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Title Page

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Name: PPD Role: PPD

Medical Monitor name and contact information will be provided separately.

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Document History Table

DOCUMENT HISTORY			
Document	**Version**	**Date**	**Comments (if applicable)**
Protocol amendment 3	**5.0**	**21 JAN 2025**	
Protocol amendment 2	4.0	19 SEP 2024	
Protocol amendment 1	3.0	19 AUG 2024	
Protocol update	2.0	23 JUL 2024	Protocol update to respond to request for information
Clinical Study Protocol	1.0	20 MAR 2024	

Protocol Amendment Summary of Changes Table

Amendment 3 (21 JAN 2025)

This amendment/modification is considered to be non-substantial based on the relevant criteria of the European Union clinical trial legislation.

Overall Rationale for the Amendment:

This is a non-substantial modification to the protocol which relates to the number of trial participants. The original sample size for the study was determined empirically and foresaw the enrollment of two populations of patients with DME or nAMD that would be treated with bilateral 8 mg aflibercept in one of 3 different treatment regimens. Each treatment regimen was to include 15 participants. The actual enrollment has been much faster than expected with a screen failure rate that has been substantially lower than anticipated, at approximately 5% (originally calculated with screen failure rate of 25%). This has resulted in an unexpected higher proportion of screened participants being eligible for enrollment and an equally unexpected imbalance in the distribution of patients assigned to the 3 treatment regimens, such that Regimen 1 and 2 have surpassed the anticipated enrollment treatment target of 15 patients.

The lower screening failure rate resulted in a recruitment of 51 participants. The increase in the study sample size from 45 to 51 participants will not impact the planned analysis for this exploratory pharmacokinetic study nor impose any safety risk to patients participating in the trial.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	The number participants was adapted	Participant number increase
Section 1.3 Schema	Note in Table 1–3 adapted and errors in table corrected.	Participant number increase and error correction
Section 4.1 Overall Design	The number participants was adapted	Participant number increase
Section 6.3 Assignment to Study Intervention	The number participants was adapted	Participant number increase
Section 9.5 Sample Size Determination	The number participants was adapted	Participant number increase

Table of Contents

Title Page **1**
Document History Table **2**
Protocol Amendment Summary of Changes Table **2**
Table of Contents **3**
Table of Tables **6**
Table of Figures **6**
List of Abbreviations **7**
1. Protocol Summary **10**
1.1 Synopsis 10
1.2 Schema 13
1.3 Schedule of Activities (SoA) 14
2. Introduction **22**
2.1 Study Rationale 22
2.2 Background 23
2.3 Benefit/Risk Assessment 24
2.3.1 Risk Assessment 24
2.3.2 Benefit Assessment 25
2.3.3 Overall Benefit: Risk Conclusion 25
3. Objectives, Endpoints, and Estimands **26**
4. Study Design **28**
4.1 Overall Design 28
4.2 Scientific Rationale for Study Design 30
4.3 Justification for Dose 30
4.4 End of Study Definition 31
5. Study Population **31**
5.1 Inclusion Criteria 31
5.2 Exclusion Criteria 32
5.3 Lifestyle Considerations 34
5.4 Screen Failures 34
5.5 Criteria for Temporarily Delaying 35
6. Study Intervention(s) and Concomitant Therapy **35**
6.1 Study Intervention(s) Administered 35
6.1.1 Medical Devices 35
6.2 Preparation, Handling, Storage, and Accountability 36
6.2.1 Packaging, Labeling, and Storage 36
6.3 Assignment to Study Intervention 37
6.4 Blinding/Masking 37
6.5 Study Intervention Compliance 37
6.6 Dose Modification 37
6.7 Continued Access to Study Intervention After the End of the Study 37
6.8 Treatment of Overdose 37
6.9 Prior and Concomitant Therapy 38

6.9.1 Prohibited Medications and Procedures 38
6.9.2 Permitted Medications and Procedures 38
6.9.3 Rescue Medicine....38

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal 38
7.1 Discontinuation of Study Intervention....39
7.2 Participant Discontinuation/Withdrawal from the Study....39
7.3 Lost to Follow-Up....40

8. Study Assessments and Procedures 41
8.1 Administrative and General Procedures 41
8.2 Ocular Efficacy and Safety Assessments....41
8.2.1 Best Corrected Visual Acuity 42
8.2.2 Slit Lamp Examination....42
8.2.3 Intraocular Pressure 42
8.2.4 Indirect Ophthalmoscopy 42
8.2.5 Spectral Domain Optical Coherence Tomography....42
8.2.6 Fundus Photography....43
8.3 Safety Assessments....43
8.3.1 Non-Ocular Safety Assessments 43
8.3.1.1 Physical Examinations 43
8.3.1.2 Vital Signs....43
8.3.1.3 Clinical Safety Laboratory Tests....44
8.3.1.4 Pregnancy Testing....44
8.3.2 Ocular Safety Assessments....44
8.4 Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting 44
8.4.1 Time Period and Frequency for Collecting AE and SAE Information....45
8.4.2 Method of Detecting AEs and SAEs 45
8.4.3 Follow-up of AEs and SAEs 45
8.4.4 Regulatory Reporting Requirements for SAEs 46
8.4.5 Pregnancy 46
8.4.6 Cardiovascular and Death Events....47
8.4.7 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs....47
8.4.8 Adverse Events of Special Interest....47
8.4.9 Medical Device Deficiencies....47
8.4.9.1 Time Period for Detecting Medical Device Deficiencies 47
8.4.9.2 Follow-up of Medical Device Deficiencies 47
8.4.9.3 Prompt Reporting of Device Deficiencies to the Sponsor 47
8.4.9.4 Regulatory Reporting Requirements for Device Deficiencies....47
8.5 Pharmacokinetics....48
8.6 Pharmacodynamics 52
8.7 Genetics 52
8.8 Biomarkers....52
8.9 Immunogenicity Assessments....52
8.10 Health Economics OR Medical Resource Utilization and Health Economics 53

9. Statistical Considerations 53
9.1 Statistical Hypotheses....53

9.2 Analysis Sets 53
9.3 Statistical Analyses 54
9.3.1 General Considerations 54
9.3.2 Pharmacokinetics 54
9.3.2.1 Primary Endpoint Analysis 54
9.3.2.2 Exploratory Endpoint Analysis 54
9.3.2.3 Other PK Analyses 54
9.3.3 Efficacy Analysis 54
9.3.4 Safety Analysis 55
9.3.4.1 Adverse Events 55
9.3.4.2 Other Safety Analyses 55
9.3.5 Analysis of Immunogenicity Data 55
9.3.6 Other Analyses 55
9.4 Interim Analysis 55
9.5 Sample Size Determination 55

10. Supporting Documentation and Operational Considerations 56
10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 56
10.1.1 Regulatory and Ethical Considerations 56
10.1.2 Financial Disclosure 57
10.1.3 Informed Consent Process 57
10.1.4 Recruitment Strategy 57
10.1.5 Data Protection 57
10.1.6 Committees Structure 58
10.1.6.1 Study Steering Committee 58
10.1.6.2 Anti-Platelet Trialists Collaboration Adjudication Committee 58
10.1.7 Dissemination of Clinical Study Data 58
10.1.8 Data Quality Assurance 58
10.1.9 Source Documents 59
10.1.10 Study and Site Start and Closure 59
10.1.11 Publication Policy 60
10.2 Appendix 2: Clinical Laboratory Tests 60
10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 62
10.3.1 Definition of AE 62
10.3.2 Definition of SAE 63
10.3.3 Recording and Follow-Up of AE and/or SAE 64
10.3.4 Reporting of SAEs 65
10.4 Appendix 4: Contraceptive and Barrier Guidance 66
10.4.1 Definitions 66
10.4.2 Contraception Guidance 68
10.5 Appendix 5: Medical Device AEs, SAEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies 69
10.5.1 Definition of Medical Device AE 69
10.5.2 Definition of Medical Device SAE 69
10.5.3 Definition of Device Deficiency 70
10.5.4 Recording and Follow-Up of Medical Device AE and/or SAE and Device Deficiencies 70

10.5.5 Reporting of Medical Device SAEs 72
10.6 Appendix 6: Country/Region-specific Requirements 72
10.6.1 Home Visits: Country-specific for Slovakia 72
10.7 Appendix 7 Protocol Amendment History 73
10.7.1 Amendment 1 73
10.7.2 Amendment 2 74

11. References 75

Table of Tables

Table 1–1: Regimen 1 Schedule of Activities (SoA) 14
Table 1–2: Regimen 2 CCI Schedule of Activities (SoA) 17
Table 1–3: Regimen 3 CCI Schedule of Activities (SoA) 19
Table 6–1: Study Intervention 35
Table 8–1: PK Sampling Schedule for Regimen 1 49
Table 8–2: PK Sampling Schedule for Regimen 2 50
Table 8–3: PK Sampling Schedule for Regimen 3 51
Table 9–1: Analysis Sets 53
Table 10–1: Protocol-required Safety Laboratory Tests* 61

Table of Figures

Figure 1-1: Study Flow Diagram 13
Figure 1-2: Dosing Schedule 13

List of Abbreviations

(A)ESI	(Adverse) events of special interest
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AMD	Age-related macular degeneration
AOBP	Automated office blood pressure
APTC	Anti-Platelet Trialists' Collaboration
AST	Aspartate aminotransferase
ATE	Arterial thromboembolic event
BCVA	Best corrected visual acuity
BP	Blood pressure
BRVO	Branch retinal vein occlusion
BUN	Blood urea nitrogen
CE	Conformité européenne
CI-DME	Central involved diabetic macular degeneration
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
C_{max}	Maximum (peak) concentration
CNV	Choroidal neovascularization
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRT	Central retinal thickness
CTFG	Clinical Trial Facilitation Group
CTIS	Clinical Trials Information System
CRVO	Central retinal vein occlusion
CSME	Clinically significant macular edema
DME	Diabetic macular edema
DBP	Diastolic blood pressure
DR	Diabetic retinopathy
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EYLEA 114.3 mg/mL	Aflibercept 8 mg
FAS	Full analysis set
FDA	Food and Drug Administration
FP	Fundus photography
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice

HbA1c	Hemoglobin A1c
HD	High dose or 8 mg aflibercept
HR	Heart rate
HRT	Hormonal replacement therapy
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committees
IOP	Intraocular pressure
IRB	Institutional Review Board
IRF	Intraretinal fluid
IRT	Interactive Response Technology
IV	Intravenous
IVT	Intravitreal
LAM	Lactational amenorrhea method
LDH	Lactate dehydrogenase
LPLV	Last Patient Last protocol-defined Visit
mCNV	Myopic choroidal neovascularization
MedDRA	Medical Dictionary for Regulatory Activities
MIGS	Minimally invasive glaucoma surgery
NAb	Neutralizing antibody
nAMD	Neovascular age-related macular degeneration
OCT	Optical coherence tomography
PK	Pharmacokinetic
PKS	Pharmacokinetic analysis set
PRP	Panretinal laser photocoagulation
PT	Preferred term
QTL	Quality tolerance limits
RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Steering committee
SD-OCT	Spectral domain optical coherence tomography
SoA	Schedule of activities
SOC	System organ class
SRF	Subretinal fluid
SDLL	Source Data Location List
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
t_{max}	Median time to peak concentration

US	United States
VA	Visual acuity
VEGF	Vascular endothelial growth factor
WBC	White blood cell
WOCBP	Woman /Women of childbearing potential
YAG	Yttrium-aluminum-garnet

1. Protocol Summary

1.1 Synopsis

Protocol Title:

An open-label, non-randomized, multi-center, phase 4 pharmacokinetic study to evaluate the systemic exposure after bilateral intravitreal administration of high dose (8 mg) aflibercept in adults with diabetic macular edema or neovascular age-related macular degeneration

Short Title:

Study to evaluate exposure after 8 mg aflibercept bilateral therapy

Regulatory Agency Identifier Number(s):

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

EU-CT number: 2024-511665-11-00

Envisaged Indications:

Diabetic macular edema and neovascular age-related macular degeneration

Rationale:

High dose (HD, 8 mg) aflibercept has been recently approved for the treatment of neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME). Bilateral treatment with HD aflibercept is likely to occur in clinical practice. While pivotal studies for HD aflibercept allowed for concurrent dosing of 8 mg aflibercept in the study eye and 2 mg aflibercept or other anti-VEGFs in the fellow eye, bilateral dosing of 8 mg aflibercept has yet to be investigated. This pharmacokinetic (PK) study is planned to evaluate systemic exposure after bilateral dosing with 8 mg aflibercept in participants with DME and nAMD.

Objectives, Endpoints, and/or Estimands:

Objectives	Endpoints
Primary	
• To evaluate the systemic pharmacokinetics after bilateral 8 mg aflibercept treatment	**Primary endpoint** • Maximum observed concentration (C_{max}) of free aflibercept **Exploratory endpoints** • Maximum observed concentration (C_{max}) of adjusted bound aflibercept • Maximum observed concentration (C_{max}) of total aflibercept • Timepoint (t_{max}) where C_{max} of free aflibercept was observed • Timepoint (t_{max}) where C_{max} of adjusted bound aflibercept was observed • In Regimen 2: Observed concentration (C_t) of free aflibercept at Weeks 4, 8, 20, 32, and 44
Exploratory	
• To evaluate immunogenicity of bilateral 8 mg aflibercept treatment	• Incidence of treatment-emergent and treatment-boosted neutralizing antibodies (NAb) and ADA anti-drug antibodies (ADA) titers
• To assess the safety of bilateral 8 mg aflibercept treatment	• Occurrence of ocular and non-ocular treatment-emergent AEs (TEAEs) and all serious adverse events (SAEs)
• To explore the relationship between dose, drug concentration and/or pharmacokinetic parameters and selected systemic response variables after bilateral 8 mg aflibercept treatment	• Maximum change from baseline of systolic/diastolic blood pressure and associated concentration of free and adjusted bound aflibercept
• To generate additional data for the effect of bilateral 8 mg aflibercept treatment on anatomical measures of response and on visual acuity	• Change from baseline in best corrected visual acuity (BCVA) at the end of the study[1] • Change from baseline in central retinal thickness (CRT) at the end of the study[1]

Footnotes:
1. End of study is CCI [redacted]

Overall Design Synopsis:

This open-label, non-randomized, multi-center, Phase 4 PK study will evaluate the systemic exposure (pharmacokinetics) of bilateral HD (8 mg) aflibercept administered to participants with DME or nAMD treated over 1 year in 3 different treatment regimens. CCI [redacted]

The primary objective of the study is to evaluate the systemic PK after bilateral 8 mg aflibercept treatment.

Number of Participants:

Two populations of patients with DME or nAMD requiring treatment with bilateral anti-VEGF treatment will be eligible for participation in this PK study.

1. The first population will be participants enrolled with active disease (as defined by inclusion criterion 2) in one eye with the fellow eye (without active disease) being already under maintenance treatment with an approved intravitreal (IVT) anti-VEGF therapy.
2. The second population will be participants with active disease in both eyes at the time of enrollment.

Up to 51 total participants (treatment naïve or previously treated) will be assigned by the study investigator based upon their clinical presentation to one of 3 treatment regimens.

At least 15 participants presenting with one eye with active disease and the fellow eye (without active disease) already under maintenance treatment with an approved intravitreal (IVT) anti-VEGF therapy will be assigned to Regimen 1. Regimen 1 participants will be administered bilateral 8 mg aflibercept injections according to the Regimen 1 dosing schedule. CCI [redacted]

At least 15 participants presenting with bilaterally active disease will be assigned to Regimen 2 and treated CCI [redacted] according to the Regimen 2 dosing schedule.

CCI [redacted]

At least 15 participants presenting with bilaterally active disease may be assigned to Regimen 3 and treated CCI [redacted] according to the Regimen 3 dosing schedule.

Study Arms and Duration:

The study duration will vary depending on the assigned treatment regimen. The study consists of an up to 21-day screening period, an up to 48-week treatment period, and an end of study (EOS) Visit 4 weeks after the last treatment administration. The maximum study duration for a participant is approximately 55 weeks CCI [redacted]

EOS is defined as the last visit of the last participant. No study treatment will be administered at the EOS visit.

8 mg aflibercept is the sponsor's study intervention under investigation. In all treatment regimens, the eyes CCI [redacted]

Data Monitoring/Other Committee: No

Study Steering Committee (SC): No

Anti-Platelet Trialists Collaboration Adjudication Committee: Yes

1.2 Schema

Figure 1-1: Study Flow Diagram

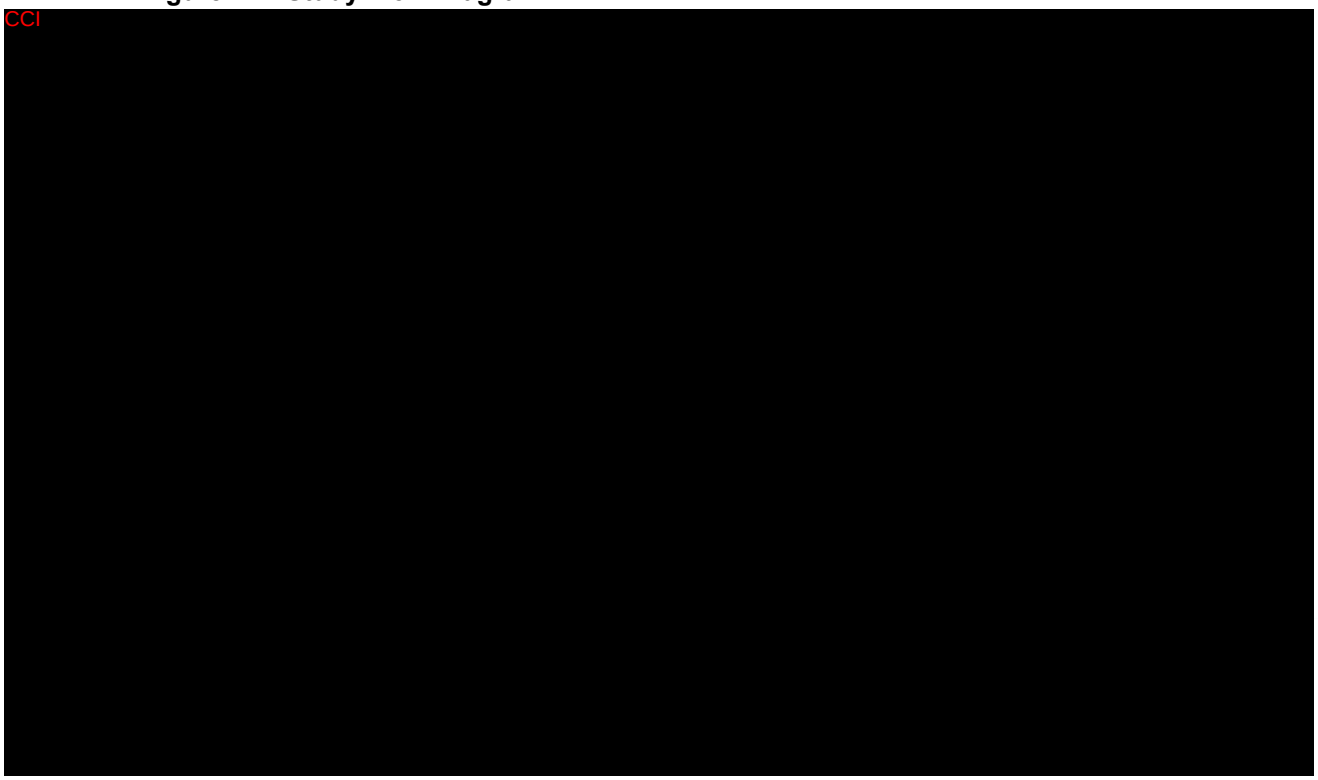
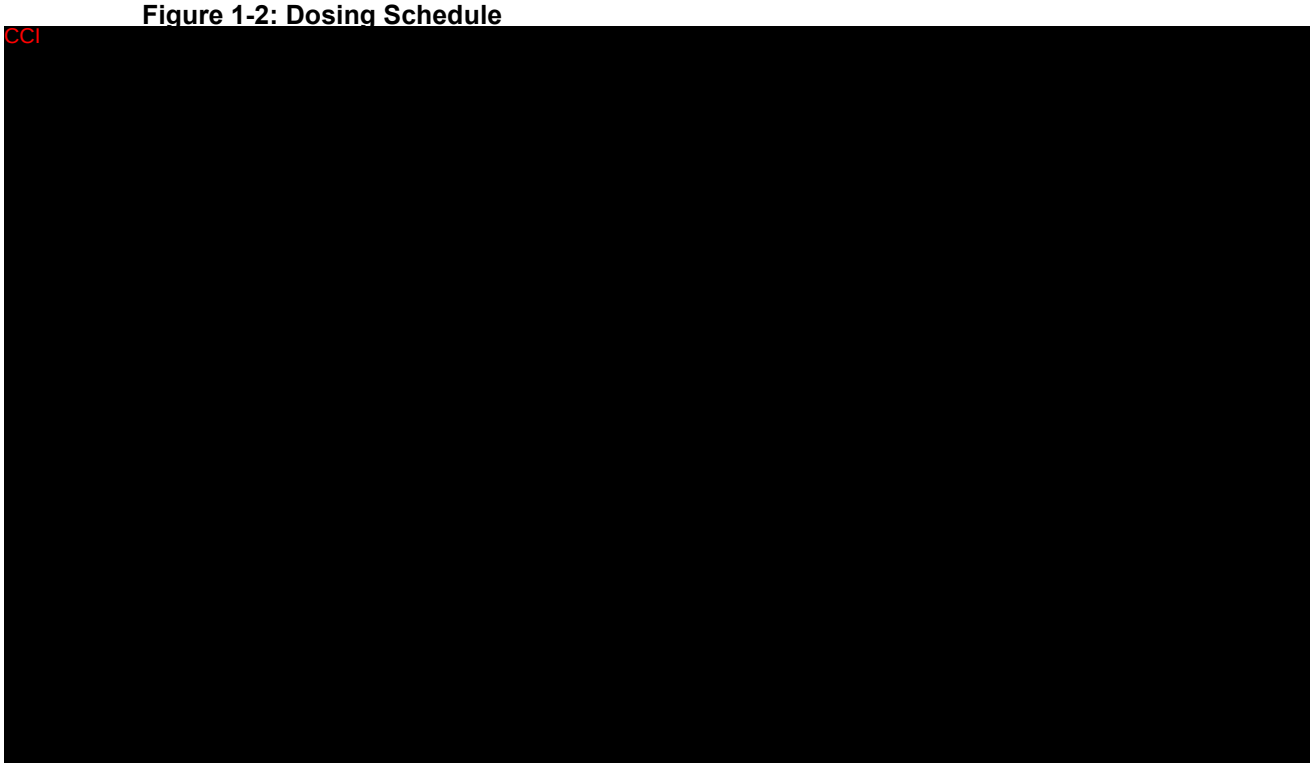


Figure 1-2: Dosing Schedule



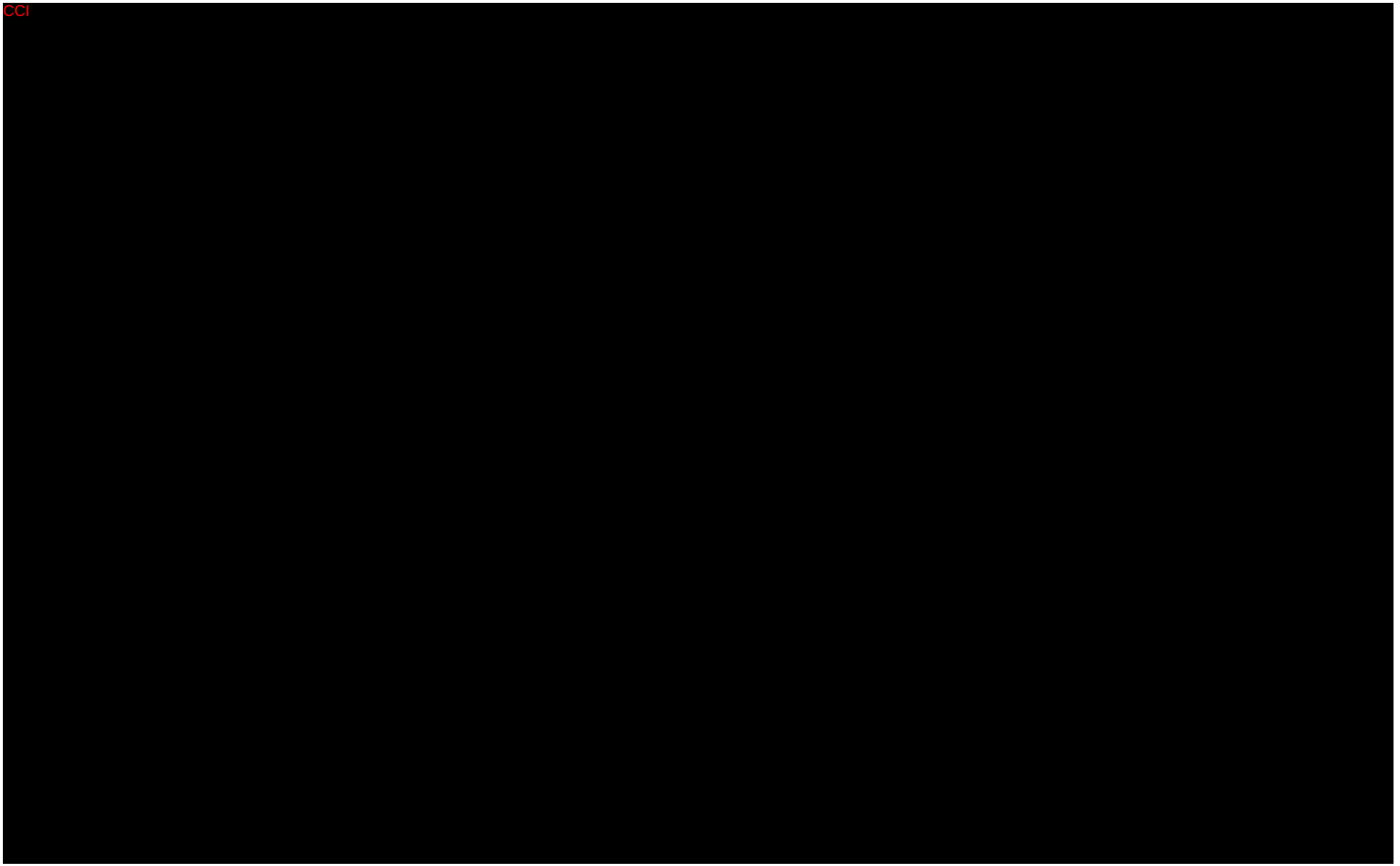
1.3 Schedule of Activities (SoA)

Study assessments and procedures are presented by regimen. The timing and intervals between visits, the dosing schedule of the intervention and the timing of the PK sampling varies in the 3 treatment regimens.

Table 1–1: Regimen 1 Schedule of Activities (SoA)

CCI

[redacted]


CCI

CCI



Table 1–2: Regimen 2 CCI Schedule of Activities (SoA)

CCI

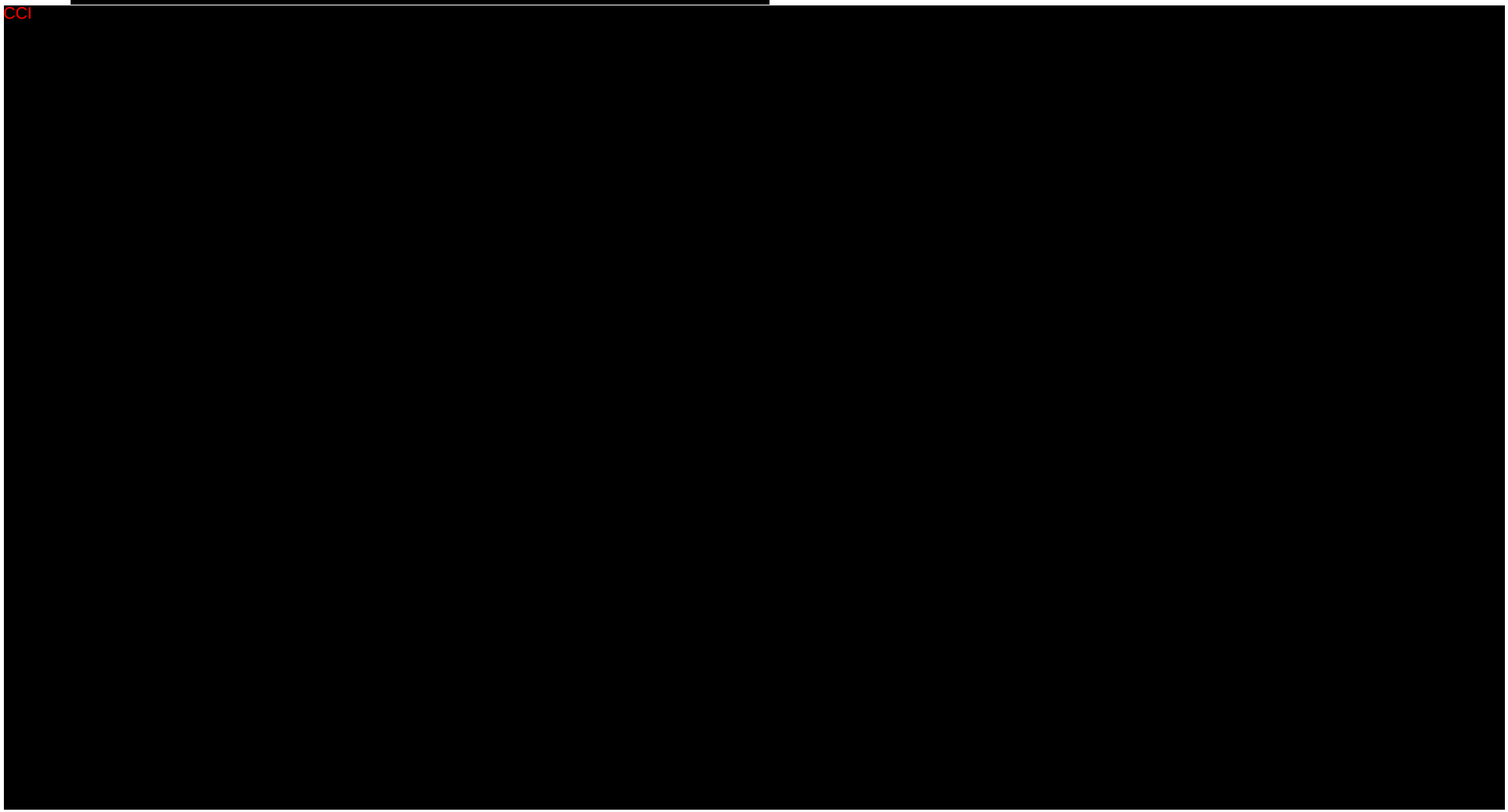
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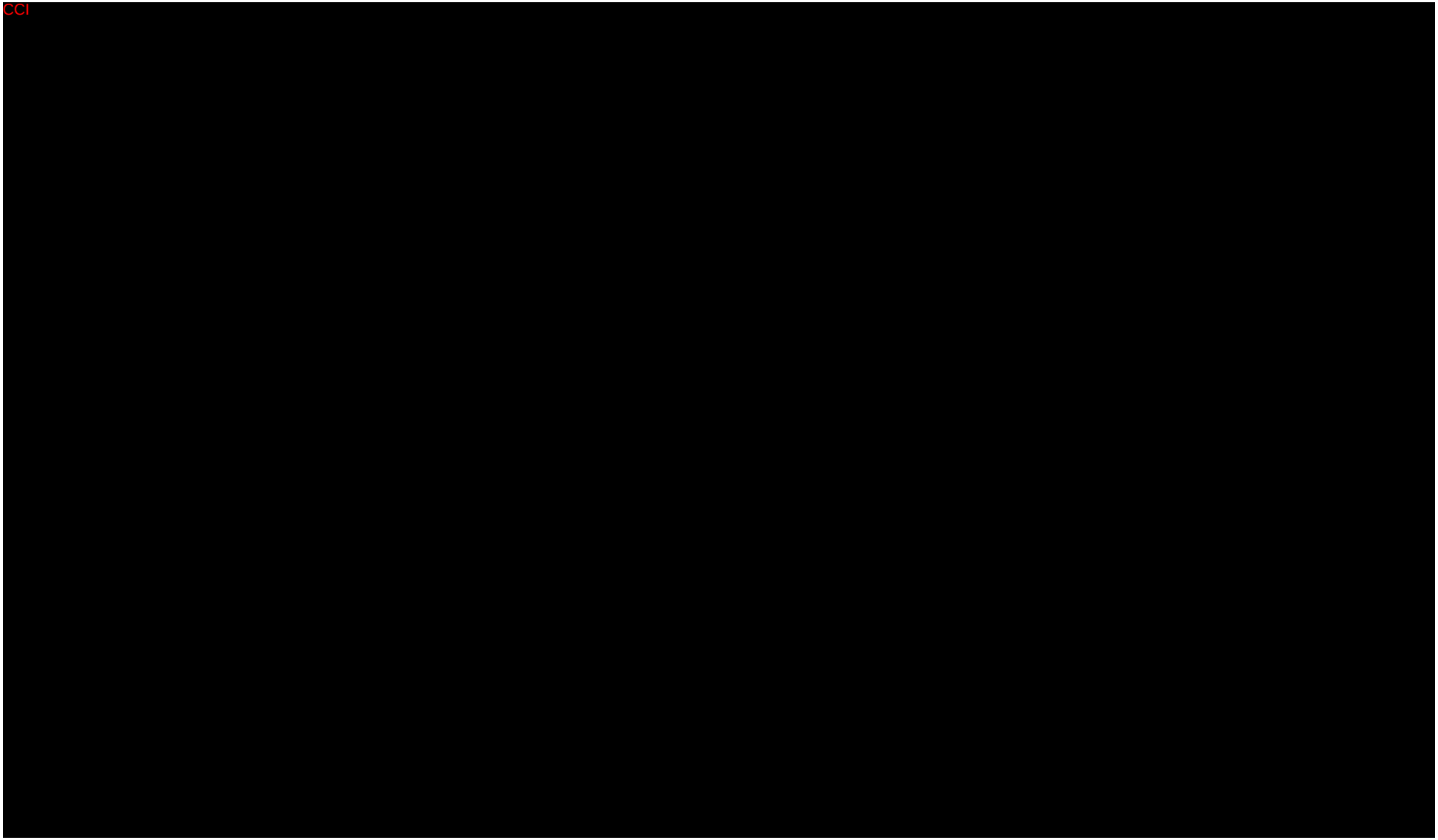
Table 1–3: Regimen 3 CCI Schedule of Activities (SoA)

CCI

CCI



CCI



CCI



2. Introduction

EYLEA (also known as intravitreal aflibercept injection) is a VEGF antagonist currently approved in over 100 countries for the treatment of DME at a dosage level of 2 mg (administered at a concentration of 40 mg/mL injected intravitreally [IVT]). EYLEA is currently approved in more than 100 countries for additional indications that include neovascular age-related macular degeneration (nAMD), macular edema following central retinal vein occlusion (CRVO) branch retinal vein occlusion (BRVO), and myopic choroidal neovascularization (mCNV). Just recently, 8 mg aflibercept (EYLEA 114.3 mg/mL) was approved in the United States (US) for the treatment of nAMD, DME and diabetic retinopathy (DR) in August 2023 and in the EU in January 2024 for the treatment of nAMD and DME.

2.1 Study Rationale

Vascular endothelial growth factor (VEGF) is a protein growth factor that both stimulates angiogenesis and increases vascular permeability, playing a key role in the pathophysiology of DME (Ferrara, 2000; Nguyen et al., 2006; Bhagat, 2009) and nAMD. Hypoxia and other metabolic factors trigger VEGF release. VEGF induces vascular leakage and neovascularization. While neovascularization is a manifestation of both macular degeneration and DR, vascular leakage leading to macular edema is the most important cause of reduced visual acuity in both conditions. Anti-vascular endothelial growth factor (anti-VEGF) compounds have become the standard of care for the treatment of DME and nAMD. This approach is highly attractive as it directly targets VEGF, one of the main mediators of DR and age-related macular degeneration (AMD).

Despite available treatments for nAMD and DME, there remained an unmet medical need for the development of anti-VEGF therapies with the potential to improve important clinical outcomes while decreasing the treatment burden via a reduction in the required frequency of intravitreal injections. 8 mg aflibercept was developed to respond to this unmet medical need.

Increased duration of pharmacological action and reduced number of injections have been demonstrated with 8 mg aflibercept (HD aflibercept). The ability to extend treatment intervals to every 12 weeks or greater following the initiation of 8 mg aflibercept has been shown in the pivotal PHOTON and PULSAR studies to reduce the number of injections required for the treatment of DME and nAMD, respectively, over 2 years compared to standard of care treatment with EYLEA. This decrease in injection-related treatment burden for patients treated with 8 mg aflibercept is expected to be a significant contribution to patient care and healthcare services.

Bilateral treatment with 8 mg aflibercept is expected to be employed in clinical practice after the launch of EYLEA 114.3 mg/mL. While pivotal studies allowed for concurrent dosing of 8 mg aflibercept in the study eye and 2 mg aflibercept or other anti-VEGFs in the fellow eye, bilateral dosing of 8 mg aflibercept has yet to be investigated. This PK study is planned to help better understand systemic exposure after bilateral dosing with 8 mg aflibercept.

PK modeling based on results from the pivotal studies with 8 mg aflibercept suggests a similar clearance of 8 mg aflibercept in both nAMD and DME patients when adjusted for age. Also, there are no expected notable differences in aflibercept clearance in patients with either condition treated at various stages of disease severity. Consequently, patients with bilateral nAMD or bilateral DME will be eligible for recruitment in this study.

Two populations of patients with DME or nAMD will be eligible for participation in this PK study. The first population will be patients who present with one eye with active disease (as defined by inclusion criteria 2 in this protocol) and the fellow eye without active disease receiving maintenance IVT anti-VEGF treatment with an approved therapy. The second population will be patients with active disease in both eyes at the time of presentation. Enrolled treatment naïve or previously treated patients will be assigned one of the 3 treatment regimens to receive bilateral 8 mg aflibercept treatment according to the regimen dosing schedule. PK sampling, blood pressure monitoring and assessment of adverse events will be carried out throughout the study.

The results of this study are expected to provide clinically relevant data on the systemic and ocular effects of bilateral dosing with 8 mg aflibercept and provide insights for how to safely treat patients suffering from bilateral ocular conditions with intravitreal 8 mg aflibercept injections.

2.2 Background

Diabetes is a chronic disease affecting 10% of the global adult population which can cause serious health complications and is among the top ten causes of death worldwide. In 2021, there were 537 million people living with diabetes, and this number is projected to increase to 783 million by 2045.

Although DR is the most common microvascular complication of diabetes, DME, a manifestation of diabetic retinopathy, is the primary cause of vision loss and blindness in patients with diabetes (Klein et al. 1984, Moss et al. 1994, Moss et al. 1998, Sivaprasad et al. 2012) and the most frequent cause of blindness in young and middle-aged adults (Klein et al. 1984, Moss et al. 1998). If left untreated, approximately half of patients with DME will lose 2 or more lines of visual acuity (VA) within 2 years (Bandello et al. 2012, Ciulla et al. 2003). Among patients with diabetes, the prevalence of clinically significant macular edema (CSME) ranges from 2.77% to 7.6% (Giuffrè 2004; Gulliford 2010; Ling 2002; McKay 2000; Minassian 2012).

Anti-VEGF compounds have become the standard of care for the treatment of DME. Other treatments include laser photocoagulation and steroids with surgery still being performed in some cases as a fall-back therapeutic option, particularly for those refractory to pharmacologic treatment or with vitreomacular traction.

Neovascular (wet) AMD is a leading cause of blindness in aging populations globally and is expected to affect approximately 7.7 million patients in the EU by 2050 (Jeany 2020; Morris 2007). 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.

Similar to DME, IVT-administered anti-VEGF therapies that inhibit neovascular growth and leakage in the retina are currently the standard of care for patients with nAMD. Anti-VEGF treatment has been demonstrated to not only maintain visual function but also provide clinically meaningful visual gains. Management of nAMD is chronic and requires long-term treatment in most patients to suppress retinal edema and recurrences of choroidal neovascularization (CNV). Although 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. In addition, long-term data in patients with nAMD and DME suggest that visual benefits achieved with anti-VEGF therapy may be lost, and not regained, if regular frequent dosing intervals are not maintained. This can 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. Consequently, prior to the recent approvals of 8 mg aflibercept, there was a significant unmet medical need to reduce the number or frequency of required IVT anti-VEGF injections while maintaining the positive visual and anatomic gains.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

Risks and Risk Management of Treatment with Bilateral 8 mg Aflibercept:

The safety profile of 8 mg aflibercept in studies in DME and nAMD patients has been shown to be similar to that of 2 mg aflibercept with no evidence of new safety concerns associated with the higher dose formulation. Identified risks for both 2 mg and 8 mg aflibercept include intraocular inflammation/infection, retinal tear, retinal detachment, transient increase in intraocular pressure (IOP), traumatic cataract, and hypersensitivity.

Other safety topics that are known to be associated with the systemic administration of anti-VEGF medications for cancer treatment including arterial thromboembolic events (ATEs), embryo-fetotoxicity, and an increase in BP remain potential risks for intravitreal 8 mg aflibercept that cannot be considered definite concerns to date. When the phase 2/3 PHOTON and phase 3 PULSAR studies evaluating 8 mg aflibercept in DME and nAMD populations, respectively, were specifically analyzed for safety topics such as non-ocular SAEs, ATEs, hypertension, non-ocular hemorrhages, VTEs, hypersensitivity and fatal events, no safety signals or increased risk of adverse drug reactions were identified in patients treated with 8 mg aflibercept compared with 2 mg aflibercept. CCI [redacted]

Now that 8 mg aflibercept is approved for the treatment of DME and nAMD, bilateral treatment with 8 mg aflibercept is expected in clinical practice. The primary objective of the study is to evaluate the systemic pharmacokinetics of 8 mg aflibercept in participants receiving treatment with 8 mg aflibercept in both eyes. While pivotal studies allowed for concurrent dosing of 8 mg aflibercept in the study eye and 2 mg aflibercept or other anti-VEGFs in the fellow eye, bilateral dosing of 8 mg aflibercept has yet to be investigated. This PK study is planned to evaluate systemic exposure and to generate safety data on bilateral dosing with 8 mg aflibercept. Safety will be assessed by collection of adverse events, vital signs (including careful monitoring of BP, heart rate, and temperature), ocular assessments and laboratory assessments.

As risk minimization measures, participants and investigators will be informed about the anticipated safety profile of 8 mg aflibercept and exclusion criteria will be applied to account for safety topics such as hypersensitivity, pregnancy, ATEs, and uncontrolled hypertension.

2.3.2 Benefit Assessment

Benefits of Treatment with 8 mg Aflibercept:

HD aflibercept by IVT injection for the treatment of DME and nAMD patients has been demonstrated to provide patient benefit through:

- Extending treatment intervals to every 16 weeks or longer
- Sustaining vision improvement and anatomic outcomes with fewer required treatments
- Reducing the number of injections, participant may benefit from:
  - Lowering the potential for injection-related risks over time
  - Increasing compliance by reducing the treatment burden on patients, caregivers, physicians, and healthcare systems

CCI [redacted]

2.3.3 Overall Benefit: Risk Conclusion

Based on the available clinical data, the benefit-risk of 8 mg aflibercept is considered positive and supports the evaluation of the systemic exposure in participants treated with 8 mg aflibercept in both eyes in the proposed study.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To evaluate the systemic pharmacokinetics after bilateral 8 mg aflibercept treatment	**Primary endpoint** • Maximum observed concentration (C_{max}) of free aflibercept **Exploratory endpoints** • Maximum observed concentration (C_{max}) of adjusted bound aflibercept • Maximum observed concentration (C_{max}) of total aflibercept • Timepoint (t_{max}) where C_{max} of free aflibercept was observed • Timepoint (t_{max}) where C_{max} of adjusted bound aflibercept was observed • In Regimen 2: Observed concentration (C_t) of free aflibercept at Weeks 4, 8, 20, 32, and 44
Exploratory	**Exploratory endpoints**
• To evaluate immunogenicity of bilateral 8 mg aflibercept treatment	• Incidence of treatment-emergent and treatment-boosted neutralizing antibodies (NAb) and ADA anti-drug antibodies (ADA) titers
• To assess the safety of bilateral 8 mg aflibercept treatment	• Occurrence of ocular and non-ocular treatment-emergent AEs (TEAEs) and all serious adverse events (SAEs)
• To explore the relationship between dose, drug concentration and/or pharmacokinetic parameters and selected systemic response variables after bilateral 8 mg aflibercept treatment	• Maximum change from baseline of systolic/diastolic blood pressure and associated concentration of free and adjusted bound aflibercept
• To generate additional data for the effect of bilateral 8 mg aflibercept treatment on anatomical measures of response and on visual acuity	• Change from baseline in BCVA at the end of the study[1] • Change from baseline in CRT at the end of the study[1]

Footnotes:
1. End of study is CCI [redacted]

Primary Estimand

The primary estimand for the primary objective is described by the following attributes:

- Population: Adult patients with DME or nAMD with either active disease in one eye and inactive disease under maintenance treatment in fellow eye OR active disease in both eyes
- Treatment condition: Aflibercept 8 mg administered to both eyes in one of 3 treatment regimens depending on the patient's clinical presentation
  - Treatment Regimen 1 (for participants with active disease in one eye and fellow eye with inactive disease under maintenance):
    - CCI [redacted]
    - CCI [redacted]
  - Treatment Regimen 2 (for participants with active disease in both eyes at screening and bilateral simultaneous treatment):
    - CCI [redacted]
  - Treatment Regimen 3 (for participants with active disease in both eyes at screening and bilateral staggered treatment):
    - CCI [redacted]
    - CCI [redacted]
- Variable: Maximum observed concentration (C_{max}) of free aflibercept
- Intercurrent events and strategies:
  - Premature treatment discontinuation prior to end of dense PK sampling – addressed by the hypothetical strategy
  - Premature treatment discontinuation after end of dense PK sampling– addressed by the while-on-treatment strategy
  - Use of prohibited medication – addressed by the treatment policy strategy
  - Missed study intervention – addressed by the treatment policy strategy
- Population-level summary: geometric mean C_{max} per treatment regimen

Rationale for estimand: For patients that discontinue treatment prior to the end of the dense PK sampling period (see Section 9.2, and Tables Table 8–1, Table 8–2, and Table 8–3), calculation of the maximum concentration of free aflibercept is not meaningful. For these events, a hypothetical strategy is applied whereby the patient is excluded from the analysis. This approach is sensible since it is not assumed that the PK profile of these patients would be systematically different from those who remained in the study, regardless of their reason for treatment discontinuation.
Regarding premature treatment discontinuation after end of the dense PK sampling period, only the on-treatment period is relevant for the estimation of C_{max} of free aflibercept. Hence the intercurrent event 'premature treatment discontinuation' is addressed using the while-on-

treatment strategy.
Intake of prohibited medication is not assumed to have an impact on the concentration of free aflibercept and is therefore addressed using the treatment policy strategy. Missing an injection may also be reflected in clinical practice and is thus addressed by the treatment policy strategy.

4. Study Design

4.1 Overall Design

This open-label, non-randomized, multi-center, phase 4 PK study to evaluate the systemic exposure after bilateral intravitreal administration of HD (8 mg) aflibercept in adults with DME or neovascular age-related macular degeneration (nAMD) will be conducted in the European Union and will evaluate up to 51 participants administered bilateral 8 mg aflibercept injections in 3 different treatment regimens. Upon enrollment participants with active central involved DME (CI-DME) or nAMD in at least one eye will be assigned by the study investigator based upon their clinical presentation to one of the 3 defined treatment regimens.

Two populations of patients with DME or nAMD will be eligible for participation in this PK study. The first population will be patients who present with one eye with active disease (as defined by inclusion criterion 2) with the fellow eye (without active disease) already under maintenance IVT anti-VEGF treatment with an approved therapy. These patients will be assigned to Regimen 1. The second population will be patients with active disease in both eyes at the time of presentation. These patients will be assigned to Regimen 2 or Regimen 3. In all treatment regimens the eyes CCI [redacted] during the up to 48-week study treatment period.

The sequence of 8 mg aflibercept IVT administrations to each eye will vary in each assigned treatment regimen as follows:

Treatment Regimen 1 CCI [redacted]

At least 15 participants presenting with one eye with active disease and the fellow eye (without active disease) already under maintenance treatment with an approved intravitreal (IVT) anti-VEGF therapy will be assigned to Regimen 1. Regimen 1 participants will be administered bilateral 8 mg aflibercept injections CCI [redacted] according to the Regimen 1 dosing schedule detailed in Figure 1-2a.

CCI [redacted]

CCI [redacted] This is primarily for 2 reasons: (i) most patients with newly diagnosed active CI-DME or nAMD in untreated eyes will likely be identified during follow-up evaluation for ongoing anti-VEGF treatment in their other eye and (ii) the clinical presentation with bilateral newly diagnosed CI-DME or nAMD is relatively uncommon (Mathenge 2014).

Treatment Regimen 2 CCI [redacted]

At least 15 participants presenting with bilaterally active disease will be assigned to Regimen 2 and treated CCI [redacted] according to the Regimen 2 dosing schedule detailed in Figure 1-2b.

CCI [redacted]

Treatment Regimen 3 CCI [redacted]

CCI [redacted]

Up to 15 participants presenting with bilaterally active disease may be assigned to Regimen 3. Participants in Regimen 3 will be treated CCI [redacted] according to the Regimen 3 dosing schedule detailed in Figure 1-2c.

CCI [redacted]

CCI [redacted] In a Swedish nAMD registry, the mean duration of treatment of the first eye was 19 months before treatment of the second eye was started (Lövestam, 2022). In the VIVID and VISTA phase 3 DME studies, the mean time to DME development in the fellow eye was about 6 months after the first eye was treated in the study (Dhoot DS et al. Retina., 2022). A more recent analysis of the PHOTON DME study and the PULSAR nAMD study reveals that the delay between treatment of the fellow eye and the treated study eye is approximately 2 months and 3 months, respectively.

During the up to 48-week treatment period, participants assigned to each regimen will undergo a battery of ocular and safety assessments as well as immunogenicity and PK sampling corresponding to the treatment regimen intervals to evaluate the systemic exposure after bilateral 8 mg aflibercept treatment. The 8 mg aflibercept dosing, safety and efficacy assessments and PK sampling schedules will vary between the 3 regimens as shown in the SoA (see Section 1.3, Table 1–1 for Regimen 1, Table 1–2 for Regimen 2 and Table 1–3 for Regimen 3 and Section 8.5 Table 8–1,Table 8–2 and Table 8–3 for the PK sampling schedules).

Participants assigned to Regimen 1 not completing treatments through Visit 8 will be replaced. However, it may not be possible to replace participants assigned to Regimen 2 or 3 prematurely discontinued from the study intervention or the study as participants with bilaterally active DME or nAMD are infrequently seen in routine clinical practice.

Baseline characteristics to be collected will include standard demography (e.g. age, race, weight, height, etc.), disease characteristics, medical history, and medication history.

In all participants, blood samples for measurement of drug concentrations (PK) and immunogenicity (ADA) will be obtained prior to the first treatment and at prespecified time points throughout the course of the study (see Section 8.5 Table 8–1 for Regimen 1, Table 8–2 for Regimen 2 and Table 8–3 for Regimen 3 PK sampling schedules). Dosing schedules appear in Figure 1-2a, 1-2b and 1-2c. Sampling time points have been derived from previous experience and expected to capture the maximum exposure as well as the overall PK profile for each regimen.

4.2 Scientific Rationale for Study Design

This study aims to provide systemic exposure information for DME and nAMD patients after bilateral 8 mg aflibercept treatment and provide some insights regarding the safety of bilateral 8 mg aflibercept treatment which was not evaluated in pivotal studies. Three options for fellow eye treatment which reflect the anticipated clinical use of bilateral 8 mg aflibercept in DME and nAMD patients will be evaluated in this open-label, non-randomized, multi-center, Phase 4 PK study. Recruited patients will be assigned to one of the 3 regimens by the study investigator based on the clinical presentation of the patient at the time of enrollment. Regimen 1 represents the scenario in which patients previously treated with an anti-VEGF for disease in one eye will develop active disease in their fellow eye. Regimens 2 and 3 address the situation where both eyes would present with active disease requiring anti-VEGF treatment. Considering that bilateral simultaneous presentation of newly diagnosed CI-DME or nAMD is infrequent in clinical practice it is expected that a smaller proportion of patients with DME or AMD recruited into this study will be assigned to Regimens 2 or 3.

4.3 Justification for Dose

Aflibercept 8 mg is the recently approved HD preparation. Initial monthly treatment for 3 consecutive doses follows the approved posology and the 12-week interval maintenance doses reflects the shortest randomized dosing interval tested in the pivotal studies. The administration of 8 mg aflibercept to both eyes on the same day following this regimen will allow an assessment of the systemic exposure resulting from the treatment of the fellow eye which was not evaluated in the pivotal trials.

In this study, both eyes of patients with DME or nAMD will receive treatment with 8 mg aflibercept to evaluate systemic exposure and to provide early insights on the appropriate use

of bilateral 8 mg aflibercept treatment which is anticipated to occur clinically. In all treatment regimens the eyes CCI [redacted] during the up to 48-week study treatment period. The sequence of the bilateral 8 mg aflibercept injections in the enrolled patients will be determined by the treatment regimen assigned by the study investigator.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedures for the EOS visit or an early discontinuation visit as shown in the SoA (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 study centers in all participating countries.

5. Study Population

Treatment naïve and previously-treated adult patients with nAMD and DME.

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

5.1 Inclusion Criteria

Participants are eligible to be included in the study only, if all the following criteria apply at both the Screening and Baseline visits (except where indicated):

Age

1. Men or women ≥18 years of age (or country's legal age of adulthood if the legal age is >18 years)

Type of Participant and Disease Characteristics

2. Participants (treatment naïve or previously treated) requiring intravitreal anti-VEGF treatment in both eyes in the opinion of the investigator
3. Participants with type 1 or type 2 diabetes mellitus and DME in both eyes with active central involvement (CI-DME) in at least one eye with CRT ≥300 µm (or ≥320 µm on Spectralis) as determined by the investigator at the screening visit, **OR** diagnosis of nAMD in both eyes with active subfoveal CNV in at least one eye with intraretinal fluid (IRF) and/or subretinal fluid (SRF) on OCT as determined by the investigator at the screening visit
4. BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 78 to 24 (approximate Snellen equivalent of 20/32 to 20/320) in eyes with active disease and decreased vision determined to be primarily the result of DME or nAMD

Sex and Contraceptive/Barrier Requirements

5. A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies: Is a woman of nonchildbearing potential (WONCBP) as defined in Appendix 4 Section 10.4 Contraceptive and Barrier Guidance
   Women of childbearing potential (WOCBP) or 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 4 months after the last administration of study intervention. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for participation in clinical studies and fulfill the conditions set in Section 10.4.2.

Informed Consent

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

Other Inclusion Criteria

7. Willing and able to comply with clinic visits and study-related procedures

5.2 Exclusion Criteria

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

Ocular Medical Conditions

1. Evidence of macular edema due to any cause other than diabetes mellitus in patients with DME or neovascular age-related macular degeneration in patients with nAMD in either eye
2. Active proliferative DR in either eye
3. Panretinal laser photocoagulation (PRP) or macular laser photocoagulation in either eye with CI-DME or active nAMD within 12 weeks (84 days) of the screening visit
4. IOP ≥25 mmHg in either eye at the screening and/or baseline visits
5. Evidence of infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye within 4 weeks (28 days) of the screening visit
6. Any intraocular inflammation/infection in either eye within 12 weeks (84 days) of the screening visit
7. History of idiopathic or autoimmune uveitis in either eye
8. Current iris neovascularization, vitreous hemorrhage, or tractional retinal detachment visible at the screening or baseline visit assessments in either eye
9. Corneal dystrophy in either eye affecting the visual axis based on investigator assessment
10. Any concurrent ocular condition in the study eyes which, in the opinion of the investigator, could either increase the risk to the patient beyond what is to be expected from standard procedures of IVT injections, or which otherwise may interfere with the injection procedure or with evaluation of safety
11. Inability to obtain photographs or SD-OCT in either eye, e.g., due to media opacity

Prior/Concomitant Ocular Therapy

12. Prior treatment with IVT 2 mg aflibercept (EYLEA) in either eye within 12 weeks (84 days) of the screening visit
13. Prior treatment with IVT 8 mg or HD aflibercept in either eye within 24 weeks (168 days) of the screening visit
14. Prior treatment with any other approved IVT agent with anti-VEGF effect (e.g. ranibizumab, bevacizumab, brolucizumab, faricimab, pegaptanib sodium or biosimilars) in either eye within 4 weeks (28 days) of the screening visit
15. Prior treatment with ocular investigational agents (e.g. IVT, suprachoroidal injections, ocular implants, etc.) in either eye at any time, that have not been approved at the time of screening
16. Prior treatment with any ocular gene or cell therapy treatment in either eye
17. Treatment with ocriplasmin (JETREA®) at any time in either eye
18. Previous use of intraocular or periocular corticosteroids in either eye within 16 weeks (112 days) of the screening visit, or OZURDEX® implant within 180 days of the screening visit or ILUVIEN® or RETISERT® implant at any time
19. History of vitreoretinal surgery (including scleral buckle) in either eye
20. Any other intraocular surgery within 12 weeks (84 days) before the screening visit in either eye
21. Yttrium-aluminum-garnet (YAG) laser capsulotomy in either eye within 4 weeks (28 days) of the screening visit
22. History of glaucoma filtration surgery (including MIGS) or likely to need for filtration surgery in either eye during course of study
23. History of corneal transplant in either eye

Non-Ocular Medical Conditions

24. 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 or that might affect interpretation of the results of the study or render the patient at high risk for treatment complications
25. Any prior systemic (IV) anti-VEGF administration
26. Patients with systolic blood pressure (SBP) >160 mmHg or diastolic blood pressure (DBP) >95 mmHg at the screening or baseline visit
27. Patients who, in the opinion of the investigator, are unlikely to have stable BP over the course of the study (e.g., due to known or suspected noncompliance with medication)
28. Patients with any changes in blood pressure medication (e.g. increase in dose, new or added medication) or medications known to affect blood pressure within 12 weeks (84 days) prior to the screening visit
29. Patients with known cardiac arrhythmia

30. History of cerebrovascular accident or myocardial infarction within 24 weeks (168 days) of screening visit
31. Renal failure, dialysis, or history of renal transplant
32. Known sensitivity to any of the compounds of the study formulation

Prior/Concurrent Clinical Study Experience

33. Participation in an investigational study that involved treatment with any drug or device within 30 days or 5 half-lives of administration of the previous study intervention, whichever is longer, prior to screening visit

Other Exclusion Criteria

34. Dependents of the investigators, the contract research organization(s) or sponsor (e.g. family members, employees, people who receive grants/education)

For patients assigned to Regimen 1, the eye meeting the criteria for active DME or nAMD will be designated as the 1st eye CCI while the fellow eye having received maintenance treatment with an anti-VEGF therapy will be designated as the 2nd eye.

For patients assigned to Regimen 2 or 3, where both eyes are expected meet the inclusion criteria for active DME or nAMD, the right eye will be designated the 1st eye and the left eye will be designated as the 2nd eye.

5.3 Lifestyle Considerations

No lifestyle restrictions are required during the study.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to a treatment regimen. 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 assigned to a treatment regimen and could not start subsequent treatment on schedule.
- 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 IOP or arterial hypertension, or initial screening occurred too early to fulfill the requirements for time intervals after specific therapeutic interventions specified in the exclusion criteria) was subsequently resolved.

Under any of the above exceptions, a participant may be rescreened once only. To be eligible, the rescreened participant must meet all inclusion criteria and none of the exclusion criteria at the Re-screening and Baseline visits. 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.

Rescreened participants will receive a new subject number.

5.5 Criteria for Temporarily Delaying

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

Study interventions are all prespecified, investigational and non-investigational medicinal products, medical devices and other interventions (e.g., surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 Study Intervention(s) Administered

The 8 mg aflibercept will be supplied for this study as an aqueous solution in sterile, sealed, single-use vials for IVT administration at a concentration of 114.3 mg/mL aflibercept which will be delivered in an injection volume of 70 µl (0.07 mL). This corresponds to 8 mg of aflibercept administered per eye.

Instructions on dose preparation are provided in the study reference manual.

Table 6–1: Study Intervention

Intervention Name	Aflibercept 8 mg
Type	Drug
Dose Formulation	Solution in vial
Unit Dose Strength(s)	114.3 mg/mL
Dosage Level(s)	8 mg (70 µL)
Route of Administration	IVT injection
Use	Experimental
IMP/AxMP	IMP
Packaging and Labeling	Study Intervention will be provided in sterile 3 mL glass vials. Each vial will be labeled as required per country requirement.

Footnotes: AxMP = Auxiliary medicinal products, IMP = Investigational Medicinal Product, IVT = intravitreal injection

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, as well as devices that are used to gather additional clinical data. These devices have been cleared (conformité européenne [CE] marked or the Food and Drug Administration [FDA] cleared) according to the regulatory requirements specific for the country where the study site is located.

The 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.

Medical devices supplied by, or on behalf of the sponsor, for use in this study to directly measure safety or efficacy endpoints include digital blood pressure monitors.

Deficiencies (including malfunctions, use error, and inadequate labeling) related to the filter needles, injection needles, syringes, and digital blood pressure monitors shall be documented and reported to the sponsor by the investigator throughout the clinical investigation (see Section 8.4.9) so they can be appropriately managed by the sponsor.

Instructions for use of additional devices not supplied by the sponsor 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, and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants assigned to one of the three study treatment regimens may receive study interventions and only authorized site staff may supply, prepare or administer study interventions.
3. All study interventions 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.
4. The investigator or the head of the institution (where applicable), or delegated site staff is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Drug returns, reconciliation and destruction return information will be captured in Interactive Response Technology (IRT).
5. Further guidance and information for the final disposition of unused study interventions are provided in the study reference manual, if applicable.

6.2.1 Packaging, Labeling, and Storage

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

- Sterile 8 mg aflibercept in sealed glass vials (see Table 6–1)
- Filter needle (18-gauge)

The study intervention kits are to be stored in the refrigerator (2°C to 8°C) and must not be frozen. The vials in the kits must be kept in the outer carton to protect them from light. When the study intervention kit is removed from the refrigerator, the solution in the vials 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. The study intervention kits 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 aflibercept.

Details on the administration of bilateral 8 mg aflibercept IVT injections are provided in study reference manual.

After the study intervention is administered, participants will be observed for at least 30 minutes.

6.3 Assignment to Study Intervention

Upon enrollment participants with active central involved DME (CI-DME) or nAMD will be assigned by the study investigator based upon their clinical presentation and the local standards of practice for the administration of IVT anti-VEGF treatments to one of the 3 defined treatment regimens.

Two populations of patients with DME or nAMD will be eligible for participation in this PK study. The first population will be patients who present with one eye with active disease with the fellow eye being already under maintenance IVT anti-VEGF treatment with an approved therapy. At least 15 of these participants will be assigned to Regimen 1. The second population will be patients with active disease in both eyes at the time of presentation. These participants will be assigned to Regimen 2 or Regimen 3. CCI [redacted] In all treatment regimens the eyes CCI [redacted] during the up to 48-week study treatment period.

The sequence of 8 mg aflibercept IVT administrations to each eye will vary in each assigned treatment regimen. Study intervention will be dispensed at the study visits summarized in the SoA (Section 1.3).

6.4 Blinding/Masking

This is an open-label study.

6.5 Study Intervention Compliance

Study intervention will be administered by a qualified ophthalmologist. Details regarding the bilateral 8 mg aflibercept IVT injections will be recorded in the eCRF (e.g., time and volume of injection, type of anesthesia, treatment site). An adequate record of receipt, dispensing, accountability and destruction of the study intervention must be captured on the dispensing log.

6.6 Dose Modification

Dose modification for an individual participant is not allowed.

6.7 Continued Access to Study Intervention After the End of the Study

The study intervention will not be supplied after the end of the study. Participants will not be restricted from pursuing available treatments for DME or nAMD as needed for their continued care.

6.8 Treatment of Overdose

For this study, any administered dose of study intervention greater 8 mg (70 µL) aflibercept per injected study 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, approximately 0 to 5 minutes, 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:

- Closely monitor the participant for elevated IOP and for any AE/SAE as medically appropriate.
- Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether study intervention should be interrupted.
- Document the overdose in the eCRF, recording to the possible extent the amount of the dose administered.

In the event of an AE/SAE, decisions regarding dose interruptions will be made by the investigator based on the clinical evaluation of the participant and in consultation with the medical monitor.

6.9 Prior and Concomitant Therapy

Any treatment administered from time of informed consent to the end of final study visit will be considered a concomitant medication. This includes medications that were started before the study and are ongoing during the study.

If a pretreatment concomitant medication is administered before the study intervention (e.g., antibiotic or anesthetic) for the 1st eye, it should be administered for the 2nd eye injections as well, if possible.

6.9.1 Prohibited Medications and Procedures

Study eye:

Participants are not allowed to receive any standard or investigational treatment for DME, DR or nAMD other than their assigned study treatment with bilateral 8 mg aflibercept treatment, until they have completed the end of study/early discontinuation visit assessments. This includes medications administered locally (e.g., IVT, topical, juxtascleral, or periorbital routes) or systemically with the intent of treating DME, DR or nAMD.

Non-ocular (systemic):

Non-ocular (systemic) standard or investigational treatments for DME, DR or nAMD are not permitted.

6.9.2 Permitted Medications and Procedures

Any other medications or procedures that are considered necessary for the participant's welfare, and that are not expected to interfere with the evaluation of the study drug, are allowed.

6.9.3 Rescue Medicine

There is no alternative rescue treatment defined for this study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1 (Section 10.1.10).

An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Participants assigned to Regimen 1 not completing treatments through Visit 8 as scheduled will be replaced. However, it may not be possible to replace participants assigned to Regimen 2 or 3 prematurely discontinued from the study intervention or the study as participants with bilaterally active DME or nAMD are infrequently seen in routine clinical practice.

7.1 Discontinuation of Study Intervention

Early discontinuation of study intervention can be triggered by the participant or by the treating investigator.

Participants for whom study intervention is planned at any time during the study but not administered 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. Following the missed study visit(s) or treatment(s), the participants should be scheduled for the next planned study visit and be administered the study intervention as indicated on the study schedule of activities (SoA, Section 1.3).

In rare instances, it may be necessary for a participant to permanently discontinue the study intervention. If the study intervention must be permanently discontinued, the participant will be asked to continue in the study without further treatment to complete the remaining scheduled study visits, if possible. If it is not possible for the participant to continue the study without treatment, the participant should be requested to complete an early discontinuation visit to be scheduled, if possible, at least 30 days after the last study intervention was administered. See the SoA EOS visit (Section 1.3, Table 1–1 for participants assigned to Regimen 1, Table 1–2 for participants assigned to Regimen 2 and Table 1–3 for participants assigned to Regimen 3) for data to be collected at the time of the early discontinuation or EOS visit. The participant will be permanently discontinued from the study upon completion of the early discontinuation visit.

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1 Section 10.1.10.

7.2 Participant Discontinuation/Withdrawal from the Study

Early or premature discontinuation of study participation, CCI [redacted] is needed under the following circumstances:

- A participant may withdraw from the study at any time at the participant's own request, for any reason (or without providing any reason) and without repercussion.
- A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing or withdrawal from the study, if possible, an early discontinuation or EOS visit should be conducted, as shown in the SoA (Section 1.3, Table 1–1 for participants assigned to Regimen 1, Table 1–2 for participants assigned to Regimen 2 and Table 1–3 for participants assigned to Regimen 3) for data to be collected at the time of early study discontinuation.
- The participant will be permanently discontinued from the study treatment and 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 must be withdrawn 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/SAE (ocular or non-ocular) that, from the participant's or the investigator's view, is severe enough to require withdrawal from the study. The investigator must notify the sponsor immediately if a participant is withdrawn because of an AE/SAE.
- Decision by the investigator or sponsor that early discontinuation is in the participant's best medical interest or administrative decision for a reason other than an AE/SAE.
- A female participant becomes pregnant (see Section 8.4.5).
- Lost to follow-up.
- Decision by the sponsor to halt the entire study.

Participants may be withdrawn if any of the following occurs:

- If any treatment for DME, DR or nAMD other than study interventions is given to either eye.
- Systemic anti-angiogenic agents are taken by the participant during the study.
- If, in the investigator's opinion, continuation in 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 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.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if the participant 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, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether 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, the participant will be considered lost to follow-up.

- Site personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants assigned, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3, Table 1–1 for Regimen 1,Table 1–2 for Regimen 2 and Table 1–3 for Regimen 3). Protocol waivers or exemptions are not allowed.
- 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. Screening (Visit 1) and Baseline (Visit 2) visits may be performed on the same day.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

The maximum amount of blood collected from each participant over the duration of the study, including safety laboratory assessments, PK (plasma), immunogenicity (serum), and any extra assessments that may be required, will not exceed approximately 120 mL. Additional repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

All attempts should be made to keep participants on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

8.2 Ocular Efficacy and Safety Assessments

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, Table 1–1 for Regimen 1,Table 1–2 for Regimen 2 and Table 1–3 for Regimen 3).

All ophthalmic examinations are to be conducted for both eyes before the study treatment and after the study treatment only in the treated eye or eyes, 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.

8.2.1 Best Corrected Visual Acuity

Visual function of the both eyes will be assessed using the ETDRS protocol (Early Treatment Diabetic Retinopathy Study research group 1985) starting at 4 meters. Refraction and BCVA are to be performed at each visit indicated on the SoA (Table 1–1 for Regimen 1, Table 1–2 for Regimen 2 and Table 1–3 for Regimen 3) for 2 regimens, respectively.

BCVA should be assessed before any other ocular procedures are performed. A detailed protocol for conducting VA testing and refraction can be found in the study reference manual.

8.2.2 Slit Lamp Examination

Participants' anterior eye structures and ocular adnexa will be examined bilaterally at each study visit as a safety assessment using a slit lamp before administration of the study treatment, as specified in Table 1–1 for Regimen 1, Table 1–2 for Regimen 2 and Table 1–3 for Regimen 3.

8.2.3 Intraocular Pressure

IOP will be measured as a safety assessment using an applanation tonometer (e.g., Goldmann) or handheld tonometer (e.g., iCare or Tono-pen®), as specified in Table 1–1 for Regimen 1, Table 1–2 for Regimen 2 and Table 1–3 for Regimen 3. The same method of IOP measurement must be used throughout the study for each individual participant, if possible.

At all visits, IOP in both eyes will be measured. Additionally, on days when the study intervention is administered, IOP will be measured at least 30 to 60 minutes after administration of study drug only in the treated eye or eyes.

Following the administration of the study treatment, the investigator (or designee) should monitor IOP closely until it reaches a value that will not be expected to cause optic nerve damage, e.g., below 25 mmHg. The exact timing is left to the discretion of the investigator. If multiple IOP measurements are taken after the study treatment, record only the last IOP measurement and related treatments in the source document and on the appropriate eCRF page.

8.2.4 Indirect Ophthalmoscopy

The posterior pole and peripheral retina of both eyes will be examined by indirect ophthalmoscopy at each study visit; before the study treatment (as a safety and efficacy assessment) and after the study treatment only in the treated eye or eyes, as specified in Table 1–1 for Regimen 1, Table 1–2 for Regimen 2 and Table 1–3 for Regimen 3. If indirect ophthalmoscopy cannot be performed immediately, approximately 0 to 5 minutes, after the administration of the study treatment, the investigator should assess the visual function of the treated eye or eyes (light perception and ability to count fingers) and then complete the indirect ophthalmoscopy assessment approximately 15 minutes after the study treatment to verify that the retina is attached and there is/are no (or no new) intraocular hemorrhage(s).

8.2.5 Spectral Domain Optical Coherence Tomography

Retinal characteristics will be evaluated using SD-OCT as an efficacy and safety assessment at each study visit specified in Table 1–1 for Regimen 1, Table 1–2 for Regimen 2 and Table 1–3 for Regimen 3. Images will be captured for both eyes and interpreted by the study

investigator at the site. All SD-OCTs will be electronically archived at the study site as part of the source documentation. A detailed protocol for acceptable SD-OCT machines and SD-OCT image acquisition can be found in the study reference manual.

The same SD-OCT imaging system used at Screening and Baseline visits must be used at all follow-up visits in each participant, if possible. The participants' eligibility to participate in the study in terms of SD-OCT will be confirmed by the investigator prior to the assignment of the participant to a treatment regimen.

8.2.6 Fundus Photography

The appearance of the retina will be evaluated as safety assessment by fundus photography as specified in Table 1–1 for Regimen 1, Table 1–2 for Regimen 2 and Table 1–3 for Regimen 3. FP will be captured for both eyes.

All FPs will be archived at the site as part of the source documentation. A detailed protocol for image acquisition can be found in the study reference manual.

The same imaging systems for FP used at Screening and Baseline visits must be used at all subsequent visits in each participant, if possible.

8.3 Safety Assessments

Procedures to assess ocular safety are included in Section 8.4. Planned timepoints for all safety assessments are provided in the SoA (Section 1.3 Table 1–1 for Regimen 1, Table 1–2 for Regimen 2 and Table 1–3 for Regimen 3).

8.3.1 Non-Ocular Safety Assessments

8.3.1.1 Physical Examinations

A physical examination, including height and weight, and a review of the cardiovascular, respiratory, gastrointestinal, and neurological systems will be performed at the screening visit to evaluate the overall health of the participant and will follow the standard practice of the site. The participant's eligibility to participate in the study will be based on the clinical judgment of the investigator following the review of the physical examination findings.

8.3.1.2 Vital Signs

Vital signs, including BP, heart rate, and temperature, are important safety measures that must be measured prior to the administration of the study treatment and any blood sampling at designated time points according to Table 1–1 for Regimen 1, Table 1–2 for Regimen 2 and Table 1–3 for Regimen 3, according to the procedures outlined in the study reference manual. Timing of all blood pressure assessments must be within ±2 hours of clock time of dosing on Day 1.

Vital sign measurements will be taken once the patient has been seated for a minimum of 5 minutes.

When possible, BP assessments will be obtained using an automated blood pressure instrument. Measures will be taken in triplicate and a mean measure as displayed by the device will be recorded in the EDC. Detailed instructions can be found in the study reference manual.

8.3.1.3 Clinical Safety Laboratory Tests

- See Section 10.2 for the list of clinical safety laboratory tests to be performed and the SoA (Section 1.3 Table 1–1 for Regimen 1, Table 1–2 for Regimen 2 and Table 1–3 for Regimen 3) for the timing and frequency.
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant 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 clinically significant 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 tests, as defined in Section 10.2, must be conducted in accordance with the study reference manual and the SoA.
    - If laboratory values from non-protocol-specified laboratory tests 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), then the results must be recorded.

8.3.1.4 Pregnancy Testing

WOCBP must have a documented negative serum pregnancy test at screening (serum) and baseline (urine) before assignment to a regimen. Urine pregnancy tests will be performed at every visit on which the study intervention is scheduled to be given, and a negative result must be documented before the study treatment can be administered.

8.3.2 Ocular Safety Assessments

Ocular safety assessments are described in Section 8.2.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3.

The definitions of device-related safety events can be found in Section 10.5. Device deficiencies are covered in Section 8.4.9.

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 (see Section 7). This includes events reported by the participant.

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.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

(S)AEs will be collected from the start of study intervention until the EOS visit at the timepoints specified in the SoA (Section 1.3). (S)AEs which are related to protocol-required study procedures (e.g., (S)AE related to invasive study procedures) will be recorded as (S)AEs from the signing of the ICF.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of learning of the event, as indicated in Section 10.3. 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 information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2 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.

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

8.4.3 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.

8.4.4 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 toward 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 (IRBs)/independent ethics committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure (IB) and will notify the IRB/IEC, if appropriate according to local requirements.
- For all studies except those using medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 4 months after the last dose of study intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy in the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner.)
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participant/pregnant female partner, 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 or be withdrawn from the study.

8.4.6 Cardiovascular and Death Events

Cardiovascular events will be reported as an AE or SAE, according to the criteria defined in Section 10.3. For deaths, the underlying or immediate cause of death should always be reported as an SAE.

8.4.7 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4.8 Adverse Events of Special Interest

Adverse events of special interest (AESI) are not defined for this study.

8.4.9 Medical Device Deficiencies

Medical devices are being provided by or on behalf of the sponsor for use in this study. To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.5.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section 10.5 of the protocol.

8.4.9.1 Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies 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 deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Section 10.5.

8.4.9.2 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.

8.4.9.3 Prompt Reporting of Device Deficiencies to the Sponsor

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

The medical device deficiency report form will be sent to the sponsor by email. If email is unavailable, then fax should be utilized.

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

8.4.9.4 Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility

to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

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

8.5 Pharmacokinetics

For the investigation of systemic exposure to aflibercept, plasma samples will be used for measurement of plasma concentrations of aflibercept (bound and free) in all participants as specified in the SoA (Section 1.3 Table 1–1 for Regimen 1, Table 1–2 for Regimen 2 and Table 1–3 for Regimen 3) and as detailed below in Table 8–1 for Regimen 1, Table 8–2 for Regimen 2 and Table 8–3 for Regimen 3.

The actual date and time (24-hour clock hour) of each PK sample will be recorded.

Please note that the timing for the collection of PK samples varies significantly between the three regimens due to the differences in the timing of the administration of the study treatment. While some flexibility is allowed with regard to timing of individual study visits, as outlined in the SoA (under “Window (days)”), the dense PK samples should be taken at the defined time after the most recent dose as described in detail in the footnotes to Table 8–1, Table 8–2, and Table 8–3. Furthermore, PK sample collection and HR/BP measurements must be taken at the same clock hour during the visit day, i.e., within a ± 2 h time window during the day.

Table 8–1: PK Sampling Schedule for Regimen 1

CCI

[redacted]

Table 8–2: PK Sampling Schedule for Regimen 2

CCI

[redacted]

Table 8–3: PK Sampling Schedule for Regimen 3

CCI

CCI

[redacted]

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

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study. Blood pressure is considered in Section 8.3 Safety Assessments and is further detailed in the SoA (Section 1.3) and above in Tables Table 8–1, Table 8–2 and Table 8–3.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Immunogenicity Assessments

Antibodies to aflibercept will be evaluated in serum samples collected from all participants according to the SoA (Table 1–1 for Regimen 1, Table 1–2 for Regimen 2, and Table 1–3 for Regimen 3).

Serum samples will be screened for antibodies binding to aflibercept and the titer of confirmed positive samples will be reported.

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).

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

8.10 Health Economics OR Medical Resource Utilization and Health Economics

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

9. Statistical Considerations

9.1 Statistical Hypotheses

No statistical hypotheses are defined for this study.

9.2 Analysis Sets

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

Table 9–1: Analysis Sets

Participant Analysis Set	Description
Full analysis set (FAS)	All participants who received at least one dose of study intervention in each eye.
Safety analysis set (SAF)	All participants who received at least one dose of study intervention in each eye.
Safety analysis set 2 (SAF2)	All participants who received any dose of study intervention.
Pharmacokinetic analysis set (PKS)	All participants who received at least one dose of study intervention in each eye and who had at least one non-missing PK result after the first dose of study intervention.
Modified PKS (mPKS)	CCI [redacted]
Immunogenicity analysis set 1 (ADA)	All participants who received at least one dose of study intervention in each eye and who had at least one non-missing result in the ADA assay after the first dose of study intervention.
Immunogenicity analysis set 2 (NAb)	All participants who received at least one dose of study intervention in each eye, were included in the ADA analysis set and tested negative at all ADA sampling times or tested positive at one or more post-dose ADA sampling times or had at least 1 non-missing post-dose NAb result (either imputed or analysis result).

PK=pharmacokinetic

The FAS is used to analyze endpoints related to efficacy, the SAF and SAF2 are used to analyze the endpoints related to safety, the PKS and mPKS are used to analyze endpoints related to PK, as appropriate, and ADA and NAb are used to analyze the endpoints related to immunogenicity.

9.3 Statistical Analyses

9.3.1 General Considerations

The statistical analysis plan (SAP) will be finalized before database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints.

Imputation of missing data is not planned. Unless specified otherwise, all available data will be used for statistical analysis.

All planned statistical analysis will be exploratory. A confirmatory statistical analysis is not intended.

9.3.2 Pharmacokinetics

9.3.2.1 Primary Endpoint Analysis

The primary endpoint is the maximum observed concentration (C_{max}) of free aflibercept.

The primary endpoint will be summarized using descriptive statistics by treatment regimen using the mPKS. The descriptive statistical assessment will include the geometric mean and the geometric coefficient of variation. No formal statistical hypothesis test will be performed.

Data of participants that discontinue early will be included in the analysis in line with the primary estimand definition and the definition of the corresponding analysis set (see Section 9.2). Furthermore, in line with the primary estimand strategy (see Section 3), data after treatment discontinuation after the dense PK sampling period will not be used for the calculation of C_{max} of free aflibercept. For this purpose, the time window from the last injection up to the next expected injection is considered to be still on-treatment.

9.3.2.2 Exploratory Endpoint Analysis

The other exploratory PK endpoints given in Section 3 will be analyzed similar to the primary endpoint. For the maximum observed concentration of total aflibercept only listings will be provided.

The maximum change from baseline of systolic/diastolic blood pressure and associated concentration of free and adjusted bound aflibercept may be analyzed graphically.

The exploratory PK endpoints will be analyzed using the PKS and/or the mPKS, as appropriate. Further details will be provided in the SAP.

9.3.2.3 Other PK Analyses

PK data may be explored using a population PK approach and, in case, will be reported separately outside of the clinical study report.

9.3.3 Efficacy Analysis

The exploratory efficacy endpoints change from baseline in BCVA at the end of the study and change from baseline in CRT at the end of the study will be analyzed using descriptive summary measures. CCI [redacted] Additional details will be provided in the SAP.

9.3.4 Safety Analysis

AEs will be analyzed for the SAF and SAF2. Treatment-emergent AEs and SAEs will be summarized through the end of the study.

9.3.4.1 Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as AEs that occurred in the time frame from first injection of study drug to the last injection plus 30 days.

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®).

The number and percentage of participants in the SAF and SAF2 with at least one TEAE/treatment-emergent SAE will be summarized by System Organ Class (SOC) and Preferred Term (PT).

Deaths and other SAEs will be listed and summarized by treatment regimen.

Treatment-emergent AEs leading to permanent treatment discontinuation will be listed and summarized by treatment group.

9.3.4.2 Other Safety Analyses

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

Vital Signs

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

9.3.5 Analysis of Immunogenicity Data

Incidence of treatment-emergent ADA response will be provided by treatment groups for the ADA analysis set, including characterization of the response with titers and neutralizing antibody status.

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

9.3.6 Other Analyses

Additional exploratory endpoints may be specified in the SAP.

9.4 Interim Analysis

No formal interim analysis is planned.

9.5 Sample Size Determination

No formal statistical sample size estimation has been performed for this study.

The selected number of patients to be included refers to the pharmacokinetic objective of the study. In previous studies of 8 mg aflibercept (CANDELA phase 2, PHOTON phase 2/3 and PULSAR phase 3) a dense PK cohort aimed to include between 8 and 15 patients per dose group. Based on the PK and population PK results generated from those studies including measures of variability, at least 8 participants were deemed sufficient to characterize the most

frequent scenarios of expected bilateral 8 mg aflibercept treatment to be implemented in routine clinical practice.

Up to 51 participants with DME or nAMD requiring anti-VEGF treatment in both eyes will be recruited and assigned to receive treatment with bilateral HD aflibercept according to one of three treatment regimens in the planned study. The sample size is expected to provide an adequate understanding of the systemic exposure resulting from bilateral 8 mg aflibercept treatment.

CCI [redacted]

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 ICH Good Clinical Practice (GCP) guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted reviewed and approved in accordance with national legislation and undergo scientific and ethical assessment 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 GCP and national and international regulations.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations

10.1.2 Financial Disclosure

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

10.1.3 Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participants and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the 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 participants.

Participants who are rescreened are required to sign a new ICF.

10.1.4 Recruitment Strategy

Detailed description of the recruitment strategy will be provided as required.

Recruitment of participants will be the responsibility of the study's clinical sites. Where permissible, additional measures will be put in place to increase the awareness to the study. These may include posters, flyers, contacts through referral networks, advertisements and others.

10.1.5 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or biological samples 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.
- Participants must be informed that their 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.
- Participants must be informed that their 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.
- The contract between sponsor and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.

- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6 Committees Structure

10.1.6.1 Study Steering Committee

A study SC is not planned for this study.

10.1.6.2 Anti-Platelet Trialists Collaboration Adjudication Committee

Potential ATEs will be evaluated by a masked adjudication committee according to criteria formerly applied and published by the Anti-Platelet Trialists' Collaboration (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 cardiologist-equivalent adjudicators, and the activities of the committee will be governed by a charter.

10.1.7 Dissemination of Clinical Study Data

Bayer fulfills its commitment to publicly disclose study results through posting the result of its studies on public registries in accordance with applicable law and regulations.

Result Summaries of Bayer's sponsored clinical studies in drug development Phases 2, 3 and 4 and Phase 1 studies in patients are provided in the Bayer Trials Explorer 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 websites, ClinicalTrials.gov, and EU Clinical Trials Information System (CTIS) in line with the applicable regulations.

In accordance with the current EU regulations, result summaries will be submitted within one year from the end of the study in all participating countries for studies in adult populations, or within 6 months from the Last Patient Last Visit (LPLV) date for studies in pediatric populations. No preliminary data analysis based on regional requirements (eg, on EU data only) will be performed, as this might compromise data integrity and the scientific validity of the study. Bayer commits to sharing upon request from qualified scientific and medical researchers' patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the US and European Union (EU) on or after January 01, 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.

10.1.8 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in eCRF completion guidance.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Quality tolerance limits (QTLs) will be predefined in the risk assessment documents to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.]
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 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.

10.1.9 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.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the Source Data Location List (SDLL) or equivalent.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of 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.

10.1.10 Study and Site Start and Closure

Study Start

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

The start of a clinical study is defined as the date on which the first site is declared by the sponsor to be ready to enroll in a country and clinical study will be open for recruitment of participants.

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

10.1.11 Publication Policy

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

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

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

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10–1 will be performed by the local laboratory. All samples collected for laboratory assessments will be obtained prior to administration of study drug.

Protocol-specific 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 Tests*

Laboratory Tests	Parameters		
Hematology	Hemoglobin	Differential:	
	Hematocrit	Neutrophils	
	Red blood cells (RBCs)	Lymphocytes	
	White blood cells (WBCs)	Monocytes	
	Red cell indices (MCV, MCH, %Reticulocytes)	Basophils	
	Platelet count	Eosinophils	
Blood chemistry	Sodium	Total protein, serum	Total bilirubin
	Potassium	Creatinine	Total cholesterol
	Chloride	Blood urea nitrogen (BUN)	Triglycerides
	Carbon dioxide	Aspartate aminotransferase (AST)	Uric acid
	Calcium	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)
	Glucose	Alkaline phosphatase	Urea (or BUN)
	Albumin	Lactate dehydrogenase (LDH)	
Routine urinalysis	Color	Glucose	RBC
	Clarity	Blood	Hyaline and other casts
	pH	Bilirubin	Bacteria
	Specific gravity	Leukocyte esterase	Epithelial cells
	Ketones	Nitrite	Crystals
	Protein	WBC	Yeast
Pregnancy testing	Women of childbearing potential must have a documented negative serum pregnancy test at screening and negative urine pregnancy test at baseline. Urine pregnancy tests will be performed at every treatment visit, and a negative result must be documented before study treatment can be administered.		
Other screening tests	Hemoglobin A1c will be measured at time points according to SoA in Section 1.2. follicle stimulating hormone (FSH) (as needed in women of nonchildbearing potential only)		

*Analysis parameters listed in table are optional if not routinely performed by the site local laboratory, except for pregnancy testing which is mandatory and must be performed.

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: AEs and SAEs: 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 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) 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. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Sign, symptoms, or the clinical sequelae of suspected medication errors, misuse and abuse of either study intervention or a concomitant medication. Medication errors, misuse and abuse per se will not be reported as an AE/SAE, unless it is resulting in AE/SAE. Such medication errors, misuse and abuse should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

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

- 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

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

a. **Results in death**

b. **Is life-threatening**

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

d. **Results in persistent or significant disability/incapacity**

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

e. **Is a congenital anomaly/birth defect**

f. **Other situations:**

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may 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, convulsions, or development of intervention dependency or intervention 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

Criteria for reporting SAEs must be followed for these events.

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.
- 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 one of the following categories:
    - Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
    - Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
    - Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes There may be situations in which an SAE has

occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to the sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a 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 submitted documents.
- 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 to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data transmission (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study 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 to the Sponsor Via Paper Data Collection Tool

- Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the sponsor.
- In rare circumstances and if email transmission is not feasible, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in the investigator site file.

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are considered WOCBP (fertile)

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below):
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal 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 postmenopausal status before study enrollment.
    - Permanent sterilization methods (for the purpose of this study) include:
        - Documented hysterectomy
        - Documented bilateral salpingectomy
        - Documented bilateral oophorectomy
        - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

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

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

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following:

a) Documented hysterectomy

b) Documented bilateral salpingectomy

c) Documented bilateral oophorectomy

d) For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

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

2. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or 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 must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
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 intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥ 1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c.) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. d) Considered effective, but not highly effective - failure rate of ≥ 1% per year. Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 Appendix 5: Medical Device AEs, SAEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to the medical devices supplied by or on behalf of the sponsor for use in the study. See Section 6.1.1 for the list of medical devices supplied by or on behalf of the Sponsor.

10.5.1 Definition of Medical Device AE

Medical Device AE

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

10.5.2 Definition of Medical Device SAE

A medical device SAE is any SAE that:

a. **Led to death**

b. **Led to serious deterioration in the health of the participant, that either resulted in:**

- A life-threatening illness or injury. The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the 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.
- Inpatient or prolonged hospitalization, planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Chronic disease (MDR 2017/745).

c. **Led to fetal distress, fetal death or a congenital abnormality or birth defect**

10.5.3 Definition of Device Deficiency

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

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

Medical Device 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.
- 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 form.
- 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 deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

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:
  A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

- Moderate:
  A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe:
  A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of Causality

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

Follow-up of Medical Device 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 postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.5.5 Reporting of Medical Device SAEs

Medical Device SAE Reporting to the Sponsor Via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study 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 table) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in the safety reporting gateway.

Medical Device SAE Reporting to the Sponsor Via Paper Data Collection Tool

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

10.6 Appendix 6: Country/Region-specific Requirements

10.6.1 Home Visits: Country-specific for Slovakia

Home visits (i.e. by a nurse or physician) can be used to reduce the burden of participation on patients and to encourage participation in case a patient is otherwise not able to travel to the site.

They may be performed at the visits indicated in the Schedule of Activities (Section 1.3), unless the patient prefers to attend the investigational site for the visit.

Samples collected at the patient’s home will be delivered to the investigational site.

Home visits will be performed by an appropriately qualified staff member fully trained on the study protocol and procedures.

10.7 Appendix 7 Protocol Amendment History

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

10.7.1 Amendment 1

Amendment 1 (19 AUG 2024)

This amendment/modification is considered to be non-substantial based on the relevant criteria of the European Union clinical trial legislation.

Overall Rationale for the Amendment:

The amendment is prepared to correct typos and inconsistencies.

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Schema	Figure updated to correct Week numbers • Regimen 1: from 1 to 0-2 • Regimen 2: from 1 to 0 • Regimen 3: from 9-13 to 9-12	Correction of inconsistency between the schema and the SoA
Section 1.3. Schedule of Activities		
Regimen 1	Pharmacy manual corrected to study manual in footnote 1 Footnote 16: „Both eyes“ added	Error correction and clarification
Regimen 2	Pharmacy manual corrected to study manual in footnote 1 PK sample: footnote 14 moved from Visit 4 to Visit 3	Error correction
Regimen 3	Pharmacy manual corrected to study manual in footnote 1 Visit windows corrected: • Visit 4, 11 and 12: from ±7 to ±1 • Visit 6: from ±0 to ±7 • Visit 7 and 8: from ±1 to ±7 • Visit 9: from ±1 to ±0 • Visit 10: from ±2 to ±1 • Visit 13: from ±7 to ±2 PK sample: footnote 14 moved from Visit 3 to Visit 4; footnote 12 added Footnote 14: Day 1/Visit 3 corrected to Day 8/Visit 3 Footnotes 15 to 19: Day 64/Visit 9 corrected to Day 64/Visit 8	Correction of errors and inconsistency between the table and footnotes
Section 2.2 Background	A small editorial correction	Editorial correction
Section 4.1 Overall Design	A small editorial correction	Editorial correction
Section 5.2 Exclusion Criteria		
Exclusion criterion 8	baseline visit was included	Correction of inconsistency between exclusion criterion and Section 5.2 instruction
Section 8.5 Pharmacokinetics		
Table 8-2 (Regimen 2)	Footnote 4: editorial correction	Error correction
Table 8-3 (Regimen 3)	Footnote 3: Day 1/Visit 3 corrected to Day 8/Visit 3 Footnotes 4 to 8: Day 64/Visit 9 corrected to Day 64/Visit 8	Error correction
9.3.4.2 Other Safety Analyses	Laboratory results will not be summarized by baseline and change from baseline.	Wrong statistical evaluation removed

10.7.2 Amendment 2

Amendment 2 (19 SEP 2024)

This amendment/modification was considered to be non-substantial based on the relevant criteria of the European Union clinical trial legislation.

Overall Rationale for the Amendment:

The amendment was prepared to correct inconsistencies between Section 8.2.2 of the protocol and Table 1–2 Regimen 2 Schedule of Activities (SoA). In Section 8.2.2 it stated that slit lamp examination should be done before the administration of the study drug treatment, however, the slit lamp examination for Visit 4 and Visit 5 for Regimen 2 was omitted on the SoA (Table 1–2).

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Missing slit lamp examination was added to Visit 4 and Visit 5 for regimen 2 (Table 1–2).	Correction of an omission (slit lamp examination for Regimen 2, Visit 4 and Visit 5) in the Schedule of Activities

11. References

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