at baseline for patients in both arms
• To assess handling satisfaction with patient Home OCT user experience questionnaire	• Number of patients for agreement levels 1 to 5 assessed at Week 36

4. Study Design

4.1 Overall Design

This is a multicenter, active-controlled, open-label, parallel-group treatment, 1:1 randomized Phase 4 study of male and/or female patients ≥50 years of age after treatment initiation with IVT aflibercept for active CNV lesions secondary to nAMD. Control arm is widely adopted and approved T&E regimen.

In total, approximately 108 patients in Europe and Canada will be randomized. The study treatment phase will be 52 weeks plus the maximal length of the screening phase (up to 4 weeks) and the 30 days (phone) follow-up phase after the last injection which may be after the last patient last visit (LPLV).

Patients must give written informed consent before any data documentation and any study procedure. The study comprises a screening phase of up to 4 weeks (Visit 1; Week -4 until Day -1), a baseline visit (Visit 2; Week 0/Day 1), and a treatment phase (which starts at baseline) of 52 weeks.

Only patients with treatment naïve eyes which have received the 3 initial injections according to the label qualify for a screening visit of the study (between Weeks 12 and 16 when counting from the treatment start of nAMD).

The 3 initial injections will be administered as routine treatment outside of the study.

In the unlikely event that 2 eyes of a patient started treatment at the same time the eye with worse BCVA will be designated as the study eye. If a patient has similar BCVA in both eyes, the eye with the clearest media will be selected as the study eye. If the ocular media of both eyes are similar in clarity, the patient's non-dominant eye (if identifiable) will be selected as the study eye. Starting at baseline (Week 0/Day 1), aflibercept 2 mg IVT treatment will be administered to the study eye as detailed below in intervals maximum of 16 weeks and minimum of 4 weeks.

Patients will be stratified based on BCVA gains from treatment initiation to study start (captured during screening) and randomized 1:1 into 1 of the following 2 arms:

- Customized treatment interval arm:
- In this treatment arm treatment interval will be extended in a single step from an extended treatment interval of 8 weeks to an 16 weeks interval (test arm, rapid treatment individualization). After the initial study injections at baseline, patients will receive their next study injection at Week 16.

  Patients in this study arm will also be issued a digital drug development tool which allows an additional layer of assessments in an ongoing way (at least 5 times a week) at home. If no abnormal assessments between preplanned visits are seen, the patient will be evaluated at these study visits and the new treatment interval be determined.

  If abnormal assessments during the treatment interval are reported by the digital drug development tool, the patient will be asked by the Investigator to return to the study site within 3 days at the latest to confirm the findings by spectral domain optical coherence tomography (SD-OCT). If fluid is verified and the treatment algorithm requires a change of treatment interval, the patient will be treated immediately, and the next treatment interval will be equal to the time between the last study injection and the SD-OCT-confirmed emergence of new fluid minus 7 days, unless fluid is verified 30 days after treatment. After reduction of the treatment interval the following intervals will be extended in 4 weeks increments up to a maximum of 16 weeks, if all extension criteria are met. If the findings are not confirmed by SD-OCT or no change is required as per treatment algorithm the patient will go on with the current treatment interval.

  The monitoring flow of the customized treatment interval arm is depicted in Appendix 10.5.
- T&E, 2 week-adjustment arm:

  In this treatment arm, starting at baseline, patients will receive treatment in intervals maintained (8 weeks) or adjusted in 2 weeks increments each time (up to a maximum of 16 weeks and minimum of 4 weeks), depending on extension/shortening criteria.

After randomization, the treatment intervals will not be less than 4 weeks nor more than 16 weeks for both arms.

During the treatment phase, the next IVT aflibercept injection will be determined by Investigators at each treatment visit according to the following criteria:

- Shortening of subsequent treatment interval from the last interval

  When any of the following criteria are met for the study eye, subsequent treatment interval will be shortened by 1 week in the customized treatment interval arm and by 2 weeks in the standard T&E, 2-week adjustment arm.

  - Presence of intraretinal fluid

    Or
  - Subretinal fluid increasing to exceed 50 µm

    Or any of the following:
  - Loss of ≥5 early treatment diabetic retinopathy study (ETDRS) letters due to disease activity
  - New neovascularization
  - New macular hemorrhage

  Minimum interval must not be less than 4 weeks during entire period of the study.
- Maintenance of last treatment interval
  - No intraretinal fluid

    And
  - Subretinal fluid

    Increasing but

    Not exceeding 50 µm in thickness
  - No loss of ≥5 ETDRS letters
  - No new neovascularization
  - No new hemorrhage
- Extension of subsequent treatment interval from the last interval
  - No intraretinal fluid

    And
  - Subretinal fluid

    Unchanged or decreased compared to previous visit
  - No loss of ≥5 ETDRS letters
  - No new neovascularization
  - No new hemorrhage

  If all of the above criteria are met for the study eye, subsequent treatment interval will be extended by 2 weeks in the standard T&E, 2-week adjustment arm and by 4 weeks in the customized treatment interval arm until a maximum treatment interval of 16 weeks is reached (e.g., if prior T&E interval was 13 weeks then there will only be an extension of 3 weeks to reach the maximum of 16 weeks).

The study patients will have study visits in accordance with the treatment interval determined by the application of the treatment algorithm (as described above).

In addition, there are 2 mandatory study visits at Weeks 36 and 52 which may or may not coincide with a treatment visit but which have to be attended by every patient as examinations are performed from which the primary and secondary outcomes are determined.

After day of final visit (Week 52 ± 7 days or early termination), administration of study drug is not allowed. Any subsequent treatment of the underlying disease of a patient is not part of the study and is at the discretion of the patient's physician. Such treatment should only occur after all study relevant assessments have been performed.

The treating Investigator must follow-up by phone on any AEs that are ongoing or may occur within 30 days of the last administration of study drug. Information regarding such events is to be reported under this protocol (i.e., not as spontaneous reports).

All ocular assessments are to be conducted in both eyes, unless indicated otherwise. Assessments of ocular efficacy and safety will include BCVA, SD-OCT, optical coherence tomography angiography (OCT-A), patient Home OCT user experience questionnaire (only applicable for patients in Home OCT arm), IOP, indirect ophthalmoscopy, slit lamp biomicroscopy, and AEs; these will be assessed at all study visits ("study visits" are all mandatory visits and injection visits and "other visits" are unscheduled visits).

A Steering Committee will be established to guide all aspects of the study.

4.2 Scientific Rationale for Study Design

The use of anti-VEGF agents in an individualized, proactive T&E for nAMD has become the standard of care. The SARS-CoV-2 pandemic has shown that there still is a major unmet need in predicting the treatment interval to optimize clinic capacity.

This study in patients with nAMD aims to assess non-inferiority of IVT aflibercept proactive customized treatment intervals compared with IVT aflibercept proactive T&E in maintaining BCVA gains following treatment initiation with aflibercept.

The non-inferiority design is adequate to assess the study objectives.

Open-label setting: Since there is no adequate way to mask home monitoring without jeopardizing its effect on treatment guidance, masking the study would disrupt the primary objective and, thus, was not considered to be a viable option.

The primary study endpoint at Week 36 corresponds to an overall treatment time of 52 weeks of the patients with nAMD. It also coincides with the completion of treatment circles of the 2 study groups. The end of study 52 weeks after study start would allow both study groups to reach the maximum treatment interval of 16 weeks.

4.3 Justification for Dose

The recommended dose for aflibercept is 2 mg (equivalent to 50 µL). Aflibercept treatment is initiated with 1 injection per month for 3 consecutive doses, followed by 1 injection after2 months. Based on the physician's judgment of visual and/or anatomic outcomes, the treatment interval may be maintained at 2 months or further extended using a T&E dosing regimen, where injection intervals are adjusted in 2- or 4-weekly increments to maintain stable visual and/or anatomic outcomes. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. There is no requirement for monitoring between injections. Based on the physician's judgment the schedule of monitoring visits may be more frequent than the injection visits.

4.4 End of Study Definition

The end of the study will be achieved as soon as the last patient has undergone their last study visit (plus AE follow-up for recently injected patients) in all centers in all participating countries.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Eligibility for participation in this study will be based on the inclusion/exclusion criteria. An individual patient may only be randomized once.

Patients eligible for this study must have had active CNV lesions secondary to nAMD at treatment initiation and 3 initial IVT aflibercept injections as per label. The patients' ability to properly handle a Home OCT device to participate in the study will be determined by the Investigator.

Only one eye will be designated as the study eye. In the rare event that a patient meets eligibility criteria in both eyes, the eye with worse BCVA will be selected. If there is no objective basis for selecting the study eye, factors such as ocular dominance, other ocular pathology and patient preference should be considered in making the selection.

Ophthalmic eligibility criteria apply to the study eye only unless otherwise specified.

Inclusion and exclusion criteria will be assessed during the screening phase and the patient must sign the informed consent form (ICF) before any of the inclusion/exclusion criteria are assessed.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

1. Written informed consent and able to read (or if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member), understand, and willing to sign the ICF.
2. Men and women ≥50 years of age.
3. At treatment initiation, active macular neovascular lesions secondary to nAMD (Patients with polypoidal choroidal vasculopathy or retinal angiomatous proliferation are eligible to participate in the study, and their condition should be captured in the electronic case report form [eCRF]).
4. Treatment initiation with 3 × monthly IVT aflibercept injections (Weeks -16, -12, and -8 to planned study baseline visit) resulting in absence of any fluid at week -8.
5. ETDRS BCVA of at least 25 letters (20/320 Snellen equivalent) in the study eye at screening visit.
6. Willing, committed, and able to return for all clinic visits and complete all study-related procedures.
7. Able to use the provided monitoring device and willing to perform 5 × weekly self-assessments in the Investigator's opinion.

8. 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 ICF and 3 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, but are not limited to, (i) condoms (male or female) with or without a spermicidal agent; (ii) diaphragm or cervical cap with spermicide; (iii) intra-uterine device; (iv) hormone-based contraception. Patients must agree to utilize 2 reliable and acceptable methods of contraception simultaneously.

5.2 Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. Any contraindication to IVT anti-VEGF treatment or treatment with Eylea® as detailed in the Summary of Product Characteristics (SmPC).
2. Any prior ocular (in the study eye) or systemic treatment (including investigational agents) or surgery for nAMD, except the 3 × monthly IVT aflibercept injections required for treatment initiation and dietary supplements or vitamins.
3. Any presence of intraretinal and subretinal fluid at screening and baseline visit.
4. Any ocular or systemic condition expected to interfere with study outcomes and procedures, including but not limited to:
   - Scar, fibrosis or other lesions (e.g., retinal pigment epithelium [RPE] tears, macular hole stage 2 or above and others) involving the center of the macula in the study eye.
   - Clinically relevant opacities or conditions involving the optic media including cataract, corneal dystrophies or s.p. corneal transplant in the study eye.
   - Uncontrolled glaucoma (defined as IOP ≥25 mm Hg despite treatment with antiglaucoma medication) in the study eye or prior trabeculectomy or other filtration surgery in the study eye.
   - Intraocular surgery, periocular surgery, or cataract surgery within 90 days before Day 1 in the study eye, except the IVT aflibercept injections required for treatment initiation and any history of vitrectomy, retinal radiation therapy, retinal detachment or treatment or surgery for retinal detachment in the study eye.
   - Aphakia or pseudophakia with absence of posterior capsule (unless as a result of an yttrium aluminum garnet posterior capsulotomy) in the study eye.
5. Participation as a patient in any clinical study within 12 weeks before screening.
6. 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).
7. Previously screen failed patients for this study.

5.3 Lifestyle Considerations

No lifestyle restrictions are required during the study.

5.4 Screen Failures

A screen failure occurs when a patient consents to participate in the clinical study but is not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study patient according to the study protocol.

6.1 Study Intervention Administered

Table 6–1: Study Intervention

Intervention Label	Investigational Drug
Intervention Name	Aflibercept 2 mg
Type	Drug
Dose Formulation	Solution in Vial
Unit Dose Strength(s)	40 mg/mL
Dosage Level(s)	2 mg (50 µL)
Route of Administration	IVT injection
Use	Experimental regimen based on Customized regimen vs. standard T&E regimen
Packaging and Labeling	Study Intervention will be provided in sterile 2 mL glass vials. Each vial will be labeled as required per country requirement

IVT=intravitreal, OCT=optical coherence tomography, T&E=treat and extend.

Each vial is for single use only.

Table 6–2: Study Arms

Arm Title	**Customized treatment interval arm**	**T&E, 2-week adjustment arm**
Arm Type	Experimental	Active comparator
Arm Description	After the initial study injection at baseline, patients will receive their next study injection at Week 16. Patients in this study arm will also be issued a home monitoring device, which will allow for regular OCT monitoring (at least 5 times a week) at home.	Patients will receive treatment in intervals maintained (8 weeks) or adjusted in 2 weeks increments each time (up to a maximum of 16 weeks and minimum of 4 weeks), as long as all extension/shortening criteria are met.
Associated Intervention Labels	Investigational drug	

OCT=optical coherence tomography, T&E=treat and extend.

6.1.1 Medical Devices

Medical devices and diagnostic devices (Home OCT devices) used in this study include both devices that help prepare the study intervention (study drug), as well as devices that are used to gather additional clinical data and Home OCT device that is an observational tool for the patients only. The Home OCT system is a diagnostic device and Sponsor will need to report device incidents and deficiencies to the legal manufacturer according to the agreement. These devices are not Conformité Européene (CE) marked (or Food and Drug Administration [FDA] cleared) according to the regulatory requirements specific for the country where the study site is located.

The Sponsor will provide 2 devices to be used in the study:

- 18-gauge filter needle to be used in the preparation of the study medication.
- The Home OCT device that is an observational tool for the patients only. The Home OCT system is a diagnostic device.

The Home OCT device (digital drug development tool) used in the study is a patient self-operated tele-connected retinal OCT imaging device for automated data transmission and remote review of images and analytics results provided by the cloud-based artificial intelligence enabled OCT Analyzer (OA). The Home OCT uses a fixed, predefined grid of 88 B-scans to cover an area of 3 × 3mm (10 × 10 image field). The specifications of the spectral domain OCT contain a central wavelength of 830 nm, a scanning speed of 10,000 A-scans per second and 500 A-scans per B-scan.

Instructions for use of these devices are provided by the legal manufacturer of these devices. Deficiencies (including malfunctions, use error, and inadequate labeling) related to the filter needles and Home OCT device shall be documented and reported to the Sponsor by the Investigator throughout the clinical investigation (see Section 8.3.7) so they can be appropriately managed by the Sponsor.

6.2 Preparation, Handling, Storage, and Accountability

The Investigator or designee must maintain a log to confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only patients randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator or the head of the institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Investigator site file, if applicable.

The study intervention will be supplied in kits that include the following:

- Sterile study intervention in sealed glass vials (see Table 6–1)
- Filter needle (18-gauge)

Study intervention is to be stored in the refrigerator (2°C to 8°C) and must not be frozen. The vials must be kept in the outer carton to protect them from light. When study intervention is removed from the refrigerator, the solution should be inspected visually and it should have no evidence of turbidity. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Study drug can withstand brief exposures to temperatures up to 25°C, such as those that may occur during finishing, shipping, and handling, without compromising either the physical or chemical stability or the potency of the protein.

6.3 Measures to Minimize Bias: Randomization

Patients will be randomly assigned in a 1:1 ratio to 1 of 2 parallel treatment arms as described in Section 4.1. Randomization will be stratified based on BCVA gains from treatment initiation to study start (captured during screening), to ensure balanced distribution of the treatment arms within each stratum (i.e., <8 or ≥8 letters gain in BCVA).

Patients will be centrally assigned to randomized study intervention using an Interactive Response System (IXRS). The treatment allocation will be done according to a generated randomization list specified by the Sponsor or delegate. Before the study is initiated, the directions for the IXRS will be provided to each site.

Study intervention will be dispensed at the study visits summarized in the Schedule of Activities (SoA) (Section 1.3).

Returned study intervention should not be re-dispensed to the patients.

6.4 Study Intervention Compliance

Study intervention will be administered by a qualified ophthalmologist. Details of IVT aflibercept injection will be recorded in the eCRF (e.g., time of injection, type of anesthesia, treatment site).

6.5 Continued Access to Study Intervention after the End of the Study

Intervention will not be supplied after the end of the study. Patients will not be restricted with regard to pursuing available approved treatments for nAMD.

6.6 Treatment of Overdose

For this study, any dose of study intervention greater than 2 mg per injected eye will be considered an overdose.

Overdosing with increased injection volume may increase IOP. In these cases, evaluation of IOP and central retinal artery perfusion should be performed immediately after the injection and monitored until normalized. If there is severe elevation of IOP causing disruption of central retinal artery perfusion, immediate performance of an anterior segment paracentesis should be considered.

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Evaluate the patient to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities.

- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

6.7 Concomitant Therapy

6.7.1 Allowed and Prohibited Medications

For prohibited drugs and procedures prior to the study, including treatments in either the study eye or the fellow eye, see Section 5.2.

Patients may not receive any standard or investigational agents for treatment of their nAMD in the study eye other than IVT aflibercept as specified in this protocol until they have completed the end of study/early termination visit assessments. This includes medications administered locally (e.g., IVT, by juxtascleral or periorbital routes), as well as those administered systemically with the intent of treating the fellow eye.

Any medication considered necessary for the patient's welfare, and that is not expected to interfere with the evaluation of the study intervention, may be given at the discretion of the Investigator.

Any medication or vaccine (including any sedation, anesthesia, eye drops used for the study procedures, blood-derived products, prescription or over-the-counter medicines, probiotics, vitamins, and herbal supplements) that the patient receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.7.2 Fellow Eye Treatment

Only 1 eye per patient may be enrolled in the study. If a patient's fellow (non-study) eye requires anti-VEGF treatment during the patient's participation in the study, the fellow eye should be treated with aflibercept 2 mg according to the approved treatment regimen in the respective country, irrespective of the randomization assignment of the patient. The costs of aflibercept 2 mg used for treatment of the fellow eye will be supported by the Sponsor in compliance with local regulations. Although the fellow eye can receive treatment, it will not be considered an additional study eye. Patients who receive treatment for the fellow eye should remain in the study. Treatment of the fellow eye will be documented in the eCRF Concomitant Medication page. Safety for the fellow eye will be monitored; AEs/SAEs will be reported in the eCRF. Once the fellow eye receives aflibercept 2 mg therapy during the study, AEs will be assessed as related/not related to "aflibercept 2 mg (fellow eye)" in addition to being assessed as related/not related to the study drug delivered to the study eye (aflibercept 2 mg), IVT aflibercept injection-procedure, and other protocol-specified procedures.

7. Discontinuation of Study Intervention and Patient Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Study intervention discontinuation can be triggered by the patient (or legally authorized representative) or by the treating Investigator.

Patients for whom study intervention is planned at any time during the study but not administrated will be considered to have temporarily discontinued study intervention. If study intervention is temporarily discontinued, it can be restarted at any time during the study but not later than 16 weeks.

In rare instances, it may be necessary for a patient to permanently discontinue study intervention. If study intervention is permanently discontinued, the patient will remain in the study to be evaluated for safety evaluation up to 30 days after the last study intervention. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.2 Patient Discontinuation/Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

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

- Relevant laboratory abnormality or SAEs, if the Sponsor or Investigator sees this as medical reason to warrant withdrawal.
- AE (ocular or non-ocular) that, from the patient's or the Investigator's view, is potent enough to require withdrawal from the study. The Investigator must notify the Sponsor immediately if a patient is withdrawn because of an AE/SAE.
- At the discretion of the treating Investigator. The development of conditions, which would have prevented a patient's entry into the study according to the selection criteria, is no reason per se for withdrawal. However, the withdrawal in such cases remains at the discretion of the treating Investigator.
- Decision by the Investigator or the Sponsor that termination is in the patient's best medical interest or administrative decision for a reason other than an AE/SAE.
- A female patient becomes pregnant. Refer to Section 8.3.5.
- Lost to follow-up. Refer to Section 7.3.
- Decision by the Sponsor to halt the entire study.

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

- Any treatment for nAMD other than study interventions in the study eye is considered a prohibited treatment, and patient must be withdrawn from the study.
- Systemic anti-angiogenic agents were taken by the patient during the study.
- If, in the Investigator's opinion, continuation of the study would be harmful to the patient's well-being.

- At the specific request of the Sponsor and in liaison with the Investigator (e.g., obvious noncompliance or safety concerns).

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The patient will be permanently discontinued from the study intervention and the study at that time.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Patients who withdraw from the study will not be replaced.

7.3 Lost to Follow-Up

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule, and ascertain whether the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls, and if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed. Patients should be seen for all visits on the designated day, with an allowed "visit window" as indicated in the SoA. Any unscheduled visits (e.g., for safety follow-up) must be documented in the eCRF.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

8.1 Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

8.1.1 Ophthalmic and General Examinations

Note: In this section, all ophthalmic examinations are described, irrespective of whether they are used for efficacy or safety assessments.

Ophthalmic evaluations will be conducted according to the SoA (Section 1.3).

All ophthalmic examinations are to be conducted pre-injection in both eyes and post-injection in the study eye only, unless indicated otherwise.

At any visit, ophthalmic examinations not stipulated by this protocol may take place outside of this protocol at the discretion of the Investigator.

8.1.1.1 Best Corrected Visual Acuity

Visual function will be assessed using the ETDRS protocol (Early Treatment Diabetic Retinopathy Study Research Group. 1985) starting at 4 meters. Refraction is to be done at each visit.

Visual acuity examiners must be certified to ensure consistent measurement of BCVA. Any certified and trained study personnel may perform this assessment (including but not limited to ophthalmologist, optometrist, or technician). For each patient, the same examiner should perform all assessments whenever possible. BCVA should be done before any other ocular procedures are performed.

8.1.1.2 Spectral Domain Optical Coherence Tomography

Retinal and lesion characteristics will be evaluated using SD-OCT. For all visits where the SD-OCT procedure is scheduled, images will be captured and read by the technician and Investigator for individual treatment decisions and sent to an independent reading center where images will be read by readers. The patients' eligibility to take part in the study in terms of SD-OCT will be reconfirmed by the central reading center. The same SD-OCT imaging system used at screening and Day 1 must be used at all follow-up visits in each patient. Images will be taken in both eyes before dosing (active injection). All SD-OCTs will be archived electronically by the study sites as part of the source documentation. The study manual will further specify the acquisition and assessment for OCT during the study.

8.1.1.3 Optical Coherence Tomography Angiography

OCT-A will be performed at sites with the relevant equipment.

The same imaging modality used at screening must be used at all follow-up visits in each patient. Images will be taken in both eyes before dosing (active injection) if applicable.

All OCT-As will be archived electronically by the study sites as part of the source documentation. The study manual will further specify the acquisition and assessment for OCT-A during the study.

8.1.1.4 Indirect Ophthalmoscopy

Indirect ophthalmoscopy will be performed according to local medical practice and applicable medical standards at the site.

Patient' posterior pole and peripheral retina will be examined by indirect ophthalmoscopy or equivalent investigation at each study visit pre-dose (bilateral) by the Investigator and post-dose (study eye) by the Investigator. Post-dose evaluation must be performed immediately after injection.

8.1.1.5 Slit Lamp Biomicroscopy

The slit lamp biomicroscopy will be performed according to local medical practice and applicable medical standards at the site.

Patients' anterior eye structure and ocular adnexa will be examined bilaterally (pre-dose on visits with active injection) at each study visit using a slit lamp by the Investigator.

8.1.1.6 Intraocular Pressure

IOP will be measured using a calibrated Goldman applanation tonometry, rebound tonometry Icare, or Tonopen and the same method of measurement must be used in each patient throughout the study.

At all visits, IOP should be measured bilaterally by the Investigator (or designee). On days when study intervention is administered, IOP should also be measured approximately 30 minutes after administration of study intervention (study eye only) by the Investigator (or designee).

If multiple post-injection measurements are performed, the final measurement before the patient leaves should be documented in the eCRF. Any injection-related clinically significant increase in IOP should be reported as AE and documented in electronic data capture (EDC) system.

8.1.2 Home OCT User Questionnaire

Patient user experience with Home OCT device will be assessed with the device vendor questionnaire (only applicable for patients in customized treatment interval arm).

8.2 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations

A routine physical examination will assess cardiovascular, respiratory, gastrointestinal, and neurological systems and will follow the standard practice of the site. Body weight, height, and body mass index (BMI) should be measured at Visit 1 (screening). The assessment will be based on the clinical judgment of the Investigator and aim to evaluate the overall health of the patient.

8.2.2 Vital Signs

Temperature, heart rate, and blood pressure will be measured according to the local medical practice and regulations.

Vital signs should be measured pre-injection, if applicable, per the procedure outlined in the study manual.

Clinically significant abnormal findings will be reported as AEs in the eCRF.

8.2.3 Pregnancy Testing

For women of childbearing potential (WOCBP), a negative urine pregnancy test at screening is required for eligibility. A negative urine pregnancy test is required before any treatment (including rescue regimen) is administered at subsequent visits in either the study eye or the fellow eye (see the SoA in Section 1.3). Pregnancy testing is not required for women not considered WOCBP. Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.

Pregnancy test results will be recorded in the eCRF.

8.3 Adverse Events, Serious Adverse Events and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.2.

The definitions of device-related safety events can be found in Section 10.4. Device deficiencies are covered in Section 8.3.7.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the patient to discontinue the study intervention or the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.2.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

(S)AEs will be collected from signing of the ICF until the last follow-up visit at the timepoints specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of learning of the event, as indicated in Section 10.2. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the

event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.2.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and Investigators.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

For all studies except those using medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.3.5 Pregnancy

Details of all pregnancies in female patients and, if indicated, female partners of male patient will be collected after the start of study intervention and until 90 days after the last dose of study intervention.

If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, and will be reported as such.

The patient/pregnant female patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient/pregnant female patient and the neonate and the information will be forwarded to the Sponsor.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study patient/pregnant female patient, he or she may learn of an SAE through spontaneous reporting.

Any female patient who becomes pregnant while participating in the study may be requested to discontinue the study intervention.

8.3.6 Adverse Events of Special Interest

No AEs of special interest are defined.

8.3.7 Medical Device Deficiencies

Medical devices are being provided for use in this study as the study intervention. To fulfill regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.4.

Device deficiencies only should be reported to the Sponsor, by completing the product technical complaints (PTC) form and submitting it to the Sponsor via the email address (ptc-imp@bayer.com) given to the site.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section 10.2 of the protocol.

8.3.7.1 Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies that result in an incident will be detected, documented, and reported to the Sponsor during all periods of the study in which the medical device is used.

If the Investigator learns of any device deficiency at any time after a patient has been discharged from the study, and such deficiency is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify the Sponsor.

The method of documenting medical device deficiencies is provided in Section 10.4.

8.3.7.2 Follow-up of Medical Device Deficiencies

Follow-up applies to all patients, including those who discontinue study intervention.

The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

8.3.7.3 Prompt Reporting of Device Deficiencies to the Sponsor

Device deficiencies will be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the protocol definition of a medical device deficiency.

The Medical Device Deficiency Report Form will be sent to the Sponsor by emailing the completed product technical complaint form (see Section 8.3.7). If email is unavailable, then fax should be utilized.

The Sponsor will be the contact for the receipt of device deficiency reports.

8.3.7.4 Regulatory Reporting Requirements for Device Deficiencies

The Investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the Sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The Investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.4 Pharmacokinetics

Pharmacokinetic(s) (PK) parameters are not evaluated in this study.

8.5 Genetics and/or Pharmacogenomics

Genetics are not evaluated in this study.

8.6 Biomarkers

Biomarkers are not evaluated in this study.

8.7 Immunogenicity Assessments

Not applicable.

8.8 Health Economics OR Medical Resource Utilization and Health Economics

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

The statistical analysis plan (SAP) will be finalized prior to first patient first visit and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoint.

9.1 Statistical Hypotheses

The test problem in relation to the primary objective and/or estimand, see Section 3, is described below. The hypothesis testing for the primary estimand will be conducted at one-sided significance level of 2.5%.

One-sided test problem (related to primary estimand):

Null hypothesis H_0: $\mu_1 \leq \mu_2 - D$ vs. alternative hypothesis H_1: $\mu_1 > \mu_2 - D$, where

- D = non-inferiority margin.
- μ_i = absolute mean change in BCVA as measured by the ETDRS letter score for the study eye from baseline to Week 36 in treatment arm i.
- i = 1: customized treatment interval arm; 2: standard T&E 2-week adjustment arm.

Note that a higher ETDRS letter score represents better vision. The aim is to show that the customized treatment interval arm is no less effective than the standard T&E 2-week adjustment arm, using a non-inferiority margin of 5 letters for the difference of the means of change from baseline in BCVA as measured by the ETDRS letter score for the study eye at Week 36.

The non-inferiority margin D is set to 5 letters and the rationale is that previous studies with anti-VEGF therapies in other indications regarded a difference of 5 letters as clinically relevant. The threshold of 5 letters has a clinical relevance and a direct meaning for the patients in terms of ETDRS chart, given that 5 letters are equal to 1 line in the chart. This choice of the non-inferiority margin is consistent with the margin used in the ARIES study.

Analyses on the key secondary and other secondary objectives/estimands will be conducted in an exploratory way and therefore no formal statistical hypothesis testing is planned.

9.1.1 Multiplicity Adjustment

The multiplicity control is not relevant for the study, given that:

- There is only one test problem in relation to the primary objective to compare the 2 study arms (i.e., customized treatment interval arm vs. standard T&E 2-week adjustment arm)
- The analyses on the key secondary and other secondary objectives will be conducted in an exploratory way.

9.2 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

- The full analysis set (FAS) includes all randomized patients who receive any study treatment injection, excluding treatment initiation prior to screening, and have a baseline and at least one post-baseline BCVA assessment. The FAS will be analyzed "as randomized".
- The safety analysis set (SAF) includes all patients who receive any study treatment injection, excluding treatment initiation prior to screening. The SAF will be analyzed "as treated".

The FAS is used to analyze endpoints related to the efficacy objectives and the SAF is used to analyze the endpoints and assessments related to safety.

9.3 Statistical Analyses

9.3.1 General Considerations

Descriptive Statistics

All variables will be analyzed descriptively with appropriate statistical methods; continuous variables will be summarized by descriptive statistics (number of patients, mean, standard deviation [STD], minimum, median and maximum) and categorical variables will be summarized by frequency tables (absolute and relative frequencies).

Baseline Definition

For efficacy endpoints, the last observed assessment prior to randomization will be considered the baseline assessment, unless otherwise specified.

For safety endpoints, the last observed assessment prior to the first injection of study treatment will be considered the baseline assessment, unless otherwise specified.

Stratification Factors

A stratification by visual outcomes at screening is planned, to ensure equal allocation of subgroups, thereby making it easier to interpret the results. Visual outcomes will be determined at the screening visit, depending on whether the patients reached <8 or ≥ 8 letters gain in BCVA relative to aflibercept initiation prior to study enrollment (i.e., treatment initiation at 16 weeks before baseline).

Missing Data Handling

In general, data will not be imputed for the safety analysis.

See the Sections 9.3.2 and 9.3.3 for the data imputations for the efficacy analyses.

Unscheduled Assessments

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.

Statistical Software

Statistical analysis will be performed using statistical analysis software; the version used will be specified in the SAP.

9.3.2 Primary Endpoint/Estimand Analysis

The estimand of primary interest will be based on a hypothetical strategy.

It describes the change in BCVA from baseline for all patients that started treatment assuming all patients have stayed on treatment until Week 36.

The estimand is specified through the following definitions of population, variable, treatment condition, intercurrent events, and population-level summary:

Population:	Target population defined by the inclusion/exclusion criteria (see Section 5).
Variable:	Absolute change from baseline to Week 36 in BCVA as measured by the ETDRS letter score for the study eye.
Treatment condition:	Aflibercept customized treatment interval arm vs. aflibercept standard T&E 2-week adjustment arm.
Intercurrent events:	Premature discontinuation from treatment/study. Start of alternative anti-VEGF treatment, prior to treatment and/or study discontinuation. Shortening/extension of the dosing interval will not be considered an intercurrent event, but as part of the randomized treatment regimen. Further intercurrent events might be specified in the SAP.
Population-level summary:	Difference in mean change from baseline to Week 36 in BCVA between the customized treatment interval arm and standard T&E 2-week adjustment arm.

The primary statistical analysis will be performed on the FAS by randomized treatment arm.

The methodological approach will be the calculation of two-sided 95% confidence interval (CI) for the difference in the least squares means (customized treatment interval arm - standard T&E 2-week adjustment arm) of the change in ETDRS letter score from baseline to Week 36 based on a mixed-effect model repeated measure (MMRM) analysis making use of all observed BCVA data from baseline up to Week 36 (including censoring for alternative anti-VEGF). The MMRM will include the fixed categorical effects of treatment, visit,

treatment-by-visit interaction and stratification variable; the fixed continuous covariate of baseline BCVA score; and visit as a repeated measure. Restricted maximum likelihood estimation will be used. An unstructured covariance matrix will be used to model the within-patient error and the Kenward-Roger approximation will be used to estimate the degrees of freedom. Further details (e.g., non-convergence of the model, handling of missing data) will be provided in the SAP.

The customized treatment interval arm will be considered to be non-inferior to the standard T&E 2-week adjustment arm if this analysis is statistically significant, i.e., if the CI of the difference lies entirely above -5 letters, where a positive difference favors the customized treatment interval arm.

The sensitivity analysis of the primary efficacy endpoint will be based on a "while on treatment" strategy.

It describes the change from baseline for all patients that started treatment until the timepoint when they discontinued treatment or had an intercurrent event with a major impact on the applied treatment regimen.

The following sensitivity analyses will be performed:

- Analysis of covariance (ANCOVA) with last observation carried forward (LOCF)
  Analysis of covariance with the BCVA measure at baseline as a covariate, and the treatment arm and the stratification variable as fixed factors.
  Missing data will be imputed using LOCF method. Observed values from both scheduled and unscheduled post-baseline visits will be used for the LOCF imputation. For patients who discontinue treatment but continue in the study and start an alternative anti-VEGF treatment, the efficacy data will be censored at the time the patient started alternative anti-VEGF treatment in the study eye. Missing data will be imputed by the last observation prior to receiving alternative anti-VEGF treatment.
- Complete case analysis
  The same main methodology will be applied but with no imputation of missing data. Patients with missing BCVA assessment at Week 36 will be excluded from the analysis.

9.3.3 Secondary Endpoints/Estimands Analysis

The estimand of key secondary interest will be based on a "while on treatment" strategy.

It describes the number of injections per patient up to study Week 52, for all patients that started treatment until the timepoint when they discontinued treatment or had an intercurrent event with a major impact on the applied treatment regimen.

The estimand is specified through the following definitions of population, variable, treatment condition, intercurrent events, and population-level summary:

Population:	Target population defined by the inclusion/exclusion criteria (see Section 5).
Variable:	Number of IVT aflibercept injections in the study eye per patient in the time frame from baseline to Week 52.
Treatment condition:	Aflibercept customized treatment interval arm vs. aflibercept standard T&E 2-week adjustment arm.

Intercurrent events:	Premature discontinuation from treatment/study. Start of alternative anti-VEGF treatment, prior to treatment and/or study discontinuation. Shortening/extension of the dosing interval will not be considered an intercurrent event, but as part of the randomized treatment regimen. Further intercurrent events might be specified in the SAP.
Population-level summary:	Difference in mean number of injections per patient in the time frame from baseline to Week 52 between the customized treatment interval arm and T&E 2-week adjustment arm.

The secondary statistical analysis will be performed on the FAS by randomized treatment arm, in a descriptive manner, by means of an analysis of covariance with the treatment arm and the stratification variable as fixed factors.

The treatment difference in the mean number of injections per patient (customized treatment interval arm vs. standard T&E 2-week adjustment arm) and its two-sided 95% CI will be estimated, as a reference.

No imputation of missing data will be performed, therefore the actual/observed number of injections per patients from baseline to Week 52 will be analyzed.

The following sensitivity analysis will be performed:

- Complete case analysis
  The same methodology will be applied but considering only data of patients who stay on treatment until Week 52. Patients who prematurely discontinue from treatment/study or who start an alternative anti-VEGF treatment, prior to treatment and/or study discontinuation or completion will be excluded from the analysis.

Analyses on the other secondary efficacy endpoints will be conducted on the FAS, by randomized treatment arm, as defined in Sections 9.2 and 9.3.1 in a descriptive manner adjusting for the stratification factors. This may include 95% CIs for treatment differences in an exploratory way.

The other secondary efficacy endpoints are:

- Mean number of IVT aflibercept injections in the study eye per patient until study Week 36.
- Proportion of patients achieving pre-defined treatment intervals (≥4, ≥8, ≥10, ≥12, ≥14, and 16 weeks) at Weeks 36 and 52.
- Mean change in BCVA [ETDRS letters score in the study eye] from baseline to Week 52.

For the mean number of IVT aflibercept injections, the same analysis as per the secondary estimand (i.e., ANCOVA analysis) will be conducted.

For the proportion of patients achieving pre-defined treatment intervals, the difference between the proportions (customized treatment interval arm - standard T&E 2-week adjustment arm) will be analyzed by means of a logistic regression with the treatment arm and the stratification variables as fixed factors.

For the mean change in BCVA, the same analysis as per the primary estimand will be conducted.

Further details will be provided in the SAP.

9.3.4 Exploratory Endpoint(s) Analysis

Analyses on exploratory variables will be conducted on the FAS, by randomized treatment arm, as defined in Sections 9.2 and 9.3.1 in a descriptive manner. This includes 95% CIs for treatment differences in an exploratory way.

The exploratory endpoints are:

For both treatment arms:

- Change in central subfield retinal thickness (CST) [µm] from baseline to Weeks 36 and 52 in the study eye.
- Change in CST compared to treatment initiation (i.e., 16 weeks before baseline) at Weeks 36 and 52 in the study eye.
- Proportion of patients without any fluid/ without intraretinal fluid (IRF)/subretinal fluid (SRF) nor sub-retinal pigment epithelium (sub-RPE) fluid at treatment-initiation (i.e., 16 weeks before baseline), baseline, Weeks 36 and 52 in the study eye.

For the customized treatment interval arm only:

- Change in retinal fluid volume and in volume by compartment (IRF and SRF) in the study eye.
- Area under the curve (AUC) of fluid volumes in the study eye.
- Agreement of home monitoring findings with SD-OCT in-office monitoring performed at the closest time prior to the office visit.

For both treatment arms:

- Change in CNV size using OCT-A (optional for center) in the study eye at study visits.
- Number of patients with newly developed CNV in fellow eye in OCT-A at Weeks 36 and 52 in eyes with dry AMD signs at baseline.

For the customized treatment interval arm only:

- Number of patients for agreement levels 1 to 5 assessed at Week 36.

Further details will be provided in the SAP.

9.3.5 Safety Analysis

The safety variables are defined in Sections 9.2 and 9.3.

The safety analysis will be conducted in the SAF by actual treatment arm.

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

Treatment-emergent ocular AEs will be presented by Medical Dictionary for Regulatory Activities (MedDRA) preferred term within the primary system organ class and summarized by actual treatment arm for the study eye and the fellow eye separately. Treatment-emergent nonocular AEs will be also summarized. Intensity and causal relationship to the study drug/IVT injection will be analyzed descriptively. SAEs including narratives will be documented separately.

Other safety variables (e.g., slit lamp assessments, indirect ophthalmoscopy assessments, IOP measurements and vital signs) will be analyzed descriptively including changes from baseline.

9.3.6 Other Analysis

Analysis of other variables and/or parameters and subgroup analyses will be further detailed in the SAP.

9.4 Interim Analysis

No formal statistical interim analysis is planned. The primary endpoint/estimand will be analyzed and the summaries up to Week 36 will be provided when all patients have completed Week 36 (or withdrew). The analysis will only use data collected up to Week 36 or premature discontinuation, whichever occurs first. No decisions on the outcome and/or study will be made (e.g., terminating the study or changing the design). Therefore, no α-adjustment seems to be necessary.

All the secondary and exploratory endpoints/estimands will be analyzed and the summaries up to Week 52 will be provided when all patients have completed the study (i.e., completed Week 52 or prematurely withdrew, whichever occurs first). The analysis will use all data collected.

9.5 Sample Size Determination

In ARIES study, patients which were dry (as no IRF and no SRF) at Weeks 8 and 16 in the early T&E arm (N=59) had a mean BCVA change of -0.5 letters from Week 16 to Week 52 with a STD of 6.6

In ALTAIR study, patients which were dry (as no IRF and no SRF) at Weeks 8 and 16 in the 2-week adjustment arm (N=55) had a mean BCVA change of -0.7 letters from Week 16 to Week 52 with a STD of 7.2 and the 4-week adjustment arm (N=61) had a mean BCVA change of -0.5 letters from Week 16 to Week 52 with a STD of 6.1.

Under the assumptions that:

- The customized treatment interval arm is similar to the 4-week adjustment arm from ALTAIR study (i.e., N=61 with a mean BCVA change of -0.5 letters from Week 16 to Week 52 with a STD of 6.1).
- The standard T&E 2-week adjustment arm is similar to the 2-week adjustment arm from ALTAIR study (i.e. N=55 with a mean BCVA change of -0.7 letters from Week 16 to Week 52 with a STD of 7.2).
- There is no true difference in mean BCVA change from baseline to Week 36 between both arms (which would be equal to the change from Week 16 to Week 52 in ALTAIR and ARIES studies).
- Both arms will have standard deviation of 7 for the mean change in BCVA from baseline to Week 36.

A sample size of N=86 patients in total would be needed to show a non-inferiority of customized treatment interval arm compared to the standard T&E 2-week adjustment arm, using a non-inferiority margin of 5 letters, for the difference of the means change from baseline in BCVA at Week 36, achieving a power of 90% using a one-sided test with a significance level α of 2.5%. Assuming an expected dropout rate of 20%, a sample size of approximately N=108 patients in total (54 patients per arm) will be randomized.

The sample size was calculated using NCSS PASS 13 “Non-Inferiority Tests for Two Means using Differences”.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
- Applicable local laws and regulations

The protocol, protocol amendments, ICF, Investigator's brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH GCP and national and international regulations.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the patients or their legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations (CFR) 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patients or their legally authorized representative.

10.1.4 Data Protection

Patients will be assigned a unique identifier by the Sponsor. Any patient records, datasets or biological samples that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees Structure

Steering Committee

A Steering Committee will be established to guide the study in all aspects of safety and efficacy and must ensure that all relevant information is provided by Investigators. The composition of the committee, the functional roles, and responsibilities will be specified in its charter.

10.1.6 Dissemination of Clinical Study Data

Result Summaries of Bayer's Sponsored clinical studies in drug development Phases 2, 3, and 4 and Phase 1 studies in patients are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition results of clinical drug studies will be provided on the publicly funded website ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical study data, study-level clinical study data, and protocols from clinical studies in patients for medicines and indications approved in the US and EU on or after January 01, 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical studies are considered for publication in the scientific literature irrespective of whether the results of the clinical studies are positive or negative.

10.1.7 Data Quality Assurance

All patient data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

Guidance on completion of case report forms (CRFs) will be provided in eCRF Completion Instructions.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site and in computer systems used by the remote monitoring service provider in case of Home OCT data.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Source Data Location List (SDLL) or equivalent.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Sponsor will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of patients.

The first act of recruitment is the first patient screened and will be the study start date.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of patients by the Investigator
- Total number of patients included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

10.1.10 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study patient, associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose, meets the one or more of the criteria listed:

a. Results in death

b. Is life-threatening

- The term life-threatening in the definition of serious refers to an event in which the patient 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

- In general, hospitalization signifies that the patient has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.2.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is not acceptable for the Investigator to send photocopies of the patient's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:
  - Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
  - Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.2.4 Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data transmission (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.
- Contacts for SAE reporting can be found in the safety reporting gateway.

SAE Reporting to via Paper Data Collection Tool

- Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Medical Monitor.
- In rare circumstances and if email transmission is not feasible, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in the Investigator site file.

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

10.3.1 Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are considered WOCBP (fertile)

1. Following menarche
2. From the time of menarche until becoming premenopausal unless permanently sterile (see below):
   - A post-menopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
     - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.
   - Permanent sterilization methods (for the purpose of this study) include:
     - Documented hysterectomy
     - Documented bilateral salpingectomy
     - Documented bilateral oophorectomy
     - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the patient's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

10.3.2 Collection of Pregnancy Information:

Male Patients With Partners Who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive study intervention.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be at least 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Patients Who Become Pregnant

- Any female patient who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.
- The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a patient's pregnancy.
- The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will be required for at least 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
  - While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
  - A spontaneous abortion (occurring at 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.5. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

10.4 Appendix 4: Adverse Events, Serious Adverse Events, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).

Both the Investigator and the Sponsor will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all Sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of Sponsor medical devices.

10.4.1 Definition of Medical Device AE

Medical Device AE Definition
• A medical device AE is any untoward medical occurrence in a clinical study patient, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the medical device (digital drug development tool). An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an medical device. This definition includes events related to the medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to devices.

10.4.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A Medical Device SAE is any SAE that:
a. Led to death
b. Led to serious deterioration in the health of the patient, that either resulted in: • A life-threatening illness or injury. The term ‘life-threatening' in the definition of serious' refers to an event in which the patient 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. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization, planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. • Chronic disease (MDR 2017/745).
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
d. Is a suspected transmission of any infectious agent via a medicinal product

10.4.3 Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

10.4.4 Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE, and Device Deficiency Recording
• When an AE/SAE/device deficiency occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE/device deficiency information in the patient’s medical records, in accordance with the Investigator’s normal clinical practice and on the appropriate form.

- It is not acceptable for the Investigator to send photocopies of the patient's medical records to the Sponsor in lieu of completion of the AE/SAE/medical device incident page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the Investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.

A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.
For PTC that are not related to an AE or SAE, a PTC form should be completed and reported to the Sponsor electronically or via the email address (ptc-imp@bayer.com).
For device deficiencies that caused an AE or SAE, complete the AE CRF and MDI CRF.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency. The Investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB in his/her assessment.

- For each AE/SAE/device deficiency, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/device Deficiency

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.4.5 Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has

been taken off-line, then the site can report this information on a paper SAE form (see next table) or to the Medical Monitor by telephone.

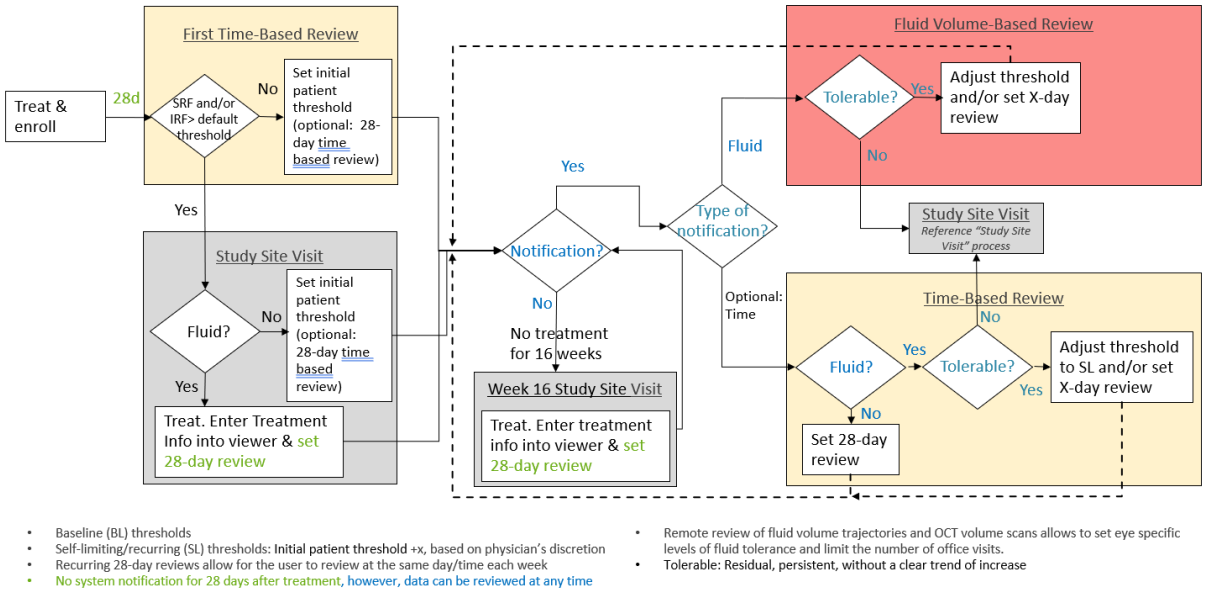
- Contacts for SAE reporting can be found in safety reporting gateway.

SAE Reporting to via Paper Data Collection Tool

- Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator site file.

10.5 Appendix 5: Customized Treatment Interval Arm Monitoring Flow

Figure 10-1: Home-OCT monitoring flow of customized Treatment Interval Arm



- Baseline (BL) thresholds
- Self-limiting/recurring (SL) thresholds: Initial patient threshold +x, based on physician's discretion
- Recurring 28-day reviews allow for the user to review at the same day/time each week
- No system notification for 28 days after treatment, however, data can be reviewed at any time
- Remote review of fluid volume trajectories and OCT volume scans allows to set eye specific levels of fluid tolerance and limit the number of office visits.
- Tolerable: Residual, persistent, without a clear trend of increase

IRF=intraretinal fluid, OCT=optical coherence tomography, SL=self-limiting, SRF= subretinal fluid

10.6 Appendix 6: Patient Training for Use of Home OCT and Monitoring of Home OCT Images

Patient Training for Use of Home OCT

- The study site will introduce the Home OCT to the patient through the Informed Consent Form and patient brochure.
- The device vendor will schedule a call prior to Home OCT device delivery to review self-imaging instructions and self-imaging frequency requirements.
- The patient will use the Home OCT's setup material to install the device in their home.
- The device vendor will provide confirmation to the patient of first Home OCT image transmission to the device vendor Health Cloud success.
- The device vendor will call patient if no transmission is received within one business day from Home OCT device delivery.
- The device vendor will perform scheduled patient engagement calls following start of home self-imaging following two (2) weeks followed by monthly for the duration of the home monitoring period.
- The device vendor will perform compliance calls to patient following a gap of 2 days in self-imaging, with a call on the next business day.

Monitoring of Home OCT images

Bayer, the device vendor, and the Principal Investigators have access to patient scan data through the cloud-based Home OCT Web Viewer. Bayer will not have access to the patient's name or other identifiable information in the viewer. After logging in, physicians can select a patient's data to review by querying patient identifiers or by scrolling through a patient or notification list.

After selecting a patient or notification, the physician will see data similar to other OCT device outputs such as: patient specific Home OCTID, eye selected, and chronological volume scans.

In the viewer tabs utilizing the OCT analyzer platform, the fluid volume information from self-imaging is presented to the physician in trajectories of IRF, SRF, and total retinal fluid (TRF) volume over the monitoring period. Also available are visualization of the original B-scans, B-scans with fluid segmentation and fluid thickness maps. In addition to the broad view of the trajectories, the fluid thickness maps guide the physician to review B-scans where fluid is present and to visualize morphology in a time efficient manner. This information allows the user to identify the fluid status and trends of increase, stability and decrease in volume (IRF/SRF) between office visits.

The physician can choose to set a periodic review of the fluid trajectory as it evolves over time. The physician should use a simple interface available on-line to request a notification upon SRF/IRF/TRF reaching a certain fluid volume threshold specific to that eye. The notification criteria are defined by the physician based on their clinical judgement on when a review of the trajectory and related B-scan data to support their decision-making process is warranted.

10.7 Appendix 7: Abbreviations

Abbreviation	Description
ADL	activities of daily living
AE	adverse event
AI	artificial intelligence
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
BCVA	best-corrected visual acuity
BMI	body mass index
CCDS	Company Core Data Sheet
CNV	choroidal neovascularization
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
CST	central subfield retinal thickness
eCRF	electronic case report form
ETDRS	early treatment diabetic retinopathy study
EU	European Union
FAS	full analysis set
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IOP	intraocular pressure
IRB	Institutional Review Board
IRF	intraretinal fluid
IVT	intravitreal
IXRS	Interactive Response System
LOCF	last observation carried forward
LPLV	last patient last visit
MDR	Medical Device Regulation
MMRM	mixed-effect model repeated measure
nAMD	neovascular (wet) age-related macular degeneration
OA	OCT Analyzer
OCT	optical coherence tomography
OCT-A	optical coherence tomography angiography
PIGF	placental growth factor
PRO	patient-reported outcome
PTC	product technical complaints
RPE	retinal pigment epithelium
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD-OCT	spectral domain optical coherence tomography
SoA	schedule of activities
SRF	subretinal fluid
STD	Standard deviation
Sub-RPE	Sub-retinal pigment epithelium
T&E	treat and extend
TEAE	treatment-emergent adverse events
TRF	total retinal fluid

Abbreviation	Description
US	United States
VEGF	vascular endothelial growth factor
WOCBP	woman (women) of childbearing potential

11. References

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