NCT04429503
EudraCT Number: 2019-003643-30
IND Number: 12462

Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A RANDOMIZED, DOUBLE-MASKED, ACTIVE-CONTROLLED PHASE 2/3 STUDY OF THE EFFICACY AND SAFETY OF HIGH-DOSE AFLIBERCEPT IN PATIENTS WITH DIABETIC MACULAR EDEMA

Compound:	High-dose aflibercept
Study Name:	PHOTON
Clinical Phase:	2/3
Protocol Number:	VGFTe-HD-DME-1934
Protocol Version:	VGFTe-HD-DME-1934 Amendment 6
Amendment 6	*See appended electronic signature page*
Amendment 5 Date of Issue	14 Sep 2022
Amendment 4 Date of Issue	28 Apr 2022
Amendment 3 Date of Issue:	07 May 2020
Amendment 2 Date of Issue:	14 Feb 2020
Amendment 1 Date of Issue:	06 Dec 2019
Original Date of Issue:	16 Oct 2019
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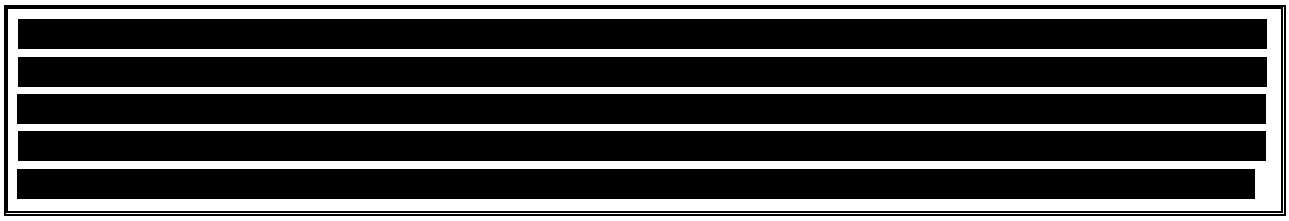
[redacted]



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AMENDMENT HISTORY

Amendment 6

The primary purpose of this amendment is to extend contraception requirements based on proposed aflibercept HD labeling language updates.

Description of Change	Brief Rationale	Section # and Name
Update the length of time contraception is required after study drug dosing.	To align with the proposed HD labeling update, which [redacted] the time contraception is needed after the last study drug dose, based on the following: the recommended duration of contraception following the last intravitreal dose increased from 3 months for 2 mg aflibercept to [redacted] for HD aflibercept. The 3-month duration of contraception for the 2-mg dose was based on the time required for all patients to reach the lower limit of quantitation (LLOQ) of free aflibercept in plasma [redacted] plus a conservative 1-month buffer. For HD aflibercept, the population PK model-predicted time for 99% of patients to reach the LLOQ of free aflibercept in plasma is [redacted] Applying the same 1-month buffer utilized for 2-mg aflibercept, the recommended duration of contraception for HD aflibercept is [redacted]	Section 7.2.2 Exclusion Criteria (# 36)
[redacted]	Clarifying the timing for investigator decision if shortening dosing interval outside of shortening criteria.	Section 6.1 Study Description and Design
Updated a reference.	The title of the referred to study was inadvertently deleted in the last version of the protocol.	Section 11.1 Statistical Hypothesis
[redacted]	The addition of this text provides clarification to the clinics for the treatment of DME in the study eye between these visits.	Section 9.1.3 [redacted]
Removal of text from sections for patients in China.	This text was removed due to the fact that no sites were opened in China for this study, and therefore, no patients were enrolled.	Section 9.2.4 Drug Concentration and Measurements Section 9.2.5 Immunogenicity Measurements and Samples

Description of Change	Brief Rationale	Section # and Name
		Section 9.2.6 Future Biomedical Research (Optional) Section 9.2.6.1 Pharmacogenomic Analysis (Optional)

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Amendment 5

[redacted]

Description of Change	Brief Rationale	Section # and Name
[redacted]	[redacted]	Clinical Study Protocol Synopsis Study Design Study Duration Section 1 Introduction Section 3.3 Risk-Benefit Section 4.1.3 Additional Secondary Endpoints Section 4.1.4 Exploratory Endpoints Section 6.1 Study Description and Duration Figure 1 Study Flow Diagram Figure 3 [redacted] Section 6.1.1 End of Study Definition Section 6.2 Planned Interim Analysis Section 6.3.3 Independent Data Monitoring Committee Section 7.1 Number of Patients Planned Section 7.2.1 Inclusion Criteria Section 7.3 Premature Withdrawal from the Study Section 8.1 Investigational and Reference Treatments Section 8.5 Masking Section 9.1.3 [redacted] Table 4 [redacted] Section 9.1.3.1 [redacted] Section 9.1.4 Early Termination Visit Section 9.2.2 Ocular Study Procedures (Efficacy and Safety) Section 9.2.3.4 Laboratory Testing Section 10.1.1 General Guidelines Section 11.4.3.2 Secondary Efficacy Analysis Section 11.5 Interim Analysis Section 13.2.1 [redacted]

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Description of Change	Brief Rationale	Section # and Name
Minor template updates, in addition to minor edits and formatting changes.	Throughout	Throughout

Amendment 4

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

To remove the initial Bonferroni-based split of the overall significance level (which had been introduced originally to allow simultaneous testing of the 2 hypotheses (8 mg aflibercept every 12 weeks [HDq12] vs 2 mg aflibercept every 8 weeks [2q8] and 8 mg aflibercept every 16 weeks [HDq16] vs 2q8) of the primary endpoint at a significance level of 0.0125 [1-sided] each) and to assign the full significance level of 0.025 (1-sided) to the first hypothesis (HDq12 vs 2q8). The reason for this change is to adjust the testing sequence to the perceived clinical probability of success, ie, since HDq12 is more likely to succeed than HDq16 (due to the higher dosing frequency after the loading phase).

1. To remove the subsequent splitting of the remaining alpha levels between 2 hypotheses, and replace it by a simpler hierarchical testing procedure in both the global statistical analysis plan (G-SAP) and the statistical analysis plan for EMA and PMDA (EP-SAP). This change allows sequential testing of hypotheses at the full significance level after successful rejection of the hypotheses which are ranked higher in the hierarchy. The reason for this change is to prioritize testing of hypotheses which are deemed to be clinically more relevant.
2. To allow formal statistical testing for superiority of the change from baseline in best corrected visual acuity (BCVA) at week 48 (and week 60, in the EP-SAP only) that controls the overall family-wise type 1 error. The formal statistical testing for superiority is added at the end of the revised testing hierarchy. Hence the testing hierarchy is extended.
3. To remove the endpoint of "Proportion of patients without retinal fluid at the foveal center at week 12" as a key secondary endpoint in the testing hierarchy (it remains as a secondary endpoint assessed at week 48). Based on recent data from another, completed study, it was determined that week 12 is not a reasonable time point to assess this endpoint. Analysis of this endpoint will be more informative at week 48 after a year of treatment.

Of note, the updated confirmatory testing hierarchy still controls the overall family-wise type 1 error at 0.025 level (1-sided). These changes will be implemented after the end of enrollment but before database lock and before any unmasking occurs.

The following table outlines the changes made to the protocol and the affected sections:

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Description of Change	Brief Rationale	Section # and Name
Replaced the figures of sequentially rejective graphical procedure for G-SAP and EP-SAP by a hierarchical testing procedure Mixed model repeated measurements (MMRM) updated to remove the random effect, variable "b," and some index updates were made to the model equation	Replace sequentially rejective graphical procedure by a hierarchical testing procedure Removed random effect, variable "b," to avoid over parameterization	Clinical Study Protocol Synopsis, Statistical Plan Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.4 Control of Multiplicity Figure 3: Hypothesis Testing (removed)
Updated the power for primary endpoint hypotheses based on hierarchical testing procedure	To clarify the power of primary endpoint hypotheses based on hierarchical testing procedure without alpha split	Clinical Study Protocol Synopsis, Statistical Plan Section 11.2 Justification of Sample Size
Removed key secondary endpoint regarding proportion of patients without fluid at foveal center at week 12 (it remains as a secondary EP at week 48)	Based on recent data from another, completed study, it was determined that week 12 is not a reasonable time point to assess this endpoint. Analysis of this endpoint is will be more informative at week 48 after a year of treatment.	Clinical Study Protocol Synopsis, Endpoint Clinical Study Protocol Synopsis , Statistical Plan Section 4.1.2 Key Secondary Endpoints Figure 1 Study Flow Diagram Section 11.1 Statistical Hypothesis Section 11.4.3.2 Secondary Efficacy Analysis
Added superiority testing for the endpoint of mean change in BCVA to the end of the statistical testing hierarchy	To control the type I error when formally testing for superiority in BCVA.	Clinical Study Protocol Synopsis, Statistical Plan Section 4.1.4 Exploratory Endpoints Section 11.1 Statistical Hypothesis Section 11.4.4 Control of Multiplicity Table 5 The Testing Order of Hierarchical Testing Procedure in G-SAP and EP-SAP (new)
Updated definition of FAS to include randomized, treated patients	To exclude from analysis patients randomized in error and not treated	Section 11.3.1 Efficacy Analysis Sets
Updated the definition of treatment-related TEAEs	To ensure that AEs are analyzed appropriately as treatment emergent	Section 11.4.5.1 Adverse Events
Removed the following exploratory endpoint "fluid on spectral domain optical coherence tomography"	This exploratory endpoint is covered by other secondary and exploratory endpoints.	Section 4.1.4 Exploratory Endpoints
Minor edits and formatting changes.	Minor edits and formatting changes.	Throughout

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Amendment 3

The primary purposes for this amendment are to clarify the machine-specific values for central retinal thickness (CRT; measured on spectral domain optical coherence tomography [SD-OCT]) defined in the inclusion criteria for the reading center's determination of eligibility, and to describe the continuity plan for conducting clinical study activities and study oversight activities during the public health emergency due to Coronavirus Disease 2019 (COVID-19).

Description of Change	Brief Rationale	Section # and Name
Added language related to the COVID-19 pandemic.	To describe the continuity plan for conducting clinical study activities and study oversight activities during the public health emergency due to COVID-19.	Section 3.3 Risk-Benefit Section 9.1.1 Schedule of Events for the Study
Updated the figure for the dosing schedule.	To show that sham injections are not administered at week 96.	Figure 2 Dosing Schedule
Inclusion criterion #2 updated to clarify the machine-specific values for CRT on SD-OCT for the reading center to determine eligibility.	While 320 µm is accurate, it is specific for the Spectralis machine, while 300 µm is the equivalent for the Cirrus and other commercially available machines.	Section 7.2.1 Inclusion Criteria (#2)
Updated urine pregnancy testing in the Schedule of Events tables. Also clarified wording in Study Procedures.	To reflect that a urine pregnancy test should be performed at all visits except optional visit 4.1 and the end of study visit.	Table 2 Schedule of Events Section 9.2.3.4 Laboratory Testing (Other Laboratory Tests)

Amendment 2

The primary purpose of this amendment is to update details of the study design, combining rescue treatment with Dose Regimen Modification (DRM) assessments in both year 1 and year 2. Patients in the HDq12 and HDq16 groups will now be eligible for a rescue regimen (8 mg aflibercept every 8 weeks) beginning at week 16.

Change and Rationale for Change	Sections Changed
Updates to the dose regimen modification (DRM) criteria to incorporate a rescue regimen defining criteria to allow high-dose aflibercept every 8 weeks for the HDq12 and HDq16 groups, beginning at week 16.	Clinical Study Protocol Synopsis: Treatments Clinical Study Protocol Synopsis: Statistical Plan Section 6.1 Study Description and Duration Section 8.2 Rescue Treatment Table 2 Schedule of Events Section 9.1.1.1 Footnotes for the Schedule of Events, footnote 6 Section 11.4.5.3 Treatment Exposure
Exploratory endpoints for best corrected visual acuity (BCVA) were added. As treatment before week 48 and week 60 are less synchronized due to the modifications introduced for the dose regimen modifications (DRMs), it is now important to assess these additional/earlier endpoints before week 48.	Section 4.1.4 Exploratory Endpoints
Inclusion criteria updated to include patients with BCVA of 24 to 78 letters to better align with clinical practice patterns.	Section 7.2.1 Inclusion Criteria (#3)
Minor additions to the exclusion criteria regarding intraocular surgery prior to screening and other systemic disease.	Section 7.2.2 Exclusion Criteria (#9, #20, #21, #26)
Updates to the masking sections to clarify roles of the masked and unmasked investigators regarding rescue treatment.	Section 8.5 Masking Table 1 Responsibilities of the Masked and Unmasked Personnel Section 9.2.2.6 Best Corrected Visual Acuity
Addition of assessment of causality to aflibercept 2mg for patients receiving injections in the fellow eye.	Section 8.8.1 Prohibited Medications and Procedures Section 10.2.4 Causality
Window for pharmacokinetic (PK) assessments clarified	Section 9.1.2 Schedule of Events for the Dense PK Substudy
Clarification of expectation for early termination visit in order to be consistent across studies in the development program for HD aflibercept.	Section 9.1.3 Early Termination Visit

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Change and Rationale for Change	**Sections Changed**
Clarification of the method of obtaining ultra-widefield angiography and color photography images.	Section 9.2.2.4 Fundus Photography/Fluorescein Angiography Section 9.1.1.1 Footnotes for the Schedule of Events, footnotes 10 and 11
Clarification that a paper questionnaire will be used.	Section 9.2.2.7 Quality of Life Questionnaire Section 12.1.2 Electronic Systems
Clarifications of expectations for pharmacokinetic and anti-drug antibody (ADA) samples and the future biomedical research (FBR) study in China.	Section 9.2.4 Drug Concentration and Measurements Section 9.2.5 Immunogenicity Measurements and Samples Section 9.2.6 Future Biomedical Research (Optional)
Clarification of reference used for assessment of expectedness for safety reporting for 2 mg aflibercept.	Section 10.4 Notifying Health Authorities, Institutional Review Board /Ethics Committee, and Investigators
Efficacy analysis estimands are further clarified Minor correction in statistical models.	Section 11.4.3 Efficacy Analyses Section 11.4.3.1 Primary Efficacy Analysis
Editorial change in description of dosing groups and randomization scheme	Synopsis, Study Design Section 6.1 Study Description and Duration Section 7.1 Number of Patients Planned
Minor edits and formatting changes.	Throughout

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Amendment 1

The purpose of this amendment is to address feedback received from European Union (EU) regulatory agencies as part of the Voluntary Harmonisation Procedure (VHP). The requested revisions include: addition of information on criteria for study and study drug discontinuation, specification that collection of adverse events (AEs) and serious adverse events (SAEs) will begin at the time of informed consent, clarification on assessment of laboratory values as AEs, clarification of some of the statistical considerations, and other minor revisions as requested.

Change	**Sections Changed**
Minor update to the definition of abstinence to include reference to "The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject" and the definition of post-menopausal to include "amenorrhoeic for at least 12 months without an alternative medical cause."	Section 7.2.2 Exclusion Criteria (#32f)
Addition of specific criteria for discontinuation of treatment in individual patients.	Section 8.3.2 Study and Study Drug Discontinuation
Update to indicate that AEs will be collected from the time of informed consent form (ICF) signing rather than from the time of first dose.	Section 10.1.1 General Guidelines
Addition of reference to Sections 9.2.3.4 and 10.1.1, which provide additional information to the investigator regarding the assessment and reporting of laboratory values as AEs.	Section 10.2.3 Severity
Addition of language regarding the rationale for the 4-letter non-inferiority margin	Section 11.1 Statistical Hypothesis
Corrections to the equations in the statistical section (MMRM analysis model)	Section 11.4.3.1 Primary Efficacy Analysis
Addition of definition of pretreatment period	Section 11.4.5.1 Adverse Events

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

2q8	2 mg aflibercept every 8 weeks
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AOBP	Automated office blood pressure
APTC	Anti-Platelet Trialists' Collaboration
AST	Aspartate aminotransferase
ATE	Arteriothromboembolic event
BCVA	Best corrected visual acuity
BP	Blood pressure
BRVO	Branch retinal vein occlusion
BUN	Blood urea nitrogen
CMH	Cochran-Mantel-Haenszel method
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
CSME	Clinically significant macular edema
DME	Diabetic macular edema
DBP	Diastolic blood pressure
DR	Diabetic retinopathy
DRCR	Diabetic Retinopathy Clinical Research
DRM	Dose regimen modification
DRSS	Diabetic Retinopathy Severity Scale
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
[redacted]	[redacted]
EMA	European Medicines Agency
EOS	End of study
EP-SAP	Statistical Analysis Plan for EMA and PMDA

ETDRS	Early Treatment Diabetic Retinopathy Study
[redacted]	[redacted]
FA	Fluorescein angiography
FAS	Full analysis set
FP	Fundus photography
GCP	Good Clinical Practice
G-SAP	Global statistical analysis plan
HbA1c	Hemoglobin A1c
HD	High-dose aflibercept
HDq12	8 mg aflibercept every 12 weeks
HDq16	8 mg aflibercept every 16 weeks
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IOP	Intraocular pressure
IRB	Institutional Review Board
IRF	Intraretinal fluid
IV	Intravenous
IVT	Intravitreal
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
mCNV	Myopic choroidal neovascularization
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measurements
NAb	Neutralizing antibody
nAMD	Neovascular age-related macular degeneration
NB	New Baseline
NEI VFQ-25	National Eye Institute Visual Function Questionnaire-25
NI	Non-inferiority
OCT	Optical coherence tomography
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per protocol set
PT	Preferred term
QoL	Quality of life

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RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SBP	Systolic blood pressure
SC	Steering committee
SD-OCT	Spectral domain optical coherence tomography
SOC	System organ class
SRF	Subretinal fluid
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
VA	Visual acuity
VEGF	Vascular endothelial growth factor
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Randomized, Double-Masked, Active-Controlled Phase 2/3 Study of the Efficacy and Safety of High-Dose Aflibercept in Patients with Diabetic Macular Edema
Site Location(s)	Approximately 180 clinical study sites in North America, Europe, and Asia.
Principal Investigator	(to be determined)
Objective(s)	The primary objective of the study is to determine if treatment with high-dose aflibercept (HD) at intervals of 12 or 16 weeks provides noninferior best-corrected visual acuity (BCVA) compared to 2 mg aflibercept dosed every 8 weeks. The secondary objectives of the study are: • to determine the effect of HD vs. 2 mg aflibercept on anatomic and other visual measures of response • to evaluate the safety, immunogenicity and pharmacokinetics (PK) of HD. Exploratory objectives of the study are: • to determine the effect of HD vs. 2 mg aflibercept on additional anatomic measures of response • to study molecular drivers of diabetic macular edema (DME) or related diseases, the mechanism of action of aflibercept, and the vascular endothelial growth factor (VEGF) pathway.
Study Design	Phase 2/3, multi-center, randomized, double-masked study in patients with DME involving the center of the macula to investigate the efficacy and safety of HD versus 2 mg aflibercept. Approximately 640 eligible patients randomized into 3 treatment groups in a 1:2:1 ratio to the following 3 treatment groups: 1) 2q8: 2 mg aflibercept every 8 weeks, following 5 initial monthly doses (n=160), 2) HDq12: HD aflibercept every 12 weeks, following 3 initial monthly doses (n=320), 3) HDq16: HD aflibercept every 16 weeks following 3 initial monthly doses (n=160). Approximately 24 patients will be included in a dense PK substudy (n=8 per group, with half Japanese and half non-Japanese per group). In all patients, blood samples for measurement of drug concentrations (PK) and anti-drug antibody (ADA) will be obtained prior to the first treatment and at prespecified time points throughout the course of the study. In addition, a DNA sample will be collected from those who sign the informed consent form (ICF) for the optional genomic substudy. [redacted]
Study Duration	The study duration for a patient during the initial phase of the study is approximately 96 weeks; [redacted]

	[redacted]
End of Study Definition	The end of study (EOS) is defined as the last visit of the last patient.
Population	
Sample Size:	Sample size is approximately 640 patients.
Target Population:	Patients with DME involving the center of the macula
Treatments	
Study Drug Dose/Route/Schedule:	High-dose aflibercept (8 mg) given by intravitreal injection in extended-dose intervals (every 12 or 16 weeks) following 3 initial monthly injections according to study group. Dosing regimen modifications (DRMs) are permitted based on clinical criteria defined in the protocol.
Reference Drug Dose/Route/Schedule:	Aflibercept 2 mg given by intravitreal injection every 8 weeks following 5 initial monthly doses.
Endpoints	
Primary:	Change from baseline in BCVA at week 48.
Secondary:	The key secondary efficacy endpoints are: • Proportion of patients with a ≥2 step improvement in the Diabetic Retinopathy Severity Scale (DRSS) at week 48 • Change from baseline in BCVA at week 60
Procedures and Assessments	Efficacy procedures: ocular examination including BCVA (Early Treatment Diabetic Retinopathy Study [ETDRS]) and refraction, intraocular pressure (IOP), slit lamp examination, indirect ophthalmoscopy, fluorescein angiography (FA), fundus photography (FP), spectral domain optical coherence tomography (SD-OCT), OCT angiography (OCTA), National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25). Safety procedures: ophthalmic exams, physical examination, vital signs, electrocardiogram (ECG), adverse events, laboratory and immunogenicity assessments. Pharmacokinetic and genomic substudies will be conducted.
Statistical Plan	The sample size calculation is based on testing 2 primary hypotheses for non-inferiority (NI) of HDq12 vs. 2q8 (control) and HDq16 vs. 2q8 (control) with respect to the primary endpoint of change from baseline in BCVA at week 48. The NI margin is set at 4 letters for each of the primary hypotheses. Under the original testing strategy (prior to Amendment 4), assuming a standard deviation of 9.07 letters for each treatment group, and dropout rate of 19%, a sample size of 160 per treatment group based on two-sample t-test will provide ≥90% power for each pairwise comparison. Sample size in the HDq12 group is doubled to meet regulatory requirements for the safety

database. Therefore, the study sample size is estimated for a total of 640 patients (160, 320, and 160 for 2q8, HDq12, and HDq16, respectively).

However, under the current hierarchical testing procedure, using the same assumptions as indicated above, a total sample size of 640 patients for 3 groups provides 98% power for rejecting the null hypothesis H_{10}, and subsequently 92% power for rejecting the null hypothesis H_{30}, for the primary endpoint assessing non-inferiority, with a 1-sided t-test at significance level of 0.025.

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

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

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

where μ_0, μ_1, μ_2, are the mean change from baseline in BCVA at week 48 for 2q8, HDq12, and HDq16, respectively. The primary efficacy analysis will be based on a mixed model for repeated measurements (MMRM) with baseline BCVA as a covariate, treatment, baseline CRT, prior DME treatment, geographical region and visit as fixed effects, and interaction terms for treatment by visit and baseline BCVA by visit; this model will use the full analysis set (FAS). Full analysis set is defined as all randomized patients who received at least 1 dose of study drug.

In addition, the HDq12 and HDq16 treatment groups will be tested for non-inferiority against the control group of 2q8 with respect to the following key secondary endpoints: change from baseline in BCVA at week 60 (non-inferiority with NI margin of 4 letters) (only for regulatory requirements for European Medicines Agency [EMA] and Pharmaceuticals and Medical Devices Agency [PMDA] of Japan) and proportion of patients with a ≥2 step improvement in DRSS at week 48 (non-inferiority with NI margin of 15%). The key secondary endpoint of change from baseline in BCVA at week 60 (SAP for EMA, PMDA [EP-SAP] only) will be analyzed with a model matching the one for the primary endpoint. The proportion of patients with a ≥2 step improvement in DRSS at week 48 will be analyzed using the Cochran-Mantel-Haenszel (CMH) method, stratified by baseline CRT, prior DME treatment, and geographical region.

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

The overall family-wise type 1 error will be controlled at 0.025 one-sided level for testing the primary and key secondary endpoints. Adjustment for multiple comparisons in the primary and key secondary endpoints will be made with a hierarchical testing procedure. For safety analysis, all treatment-emergent adverse events (TEAEs) will be summarized for each treatment group by the primary system organ class (SOC) and preferred terms (PT) using the Medical Dictionary for Regulatory Activities dictionary (MedDRA®). Severity and relationship to treatment will also be presented by SOC and PT. Deaths, serious adverse events (SAEs), and TEAEs leading to permanent treatment discontinuation will also be listed and summarized by treatment group. In addition, vital signs and laboratory tests results will be descriptively tabulated and/or graphically presented as well as patient listings provided. Treatment exposure will be summarized in terms of total number of treatments, duration of treatment, and proportion of patients maintaining, shortening, or extending the dosing interval.

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1. INTRODUCTION

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes. Diabetic macular edema (DME), a manifestation of diabetic retinopathy, is the primary cause of vision loss and blindness in patients with diabetes (Klein, 1984) (Moss, 1994) (Moss, 1998) (Sivaprasad, 2012) and the most frequent cause of blindness in young and middle-aged adults (Klein, 1984) (Moss, 1998). If left untreated, approximately half of patients with DME will lose 2 or more lines of visual acuity (VA) within 2 years (Bandello, 2012) (Ciulla, 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).

The World Health Organization (WHO) reported the number of people with diabetes at 422 million in 2014, and a global prevalence of diabetes among adults at 8.5% in 2014, increased from 4.7% in 1980, with a continued rise in these numbers expected in coming years (Danaei, 2011) (NCD Risk Factor Collaboration, 2016).

Treatment options for DME include laser photocoagulation and pharmacologic interventions, specifically vascular endothelial growth factor (VEGF) inhibitors and steroids. Surgery is also performed in some cases as a fall-back therapeutic option, particularly for those refractory to treatment or with vitreomacular traction.

However, anti-VEGF compounds have become the standard of care for the treatment of DME. This approach is highly attractive as it directly targets VEGF, one of the main mediators of DR and DME. Vascular endothelial growth factor 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, 2006) (Bhagat, 2009). Hypoxia and other metabolic factors trigger VEGF release. VEGF induces vascular leakage and neovascularization. While neovascularization is the most severe manifestation of DR, vascular leakage leading to macular edema is an important cause of reduced visual acuity.

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 [redacted] injected intravitreally [IVT]). EYLEA is currently approved in at least 100 countries for additional indications that include neovascular age-related macular degeneration (nAMD), macular edema following central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO), and in 99 countries for the treatment of myopic choroidal neovascularization (mCNV). EYLEA is also approved in the United States for the treatment of diabetic retinopathy. (See the Investigator's Brochure for additional details).

Ranibizumab (LUCENTIS®, Novartis AG), a VEGF inhibitor, has been approved in the US and in the European Union for the treatment of DME. The results of the pivotal studies used to support the approval of LUCENTIS (Massin, 2010) (Mitchell, 2011) (Nguyen, 2012) and aflibercept (Brown, 2015) (Korobelnik, 2014), as well as data from large, randomized trials sponsored by the Diabetic Retinopathy Clinical Research (DRCR) Network (Elman, 2010) (Wells, 2015) using ranibizumab, bevacizumab, and aflibercept, support the assertion that anti-VEGF therapy may be the treatment option of choice, leading to vision gains for a significant number of patients. Additionally, in the 1-year data from DRCR Protocol T that compared aflibercept, bevacizumab, and ranibizumab, aflibercept demonstrated superior efficacy in the overall population with a more

pronounced benefit in patients with baseline best-corrected visual acuity (BCVA) worse than 20/40 (Wells, 2015).

Despite available treatments, there remains an unmet medical need for the development of therapies with the potential to improve important clinical outcomes. This unmet need includes decreasing the treatment burden via a reduction in the required frequency of intravitreal injections, improving visual and anatomic outcomes over currently available standards of care, and slowing or even reversing the underlying pathophysiology of the disease itself, specifically retinal ischemia.

Increasing the drug product concentration of aflibercept allows a greater amount of drug to be delivered IVT and thus has the potential to increase aflibercept's pharmacological duration of action, and thereby provide additional benefit to patients with DME. The resulting extension of treatment intervals to every 12 weeks or 16 weeks, early after the initiation of treatment, would reduce the number of injections in the first treatment year. A potential decrease in injection-related treatment burden and safety events could be a significant contribution to patient care and healthcare services.

This study will investigate the safety and efficacy of a high-dose aflibercept with the intent of extending the dosing interval, with at least similar functional and potentially improved anatomic outcomes compared to 2 mg aflibercept.

[redacted]

Additional background information on the study drug and development program can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to determine if treatment with high-dose aflibercept (HD) at intervals of 12 or 16 weeks provides noninferior BCVA compared to 2 mg aflibercept dosed every 8 weeks.

2.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To determine the effect of HD vs. 2 mg aflibercept on anatomic and other visual measures of response
- To evaluate the safety, immunogenicity, and pharmacokinetics (PK) of aflibercept

2.3. Exploratory Objectives

The exploratory objectives of the study are as follows:

- To determine the effect of HD vs. 2 mg aflibercept on additional anatomic measures of response
- To study molecular drivers of DME or related diseases, the mechanism of action of aflibercept, and the VEGF pathway

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3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

Treatment with high-dose aflibercept with longer treatment intervals of at least 12 weeks will result in noninferior changes from baseline in BCVA at week 48 compared to 2 mg aflibercept dosed every 8 weeks.

3.2. Rationale

3.2.1. Rationale for Study Design

There remains an unmet medical need in the treatment of DME. Although many patients benefit from treatment with currently available anti-VEGF agents, a sizable proportion of patients still need frequent IVT injections. Long-term data suggest that visual benefits may be lost if regular dosing is not maintained. In addition, dosing at an insufficient frequency may result in fluctuations in visual and anatomic manifestations of the disease, leading ultimately to irreversible loss of vision below certain visual thresholds, eg driving vision. Longer treatment intervals will lead to better treatment compliance and improved long-term clinical benefit.

Increasing the drug product concentration of aflibercept allows a greater amount of drug to be delivered intravitreally, with the potential for both added efficacy and an increase in aflibercept's pharmacological duration of action, thereby providing additional benefit to patients with DME while reducing burden on both patients and physicians. In addition, higher intravitreal aflibercept concentrations sustained over a longer period of time may provide better control of the anatomic features of DME.

Anatomic measures of retinal thickness and retinal fluid are well-known markers of disease activity. These parameters are used by clinicians to determine treatment success and/or the timing of further retreatment. These measures will be used as secondary and exploratory endpoints in this phase 2/3 study, as these endpoints will help determine the timing and degree to which HD can extend the dosing interval relative to 2 mg aflibercept.

The study aims to investigate the efficacy and safety of HD with the objectives of achieving noninferior BCVA with an extended dosing interval and potential improvements in anatomic outcomes vs. 2 mg aflibercept. The study is designed to investigate HD dosed every 12 or 16 weeks after 3 initial monthly injections vs. 2 mg aflibercept dosed every 8 weeks (2q8) after 5 initial monthly injections in patients diagnosed with DME.

3.2.2. Rationale for Dose Selection

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

In a nonclinical rabbit model of chronic retinal neovascularization and vascular leak, dose-dependent duration of leak suppression was observed after single IVT doses equivalent of up to 8 mg in humans. Pharmacokinetic simulations of free aflibercept concentration-time profiles in human vitreous using a 1-compartment ocular model predicted [redacted]

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[redacted]

Studies with intravenous (IV) aflibercept indicated that blood pressure (BP) increase was the earliest pharmacodynamic indicator of systemic effect. Two studies (PDY6655 and PDY6656) evaluated the effects of IV and subcutaneous aflibercept on BP via 24-hour ambulatory BP monitoring in healthy subjects. At the lowest IV dose tested in these studies (1 mg/kg; PDY6656), a maximal increase of ~5 mmHg in 24-hour mean change from baseline in systolic BP (SBP) occurred by day 6 after a single dose, SBP returning to baseline by ~30 days post-dose. Assuming linear PK and extrapolating C_{max} and AUC_{last} values (for both mean and maximum individual patient values) from 2 mg IVT, estimated free aflibercept systemic C_{max} and AUC_{last} for an 8 mg IVT dose are approximately 60-142x and 98-221x lower, respectively, than the corresponding values associated with a 1 mg/kg IV dose. Although systemic concentrations of free aflibercept at these IVT doses are appreciably lower than those required to saturate the target-mediated elimination pathway, linear extrapolation may overestimate the exposure margins for an 8 mg IVT dose. A threshold dose and/or concentration of free aflibercept associated with BP increase has not yet been determined.

In phase 1 and 2 clinical trials, doses up to 4 mg per eye in monthly intervals, with injection volumes up to 100 µl, were generally well tolerated in patients with both DME and nAMD. In a small number of patients with nAMD, isolated cases of unintentional dosing with 8 mg per eye occurred and were also well tolerated. It is expected that an 8 mg IVT dose will extend the dosing interval relative to 2 mg IVT, thereby reducing the number of injections needed for successful treatment. Hence, with the expectation of both a longer dosing interval resulting in a lower annualized number of injections, and similar safety profile, the 8 mg dose was selected for evaluation in this study.

3.3. Risk-Benefit

Benefits of Treatment with HD:

High-dose aflibercept for IVT injection may provide improved patient benefit through:

- Longer treatment intervals of every 12 weeks or longer for all patients
- Potential for improved functional and anatomic efficacy
- Less injection-related risk over time
- Increased compliance by reducing the treatment burden on patients, caregivers, physicians, and healthcare systems

Extrapolated safety margins for free aflibercept after an 8 mg IVT dose, derived from linear extrapolation of available PK data for 2 mg IVT aflibercept, suggest an acceptable systemic safety profile of HD aflibercept 8 mg. Robust generation of safety data is further planned in the phase 2 and phase 3 trials.

[redacted]

[redacted]

Risks and Risk Management of Treatment with HD:

The safety profile of aflibercept 2 mg has been thoroughly investigated in a comprehensive clinical trial program including 9 phase 3 studies in the indications nAMD, CRVO, BRVO, mCNV, DME, and DR. Overall, more than 4900 patients were treated with aflibercept in clinical trials. Patients were treated for up to 148 weeks with aflibercept during these phase 3 studies. No new safety findings were observed with long-term treatment with aflibercept.

The safety profile of HD is anticipated to be similar to that of 2 mg aflibercept, and includes identified risks such as 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 include arteriothromboembolic events (ATEs), embryo-fetotoxicity, and an increase in BP. However, pharmacokinetic and clinical safety data of IVT 2 mg aflibercept have indicated that the known potential risks from systemic administration of anti-VEGF treatments in oncology indications were not identified with IVT dosing of 2 mg. Studies performed with IV administration of aflibercept demonstrated that increases in BP were the earliest pharmacodynamic (PD) indicator of systemic effects. Based on the estimated exposure margins for free aflibercept after an 8 mg IVT dose for a 5 mmHg mean increase in SBP as described above, a meaningful increase in BP is not anticipated for the 8 mg IVT dose.

An objective of this study in DME patients is to assess patient safety. Robust generation of safety data is planned in this phase 2/3 trial to evaluate potential systemic exposure-related adverse events (AEs) such as changes in BP and incidence of ocular safety events. Safety will be assessed by collection of vital signs (including careful monitoring of blood pressure, heart rate, and temperature), ocular assessments, AEs, laboratory assessments, and sparse PK sampling. Additionally, the aflibercept PK profile (via dense sampling for drug concentration and PK evaluation) and PD effects (ie, BP changes) will be evaluated in a dense PK substudy.

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

Overall Risk-Benefit Balance:

Based on the available preclinical and clinical data, the benefit-risk assessment of HD aflibercept is considered as positive and supports the participation of patients with DME in the clinical trial program.

Recognizing that "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, the Sponsor does not intend to screen any patient in this study in a specific location or area until the COVID-19 pandemic is controlled such that patients can safely participate in the study. Until then, the Sponsor plans to continue to obtain approvals from Health Authorities/Ethics Committees (ECs) to enable initiation of study sites for this study, as allowed by local laws and regulations. Site initiation visits will then be determined based on the sites' ability to proceed.

4. ENDPOINTS

4.1. Primary and Secondary Endpoints

4.1.1. Primary Endpoint

The primary endpoint is the change from baseline in BCVA at week 48.

4.1.2. Key Secondary Endpoints

The key secondary efficacy endpoints are:

- Proportion of patients with a ≥2 step improvement in Diabetic Retinopathy Severity Scale (DRSS) at week 48
- Change from baseline in BCVA at week 60 (for EMA/PMDA [European Medicines Agency/Pharmaceuticals and Medical Devices Agency] Analysis Plan only, see Section 11)

4.1.3. Additional Secondary Endpoints

The secondary efficacy endpoints are:

- Proportion of patients gaining ≥15 letters at week 48
- Proportion of patients with BCVA ≥69 letters at week 48
- Proportion of patients without fluid at foveal center at week 48
- Change from baseline in central retinal thickness (CRT) at week 48
- Proportion of patients without leakage on fluorescein angiography (FA) at week 48
- Change from baseline in National Eye Institute Visual Function Questionnaire (NEI-VFQ) total score at week 48
- Systemic PK of aflibercept as assessed from baseline through week 48
- Assessment of immunogenicity to aflibercept through end of study (EOS) week (week 96).

The secondary safety endpoint is:

- Safety evaluation by assessment of AEs and serious adverse events (SAEs) through weeks 48, 60, 96, [redacted]

4.1.4. Exploratory Endpoints

The exploratory endpoints are:

- Proportion of patients without retinal fluid (total fluid, intraretinal fluid [IRF] and/or subretinal fluid [SRF]) at the foveal center and in center subfield at week 48 and week 96
- Time to fluid-free retina over 48 weeks and 96 weeks (total fluid, IRF and/or SRF at foveal center and in the center subfield)

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- Proportion of patients with sustained fluid-free retina over 48 weeks and 96 weeks (total fluid, IRF and/or SRF at foveal center and in the center subfield)
- Proportion of patients without CSME at week 48 and week 96
- Proportion of patients with a ≥3 step improvement in DRSS at week 48 and week 96
- Change from baseline in BCVA averaged over the period from week 36 to week 48
- Change from baseline in BCVA averaged over the period from week 48 to week 60
- Proportions of patients gaining and losing ≥5 or ≥10 letters at week 48 and week 96
- Proportion of patients losing ≥15 letters at week 48 and week 96
- Proportion of patients randomized to HDq16 maintaining q16 dosing interval or longer through weeks 48, 60, and 96
- Proportion of patients randomized to HDq12 maintaining q12 dosing interval or longer through weeks 48, 60 and 96
- Proportion of patients with an assigned injection interval of ≥16 or ≥20 weeks based on assessment at the last injection visit

In addition to those specified above, all primary, secondary, and exploratory endpoints may be analyzed in an exploratory manner at weeks 60 and 96. [redacted]

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc.), disease characteristics, medical history, and medication history.

5.2. Efficacy Variables

The efficacy variable relevant to the primary efficacy endpoint is visual acuity.

The efficacy variables relevant to the secondary endpoints are:

- BCVA
- Assessment of retinal fluid levels and retinal thickness on spectral domain optical coherence tomography (SD-OCT)
- Dosing interval
- Quality of life using the NEI VFQ-25
- Diabetic retinopathy severity level using the DRSS

The efficacy variables relevant to the exploratory endpoints are:

- Assessment of retinal fluid levels and retinal thickness on SD-OCT
- BCVA
- Dosing interval

5.3. Safety Variables

Safety will be evaluated by assessment of AEs and SAEs, ocular exams, IOP, vital signs (including BP, heart rate, and temperature), and clinical laboratory values.

5.4. Pharmacokinetic Variables

The PK variables are the concentrations of free, bound, adjusted bound, and total aflibercept in plasma at each time point (Table 2).

5.5. Immunogenicity Variables

The immunogenicity variables are anti-drug antibody (ADA) status, titer, and neutralizing antibody (NAb) status at each study visit time point (Table 2).

6. STUDY DESIGN

6.1. Study Description and Duration

This phase 2/3, multi-center, randomized, double-masked study in patients with DME involving the center of the macula will investigate the efficacy and safety of HD aflibercept versus 2 mg aflibercept (through week 96; year 2) [redacted]

The study consists of a screening/baseline period, a treatment period, and an EOS visit at week 96. [redacted]

A total of approximately 640 eligible patients will be randomized into 3 treatment groups in a 1:2:1 ratio as follows: 1) 2q8: 2 mg aflibercept every 8 weeks, following 5 initial monthly doses (n=160), 2) HDq12: HD aflibercept every 12 weeks, following 3 initial monthly doses (n=320), 3) HDq16: HD aflibercept every 16 weeks following 3 initial monthly doses (n=160) (Figure 1).

Patients will be stratified based on baseline CRT (<400µm, ≥400 µm), prior DME treatment (yes, no), and geographical region (Rest of world, Japan). Sham injections will be given at all visits when an active injection is not planned. All patients will be followed every 4 weeks through week 96.

The primary analysis will take place once all patients have completed week 48 (or prematurely discontinued), with additional analyses after all patients have completed week 60, and after all patients have completed the study at week 96.

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

Approximately 24 patients will be included in a dense PK substudy (n=8 per group, with half Japanese and half non-Japanese per group). For details refer to Table 3.

In all patients, blood samples for measurement of drug concentrations (PK) and ADA will be obtained prior to the first treatment and at prespecified time points throughout the course of the study (see Schedule of Events, Table 2). In addition, a DNA sample will be collected from those who sign the informed consent form (ICF) for the optional genomic substudy.

Dosing schedules appear in Figure 2 and [redacted] are described below.

Figure 1: Study Flow Diagram

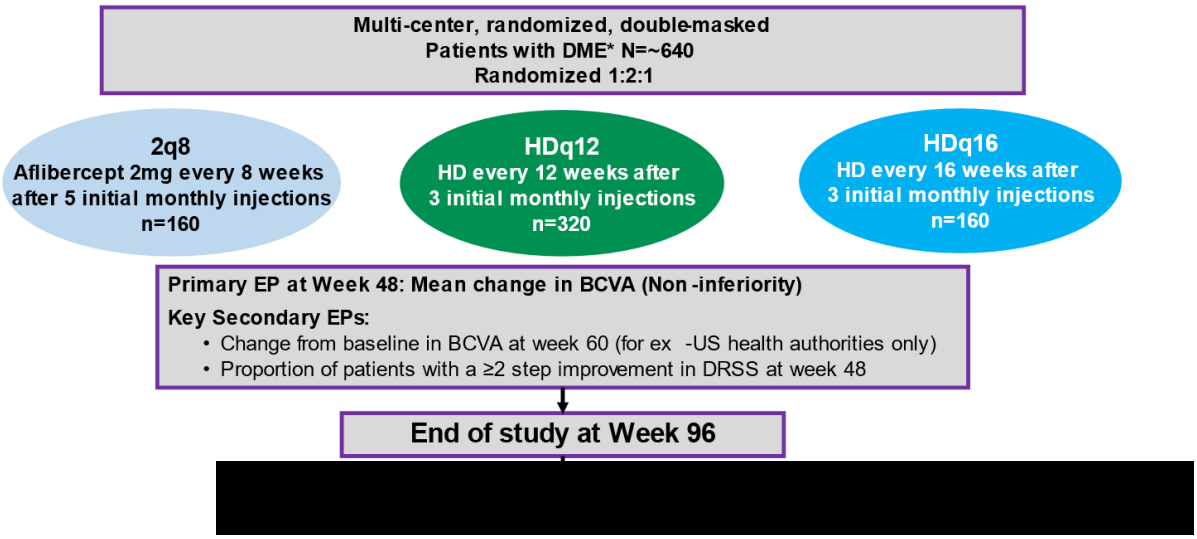

Figure 2: Dosing Schedule

PHOTON: Dosing Schedule

	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24* (1° Endpoint)	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48
2q8	X	X	X	X	X	o	X	o	X	o	X	o	X
HDq12	X	X	X	o	o^	X^	o	o	X[a]	o	o	X[a]	o
HDq16	X	X	X	o	o*	o*	X*	o	o	o	X[a]	o	o

X=active injection
o=sham injections

Dose Regimen Modifications in Year 1
^Q12 group: If criteria are met, patients will continue q8.
*HDq16 group: If criteria are met at week 16 or 20, patient will continue q8. If criteria are met at week 24, patient will continue q12.
[a]For patients on a dosing interval of q12 or q16 weeks, DRM criteria will be assessed at dosing visits and if DRM criteria are met the next dosing interval will be reduced by 4 weeks.

	Wk 52	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96
2q8	o	X	o	X	o	X	o	X	o	X	o	
HDq12	o	X[a]	o	o	X[a]	o	o	X[a]	o	o	X[a]	
HDq16	o	X[a]	o	o	o	X[a]	o	o	o	X[a]	o	

Dose Regimen Modifications in Year 2
[a]Patients that continue on a dosing interval >8 weeks will be assessed at their dosing visits for DRM criteria for both shortening and extension of the interval by 4 week increments

Note: Figure does not reflect all dosing options, once a patient is shortened or extended.

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Figure 3 [redacted]

Dose Regimen Modifications/Rescue Regimen

For masking purposes, assessments for dose regimen modifications (DRMs) will be performed in all participants at all visits (through the IWRS) beginning at week 16. Based on these assessments, patients in the HD groups may have their treatment intervals shortened (year 1 and year 2) or extended (year 2). The minimum interval between injections will be 8 weeks which is considered a rescue regimen for patients randomized to HD aflibercept and unable to tolerate a dosing interval greater than every 8 weeks. Patients in the aflibercept 2 mg group will remain on fixed q8 dosing throughout the study (ie, will not have modifications of their treatment intervals regardless of the outcomes of the DRM assessments).

Year 1: Baseline to Week 52

Beginning at week 16, patients in the HD groups will have the dosing interval **shortened** (at the visits described below) if BOTH of the following criteria are met:

1. >10 letter loss in BCVA from week 12 in association with persistent or worsening DME AND
2. >50 μm increase in CRT from week 12

(It should be noted that the change in CRT for these criteria will be assessed at the site.)

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

For patients whose interval was not shortened to q8 dosing at or before week 24, the interval will be shortened if the DRM criteria are met at a subsequent dosing visit. Patients in the HDq12 group who meet the criteria will receive the planned dose at that visit and will then continue on a rescue

regimen (aflibercept 8 mg, every 8 weeks). Patients in the HDq16 group who meet these criteria will receive the planned dose at that visit and will then continue to be dosed every 12 weeks if they were on a 16-week interval, or switch to the rescue regimen (aflibercept 8mg, every 8 weeks) if they were previously shortened to a 12-week interval. Therefore, a patient randomized to HDq16 whose injection interval has been shortened to q12 will have their injection interval further shortened to q8 if these criteria are met at any subsequent dosing visit.

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

From week 52 through the end of study (year 2), all patients in the HD groups will continue to have the interval shortened in 4-week intervals if the DRM criteria for shortening are met at dosing visits using the DRM criteria described above for year 1. As in year 1, the minimum dosing interval for patients in all treatment groups is every 8 weeks.

In addition to shortening of the interval, all patients in the HD groups (including patients whose interval was shortened during year 1) may be eligible for interval **extension** (by 4-week increments), if BOTH the following criteria are met at dosing visits in year 2:

1. <5 letter loss in BCVA from week 12 AND
2. CRT <300 μm on SD-OCT (or <320 μm on Spectralis SD-OCT)

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

As in year 1, all patients in all treatment groups (including the 2q8 group) will be evaluated against both DRM criteria at all visits through the IWRS for masking purposes. However, changes to dosing schedule will only be implemented as described above for those patients randomized to HDq12 or HDq16 treatment groups. No changes to the dosing schedule will be made to the 2q8 treatment group at any time.

[redacted]

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[redacted]

6.2. Planned Interim Analysis

No formal interim analysis is planned. However, the primary analysis for this study will be performed once all patients reach week 48, with a subsequent analysis performed when all patients reach week 60. The study will continue through week 96 for the main phase [redacted]

Another analysis will be conducted after all patients have completed the main phase of study at week 96 (or prematurely discontinued). [redacted]

A description of the statistical methods to be employed is in Section 11.4 and masking implications are discussed in Section 8.5.

6.3. Study Committees

6.3.1. Study Steering Committee

A study steering committee (SC) will be established to help guide the study in regard to safety and efficacy. All members of the SC are masked with regard to treatment assignments throughout the study.

6.3.2. 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). Arterial thromboembolic events 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.

6.3.3. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will meet periodically to review the ongoing safety of patients in the study and provide recommendations to continue or terminate the study depending upon these reviews. The operation of the IDMC is governed by a charter that describes the group's frequency of meeting, procedures (including but not limited to periodic safety monitoring), and requirements for reporting its observations to the sponsor. The IDMC oversight will continue through the last patient's completion of visit 26 EOS visit (week 96) [redacted]

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

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7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

The study will enroll approximately 640 patients to be randomized 1:2:1 (160 patients each in the 2q8 and the HDq16 groups, and 320 patients in the HDq12 group). [redacted]

7.2. Study Population

The study population will comprise patients with DME with central involvement.

7.2.1. Inclusion Criteria

A patient must meet the following criteria at both the screening and randomization visits (except where indicated) to be eligible for inclusion in the study:

1. Men or women ≥18 years of age (or country's legal age of adulthood if the legal age is >18 years) with type 1 or type 2 diabetes mellitus
2. DME with central involvement in the study eye with CRT ≥300 µm (or ≥320 µm on Spectralis) as determined by the reading center at the screening visit
3. BCVA early treatment diabetic retinopathy study (ETDRS) letter score of 78 to 24 (approximate Snellen equivalent of 20/32 to 20/320) in the study eye with decreased vision determined to be primarily the result of DME
4. Willing and able to comply with clinic visits and study-related procedures
5. Provide informed consent signed by study patient or legally acceptable representative

[redacted]

7.2.2. Exclusion Criteria

A patient who meets any of the following criteria at either the screening or randomization visits will be excluded from the study:

1. Evidence of macular edema due to any cause other than diabetes mellitus in either eye
2. Active proliferative diabetic retinopathy in the study eye
3. Panretinal laser photocoagulation (PRP) or macular laser photocoagulation in the study eye within 12 weeks (84 days) of the screening visit
4. IVT anti-VEGF treatment (aflibercept, ranibizumab, bevacizumab, brolucizumab, pegaptanib sodium) in the study eye within 12 weeks (84 days) of the screening visit

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5. Prior IVT investigational agents in either eye (eg, anti-ang-2/anti-VEGF bispecific monoclonal antibodies, gene therapy, etc.) at any time
6. Treatment with ocriplasmin (JETREA®) in the study eye at any time
7. Previous use of intraocular or periocular corticosteroids in the study eye within 16 weeks (112 days) of the screening visit, or ILUVIEN® or OZURDEX® IVT implants at any time
8. History of vitreoretinal surgery (including scleral buckle) in the study eye
9. Any other intraocular surgery within 12 weeks (84 days) before the screening visit
10. Yttrium-aluminum-garnet (YAG) laser capsulotomy in the study eye within 4 weeks (28 days) of the screening visit
11. IOP ≥25 mmHg in the study eye
12. History of glaucoma filtration surgery in the past, or likely to need filtration surgery in the future in the study eye
13. Evidence of infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye within 4 weeks (28 days) of the screening visit
14. Any intraocular inflammation/infection in either eye within 12 weeks (84 days) of the screening visit
15. History of idiopathic or autoimmune uveitis in the study eye
16. Vitreomacular traction or epiretinal membrane in the study eye evident on biomicroscopy or OCT that is thought to affect central vision
17. Preretinal fibrosis involving the macula in the study eye
18. Any history of macular hole of stage 2 and above in the study eye
19. Current iris neovascularization, vitreous hemorrhage, or tractional retinal detachment visible at the screening assessments in the study eye
20. History of corneal transplant or corneal dystrophy in study eye
21. Any concurrent ocular condition in the study eye 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 efficacy or safety
22. Only 1 functional eye, even if that eye was otherwise eligible for the study (eg, BCVA of counting fingers or less in the eye with worse vision)
23. Structural damage to the center of the macula in the study eye that is likely to preclude improvement in BCVA following the resolution of macular edema including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia, or organized hard exudates
24. Ocular conditions with poorer prognosis in the fellow eye
25. Inability to obtain photographs, FA, or SD-OCT in the study eye, eg, due to media opacity, allergy to fluorescein dye, or lack of venous access

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26. 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
27. Any prior systemic (IV) anti-VEGF administration
28. Uncontrolled diabetes mellitus as defined by hemoglobin A1c (HbA1c) > 12%
29. Uncontrolled blood pressure (defined as systolic >160 mmHg or diastolic >95 mmHg). Patients may be treated with up to 3 agents known to have anti-hypertensive effects for arterial hypertension to achieve adequate blood pressure control. This limit applies to drugs that could be used to treat hypertension even if their primary indication in the patient was not for blood pressure control. Any recent changes in medications known to affect blood must be stable for 12 weeks (84 days) prior to screening.
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
33. Participation in an investigational study within 30 days prior to screening visit that involved treatment with any drug (excluding vitamins and minerals) or device
34. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the sponsor
35. Pregnant or breastfeeding women
36. Men or women of childbearing potential (WOCBP)* who are unwilling to practice 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 dose. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
    b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS)
    c. bilateral tubal ligation
    d. vasectomy**
    e. condom plus contraceptive sponge, foam, or jelly, or diaphragm plus contraceptive sponge, foam, or jelly
    f. and/or sexual abstinence†, ‡.

    *Postmenopausal women must be amenorrhoeic for at least 12 months without an alternative medical cause in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

**Vasectomized partner or vasectomized study participant must have received medical assessment of the surgical success.

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

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

Additional Exclusion Criteria for the PK Substudy:

1. Prior treatment with IVT aflibercept in the fellow eye within 12 weeks (84 days) of the screening visit
2. Other IVT anti-VEGF treatment (ranibizumab, bevacizumab, brolucizumab, pegaptanib sodium) in the fellow eye within 4 weeks (28 days) of the screening visit
3. Patients with SBP >140 mmHg or diastolic blood pressure (DBP) >90 mmHg
4. Patients with known cardiac arrhythmia
5. Patients who, in the opinion of the investigator, are unlikely to have stable BP over the course of the study (eg, due to known or suspected non-compliance with medication)
6. Variation by more than 10% in the 3 pre-randomization BP measures recorded at the screening visits and at randomization

7.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who are withdrawn prematurely from the study will be asked to complete the early termination visit (EOS visit, [visit 26] [redacted] as described in Section 9.1.4.

Rules for discontinuation of the study or study treatment (permanent or temporary) are discussed in Section 8.3.2.

7.4. Replacement of Patients

Patients prematurely discontinued from study/study drug will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

The HD drug product 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).

Intravitreal aflibercept injection 2 mg will be supplied for this study as an aqueous solution in sterile, sealed, single-use vials for IVT administration at a concentration of 40 mg/mL delivered in an injection volume of 50 µL (0.05 mL).

Empty vials will be supplied in sham injection kits.

Instructions on dose preparation are provided in the pharmacy manual.

Fellow eye treatment will be allowed with 2 mg aflibercept, throughout the main study phase [redacted], at the investigator's discretion for indications approved by governing authorities. The treated fellow eye will not be considered an additional study eye.

8.2. Rescue Treatment

There is no alternative rescue treatment defined for this study. However, patients in the HDq12 and HDq16 groups meeting the DRM criteria for shortening may be shortened to intervals as short as every 8 weeks, which is considered a rescue regimen. See Section 6.1.

8.3. Dosing Modification and Study Treatment Discontinuation Rules

8.3.1. Dosing Modification

Dosing modification for an individual patient is not allowed.

8.3.2. Study and Study Drug Discontinuation

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

Patients 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 (ocular or nonocular) that, from the patient's or the investigator's view, is severe enough to require withdrawal from the study. The investigator must notify the sponsor immediately if a patient is withdrawn because of an AE/SAE.
- At the discretion of the treating investigator. The development of conditions, which would have prevented a patient's entry into the study according to the selection criteria, is no reason per se for withdrawal. However, the withdrawal in such cases remains at the discretion of the treating investigator.

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- Decision by the investigator or sponsor that termination is in the patient's best medical interest or administrative decision for a reason other than an AE/SAE.
- A female patient becomes pregnant (see Section 10.1.3).
- Lost to follow-up.
- Decision by the sponsor to halt the entire study.

Patients may be withdrawn if any of the following occurs:

- If any treatment for DME other than study interventions is given in the study eye.
- Systemic anti-angiogenic agents are taken by the patient during the study.
- If, in the investigator's opinion, continuation in the study would be harmful to the patient's well-being.
- At the specific request of the sponsor and in liaison with the investigator (eg, obvious noncompliance or safety concerns).

Patients who permanently discontinue from study drug should be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 9.1.3.

8.4. Method of Treatment Assignment

Approximately 640 patients will be randomized into 3 treatment groups in a ratio of 1:2:1 to receive either 2 mg aflibercept every 8 weeks following 5 initial monthly doses (2q8), HD every 12 weeks following 3 initial monthly doses (HDq12), or HD every 16 weeks following 3 initial monthly doses (HDq16), according to a central randomization scheme provided by an interactive web response system (IWRS) to the designated, unmasked investigator or study coordinator (or unmasked qualified designee). Randomization will be stratified according to baseline CRT (<400 µm, ≥400 µm), prior treatment for DME (yes, no) and geographic region (Rest of world, Japan).

8.5. Masking

The study will be conducted in double-masked fashion. Study patients and masked study site personnel will remain masked to all randomization assignments throughout the main study. The Regeneron Medical/Study Director, study monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain masked to all patient randomization assignments.

To preserve masking, sham injections will be performed for all patients at treatment visits in which patients do not receive an active injection through week 92.

A masked physician will be assigned to do the following: 1) assess AEs, 2) perform all study procedures except those related to study drug injection, and 3) perform the masked assessment of

efficacy. A separate, unmasked physician will administer treatment in the study eye (ie, perform study drug injection or sham injection) (Table 1).

The unmasked physician or designee will not have any role in the study beyond the receipt, tracking, preparation, destruction, and administration of study drug, and assessing safety during the observation period following study drug administration. The masked physician will provide assessments for the IWRS to determine whether the patient has met DRM criteria for shortening or extending the interval.

Every effort must be made to ensure that all other study site personnel other than those designated as unmasked remain masked to treatment assignment.

Masked and unmasked roles will be assumed for the entire study, and switching from an unmasked to a masked role after the first patient is randomized at a site is not permitted. Any deviation to the roles above must first be approved by the sponsor. This must be properly documented before any patients are treated, and the site signature and delegation log must be maintained as new personnel are added to the study team.

[redacted]

Table 1: Responsibilities of the Masked and Unmasked Personnel

Masked or Unmasked Personnel
• Performs all screening procedures up until randomization • Assesses inclusion/exclusion criteria • Obtains medical/ophthalmic history • Obtains informed consent • Collects samples for laboratory testing and antibody sampling • Performs electrocardiograms (ECGs) and transfers to reading center
Masked Personnel
• Assesses AEs, including severity and relationship • Assesses efficacy • Performs ophthalmic examinations, including IOP, at all study visits (except post-dose examinations immediately after treatment) • Evaluates all safety, including vital signs and review of images for safety concerns (except those immediately after IVT injection) • May perform fellow eye injections at any unscheduled visits where only the fellow eye is treated • Tests refraction and BCVA (no exceptions will be granted) • Performs and assesses OCT, fundus photography (FP), and FA images and transfers them to reading centers
Unmasked Personnel
• Coordinates randomization • Performs receipt and accountability of study drug • Performs study drug (HD or 2 mg aflibercept) or sham injections in study eye • Performs fellow eye injection (if treatment is administered bilaterally/in conjunction with study eye treatment) • Observes safety through the end of the observation period (approximately 30 minutes following study treatment) • Checks IOP post-dose (study eye) before the end of the approximately 30-minute observation period • Checks indirect ophthalmoscopy post-dose (study eye)

8.6. Emergency Unmasking

Unmasking of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy) and when a treatment decision is contingent on knowing the patient's treatment assignment. Study drug will be discontinued for patients whose treatment has been unmasked (Section 8.3.2).

- If unmasking is required:
  - Only the investigator will make the decision to unmask the treatment assignment.
  - Only the affected patients will be unmasked.
  - Unmasking is performed using the IWRS which will notify Regeneron.
  - The investigator will also notify Regeneron and/or designee as soon as possible after unmasking the patient.

Treatment assignment is not to be provided to site personnel, other than the unmasked site personnel, at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the patient's treatment assignment.

8.7. Treatment Logistics and Accountability

8.7.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the mask, these lists will not be accessible to individuals involved in study conduct.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

8.7.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed / returned to the sponsor or designee.

8.7.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- dispensed to each patient
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

8.7.4. Treatment Compliance

Study drug treatments will be administered by clinical personnel during study visits. All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

8.8. Concomitant Medications and Procedures

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

If a pretreatment concomitant medication is administered in the study eye before injection (eg, antibiotic or anesthetic), it must be administered for sham and fellow eye injections as well.

8.8.1. Prohibited Medications and Procedures

Study Eye:

Patients are not allowed to receive any standard or investigational treatment for DME in the study eye other than their assigned study treatment with HD or 2 mg aflibercept, as specified in the protocol. This includes medications administered locally (eg, IVT, topical, juxtascleral, or periorbital routes) with the intent of treating DME in the study eye.

Fellow Eye:

If the fellow eye has DME, or any other approved indication, 2 mg aflibercept will be allowed and supplied through the IWRS. Once the fellow eye receives aflibercept 2 mg therapy during the study, AEs/SAEs will be assessed as related/not related to aflibercept 2 mg treatment in the fellow eye in addition to being assessed as related/not related to the study drug (delivered to the study eye), IVT injection-procedure, and other protocol-specified procedures. Patients are not allowed to receive any other anti-VEGF agent in the fellow eye.

Patients enrolled in the dense PK substudy cannot receive 2 mg aflibercept in the fellow eye before providing a PK sample at visit 3, week 4.

Non-Ocular (Systemic):

Non-ocular (systemic) standard or investigational treatments for DME of the study or fellow eye are not permitted.

8.8.2. Permitted Medications and Procedures

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

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

9.1.1. Schedule of Events for the Study

Study assessments and procedures are presented by study period and visit in Table 2.

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

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Table 2: Schedule of Events

Baseline to Week 48

Study Procedure	Screening Visit 1	Baseline Visit 2	Visit 3	Visit 4	Optional Visit 4.1[1]	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14
Week		0	4	8		12	16	20	24	28	32	36	40	44	48
Day	-21 to -1	1	29	57	60-64	85	113	141	169	197	225	253	281	309	337
Window (day)			±5	±5		±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Screening/Baseline:															
Informed consent form(ICF)	X														
Dense PK substudy ICF[2]	X														
Genomic substudy ICF[3]	X														
Future Biomedical Research ICF[4]	X														
Inclusion/Exclusion	X	X													
Medical history	X														
Demographics	X														
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X													
Administer Study Drug[5]															
Study drug (active or sham)		X	X	X		X	X	X	X	X	X	X	X	X	X
DRM assessment							X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
Ocular Efficacy and Safety (bilateral unless indicated):															
BCVA (ETDRS) and Refraction[7]	X	X	X	X		X	X	X	X	X	X	X	X	X	X
IOP[8]	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Slit lamp examination	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy[9]	X	X	X	X		X	X	X	X	X	X	X	X	X	X
FA, FP[10]	X					X			X			X			X
SD-OCT[10]	X	X	X	X		X	X	X	X	X	X	X	X	X	X

Table 2: Schedule of Events

Baseline to Week 48 (continued)

Study Procedure	Screening Visit 1	Baseline Visit 2	Visit 3	Visit 4	Optional Visit 4.1[1]	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14
Week		0	4	8		12	16	20	24	28	32	36	40	44	48
Day	-21 to -1	1	29	57	60-64	85	113	141	169	197	225	253	281	309	337
Window (day)			±5	±5		±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
OCTA substudies[11]	X					X			X			X			X
NEI-VFQ-25	X								X						X
Nonocular Safety:															
Physical examination	X														
Vital signs[12]	X	X	X	X	X[1]	X	X	X	X	X	X	X	X	X	X
ECG	X														X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[13]															
Hematology	X														X
Blood chemistry	X														X
HbA1c	X														X
Pregnancy test (women of childbearing potential)[14]	X Serum	X Urine	X Urine	X Urine		X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine
Urinalysis/UPCR	X														X
Pharmacokinetics and Other Sampling															
PK samples (Dense)[15, 17]		See schedule below	X		X[1]	X				X					X
PK samples (Sparse)[16, 17]		X	X		X[1]	X				X					X
Genomic DNA sample[3]		X													
Immunogenicity sample[16, 17]		X													X

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Table 2 continued: Schedule of Events

Week 52 to Week 96

Study Procedure	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22	Visit 23	Visit 24	Visit 25	EOS Visit[18] 26
Week	52	56	60	64	68	72	76	80	84	88	92	96
Day	365	393	421	449	477	505	533	561	589	617	645	673
Window (day)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Screening/Baseline:												
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Administer Study Drug[5]												
Study Drug (active or sham)	X	X	X	X	X	X	X	X	X	X	X	
DRM assessment	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	
Ocular Efficacy and Safety (bilateral unless indicated):												
BCVA (ETDRS) and refraction[7]	X	X	X	X	X	X	X	X	X	X	X	X
IOP[8]	X	X	X	X	X	X	X	X	X	X	X	X
Slit lamp examination	X	X	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy[9]	X	X	X	X	X	X	X	X	X	X	X	X
FA, FP[10]			X			X			X			X
SD-OCT[10]	X	X	X	X	X	X	X	X	X	X	X	X
OCTA Substudies[11]			X			X			X			X
NEI VFQ-25			X									X
Nonocular Safety:												
Physical examination												
Vital signs[12]	X	X	X	X	X	X	X	X	X	X	X	X
ECG												X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[13]												
Hematology												X
Blood chemistry												X
HbA1c												X

Study Procedure	**Visit 15**	**Visit 16**	**Visit 17**	**Visit 18**	**Visit 19**	**Visit 20**	**Visit 21**	**Visit 22**	**Visit 23**	**Visit 24**	**Visit 25**	**EOS Visit[18] 26**
Week	52	56	60	64	68	72	76	80	84	88	92	96
Day	365	393	421	449	477	505	533	561	589	617	645	673
Pregnancy test (women of childbearing potential)[14]	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	
Urinalysis/UPCR												X
Pharmacokinetics and Other Sampling												
PK samples(Dense)[15,17]												
PK samples(Sparse)[16,17]												
Genomic DNA sample[3]												
Immunogenicity sample[16, 17]												X

BCVA=Best corrected visual acuity, DRM = Dose regimen modification, ECG=electrocardiogram, ETDRS=Early Treatment Diabetic Retinopathy Study, FA=fluorescein angiography, FP=fundus photography, IOP=Intraocular pressure, OCTA = optical coherence tomography angiography, PK=pharmacokinetics, SD-OCT=spectral domain optical coherence tomography, UPCR=urine protein:creatinine ratio.

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9.1.1.1. Footnotes for the Schedule of Events Table

1. An optional visit for all patients on days 60 to 64 (after the third injection) to collect a PK sample and assess heart rate and BP (no temperature measures required) as well as concomitant medications and AEs.
2. Signed only by patients participating in the dense PK substudy and in addition to the study ICF.
3. The optional genomic substudy ICF should be presented to patients at the screening visit and may be signed at any subsequent visit at which the patient chooses to participate after screening. The genomic DNA sample should be collected on day 1/baseline (pre-dose) or at any study visit from patients who have signed the substudy ICF.
4. The optional future biomedical research substudy ICF should be presented to patients and signed at the screening visit.
5. Refer to pharmacy manual for study drug injection guidelines. Following study drug injection, patients will be observed for approximately 30 minutes.
6. Assessments for DRM criteria will occur in all patients at all visits for masking purposes beginning at week 16. Actual DRMs will be implemented as described in Section 6.1.
7. Patients enrolled at sites participating in the optional visual function substudy may undergo additional visual function tests. See study procedure manual for details.
8. Intraocular pressure will be measured at all study visits (bilateral). On days when study drug is administered, IOP should be measured pre-dose (bilaterally) by the masked investigator (or designee) and approximately 30 minutes after administration of study drug (study eye only) by the unmasked investigator (or designee). IOP will be measured using Goldmann applanation tonometry or Tono-pen™ and the same method of measurement must be used in each patient throughout the study.
9. Indirect ophthalmoscopy will be performed bilaterally at all visits by the masked investigator. On days when study drug is administered, it should also be performed immediately after administration of study drug (study eye only) by the unmasked investigator.
10. The same SD-OCT/FA/FP imaging system used at screening and day 1 must be used at all follow-up visits in each patient. Images will be taken in both eyes before dosing at each required visit. For FA, the study eye will be the transit eye and images should be collected using the widest field available. If available, sites should also submit an optional ultra-widefield color photograph.
11. Details on an optional substudy evaluating OCTA are provided in study procedure manual. Images will be collected at the same time points as FA/FP.
12. Vital signs (BP, heart rate, temperature) should be measured prior to injection and any blood sampling. When possible, timing of all BP assessments should be within 2 hours of clock time of dosing on day 1. Table 3 shows additional measurements for patients enrolled in the dense PK substudy.

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13. All samples collected for laboratory assessments should be obtained prior to administration of fluorescein and prior to administration of study drug.
14. For women of childbearing potential, a negative serum pregnancy test at screening is required for eligibility. A negative urine pregnancy test is required before treatment is administered at subsequent visits.
15. Dense PK sampling will be performed in approximately 24 patients (n=8/group) as indicated in Table 2. Additional samples will be drawn according to the dense PK substudy schedule defined in Table 3. On dosing visits, PK sampling should be performed prior to the administration of study drug and within 2 hours of the clock time of dosing on day 1.
16. On dosing visits, PK and ADA sampling will be performed prior to dosing.
17. PK and ADA samples may also be drawn at any non-specified scheduled visit or any unscheduled visit if a patient experiences an unexpected SAE.
18. The EOS will also represent the early termination visit.

9.1.2. Schedule of Events for the Dense PK Substudy

Additional study assessments and procedures for the Dense PK Substudy are presented by study period and visit in Table 3.

Table 3: Schedule of Events: (Dense PK Substudy)

Visit	Dose	Assessment Day	Assessment Time (h)	PK Sample	Heart Rate and Blood Pressure[3]
Screening 2[1]		-20 to -1	±2h		X[2]
Visit 2		1	Predose[3]	X	X[2]
	X		4h ±30min	X	
			8h ±2h	X	
		2	±2h[3]	X	X[2]
		3	±2h[3]	X	X[2]
		5	±2h[3]	X	X[2]
		8	±2h[3]	X	X[2]
		15	±2h[3]	X	X[2]
		22	±2h[3]	X	X[2]

9.1.2.1. Footnotes for the Dense PK Substudy Schedule of Events Table 3

1. Additional BP assessment to confirm eligibility for patients in the dense PK substudy between screening and baseline
2. Timing of all BP assessments must be within 2 hours of the clock time of dosing on day 1. Blood pressure assessments for patients in the dense PK substudy will be obtained prior to blood sample collection, using automated office blood pressure (AOBP) measurement with the Omron Model HEM 907XL (or comparable). Measures displayed by the device will be recorded in the electronic data capture (EDC). Detailed instructions can be found in the study procedure manual.
3. PK sampling is to be performed within ±2 hours of the clock time of dosing on day 1.

9.1.3. [redacted]

[redacted]

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Table 4: [redacted]

[redacted]

9.1.3.1. [redacted]

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[redacted]

9.1.4. Early Termination Visit

Patients who are withdrawn from the study will be asked to return to the clinic for an early termination visit consisting of the end of study assessments described in Table 2 (EOS, visit 26) [redacted]

9.1.5. Unscheduled Visits

All attempts should be made to keep patients 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.

9.2. Study Procedures

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population: medical history, demographics, and physical examination. Signatures for ICFs will also be obtained.

9.2.2. Ocular Study Procedures (Efficacy and Safety)

[redacted]

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[redacted]

9.2.2.1. Intraocular Pressure

Intraocular pressure of the study eye will be measured in both eyes at every visit using Goldmann applanation tonometry or Tono-pen®, as specified in Table 2 and Table 4. The same method of IOP measurement must be used throughout the study for each individual patient. Intraocular pressure will be measured pre-dose (bilateral) by the masked physician (or designee), and at approximately 30 minutes post-dose (study eye) by the unmasked physician (or designee).

9.2.2.2. Slit Lamp Examination

Patients' anterior eye structure and ocular adnexa will be examined bilaterally pre-dose at each study visit using a slit lamp by the masked investigator, as specified in Table 2 and Table 4.

9.2.2.3. Indirect Ophthalmoscopy

Patients' posterior pole and peripheral retina will be examined by indirect ophthalmoscopy at each study visit pre-dose (bilateral) by the masked investigator and post-dose (study eye) by the unmasked investigator, as specified in Table 2 and Table 4. Post-dose evaluation must be performed immediately after injection.

9.2.2.4. Fundus Photography/Fluorescein Angiography

The anatomical state of the retinal vasculature, including the DRSS level, leakage, and perfusion status will be evaluated by FP and FA as specified in Table 2 and Table 4. Fundus photography and FA will be captured and transmitted to an independent reading center for both eyes. For FA, the study eye will be the transit eye and images should be collected using the widest field available. If available, sites should also submit an optional ultra-widefield color photograph.

Fundus and angiographic images will be sent to an independent reading center where images will be read by masked readers. All FPs and FAs will be archived at the site as part of the source documentation. Photographers must be masked to treatment assignment and must be certified by the reading center to ensure consistency and quality in image acquisition. A detailed protocol for image acquisition and transmission can be found in the study procedure manual.

Details on an optional substudy evaluating an exploratory OCT-angiography procedure are provided in the study procedure manual.

9.2.2.5. Spectral Domain Optical Coherence Tomography

Retinal characteristics will be evaluated at each study visit specified in Table 2 and Table 4 using SD-OCT. Images will be captured and transmitted for both eyes. Images will be sent to an independent reading center where they will be read by masked readers. All OCTs will be electronically archived at the study site as part of the source documentation. Optical coherence tomography technicians must be masked to treatment assignment and must be certified by the reading center to ensure consistency and quality in image acquisition. A detailed protocol for acceptable OCT machines and OCT image acquisition/transmission can be found in the study procedure manual.

9.2.2.6. Best Corrected Visual Acuity

Visual function of the study eye and the fellow eye will be assessed using the ETDRS protocol (Early Treatment Diabetic Retinopathy Study Research Group, 1985) at 4 meters at each study visit specified in Table 2 and Table 4. Visual acuity examiners must be certified to ensure consistent measurement of BCVA. They must remain masked per Section 8.5, but whenever possible, should also remain masked to prior BCVA measures and study eye. Best corrected visual acuity should be assessed before any other ocular procedures are performed. A detailed protocol for conducting visual acuity testing and refraction can be found in the study procedure manual. Patients enrolled at sites participating in the optional visual function substudy may undergo additional visual function tests.

9.2.2.7. Quality of Life Questionnaire

Vision-related quality of life (QoL) will be assessed using the NEI VFQ-25 (see study procedure manual) in the interviewer-administered format at visits specified in Table 2 and Table 4. The NEI VFQ-25 will be administered by masked certified personnel.

9.2.3. Safety Procedures (non-ocular)

Safety procedures to assess AEs and SAEs include:

9.2.3.1. Vital Signs

Vital signs, including BP, heart rate, and temperature, will be collected pre-dose at designated time points according to Table 2 and Table 4. [redacted]

When possible, BP assessments will be obtained using AOBP measurement with the Omron Model HEM 907XL (or comparable). 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 procedure manual.

9.2.3.2. Physical Examination

A physical examination, including height and weight, will be performed at the screening visit.

9.2.3.3. Electrocardiogram

A standard 12-lead ECG measurement will be measured at visits specified in Table 2. Heart rate will be recorded from the ventricular rate and the PR, QRS, RR, and QT intervals will be recorded. The ECG strips or report will be retained with the source documentation. Electrocardiograms will be forwarded to a central reader.

9.2.3.4. Laboratory Testing

Hematology, blood chemistry, HbA1c, urinalysis, and serum pregnancy testing samples will be analyzed by a central laboratory. All samples collected for laboratory assessments will be obtained prior to administration of study drug. At visits at which FA is performed, urinalysis samples must be collected before FA to avoid false elevations in urine protein values. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at visits according to Table 2 (main study) and Table 4 [redacted] Tests will include:

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	
Albumin	Lactate dehydrogenase (LDH)	

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

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
Urine protein:creatinine ratio (UPCR)		

Other Laboratory Tests

Hemoglobin A1c will be measured at time points according to Table 2.

Women of childbearing potential must have a documented negative serum pregnancy test before randomization. Urine pregnancy tests will be performed at every treatment visit, and a negative result must be documented before study eye treatment (active or sham) or fellow eye treatment can be administered.

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the masked investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or

conditions unrelated to the study medication or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the masked investigator.

Criteria for reporting laboratory values as an AE are provided in Section 10.1.1.

9.2.4. Drug Concentration and Measurements

Blood samples for concentrations of free, bound, adjusted bound, and total aflibercept in plasma will be collected at the visits and time points listed in Table 2 and Table 3. Instructions for PK blood sample collection will be included in the laboratory manual provided to study sites.

9.2.5. Immunogenicity Measurements and Samples

Serum samples for ADA and NAb assessment will be collected at time points listed in Table 2.

9.2.6. Future Biomedical Research (Optional)

Additional analyses may be performed on leftover PK and ADA samples from patients who consent to participate in the optional future biomedical research substudy. Samples will be banked in long-term storage. The unused PK/ADA samples will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for future biomedical research of DME, related diseases or pathways blocked by study treatment, and any adverse reactions that may emerge. These samples may also be used for assay development and assay validation purposes. After 15 years, any residual samples will be destroyed. The results of these future biomedical research analyses will not be presented in the clinical study report.

9.2.6.1. Pharmacogenomic Analysis (Optional)

Patients who agree to participate in the genomics substudy will be required to consent to this optional substudy before collection of the samples. Whole blood samples for DNA extraction should be collected on day 1/baseline (predose) but can be collected at a later study visit. DNA samples will be collected for pharmacogenomics analyses to understand the genetic determinants of efficacy and safety associated with the treatments in this study and the molecular basis of DME and related diseases. These samples will be single-coded as defined by the International Council on Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock. If there are specific site or country requirements involving the pharmacogenomic analyses which the sponsor is unable to comply with, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker response to aflibercept, other DME clinical outcome measures, and possible AEs. In addition, associations between genomic variants and prognosis or progression of DME as well as related diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug, target pathway, or DME and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods including whole-exome

sequencing, whole-genome sequencing, and DNA copy number variation may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic analyses will not be reported in the CSR.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection period from the time of signing of the ICF to the end of the on-treatment period (defined as the time from signing of the ICF to the last dose of study drug (active or sham) plus 30 days, or to the last study visit (week 96 [redacted] (see Section 11.4.5.1). Medical conditions that existed or were diagnosed prior to the first dose of study drug will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of informed consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the patient. Adverse events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The masked investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The masked investigator's assessment must be clearly documented in the site's source documentation with the masked investigator's signature. The investigator should follow up on SAEs until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the masked investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation or dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to first dose of study drug) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for Definitions).

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For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (after the end of the on-treatment period) that the masked investigator assesses as related to study drug should also be reported.

All AEs, SAEs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3.

10.1.2. Reporting Procedure

All events (serious and non-serious) must be reported with masked investigator's assessment of the event's seriousness, severity, and causality to the study drug, study conduct, and/or injection procedure. For SAEs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE case report form (CRF). Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc.) will be summarized in the narrative on the AE CRF, and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

- **SAEs**
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female or female partner of a male, during the study or within 90 days of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria, must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

10.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital (any duration) or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect.**
- Is an **important medical event**. Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

An ocular important medical event may include the following:

- An AE that requires either surgical or medical intervention to prevent permanent loss of vision
- Substantial, unexplained vision loss or an AE that causes substantial vision loss

Criteria for reporting SAEs must be followed for these events.

10.2.3. Severity

The severity of AEs will be graded according to the following scale:

Mild: Does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms but may be given because of personality of the patient.

Moderate: Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.

Severe: Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

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If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates (see Section 9.2.3.4 and Section 10.1.1 for further information regarding the assessment of laboratory values as AEs).

10.2.4. Causality

The masked investigator must provide causality assessment as to whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset vs. time drug was administered
- Nature of the reactions: immediate vs. long term
- Clinical and pathological features of the events
- Existing information about the drug and same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction, when applicable
- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Patient's medical and social history

Causality to the study drug:

The relationship of AEs to study drug will be assessed by the masked investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the nature of the reaction, patient's clinical condition (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its class of drugs, or is predicted by known pharmacology.
- Not Related:

- The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

For patients receiving fellow eye injections, AEs will also be assessed as related/ not related to "aflibercept 2mg (fellow eye)".

Causality to the Injection Procedure

The relationship of AEs to the injection procedure will be assessed by the masked investigator, and is a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the injection procedure?

The possible answers are:

- **Related:** There is a reasonable possibility that the event may have been caused by the injection procedure.
- **Not Related:** There is no reasonable possibility that the event may have been caused by the injection procedure.

Causality to the other protocol-specified procedures (excluding injection procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol-specified procedure, and cannot be reasonably explained by the nature of the reaction, patient's clinical condition (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol-specified procedure, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance; Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic, cumulative aggregate basis. In addition, the IDMC will review the ongoing safety of patients in the study and provide recommendations to continue or terminate the study depending upon these reviews (see Section 6.3.3).

10.4. Notifying Health Authorities, Institutional Review Board /Ethics Committee, and Investigators

During the study, the sponsor and/or the CRO will inform health authorities, ECs/Institutional Review Boards (IRBs), and the participating investigators of any SUSARs (suspected unexpected serious adverse reactions) occurring in other study centers or other studies of the active study drug (HD), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only masked information.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the ECs/IRBs unless delegated to the sponsor.

Event expectedness for high-dose and for 2 mg aflibercept is assessed against the reference safety information section of the current Investigator's Brochure that is effective for expedited safety reporting.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the clinical study report to health authorities and ECs/IRBs as appropriate.

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11. STATISTICAL PLAN

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

11.1. Statistical Hypothesis

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

Justification of Non-inferiority Margin:

Based on the pooled data analysis of VIVID and VISTA studies in patients with DME treated with aflibercept 2q8, the mean change from baseline in BCVA at week 48 was 10.4 (95% CI: 9.41 to 11.4) letters. Using the lower limit of this confidence interval, a non-inferiority (NI) margin of 4 letters would preserve greater than 50% (57.5%) of the treatment effect of aflibercept 2q8 when compared to a putative placebo. The assumption that mean change in vision for a placebo group would be 0 letters is considered conservative as studies that included sham/placebo treatment demonstrated larger proportions of patients losing vision compared to laser treated groups (Blankenship, 1979) (Early Treatment Diabetic Retinopathy Study Research Group, 1985). This provides justification of the NI margin based on statistical considerations.

Regarding clinical relevance of the NI margin for the BCVA endpoint, previous studies with anti-VEGF therapies in other indications regarded a difference of 5 letters as clinically relevant. For example, the CLARITY (Sivaprasad, 2017) study in diabetic retinopathy (comparing aflibercept to panretinal photocoagulation) and the CATT study (CATT Research Group, 2011) in nAMD (comparing ranibizumab and bevacizumab), used a non-inferiority margin of 5 letters in BCVA. Recently, controlled phase 3 clinical trials studying nAMD (HARBOR study [Ho, 2014] and HAWK and HARRIER study [Dugel, 2019]) were based on a reduced margin of 4 letters.

Null and Alternative Hypotheses:

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

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

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

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

In addition, the HDq12 and HDq16 treatment groups will be tested for non-inferiority against the control group of 2q8 with respect to the following key secondary endpoints. The hypotheses (null vs. alternative) are, respectively, stated as below.

1. Change from baseline in BCVA at week 60 (non-inferiority) (included as part of the primary family of hypotheses only for the EP-SAP)

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

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

where μ_0, μ_1, μ_2, are the mean change from baseline in BCVA at week 60 for 2q8, HDq12, and HDq16, respectively. The non-inferiority margin is set at 4 letters.

2. Proportion of patients with a ≥2 step improvement in DRSS at week 48 (non-inferiority)

H_{50}: $p_1 \leq p_0 - 0.15$ vs. H_{51}: $p_1 > p_0 - 0.15$ (ie, HDq12 vs. 2q8)

H_{60}: $p_2 \leq p_0 - 0.15$ vs. H_{61}: $p_2 > p_0 - 0.15$ (ie, HDq16 vs. 2q8)

where p_0, p_1, p_2, are the proportion of patients with ≥2 step improvement in DRSS at week 48 for 2q8, HDq12, and HDq16, respectively. The non-inferiority margin is set at 15%.

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

3. Change from baseline in BCVA at week 48 (superiority)

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

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

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

4. Change from baseline in BCVA at week 60 (superiority) (included only for the EP-SAP)

H_{80}: $\mu_1 \leq \mu_0$ vs. H_{81}: $\mu_1 > \mu_0$ (ie, HDq12 vs. 2q8)

H_{100}: $\mu_2 \leq \mu_0$ vs. H_{10_1}: $\mu_2 > \mu_0$ (ie, HDq16 vs. 2q8)

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

11.2. Justification of Sample Size

The sample size calculation is based on the primary endpoint, the change from baseline in BCVA at week 48 in 2 pairwise comparisons: (1) HDq12 vs. 2q8; (2) HDq16 vs. 2q8. The non-inferiority margin is defined to be 4 letters.

Under the original testing strategy (prior to Amendment 4), assuming a standard deviation of 9.07 letters for each treatment group (Brown, 2015), a sample size of 129 patients per group will provide 90% power using a two-sample t-test to demonstrate non-inferiority with one-sided alpha=0.0125 (=0.025/2) for each comparison. The overall family-wise type I error rate of 0.025 (one-sided) will be preserved. Allowing for a dropout rate of 19%, 160 patients per group will be required to provide 90% power for each pairwise comparison. However, the sample size in the HDq12 group has been doubled to meet regulatory requirements for the safety database. This results in a total of 640 patients for 3 groups (160, 160, and 320 patients for groups 2q8, HDq16, and HDq12, respectively). Therefore, with these sample sizes, the power for the pairwise comparisons will be: 90% for HDq16 vs. 2q8, and approximately 97% for HDq12 vs. 2q8. The power to reject each of

the primary hypotheses with the proposed multiple testing procedure will be at least as high. Sample size/power calculations were performed using East 6 software.

However, under the current hierarchical testing procedure, using the same assumptions as indicated above, a total sample size of 640 patients for 3 groups provides 98% power for rejecting the null hypothesis H_{10}, and subsequently 92% power for rejecting the null hypothesis H_{30}, for the primary endpoint assessing non-inferiority, with a 1-sided t-test at significance level of 0.025.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized patients who received at least 1 dose of study drug. Analysis of the FAS will be done according to the treatment assigned to the patient at baseline (as randomized). All efficacy endpoints will be analyzed using the FAS. The FAS will be used for primary analysis (statistical evaluation of non-inferiority) and the analysis of key secondary hypotheses.

The per protocol set (PPS) includes all patients in the FAS who had a baseline and at least 1 post-baseline assessment of BCVA, and do not have any relevant important protocol violations that affect the primary efficacy endpoint. Treatment assignment is based on the treatment received (as treated). The final determination on the exclusion of patients from the PPS will be made on the masked data prior to the first database lock. The PPS will be used for supplementary analyses of change from baseline in BCVA (non-inferiority only) at week 48 (primary endpoint) and week 60 (key secondary endpoint, under the EP-SAP).

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study treatment; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF. The safety analysis will be performed on the observed safety data.

11.3.3. Pharmacokinetic Analysis Sets

The PK analysis population includes all patients who received any study drug and who had at least 1 non-missing result following the first dose of study drug. Patients will be analyzed based on actual treatment received.

11.3.4. Immunogenicity Analysis Sets

The ADA analysis set includes all patients who received study drug and had at least 1 non-missing result in the ADA assay following the first study dose. Samples positive in the ADA assay will be analyzed in the NAb assay.

The NAb analysis set includes all patients who received any study drug and who are negative in the ADA assay or with at least 1 non-missing result in the NAb assay. Patients who are ADA negative are set to negative in the NAb analysis set.

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

Subgroups will be defined by key baseline factors (ie, demographics, disease characteristics, and medical history). Subgroup analyses will be performed on efficacy and safety endpoints. Details will be described in the SAPs.

All statistical analyses will be performed using Statistical Analysis Software (SAS), version 9.4 or higher.

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients who have signed the ICF
- The total number of randomized patients: received a randomization number
- The total number of patients who discontinued the study, and the reasons for discontinuation
- The total number of patients who discontinued from study treatment, and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation
- The FAS (defined in Section 11.3.1)
- The PPS (defined in Section 11.3.1)
- The SAF (defined in Section 11.3.2)

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all patients combined. No formal comparison between treatment groups will be conducted.

11.4.3. Efficacy Analyses

Efficacy analyses will be conducted using the FAS population.

The primary analysis is based on the estimand concept. The estimand of primary interest will be mainly based on a hypothetical strategy (ICH E9 [R1], 2017). It describes the change from baseline for all patients who started treatment, assuming all patients have stayed on treatment until week 48.

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

- Population: Defined by the inclusion/exclusion criteria
- Variable: Change from baseline to week 48 in BCVA
- Treatment condition: HD aflibercept administered every 12 weeks (HDq12) after 3 initial monthly injections or every 16 weeks (HDq16) after 3 initial monthly injections versus aflibercept 2 mg administered every 8 weeks (2q8) after 5 initial monthly injections; dose regimen may be modified as detailed in Section 6.1. For primary analysis, data for patients will be analyzed according to their randomized treatment group regardless of dose regimen modifications.
- Intercurrent events: Premature discontinuation from treatment;
- shortening/extension of the interval (DRM / rescue regimen) will not be considered an intercurrent event but as part of the randomized treatment regimen.
- Population-level summary: Difference in least squares (LS) mean change from baseline to week 48 in BCVA between HDq12 and 2q8 (and HDq16 and 2q8) resulting from a mixed-model for repeated measurements (MMRM).

11.4.3.1. Primary Efficacy Analysis

Primary Efficacy Analysis:

The primary efficacy analysis will be a multiple-comparison between the following 2 comparative arms: 1) HDq12 vs. 2q8; and 2) HDq16 vs. 2q8. The primary efficacy variable (change in BCVA from baseline to week 48) will be analyzed using FAS with an MMRM analysis model. The model is specified below and includes baseline BCVA as a covariate, treatment group, baseline CRT category, prior DME treatment, geographical region and visit as fixed effects, and interaction terms for treatment by visit and baseline BCVA by visit. A Kenward-Roger approximation will be used for the denominator degrees of freedom. More details (including the handling of missing data as well as the missing at random assumption) will be in the SAP.

$$Y_{ijk} = \beta_0 + \beta_{baseBCVA}x_i + \beta_{t_k} + \beta_{baseCRT_n} + \beta_{pDME_l} + \beta_{region_m} + \beta_{visit_j} + \beta_{t_k * visit_j} + \beta_{baseBCVA*visit_j}x_i + \varepsilon_{ijk},$$

where:

Y_{ijk} is the change from baseline BCVA at week 48 for i^{th} patient at j^{th} visit for k^{th} treatment group,

β_0 is an intercept term,

$\beta_{baseBCVA}$ is the regression coefficient of the covariate,

x_i for the baseline BCVA of i^{th} patient,

β_{t_k} is the fixed effect of treatment group k,$\beta_{baseCRT_n}$ is the fixed effect of categorized baseline CRT n,

β_{pDME_l} is the fixed effect of prior DME treatment l,

β_{visit_j} is the fixed effect of visit j,

β_{region_m} is the fixed effect of region m,

$\beta_{t_k * visit_j}, \beta_{baseBCVA*visit_j}$ are the interaction terms for treatment by visit and baseline BCVA by visit, and ε_{ijk} is the residual error term.

In terms of the model parameters, the estimand of interest, ie, treatment effect can be expressed, for example, as $(\beta_{t_1} + \beta_{t_1 * Week\ 48}) - (\beta_{t_2} + \beta_{t_2 * Week\ 48})$.

A supplementary analysis of the primary endpoint will be conducted using the MMRM model using the PPS.

Superiority testing for change from baseline in BCVA at week 48 will be performed as described in Section 11.1 and placed in hierarchy as described in Section 11.4.4. Further details will be described in the SAP.

11.4.3.2. Secondary Efficacy Analysis

Analysis for Key Secondary Endpoints:

The key secondary endpoint of change from baseline in BCVA at week 60 (EP-SAP only) will be analyzed with a model matching the one for the primary endpoint. The other key secondary efficacy endpoint (proportion of patients with ≥2 step improvement in DRSS at week 48) will be analyzed using the Cochran-Mantel-Haenszel (CMH) method, stratified by baseline CRT, prior DME treatment, and geographical region as specified for the primary endpoint. The key secondary hypotheses for non-inferiority (see Section 11.1) will be tested according to the multiplicity adjustment method specified in Section 11.4.4. In addition, two-sided 95% confidence intervals will be reported.

Superiority testing for the change from baseline in BCVA at week 60 will be performed as described in Section 11.1 and placed in hierarchy as described in Section 11.4.4. Further details will be described in the SAP.

Analysis for Additional Secondary and Exploratory Endpoints:

All additional efficacy variables (see Section 4.1.3 and Section 4.1.4) will be analyzed descriptively at each scheduled visit from baseline to week 48, week 60, week 96, [redacted] These descriptive analyses may include statistical tests (with nominal p-values) for the efficacy variables and two-sided 95% confidence intervals, in the same way as described for the primary and secondary efficacy variable analyses (see Section 11.4.3.1 and Section 11.4.3.2). Time-to-event variables will be analyzed using the Kaplan-Meier method. No multiplicity adjustments will be made for the additional efficacy analyses. Further details will be described in the SAP.

11.4.4. Control of Multiplicity

The overall family-wise type 1 error will be controlled at 0.025 one-sided level for testing the primary and key secondary endpoints. Adjustment for multiple comparisons in the primary and key secondary endpoints will be made with the hierarchical testing procedure. This approach allows the confirmatory testing of a hypothesis at the full alpha level of 0.025 after successful rejection of the hypotheses which are ranked higher in the hierarchy. The testing hypotheses will be tested in the order as specified in Table 5 for G-SAP and EP-SAP, respectively.

Table 5: The Testing Order of Hierarchical Testing Procedure in G-SAP and EP-SAP

G-SAP	EP-SAP
H_{10} : Q12 BCVA Week 48 non-inferiority	H_{10} : Q12 BCVA Week 48 non-inferiority
	H_{20} : Q12 BCVA Week 60 non-inferiority
H_{30} : Q16 BCVA Week 48 non-inferiority	H_{30} : Q16 BCVA Week 48 non-inferiority
	H_{40} : Q16 BCVA Week 60 non-inferiority
H_{50} : Q12 DRSS Week 48 non-inferiority	H_{50} : Q12 DRSS Week 48 non-inferiority
H_{60} : Q16 DRSS Week 48 non-inferiority	H_{60} : Q16 DRSS Week 48 non-inferiority
H_{70} : Q12 BCVA Week 48 superiority	H_{70} : Q12 BCVA Week 48 superiority
	H_{80} : Q12 BCVA Week 60 superiority
H_{90} : Q16 BCVA Week 48 superiority	H_{90} : Q16 BCVA Week 48 superiority
	H_{100} : Q16 BCVA Week 60 superiority

11.4.5. Safety Analysis

11.4.5.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The on-treatment period (to determine treatment-emergent adverse events [TEAEs]) is defined as the time from first dose of study drug to the last dose of study drug (active or sham) plus 30 days.
- The post-treatment period is defined as after the end of the on-treatment period.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period.

Analysis

All AEs reported in this study will be coded using MedDRA®.

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.2.3), presented by SOC and PT
- All treatment-related TEAEs, presented by SOC and PT

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

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

11.4.5.2. Other Safety

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.

Laboratory Tests

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

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

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

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

11.4.5.3. Treatment Exposure

Exposure to study drug will be examined for each patient. The total number of treatments administered to each patient and the duration of treatment will be analyzed and summarized using descriptive statistics by treatment group in the SAF and FAS populations. Proportions of patients maintaining, shortening, or extending the dosing interval at various time points will be summarized as well.

11.4.5.4. Treatment Compliance

Compliance with protocol-defined study medication will be calculated as follows:

Treatment compliance = (number of received injections through a given week)/(number of planned injections during the period of participation in the study through the given week)x100%.

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

Main Study:

The concentrations of free, bound, adjusted bound, and total aflibercept over time will be summarized by descriptive statistics for each treatment group. Concentrations may be further grouped by factors such as age, renal function, HbA1c level, hepatic function, concomitant medications, body weight, ethnicity, etc. No formal statistical hypothesis testing will be performed.

Dense PK Substudy:

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

- C_{max}
- C_{max}/Dose
- t_{max}
- t_{last}
- C_{last}
- AUC_{last}
- AUC_{inf}
- AUC_{inf}/Dose
- $t_{1/2}$
- C_{trough}

After repeat dosing in the dense PK substudy, PK parameters to be determined may include, but are not limited to, C_{trough}, time to reach steady-state, and accumulation ratio. PK parameters will be summarized by descriptive statistics by treatment group, and geographical region as appropriate. This descriptive statistical assessment may include the geometric means and ratios of the geometric means for selected PK parameters, as deemed appropriate. No formal statistical hypothesis testing will be performed.

11.4.6.2. Pharmacokinetics/Pharmacodynamics Analyses

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

11.4.7. Analysis of Immunogenicity Data

Incidence of treatment-emergent ADA response will be provided by treatment groups, 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 PK profiles evaluated. Assessment of impact of ADA and NAbs on safety and efficacy may be provided.

11.5. Interim Analysis

No formal interim analysis is planned. The primary analysis for this study will be performed once all patients reach week 48, with a subsequent analysis when all patients reach week 60. The study will continue through week 96 for the main phase [redacted]

Another analysis will be conducted after all patients have completed the main phase of the study at week 96 (or prematurely discontinued). [redacted]

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron Pharmaceuticals, Inc. (sponsor).

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history/surgical history/ophthalmic history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an EDC system (Medidata RAVE).

12.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IWRS system – randomization, study drug supply
- EDC system – data capture – Medidata RAVE
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

The study monitor and/or designee (eg, [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. This study will use the principles of risk-based monitoring (ICH). This means that the number of visits for any given site may vary based on site risk indicators. The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current, approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and CRF data are timely, accurate, and complete.

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final eCRFs that will be provided to the sponsor.

12.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

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13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in the presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original, signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

13.2.1. [redacted]

[redacted]

13.3. Patients Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patient (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patient, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site after study completion.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and health authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Randomized, Double-Masked, Active-Controlled Phase 2/3 Study of the Efficacy and Safety of High-Dose Aflibercept in Patients with Diabetic Macular Edema, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

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SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the planned conduct of the study.

Study Title: A Randomized, Double-Masked, Active-Controlled Phase 2/3 Study of the Efficacy and Safety of High-Dose Aflibercept in Patients with Diabetic Macular Edema

Protocol Number: VGFTe-HD-DME-1934

Protocol Version: VGFTe-HD-DME-1934 Amendment 6

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

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Sponsor's Responsible Biostatistician

VV-RIM-00179129-4.0 Approved - 27 Feb 2023 GMT-5:00

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