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Title Page

Protocol Title: Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of High Dose Aflibercept in Patients With Neovascular Age-Related Macular Degeneration

Protocol Number:	20968
Protocol Version:	5.0
Amendment Number:	4
Compound Number:	BAY 86-5321 / aflibercept
Short Title:	Efficacy and Safety of High Dose Aflibercept in Patients With Neovascular Age-Related Macular Degeneration (nAMD)
Study Phase:	3
Acronym:	PULSAR
Sponsor Name:	Bayer AG

Legal Registered Address:

Bayer AG, 51368 Leverkusen, Germany

Regulatory Agency Identifier Numbers:

Investigational New Drug (IND): 12462 (Regeneron Pharmaceuticals, Inc.)

European Clinical Trials Database (EudraCT): 2019-003851-12

Protocol Date: 27-February-2023

Name: PPD Role: PPD

This is an electronically generated document that does not bear any sponsor signatures. The signature of the sponsor's medically responsible person is filed in the TMF and available on request.

Medical Monitor name and contact information will be provided separately.

Document History Table

DOCUMENT HISTORY			
Document	**Version**	**Date**	**Comments (if applicable)**
Amendment 4	5.0	27 FEB 2023	-
Amendment 3	4.0	13 SEP 2022	Version approved by health authorities and used in the study
Amendment 2	3.0	26 APR 2022	Version approved by health authorities and used in the study
JPN-1		06 MAY 2021	-
FRA-2		11 MAR 2021	-
SS-1		23 FEB 2021	-
FRA-1	-	17 SEP 2020	-
DEU-1	-	03 AUG 2020	-
USA-1	-	12 MAY 2020	-
Amendment 1	2.0	14 FEB 2020	Version approved by health authorities and used in the study
Clinical Study Protocol	1.0	09 DEC 2019	-

Protocol Amendment Summary of Changes Table

Amendment 4 (27 FEB 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to align with the proposed HD labeling update which CCI the time contraception is needed after the last study drug dose, based on the following: the recommended duration of contraception following the last intravitreal dose CCI from 3 months for 2 mg aflibercept to CCI for HD aflibercept. The 3 month duration of contraception for the 2-mg dose was based on the time required for all subjects to reach the lower limit of quantitation (LLOQ) of free aflibercept in plasma CCI, plus a CCI For HD aflibercept, the population PK model-predicted time for 99% of subjects to reach the LLOQ of free aflibercept in plasma is CCI. Applying the CCI utilized for 2-mg aflibercept, the recommended duration of contraception for HD aflibercept is CCI.

In addition, the amendment clarifies that exploratory analyses may be performed before Week 96 (but after the completion of the confirmatory analyses at Week 48 and Week 60) as necessary to, e.g. to address health authority requests and queries, as well as to perform editorial corrections.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA) Table 1-3	Removed Study extension FBR ICF	Not necessary in the Extension Period
	Added footnote when Study extension ICF can be signed.	To clarify that the ICF can be signed before the Extension Period starts
	Updated footnotes to clarify visit schedule deviations and when DRM or E-DRM is used.	To prevent ambiguity in the wording
4.1 Overall Design	Clarification added that additional exploratory analyses may be performed before Week 96 (but after the completion of the confirmatory analyses at Week 48 and Week 60) as necessary.	To be able to address potential health authority requests and queries
	Existing wording regarding exploratory analyses during the extension phase updated.	To harmonize with existing wording in section 9.5.
5.1 Inclusion Criteria	Contraceptive use CCI from 3 months to CCI	To update the recommendation of duration of contraceptive use to align with most recent pharmacokinetic data

Section # and Name	Description of Change	Brief Rationale
6.6.3 Year 3 (Masked Transition Period and Open-label Extension Part): Week 96 to Week 156 (End of Study) / E-DRM Criteria	Added clarifying language.	To provide detail on E-DRM Criteria
9.5 Interim Analyses	Clarification added that additional exploratory analyses may be performed before Week 96 (but after the completion of the confirmatory analyses at Week 48 and Week 60) as necessary.	To be able to address potential health authority requests and queries

DRM=dose regimen modification, E-DRM=dose regimen modification criteria for extension period, FBR=future biomedical research, ICF=informed consent form

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1. Protocol Summary

1.1 Synopsis

Protocol Title: Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of High Dose Aflibercept in Patients With Neovascular Age-Related Macular Degeneration

Short Title: Efficacy and Safety of High Dose Aflibercept in Patients With Neovascular Age-Related Macular Degeneration (nAMD)

Regulatory Agency Identifier Numbers:

Investigational New Drug (IND):	12462 (Regeneron Pharmaceuticals, Inc.)
European Clinical Trials Database (EudraCT):	2019-003851-12

Rationale:

There remains an unmet medical need in the treatment of neovascular (wet) age-related macular degeneration (nAMD). Although many patients benefit from treatment with currently available anti-vascular endothelial growth factor (VEGF) agents, a sizable proportion of patients still need intravitreal (IVT) injections as frequently as every 4 to 8 weeks, specifically in the first year of treatment. A continued need for treatment in intervals as short as 4 to 8 weeks poses significant treatment burden to patients, physicians, and to healthcare systems. In addition, long-term data in patients with nAMD suggest that visual benefits achieved in the first year of treatment may be lost if regular dosing is not maintained. In real-world settings, visual loss also occurs to patients being treated under a treat-and-extend regimen with inappropriate dosing interval extension strategy. In fact, in nAMD, lost vision may not be regained, even with increases of treatment frequency after the vision loss has occurred. Furthermore, dosing with an insufficient frequency may result in a patient's vision deteriorating below certain visual thresholds that would preclude certain activities of daily living, e.g., driving a car or reading.

EYLEA® (also known as aflibercept 2 mg) is a VEGF antagonist approved as of 07 OCT 2019 in over 109 countries for the treatment of nAMD at a dosage level of 2 mg (administered at a concentration of 40 mg/mL injected IVT) administered every 8 (q8) weeks. This study will investigate the efficacy and safety of a high dose (HD) aflibercept (8 mg; provided at a concentration of CCI mg/mL) with the intent of achieving non-inferior best corrected visual acuity (BCVA), while extending the dosing interval and potentially improving visual and/or anatomic outcomes for HD versus the currently approved aflibercept 2 mg dose regimen. The study will compare HD aflibercept administered every 12 (q12) or every 16 (q16) weeks, after 3 initial injections at 4-week intervals (HDq12 and HDq16) versus aflibercept 2 mg administered q8 weeks (2q8), after 3 initial injections at 4-week intervals in participants with nAMD.

In order to investigate the long-term efficacy and safety of HD aflibercept beyond 2 years of treatment, this study will be extended in an open-label part (after a masked transition period of 12 weeks) for approximately one additional year (60 weeks) in countries and sites selected by the sponsor. The reason for the masked transition period is to prevent study staff and participants from being able to determine the participant's treatment assignment during the masked part of the study before data cleaning is completed for the masked part, preserving

data quality for the Week 60 database lock, and giving a time frame for data cleaning. During this third year of treatment, CCI who consent to continue in the study, CCI CCI . The treatment intervals for all groups will be adjusted according to individual participant response as determined by the E-DRM criteria in Year 3.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To determine if treatment with aflibercept 8 mg (HD) at intervals of 12 or 16 weeks provides non-inferior BCVA change compared to aflibercept 2 mg every 8 weeks in participants with nAMD	Primary Endpoint • Change from baseline in BCVA measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at Week 48
Secondary - Efficacy	
To determine the effect of HD versus 2 mg aflibercept on other visual and anatomic measures of response To assess the efficacy of HD compared to 2 mg aflibercept on vision-related quality of life	Key Secondary Efficacy Endpoints • Change from baseline in BCVA measured by the ETDRS letter score at Week 60 (for regulatory submissions to European Medicines Agency/Pharmaceuticals and Medical Devices Agency [EMA/PMDA] Analysis Plan only, see Section 9) • Proportion of participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in central subfield at Week 16 Additional Secondary Efficacy Endpoints • Proportion of participants gaining at least 15 letters in BCVA from baseline at Week 48 • Proportion of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Week 48 • Change in choroidal neovascularization (CNV) size from baseline to Week 48 • Change in total lesion area from baseline to Week 48 • Proportion of participants with no IRF and no SRF in the center subfield at Week 48 • Change from baseline in central subfield retinal thickness (CST) at Week 48 • Change from baseline in National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) total score at Week 48
Secondary - Safety	
To evaluate the safety of aflibercept	• Treatment-emergent adverse events (AEs) and serious AEs (SAEs) through Week 48, 60, 96 and, for participants who continue in the study extension, through Week 156
Secondary - Other	
To evaluate the pharmacokinetics (PK) and immunogenicity of aflibercept	• Systemic exposure to aflibercept as assessed by plasma concentrations of free, adjusted bound and total aflibercept from baseline through Week 48 • Assessment of immunogenicity to aflibercept through end of masked study (Week 96)

Overall Design

Disclosure Statement: This is a randomized, double-masked (participant and investigator masked), active-controlled, multi-center study with 3 groups. After completion of the double-masked part (Week 96), this study will be extended through a masked transition period (Week 96 to Week 108) to an open-label part until Week 156.

Intervention Model: Parallel.

Primary Purpose: Treatment.

Number of Groups: 3

Masking: In the masked part (up to Week 96): participant and investigator masked; in the transition period of study extension (Week 96 to Week 108): participant and investigator masked; in the open-label part of study extension (after Week 108 to Week 156): participant and investigator unmasked to treatment intervals in the extension period (CCI [redacted]) (refer to Section 6.3.2 for details).

Number of Participants: Approximately 960 participants will be randomly assigned in a 1:1:1 ratio (320 in each group) such that approximately 288 evaluable participants per treatment group complete the primary endpoint evaluation. Refer to Section 9.2 for justification of the sample size. Randomization will be stratified by geographic region (Japan vs. Rest of World), and baseline (Day 1) BCVA (<60 vs. ≥60). Approximately 24 participants (12 Japanese participants from Japan sites and 12 non-Asian participants from Europe or US sites, distributed across all 3 treatment groups) will undergo additional pharmacokinetic (PK) testing in a Dense PK Substudy.

Approximately 380 sites in approximately 36 countries in Europe, North America, Latin America, Australia, and Asia Pacific (including at least 10% of participants in Japan [n=96]) will participate in the masked part of this study (up to Week 96).

A total of 660 participants (220 per group) are estimated to consent to continue in the study extension.

Approximately 160 sites in approximately 18 countries in Europe, North America, Australia, and Asia Pacific will participate in the extension period of this study.

Intervention Groups and Duration:

In the double-masked study part (Years 1 and 2), treatment groups and duration will be as follows:

- 2q8: aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
- HDq12: high dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals.
- HDq16: high dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals.

Only one eye can be treated within the study. Sham procedures will be done on visits when an active injection is not planned. No sham procedures will be done at the non-treatment visit at Week 12. At all subsequent visits, all participants will receive either active study treatment injection or sham procedure (for masking purposes), depending on their assigned treatment schedule and eligibility for dose regimen modification (DRM). All participants will be followed every 4 weeks through Week 96.

For each participant, the total duration of participation in the double-masked study part will be approximately 99 weeks, including a 3-week screening period, Year 1 (48 weeks), and Year 2 (48 weeks).

At sites where the study will be extended, participants who are planned to complete the masked part of the study (i.e., the end of masked study visit at Week 96) will be asked to provide their informed consent to continue in the study for a 1-year extension until the end of Year 3. Participants must complete the Week 96 visit to be eligible to enter the extension.

In this extension period (Year 3), treatment groups and duration will be as follows:

- 2q8: For participants CCI assigned to 2q8 at the beginning of the study, CCI thereafter, CCI according to individual participant response as determined by the E-DRM in Year 3. If the E-DRM criteria are met at CCI, these participants will receive a dose at CCI and their subsequent treatment interval will be CCI.
- HDq12: For participants CCI assigned to HDq12 at the beginning of the study, CCI according to individual participant response as determined by the E-DRM in Year 3.
- HDq16: For participants CCI assigned to HDq16 at the beginning of the study, CCI according to individual participant response as determined by the E-DRM in Year 3.

Study eye and fellow eye assignments will be kept the same in the extension period as in the core study. The study extension will start immediately after completion of the end of masked study visit at Week 96 for Year 2 and consists of a masked transition period of 12 weeks, during which study intervention will still be administered in a masked fashion, followed by an open-label treatment part with duration of 44 weeks, and an end of study visit 4 weeks after the last treatment at Week 156 for Year 3. During the masked transition period, from Week 96 through Week 108, sham injections will be done at visits when an active injection is not planned.

Thereafter, in the open-label part, no sham injections will be done. At any visit, participants will receive either active or no study treatment. All participants in the open-label part will have treatment visits according to their treatment schedule. At treatment visits, if E-DRM criteria are met, treatment intervals will be modified CCI CCI. In addition, there will be mandatory monitoring visits for all participants at Weeks CCI to ensure that data collection occurs at least every CCI weeks. If shortening criteria are met at any treatment, monitoring or unscheduled visit, the participant will be dosed at the same visit, unless the previous dose was administered less than 8 weeks before, and the subsequent treatment interval will be shortened to the time from the most recent dose CCI.

For each participant in the extension period, the total duration of participation in the whole study will be approximately 159 weeks, including the initial 3-week screening period, Year 1 (48 weeks), Year 2 (48 weeks), and Year 3 (60 weeks).

Data Monitoring Committee: Yes

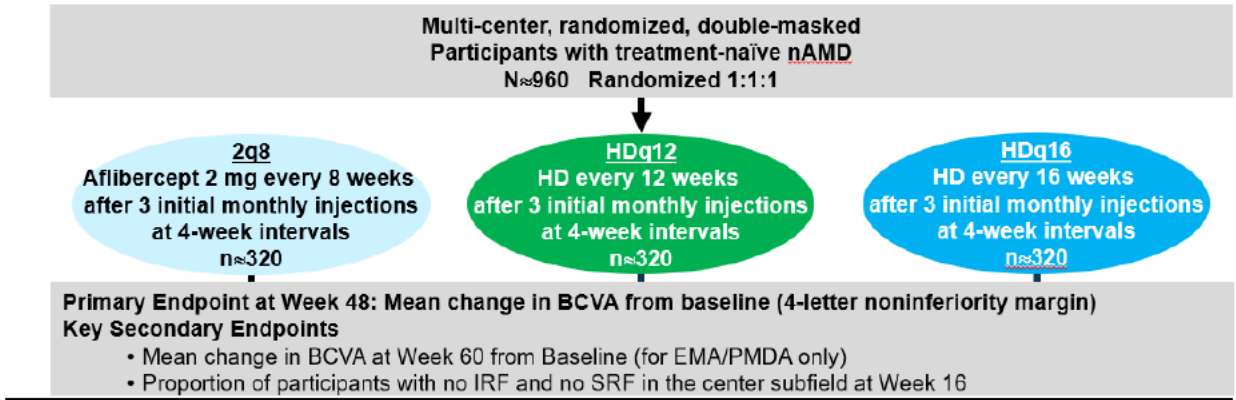
The independent data monitoring committee (DMC) oversight will continue through the last participant's completion of the end of masked study visit (Week 96) and until completion of the masked transition period (Week 108).

Steering Committee: Yes

Adjudication Committee for Arterial Thromboembolic Events? Yes

1.2 CCI

CCI



CCI

2q8=aflibercept 2 mg administered every 8 weeks until Week 92, after 3 initial injections at 4-week intervals. Participants who consent to continue in the extension period from Week 96 in Year 3 CCI; thereafter, CCI CCI according to individual participant response as determined by E-DRM in Year 3. If the E-DRM criteria are met at CCI, these participants will CCI and their subsequent treatment interval will be CCI

HDq12=high dose aflibercept 8 mg administered every 12 weeks until Week 92, after 3 initial injections at 4-week intervals. Participants who consent to continue in the extension period from Week 96 in Year 3 CCI according to individual participant response as determined by the E-DRM in Year 3.

HDq16=high dose aflibercept 8 mg administered every 16 weeks until Week 92, after 3 initial injections at 4-week intervals. Participants who consent to continue in the extension period from Week 96 in Year 3 CCI according to individual participant response as determined by the E-DRM in Year 3.

BCVA=best corrected visual acuity, E-DRM=dose regimen modification criteria for extension period, EMA=European Medicines Agency, HD=high dose, IRF=intraretinal fluid, N=total number of participants, n=number of participants per group, nAMD=neovascular (wet) age-related macular degeneration, PMDA=Pharmaceuticals and Medical Devices Agency, SRF=subretinal fluid

Figure 1–2 Dosing Schedule

	Day 1	Wk 4	Wk 8	Wk 12	Key 2° Endpoint Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	1° Endpoint Wk 48
2q8	X	X	X		X	o	X	o	X	o	X	o	X
HDq12	X	X	X		CCI			o	X[c]	o	o	X[c]	o
HDq16	X	X	X					o	o	o	X[c]	o	o

	Wk 52	Wk 56	Key 2° Endpoint Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96	
2q8	o	X	o	X	o	X	o	X	o	X	o	EOMS	CCI
HDq12	o	X[d]	o	o	X[d]	o	o	X[d]	o	o	X[d]	EOMS	
HDq16	o	X[d]	o	o	o	X[d]	o	o	o	X[d]	o	EOMS	

CCI

For masking purposes, DRM assessments will be performed in all participants at all visits (through the IXRS) starting from Week 16.

a HDq12 group: If DRM criteria are met, participants will continue on q8 rescue regimen.
b HDq16 group: If DRM criteria are met at Week 16 or 20, participant will continue on q8 rescue regimen. If DRM criteria are met at Week 24, participant will continue on q12 regimen.
c For participants remaining on a dosing interval of q12 or q16 weeks after Week 24, if DRM criteria are met at an active injection visit, the next dosing interval will be reduced by 4 weeks (to a minimum of q8).
d From Week 52, all participants in HD groups will be eligible for dose interval shortening (to a minimum of q8) or extension (by 4-week increments) according to pre-specified DRM criteria. If DRM criteria are met at an active injection visit, the next dosing interval will be changed by 4 weeks.
e Decision on treatment interval shortening at CCI. If E-DRM shortening criteria in Year 3 are met, interval will be shortened to 8 weeks and the participants will be dosed CCI at the same visit, and thus will not be dosed at CCI.
f CCI will be administered according to individual participant response as determined by the E-DRM in Year 3.
g During the open-label part: CCI will be administered according to individual participant response as determined by the E-DRM in Year 3. Visit windows will be increased to CCI to allow CCI apart. Decision on treatment interval shortening can be done at any visit: If E-DRM shortening criteria in Year 3 are met, dosing should be done at the same visit. Decision on treatment interval extension can only be done at treatment visits.
h Mandatory monitoring visits must be performed to ensure that data collection occurs at least every 12 weeks. They will be performed with or without treatment according to individual participant response as determined by the E-DRM in Year 3.

This figure does not reflect all available dosing options, once a participant's dose regimen is shortened or extended.

X=active injection, o=sham procedure
2q8=aflibercept 2 mg administered every 8 weeks until Week 92, after 3 initial injections at 4-week intervals. Participants who consent to continue in the extension period from Week 96 in Year 3 CCI according to individual participant response as determined by the E-DRM in Year 3. If the E-DRM criteria are met at Week 104, these participants will receive a dose at CCI and their subsequent treatment interval will be shortened to every 8 weeks.
HDq12=high dose aflibercept 8 mg administered every 12 weeks until Week 92, after 3 initial injections at 4-week intervals. Participants who consent to continue in the extension period from Week 96 in Year 3 CCI according to individual participant response as determined by the E-DRM in Year 3.
HDq16=high dose aflibercept 8 mg administered every 16 weeks until Week 92, after 3 initial injections at 4-week intervals. Participants who consent to continue in the extension period from Week 96 in Year 3 CCI according to individual participant response as determined by the E-DRM in Year 3.
1º=primary, 2º=secondary, DRM=dose regimen modification, E-DRM=dose regimen modification criteria for extension period, EOMS=end of masked study, HD=high dose, IXRS=Interactive Response System, q8=every 8 weeks, q12=every 12 weeks, q16=every 16 weeks, Wk=Week

1.3 Schedule of Activities (SoA)

Table 1–1 Schedule of Activities – Year 1

Visit	1 Screening	2 Baseline	3	4	5	6	7	8	9	10	11	12	13	14	15
Week			4	8		12	16	20	24	28	32	36	40	44	48
Day	-21 to -1	1	29	57	60-64	85	113	141	169	197	225	253	281	309	337
Window (day)[a]			±5	±5	[b]	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Administrative:															
Informed Consent (ICF)	X														
Dense PK Substudy ICF[c]	X														
Genomic Substudy ICF[d]	X														
FBR ICF[e]	X														
Inclusion/Exclusion Eligibility	X	X[f]													
Medical History	X														
Demographics	X														
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X													
Study Intervention[g]:															
Study Intervention (active or sham)		X	X	X			X	X	X	X	X	X	X	X	X
DRM Assessment[h]							X	X	X	X	X	X	X	X	X
Ocular Efficacy and Safety (bilateral unless indicated):															
NEI-VFQ-25[i]		X							X						X
BCVA (ETDRS) and Refraction	X	X	X	X		X	X	X	X	X	X	X	X	X	X
IOP[j]	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Slit Lamp Examination[k]	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Indirect Ophthalmoscopy[l]	X	X	X	X		X	X	X	X	X	X	X	X	X	X
FA, FP[m]	X					X			X			X			X
SD-OCT[m]	X	X	X	X		X	X	X	X	X	X	X	X	X	X
ICGA[n]	X														X
OCT-A[o]	X					X			X			X			X

Table 1–1 Schedule of Activities – Year 1

Visit	1 Screening	2 Baseline	3	4	5	6	7	8	9	10	11	12	13	14	15
Week			4	8		12	16	20	24	28	32	36	40	44	48
Day	-21 to -1	1	29	57	60-64	85	113	141	169	197	225	253	281	309	337
Window (day)[a]			±5	±5	[b]	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Nonocular Safety:															
Physical Examination	X														
Vital Signs[p]	X	X	X	X	X[o]	X	X	X	X	X	X	X	X	X	X
ECG	X														X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[q]:															
Hematology	X														X
Blood Chemistry	X														X
Pregnancy Test (WOCBP)[r]	X Serum	X Urine	X Urine	X Urine		X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine
Urinalysis, UPCR	X														X
Pharmacokinetics and Other Sampling:															
PK Samples (Sparse)[s]		X	X		X	X				X					X
PK Samples (Dense)[c]		See Table 1–4													
Anti-drug Antibody Serum Sample[q,t]		X													X
Genomic DNA Sample (optional)[d]		X													

BCVA=best corrected visual acuity, DNA=deoxyribonucleic acid, DRM=dose regimen modification, ECG=electrocardiogram, ETDRS=Early Treatment Diabetic Retinopathy Study, FA=fluorescein angiography, FBR=future biomedical research, FP=fundus photography, ICF=informed consent form, ICGA=indocyanine green angiography, IOP=Intraocular pressure, NEI-VFQ-25=National Eye Institute Visual Functioning Questionnaire-25, OCT-A=optical coherence tomography angiography, PK=pharmacokinetics, SD-OCT=spectral domain optical coherence tomography, UPCR=urine protein:creatinine ratio, WOCBP=women of childbearing potential

Table 1–2 Schedule of Activities – Year 2

Visit	16	17	18	19	20	21	22	23	24	25	26	27 EOMS or ED
Week	52	56	60	64	68	72	76	80	84	88	92	96
Day	365	393	421	449	477	505	533	561	589	617	645	673
Window (day)[a]	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Administrative:												
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Study Intervention[g]**:**												
Study Intervention (active or sham)	X	X	X	X	X	X	X	X	X	X	X	
DRM Assessment[h]	X	X	X	X	X	X	X	X	X	X	X	
Ocular Efficacy and Safety (bilateral unless indicated):												
NEI-VFQ-25[i]			X									X
BCVA (ETDRS) and refraction	X	X	X	X	X	X	X	X	X	X	X	X
IOP[j]	X	X	X	X	X	X	X	X	X	X	X	X
Slit lamp examination[k]	X	X	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy[l]	X	X	X	X	X	X	X	X	X	X	X	X
FA, FP[m]			X									X
SD-OCT[m]	X	X	X	X	X	X	X	X	X	X	X	X
ICGA[n]												X
OCT-A[o]			X									X
Nonocular Safety:												
Physical examination												X
Vital signs[p]	X	X	X	X	X	X	X	X	X	X	X	X
ECG												X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[q]**:**												
Hematology												X
Blood Chemistry												X
Pregnancy Test (women of childbearing potential)[r]	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine
Urinalysis, UPCR												X
Anti-drug Antibody Serum Sample[q,t]												X

BCVA=best corrected visual acuity, DRM=dose regimen modification, ECG=electrocardiogram, ED=Early Discontinuation, EOMS=End of Masked Study, ETDRS=Early Treatment Diabetic Retinopathy Study, FA=fluorescein angiography, FP=fundus photography, ICF=informed consent form, ICGA=indocyanine green angiography, IOP=Intraocular pressure, NEI-VFQ-25=National Eye Institute Visual Functioning Questionnaire-25, OCT-A=optical coherence tomography angiography, PK=pharmacokinetics, SD-OCT=spectral domain optical coherence tomography, UPCR=urine protein:creatinine ratio, WOCBP=women of childbearing potential

[redacted] CCI [redacted]

	Mandatory Masked Transition Period				Open-label Part							
[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]								
[redacted]	[redacted]	CCI [redacted]	CCI [redacted]	CCI [redacted]	CCI [redacted]	[redacted]	CCI [redacted]	[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]	CCI [redacted]	CCI [redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]	[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit type	T^u	T^u	T^u	T^u	T^v	M^w	T^v	M^w	T^v	M^w	T^v	
Administrative:												
Study extension ICF[x]	X											
Additional inclusion criteria for study extension	X											
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X
Study Intervention[g]:												
Study Intervention	X	X	X	X	X (active)	X (active or none)	X (active)	X (active or none)	X (active)	X (active or none)	X (active)	
	active or sham											
E-DRM Assessment[h]		X	X	X	X	X	X	X	X	X	X	
Ocular Efficacy and Safety (bilateral unless indicated):												
NEI-VFQ-25[i]												X
BCVA (ETDRS) and refraction		X	X	X	X	X	X	X	X	X	X	X
IOP[j]		X	X	X	X	X	X	X	X	X	X	X
Slit lamp examination[k]		X	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy[l]		X	X	X	X	X	X	X	X	X	X	X
FA, FP[m]								X				X
SD-OCT[m]		X	X	X	X	X	X	X	X	X	X	X
ICGA[n]												X
OCT-A[o]								X				X
Nonocular Safety:												
Vital signs[p]		X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X

Table 1–3 Schedule of Activities – Extension Period (Year 3)

	Mandatory Masked Transition Period				Open-label Part							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] CCI								
[redacted]	[redacted]	[redacted] CCI	[redacted] CCI	[redacted] CCI	[redacted] CCI	[redacted]	[redacted] CCI	[redacted]	[redacted] CCI	[redacted]	[redacted]	
[redacted] CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] CCI	[redacted] CCI	[redacted] CCI
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] CCI	[redacted]	[redacted] CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit type	T^u	T^u	T^u	T^u	T^v	M^w	T^v	M^w	T^v	M^w	T^v	
Laboratory Testing[q]:												
Pregnancy Test (WOCBP)[r]		X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine

BCVA=best corrected visual acuity, DRM=dose regimen modification, ED=Early Discontinuation, E-DRM=dose regimen modification criteria for the extension period, EOS=End of Study, ETDRS=Early Treatment Diabetic Retinopathy Study, FA=fluorescein angiography, FBR=future biomedical research, FP=fundus photography, ICF=informed consent form, ICGA=indocyanine green angiography, IOP=Intraocular pressure, M=monitoring visit, NEI-VFQ-25=National Eye Institute Visual Functioning Questionnaire-25, OCT-A=optical coherence tomography angiography, SD-OCT=spectral domain optical coherence tomography, T=treatment visit, UPCR=urine protein:creatinine ratio, WOCBP=women of childbearing potential

Footnotes for the Schedule of Activities Tables

a Visit schedules may deviate by up to ±5 days during Year 1 and Year 2 and for Visit E01 in Year 3. For the remainder of Year 3, visit schedules may deviate by up to [redacted] (for mandatory visits by up to [redacted]) to allow [redacted] apart. Set schedule visits (except Visit 5) use baseline for the calculation. The procedures required at each visit have to be complete within 3 days, i.e., split visits are allowed. Additionally, all procedures have to be complete within the 5-day window. Slit lamp (anterior segment), IOP measurement, and indirect ophthalmoscopy are recommended to take place on the same day as the IVT injection (see Section 8.1.1 for details).

b Visit 5 must be within 3 to 7 days after the Week 8 injection. This visit uses the date of Visit 4 for calculation.

c Dense PK sampling will be performed in a subgroup including participants at Japanese and non-Asian sites. The Dense PK Substudy ICF should be presented and signed at the screening visit. Refer to Table 1–4. Participants in the Dense PK Substudy have extra visits but otherwise participate in the

main study with a 96 week duration.

d The optional genomic substudy ICF should be presented to participants at the screening visit and may be signed at any subsequent visit at which the participant chooses to participate after screening. The genomic DNA blood sample should be collected on Day 1/baseline (pre-injection) or at any time during the study, only from participants who consent to participate in the genomic substudy. Participants from China will not be enrolled in this optional substudy.

e The optional FBR ICF should be presented to participants and signed at the screening visit. No additional blood sample is required – remaining blood samples (from e.g., PK or anti-drug antibody [ADA] sampling) may be used.

f Inclusion/exclusion criteria will be evaluated at screening and baseline to confirm subject's eligibility. The investigator is responsible for confirming that any changes between screening and baseline do not affect the participant's eligibility.

g Refer to Section 10.7 for study intervention injection guidelines. Following study intervention injection or sham procedure, participants will be observed for at least 30 minutes.

h For masking purposes, assessments for dose regimen modification (DRM) will be performed in all participants at all visits starting from Week 16 through Week 92. At Week 96 no interval adjustments will be performed. Thereafter, E-DRM assessments will be performed in all participants at all individually scheduled visits (including treatment and mandatory monitoring visits) and unscheduled visits through Week 152. Actual DRMs and E-DRMs will be implemented as described in Section 6.6.

i NEI-VFQ-25 to be administered in a quiet room by a masked study-related person trained to administer this type of questionnaire, preferably before other visit procedures are performed.

j IOP will be measured at all study visits (bilateral). On days when study intervention is administered, IOP should be measured pre-injection (bilaterally) and approximately 30 to 60 minutes after administration of study intervention (study eye only). The exact timing is left to the discretion of the unmasked investigator. IOP will be measured using Goldmann applanation tonometry, rebound tonometry Icare, or Tonopen and the same method of measurement must be used in each participant throughout the study. For visits after Week 108, no distinction between masked and unmasked study teams (or tasks) will be made.

k Slit lamp examination will be performed bilaterally.

l Indirect ophthalmoscopy will be performed bilaterally at all visits. On days when study intervention is administered, it should also be performed as soon as possible, approximately 0 to 15 minutes after administration of study intervention (study eye only). The exact timing is left to the discretion of the unmasked investigator. If the indirect ophthalmoscopy cannot be performed immediately after injection, see Section 10.7.2.3. For visits after Week 108, no distinction between masked and unmasked study teams (or tasks) will be made.

m The same SD-OCT/FA/FP imaging system used at screening and Day 1 must be used at all follow-up visits in each participant. Images will be taken in both eyes before dosing (active or sham injection).

n Optional at all sites that have the relevant equipment. ICGA will be used to diagnose and characterize the polypoidal choroidal vascularization (PCV) subtype of nAMD. If ICGA cannot be performed at screening visit, it may be done at baseline visit.

o OCT-A is optional at all sites that have the relevant equipment. If OCT-A cannot be performed at screening visit, it may be done at baseline visit.

p Vital signs (temperature, blood pressure, heart rate) should be measured per the procedure outlined in the study manual. At Visit 5, only blood pressure and heart rate are required. Vital signs should be measured prior to injection and any blood sampling. When possible, timing of all blood pressure assessments should be within 2 hours of clock time of dosing on Day 1. Measurements will be taken pre-dose (active or sham injection).

q All samples collected for laboratory assessments should be obtained prior to administration of fluorescein and/or indocyanine green, and prior to administration of study intervention.

r For women of childbearing potential, a negative serum 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.

s Sparse PK sampling will be performed in all participants (optional for participants in China). Any PK sampling will be done prior to dosing if scheduled at the sampling time point.

t Anti-drug antibody sample collection is optional for participants in China.

u Treatment visits during the mandatory masked transition period (Week 96 to Week 108):
2q8 group: For participants originally assigned to 2q8 at the beginning of the study, CCI starting at Week 96; thereafter, CCI administered according to individual participant response as determined by E-DRM in Year 3. If the E-DRM criteria are met at Week CCI these participants will receive a dose at Week CCI and their subsequent treatment interval will be shortened to every 8 weeks.
HDq12 and HDq16 groups: For participants originally assigned to HDq12 and HDq16 at the beginning of the study, CCI participants will CCI CCI according to their individual participant response as determined by the E-DRM in Year 3.
Visit E01 at Week 96: All participants from selected countries/sites will be asked for consent to continue in the 1-year extension period of the study starting at Week 96. For all other procedures scheduled for the first extension visit, every effort should be made to ensure that they are performed on the same date as the end of Year 2, Week 96 visit. In cases where this is not possible, the procedures for the first extension visit may be conducted up to 4 weeks after the date of the end of Year 2, Week 96 visit. The schedule for subsequent extension visits will be adjusted to start counting from the actual date when initial extension procedures were performed.
Any visit scheduled for Week 110 will actually be combined with the visit at Week 108 by making use of the overlapping visit windows (i.e., no visits with 2-week intervals will occur).

v Treatment visits during the open-label part (to be modified CCI): CCI will be administered open label according to individual participant response as determined by the E-DRM in Year 3. If E-DRM shortening criteria are met at any visit in Year 3, treatment interval shortening and dosing should be done at the same visit. Treatment intervals may not be adjusted to less than 8 weeks. Decision on treatment interval extension can only be done at treatment visits.

w Mandatory monitoring visits: these must be performed to ensure that data collection occurs at least every 12 weeks. They will be performed with or without treatment. If E-DRM shortening criteria in Year 3 are met at a monitoring visit, dosing should be done at the same visit. Dosing visits should be scheduled as close to the planned dosing date as possible, but should be combined with mandatory visits when visit windows overlap.

x ICF has to be signed before or at Visit 1 of the Extension Period.

Table 1–4 Schedule of Activities – Dense PK Substudy

Visit	Dose	Assessment Day	Assessment Time (h)	PK Sample	Heart Rate and Blood Pressure[a]
Screening 2[b]		-21 to -1	±2h		X
Visit 2 (Baseline)		1	Pre-dose[c]	X (pre-injection)	X
	X		4[c]	X	
			8[c]	X	
		2	±2h[c]	X	X
		3	±2h[c]	X	X
		5	±2h[c]	X	X
		8	±2h[c]	X	X
		15	±2h[c]	X	X
		22	±2h[c]	X	X

PK=pharmacokinetics

Participants enrolled in the Dense PK Substudy will also have blood pressure and heart rate assessed at each visit within the substudy.

a Timing of all blood pressure assessments must be within ±2 hours of the clock time of dosing on Day 1. Blood pressure assessments for participants in the Dense PK Substudy will be taken prior to blood sample collection using automated office blood pressure (AOBP) measurement with the Omron Model HEM 907XL (or comparable). Measures will be recorded in the electronic case report form (eCRF). Detailed instructions can be found in the study manual.

b Additional blood pressure assessment between screening and baseline, to confirm eligibility for participants in the Dense PK Substudy. Screening 2 may occur on the same day as the screening visit.

c On Day 1, the 4 hour and 8 hour PK sampling is to be within ±30 minutes and ±2 hours, respectively, of the scheduled time. For subsequent days, PK sampling is to be performed within ±2 hours of the clock time of dosing on Day 1.

2. Introduction

2.1 Study Rationale

There remains an unmet medical need in the treatment of neovascular (wet) age-related macular degeneration (nAMD). Although many patients benefit from treatment with currently available anti-vascular endothelial growth factor (VEGF) agents, a sizable proportion of patients still need intravitreal (IVT) injections as frequently as every 4 to 8 weeks, specifically in the first year of treatment. A continued need for treatment in intervals as short as 4 to 8 weeks poses significant treatment burden to patients, physicians, and to healthcare systems. In addition, long-term data in patients with nAMD suggest that visual benefits achieved in the first year of treatment may be lost if regular dosing is not maintained. In real-world settings, visual loss also occurs to patients being treated under a treat-and-extend regimen with inappropriate dosing interval extension strategy. In fact, in nAMD, lost vision may not be regained, even with increases of treatment frequency after the vision loss has occurred. Furthermore, dosing with an insufficient frequency may result in a patient's vision deteriorating below certain visual thresholds that would preclude certain activities of daily living, e.g., driving a car or reading.

EYLEA (also known as aflibercept 2 mg) is a VEGF antagonist approved as of 07 OCT 2019 in over 109 countries for the treatment of nAMD at a dosage level of 2 mg (administered at a concentration of 40 mg/mL injected IVT) administered every 8 (q8) weeks. This study will investigate the efficacy and safety of a high dose (HD) aflibercept (8 mg; provided at a concentration of CCI mg/mL) with the intent of achieving non-inferior best corrected visual acuity (BCVA), while extending the dosing interval and potentially improving visual and/or anatomic outcomes for HD versus the currently approved aflibercept 2 mg dose regimen. The study will compare HD aflibercept administered every 12 (q12) or every 16 (q16) weeks, after 3 initial injections at 4-week intervals (HDq12 and HDq16) versus aflibercept 2 mg administered q8 weeks (2q8), after 3 initial injections at 4-week intervals in participants with nAMD.

In order to investigate the long-term efficacy and safety of HD aflibercept beyond 2 years of treatment, this study will be extended in an open-label part (after a masked transition period of 12 weeks) for approximately one additional year (60 weeks) in countries and sites selected by the sponsor. The reason for the masked transition period is to prevent study staff and participants from being able to determine the participant's treatment assignment during the masked part of the study before data cleaning is completed for the masked part, preserving data quality for the Week 60 database lock and giving a time frame for data cleaning. During this third year of treatment, CCI participants who consent to continue in the study, [redacted] CCI [redacted], will be treated with CCI [redacted]. The treatment intervals for all groups will be adjusted according to individual participant response as determined by E-DRM criteria in Year 3.

2.2 Background

Neovascular (wet) AMD is a major health issue in aging populations globally. Vision loss in nAMD results from the abnormal growth and leakage of blood vessels in the macula. In elderly patients affected by nAMD, vision loss frequently has an even greater impact, as it substantially reduces the visual compensation of functional impairment by other age-related comorbidities, such as arthritis and osteoporosis.

IVT-administered anti-VEGF therapies like EYLEA (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 choroidal neovascularization (CNV). Although the globally approved IVT anti-VEGF therapies are efficacious and well tolerated, the need for IVT 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. Despite the recent US Food and Drug Administration (FDA) approval of brolucizumab for q8 to q12 use following 3 initial monthly loading doses in nAMD, there is limited clinical experience with this drug and the proposed dosing regimen. 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.

Increasing the concentration of aflibercept in the dosing solution allows a greater amount of drug to be delivered via IVT administration. To achieve an optimized IVT aflibercept injection, a HD formulation has been developed with an aflibercept concentration of CCI mg/mL, allowing a dose of 8 mg in an injection volume of CCI µL. Quadrupling the IVT dose to 8 mg is estimated to increase the duration of exposure relative to the 2 mg formulation (see Section 4.3). This increased exposure and putative prolonged duration of pharmacological action carries the potential to extend treatment intervals in the maintenance phase to CCI, which will provide meaningful additional benefit to patients with nAMD.

High dose aflibercept offers the potential for a similar efficacy benefit compared to aflibercept 2 mg, with a reduced number of IVT injections per time period. Extending the treatment interval to injections CCI will reduce the burden on patients, physicians, and healthcare systems. In addition, higher aflibercept concentrations over a longer period of time may provide better visual outcomes and/or control of the anatomic features of nAMD.

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

This study will investigate the safety and efficacy of HD aflibercept at treatment intervals of 12 weeks or longer.

2.3 Benefit/Risk Assessment

Aflibercept is marketed for the treatment of adult patients with several retinal diseases that are characterized by upregulation of VEGF, are related to pathological neovascularization 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.

Anticipated Benefits of HD Aflibercept

High dose IVT aflibercept may provide improved patient benefit through:

- Longer treatment intervals (every 12 weeks or longer for most patients after initial monthly dosing).
- Potential for improved visual, functional and/or anatomic efficacy.
- Lower injection-related risk over time.
- Increased patient compliance due to reduced treatment burden on patients, caregivers, physicians, and healthcare systems.

Participation in the extension period may provide benefits to participants CCI [redacted], allowing extension of treatment intervals for these participants with the aforementioned advantages. Additionally, participants CCI [redacted] d, may benefit from continued treatment on HD aflibercept with potential for CCI [redacted] of their treatment intervals.

Risks and Risk Management of Treatment with HD Aflibercept

The safety profile of HD aflibercept is expected to be similar to that of the currently approved regimen of IVT aflibercept, 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. Potential risks for aflibercept include embryofetotoxicity and the development of arterial thromboembolic events (ATEs). For a dedicated assessment and categorization, a masked Anti-Platelet Trialists' Collaboration (APTC) adjudication committee will centrally evaluate all potential ATE reports in this study (see Section 9.5.1).

Pharmacokinetic (PK) and clinical safety data of IVT aflibercept have indicated that the known potential risks from systemic administration of anti-VEGF treatments in oncology indications were not identified with local treatment with IVT aflibercept. Studies performed with intravenous (IV) administration of aflibercept demonstrated that increases in blood pressure were the earliest pharmacodynamic indicator of systemic effects. Estimated exposure margins for free aflibercept after an 8 mg IVT dose, derived from linear extrapolation of available PK data for IVT-administered 2 mg IVT aflibercept, suggest adequate safety margins will be observed and maintained.

Nonclinical pharmacology evidence from the chronic DL-alpha-aminoadipic acid toxin induced leakage model in rabbits (1) and additional clinical extrapolation data collectively suggest that a higher dose of aflibercept could extend the dosing interval on average by approximately CCI [redacted] (see also Section 4.3) and thereby reduce the number of injections needed for successful treatment.

In initial clinical trials, doses of up to 4 mg per eye in monthly intervals with injection volumes up to 100 µL and isolated cases of unintentional dosing with 8 mg per eye, which occurred in early studies of the development program of aflibercept 2 mg, were generally well tolerated in participants with nAMD.

The recently completed Phase 2 proof-of-concept study, CANDELA, evaluated for the first time the efficacy and safety of the 8 mg aflibercept dose compared to the 2 mg dose for the treatment of nAMD. The study met the primary safety endpoint and no new safety signals

were seen through Week 44. Moreover, results favored aflibercept 8 mg in visual acuity, drying and other anatomical measures through Week 44 (2).

Hence, with a safety profile expected to be consistent with aflibercept 2 mg, the overall risk/benefit profile for HD should be maintained or improved over the currently approved dose of aflibercept (EYLEA 2 mg).

As risk minimization measures, participants and investigators will be informed about the anticipated safety profile of HD and exclusion criteria will be applied to account for potential safety concerns such as hypersensitivity, pregnancy, and uncontrolled hypertension.

Overall Risk-Benefit Balance:

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with HD aflibercept are justified by the anticipated benefits that may be afforded to participants 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 Investigator's Brochure.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine if treatment with aflibercept 8 mg (HD) at intervals of 12 or 16 weeks provides non-inferior BCVA change compared to aflibercept 2 mg every 8 weeks in participants with nAMD	Primary Endpoint • Change from baseline in BCVA measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at Week 48
Secondary - Efficacy	
To determine the effect of HD versus 2 mg aflibercept on other visual and anatomic measures of response To assess the efficacy of HD compared to 2 mg aflibercept on vision-related quality of life	<u>Key Secondary Efficacy Endpoints</u> • Change from baseline in BCVA measured by the ETDRS letter score at Week 60 (for regulatory submissions to European Medicines Agency/Pharmaceuticals and Medical Devices Agency [EMA/PMDA] Analysis Plan only, see Section 9) • Proportion of participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in central subfield at Week 16 <u>Additional Secondary Efficacy Endpoints</u> • Proportion of participants gaining at least 15 letters in BCVA from baseline at Week 48 • Proportion of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Week 48 • Change in choroidal neovascularization (CNV) size from baseline to Week 48 • Change in total lesion area from baseline to Week 48 • Proportion of participants with no IRF and no SRF in the center subfield at Week 48 • Change from baseline in central subfield retinal thickness (CST) at Week 48 • Change from baseline in National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) total score at Week 48

Objectives	Endpoints
Secondary - Safety	
To evaluate the safety of aflibercept	• Treatment-emergent adverse events (AEs) and serious AEs (SAEs) through Week 48, 60, 96, and through Week 156
Secondary - Other	
To evaluate the pharmacokinetics (PK) and immunogenicity of aflibercept	• Systemic exposure to aflibercept as assessed by plasma concentrations of free, adjusted bound and total aflibercept from baseline through Week 48 • Assessment of immunogenicity to aflibercept through end of masked study (Week 96)
Exploratory	
To determine the effect of HD versus 2 mg aflibercept on functional and anatomic measures of response as well as on vision-related quality of life	• Change from baseline in BCVA measured by the ETDRS letter score at Week 96 and through Week 156 • Change from baseline in BCVA averaged over the period from Week 36 to Week 48 and from Week 48 to Week 60 • Proportion of participants gaining at least 15 letters in BCVA from baseline at Week 60, Week 96, and through Week 156 • Proportion of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Week 60, Week 96, and through Week 156 • Proportions of participants gaining and losing at least 5 or at least 10 letters in BCVA from baseline at Week 48, Week 60, Week 96, and through Week 156 • Proportion of participants losing at least 15 letters in BCVA from baseline at Week 48, Week 60, Week 96, and through Week 156 • Change in CNV size from baseline to Week 60, Week 96, and through Week 156 • Change in total lesion area from baseline to Week 60, Week 96, and through Week 156 • Change from baseline in CST at Week 60, Week 96, and through Week 156 • Proportion of participants with no IRF and no SRF in the center subfield at Week 96 and through Week 156 • Proportion of participants without retinal fluid (total fluid, IRF, and/or SRF) and subretinal pigment epithelium fluid in center subfield at Week 48, Week 60, Week 96, and through Week 156 • Time to fluid-free retina over 48 weeks, 60 weeks, 96 weeks, and 156 weeks (total fluid, IRF, and/or SRF in the center subfield) • Proportion of participants with sustained fluid-free retina over 48 weeks, 60 weeks, 96 weeks, and through 156 weeks (total fluid, IRF, and/or SRF in the center subfield) • Change from baseline in NEI-VFQ-25 total score at Week 60, Week 96, and through Week 156 • Proportion of participants without leakage on fluorescein angiography (FA) at Week 48, Week 60, Week 96, and through Week 156
To evaluate the duration of effect of HD after 3 initial doses at	• Proportion of participants with q16 or longer treatment interval through Week 48, Week 60, and Week 96 in

Objectives	Endpoints
4-week intervals followed by dosing q12 or q16	HDq16 group • Proportion of participants with q12 or longer treatment interval through Week 48, Week 60, and Week 96 in the HDq12 and HDq16 groups • Proportion of participants with q12 or longer treatment interval as the last treatment interval at Week 48, Week 60, and Week 96 in HDq12 and HDq16 groups, respectively • Proportion of participants with q12 or longer treatment interval during Year 3 in the HDq12 and HDq16 groups
To evaluate the duration of effect of HD after switching from treatment with 2 mg	• Proportion of participants extended to q12 or longer treatment intervals during Year 3 in 2q8 group • Proportion of participants with q12 or longer treatment interval as the last treatment interval at Week 156 in 2q8 group
Based on dense PK sampling, characterize the concentrations in plasma over time, and corresponding PK parameters for aflibercept	• Concentrations of free, adjusted bound and total aflibercept over time, and PK parameters
For all participants, explore the relationship between PK and selected systemic and ocular response variables	• Relationship of free aflibercept concentrations and blood pressure • Dose and/or exposure-response analyses for select safety and efficacy endpoints, as appropriate.
Other Pre-specified Objectives	
To study molecular drivers of nAMD or related diseases, clinical efficacy of aflibercept, and affected molecular pathways	• Evaluation of clinical efficacy parameters by repertoire or frequency of genetic alterations (genomics substudy) • Treatment related changes in circulating biomarkers (future biomedical research [FBR])

4. Study Design

4.1 Overall Design

This phase 3, multi-center, randomized, double-masked, active-controlled study will investigate the efficacy, safety, and tolerability of IVT administration of aflibercept 8 mg (HD) versus aflibercept 2 mg in participants with treatment-naïve nAMD.

The masked part of the study (up to Week 96) consists of a screening/baseline period, a treatment period with duration of 92 weeks, and a last study visit at Week 96 for Year 2 (i.e., end of main study visit). The extension period of the study starts immediately after the last scheduled procedure at the end of the Week 96 study visit and consists of a transition period of 12 weeks, during which study intervention will still be administered in a masked fashion, an open-label treatment period with duration of 48 weeks, and an end of study visit at Week 156 for Year 3.

No study intervention will be administered at the end of masked study visit at Week 96 for Year 2 for participants who do not consent to participate in the extension period part of the study in Year 3 and complete the study at that visit. In contrast, participants who consent to continue in the extension period in Year 3 will receive masked study intervention at that visit, which will be considered the first visit for Year 3. [redacted]
CCI [redacted]

CCI [redacted]. All participants will continue to receive masked study intervention during the transition period of 12 weeks (through Week 108). Thereafter, CCI participants who remain in the extension period of the study will receive CCI [redacted]t in an open-label fashion according to their individual dosing schedule.

Approximately 960 eligible participants with nAMD will be randomly assigned to receive IVT injections of HD or 2 mg in a 1:1:1 ratio to 3 parallel treatment groups for 2 years:

- 2q8: aflibercept 2 mg administered every 8 weeks until Week 92, after 3 initial injections at 4-week intervals.
- HDq12: aflibercept 8 mg administered every 12 weeks until Week 92, after 3 initial injections at 4-week intervals. Participants in this group can move to q8 dosing regimen at Weeks 16 or 20 according to pre-specified criteria.
- HDq16: aflibercept 8 mg administered every 16 weeks until Week 92, after 3 initial injections at 4-week intervals. Participants in this group can move to q8 dosing regimen at Weeks 16 or 20, or q12 dosing regimen at Week 24, according to pre-specified criteria.

Upon approaching completion of the first 2 years, all participants from selected countries/sites will be asked for consent to continue in the 1-year extension period of the study starting at Week 96. For all other procedures scheduled for the first extension visit, every effort should be made to ensure that they are performed on the same date as the end of Year 2, Week 96 visit. In cases where this is not possible, the procedures for the first extension visit may be conducted up to 4 weeks after the date of the end of Year 2, Week 96 visit. The schedule for subsequent extension visits will be adjusted to start counting from the actual date when initial extension procedures were performed. During this extension period, CCI participants – CCI [redacted] according to individual participant response as determined by the E-DRM in Year 3.

For initial randomization at the beginning of the study, participants will be stratified based on baseline BCVA and geographical region, to ensure balanced distribution of the treatment groups within each stratum. Only one eye can be treated within the study. In the masked study part, sham procedures will be done on visits when an active injection is not planned. No sham procedures will be done at the non-treatment visit at Week 12. At all subsequent visits up until Week 92, all participants will receive either active study treatment injection or sham procedure (for masking purposes), depending on their assigned treatment schedule and eligibility for dose regimen modification. Participants who consent to continue in the extension period of the study from Week 96 in Year 3 will continue to receive either active study treatment injection or sham procedure, depending on their assigned treatment schedule, for masking purposes during the transition period. The reason for this masked transition period is to prevent study staff and participants from being able to determine the participant's treatment assignment before data cleaning is completed, preserving data quality for the Week 60 database lock, and giving a time frame for data cleaning.

Starting at Week 52, all participants randomized to HDq12 or HDq16 will be eligible for adjustments of their treatment intervals (shortening or extension) based on pre-specified DRM criteria, with the dose interval adjustments (shortening or extension) becoming effective at or after Week 60 (after data collection for key secondary efficacy endpoint). All participants will be followed every 4 weeks through Week 96. After completion of the last scheduled procedure at the end of masked study visit at Week 96 for Year 2, all participants in the 2q8,

HDq12, and HDq16 groups who consent to continue in the extension period of the study will be eligible for DRM to be followed for the extension period in Year 3 (E-DRM criteria).

During the open-label extension, no sham procedures will be done at any visit so that all participants will receive either active or no study treatment injection according to their individual treatment and visit schedule. All participants will have treatment visits according to their treatment schedule and eligibility for DRM, as well as mandatory monitoring visits at Weeks CCI and CCI to ensure synchronized observations, participant monitoring, and data capture at least once every CCI weeks. In the open-label part, the visit schedule will be individualized and dependent on the injection schedule in multiples of CCI CCI visit schedule required during the masked part of the study.

An analysis of data up to Week 48 (including the primary efficacy analysis) will take place once all participants have completed Week 48 (or prematurely discontinued). Another analysis of data up to Week 60 (including a confirmatory analysis at this timepoint for regulatory submissions to EMA and PMDA) will take place once all participants have completed Week 60 (or prematurely discontinued). Furthermore, an analysis of all data will be conducted after all participants have completed the study at Week 96 (or prematurely discontinued). In addition, exploratory analyses may be performed at earlier time points (after the completion of the confirmatory analyses at Week 48 and Week 60) as necessary, e.g. to address health authority requests and queries. A final exploratory analysis of all data will be conducted after all participants who continued the study beyond Week 96 have completed the study at Week 156 (or prematurely discontinued). In addition, exploratory analyses may be performed at earlier time points during the extension phase as necessary. Masking of the study site personnel will continue until the end of the masked transition period of the study (see Section 6.3.2). Masking/unmasking of the study team will be described in a blinding maintenance plan.

The exact test sequence for confirmatory testing is outlined in Section 9.4 and will be described in detail in the study's statistical analysis plan (SAP).

Indocyanine green angiography (ICGA) will be used to diagnose and characterize the polypoidal choroidal vascularization (PCV) subtype of nAMD at sites that have the appropriate equipment.

Safety will be assessed by ophthalmic examinations, vital signs (including heart rate, blood pressure and temperature), electrocardiogram (ECG), AEs, and laboratory assessments. All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®).

In all participants, blood samples for measurement of drug concentrations (for PK) will be obtained prior to the first treatment and at pre-specified time points throughout the course of the study (see Schedule of Activities [SoA] in Section 1.3). In addition, a deoxyribonucleic acid (DNA) blood sample will be collected from those who sign the informed consent form (ICF) for the optional genomic substudy.

The study also includes a PK substudy, with dense PK blood sampling for systemic drug concentrations and PK assessments for approximately 12 Japanese participants from Japan sites and 12 non-Asian participants from Europe or US sites (distributed across all 3 treatment groups). All participants in the PK substudy will participate in the main study but will have extra visits as outlined in Table 1–4. Participants in the PK substudy will also be eligible to participate in the extension period. Blood pressure and heart rate measurements will also be taken in these participants at the same time points as for the PK sampling.

A total of 960 participants (320 per group) is planned to be enrolled in this study. Refer to Section 9.2 for justification of the sample size. A total of 660 participants (220 per group) are estimated to consent to continue in the study extension.

For each participant, the total duration of participation in the double-masked study part (up to Week 96) will be approximately 99 weeks, including a 3-week screening period, Year 1 (48 weeks), and Year 2 (48 weeks). For each participant in the extension period, the total duration of participation will be approximately 155 weeks, including the initial 3-week screening period, Year 1 (48 weeks), Year 2 (48 weeks), and Year 3 (60 weeks).

Approximately 380 sites in approximately 36 countries in Europe, North America, Latin America, Australia, and Asia Pacific (including at least 10% of participants in Japan [n=96]) will participate in the masked part of the study.

This study includes an independent DMC to monitor safety. A Steering Committee will be established to guide all aspects of the study. An adjudication committee will evaluate all potential ATEs. Refer to Section 9.5.1 for details.

4.2 Scientific Rationale for Study Design

The general patient population included in this study is considered to be representative of the population under treatment in the clinic, while the eligibility criteria minimize population variability and maximize the potential to measure clinically meaningful outcomes relevant to the study.

This study includes an active control group, rather than placebo/sham control. Aflibercept, administered according to a widely approved dose and regimen (2 mg, q8 weeks) is the active control, as this treatment regimen provides outcomes and an appropriate control for assessment of this HD regimen.

This study uses a double-masked design, with sham procedures at visits where active study intervention is not scheduled, to prevent participant and investigator bias during assessment of the safety and effectiveness of treatment.

The primary endpoint (change from baseline in BCVA measured by the ETDRS letter score at Week 48) was chosen as BCVA is a clinically relevant and well accepted measure of efficacy in clinical trials of patients with nAMD. For EMA and PMDA, confirmatory analysis at Week 60 will include the key secondary endpoint change from baseline in BCVA measured by the ETDRS letter score at Week 60.

Anatomic measures of retinal thickness and retinal fluid are well-known markers of disease activity. These parameters are used by clinicians to determine treatment success and/or the timing of further re-treatment. These measures will be used as secondary endpoints in this phase 3 study to help to determine the degree to which HD can extend the dosing interval relative to aflibercept 2 mg. Additional endpoints are included to determine whether higher aflibercept concentrations over a longer period of time may also provide potential additional functional benefits to patients with nAMD.

The extension period aims to further evaluate the efficacy and safety of CCI [redacted]. It will evaluate [redacted] CCI [redacted] It will also allow evaluation of potential benefits experienced by participants CCI [redacted].

4.3 Justification for Dose

Based on considerations of manufacturing capabilities, formulation, stability, and the likelihood of achieving a meaningful extension of the duration of effect, an 8 mg IVT dose was selected for evaluation in the present study.

In a nonclinical rabbit model of chronic retinal neovascularization and vascular leak, dose-dependent duration of leak suppression was observed after single IVT doses equivalent of up to 8 mg in humans. Pharmacokinetic simulations of free aflibercept concentration-time profiles in human vitreous using a CCI (assuming a vitreous humor volume of [redacted] mL and half-life of CCI) predicted that the concentration at the end of an [redacted]-week dosing interval for a 2 mg IVT dose would be achieved CCI later for an 8 mg IVT dose, suggesting a longer duration of pharmacological activity for this dose relative to 2 mg IVT dose. This increase in IVT exposure and duration of pharmacological effect is expected to allow clinical treatment intervals of CCI.

Clinical studies with intravenous aflibercept indicated that blood pressure increase was the earliest pharmacodynamic indicator of systemic effect. Two studies (PDY6655 and PDY6656) evaluated the effects of IV and subcutaneous aflibercept on blood pressure via 24-hour ambulatory monitoring in healthy subjects. At the lowest IV dose tested in these studies (1 mg/kg; PDY6656), a maximal increase of about 5 mmHg in 24-hour mean change from baseline in systolic blood pressure occurred by Day 6 after a single dose, returning to baseline by about 30 days post-dose. Assuming CCI PK and extrapolating maximum concentration (C_{max}) and area under the curve to the last quantifiable concentration (AUC_{last}) values (for both mean and maximum individual patient values) from 2 mg IVT, estimated free aflibercept systemic C_{max} and AUC_{last} for an 8 mg IVT dose are approximately CCI times and CCI times CCI respectively, than the corresponding values associated with a 1 mg/kg IV dose. Although systemic concentrations of free aflibercept at these IVT doses are appreciably lower than those required to saturate the target-mediated elimination pathway, CCI. A threshold dose and/or concentration of free aflibercept associated with blood pressure increase has not yet been determined.

In the early phase 1 and 2 clinical studies, 93 patients have been exposed to 4 mg of IVT aflibercept, with dosing for up to approximately 1 year and injection volumes up to CCI µL. Furthermore, 3 patients (4 injections) were erroneously treated with a [redacted] mg aflibercept dose instead of the intended dose of [redacted] mg VEGF Trap-Eye, in an injection volume of CCI µL instead of the protocol-specified 50 µL in the phase 1 study VGFT-OD-0603. Adverse events reported in these patients were consistent with the adverse event profile observed for patients receiving EYLEA 2 mg.

The target for the current development plan is to achieve at least similar efficacy to the current standard of care (EYLEA 2 mg) while allowing for a reduced frequency of treatment by increasing the dose. Building on the established safety profile of EYLEA 2 mg, the 8 mg IVT aflibercept may provide additional patient benefits through longer treatment intervals (12 weeks or 16 weeks after initial dosing at 4-week intervals), improved anatomical efficacy (better and/or more durable retinal drying), lower injection-related risk over time related to longer treatment intervals with need for fewer injections over time and increased patient compliance due to reduced treatment burden on patients, caregivers, physicians, and healthcare systems. Better patient compliance in practice is thought to translate to better visual outcomes due to maintaining an adequate injection frequency.

With the expectation of both a longer dosing interval, resulting in a lower annualized number of injections, similar safety profile, and relatively small increase in injection volume, the 8 mg dose was selected for evaluation in this study. Although the planned dose intervals in the HD groups are q12 and q16, DRM is allowed on an individual basis according to pre-specified criteria (see Section 6.6), tailoring the interval to the needs of the participant.

4.4 End of Study Definition

A participant is considered to have completed the masked part of the study if he/she has completed all phases of the study up until and including the last scheduled procedure for Year 2 at the end of masked study visit at Week 96, as shown in the SoA in Table 1–2 (Section 1.3).

A participant is considered to have completed the extension period of study if he/she has completed all phases of the study including the last scheduled procedure at the end of study visit at Week 156, as shown in the SoA in Table 1–3 (Section 1.3).

The end of the study as a whole is defined as the date of the last visit of the last participant in the study in all centers of 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.

The participants' eligibility to be included in the study in terms of optical coherence tomography (OCT) and fluorescein angiography (FA) will be confirmed by the central reading center before randomization.

Re-screening is permitted under certain conditions (see Section 5.4).

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply at both screening and baseline:

Age

1. At least 50 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Active subfoveal CNV secondary to nAMD, including juxtafoveal lesions that affect the fovea as assessed in the study eye.
3. Total area of CNV (including both classic and occult components) must comprise greater than 50% of the total lesion area in the study eye.
4. BCVA ETDRS letter score of 78 to 24 (corresponding to a Snellen equivalent of approximately 20/32 to 20/320) in the study eye.
5. Decrease in BCVA determined to be primarily the result of nAMD in the study eye.
6. Presence of IRF and/or SRF affecting the central subfield of the study eye on OCT. The central subfield is defined as a circle with diameter 1 mm, centered on the fovea.

Sex

7. Male or female.

Contraception

8. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male participants: Men who are sexually active with partners of childbearing potential must agree to use highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least CCI after the last administration of study intervention.

b. Female participants: Women of childbearing potential (WOCBP) must practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least CCI after the last administration of study intervention. Refer to Section 10.5 for definitions of WOCBP. Pregnancy testing and contraception are not required for women not considered WOCBP.

Highly effective contraceptive measures include:

- Stable use of combined (estrogen- and progestogen- containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening.
- Intrauterine device (IUD); intrauterine hormone releasing system (IUS).
- Bilateral tubal ligation.
- Vasectomized partner or vasectomized study participant.
    - Must have received medical assessment of the surgical success.
- Sexual abstinence.[†‡]

[†] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

[‡] Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

Informed Consent

9. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.1.1 Additional Inclusion Criteria for the Extension Period

All randomized participants that complete Week 96 are eligible for the extension period, as long as the following criteria apply:

1. The participant provides signed informed consent to participate in the extension period as described in Section 10.1.3.1, and no treatment for nAMD has been given in the study eye outside of the randomized study treatment.
2. At least one BCVA value and one central subfield retinal thickness (CST) value from measurements at one of the following visits: Visit 24 (Week 84), Visit 25 (Week 88) or Visit 26 (Week 92).
3. Participant is enrolled at a site that participates in the extension period.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply at either screening or baseline:

Medical Conditions – Per Eye

1. Causes of CNV other than nAMD in the study eye.
2. Prior or concomitant conditions in the study eye:
   a. Subretinal hemorrhage that is at least 50% of the total lesion area, or if the blood under the fovea is 1 or more disc areas in size in the study eye.
   b. Scar or fibrosis making up more than 50% of the total lesion in the study eye.
   c. Scar, fibrosis, or atrophy involving the central subfield in the study eye.
   d. Presence of retinal pigment epithelial tears or rips involving the central subfield in the study eye.
   e. Total lesion size >12 disc areas (30.5 mm^2, including blood, scars, and neovascularization) as assessed by FA in the study eye.
   f. Uncontrolled glaucoma (defined as IOP >25 mmHg despite treatment with anti-glaucoma medication) in the study eye.
   g. History of idiopathic or autoimmune uveitis in the study eye.
   h. Vitreomacular traction or epiretinal membrane in the study eye evident on biomicroscopy or OCT that is thought to affect central vision.
   i. Any history of macular hole of stage 2 and above in the study eye.
   j. Structural damage to the center of the macula in the study eye that is likely to preclude improvement in BCVA following the resolution of retinal fluid including but not limited to, atrophy of the retinal pigment epithelium, subretinal fibrosis or scar or significant macular ischemia.
   k. History of, or likely future need of, filtration or tube shunt surgery on the study eye.
   l. Aphakia, or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium-aluminum-garnet [YAG] posterior capsulotomy performed more than 30 days before screening), in the study eye.

m. Myopia of a spherical equivalent of at least 8 diopters in the study eye prior to any refractive or cataract surgery.

n. Significant media opacities, including cataract, that interfere with BCVA assessment, fundus photography or OCT imaging in the study eye.

o. History of corneal transplant or corneal dystrophy in the study eye.

p. History of irregular astigmatism or amblyopia with chronic limitation of BCVA in the study eye.

Medical Conditions – Per Participant

3. Prior or concomitant conditions:

   a. History or clinical evidence of diabetic retinopathy, diabetic macular edema, or any retinal vascular disease other than nAMD in either eye.

   b. Evidence of extraocular or periocular infection or inflammation (including infectious blepharitis, keratitis, scleritis, or conjunctivitis) in either eye at the time of screening/randomization.

   c. Any intraocular inflammation/infection in either eye within 12 weeks (84 days) of the screening visit.

   d. Only 1 functional eye, even if that eye was otherwise eligible for the study (e.g., BCVA of counting fingers or less in the eye with worse vision).

   e. Ocular conditions with poorer prognosis in the fellow eye.

4. Uncontrolled blood pressure (defined as systolic >160 mmHg or diastolic >95 mmHg).
   Participants may be treated with up to 3 agents known to have anti-hypertensive effects for arterial hypertension to achieve adequate blood pressure control. This limit applies to drugs that could be used to treat hypertension even if their primary indication in the participant was not for blood pressure control. Any recent changes in medications known to affect blood pressure need to be stable for 12 weeks prior to screening.

5. History of cerebrovascular accident or myocardial infarction within 24 weeks (168 days) before the screening visit.

6. Renal failure requiring dialysis, or renal transplant at screening or potentially during the study.

7. Allergy or hypersensitivity to any of the compounds/excipients in the study interventions formulations.

8. Presence of any contraindications indicated in the locally approved label for aflibercept.

9. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, might affect interpretation of the results of the study, or renders the participant at high risk for treatment complications.

10. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the sponsor.

11. Pregnant or breastfeeding women.

Prior Therapy

12. Any prior or concomitant ocular (in the study eye) or systemic treatment (with an investigational or approved, anti-VEGF or other agent) or surgery for nAMD, except dietary supplements or vitamins.
13. Prior treatment of the study eye with any of the following drugs (any route of ophthalmic administration) or procedures before baseline visit (Day 1):
    a. Anti-angiogenic drugs at any time including investigational therapy (e.g., with anti-angiopoietin/anti-VEGF bispecific monoclonal antibodies).
    b. Long-acting steroids, within 16 weeks (112 days) before the screening visit, or any treatment with IVT implant, gene therapy, or cell therapy at any time.
    c. Ocriplasmin (Jetrea®) at any time.
    d. Vitreoretinal surgery and/or including scleral buckling at any time.
    e. Any other intraocular surgery within 90 days before the screening visit.
    f. Panretinal laser photocoagulation or macular laser photocoagulation within 90 days before the screening visit.
    g. YAG capsulotomy in the study eye within 30 days before the screening visit.
14. Prior treatment of the fellow eye with any of the following:
    a. Investigational therapy (e.g., with anti-angiopoietin/anti-VEGF bispecific monoclonal antibodies) within 180 days before the screening visit.
    b. IVT implant, gene therapy, or cell therapy at any time.

    Prior treatment in the fellow eye with approved anti-VEGF therapy is allowed. Prior treatment in the fellow eye with bevacizumab (although not approved but a component of standard of care in some countries) is also allowed.

Prior/Concurrent Clinical Study Experience

15. Participation in other clinical trials requiring administration of investigational treatments (other than vitamins and minerals) at the time of screening, or within 30 days or 5 half-lives of administration of the previous study intervention, whichever is longer.

5.2.1 Additional Exclusion Criteria for the Dense PK Substudy

Participants who meet any of the following criteria will be not be eligible for the Dense PK Substudy:

1. Prior treatment with IVT aflibercept in the fellow eye within 12 weeks (84 days) before the screening visit.
2. Active CNV in the fellow eye requiring anti-VEGF treatment at the time of screening visit.
3. Other IVT anti-VEGF treatment (ranibizumab, bevacizumab, brolucizumab, conbercept, pegaptanib sodium) in the fellow eye within 4 weeks (28 days) before the screening visit.

4. Systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg.
5. Known cardiac arrhythmia, based on medical history and/or outcome of ECG at screening.
6. Variation by more than 10% in the 3 pre-randomization blood pressure measures recorded at the screening visits and at randomization (see Table 1–4).
7. Participants who, in the opinion of the investigator, are unlikely to have stable blood pressure over the course of the study (e.g., due to known or suspected non-compliance with medication).

5.3 Lifestyle Considerations

No lifestyle restrictions are required during the study.

5.4 Screen Failures and Re-Screening

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Re-starting the defined set of screening procedures to enable a "screening failure" participant to re-screen at a later time point is not allowed, with the following exceptions:

- The participant had successfully passed the screening procedures, but was not randomized and could not start subsequent treatment on schedule.
- Initial screening occurred too early to fulfil the requirements for time intervals after specific therapeutic interventions specified in the exclusion criteria.
- The in/exclusion criteria preventing the participant's initial attempt to participate have been changed (via protocol amendment).
- The reason for the screening failure (e.g., uncontrolled glaucoma or arterial hypertension) was subsequently resolved.

Under any of the above exceptions, a participant may be re-screened once only. To be eligible, the re-screened participant must meet all inclusion criteria and none of the exclusion criteria at the re-screening visit.

In any case, the investigator must ensure that the repeated screening procedures do not expose the participant to an unjustifiable health risk. Also, for re-screening, the participant must re-sign the ICF, even if it was not changed since the participant's previous screening.

Re-screened participants should be assigned the same participant number as for the initial screening.

6. Study Intervention

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

6.1 Study Intervention(s) Administered

Table 6–1 Study Interventions

Masked part of study (up to Week 96)			
Group Name	**HDq12, HDq16**	**2q8**	**Sham**
Intervention Name	Aflibercept HD	Aflibercept 2 mg	Sham
Type	Drug	Drug	Not applicable
Dose Formulation	Solution in Vial	Solution in Vial	Not applicable
Unit Dose Strength(s)	CCI mg/mL	40 mg/mL	Not applicable
Dosage Level(s)	8 mg (CCI µL)	2 mg (50 µL)	Not applicable
Route of Administration	IVT injection	IVT injection	Not applicable
Use	Experimental	Active comparator	Sham procedure
Packaging and Labeling	Study Intervention will be provided in sterile 3 mL glass vials. Each vial will be labeled as required per country	Study Intervention will be provided in sterile 2 mL glass vials. Each vial will be labeled as required per country	Empty kit

CCI

2q8=aflibercept 2 mg administered every 8 weeks until Week 92, after 3 initial injections at 4-week intervals. Participants who consent to continue in the extension period from Week 96 in Year 3 CCI starting at Week 96; thereafter, CCI CCI to individual participant response as determined by dose regimen modification criteria for extension period (E-DRM) in Year 3. If the E-DRM criteria are met at Week CCI, these participants will receive a dose at Week CCI and their subsequent treatment interval will be shortened to every 8 weeks.
HDq12=high dose aflibercept 8 mg administered every 12 weeks until Week 92, after 3 initial injections at 4-week intervals. Participants who consent to continue in the extension period from Week 96 in Year 3 receive CCI according to individual participant response as determined by the E-DRM in Year 3.
HDq16=high dose aflibercept 8 mg administered every 16 weeks until Week 92, after 3 initial injections at 4-week intervals. Participants who consent to continue in the extension period from Week 96 in Year 3 receive CCI according to individual participant response as determined by the E-DRM in Year 3.
HD=high dose, IVT=intravitreal

a Only applicable during the masked transition period (Week 96 to Week 108).

Each vial is for single use only.

6.1.1 Medical Devices

Medical devices used in this study include both devices that help prepare and deliver the study intervention (study drug and comparator), as well as devices that are used to gather additional

clinical data. These devices are CE marked (or FDA cleared) according to the regulatory requirements specific for the country where the study site is located.

Sponsor provides an 18-gauge filter needle for use preparing the study medication in this study. Other medical devices (not manufactured by or for Bayer) to be used in this study to deliver the medication according to Table 6–1 include syringes and injection needles. Instructions for use of these medical devices are provided by the legal manufacturer of these devices. Deficiencies (including malfunctions, use error, and inadequate labelling) related to the filter needles, injection needles, and syringes 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.

Additional devices (Omron Model HEM 907XL (or comparable), Goldmann applanation tonometry / rebound tonometry Icare / Tonopen, standard digital 12-Lead ECG, etc.) are used for gathering additional clinical data (measuring blood pressure, IOP, heart rate, etc.). Instructions for use of these medical device are provided by the legal manufacturer of these devices. Deficiencies related to these devices should be reported directly to the legal manufacturer of the deficient medical device.

6.2 Preparation/Handling/Storage/Accountability

The investigator or designee must 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 participants enrolled 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 (study drug and comparator) 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 (study drug and comparator) 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 medication (study drug and comparator) 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.

Sham kits will assigned for visits requiring sham procedures. The sham kits are empty but should be handled same as a study intervention kit.

Sham procedure will be given on visits when an active injection is not planned. No sham procedures will be given at the non-treatment visit at Week 12. Thereafter, all participants in the masked part of study and the masked transition period will receive either active study treatment or sham procedure (for masking purposes) following their assigned treatment group and eligibility for DRM.

Details on the administration of aflibercept IVT injection, sham procedure, and post-injection procedures are provided in Section 10.7.

After study intervention injection or sham procedure, participants will be observed for at least 30 minutes.

Dose modification procedures are detailed in Section 6.6.

6.3 Measures to Minimize Bias: Randomization and Masking

6.3.1 Intervention Assignment

Participants will be randomly assigned in a 1:1:1 ratio to 1 of 3 parallel treatment groups as described in Section 4.1. Randomization will be stratified by geographic region (Japan vs. Rest of World), and baseline (Day 1) BCVA (<60 vs. ≥60), to ensure balanced distribution of the treatment groups within each stratum.

Participants will be centrally assigned to randomized study intervention using an Interactive Response System (IXRS). 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 SoA (Section 1.3).

6.3.2 Masking

6.3.2.1 Masked Part (Screening to Week 96) and Masked Transition Period for Extension (Week 96 to Week 108)

All study site personnel (except for those performing the unmasked roles as described below and in Table 6–2), must remain masked to treatment assignment of participants in order to ensure an unbiased assessment of visual acuity, safety, and ancillary study measures. Masking will continue until the end of the masked transition period of the study extension. Any visit scheduled for Week 110 will actually be combined with the visit at Week 108 by making use of the overlapping visit windows (i.e., CCI [redacted]). At the end of Week 108 visit, only the date of the next planned visit will be known. On the actual date of the visit subsequent to Week 108, the date of the immediate previous treatment will also be disclosed to allow accurate interval adjustment. Subsequently (after a participant reaches Visit E04, Week 108), only the BCVA examiners will remain masked throughout the study (i.e., with no access to the participant file, only to the BCVA file); all other tasks for that participant previously assigned to masked or unmasked teams can be performed by any study personnel.

Masking/unmasking of the study team will be described in a blinding maintenance plan.

An unmasked monitor will be responsible for unmasked site visits and will be unmasked to study treatment. Participants, all other study personnel, central reading center, and Steering

Committee members must remain masked to treatment assignment. A masked monitor will be responsible for the masked site visits.

Site personnel must not change from unmasked to masked roles after the first participant is randomized at the site. Masked staff are allowed to change to unmasked role under exceptional circumstances, if approved by the sponsor.

Active and sham treatments will be masked and will be administered by an unmasked investigator (or designee).

Masked Roles

The masked personnel are responsible to (i) assess AEs (except for the post-injection evaluation), (ii) perform the masked assessment of efficacy and safety, iii) assess if a participant has met pre-specified criteria for dose regimen shortening at Weeks 16, 20, and 24 and for dose regimen shortening or extending at and after Week 52, (iv) report any medical device AEs/SAEs/device deficiencies relating to devices used for gathering clinical data (see Section 6.1.1).

Depending on their function, masked personnel are also responsible for performing the masked assessments of visual acuity, ophthalmologic assessments, non-ophthalmologic assessments, and blood samples collection and laboratory assessments.

Every effort will be made to ensure that the visual acuity examiner remains masked to treatment assignment in order to allow for an unbiased assessment of visual acuity. The visual acuity examiner should only perform the assigned task of visual acuity assessments and should make every effort to remain masked to participant's previous letter score and study eye; another masked team member will document BCVA values in source and electronic case report form (eCRF).

Unmasked Roles

An unmasked investigator (or designee), separate from the masked personnel, will perform active injection / sham procedure (including rescue regimen), post-injection indirect ophthalmoscopy, and post-injection IOP assessment. The participant must remain unaware of the treatment assignment; thus, the study intervention and syringe must be covered and remain unidentifiable to the participant. The unmasked investigator will not have any role in the study beyond the i) receipt, tracking, preparation, destruction, and administration of study intervention, and ii) reporting any AEs relating to the injection procedure or medical device AEs/SAEs/device deficiencies relating to the filter needle, injection needle, or syringe, during the post-injection period until the next scheduled visit. An unmasked drug handler (e.g., pharmacist) may be assigned to handle receipt, storage, and preparation of active and sham kits. Unmasked personnel are also allowed to do screening/baseline procedures such as initial informed consent (reconsent must be undertaken by masked personnel).

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

An overview of the masked and unmasked site personnel is presented in Table 6–2.

Table 6–2: Masked and Unmasked Site Personnel

Study Procedure	Masked Study Staff [a]	Unmasked Study Staff [b]	Certification needed
Study intervention:			
Study intervention (study drug) accountability		X	
Injection-related procedures:			
IXRS access [c]	X	X	
(Pre-)injection procedures		X	
IVT injection (active, sham)		X	
Post-injection assessment (post-injection indirect ophthalmoscopy, and post-injection IOP)		X	
AE reporting:			
AEs and device-related AEs/SAEs/deficiencies relating to filter needle, injection needle, or syringe during injection procedure and post-injection assessment		X	
All other AEs, device-related AEs/SAEs/ deficiencies for devices used for gathering clinical data	X		
Ophthalmic assessment:			
BCVA examination BCVA recording in eCRF (different from BCVA examiner)	X X		X
Full ophthalmic examination (IOP, slit lamp, indirect ophthalmoscopy)	X		
FA, FP	X		X
SD-OCT	X		X
ICGA, if applicable	X		X
OCT-A, if applicable	X		X
NEI-VFQ-25 questionnaire	X		X
Other procedures:			
Informed consent	X [d]	X [d]	
Demography, medical and ocular history	X [d]	X [d]	
Record concomitant medications / treatments / interventions [e]	X		
Blood sampling (e.g., serum pregnancy test, immunogenicity, PK sampling)	X		
Blood pressure measurement	X		
Urine pregnancy test	X		

AE=adverse event, BCVA=best corrected visual acuity, eCRF=electronic case report form, FA=fluorescein angiography, FP=fundus photography, ICGA=indocyanine green angiography, IOP=intraocular pressure, IVT=intravitreal, IXRS=Interactive Response System, NEI-VFQ-25=National Eye Institute Visual Functioning Questionnaire-25, OCT-A=optical coherence tomography angiography, PK=pharmacokinetic, SAE=serious adverse event, SD-OCT=spectral domain optical coherence tomography.

a Includes masked investigator, masked study nurse/study coordinator, and study personnel for ocular assessments.

b Includes, unmasked investigator administering active/sham study intervention and assessing post-injection ocular assessments, and drug handler/pharmacist dispensing active/sham study intervention.

c For the purpose of treatment assignments/kit numbers, only the unmasked staff should have access to IXRS. Masked staff will have limited access to IXRS.

d Masked or unmasked personnel are allowed to do screening/baseline procedures such as initial informed consent. Reconsent must be undertaken by masked personnel.

e Except concomitant medications due to AE occurring during the injection or in the immediate post-injection period, which must be reported by unmasked investigator.

Masked study intervention kits coded with a medication numbering system will be used. In order to maintain the mask, lists linking these codes with product lot numbers will not be accessible to individuals involved in study conduct.

In compliance with applicable regulations, in the event of a suspected unexpected serious adverse reactions (SUSAR) (see Section 8.3.4) related to the masked treatment, the participant's treatment code will usually be unmasked before reporting to the health authorities, ethics committees and investigators (Section 10.3.4).

Emergency Unmasking

The IXRS will be programmed with mask-breaking instructions. In case of an emergency, the investigator has the responsibility for determining if unmasking of a participant's intervention assignment is warranted. If the investigator is unavailable, and a treating physician not associated with the study requests emergency unmasking, the emergency unmasking requests are forwarded to the study specific emergency medical advice 24 hours/7 day service. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unmasking is warranted, the investigator should make every effort to contact the sponsor or the sponsor representative prior to unmasking a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unmasked, the sponsor must be notified within 24 hours after breaking the mask. The date and reason that the mask was broken must be recorded in the source documentation and eCRF, as applicable.

6.3.2.2 Open-label Part (After Week 108 to Week 156)

In the open-label part of the study, CCI [redacted] according to their individual treatment schedule. The group assignment used during the masked part will not be disclosed. Sites are required to enter all available data from the masked part of the study before being able to see the treatment schedule for the open-label part. The BCVA examiner will remain masked to treatment received during the open-label part of the study. All other team members, as well as the study participants, will be aware of the treatment schedule starting from the first visit after Week CCI

6.4 Study Intervention Compliance

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

6.5 Concomitant Therapy

6.5.1 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.

Participants 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 participant'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 participant is receiving at the time of enrollment or 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

If a pre-treatment concomitant medication is administered in the study eye before injection (e.g., antibiotic, topical anesthetic), it must be administered for sham procedures as well.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.2 Fellow Eye Treatment

Only 1 eye per participant may be enrolled in the study. If a participant's fellow (non-study) eye requires anti-VEGF treatment during the participant'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 participant. 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. Participants 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/aflibercept HD treatment), IVT injection-procedure, and other protocol-specified procedures.

For participants enrolled in the Dense PK Substudy, if a participant's fellow (non-study) eye requires anti-VEGF treatment prior to Week 12, PK sample(s) should be collected prior to administration of study intervention in the study eye and aflibercept (2 mg) in the fellow eye.

6.6 Dose Regimen Modification/Rescue Regimen

For masking purposes, assessments for DRM will be performed in all participants at all visits (through the IXRS) starting from Week 16. Based on these assessments, participants in the HD groups may have their treatment intervals shortened or extended. The minimum interval between injections will be 8 weeks, which is considered a rescue regimen for participants randomized to HD aflibercept who are unable to tolerate a dosing interval greater than every 8 weeks. Participants in the aflibercept 2 mg group will remain on fixed q8 dosing throughout the study until the end of masked study visit at Week 96 (i.e., will not have modifications of their treatment intervals regardless of the outcomes of the DRM assessments).

6.6.1 Year 1: Baseline to Week 48

Beginning at Week 16, participants in the HD groups will have the dosing interval shortened (at the visits described below) if BOTH the following DRM criteria are met:

1. BCVA loss >5 letters from Week 12, AND
2. >25 µm increase in central retinal thickness (CRT) from Week 12 OR new foveal hemorrhage OR new foveal neovascularization

In case the Week 12 measurement is not available, the Week 8 measurement should be used instead. If both, Week 12 and Week 8 measurements are not available, the Week 4 measurement should be used instead.

If a participant in the HDq12 group or the HDq16 group meets both criteria at Week 16 or Week 20, the participant will be dosed with 8 mg aflibercept at that visit and will continue on rescue regimen (aflibercept 8 mg, every 8 weeks). If a participant in the HDq16 group who has not met the criteria at Week 16 or Week 20 meets both criteria at Week 24, the participant will be dosed with 8 mg aflibercept at that visit and will continue on q12 dosing.

For participants whose interval was not shortened to q8 dosing at or before Week 24, the interval will be shortened if the DRM criteria are met at subsequent visits with active injection. Participants in the HDq12 group who meet the criteria will receive the planned dose at that visit and will then continue on rescue regimen (aflibercept 8 mg, every 8 weeks). Participants in the HDq16 group who meet these criteria will receive the planned dose at that visit and will then continue to be dosed every 12 weeks if they were on a 16-week interval, or switch to the rescue regimen (aflibercept 8 mg, every 8 weeks) if they were on a 12-week interval. Therefore, a participant randomized to HDq16 whose injection interval has been shortened to q12 will have their injection interval further shortened to q8 if these criteria are met at any subsequent assessment.

6.6.2 Year 2: Week 52 to Week 96 (End of Masked Part of Study)

From Week 52 through the end of the masked part of study (Year 2), all participants in the HD groups will continue to have the interval shortened in 4-week intervals (to a minimum of q8) if the DRM criteria for shortening are met at visits with active injection, using the criteria described above for Year 1.

In addition to shortening of the interval, all participants in the HD groups (including HD group participants whose interval was shortened during Year 1) may be eligible for interval extension (by 4-week increments) if the following DRM criteria are met at visits with active injection in Year 2:

1. BCVA loss <5 letters from Week 12, AND
2. No fluid at the central subfield on OCT, AND
3. No new onset foveal hemorrhage or foveal neovascularization

For participants who do not meet the criteria for shortening or extension of the interval, the dosing interval will be maintained.

As in Year 1, all participants in all treatment groups (including the 2q8 group) will be evaluated against both DRM criteria at all visits through the IXRS for masking purposes. However, changes to dosing schedule will only be implemented as described above. No changes to the dosing schedule will be made to the 2q8 treatment group at any time. All

anatomic criteria will be based on the site evaluations/OCT assessments, not on the reading center assessments.

6.6.3 Year 3 (Masked Transition Period and Open-label Extension Part): Week 96 to Week 156 (End of Study) / E-DRM Criteria

The E-DRM criteria refer to new baseline (NB) which will be defined as the CCI values CCI).

At Week 96, no interval adjustments will be performed for any group.

Beginning at Week CCI all participants will have the dosing interval **shortened** if the following criteria are met at ANY visit (scheduled or unscheduled, with or without active injection):

1. BCVA loss >5 letters from NB BCVA due to persistent or worsening AMD, AND
2. Any of the following
   - >25 µm increase in CRT from NB CRT
   - new onset of foveal neovascularization
   - new foveal hemorrhage

OR

3. BCVA loss >10 letters NB due to worsening AMD

If the E-DRM shortening criteria are met at any treatment, monitoring or unscheduled visit, the participant will be dosed at the same visit unless the previous dose was administered less than 8 weeks before.

If the E-DRM criteria are met at a dosing visit the subsequent interval will be shortened by CCI weeks. If the E-DRM criteria are met at a non-dosing visit, the subsequent interval will be shortened to the time from the most recent dose minus CCI weeks. Participants can be seen for unscheduled visits at any time at the investigator's discretion. Treatment intervals may not be adjusted to less than 8 weeks. Actual intervals may be slightly shorter due to the windows allowed for visits planned 8 weeks apart.

Starting from Week CCI, if a participant does not meet any of the E-DRM criteria but is deemed at high risk for vision loss, the participant should be brought back for evaluation within approximately 2 weeks. If E-DRM criteria are still not met, and the investigator feels there is high risk for irreversible disease progression, a dose can be given at that visit, and the subsequent interval will be shortened to the time from the most recent dose minus CCI weeks. The minimum dosing interval remains every 8 weeks (q8).

Similarly to Year 2, all participants in all groups (including participants whose interval was shortened during Year 1, Year 2, or Year 3) are eligible for interval **extension** CCI to a CCI interval of CCI weeks, but in contrast to Year 2, intervals will now be modified by CCI, if all of the following E-DRM criteria are met at visits with active injection:

1. BCVA loss <5 letters from the NB, AND
2. No fluid at the central subfield on OCT, AND
3. No new onset foveal hemorrhage or foveal neovascularization

For participants who do not meet the criteria for shortening or extension of the interval, the dosing interval will be maintained.

For E-DRM adjustment purposes, similar to the masked study part, all anatomic criteria will be based on the local site evaluations/OCT assessments, not on the assessments of the central reading center.

6.7 Intervention After the End of the Study

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

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Study intervention (study drug or comparator) discontinuation can be triggered by the participant (or legally authorized representative) or by the treating investigator.

Participants 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.

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

7.2 Participant Discontinuation/Withdrawal from the Study

A participant 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, compliance, or administrative reasons. This is expected to be uncommon.

Participants 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 nonocular) that, from the participant’s or the investigator’s view, is potent enough to require withdrawal from the study. The investigator must notify the sponsor immediately if a participant is withdrawn because of an AE/SAE.
- At the discretion of the treating investigator. The development of conditions, which would have prevented a participant’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 sponsor that termination is in the participant's best medical interest or administrative decision for a reason other than an AE/SAE.
- A female participant 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.

Participants 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 participant must be withdrawn from the study.
- Systemic anti-angiogenic agents were taken by the participant during the study.
- If, in the investigator's opinion, continuation of the study would be harmful to the participant'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. 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 participant will be permanently discontinued both from the study intervention and from the study at that time.

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

Participants who withdraw from the study will not be replaced.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or 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 participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known

mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant 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. Protocol waivers or exemptions are not allowed. Participants 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 participant 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 participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) 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 time frame defined in the SoA.

The maximum amount of blood collected from each participant over the duration of the study, including safety laboratory assessments, sparse PK, Dense PK Substudy, optional genomic substudy, and any extra assessments that may be required, will not exceed 120 mL. Additional repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

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 (BCVA)

Visual function will be assessed using the ETDRS protocol (3) 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) and must remain masked to treatment assignment. For each participant, the same examiner must perform all assessments whenever possible. BCVA should be done before any other ocular procedures are performed.

8.1.1.2 Intraocular Pressure (IOP)

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

At all visits, IOP should be measured bilaterally by the masked investigator (or designee). On days when study intervention is administered, IOP should also be measured approximately 30 to 60 minutes after administration of study intervention (study eye only) by the unmasked investigator (or designee). The exact timing is left to the discretion of the unmasked investigator.

If multiple post-injection measurements are performed, the final measurement before the participant leaves should be documented in the eCRF. Any injection-related increase in IOP (and treatment) should be documented in a masked fashion.

8.1.1.3 Slit Lamp Examination

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

Participants' 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 masked investigator, as specified in Table 6–2.

8.1.1.4 Indirect Ophthalmoscopy

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

Participants' posterior pole and peripheral retina will be examined by indirect ophthalmoscopy at each study visit pre-dose (bilateral) by the masked investigator and post-dose (study eye) by the unmasked investigator, as specified in Table 6–2. Post-dose evaluation should be performed as soon as possible, approximately 0 to 15 minutes after injection. The exact timing is left to the discretion of the unmasked investigator. If the indirect ophthalmoscopy cannot be performed immediately after injection, see Section 10.7.2.3.

8.1.1.5 Fundus Photography (FP) and Fluorescein Angiography (FA)

The anatomical state of the retinal vasculature of the study eye will be evaluated by FP and FA at visits specified in Table 6–2. The treating investigator may perform additional FA/FP at other times during the study based on his/her medical judgment and standard of care. Photographers must be masked to treatment assignment and must be certified by the reading center to ensure consistency and quality in image acquisition.

FP and FA images will be read by the investigator for individual treatment decisions and sent to an independent reading center where images will be read by masked readers. The participants' eligibility to participate in the study in terms of FA will be confirmed by the central reading center before randomization.

The same FA/FP imaging system used at screening and Day 1 must be used at all subsequent visits in each participant. Images will be taken in both eyes before dosing (active or sham injection). Detailed instructions can be found in the imaging manual.

All FA and FP images will be archived electronically at the site as part of the source documentation.

The study manual will further specify the acquisition and assessment for FA/FP during the study.

8.1.1.6 Spectral Domain Optical Coherence Tomography (SD-OCT)

Retinal and lesion characteristics will be evaluated using SD-OCT. Technicians must be masked to treatment assignment and must be certified by the reading center to ensure consistency and quality in image acquisition and segmentation. 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 masked readers. The participants' eligibility to take part in the study in terms of SD-OCT will be confirmed by the central reading center before randomization.

The same SD-OCT imaging system used at screening and Day 1 must be used at all follow-up visits in each participant. Images will be taken in both eyes before dosing (active or sham 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.

8.1.1.7 Indocyanine Green Angiography (ICGA)

ICGA will be optional, performed at sites with the appropriate equipment. ICGA will be used to diagnose and characterize the PCV subtype of nAMD. Technicians must be masked to treatment assignment and must be certified by the reading center to ensure consistency and quality in image acquisition.

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

All ICGAs 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 ICGA during the study.

8.1.1.8 Optical Coherence Tomography Angiography (OCT-A)

Optical coherence tomography angiography (OCT-A) will be optional, performed at sites with the relevant equipment. Technicians must be masked to treatment assignment and must be certified by the reading center to ensure consistency and quality in image acquisition.

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

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.

8.1.2 National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25)

Vision-related quality of life (QoL) will be assessed using the NEI-VFQ-25 questionnaire (4) in the interviewer-administered format. It is a reliable and valid 25-item version of the 51-item NEI-VFQ.

The questionnaire will be presented in the local language and should be administered in a quiet room by a masked study-related person trained to administer this type of questionnaire, preferably before other visit procedures are performed.

8.2 Safety Assessments

Planned time points 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 should be measured at Visit 1. The assessment will be based on the clinical judgment of the investigator and aim to evaluate the overall health of the participant.

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, and before any blood draws, if applicable, per the procedure outlined in the study manual. When possible, timing of all blood pressure assessments should be within ±2 hours of clock time of dosing on Day 1.

Where possible, blood pressure assessments will be taken using automated office blood pressure (AOBP) with the Omron Model HEM 907XL (or comparable). Measures will be recorded in the eCRF. Detailed instructions can be found in the study manual.

Participants in the Dense PK Substudy will also have blood pressure and heart rate assessed at each visit within the substudy. These assessments must be within ±2 hours of the clock time of dosing on Day 1.

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

8.2.3 Electrocardiograms

A standard digital 12-lead ECG will be performed. Heart rate will be recorded from the ventricular rate and the PR, QRS, RR, and QT intervals will be recorded. The ECG strips or report will be retained with the source documentation.

Electrocardiograms will be forwarded to a central reader.

8.2.4 Clinical Safety Laboratory Assessments

See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal

laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 4 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the Medical Monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

All samples collected for laboratory assessments should be obtained prior to administration of fluorescein and/or indocyanine green and prior to administration of study intervention.

At visits at which FA or ICGA are performed, urinalysis samples must be collected before FA/ICGA to avoid false elevations in urine protein values.

Laboratory (hematology, chemistry, and urinalysis) analyses will be performed and reviewed at screening (Visit 1). A sample is not needed if results from laboratory tests within 8 days prior to screening are available and there was no change in the clinical situation from the time of the sample to the screening visit.

Additional samples, including blood samples for immunogenicity, may be collected at any time during the study as determined necessary by the investigator or required by local regulations. This might be true for participants receiving rescue regimen with aflibercept.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE and SAE can be found in Section 10.3. The definitions of device-related safety events (adverse device effects [ADEs] and serious adverse device effects [SADEs]) can be found in Section 10.4. Device deficiencies are covered in Section 8.3.7.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant'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 participant to discontinue the study intervention or the study (see Section 7).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the moment when informed consent is obtained until the last follow-up visit at the time points specified in the SoA (Section 1.3).

All AE will be collected from the moment when informed consent is obtained until the last follow-up visit at the time points 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, as indicated in Section 10.3. 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 AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant 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 AEs and SAEs

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 10.3.

For participants receiving fellow eye injections, AEs will also 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/aflibercept HD treatment), IVT injection-procedure, and other protocol-specified procedures.

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants 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 (IRB)/Independent Ethics Committees (IEC), and investigators.

For all studies except those utilizing medical devices investigator safety reports must be prepared for SUSAR according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female participants or female partner of a male participant 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 should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Outcome for all pregnancies should be reported to the sponsor.

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 described in Section 6.1.1. In order to fulfil 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.

Deficiencies should be reported by completing the product technical complaint (PTC) form and then sending PTC form via email ptc-imp@bayer.com. Included in this PTC reporting requirement are devices used to prepare the dose (filter needle / syringe) or deliver the dose (injection needle /syringe).

Device deficiencies for all devices used for gathering additional clinical data (measuring blood pressure, IOP, heart rate, etc.) should be reported directly to the legal manufacturer of the medical device.

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

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Section 10.3 of the protocol.

8.3.7.1 Time Period for Detecting Medical Device Deficiencies

Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported 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 participant has been discharged from the study, and such incident 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 participants, 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 Medical Device Deficiencies to Sponsor

For device deficiencies related to medical devices used to prepare, apply, or deliver the study medication:

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 PTC 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 medical device deficiency reports.

8.3.7.4 Regulatory Reporting Requirements for Medical 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 fulfil 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 Treatment of Overdose

For this study, any administered dose of study intervention greater than 2 mg (for the 2q8 group during the masked part of study up until Week 96) or greater than 8 mg (for the HDq12 or HDq16 groups during the entire study; for the 2q8 group during the extension period of study from Week 96) 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:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. 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 participant.

8.5 Pharmacokinetics

Blood samples for analysis of systemic concentrations of aflibercept (bound and free) will be collected. Collection of PK samples for all participants (sparse schedule) will be optional in China.

A blood sample for plasma concentrations of aflibercept will be collected according to the time points in the SoA (Section 1.3). For participants in the Dense PK Substudy, blood samples will be collected as outlined in Table 1–4.

Additional samples may be collected at any time during the study as determined necessary by the investigator or required by local regulations. PK (and anti-drug antibody [ADA]) samples may be collected in the event of an SAE.

If the fellow eye needs to be treated with aflibercept on a day with PK sample collection, the PK sample should be collected first.

To ensure accuracy of the PK analyses, it is critical to accurately record the exact date and time (24-hour clock) of all blood samples taken on the eCRF.

Details about the collection, processing, storage and shipment of samples will be provided separately (e.g., sample handling sheets or laboratory manual).

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study. Blood pressure is considered under safety endpoints.

8.7 Genetics

8.7.1 Optional Genomic Substudy

Optional participation in genomic substudy will be offered to all participants, except those in China, who will not be enrolled in this optional substudy. See Section 10.6 for details.

8.8 Future Biomedical Research

Participation is optional. Participants who do not wish to participate in the FBR component of the study may still participate in the main study. Participants from China will not be enrolled in the optional FBR component of the study.

No additional blood sample is required – analysis may be performed on remaining blood samples (from e.g., PK or ADA sampling).

Samples will be banked in long-term storage. The unused PK samples will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for FBR of nAMD, related diseases or pathways blocked by study treatment, and any adverse reactions that may emerge. These samples may also be used for unrelated assay development and validation purposes. After 15 years, any residual samples will be destroyed.

The results of these FBR analyses will not be presented in the clinical study report.

8.9 Biomarkers

Not applicable.

8.10 Immunogenicity Assessments

Antibodies to aflibercept will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3). These samples will be tested by the sponsor or sponsor's designee. Collection of ADA and neutralizing antibody (NAb) samples will be optional in China.

Serum samples will be screened for antibodies binding to aflibercept and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to aflibercept and/or further characterize the immunogenicity of aflibercept.

The detection and characterization of antibodies to aflibercept will be performed using a validated assay method by or under the supervision of the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s).

Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor, to enable further analysis of immune responses to aflibercept.

8.11 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

Due to differing requirements for the submission to regulatory authorities, 2 different testing strategies will be applied, which will be detailed in the SAP: a Global plan (G-SAP) and an EMA/PMDA plan (EP-SAP). This section provides the basis for these plans, which will be used to govern the detailed analysis of the study. The G-SAP plan will constitute the primary analysis for the study. The EP-SAP plan will be used for submission to the EMA/PMDA regulatory authorities.

9.1 Statistical Hypotheses

The 2 primary hypotheses to be tested are the non-inferiority of HDq12 vs. 2q8 (control) and HDq16 vs. 2q8 (control) with respect to the primary endpoint of change from baseline in BCVA at Week 48. The non-inferiority margin is set at 4 letters for each of the primary hypotheses.

Justification of the Non-inferiority Margin

Previous studies with anti-VEGF therapies in other indications regarded a difference of 5 letters as clinically relevant. For example, the CATT study in AMD, comparing ranibizumab and bevacizumab in a setting close to real life, used a non-inferiority margin of 5 letters in the in BCVA (5). Recently, controlled phase 3 clinical trials studying AMD (HARBOR study (6) and HAWK and HARRIER (7)) were based on a reduced margin of 4 letters.

Null and Alternative Hypotheses

The primary family of hypotheses (null vs. alternative) are stated as below.

1. Change from baseline in BCVA at Week 48 (non-inferiority at a margin of 4 letters):

   H_{10}: $\mu_1 \leq \mu_0 - 4$ vs. H_{11}: $\mu_1 > \mu_0 - 4$ (i.e., HDq12 vs. 2q8)

   H_{30}: $\mu_2 \leq \mu_0 - 4$ vs. H_{31}: $\mu_2 > \mu_0 - 4$ (i.e., HDq16 vs. 2q8)

where μ_0, μ_1, μ_2 are the mean change from baseline in BCVA at Week 48 for 2q8, HDq12, and HDq16, respectively. In addition, the HDq12 and HDq16 treatment groups will be tested

for non-inferiority or superiority against the control group of 2q8 with respect to the following key secondary endpoints. The hypotheses (null vs. alternative) are, respectively, stated as below:

2. Only included in the EP-SAP for EMA and PMDA:
   Change from baseline in BCVA at Week 60 (non-inferiority at a margin of 4 letters)

   H_{20}: $\mu_1 \leq \mu_0 - 4$ vs. H_{21}: $\mu_1 > \mu_0 - 4$ (i.e., HDq12 vs. 2q8)

   H_{40}: $\mu_2 \leq \mu_0 - 4$ vs. H_{41}: $\mu_2 > \mu_0 - 4$ (i.e., HDq16 vs. 2q8)

   where μ_0, μ_1, μ_2 are the mean change from baseline in BCVA at Week 60 for 2q8, HDq12, and HDq16, respectively.

3. Proportion of participants with no IRF and no SRF in central subfield at Week 16 (superiority)

   H_{50}: $p_1 \leq p_0$ vs. H_{51}: $p_1 > p_0$ (i.e., pooled high dose vs. 2q8)

   where p_0, p_1 are the proportion of participants with no IRF and no SRF in central subfield at Week 16 for 2q8, and the pooled high dose groups (HDq12 and HDq16), respectively. HDq12 and HDq16 high dose groups have same dosing regimen up to Week 16.

The HDq12 and HDq16 treatment groups will also be tested for superiority against the control group of 2q8 with respect to the change from baseline in BCVA at Week 48 (and Week 60, only for EP-SAP).

4. Change from baseline in BCVA at Week 48 (superiority):

   H_{60}: $\mu_1 \leq \mu_0$ vs. H_{61}: $\mu_1 > \mu_0$ (i.e., HDq12 vs. 2q8)

   H_{80}: $\mu_2 \leq \mu_0$ vs. H_{81}: $\mu_2 > \mu_0$ (i.e., HDq16 vs. 2q8)

where μ_0, μ_1, μ_2 are the mean change from baseline in BCVA at Week 48 for 2q8, HDq12, and HDq16, respectively.

5. Only included in the EP-SAP for EMA and PMDA:
   Change from baseline in BCVA at Week 60 (superiority)

   H_{70}: $\mu_1 \leq \mu_0$ vs. H_{71}: $\mu_1 > \mu_0$ (i.e., HDq12 vs. 2q8)

   H_{90}: $\mu_2 \leq \mu_0$ vs. H_{91}: $\mu_2 > \mu_0$ (i.e., HDq16 vs. 2q8)

where μ_0, μ_1, μ_2 are the mean change from baseline in BCVA at Week 60 for 2q8, HDq12, and HDq16, respectively.

Control of Multiplicity

The overall family-wise type 1 error will be controlled at 0.025 (one-sided tests) for testing the primary and key secondary endpoints. Adjustment for multiple comparisons in the primary and key secondary endpoints will be made with a hierarchical testing procedure (see Table 9–1). This approach allows the confirmatory testing of a hypothesis at the full alpha level of 0.025 after successful rejection of the hypotheses which are ranked higher in the hierarchy. Further details will be described in the SAP.

Table 9–1 Testing Order of Hierarchical Testing Procedure in G-SAP and EP-SAP

G-SAP	EP-SAP
H_{10}: non-inferiority of HDq12 vs. 2q8 in primary endpoint "Change from baseline in BCVA at Week 48"	H_{10}: non-inferiority of HDq12 vs. 2q8 in primary endpoint "Change from baseline in BCVA at Week 48"
	H_{20}: non-inferiority of HDq12 vs. 2q8 in key secondary endpoint "Change from baseline in BCVA at Week 60"
H_{30}: non-inferiority of HDq16 vs. 2q8 in primary endpoint "Change from baseline in BCVA at Week 48"	H_{30}: non-inferiority of HDq16 vs. 2q8 in primary endpoint "Change from baseline in BCVA at Week 48"
	H_{40}: non-inferiority of HDq16 vs. 2q8 in key secondary endpoint "Change from baseline in BCVA at Week 60"
H_{50}: superiority of pooled high dose vs. 2q8 in key secondary endpoint "Proportion of participants with no IRF and no SRF in central subfield at Week 16"	H_{50}: superiority of pooled high dose vs. 2q8 in key secondary endpoint "Proportion of participants with no IRF and no SRF in central subfield at Week 16"
H_{60}: superiority of HDq12 vs. 2q8 in primary endpoint "Change from baseline in BCVA at Week 48"	H_{60}: superiority of HDq12 vs. 2q8 in primary endpoint "Change from baseline in BCVA at Week 48"
	H_{70}: superiority of HDq12 vs. 2q8 in key secondary endpoint "Change from baseline in BCVA at Week 60"
H_{80}: superiority of HDq16 vs. 2q8 in primary endpoint "Change from baseline in BCVA at Week 48"	H_{80}: superiority of HDq16 vs. 2q8 in primary endpoint "Change from baseline in BCVA at Week 48"
	H_{90}: superiority of HDq16 vs. 2q8 in key secondary endpoint "Change from baseline in BCVA at Week 60"

2q8=aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals, BCVA=best corrected visual acuity, EMA=European Medicines Agency, EP-SAP=EMA/PMDA statistical analysis plan, G-SAP=global statistical analysis plan, HDq12=aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals, HDq16=aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals, IRF= intraretinal fluid, IVT=intravitreal, PMDA=Pharmaceuticals and Medical Devices Agency, SRF=subretinal fluid

9.2 Sample Size Determination

The sample size calculation is based on the primary endpoint analysis, "change from baseline in BCVA in ETDRS letters to Week 48" in 2 comparisons to assess non-inferiority: HDq12 versus 2q8, and HDq16 versus 2q8.

The sample size has been calculated under the following assumptions:

- The changes in BCVA letter score from baseline are normally distributed.
- The true difference in the mean change in BCVA between HDq12 and 2q8, and between HDq16 and 2q8 is 0 letters.
- The standard deviation of the residuals is CCI (derived from the residuals of an analysis of covariance (ANCOVA) analysis of the CCI studies).

Under the hierarchical testing strategy, a sample size of 288 evaluable participants per group provides 94% power for rejecting the initial null hypothesis (HDq12 vs 2q8) for the primary endpoint assessing non-inferiority with a 1-sided t-test at significance level of 0.025. The

power to reject both primary null hypotheses (HDq12 vs 2q8 and HDq16 vs 2q8) is 88%. Under the prior testing strategy that was planned originally (before Protocol version 3.0, Global Amendment 2), a sample size of 288 evaluable participants per group provides 90% power for rejecting each of the null hypotheses for the primary endpoints assessing non-inferiority (HDq12 vs 2q8 and HDq16 vs 2q8) with a 1-sided t-test at significance level of 1.25% (=2.5%/2 Bonferroni correction).

Approximately 10% of the participants are assumed to drop out before Week 48 (time point of the primary endpoints). Therefore, approximately 320 participants are to be randomized in each group, leading to a total sample size of approximately 960 participants.

Approximately 1600 participants will be screened to achieve 960 randomly assigned to study intervention and 864 evaluable participants for an estimated total of 288 evaluable participants per treatment group.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process.

Justification of Japanese Sample Size

Out of the total sample size of approximately 960 participants, at least 96 (10%) are to be enrolled in Japan in order to provide consistent results with a certain probability.

For superiority trials, the PMDA guidance (8) proposes to determine the number of Japanese participants so that $D_{Japan} / D_{all} > \pi$ will occur with a probability of 80 % or higher, whereas D_{all} is the treatment difference in the entire study population across regions, and D_{Japan} is the treatment difference within the Japanese sub-population. Furthermore, $\pi = 0.5$ is generally recommended.

As the present study is a non-inferiority trial, this consistency criterion is adapted as follows: (D_{Japan} + non-inferiority margin) / (D_{all} + non-inferiority margin) > π.

With the sample size of at least 96 Japanese participants and $\pi = 0.5$:

- the probability to show a consistent result in at least one of the 2 hypothesis tests for the primary endpoints assessing non-inferiority (HDq12 vs. 2q8 and HDq16 vs. 2q8) is 81%.
- the probability to show a consistent result in one particular hypothesis test for the primary endpoints is 71%.

9.3 Populations for Analyses

The primary analysis is based on the estimand framework including the definition of the population which is of interest (see Section 9.4.1). The population of interest for the primary and key secondary endpoints is represented by the full analysis set (FAS).

The following populations are defined:

Population	Description
Full analysis set (FAS)	All participants randomly assigned to study intervention and who received at least 1 dose of study intervention.
Per protocol set (PPS)	All participants in the FAS, who did not have an important deviation from the protocol affecting primary efficacy endpoint.
Safety analysis set (SAF)	All participants randomly assigned to study intervention and who received at least 1 dose of study intervention.

PK analysis set (PKS)	The PK analysis population includes all participants who received any study intervention and who had a at least 1 non-missing result following the first dose of study intervention. Participants will be analyzed based on the actual treatment received.
Immunogenicity analysis set	The ADA analysis set includes all participants who received study intervention and had at least 1 non-missing result in the ADA assay following the first study dose. The NAb analysis set includes all participants who received any study intervention and who are negative in the ADA assay or with at least 1 non-missing result in the NAb assay [participants who are ADA negative are set to negative in the NAb analysis set]. Participants will be analyzed based on the actual treatment received.

9.4 Statistical Analyses

The SAP for the masked part of the study (Years 1 and 2) will be finalized prior to unmasking and will include a more technical and detailed description of the statistical analyses described in this section (statistical analyses related to the study extension [Year 3] will present results split by initial treatment assignment, pooled groups and overall. The analysis is exploratory and details will be described in a SAP document). This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

The testing of the primary and key secondary endpoints is performed at an overall significance level of 2.5% for the one-sided tests. The confirmatory testing strategy for the primary and the key secondary endpoints is defined in Section 9.1. For descriptive purposes 95% two-sided confidence intervals will be provided where applicable.

More details (including any subgroup analyses) will be described in the SAP.

9.4.2 Primary Efficacy Endpoint

The primary endpoint is the change in BCVA (as measured by ETDRS letter score) from baseline at Week 48.

The primary analysis is based on the estimand concept. The estimand of primary interest will mainly be based on a hypothetical strategy. It describes the change from baseline for all participants that started treatment assuming all participants have stayed on treatment until Week 48.

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

Target population: Defined by the inclusion/exclusion criteria.

Variable: Absolute change from baseline to Week 48 in BCVA.

Treatment condition: HD aflibercept administered HDq12 with option for DRM/rescue regimen (Section 6.6), or HDq16 with option for DRM/rescue regimen (Section 6.6), versus aflibercept 2 mg administered 2q8.

Intercurrent events: Premature discontinuation from treatment. Shortening/extension of the dosing interval (DRM/rescue regimen) will not be

considered an intercurrent event but as part of the randomized treatment regimen.

Population-level summary: Difference in least squared (LS) change from baseline to Week 48 in BCVA between HDq12 and 2q8 (HDq16 and 2q8, respectively).

The following 2 hypotheses will be tested in the primary analysis, to assess non-inferiority in the primary endpoint:

- HDq12 is non-inferior to 2q8 regarding the mean change in BCVA from baseline to Week 48 using a non-inferiority margin of 4 letters.
- HDq16 is non-inferior to 2q8 regarding the mean change in BCVA from baseline to Week 48 using a non-inferiority margin of 4 letters.

For the analysis, a mixed model for repeated measurements (MMRM) will be used with baseline BCVA measurement as a covariate and treatment group and the stratification variables as fixed factors as well as terms for the interaction between baseline and the visit and for the interaction between treatment and visit. A Kenward-Roger approximation will be used for the denominator degrees of freedom. More details (including the handling of missing data as well as the missing at random assumption) will be described in the SAP.

$$Y_{ijk} = \beta_0 + x_i \times \beta_{base} + \beta_{reg}^{(l)} + \beta_{base\_cat}^{(m)} + \beta_{treat}^{(k)} + \beta_{visit}^{(j)} + x_i \times \beta_{base*visit}^{(j)} + \beta_{treat*visit}^{(k,j)} + \epsilon_{ijk}$$

with

- Y_{ijk} being the change from baseline to visit j for the ith participant receiving treatment k
- β_0 being the intercept
- x_i being the baseline BCVA measurement of participant i
- β_{base} the fixed effect of the baseline BCVA measurement
- $\beta_{reg}^{(l)}$ the fixed effect of region l
- $\beta_{base\_cat}^{(m)}$ the fixed effect of categorized baseline BCVA measurement m
- $\beta_{treat}^{(k)}$ the fixed effect of treatment k
- $\beta_{visit}^{(j)}$ the fixed effect of visit j
- $\beta_{base*visit}^{(j)}$ the interaction between baseline BCVA and visit j
- $\beta_{treat*visit}^{(k,j)}$ the interaction between treatment k and visit j
- ϵ_{ijk} the residual error with $\epsilon_{ijk} \sim N(0, {\sigma_k}^2)$ and $corr(\epsilon_{ijk}, \epsilon_{ij'k}) = \rho^{(k)}\_\{j, j'\}$.

In terms of the model parameters the population-level summary of the estimands (i.e., the treatment effect at Week 48) can then be expressed as

$$\left[\beta_{treat}^{(1)} + \beta_{treat*visit}^{(1,w48)}\right] - \left[\beta_{treat}^{(2)} + \beta_{treat*visit}^{(2,w48)}\right].$$

In line with the definition of estimands (see above), the primary analysis will be performed on the FAS and participants will be analyzed within their original randomized group (regardless of any changes to dose interval).

The analysis described above will be repeated on the PPS as supplementary analysis.

Furthermore, the following 2 hypotheses will be tested (within the pre-defined testing strategy, see Section 9.1), using the MMRM described above, to assess superiority in the primary endpoint:

- HDq12 is superior to 2q8 regarding the mean change in BCVA from baseline to Week 48.
- HDq16 is superior to 2q8 regarding the mean change in BCVA from baseline to Week 48.

To control the nominal family-wise type I error rate of 0.025, a hierarchical testing procedure will be applied that also includes the confirmatory testing of the key secondary endpoints (see Section 9.1) and the confirmatory testing of change from baseline in BCVA at Week 48 (and Week 60, only for EP-SAP) for superiority at the end of the confirmatory testing hierarchy.

9.4.3 Secondary Efficacy Endpoints

Key Secondary Endpoints

The key secondary endpoint "change from baseline to Week 60 in BCVA" will be analyzed with the same methodology as the primary endpoint under the EP-SAP only. The HDq12 and HDq16 treatment groups will be tested for non-inferiority and superiority against the control group of 2q8, according to the confirmatory testing strategy outlined in Section 9.1.

The key secondary endpoint "the proportion of participants with no IRF and no SRF in central subfield at Week 16" will be analyzed by a Cochran-Mantel-Haenszel test stratified by geographic region (Japan vs. Rest of World) and baseline (Day 1) BCVA (<60 vs. ≥60). The pooled high dose groups (HDq12 and HDq16) will be tested for superiority against the control group of 2q8, according to the confirmatory testing strategy outlined in Section 9.1.

Other Secondary Endpoints

All other secondary efficacy endpoints will only be analyzed descriptively. Continuous variables will be analyzed by similar repeated measurement models as for the primary endpoint. Binary endpoints will be analyzed by Cochran-Mantel-Haenszel methodology.

Two-sided 95% confidence intervals and p-values might be provided for descriptive purposes.

Details will be provided in the SAP.

9.4.4 Secondary Safety Endpoints

9.4.4.1 Adverse Events

Treatment-emergent AEs and SAEs will be summarized through Week 48, Week 60, Week 96, and through Week 156.

Definitions

Treatment-emergent AEs (TEAEs) are defined as AEs that occurred in the time frame from first injection to the last injection (active or sham) in the study plus 30 days.

All AEs reported in this study will be coded using the currently available version of the MedDRA®. Coding will be to lowest level terms.

The number and percentage of participants in the SAF with at least one TEAE (TESAE) will be summarized by System Organ Class (SOC) and Preferred Term (PT).

9.4.4.2 Immunogenicity Data

Incidence of treatment-emergent ADA response will be provided by treatment groups, including characterization of the response with titers and NAb status.

Plots of drug concentrations will be examined and the influence of ADAs and NAbs on individual PK profiles evaluated. Assessment of impact of ADA and NAbs on safety and efficacy may be provided.

9.4.5 Other Safety Analyses

All other safety variables will be analyzed in the SAF by descriptive methods.

9.4.5.1 Vital Signs

Vital signs (temperature, heart rate, and blood pressure) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

9.4.5.2 Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of participants with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for each clinical laboratory test for all participants and separately for participants in whom the PCSV criterion was normal or missing at baseline.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out of laboratory range values.

9.4.6 Pharmacokinetics Endpoints

Main Study:

The concentrations of free, adjusted bound, and total aflibercept over time will be summarized by descriptive statistics for each treatment group. Concentrations may be further grouped by factors such as age, renal function, hepatic function, concomitant medications, body weight, ethnicity, etc. No formal statistical hypothesis testing will be performed.

Dose and/or exposure-response analyses may be performed for select safety and efficacy endpoints, as appropriate.

Dense PK Substudy:

The PK parameters to be determined, if possible, after the first dose for free, adjusted bound, and total aflibercept may include, but are not limited to:

- C_{max}
- C_{max}/Dose
- Time of C_{max} (t_{max})
- Last time point (t_{last})
- Last concentration (C_{last})
- AUC_{last}
- Area under the curve from time zero to infinity (AUC_{inf})
- AUC_{inf}/Dose
- Half-life ($t_{1/2}$)
- Trough concentration (C_{trough})

After repeat dosing, PK parameters to be determined, if possible, may include, but are not limited to, C_{trough}, time to reach steady-state, and accumulation ratio. PK parameters will be summarized by descriptive statistics by treatment group, and geographical region as appropriate.

This descriptive statistical assessment may include the geometric means and ratios of the geometric means for selected PK parameters, as deemed appropriate. No formal statistical hypothesis testing will be performed.

Relationship of free aflibercept concentrations and blood pressure will be explored for all participants (if data available). Dose and/or exposure-response analyses may be performed for select safety and efficacy endpoints, as appropriate.

PK data may also be explored using a population PK approach and, in case, will be reported separately.

9.4.7 Other Analyses

All exploratory endpoints will only be analyzed descriptively. Continuous variables will be analyzed by similar repeated measurement models as for the primary endpoint. Binary endpoints will be analyzed by Cochran-Mantel-Haenszel methodology.

Two-sided 95% confidence intervals and p-values might be provided for descriptive purposes.

Details will be provided in the SAP.

9.5 Interim Analyses

No interim analyses are planned.

An analysis of data up to Week 48 (including the primary efficacy analysis) will take place once all participants have completed Week 48 (or prematurely discontinued). Another analysis of data up to Week 60 (including a confirmatory analysis at this timepoint for regulatory submission to EMA and PMDA) will take place once all participants have completed Week 60 (or prematurely discontinued). Another analysis will be conducted after all participants have completed the masked part of study at Week 96 (or prematurely discontinued). In addition, exploratory analyses may be performed at earlier time points (after the completion of the confirmatory analyses at Week 48 and Week 60) as necessary, e.g. to address health authority requests and queries. A final exploratory analysis will be conducted after all participants who continued the study beyond Week 96 have completed the Week 156

visit (or prematurely discontinued), and additional exploratory analyses may be performed at earlier time points during the extension phase as necessary.

9.5.1 Data Monitoring Committee (DMC) and Other Committees

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. All members of the Steering Committee will be masked with regard to treatment assignments throughout the study. The composition of the committee, the functional roles, and responsibilities will be specified in its charter.

Data Monitoring Committee

An independent DMC will meet periodically to review the ongoing safety of participants in the study and to provide recommendations to continue or terminate the study depending upon these reviews. The operation of the DMC is governed by a charter that describes the group's frequency of meeting, procedures (including but not limited to periodic safety monitoring), and requirements for reporting its observations to the sponsor. The DMC oversight will continue through the last participant's completion of the end of masked study visit (Week 96) and until completion of the masked transition period (Week 108).

During the course of the study, the Steering Committee and DMC will keep each other informed in order to assess all relevant safety information in a timely and efficient manner. Communications between Steering Committee and DMC will only include masked data.

Anti-Platelet Trialists' Collaboration (APTC) Adjudication Committee

Potential ATEs will be evaluated by a masked adjudication committee according to criteria formerly applied and published by the APTC prior to database unmasking (Antithrombotic Trialists' Collaboration 1994, Antithrombotic Trialists' Collaboration 2002). ATEs as defined by the APTC criteria include nonfatal myocardial infarction, nonfatal ischemic stroke, nonfatal hemorrhagic stroke, or death resulting from vascular or unknown causes. The committee will include at least 2 cardiologists and the provision of data and activities of the committee will be governed by a charter.

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 laws and regulations.

The protocol, protocol amendments, ICF, Investigator 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 participants. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH Good Clinical Practice and national and international regulations.

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 and 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 to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) 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 participant 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.

Participants 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 participant or the participant's legally authorized representative.

A new ICF is required if a participant is re-screened.

A separate ICF will address the use of remaining samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.3.1 Informed Consent for Study Extension

Participants who are asked and choose to remain in the study for a 1-year extension period after Week 96 are required to sign separate ICFs for the study extension period.

10.1.4 Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant 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 participant who will be required to give consent for their data to be used as described in the informed consent

The participant 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 Dissemination of Clinical Study Data

Result summaries of Bayer's sponsored clinical trials in drug development phases 2, 3, and 4 and phase 1 studies in participants 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 trials will be provided on the publicly funded website www.ClinicalTrials.gov and European Union (EU) Clinical Trials Register in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers participant-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in participants for medicines and indications approved in the United States (US) and EU on or after 01 JAN 2014 as necessary for conducting legitimate research.

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

10.1.6 Data Quality Assurance

All participant data relating to the study will be recorded on printed or eCRF 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 electronically signing the eCRF.

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

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 (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).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants 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.

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.

10.1.7 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

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

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 can be found in ICH GCP guidelines E6(R2) §1.51, 1.52.

10.1.8 Study and Site Start and Closure

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

The sponsor 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:

- 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 recruitment of participants by the investigator
- Discontinuation of further study intervention development

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 participant and should assure appropriate participant therapy and/or follow-up.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10–1 will be performed by the central laboratory.

Local laboratory results are only required in the event that central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, and meet the criteria for an AE, such AEs must be recorded in the eCRF.

Protocol-specific laboratory requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10–1: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**		
Hematology	Platelet count RBC count Hemoglobin Hematocrit RBC Indices	WBC count Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry	Sodium Potassium Chloride Carbon dioxide Calcium Creatinine Glucose (non-fasting) Albumin	AST/SGOT ALT/SGPT Alkaline phosphatase Total and direct bilirubin Urea (or BUN) LDH	Total protein, serum Total cholesterol Triglycerides LDL HDL Uric acid Creatinine CPK
Routine Urinalysis	• Specific gravity, color, clarity, crystals • pH, glucose (non-fasting), protein, blood, ketones, bilirubin, nitrite, leukocyte esterase by dipstick • WBC, RBC, hyaline and other casts, bacteria, epithelial cells, yeast • Creatinine • UPCR		
Other Screening Tests	• Follicle stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Highly sensitive serum hCG pregnancy test (as needed for WOCBP)[a] The results of each test must be entered into the eCRF.		

ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CPK=creatine phosphokinase, eCRF=electronic case report form, hCG=human chorionic gonadotropin, HDL=high density lipoprotein, LDH=lactate dehydrogenase, LDL=low density lipoprotein, RBC=red blood cell, SGOT=serum glutamic-oxaloacetic transaminase, SGPT=serum glutamic-pyruvic transaminase, UPCR=urine protein:creatinine ratio, WBC=white blood cell, WOCBP=women of childbearing potential

[a] For WOCBP, a negative serum pregnancy test at screening is required for eligibility.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unmask the study will not be reported to investigative sites or other masked personnel until the study has been unmasked. However, no laboratory data are anticipated to cause unmasking.

Pregnancy Testing

For WOCBP, a negative serum 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.

10.3 Appendix 3: Adverse Events (AEs): Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, 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) temporally 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 drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. 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 fulfil the definition of an AE or SAE.

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

- 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.

10.3.2 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:

a. Results in death

b. Is life-threatening

- The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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 participant has been detained (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 fulfils 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 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) which 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 in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant 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 in an emergency room or at home for allergic bronchospasm, blood

dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- An ocular important medical event may include the following:
  - An AE that requires either surgical or medical intervention to prevent permanent loss of vision
  - Substantial, unexplained vision loss or an AE that causes substantial vision loss

10.3.3 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 in the eCRF.
- It is not acceptable for the investigator to send photocopies of the participant'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 participant identifiers, with the exception of the participant 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 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
  - Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- 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 Investigator's Brochure 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.
- 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 participant 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 completed eCRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 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) in order to report the event to the sponsor within 24 hours after awareness.
- 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 participant 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 via Paper Case Report Form (CRF)

- Email transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor.
- 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 CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the investigator site file.

10.4 Appendix 4: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization (ISO) 14155.

Both the investigator and the sponsor will comply with all local medical device reporting requirements.

The detection and documentation procedures described in this protocol apply to medical devices provided for use in the study (see Section 6.1.1).

10.4.1 Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition:
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational 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 investigational devices. • An adverse device effect (ADE) is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.4.2 Definition of Medical Device SAE, Serious ADE (SADE) and Unexpected SADE (USADE)

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 an AE that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: 1. A life-threatening illness or injury. The term 'life-threatening' in the definition of serious' refers to an event in which the participant 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,

2. 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
c. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
d. Led to fetal distress, fetal death or a congenital abnormality or birth defect
Medical Device SADE Definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Medical Device USADE Definition
• A USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

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 inadequate labeling.

10.4.4 Recording and Follow-Up of Medical Device 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 participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the eCRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE/SAE/device deficiency eCRF page. • There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant 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 incident.
    - 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.

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: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- 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 Product Information, 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 a 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 participant 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 completed eCRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.4.5 Reporting of Medical Device 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) in order to report the event to the sponsor within 24 hours after awareness. • 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 participant 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.

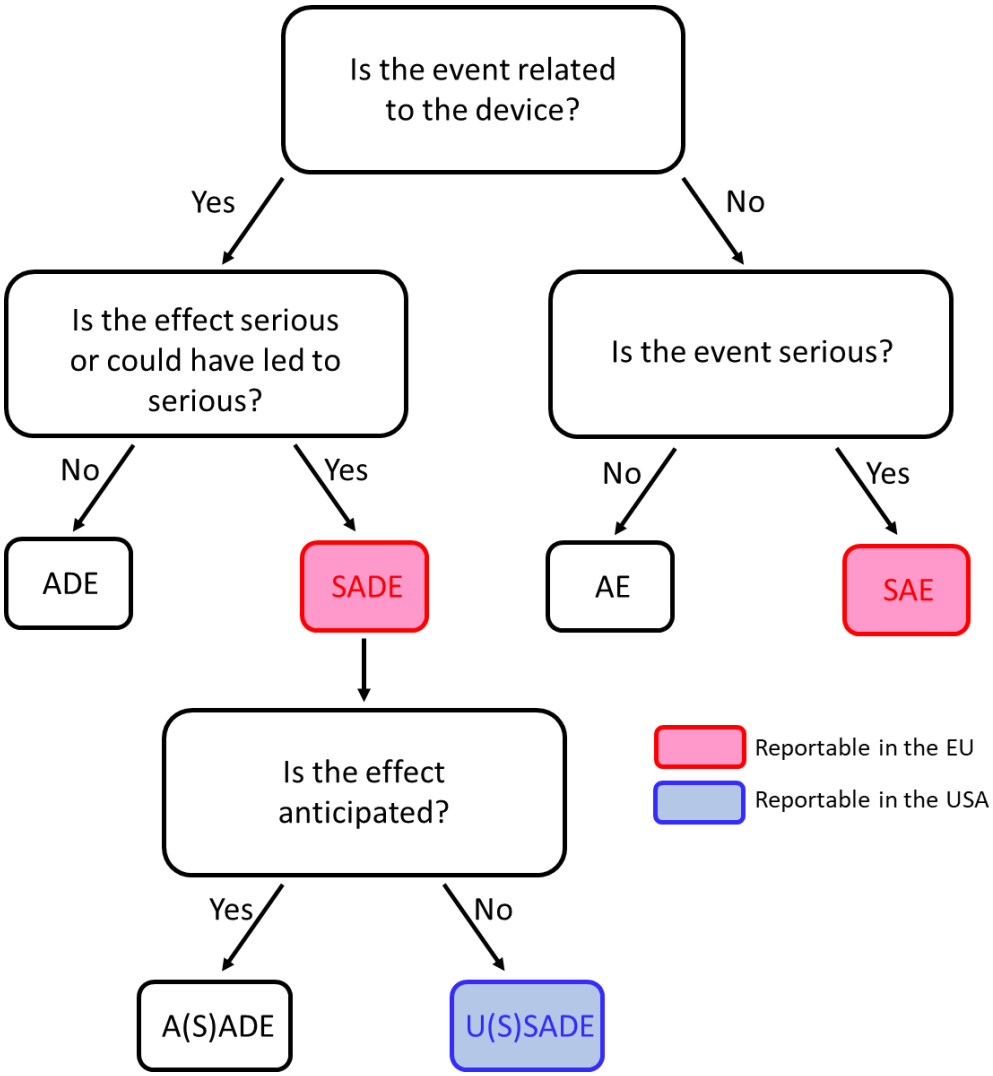
SAE Reporting via Paper CRF
• Email transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor. • In rare circumstances and if email transmission is not feasible, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight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

10.4.6 Reporting of Medical Device SADEs

SADE Reporting
NOTE: There are additional reporting obligations for medical device incidents that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/IECs as required by national regulations. • Contacts for SAE reporting can be found in the safety reporting gateway.

10.4.7 Medical Device AE, ADE, SAE, SADE Determination Flow Chart

Note: Adverse event reporting for countries/regions other than the USA and EU must follow the regulatory and ethical requirements for that country.



10.5 Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

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 not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - 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), investigator discretion should be applied to determining study entry.

    Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Post-menopausal female
    - 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.

Contraception Guidance:

Refer to Section 5.1, Inclusion Criteria, for details of contraception requirements for this study.

Collection of Pregnancy Information:

Male Participants With Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants 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 Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant 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 participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant 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) or still birth (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 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

10.6 Appendix 6: Genetics

Genetic predisposition that might be associated with treatment response to aflibercept and/or disease progression will be investigated as a voluntary genomic substudy.

- The participation in the genomic substudy is voluntary and has no influence on the participation in the main study.
- A whole blood sample will be obtained from those participants, who have signed a separate ICF for genomic substudy. The sample may be used as source of germline DNA.
- DNA sample will be utilized for genotyping of candidate genes suggested to play a role in retinal diseases and may include analysis of the entire genome for discovery of new variants.
- Genomic analyses may include sequencing of the candidate genes and allele specific polymerase chain reaction (PCR) analyses, for example. The methods will be chosen according to current state of the art utilizing analytically validated assays.
- Details on the collection and handling of samples will be provided in separate documents (e.g., sample handling sheets or laboratory manual), available at the Investigator Site File.
- Results will be reported separately (e.g. in a biomarker evaluation report).

10.7 Appendix 7: Study Intervention Administration and Procedures

10.7.1 Preparation of Study Intervention

Only designated unmasked individuals may prepare study intervention for administration.

10.7.1.1 Aflibercept HD and 2 mg

Refer to Section 6.1 for details of study intervention presentation.

The volume of injection will be 50 µL (0.05 mL) for the 2q8 group during the masked part of study through Week 96.

The volume of injection will be CCI µL CCI mL) for HDq12 and HDq16 groups during the CCI study; CCI during the CCI period of the study from CCI.

The study intervention will be withdrawn using aseptic technique through an 18-gauge filtered needle attached to a 1-mL syringe. The needle will be discarded after withdrawal of the vial contents and shall not be used for IVT injection. The needle shall be replaced with a sterile 30-gauge needle for the IVT injection. The contents should be expelled until the plunger is aligned with the line that marks 0.05 mL (for CCI group during the CCI part of study through Week CCI) or CCI mL (for CCI and CCI during the CCI study; and for the CCI CCI during the CCI period of the study from Week CCI) on the syringe. The plunger alignment should be double-checked for accuracy.

Injections will follow the procedures described below.

10.7.1.2 Sham

The sham procedure will use a syringe without a needle. No IVT or intraocular penetration will be performed and no drug will be administered intravitreally.

For the sham procedure, the unmasked injector will ensure that all procedures besides the actual injection are identical to an intravitreal injection of study intervention and will take precaution to ensure that the participant remains masked during the procedure.

10.7.2 Injection Procedure

The sequence of steps described below is recommended. This drug administration protocol is based upon recommendations from the Euretina Expert Consensus (9).

Use of Topical Antibiotic Agents

At the time of this study, the use of topical antibiotics as prophylaxis in intravitreal injections, both in the preparation and post-injection, varies considerably between different practices. There is no consensus on the use of topical antibiotics, the agent to be used, and the dose administered. Therefore, topical antibiotic prophylaxis is allowed in line with local practices and at the discretion of the investigator.

10.7.2.1 Preparation

The investigator or designee will prepare the participant for the injection.

Only designated unmasked individuals may administer study intervention. Individuals involved in performing participants' assessments must remain masked to treatment assignment.

1. Apply topical anesthetic.
2. Apply povidone iodine to eyelid margins, eyelashes, and conjunctival surface.

3. Place 1 or 2 drops of 5% povidone iodine on the ocular surface at the intended injection site.
4. Use sterilized forceps and calipers (speculum) to stabilize the globe and measure the injection site.
5. Optional: Inject 0.5 mL of 2% xylocaine without epinephrine subconjunctivally at the intended injection site (the entry site of the needle for the intravitreal injection should be in the inferotemporal quadrant, 3.0 to 3.5 mm from the limbus in aphakic/pseudophakic participants, and 3.5 to 4.0 mm in the phakic participants).
6. Drape.
7. Apply additional drop of 5% povidone iodine to site of injection.

10.7.2.2 Study Intervention Administration

Active Drug Procedure:

1. Insert needle at marked injection point.
2. Gently inject study intervention.
3. As the needle is withdrawn, a sterile cotton tip applicator should be rolled over the entry site to minimize the risk of drug reflux. This should be held in place for a full 10 seconds.

Sham Procedure:

1. Prepare injection site as above.
2. Use syringe without needle attached.
3. Apply syringe hub to conjunctival surface, pressing gently to simulate force of actual injection.

10.7.2.3 Post-injection Procedures

1. Indirect ophthalmoscopy in the study eye only as soon as possible, approximately 0 to 15 minutes after injection. The exact timing is left to the discretion of the unmasked investigator. If the indirect ophthalmoscopy cannot be performed immediately after injection, the unmasked investigator needs to assess the visual function of the injected eye: light perception and ability to count fingers within 0 to 5 minutes after the injection.
2. Measure IOP approximately 30 to 60 minutes after injection in the study eye only. The exact timing is left to the discretion of the unmasked investigator.

Additional post-injection management procedures as recommended by the guidelines are as follows:

3. Instruct the participant to self-administer 1-2 drops of a topical antibiotic to the injected eye, 3 times a day, for an additional 3 days.
4. Post-injection reperfusion of the optic nerve:
    a. Visualize the optic nerve to verify reperfusion of the central retinal artery in the immediate post-injection period.
    b. Verify IVT location of therapeutic agent when possible.
    c. Verify that the retina is attached and that there is no new intraocular hemorrhage.
5. Intraocular pressure:

IOP may be lowered by pharmaceutical or surgical intervention, if required. If a Tonopen is used to check pressure, a clean Tonopen condom should be placed on the tip before taking each measurement. If an Icare tonometer is used, a clean probe should be used. If applanation tonometry is used, a disposable prism should be used or, in case this is not available, the non-disposable prism should be disinfected (e.g., swabbing tip with alcohol and allowing to dry before using it to measure IOP).

a. Monitor IOP for at least 30 minutes after each injection. The exact timing is left to the discretion of the unmasked investigator.

b. Check IOP while maintaining a clean field.

c. Monitor IOP closely until it reaches a value that will not be expected to cause damage, e.g., below 25 mm Hg.

d. Treatment should be initiated whenever IOP is increased to the extent that the central retinal artery remains closed and the participant has no light perception for more than 1 to 2 minutes.

e. Transient graying or obscuration of vision following injection is expected and should not be treated.

f. Paracentesis should be used only in extreme circumstances when the degree of pressure elevation poses an imminent and irreversible threat to vision. In the rare situation when a paracentesis is warranted, IOP should be recorded both before and after the procedure. A 0.1- to 0.2-mL paracentesis may be performed at the temporal limbus using a 27- or 30-gauge needle or surgical knife, if judged to be necessary by the investigator.

g. Record the last IOP measurement and related treatments in the source document and on the appropriate eCRF page.

10.7.2.4 Discharge

No special precautions are required before discharge of a participant who has had an uneventful recovery from IVT injection, but participants and/or caregivers should be educated to avoid rubbing the eye and to recognize the signs and symptoms of endophthalmitis, retinal detachment, or intraocular hemorrhage. These signs and symptoms include eye pain or increased discomfort, increased redness of the eye (compared to immediately after injection), blurred or decreased vision, and increased ocular sensitivity to light.

Participants should be informed that some blurring of vision is common after an injection, which is often described as seeing spots floating in the eye. Floaters usually resolve after a few days or weeks.

Participants who experience AEs after injection that require additional monitoring should remain in the clinic until the condition is resolved, and should be treated according to the investigator’s medical judgment.

10.8 Appendix 8: Abbreviations

2q8	aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals
ADA	anti-drug antibody(ies)
ADE	adverse device effect
AE	adverse event
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
AOBP	automated office blood pressure
APTC	Anti-Platelet Trialists' Collaboration
ATE	arterial thromboembolic events
AUC_{last}	area under the curve to the last quantifiable concentration
AUC_{inf}	area under the curve from time zero to infinity
BCVA	best corrected visual acuity
C_{max}	maximum concentration
CNV	choroidal neovascularization
CRF	(paper) case report form
CRT	central retinal thickness
CST	central subfield retinal thickness
C_{trough}	trough concentration
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DRM	dose regimen modification
ECG	electrocardiogram
eCRF	electronic case report form
E-DRM	dose regimen modification criteria for the extension period
EMA	European Medicines Agency
EOS	end of study
EP-SAP	EMA/PMDA statistical analysis plan
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	fluorescein angiography
FAS	full analysis set
FBR	future biomedical research
FDA	Food and Drug Administration
FP	fundus photography
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
G-SAP	Global statistical analysis plan
HD	high dose (aflibercept)

HDq12	high dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals
HDq16	high dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals
HRT	hormonal replacement therapy
ICF	informed consent form
ICGA	indocyanine green angiography
IEC	Independent Ethics Committee
IOP	intraocular pressure
IRB	Institutional Review Board
IRF	intraretinal fluid
IUD	intrauterine device
IUS	intrauterine hormone releasing system
IV	intravenous
IVT	intravitreal
IXRS	Interactive Response System
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
NAb	neutralizing antibody(ies)
nAMD	neovascular (wet) age-related macular degeneration
NB	new baseline
NEI-VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
OCT	optical coherence tomography
OCT-A	optical coherence tomography angiography
PCSV	potentially clinically significant value
PCV	polypoidal choroidal vascularization
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	per protocol set
PTC	product technical complaint
q8	every 8 weeks
q12	every 12 weeks
q16	every 16 weeks
SADE	serious adverse device effect
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SD-OCT	spectral domain optical coherence tomography
SoA	Schedule of Activities
SRF	subretinal fluid
SUSAR	Suspected Unexpected Serious Adverse Reaction

TEAE	treatment-emergent adverse event
UPCR	urine protein:creatinine ratio
USADE	unexpected serious adverse device effect
VEGF	vascular endothelial growth factor
WOCBP	women of childbearing potential
YAG	yttrium-aluminum-garnet

10.9 Appendix 9: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 3 (13 SEP 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to investigate the long-term efficacy and safety of HD aflibercept beyond 2 years of treatment. Therefore, the study will be extended in an open-label part (after a masked transition period of 12 weeks) for approximately one additional year (60 weeks) in countries and sites selected by the sponsor. During this third year of treatment, CCI participants who consent to continue in the study, CCI those CCI assigned to the CCI CCI, will be treated with CCI The treatment intervals for all groups will be adjusted according to individual participant response as determined by dose regimen modification criteria for the extension period (E-DRM) in Year 3.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema Figure 1-1, Figure 1-2 1.3 Schedule of Activities (SoA) Table 1-3 2.1 Study Rationale 2.3 Benefit/Risk Assessment 3. Objectives and Endpoints 4.1 Overall Design 4.2 Scientific Rationale for Study Design 4.4 End of Study Definition 5.1.1 Additional Inclusion Criteria for the Extension Period 6.1 Study Intervention(s) Administered Table 6–1 Study Interventions 6.2 Preparation/Handling/Storage/Accountability 6.3.2.1 Masked Part (Screening to Week 96) and Masked Transition Period for Extension (Week 96 to Week 108) 6.3.2.2 Open-label Part (After Week 108 to Week 156) 6.6 Dose Regimen Modification/Rescue Regimen 6.6.2 Year 2: Week 52 to Week 96 (End of Masked Part of Study) 6.6.3 Year 3 (Masked Transition Period and Open-label Extension Part): Week 96 to Week 156 (End of Study) / E-DRM Criteria 8.4 Treatment of Overdose 9.4 Statistical Analyses 9.4.4.1 Adverse Events 9.5 Interim Analyses 9.5.1 Data Monitoring Committee (DMC) and Other Committees 10.1.3.1 Informed Consent for Study Extension 10.7.1.1 Aflibercept HD and 2 mg 10.8 Appendix 8: Abbreviations	Added or updated language to describe the extension period of the study throughout the document	To update or add the sections needed to accommodate the additional language required to implement an extension period into the study.
Throughout	Minor editorial changes for consistency of the updates described above, company template updates, spelling, and document formatting.	Minor, therefore have not been summarized.

E-DRM=dose regimen modification criteria for extension period

Amendment 2 (26 APR 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to simplify and extend the confirmatory testing hierarchy:

1. To remove the initial Bonferroni-based split of the overall significance level (which had been introduced originally to allow simultaneous testing of the 2 hypotheses (HDq12 vs. 2q8 and HDq16 vs. 2q8) of the primary endpoint at a significance level of 0.0125 [one-sided] each) and to assign the full significance level of 0.025 (one-sided) to the first hypothesis (HDq12 vs. 2q8).
   The reason for this change is to adjust the testing sequence to the perceived clinical probability of success, i.e., since HDq12 is more likely to succeed than HDq16 (due to the higher dosing frequency after the loading phase).
2. To remove the subsequent splitting of the remaining alpha levels between 2 hypotheses and replace it by a simpler hierarchical testing procedure in both the global statistical analysis plan (G-SAP) and the European Medicines Agency/Pharmaceuticals and Medical Devices Agency (EMA/PMDA) statistical analysis plan (EP-SAP). This change allows sequential testing of hypotheses at the full significance level after successful rejection of the hypotheses which are ranked higher in the hierarchy.
   The reason for this change is to prioritize testing of hypotheses which are deemed to be clinically more relevant.
3. To allow formal statistical testing for superiority of the change from baseline in best corrected visual acuity (BCVA) at Week 48 (and Week 60, for regulatory submissions to EMA/PMDA Analysis Plan only) that controls the overall family-wise type 1 error. The formal statistical testing for superiority is added at the end of the revised testing hierarchy.

Of note, the updated confirmatory testing hierarchy still controls the overall family-wise type 1 error. The change was implemented after the end of enrollment but before the database lock and before any unmasking occurred.

In addition, the definition of the Full Analysis Set (FAS) was updated to include all participants who received at least 1 dose of study intervention.

This amendment also clarifies a discrepancy in the following exclusion criteria:

- Section 5.2, Exclusion Criterion 2.l: Aphakia, or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium-aluminum-garnet [YAG] posterior capsulotomy performed more than 4 weeks (28 days) before screening), in the study eye.
- Section 5.2, Exclusion Criterion 13.g: YAG capsulotomy in the study eye within 30 days before the screening visit.

Eligibility requires that none of the exclusion criteria are met, therefore, this amendment confirms that the strictest definition, as used in Section 5.2, Exclusion Criterion 13.g, needs to be applied, i.e., a patient is not eligible if YAG was applied in the study eye within 30 days before the screening visit.

Additionally, this amendment includes updates of secondary-other and exploratory endpoints, clarifications with regard to the type and follow-up time of adverse events (AEs) during the post-injection period by the unmasked team, the contact information in case unmasking of a

participant's intervention assignment is warranted, the baseline to be used for the dose regimen modification (DRM), the definition of treatment-emergent adverse events (TEAEs), and the timing of indirect ophthalmoscopy and intraocular pressure (IOP) measurements performed after study intervention.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis and 3 Objectives and Endpoints Secondary – Other Objective: To evaluate the pharmacokinetics (PK) and immunogenicity of aflibercept	Modified secondary – other endpoint: • Systemic exposure to aflibercept as assessed by plasma concentrations of free, adjusted bound and total aflibercept from baseline through Week 48	Removal of concentrations of "bound" aflibercept from the secondary – other and the exploratory endpoints related to PK as concentrations of "adjusted bound" aflibercept were considered sufficient.
3 Objectives and Endpoints Exploratory Objective: Based on dense PK sampling, characterize the concentrations in plasma over time, and corresponding PK parameters for aflibercept	Modified exploratory endpoint: • Concentrations of free, adjusted bound and total aflibercept over time, and PK parameters	
9.4.6 Pharmacokinetics Endpoints Main Study and Dense PK Substudy	Text was updated to reflect the removal of "bound" aflibercept from the secondary – other and the exploratory endpoints	
3 Objectives and Endpoints Exploratory Objective: To determine the effect of HD versus 2 mg aflibercept on functional and anatomic measures of response as well as on vision related quality of life	Removed exploratory endpoint: • Change from baseline in BCVA at each visit in relation to fluid outcomes	Correlation between OCT and vision has never been formally established; Change from baseline in BCVA at each visit in relation to fluid outcomes is to be assessed in a post-hoc analysis, as appropriate.
	Added exploratory endpoint: • Proportion of participants without leakage on fluorescein angiography (FA) at Week 48, Week 60, and Week 96	To explore the effect of treatment on the inhibition of vascular leakage.

Section # and Name	Description of Change	Brief Rationale
3 Objectives and Endpoints Exploratory Objective: To evaluate the duration of effect of HD after 3 initial doses at 4 week intervals followed by dosing q12 or q16	Modified exploratory endpoints: • Proportion of participants with q16 or longer treatment interval through Week 48, Week 60, and Week 96 in HDq16 group • Proportion of participants with q12 or longer interval through Week 48, Week 60, and Week 96 in the HDq12 and HDq16 groups • Proportion of participants with q12 or q16 or longer treatment interval as the last treatment interval at Week 48, Week 60, and Week 96 in HDq12 and HDq16 groups, respectively	To also identify the proportion of participants who did not require any shortening of their treatment intervals throughout the study duration and to delete the inappropriate word “maintained“ from the endpoint to clarify the intention of the analysis referring to the last treatment interval.
5.2.2.l Exclusion Criteria Medical Conditions – Per Eye	Correction of restrictive period of YAG posterior capsulotomy in Section 5.2.2.l to more than 30 days before screening.	Clarification of discrepancy between Section 5.2.2.l and Section 5.2.13.g.
6.3.2 Masking Unmasked Roles	Text was amended to clarify that AEs relating to the injection procedure and AEs/SAEs/device deficiencies should be reported during the post-injection period until the next scheduled visit.	To clarify which AEs should be reported by the unmasked investigator and during which period of time.
6.3.2 Masking Emergency Unmasking	Update of contact information.	To clarify who should be contacted if the investigator decides that unmasking is warranted.
6.6.1 Year 1: Baseline to Week 48	Added paragraph: In case the Week 12 measurement is not available, the Week 8 measurement should be used instead. If both, Week 12 and Week 8 measurements are not available, the Week 4 measurement should be used instead.	Clarification of the baseline to be used for the DRM if the Week 12 measurement is not available.
1.3 Schedule of activities, Tables 1-1 and 1-2, footnote ‘j’ 8.1.1.2 Intraocular Pressure (IOP)	Text was amended to clarify that on days when study intervention is administered, IOP should also be measured approximately 30 to 60 minutes after administration of study intervention and that the exact timing is left to the discretion of the unmasked investigator.	To clarify the timing of indirect ophthalmoscopy and intraocular pressure IOP measurements performed after study intervention administration.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities, Tables 1-1 and 1-2, footnote 'l' 8.1.1.4 Indirect Ophthalmoscopy	Text was amended to clarify that post-dose evaluation should be performed as soon as possible, approximately 0 to 15 minutes after injection and that the exact timing is left to the discretion of the unmasked investigator. For post-injection procedures if the indirect ophthalmoscopy cannot be performed immediately after injection, a reference to Section 10.7.2.3 was added.	
9.1 Statistical Hypotheses Null and Alternative Hypotheses	Added bullet point: 1. Change from baseline in BCVA at Week 48 (non-inferiority at a margin of 4 letters):	To add a subheader for the primary family of hypotheses for more clarity and to distinguish between the different hypotheses tested.
	Null and alternative hypotheses renumbered.	To match the order in the revised hierarchical testing procedure.
	Added text: The HDq12 and HDq16 treatment groups will also be tested for superiority against the control group of 2q8 with respect to the change from baseline in BCVA at Week 48 (and Week 60, only for EP-SAP). 4. Change from baseline in BCVA at Week 48 (superiority): H_{60}: $\mu_1 \leq \mu_0$ vs. H_{61}: $\mu_1 > \mu_0$ (i.e., HDq12 vs. 2q8) H_{80}: $\mu_2 \leq \mu_0$ vs. H_{81}: $\mu_2 > \mu_0$ (i.e., HDq16 vs. 2q8) where μ_0, μ_1, μ_2 are the mean change from baseline in BCVA at Week 48 for 2q8, HDq12, and HDq16, respectively. 5. Only included in the EP-SAP for EMA and PMDA: Change from baseline in BCVA at Week 60 (superiority) H_{70}: $\mu_1 \leq \mu_0$ vs. H_{71}: $\mu_1 > \mu_0$ (i.e., HDq12 vs. 2q8) H_{90}: $\mu_2 \leq \mu 0$ vs. H_{91}: $\mu_2 > \mu_0$ (i.e., HDq16 vs. 2q8) where μ_0, μ_1, μ_2 are the mean change from baseline in BCVA at Week 60 for 2q8, HDq12, and HDq16, respectively.	To add the description of the additional superiority hypotheses.

Section # and Name	Description of Change	Brief Rationale
9.1 Statistical Hypotheses Control of Multiplicity; Figure 9-1- Adjustment for Multiplicity	Text was amended and the 2 figures replaced showing Global SAP (G-SAP) EMA/PMDA SAP(EP-SAP) by a table summarizing the testing order of the hierarchical testing procedure in the G-SAP and EP-SAP.	To replace the graphical representations of the adjustment for multiplicity by a hierarchical testing procedure, and including the superiority hypotheses at the end of the confirmatory testing hierarchy.
9.2 Sample Size Determination	Text was amended to clarify that sample size determination is still based on the non-inferiority tests but not on the superiority tests.	Clarification required since both non-inferiority tests and superiority tests are now applied to the primary endpoint.
	Text was added to describe the power, based on the revised confirmatory testing hierarchy (according to Protocol version 3.0, Global Amendment 2).	Clarification required of the power based on the revised testing strategy, i.e., the hierarchical confirmatory testing procedure without alpha split.
	Text was removed which referred to the initial alpha split and Figure 9-1 which are no longer applicable.	Text no longer applicable due to revision of confirmatory testing hierarchy.
9.3 Populations for Analyses	The definition of the FAS was amended.	To include randomized participants who received at least 1 dose of study intervention in the FAS.
	The definition of the PPS was amended.	To clarify that patients should not have an important protocol deviation affecting the primary efficacy endpoint.

Section # and Name	Description of Change	Brief Rationale
9.4.2 Primary Efficacy Endpoint	Text was amended to clarify that the estimand of primary interest will mainly be based on a hypothetical strategy, that the population defined is the target population, and that the population-level summary is defined as the difference in the least squared (LS) rather than the mean change from baseline. It was also clarified that the analysis will be repeated on the PPS as a supplementary rather than a sensitivity analysis. Text was amended to clarify that the first 2 hypotheses in the primary analysis will be tested to assess non-inferiority in the primary endpoint.	Clarification required since both non-inferiority tests and superiority tests are now applied to the primary endpoint.
	MMRM updated to remove random effect b_i, to add index k to Y and ϵ; clarification of ϵ updated.	Random effect b_i removed, to avoid over parametrization.
	Paragraphs were re-ordered and text added: Furthermore, the following 2 hypotheses will be tested (within the pre-defined testing strategy, see Section 9.1), using the MMRM described above, to assess superiority in the primary endpoint: • HDq12 is superior to 2q8 regarding the mean change in BCVA from baseline to Week 48. • HDq16 is superior to 2q8 regarding the mean change in BCVA from baseline to Week 48.	To replace the original sentence: “Two-sided confidence intervals will be provided to allow the assessment of superiority if non-inferiority could be concluded.” by a formal test for superiority at the end of the testing strategies.
	Text was amended to indicate that a hierarchical testing procedure will be applied which also includes the confirmatory testing for superiority at the end of the confirmatory testing hierarchy.	To refer to the updated hierarchical testing procedure and to remove the reference to the graphical representations of the adjustment for multiplicity, which are no longer applicable.

Section # and Name	Description of Change	Brief Rationale
9.4.3 Secondary Efficacy Endpoints	Added text: The HDq12 and HDq16 treatment groups will be tested for non-inferiority and superiority against the control group of 2q8, according to the confirmatory testing strategy outlined in Section 9.1.	To clarify the testing strategy on key secondary endpoint “change from baseline to Week 60 in BCVA”.
	Added text: The pooled high dose groups (HDq12 and HDq16) will be tested for superiority against the control group of 2q8, according to the confirmatory testing strategy outlined in Section 9.1.	To clarify the testing strategy on key secondary endpoint “proportion of participants with no IRF and no SRF in central subfield at Week 16”.
9.4.4.1 Adverse Events	Text was amended to clarify that TEAEs are defined as AEs that occurred in the time frame from first injection to the last injection (active or sham) in the study plus 30 days.	Clarification of the definition of TEAEs by deleting references to the rescue regimen, which is inherent in the DRM/rescue regimen paradigm, and to delete sham from the first injection as no sham procedure is done at the first injection.
9.4.6 Pharmacokinetics Endpoints	Text was amended to clarify that the PK parameters mentioned are to be determined if possible.	To clarify that PK parameters are to be determined based on their availability.
10.7.2.3 Post-injection Procedures	Text was amended to update the following procedures: 1. Indirect ophthalmoscopy in the study eye only as soon as possible, approximately 0 to 15 minutes after injection. The exact timing is left to the discretion of the unmasked investigator. If the indirect ophthalmoscopy cannot be performed immediately after injection, the unmasked investigator needs to assess the visual function of the injected eye: light perception and ability to count fingers within 0 to 5 minutes after the injection. 2. Measure IOP approximately 30 to 60 minutes after injection in the study eye only. The exact timing is left to the discretion of the unmasked investigator. ... 5a. Monitor IOP for at least 30 minutes after each injection. The exact timing is left to the discretion of the unmasked investigator.	To clarify the timing of indirect ophthalmoscopy and intraocular pressure IOP measurements performed after study intervention administration.

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial changes for consistency of the updates described above, company template updates and document formatting.	Minor, therefore have not been summarized.

AE=adverse event, BCVA=best corrected visual acuity, DRM= dose regimen modification, EMA=European Medicines Agency, EP-SAP=EMA/PMDA statistical analysis plan, FAS=full analysis set, G-SAP=global statistical analysis plan, HD=high dose, IOP=intraocular pressure, IRF=intraretinal fluid, MMRM=mixed model for repeated measurements, OCT=optical coherence tomography; PK=pharmacokinetic; PMDA= Pharmaceuticals and Medical Devices Agency, PPS=per protocol set, q8=every 8 weeks, q12=every 12 weeks, q16=every 16 weeks, SAE= serious adverse event, SRF=subretinal fluid, TEAE=treatment-emergent adverse event, YAG=yttrium aluminum garnet

DOCUMENT HISTORY	
Document	**Date**
Protocol Amendment 1	14-February-2020
Original Protocol	09-December-2019

Amendment 1 (14-February-2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to update the study design to simplify implementation of dose regimen modifications (DRMs) and rescue regimen. The updated design encompasses combining rescue regimen with DRM assessments in both Year 1 and Year 2, allowing dose regimen flexibility while maintaining participant safety. In Year 1, participants in the high dose (HD) groups will be eligible for dose interval shortening (to a rescue regimen with 8 mg aflibercept every 8 weeks) beginning at Week 16. In Year 2, all participants in HD groups will be eligible for dose interval adjustments (shortening or extension) based on DRM criteria from Week 52 onwards, with the dose interval adjustments (shortening or extension) becoming effective at or after Week 60 (after data collection for key secondary efficacy endpoint). To improve dosing flexibility, all participants in HD groups whose dosing intervals were shortened during Year 1 will be eligible for dose interval extension in Year 2 if they meet pre-specified criteria.

Additionally, recent shifts in disease characteristics at presentation led to the adjustment (broadening) of the inclusion criterion for best corrected visual acuity (BCVA) to allow inclusion of participants with BCVA scores between 78 and 24 letters (20/32 to 20/320).

Section # and Name	Description of Change	Brief Rationale
1.2 Schema, Figure 1-2 Dosing Schedule	Updated to reflect the updated DRM and rescue regimen assessments.	To provide detail on combined rescue regimen and DRM

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA), Table 1-1 and Table 1-2	Rows for Rescue Treatment and DRM Assessment were combined, footnote 'g' was deleted, and footnote 'h' was amended to reflect combined DRM and rescue regimen assessments.	assessments in Year 1 and Year 2. In Year 1, participants in HD groups will be eligible for dose interval shortening (rescue regimen with 8 mg aflibercept q8 or reduction to q12 dosing, if applicable) beginning at Week 16, according to pre-specified criteria. From Week 52, all participants in HD groups will be eligible for dose interval shortening (to a minimum of q8) or extension (by 4-week increments) according to pre-specified DRM criteria. All participants in HD groups whose dosing intervals were shortened during Year 1 will eligible for dose interval extension in Year 2 if they meet pre-specified criteria.
4.1 Overall Design	Text was amended to update information on potential dose interval changes during Year 1 and Year 2.	
6.3.2 Masking	Masked roles were updated to reflect the current DRM activities.	
6.5.3 Rescue Treatment	The section was deleted. Relevant information has now been combined and included into Section 6.6 Dose Regimen Modification.	
6.6 Dose Regimen Modification	The section was renamed to "Dose Regimen Modification/Rescue Regimen". Section completely replaced with new text describing the combined DRM and rescue regimen criteria for Years 1 and 2.	
9.4.2 Primary Efficacy Endpoint	Estimand definitions updated to reflect the updated DRM and rescue regimen assessments. Text that was previously in Section 6.6 was added for completeness: For primary analysis, participants will be analyzed within their original randomized group, regardless of any changes to dose interval.	
5.1 Inclusion Criteria, criterion 4	Upper limit of BCVA ETDRS letter score for the study eye was updated from 73 to 78 (corresponding to a Snellen equivalent of approximately 20/32).	Broadened to better reflect patient population disease characteristics at presentation.
3 Objectives and endpoints	Two additional exploratory endpoints were added: • Change from baseline in BCVA averaged over the period from Week 36 to Week 48 and from Week 48 to Week 60. • Change from baseline in BCVA at each visit in relation to fluid outcomes.	As treatment before Week 48 and Week 60 are less synchronized due to the modifications introduced for the DRMs, it is now important to assess these additional/earlier endpoints.
6.5.2 Fellow Eye Treatment	Added text: The costs of aflibercept 2 mg used for treatment of the fellow eye will be supported by the sponsor in compliance with local regulations.	To clarify that, although aflibercept 2 mg for fellow eye treatment will not be provided by the sponsor through study medication supplies, costs for purchase of EYLEA® 2 mg will be reimbursed where allowed.

Section # and Name	Description of Change	Brief Rationale
6.5.2 Fellow Eye Treatment 8.3.2 Method of Detecting AEs and SAEs	New text: Once the fellow eye receives aflibercept 2 mg therapy during the study, AEs will be assessed as related/not related to aflibercept 2 mg treatment in the fellow eye in addition to being assessed as related/not related to the study drug (aflibercept 2 mg/aflibercept High Dose treatment in the study eye), IVT injection-procedure, and other protocol-specified procedures.	To improve characterization of the safety profile of investigational aflibercept, separate documentation of potential relationship of AEs to commercial or investigational aflibercept.
1.3 Schedule of activities, Table 1-1	Addition of new footnote 'f' associated with Inclusion/Exclusion Eligibility at Visit 2: Inclusion/exclusion criteria will be evaluated at screening and baseline to confirm subject's eligibility. The investigator is responsible for confirming that any changes between screening and baseline do not affect the participant's eligibility.	To clarify which data are to be used to confirm eligibility.
1.3 Schedule of activities, Table 1-3	On Day 1, the 4 and 8 hour PK sampling is to be within ±30 minutes and ±2 hours, respectively, of the scheduled time.	To allow flexibility while still ensuring accuracy of PK sampling time-points.
1.3 Schedule of activities, Table 1-1 8.10 Immunogenicity Assessments	PK sample time pre-dose changed from Screening (Visit 1) to Baseline (Visit 2). Deleted paragraph about evaluation of aflibercept serum concentrations at same time points as immunogenicity assessments.	Alignment of PK and anti-drug antibody sampling times. Text in Section 8.10 is unnecessary due to correspondence of PK and anti-drug antibody sampling at baseline and Week 48. The PK profile is sufficiently characterized.
1.3 Schedule of activities, Table 1-1, footnote 'd' 8.7.1 Optional Genomic Substudy	Participants from China will not be enrolled in the optional genomic substudy.	Clarification that participants in China will not take part in the optional substudy.
8.2.1 Physical Examination	Addition of body weight at Visit 1.	Body weight should be measured in all participants.
Throughout	Minor editorial changes for improved clarity/readability, company template updates, and document formatting.	Minor, therefore have not been summarized.

AE=adverse event, BCVA=best corrected visual acuity, DRM=dose regimen modification, ETDRS=Early Treatment Diabetic Retinopathy Study, HD=high dose, IVT=intravitreal, PK=pharmacokinetic, q8=every 8 weeks, q12=every 12 weeks, SAE=serious adverse event

11. References

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