REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: 2.0

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
Protocol Number:	VGFTe-HD-DME-1934
Clinical Phase:	2/3
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatisticians:	[redacted]
Project Biostatisticians:	[redacted]
Clinical Trial Manager:	[redacted]
Study Medical Director:	[redacted]
Version/Date:	Original (Version 1.0) / 05 JUL 2022 Amendment Version 2.0 / 19 AUG 2022

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

2q8	2 mg aflibercept every 8 weeks
AAS	ADA analysis set
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APTC	Anti-Platelet Trialists' Collaboration
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BCVA	Best corrected visual acuity
BMI	Body mass index
BP	Blood pressure
BRVO	Branch retinal vein occlusion
BUN	Blood urea nitrogen
CI	Confidence interval
CMH	Cochran Mantel Haenszel
CPK	Creatine phosphokinase
CRF	Case report form
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
CSME	Clinically Significant Macular Edema
DME	Diabetic macular edema
DPKS	Dense PK analysis set
DR	Diabetic retinopathy
DRM	Dose Regimen Modification
DRSS	Diabetic Retinopathy Severity Scale
ECG	Electrocardiogram
EMA	European Medicines Agency
EP-SAP	Statistical analysis plan for EMA and PMDA
EOS	End of study
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FAS	Full analysis set
G-SAP	Global statistical analysis plan

HbA1c	Hemoglobin A1c
HD	High-dose
HDq12	High-dose aflibercept every 12 weeks
HDq16	High-dose aflibercept every 16 weeks
HDL	High-density lipoprotein
ICF	Informed consent form
ICE	Intercurrent event
ICH	International Council for Harmonisation
IOP	Intraocular pressure
IRF	Intraretinal fluid
IVT	Intravitreal
IWRS	Interactive web response system
LOCF	Last observation carry forward
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LS	Least square
MAR	Missing at random
MI	Multiple imputation
MCMC	Markov Chain Monte Carlo
mCNV	Myopic choroidal neovascularization
MedDRA	Medical Dictionary for Regulatory Activities
(MedDRA) HLT	High Level Term
MMRM	Mixed-model repeated measures
NAb	Neutralizing antibody
NAbAS	NAb analysis set
nAMD	Neovascular “wet” age-related macular degeneration
NEI-VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
OC	Observed case
OCT	Optical coherence tomography
PCSV	Potentially clinically significant value
PK	Pharmacokinetic
PKAS	PK analysis set
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per protocol set
PT	Preferred term
RBC	Red blood cell

SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Standard deviation
SD-OCT	Spectral domain optical coherence tomography
SI	Standard international
SOC	System organ class
SRF	Subretinal fluid
TEAE	Treatment-emergent adverse event
UPCR	Urine protein:creatinine ratio
VA	Visual acuity
VEGF	Vascular endothelial growth factor
WBC	White blood cell
WHODD	World Health Organization Drug Dictionary

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for the phase 2/3 PHOTON, VGFTe-HD-DME-1934, study of high-dose (HD) aflibercept in patients with Diabetic Macular Edema (DME). This SAP is based on Protocol Amendment 4 dated April 28, 2022.

1.1. Background/Rationale

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

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. 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 40 mg/mL 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.

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 Phase 2/3 study (hereafter referred to as PHOTON) is designed as a randomized, double-masked, active-controlled non-inferiority study to evaluate the safety and efficacy of a HD aflibercept with the intent of extending the dosing interval, with at least similar functional and potentially improved anatomic outcomes compared to the active control arm of 2 mg aflibercept (EYLEA). The PHOTON study will investigate HD aflibercept dosed every 12 weeks (HDq12) or 16 weeks (HDq16) after 3 initial monthly injections vs. 2 mg aflibercept dosed every 8 weeks (2q8) after 5 initial monthly injections in patients diagnosed with DME.

1.2. Study Objectives

1.2.1. Primary Objectives

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

1.2.2. 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.

1.2.3. 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

1.2.4. Modifications from the Statistical Section in the Final Protocol

Additional secondary efficacy endpoints and their analyses are added to this SAP for submission to the US FDA (based on the G-SAP that constitutes the primary analysis for the study). See Appendix 10.9 for details.

1.2.5. Revision History for SAP Amendments

Version	Date	Version history
1.0	05 July 2022	Initial version
2.0	19 August 2022	Additional secondary efficacy variables and their analyses are added to the Appendix 10.9 of the SAP

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

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.

The study consists of a screening/baseline period, a treatment period, and an end of study (EOS) visit at week 96. A total of approximately 640 eligible patients will be randomized into 3 treatment groups in a 1:2:1 ratio as follows (Figure 1):

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).

Randomization of patients will be stratified based on

- baseline central retinal thickness (CRT) (<400 µm, ≥400 µm),
- prior DME treatment (yes, no), and
- geographical region (Japan, Rest of world).

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.

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 Appendix 10.2.2.

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 (see Schedule of Events in Appendix 10.2). 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 are described below.

Figure 1: Study Flow Diagram

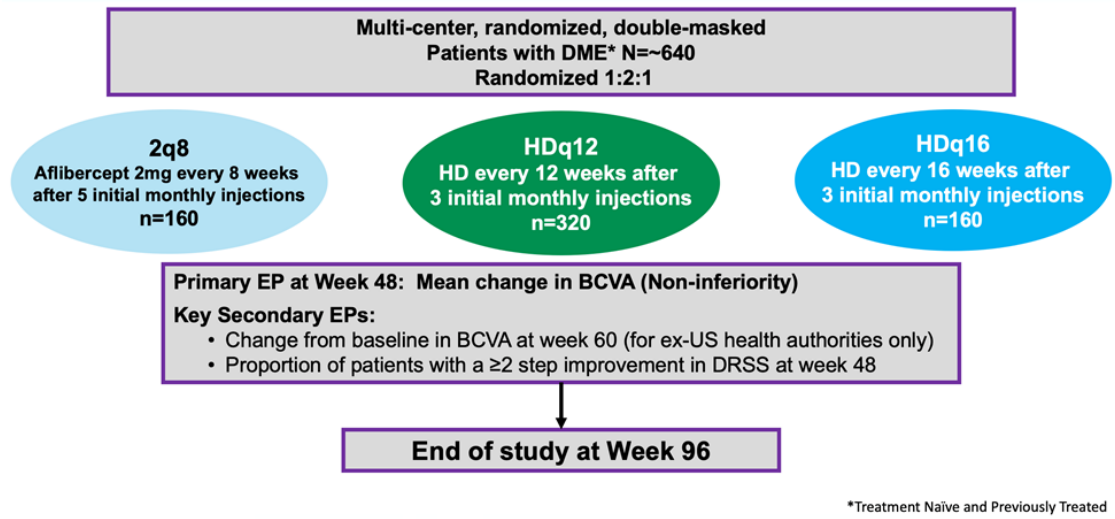
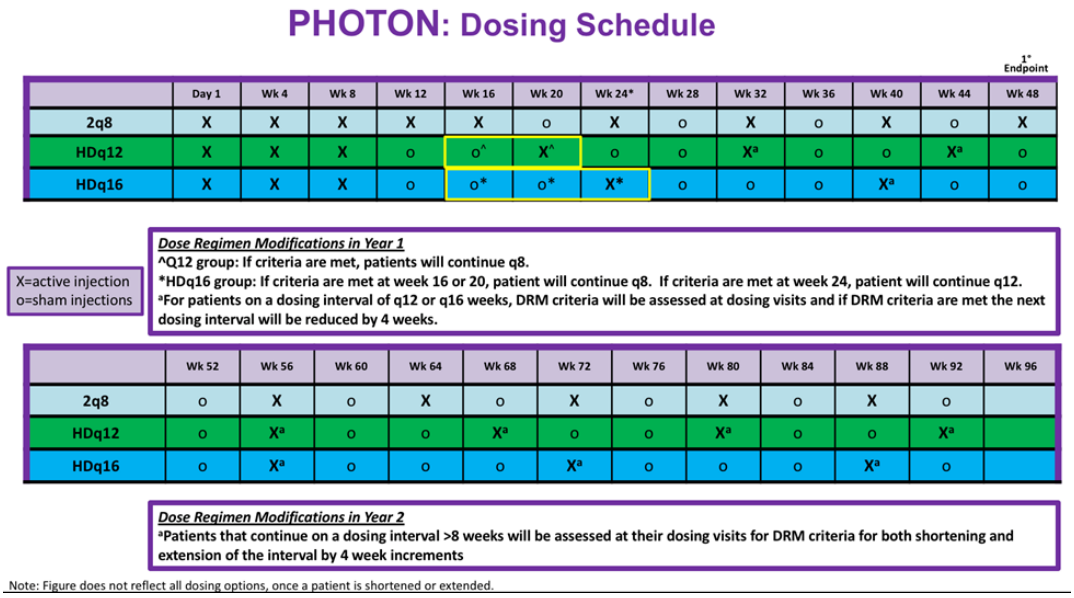


Figure 2: Dosing Schedule



Dose Regimen Modifications/Rescue Regimen

For masking purposes, assessments for dose regimen modifications (DRMs) will be performed in all patients at all visits (through the interactive web response system [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 Spectral domain optical coherence tomography (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.

2.2. Sample Size and Power Considerations

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 the comparison of HDq12 vs. 2q8, and subsequently 92% power for the comparison of HDq16 vs. 2q8, for the primary endpoint assessing non-inferiority, with a 1-sided t-test at significance level of 0.025.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998), the following population of analysis will be used for all statistical analysis:

3.1. The Full Analysis Set (FAS)

The full analysis set (FAS) includes all randomized patients who received at least 1 dose of study medication; it is based on the treatment assigned to the patient at baseline (as randomized). FAS is the primary analysis set for efficacy endpoints.

3.2. The Per Protocol Set (PPS)

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 did not have any relevant important protocol violations that affect the primary efficacy variable. The final determination on the exclusion of patients from the PPS will be made on the masked data prior to the first database lock and described in a separate document. The PPS will be used for supplementary analysis of change from baseline in BCVA (non-inferiority only) at week 48 (primary endpoint) and week 60 (key secondary endpoint).

Treatment assignment is based on the treatment received (as treated). In general, the randomized treatment group will be considered as the actual treatment group, unless the patient has not been treated at all after randomization. Isolated incorrect treatments will not constitute a change in the "as treated" assignment but will be considered as intercurrent events (refer to Section 5.6.1).

3.3. The Safety Analysis Set (SAF)

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.

3.4. Pharmacokinetic Analysis Sets

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

The dense PK analysis set (DPKS) includes all patients who did not meet any of the additional exclusion criteria for Dense PK substudy who consented to Dense PK sampling (enrolled in PK sub study), received any study treatment, and with at least 1 non-missing dense PK result post first dose. Patients will be analyzed based on actual treatment received.

3.5. Immunogenicity Analysis Sets

The ADA analysis set (AAS) includes all treated patients 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 Neutralizing antibody (NAb) assay.

The NAb analysis set (NAbAS) includes all treated patients that are included in the ADA analysis set and that tested negative at all ADA sampling times or tested positive at one or more post-dose ADA sampling times and had at least one non-missing post-dose NAb result (either imputed or analysis result). Samples that tested negative for ADA are not assayed in the NAb assay and the corresponding NAb result are imputed as negative and included as such in the NAb analysis set. Patients in the NAbAS with multiple post-dose ADA results which consist of both imputed NAb-negative result(s) for ADA negative samples and only missing NAb results for all ADA-positive result(s), are set to NAb negative. Patients in the NAbAS that have at least one post-dose positive NAb analysis result are set to NAb positive even if other NAb results are missing.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic variables and baseline assessments will be summarized:

- Age
- Age category (<55 years, ≥55 years to <65 years, ≥65 years to <75 years, ≥75 years)
- Sex (Female, Male)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Not Reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)
- Geographical region (Japan, Rest of World).
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m²)
- BMI category (≤30 kg/m², >30 to ≤35 kg/m², >35 kg/m²)
- Smoking history (Yes, No)
- Hemoglobin A1c (HbA1c)
- HbA1c category (≤8%, >8%)
- Vital Signs (heart rate, blood pressure [BP] [systolic and diastolic], and temperature)
- Intraocular pressure (IOP) in the study eye
- Medical history: renal impairment (Normal, Mild, Moderate, Severe), hepatic impairment (Yes, No), hypertension (Yes, No), cerebrovascular disease (Yes, No), ischaemic heart disease (Yes, No). Detailed definitions are presented in Appendix 10.4.
- Duration of diabetes (years): defined as time from diagnosis (based on medical history data (MedDRA High Level Term (HLT) “diabetes mellitus”) to randomization
- Diabetes type (Type 1, Type 2)
- Diabetic Retinopathy Severity Scale (DRSS) in the study eye
- BCVA (measured by Early Treatment Diabetic Retinopathy Study [ETDRS] letters) in the study eye
- BCVA category (≤73 letters, >73 letters)
- CRT in the study eye
- Categorized CRT (<400 µm, ≥400 µm)

- National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) total score
- Prior DME treatment in the study eye (Yes, No)
- Presence of Clinically Significant Macular Edema (CSME)

4.2. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA®).

4.3. Pre-Treatment / Concomitant Medication

Medications taken during the study will be recorded and will be coded using the World Health Organization Drug Dictionary (WHODD).

Medications will be summarized as follows:

- **Prior medication** is defined as medication that was started before a patient received first study treatment regardless of when it was stopped.
- **Concomitant medication** is defined as medication that was ongoing at, or began after, the start of study treatment

4.4. Exposure, Compliance, Additional Treatment to Study Treatment

Exposure

For each patient, the following variables will be used to examine exposure to study treatment for the study eye:

- Total number of active injections through weeks 48, 60, and 96
- Total number of sham injections through weeks 48, 60, and 96
- Duration of treatment calculated (Weeks) as: [(last study treatment [active or sham] date) - (first study treatment [active or sham] date) + 28]/7 (28 days are added because of the minimum 4-week dosing interval in the study)
- Proportion of patients in HDq16 group maintaining q16 dosing interval or longer through weeks 48, 60, and 96
- Proportion of patients in HDq12 and HDq16 groups maintaining q12 dosing interval or longer through weeks 48, 60, and 96
- Proportion of patients in HDq12 and HDq16 groups with q12 or q16 or longer dosing interval as the last intended dosing interval at week 48, week 60, and week 96
- Proportion of patients in HDq12 and HDq16 groups shortening dosing interval to q8 at week 16 or week 20
- Proportion of HDq12 and HDq16 patients with a shortened dosing interval anytime through weeks 48, 60 and 96

The following variables will be used to evaluate the fellow eye treatment

- Total number of aflibercept injections
- Duration of fellow eye treatment calculated (Weeks) as: [(last fellow eye treatment date) - (first fellow eye treatment date) + 28]/7 (28 days are added because of the minimum 4-week dosing interval in the fellow eye in the study)

Compliance

Compliance with protocol-defined study treatments (active and sham) from baseline through the following time points will be assessed per patient: 48 weeks, 60 weeks and 96 weeks will be calculated as follows:

Treatment Compliance = (Number of received injections [sham or active] through a given time period)/(Number of planned injections [sham or active] during period of participation in the study through the given time period) x 100%

For the calculation of compliance all injections (regardless if they were sham or active) will be used.

4.5. Efficacy Variable

4.5.1. Primary Efficacy Variable (s)

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

4.5.2. Key Secondary Efficacy Variable(s)

The key secondary efficacy endpoints are:

- Proportion of patients with a ≥2 step improvement in 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 5.6)

4.5.3. Additional Secondary Efficacy Variable(s)

The additional secondary efficacy endpoints are:

Proportion of patients gaining ≥ 15 letters in BCVA from baseline 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 CRT at week 48
- Proportion of patients without leakage on fluorescein angiography (FA) at week 48
- Change from baseline in NEI-VFQ-25 total score at week 48 (scoring details can be found in Appendix 10.3)

4.5.4. Exploratory Efficacy Variable(s)

The exploratory efficacy endpoints will include the following:

- Change from baseline in BCVA at week 96
- Proportion of patients gaining ≥ 15 letters in BCVA from baseline at week 60 and 96
- Proportion of patients with BCVA ≥ 69 letters at week 60 and 96
- Change from baseline in CRT at week 60 and 96
- Proportion of patients without leakage on FA at week 60 and 96
- Change from baseline in NEI-VFQ-25 total score at week 60 and 96
- Proportion of patients without retinal fluid (total fluid, intraretinal fluid [IRF], subretinal fluid [SRF]) at the foveal center and in center subfield at week 48, week 60, and week 96
- Time to fluid-free retina over 48 weeks, 60 weeks, and 96 weeks (total fluid, IRF, SRF at foveal center and in the center subfield)
- Proportion of patients with sustained fluid-free retina (defined as the absence of fluid for at least 2 consecutive visits and for all subsequent study visits) over 48 weeks, 60 weeks, and 96 weeks (total fluid, IRF, SRF at foveal center and in the center subfield)

  Sustained fluid-free retina is defined as the absence of fluid for at least 2 consecutive visits and for all subsequent study visits. The first 2 consecutive visits cannot have missing assessment between these two consecutive visits. After the 2 consecutive visits, the missing assessments at subsequent visits can be ignored or treated them as dry when determined sustained fluid free retina.
- Time to sustained fluid-free retina over 48 weeks, 60 weeks, and 96 weeks (total fluid, IRF, SRF at foveal center and in the center subfield)
- Proportion of patients without CSME at week 48, week 60, and week 96
- Proportion of patients with a ≥ 3 step improvement in DRSS at week 48, week 60, and week 96
- Change from baseline in BCVA averaged over the period from Week 36 to Week 48
- Change from baseline in BCVA average over the period from Week 48 to Week 60
- Proportions of patients gaining and losing ≥ 5 or ≥ 10 letters at week 48, week 60, and week 96
- Proportion of patients losing ≥ 15 letters at week 48, week 60, 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 (Week 96)

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events

An adverse event (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.

All AEs are to be coded according to MedDRA.

A Serious Adverse Event (SAE) is an AE that is classified as serious according to the criteria.

Other variables for AE description and analysis will include AE Verbatim Term, AE start date and end date/ongoing and corresponding study day, AE duration, relationship of AE to study drug, relationship of AE to 2 mg aflibercept in the fellow eye, relationship of AE to injection procedure, relationship of AE to study conduct, seriousness, severity, action due to AE, treatment of AE and outcome.

4.6.2. Laboratory Safety Variables

The clinical laboratory data consists of serum chemistry, hematology, urinalysis and HbA1c.

Clinical laboratory values will be converted to standard international (SI) units and grouped by function in summary tables. Functions are defined as follows:

- Blood chemistry panel: Sodium, Potassium, Chloride, Carbon dioxide, Calcium, Glucose, Albumin, Total Protein (serum), Creatine, Blood urea nitrogen (BUN), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase, Lactate dehydrogenase (LDH), Total bilirubin, Total cholesterol (Low-density lipoprotein [LDL] + high-density lipoprotein [HDL]), Triglycerides, Uric acid, Creatine phosphokinase (CPK)
- Hematology panel: Hemoglobin, Hematocrit, Red blood cells (RBCs), White blood cells (WBCs), Red Cell Indices, Platelet count and Differential count (Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils)
- Urinalysis: Color, Clarity, pH, Specific gravity, Ketones, Protein, Urine protein:creatinine ratio (UPCR), Glucose, Blood, Bilirubin, Leukocyte esterase, Nitrite, WBC, RBC, Hyaline and other casts, Bacteria, Epithelial cells, Crystals, Yeast
- HbA1c

4.6.3. Vital Signs

Variables of analysis for vital signs include temperature, BP (systolic and diastolic) and heart rate.

4.6.4. 12-Lead Electrocardiography (ECG)

Variables of 12-Lead Electrocardiogram (ECG) include PR interval, QRS interval, RR interval, QT interval, QTc with Fridericia corrections, and heart rate.

4.6.5. Other Ocular Safety Variables

Other ocular safety variables include intraocular pressure pre-dose in the study eye and fellow eye and post-dose in the study eye.

4.6.6. Surgeries

All the surgeries after informed consent are collected on the case report form (CRF) and are coded by MedDRA. Treatment emergent surgery is defined as surgery performed during the on-treatment period (see Section 5.7.1).

4.7. Pharmacokinetic Variables

The PK variables are the concentrations of free, bound, adjusted bound, and total aflibercept in plasma at each time point. Plasma samples for drug concentration will be collected at the clinic visits specified in the protocol schedule of events.

4.8. Immunogenicity Variables (ADA)

The immunogenicity variables include ADA status, NAb status and titer at nominal sampling time/visit. Serum samples for ADA will be collected at the clinic visits specified in Appendix 10.2.

5. STATISTICAL METHODS

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

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

5.1. Demographics and Baseline Characteristics

Demographic data and baseline characteristics variables will be summarized, by treatment group and overall, using descriptive statistics for FAS, SAF, and PPS. Disease characteristics of the study eye will be presented in a separate table.

5.2. Medical History

Medical history will be descriptively summarized, by treatment group and overall, for SAF. Summaries will show number and percentage of patients by primary system organ class (SOC) and preferred term (PT). The tables will be sorted by decreasing frequency of primary SOC. Within each primary SOC, PTs will be sorted by decreasing frequency in the total group. It will be summarized separately by ocular medical history in the study eye, ocular medical history in the fellow eye, and non-ocular medical history.

5.3. Prior/concomitant Medications

All prior/concomitant medications, dictionary coded by WHODD, will be descriptively summarized by treatment group for SAF. Summaries will present number and percentage of patients for the medication groups described in Section 4.3 for all medications, by decreasing frequency of Anatomical Therapeutic Chemical (ATC) level 1 followed by ATC level 2 in the total group. In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

Concomitant medications will be summarized by the following periods:

- Day 1 up to week 48
- Day 1 up to week 60
- Day 1 up to End of study (week 96)

When medication start/end date is missing, the rules for determining whether a medication is prior, concomitant, or post-treatment, are specified in Section 6.5.

5.4. Patient Disposition

The disposition of patients in the study will be summarized by treatment group and overall. Percentages will be calculated using the number of randomized patients as the denominator. The following summaries will be provided:

- The total number of screened patients who have signed the ICF, the number of screen failure and the reasons for screen failure.
- The total number of randomized patients who received a randomization number

- The total number of patients in each analysis set
- The total number of patients who prematurely discontinued the study, and the reasons for discontinuation, and who completed the Week 48, Week 60, and Week 96 visits

5.5. Extent of Study Treatment Exposure and Compliance

The variables for dose exposure and compliance described in Section 4.4 will be summarized for the SAF, FAS, and PPS populations, using descriptive statistics by the following time periods:

- Day 1 to week 48 (excluding treatment at week 48)
- Day 1 to week 60 (excluding treatment at week 60)
- Day 1 to End of study (week 96)

5.6. Analyses of Efficacy Variables

Due to differing requirements for the submission to regulatory authorities, 2 different analysis strategies will be applied, which will be detailed in this SAP document: a global statistical analysis plan (G-SAP), and a plan that specifically addresses requirements from EMA and PMDA (EP-SAP). 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.

All efficacy analyses will be conducted using the FAS population. In addition, the change from baseline in BCVA at week 48 and week 60 will be analyzed using the PPS population as supplementary analyses.

5.6.1. Analysis of Primary Efficacy Variable

The primary analysis is based on the estimand concept. The estimand of primary interest will be based mainly 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. All efficacy analyses will be conducted using the FAS.
- Variable: Change from baseline to week 48 in BCVA
- Treatment condition: Intention to treat with HD aflibercept administered every 12 weeks (HDq12) after 3 initial monthly injections or every 16 weeks (HDq16) after 3 initial monthly injections each versus aflibercept 2 mg administered every 8 weeks (2q8) after 5 initial monthly injections; dose regimen modifications as detailed in Section 2.1 do not affect patient's assigned ITT regimen.
- Intercurrent events: Premature discontinuation from treatment; missed injections; use of prohibited medication; wrong study intervention administered, as displayed in Table 1.

- Population-level summary: Difference in least-square (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).

Table 1: Strategies for occurrence of intercurrent events (ICE)

Potential post-randomization event	Intercurrent event (yes/no)	Estimand strategy	Analysis strategy
Premature discontinuation of study intervention before Week 48			
- Discontinuation of study at the same time	Yes	Hypothetical	Non-observed data beyond discontinuation will be covered implicitly in the MMRM
- Continuation of study beyond discontinuation of study intervention^	Yes	Hypothetical	Observed data beyond last active injection prior to discontinuation + current treatment interval + 5 days will be excluded from analysis. Missing and excluded data will be covered by the MMRM.
Missed injection for any reason before Week 48			
- Planned to be sham	Yes, but no impact	N/A	All observed data will be included in the analysis
- Planned to be active, make-up given at next visit	Yes	Treatment policy	All observed data will be included in the analysis
- Planned to be active, make-up or scheduled active injection not given at next visit	Yes	Hypothetical	Observed data beyond last active injection prior to the missed dose + current treatment interval + 5 days will be excluded from analysis. Missing and excluded data will be covered by the MMRM.
Shortening of dosing interval according to DRM criteria before Week 48	No, DRM is considered part of the treatment regimen	N/A	

Use of a prohibited medication after the first dose of study medication (	Yes	Hypothetical	Observed data beyond first administration of prohibited medicine will be excluded from analysis. Missing and excluded data will be covered by the MMRM.
Wrong study intervention before Week 48			
- Active injection given instead of sham	Yes	Treatment policy	All observed data will be included in the analysis
- Sham injection instead of active	Yes	Hypothetical	Observed data beyond last active injection prior to the wrong dose + current treatment interval + 5 days will be excluded from analysis. Missing and excluded data will be covered by the MMRM.
- Wrong dose level given (eg, 2mg given instead of 8mg)	Yes	Treatment policy	All observed data will be included in the analysis

^ This ICE will be handled in the same way as "Missed injection: Planned to be active, make-up or scheduled active injection not given at next visit, since the info of discontinuation from study intervention was not collected in the database.

The following 2 hypotheses will be tested in the primary analysis:

- HDq12 is non-inferior to 2q8 regarding the mean change in BCVA from baseline to week 48 using a non-inferiority margin of 4 letters:
  H_{10}: $\mu_1 \leq \mu_0 - 4$ vs. H_{11}: $\mu_1 > \mu_0 - 4$,
  where μ_0, μ_1, are the mean change from baseline in BCVA at week 48 for 2q8 and HDq12, respectively.
- HDq16 is non-inferior to 2q8 regarding the mean change in BCVA from baseline to week 48 using a non-inferiority margin of 4 letters:
  H_{30}: $\mu_2 \leq \mu_0 - 4$ vs. H_{31}: $\mu_2 > \mu_0 - 4$,
  where μ_0, μ_2 are the mean change from baseline in BCVA at week 48 for 2q8, and HDq16, respectively.

5.6.1.1. Primary Analysis for Primary Efficacy Variable

For the analysis of the primary efficacy variable, a mixed model for repeated measurements (MMRM) will be used with baseline BCVA measurement as a covariate and treatment group (HDq16 vs. 2q8 and HDq12 vs. 2q8) and baseline CRT category (<400 μm, ≥400 μm), prior

DME treatment (yes, no), geographical region (Rest of world, Japan), and visit as fixed effects as well as terms for the interaction between baseline BCVA and visit and for the interaction between treatment and visit. A Kenward-Roger approximation will be used for the denominator degrees of freedom. Further, an unstructured covariance structure will be used. If the model does not converge, an appropriate covariance structure will be used instead. Only data up to Week 48 will be used in this analysis.

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

where:

Y_{ijk} is the change from baseline BCVA 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,

$\beta_{treat}^{(k)}$ is the fixed effect of treatment group k

$\beta_{base\_CRT}^{(n)}$ is the fixed effect of categorized baseline CRT n,

$\beta_{pDME}^{(l)}$ is the fixed effect of prior DME treatment l,

$\beta_{reg}^{(m)}$ is the fixed effect of region m,

$\beta_{visit}^{(j)}$ is the fixed effect of visit j,

$\beta_{base*visit}^{(j)}$ the interaction between baseline BCVA and visit j,

$\beta_{treat*visit}^{(k,j)}$ the interaction between treatment k and visit j,

ϵ_{ijk} is the residual error with $\epsilon_{ijk} \sim N(0, \sigma^2)$ and $corr(\epsilon_{ijk,}\, \epsilon_{ij'k,}) = \rho^{(k)}\_\{i, j'\}$, or 0 otherwise.

In terms of the estimators the population-level summary of the estimands (ie, the treatment effect at week 48) can then be expressed as

$$D_{HDQ12} = \left[\beta_{treat}^{(HDQ12)} + \beta_{treat*visit}^{(HDQ12,w48)}\right] - \left[\beta_{treat}^{(2Q8)} + \beta_{treat*visit}^{(2Q8,w48)}\right]$$

and

$$D_{HDQ16} = \left[\beta_{treat}^{(HDQ16)} + \beta_{treat*visit}^{(HDQ16,w48)}\right] - \left[\beta_{treat}^{(2Q8)} + \beta_{treat*visit}^{(2Q8,w48)}\right].$$

Summary tables will include number of patients, LS mean change, (unadjusted) mean change and standard deviation (SD) and baseline means of each treatment group. For non-inferiority testing, the population level estimates comparing HDq16 vs. 2q8 (D_{HDQ16}) and HDq12 vs. 2q8 (D_{HDQ12}), expressed as LS mean change, the test statistics, the degrees of freedom, and

corresponding p-values will be presented. Two-sided 95% confidence intervals will also be provided.

In line with the definition of estimands (see above), the primary analysis will be performed on the FAS and patients will be analyzed within their original randomized group (regardless of any changes to dose interval). The MMRM assumes missing at random (MAR) for patients who discontinue the study prematurely, ie, missingness only depends on observed data.

The following superiority testings will be performed as described in Section 5.6.4 for G-SAP strategy and EP-SAP strategy.

- HDq12 is superior to 2q8 regarding the mean change in BCVA from baseline to week 48:
  H_{70}: $\mu_1 \leq \mu_0$ vs. H_{71}: $\mu_1 > \mu_0$,
  where μ_0, μ_1, are the mean change from baseline in BCVA at week 48 for 2q8 and HDq12, respectively.
- HDq16 is superior to 2q8 regarding the mean change in BCVA from baseline to week 48:
  H_{90}: $\mu_2 \leq \mu_0$ vs. H_{91}: $\mu_2 > \mu_0$,
  where μ_0, μ_2 are the mean change from baseline in BCVA at week 48 for 2q8, and HDq16, respectively.

An example of Statistical Analysis System (SAS) code for MMRM is presented in Appendix 10.8

5.6.1.2. Sensitivity Analyses for Primary Efficacy Variable

Last observation carried forward (LOCF) will be conducted for patients who had at least one post-baseline value but discontinued prematurely or had an ICE as defined in Table 1 before week 48 and ANCOVA will be applied for the change from baseline in BCVA at week 48. Another approach assuming MAR will be implemented by using multiple imputation (MI). In addition, the tipping point analysis will be performed as a sensitivity analysis if the MI analysis results under MAR assumption show non-inferiority of the high dose groups compared to the low dose group.

5.6.1.2.1. ANCOVA using LOCF

For this sensitivity analysis of the primary efficacy variable, an analysis of covariance (ANCOVA) will be used with baseline BCVA measurement as a covariate and treatment group (HDq16 vs. 2q8 and HDq12 vs. 2q8) and the stratification variables (baseline CRT category [<400 µm, ≥400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]) as fixed factors. A separate variance term will be estimated for the three treatment groups.

The observation at week 48 of patient i receiving treatment t can be written as follows:

$$Y_{itrb} = \mu_t + \gamma_r + \eta_c + \pi_p + x_i\beta + \epsilon_{itrb}$$

where

Y_{itrb} is the change from baseline to week 48 for the ith patient,

μ_t is the treatment effect,

γ_r is the geographic region effect (Rest of world, Japan),

η_c is the categorized baseline CRT (<400 µm, ≥400 µm),

π_p is the prior DME treatment (yes, no)

x_i is the baseline BCVA of patient i,

ϵ_{itrb} is the residual error with $\epsilon_{itrb} \sim N(0, \sigma_t^2)$ for treatment arm t.

For this analysis missing week 48 BCVA data will be imputed by using LOCF. That means that the last non-missing post-baseline BCVA measurement prior to an ICE will be carried forward to week 48.

Summary tables will include number of patients, LS mean change, (unadjusted) mean change and SD and baseline means of each treatment group. For non-inferiority testing the one-sided α of 0.025 for the population level estimates comparing HDq16 vs. 2q8 and HDq12 vs. 2q8, the estimates expressed as LS mean change including the one-sided confidence intervals (CIs) for α of 0.025, the test statistics, the degrees of freedom and corresponding p-values will be presented.

This sensitivity analysis will be analyzed for the FAS.

An example of SAS code for ANCOVA is presented in Appendix 10.8.

5.6.1.2.2. ANCOVA with Multiple Imputation

The primary efficacy variable at week 48 will be analyzed using MI with ANCOVA model based on the FAS. Data after occurrence of an ICE as defined in Table 1 will be excluded. MI methods involve three steps.

I. Imputation

Missing data up to week 48 will be imputed 50 times to generate 50 complete data sets by using the SAS procedure MI following the 2 steps below:

Step 1: The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure using seed number 01934.

Step 2: The missing data at subsequent visits will be imputed using the regression method for the monotone pattern with seed number 01934 and adjustment for covariates including treatment groups, baseline CRT category (<400 µm, ≥400 µm), prior DME treatment (yes, no), geographical region (Rest of world, Japan), baseline BCVA and all BCVA values at preceding visits.

If the imputed data is outside the range of 0 to 100 in either step of imputation, truncation will be applied to the imputed data.

II. Analysis

The week 48 data of each of the 50 complete datasets will be analyzed using an ANCOVA model as specified in Section 5.6.2.2.1.

III. Pooling

The SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 50 analyses using Rubin's formula (Rubin, 1987).

An example of SAS code for MI is presented in Appendix 10.8.

5.6.1.2.2.1. Tipping Point Analysis

In order to check the assumption that the missing data are not MAR, a tipping point analysis will be conducted based on the multiple imputation analysis in Section 5.6.1.2.2. The objective of the tipping point analyses is to identify assumptions about the missing data under which the conclusions from the main analysis change, ie, under which non-inferiority cannot be shown anymore. These tipping point analyses will only be performed if the multiple imputation analysis results show non-inferiority of the high dose groups compared to the low dose group. In case the non-inferiority is shown, additional tipping point analyses will be repeated after reducing the imputed BCVA values in the high dose arms by ascending natural number of letters (1, 2, 3… etc.), with the goal to find for each high dose treatment group the "tipping point" that will significantly reverse the analysis result. The smallest delta, for which non-inferiority cannot be shown anymore, will be the "tipping point".

For each value of delta, summary tables will include number of patients, LS mean change, (unadjusted) mean change and SD and baseline means of each treatment group as well as the estimates expressed as LS mean change including the two-sided CIs, the test statistics, the degrees of freedom and corresponding p-values.

An example of SAS code for tipping point analysis is presented in Appendix 10.8.

5.6.1.3. Supplementary Analyses for Primary Efficacy Variable

The primary analysis described in Section 5.6.1.1 will be repeated using the PPS.

5.6.1.4. Subgroup Analyses for Primary Efficacy Variable

Analyses will be performed in the following subgroups:

- Sex: male, female
- Age at enrollment: <55 years, ≥55 years to <65 years, ≥65 years to < 75 years, ≥75 years
- Race (only subgroups with sufficient sample size): White, Black or African American, Asian
- Ethnicity: Not Hispanic or Latino, Hispanic or Latino
- Baseline BCVA (≤73 letters, >73 letters)
- Geographic region: Japan, Rest of the world
- Baseline CRT category (<400 µm, ≥400 µm)
- Prior DME treatment (yes, no)

Subgroup analyses will be performed using the same model as in Section 5.6.1.1, except for those subgroups that are also stratification factors (geographic region, baseline CRT category,

and prior DME treatment), where these terms will be individually removed from the model (leaving the other 2 factors in).

5.6.2. Analysis of Key Secondary Efficacy Variables

5.6.2.1. Change from Baseline in BCVA Measured by the ETDRS Letter Score at Week 60

The following 2 non-inferiority hypotheses will be tested for this key secondary endpoint under the EP-SAP only:

- HDq12 is non-inferior to 2q8 regarding the mean change in BCVA from baseline to week 60 using a non-inferiority margin of 4 letters:
  H_{20}: $\mu_1 \leq \mu_0 - 4$ vs. H_{21}: $\mu_1 > \mu_0 - 4$,
  where μ_0, μ_1, are the mean change from baseline in BCVA at week 60 for 2q8 and HDq12, respectively.
- HDq16 is non-inferior to 2q8 regarding the mean change in BCVA from baseline to week 60 using a non-inferiority margin of 4 letters:
  H_{40}: $\mu_2 \leq \mu_0 - 4$ vs. H_{41}: $\mu_2 > \mu_0 - 4$,
  where μ_0, μ_2 are the mean change from baseline in BCVA at week 60 for 2q8, and HDq16, respectively.

The analysis of key secondary endpoints will be required for the submission to the EMA/PMDA regulatory authorities. The change from baseline in BCVA at week 60 will be analyzed with the same methods and main and sensitivity summaries as for the primary endpoint described in Section 5.6.1. Only data up to Week 60 will be used in this analysis.

The following superiority testings will also be performed as described in Section 5.6.4 (under the EP-SAP only) for this endpoint.

- HDq12 is superior to 2q8 regarding the mean change in BCVA from baseline to week 60:
  H_{80}: $\mu_1 \leq \mu_0$ vs. H_{81}: $\mu_1 > \mu_0$,
  where μ_0, μ_1, are the mean change from baseline in BCVA at week 48 for 2q8 and HDq12, respectively.
- HDq16 is superior to 2q8 regarding the mean change in BCVA from baseline to week 60:
  H_{100}: $\mu_2 \leq \mu_0$ vs. H_{101}: $\mu_2 > \mu_0$,
  where μ_0, μ_2 are the mean change from baseline in BCVA at week 48 for 2q8, and HDq16, respectively.

Subgroup analyses will be performed on those subgroups listed in Section 5.6.1.4 using the same model described above, except for those subgroups that are also stratification factors (geographic region, baseline CRT category, and prior DME treatment), where these terms will be individually removed from the model (leaving the other 2 factors in).

5.6.2.2. Proportion of patients with a ≥2 step improvement in DRSS at week 48

The following 2 non-inferiority hypotheses will be tested for this key secondary variable on the FAS:

- HDq12 is non-inferior to 2q8 regarding the proportion of patients with a ≥2 step improvement in DRSS at week 48:
  H_{50}: $p_{HDq12} \leqslant p_{2Q8} - 0.15$ vs. H_{51}: $p_{HDq12} > p_{2Q8} - 0.15$,
  where p_{2Q8}, p_{HDq12}, are the proportion of patients with a ≥2 step improvement in DRSS at week 48 for 2q8, and HDq12, respectively.
- HDq16 is non-inferior to 2q8 regarding the proportion of patients with a ≥2 step improvement in DRSS at week 48:
  H_{60}: $p_{HDq16} \leqslant p_{2Q8} - 0.15$ vs. H_{61}: $p_{HDq16} > p_{2Q8} - 0.15$,
  where p_{2Q8}, p_{HDq16}, are the proportion of patients with a ≥2 step improvement in DRSS at week 48 for 2q8, and HDq16, respectively.

The non-inferiority margin is set at 15%. This endpoint will be analyzed by a Cochran-Mantel-Haenszel (CMH) test stratified by baseline CRT category (<400 µm, ≥400 µm), prior DME treatment (yes, no), geographical region (Rest of world, Japan). Missing or non-gradable post-baseline values will be imputed using LOCF procedure. Patients will be considered as non-responders if all post-baseline measurements are missing or non-gradable. Strategies for occurrence of intercurrent events will be similar to Table 1, except the excluded data will be implemented by LOCF procedure.

Additionally, a two-sided 95% Mantel-Haenszel confidence interval (Koch et al, 1990) for the difference of proportion adjusted for stratification factors (baseline CRT category [<400 µm, ≥400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]) will be calculated using normal approximation.

Subgroup analyses will be performed on those subgroups listed in Section 5.6.1.4 using the same model described above, except for those subgroups that are also stratification factors (geographic region, baseline CRT category, and prior DME treatment), where these terms will be individually removed from the model (leaving the other 2 factors in).

5.6.2.2.1. Sensitivity Analyses

The following sensitivity analysis will be performed for the proportion of patients with a ≥2 step improvement in DRSS at week 48 for the FAS:

The above analysis will be repeated but for observed cases (OC) only, ie, observed data prior to the occurrence of an ICE.

5.6.3. Analysis of Additional Secondary and Exploratory Efficacy Variables

All additional secondary and exploratory efficacy variables (see Section 4.5.3 and Section 4.5.4) will be analyzed descriptively at each scheduled visit from baseline to week 48, week 60, and week 96, as applicable. These descriptive analyses will include statistical tests (with nominal p-values) for the efficacy variables and two-sided 95% confidence intervals.

For these statistical tests, continuous variables will be analyzed by the same repeated measurement models as for the primary endpoint.

Binary endpoints will be analyzed by CMH methods adjusted by the stratification factors based on LOCF (ie, missing/non-gradable data will be imputed by the last valid data prior to ICE). The endpoint of proportion of patients with a ≥ 3 step improvement in DRSS will analyzed by the

same method as the proportion of patients with a ≥ 2 step improvement in DRSS as specified in Section 5.6.2.2. For the other binary endpoints, only valid data (excluding missing/non-gradable) will be included in the denominator when calculated the proportion. Sensitivity analysis will be performed by OC method (ie, observed data prior to an ICE).

Time-to-event variables will be analyzed using the Kaplan-Meier method. Time to event will be calculated as duration from date of randomization to the event for the first time whereas intercurrent events are handled according to Table 1. Patients without the event will be censored at their last assessment date. The analysis will be using the study visits (ie, multiples of 4 weeks) and not the calendar time as unit. Each of the HD groups will be compared with the 2q8 group using a stratified log-rank test. Hazard ratios will be calculated using a stratified Cox proportional hazards model, including treatment group as factor and baseline CRT category (<400 μm, ≥400 μm), prior DME treatment (yes, no), geographical region (Rest of world, Japan) as strata.

No multiplicity adjustments will be made for these efficacy analyses.

5.6.4. Adjustment for Multiple Comparisons

For the G-SAP strategy, statistical hypotheses of the primary endpoint (BCVA at week 48) and the key secondary endpoint (≥2 step improvement in DRSS at week 48) will be assessed together, after all patients completed week 48 (or discontinued prematurely) using the below described methods.

For the EP-SAP strategy, statistical hypotheses of the primary endpoint (BCVA at week 48) and the key secondary endpoints (BCVA at week 60, ≥2 step improvement in DRSS at week 48) will be assessed together, after all patients completed week 60 (or prematurely discontinued) using the below described methods.

The overall family-wise type 1 error will be controlled at 0.025 (one-sided tests) for testing the primary and key secondary endpoints. Adjustment for multiple comparisons in the primary and key secondary endpoints will be made with a hierarchical testing procedure. 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 hypotheses will be tested in the order as specified in Table 2 for G-SAP and EP-SAP, respectively.

Table 2: 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

5.7. Analysis of Safety Data

The safety variables as defined in Section 4.6 will be analyzed on the SAF for the periods from baseline/day 1 through week 48, week 60 and the end of study (week 96). The summary of safety results will be presented for each treatment group. Data will not be imputed for the safety analysis.

5.7.1. Adverse Events

Period of observation: The observation period will be divided into three segments:

- 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 the first dose of study drug to the last dose of study drug (active or sham) plus 30 days. In the week 48 (week 60) analysis, for patients who are still participating in the study (ie, have not been withdrawn), all AEs up through the date of that visit will be considered on-treatment.
- The post-treatment period is defined as after the end of the on-treatment period

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

TEAEs will further be summarized by the following categories:

- Ocular TEAEs in the study eye
- Ocular TEAEs in the fellow eye
- Non-ocular TEAEs

The following TEAE categories will also be summarized as described for TEAEs:

- Study drug related TEAEs
- Injection related TEAEs
- Study conduct related TEAEs
- 2mg aflibercept in the fellow eye related TEAEs
- TEAEs leading to discontinuation

- TEAEs by maximum severity
- TE SAEs
- Study drug related TE SAEs
- Injection related TE SAEs
- TE SAEs by maximum severity

Counts will be provided according to treatment group for each PT within each SOC. Percentages will be calculated using the number of patients from the SAF in each treatment group.

Primary SOCs will be sorted according to alphabetical order. Within each primary SOC, PTs will be sorted by alphabetical order as well. For tables presenting severity of events, the worst severity will be chosen for patients with multiple instances of the same event.

Treatment emergent APTC events (adjudicated), hypertension, intraocular inflammation, and nasal mucosal events will be tabulated. Detailed definitions for the latter 3 of these types of AEs are presented in Appendix 10.4. Please refer to APTC charter for more information for adjudication of APTC events.

The following study periods will be used for TEAE summaries:

- Day 1 to week 48
- Day 1 to week 60
- Day 1 to week 96

5.7.1.1. Subgroup Analyses

Subgroup analyses in TEAE reporting will be performed for the following subgroups:

- Sex: male, female
- Age at enrollment: <55 years, ≥55 years to <65 years, ≥65 years to < 75 years, ≥75 years
- Race (only subgroups with sufficient sample size): White, Black or African American, Asian
- Ethnicity: Not Hispanic or Latino, Hispanic or Latino
- Geographic region: Japan, Rest of the world
- Medical history of renal impairment
- Medical history of hepatic impairment
- Medical history of hypertension
- Medical history of cerebrovascular disease
- Medical history of ischaemic heart disease

The medical history subgroups are defined in more detail in Appendix 10.4.

Summaries (by SOC and PT) of patients with each of the following types of TEAE will be provided for the above subgroups:

- Ocular TEAEs in the study eye
- Non-ocular TEAEs
- Serious ocular TEAEs in the study eye
- Serious non-ocular TEAEs

5.7.2. Clinical Laboratory Measurements

Baseline clinical laboratory analytes and change from Baseline in clinical laboratory analytes to each scheduled assessment time will be summarized with descriptive statistics.

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 normal range values.

Treatment-emergent high abnormalities are laboratory values that were normal or low at Baseline but high after treatment with study drug. Treatment-emergent high abnormalities will be summarized using SAF for patients who were normal or low at Baseline.

Treatment-emergent low abnormalities are laboratory values that were normal or high at Baseline but low after treatment with study drug. Treatment-emergent low abnormalities will be summarized using SAF for patients who were normal or high at Baseline.

A treatment-emergent potentially clinically significant value (PCSV) is a laboratory value that was normal at Baseline but met PCSV criteria after treatment with study drug. Definitions of PCSVs are listed in Appendix 10.5. Treatment Emergent PCSVs will be summarized using SAF for patients who did not meet the PCSV criterion at baseline.

5.7.3. Analysis of Vital Signs

The assessments of vital signs (heart rate, systolic/diastolic BP, and temperature) and their changes from Baseline will be summarized by visit. The Baseline for BP is defined as the average of all valid measurements taken prior to administration of study drug. The Baseline for other vital signs endpoints will be the latest available valid measurement taken prior to the administration of study drug, as specified in 6.1.

Treatment Emergent PCSV for systolic/diastolic blood pressure will be summarized based on the using SAF and in the SAF for patients who do did not meet the PCSV criterion at baseline. Definition of PCSVs for blood pressure are listed in Appendix 10.5.

5.7.4. Analysis of 12-Lead ECG

The assessments of ECG parameters (P-R interval, QT interval, QTc interval, QRS interval, Ventricular rate and Heart rate) and their changes from Baseline will be summarized by visit.

ECG status (ie, normal, abnormal) will be reported. Shift tables may be provided to present the post-baseline status according to the baseline status (normal or missing / abnormal) by treatment group.

5.7.5. Analysis of Other Ocular Safety Variables

Pre-dose IOP measurements and their changes from baseline will be summarized by visit using descriptive statistics for the study eye and the fellow eye, respectively. Post-dose IOP measurements and their changes from pre-dose will be summarized for study eye. The proportion of patients who meet the following criteria will be summarized descriptively:

- ≥ 10 mmHg increase in IOP measurement from baseline to pre-dose measurement in the study eye (by visit and at any time)
- ≥ 10 mmHg increase in IOP measurement from baseline to pre-dose measurement in the fellow eye (by visit and at any time)
- > 21 mmHg for any pre-dose measurement in the study eye (by visit and at any time)
- > 21 mmHg for any pre-dose measurement in the fellow eye (by visit and at any time)
- ≥ 25 mmHg for any pre-dose measurement in the study eye (by visit and at any time)
- ≥ 25 mmHg for any pre-dose measurement in the fellow eye (by visit and at any time)
- ≥ 35 mmHg at any time (pre- or post-dose) in the study eye (by visit and at any time)
- ≥ 35 mmHg at any time (pre- or post-dose) in the fellow eye (by visit and at any time)

5.7.6. Surgeries

Treatment emergent surgeries will be summarized by the following categories:

- Ocular treatment emergent surgeries in the study eye
- Ocular treatment emergent surgeries in the fellow eye
- Non-ocular treatment emergent surgeries

5.8. Analysis of Pharmacokinetic Data

5.8.1. 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.

5.8.2. Pharmacokinetics/Pharmacodynamics Analyses

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

5.9. Analysis of Immunogenicity Data

The immunogenicity variables described in Section 4.8 will be summarized using descriptive statistics. Immunogenicity will be characterized per drug molecule by ADA status, ADA category and maximum titer observed in patients in the ADA analysis sets.

The ADA status of each patient may be classified as one of the following:

- Positive
- Pre-existing - If the baseline sample is positive and all post baseline ADA titers are reported as less than 4-fold the baseline titer value
- Negative - If all samples are found to be negative in the ADA assay.

The ADA category of each positive patient is classified as:

Treatment-boosted - A positive result at baseline in the ADA assay with at least one post baseline titer result ≥4-fold the baseline titer value

Treatment-emergent - A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay. Patients that are treatment-emergent will be further categorized as follows:

Persistent - A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a 16-week post baseline period [based on nominal sampling time], with no ADA-negative results in-between, regardless of any missing samples

Transient - Not persistent or indeterminate, regardless of any missing samples

Indeterminate - A positive result in the ADA assay at the last collection time point only, regardless of any missing samples

The maximum titer category of each patient is classified as:

Low (titer <1,000)

Moderate (1,000 ≤ titer ≤ 10,000)

High (titer >10,000)

The following will be summarized by treatment group and ADA titer level:

Number (n) and percent (%) of ADA-negative patients

Number (n) and percent (%) of pre-existing patients

Number (n) and percent (%) of treatment-emergent ADA positive patients

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline

Unless otherwise specified, the Baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of study drug.

6.2. Visit Windows

The visits used for the analysis will be based on the nominal visits, ie, according to the case report form (CRF) assessment recorded by the investigator. No visit windows will be further defined.

6.3. Unscheduled Assessments

Unscheduled assessments will not be included in the summaries unless specified.

If more than one value is available for a given visit, the visit value actually used for statistical summaries and analyses will be as follows:

- The last non-missing repeated measurement, if respective visit is before start of treatment
- The first non-missing repeated measurement, if respective visit is after start of treatment

If an early termination visit is performed within the protocol-defined window of the next scheduled visit after the last previous visit, the visit-dependent assessments will be re-slotted to the next scheduled visit.

6.4. Handling of Patients who Discontinue

Patients who discontinue this study will not be replaced. The details for the handling of missing data due to patients who discontinue the study and study medication are described in Section 6.5.

6.5. Data Handling Convention for Missing Data

For the primary and secondary efficacy variables, missing observations will be dealt with as described in the efficacy analysis (Section 5.6) based on the analysis being performed.

Pretreatment/concomitant medication

For the tabulation of prior and concomitant medication, partially missing start dates of the medication will be imputed by the earliest possible time point, partially missing stop dates will be imputed by the latest possible time point.

Adverse event

It is important to determine whether AEs started during the on-treatment period. AEs with partial start dates will be imputed based on the following rules:

1. If AE partial start date indicates it is before the first dose of study drug, then it will be imputed as the latest possible date

2. If AE partial start date has the same partial date as the first dose of study drug, then it will be imputed as the date of the first dose of study drug
3. If AE partial start date indicates it is after the first dose of study drug, then it will be imputed as the earliest possible date.
4. If imputed AE start date is later than AE end date, then impute the AE start date to AE end date.

7. INTERIM ANALYSIS

No formal interim analyses will be performed. 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.

8. SOFTWARE

All analyses will be done using SAS Version 9.4 (or higher) or R version 3.5.1 (or higher).

9. REFERENCES

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10. APPENDIX

10.1. Summary of Statistical Analyses

Efficacy Analysis:

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint						
Change from baseline in BCVA at Week 48	FAS, PPS	Non-inferiority of HDq12 vs 2q8 and non-inferiority of HDq16 vs 2q8 in FAS	MMRM	LOCF ANCOVA: MI with ANCOVA, tipping point analysis	Yes, for subgroups sex, age, race, ethnicity, geographic region, baseline BCVA category, baseline CRT category, prior DME treatment	Superiority of HDq12 vs 2q8 and superiority of HDq16 vs 2q8
Secondary Endpoints						
Change from baseline in BCVA at Week 60	FAS, PPS	Non-inferiority of HDq12 vs 2q8 and non-inferiority of HDq16 vs 2q8 in FAS	MMRM	Non-inferiority in PPS; LOCF ANCOVA: MI with ANCOVA	Yes, for subgroups sex, age, race, ethnicity, geographic region, baseline BCVA category, baseline CRT category, prior DME treatment	Superiority of HDq12 vs 2q8 and superiority of HDq16 vs 2q8
Proportion of patients with a ≥2 step improvement in DRSS at week 48	FAS	Non-inferiority of HDq12 vs 2q8 and non-inferiority of HDq16 vs 2q8 in FAS	CMH test with LOCF	OC	Yes, for subgroups sex, age, race, ethnicity, geographic region, baseline BCVA category, baseline CRT category, prior DME treatment	No

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Proportion of patients gaining ≥ 15 letters in BCVA from baseline at week 48	FAS	HDq12 vs 2q8 and HDq16 vs 2q8	CMH test with LOCF	OC	No	No
Proportion of patients with BCVA ≥ 69 letters at week 48	FAS	HDq12 vs 2q8 and HDq16 vs 2q8	CMH test with LOCF	OC	No	No
Change from baseline in CRT at week 48	FAS	HDq12 vs 2q8 and HDq16 vs 2q8	MMRM	No	No	No
Proportion of patients without leakage on FA at week 48	FAS	HDq12 vs 2q8 and HDq16 vs 2q8	CMH test with LOCF	No	No	No
Change from baseline in NEI-VFQ total score at week 48	FAS	HDq12 vs 2q8 and HDq16 vs 2q8	MMRM	No	No	No
Proportion of patients without retinal fluid (total fluid, IRF, and/or SRF) at the foveal center and in center subfield at week 48, 60, and 96	FAS	HDq12 vs 2q8 and HDq16 vs 2q8	CMH test with LOCF	No	No	No
Time to fluid-free retina over 48, 60, and 96 weeks (total fluid, IRF and/or SRF at foveal center and in the center subfield)	FAS	HDq12 vs 2q8 and HDq16 vs 2q8	Kaplan-Meier	No	No	No

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Proportion of patients with sustained fluid-free retina over 48, 60, and 96 weeks (total fluid, IRF and/or SRF at foveal center and in the center subfield)	FAS	HDq12 vs 2q8 and HDq16 vs 2q8	CMH test with LOCF	No	No	No
Time to sustained fluid-free retina over 48, 60, and 96 weeks (total fluid, IRF and/or SRF at foveal center and in the center subfield)	FAS	HDq12 vs 2q8 and HDq16 vs 2q8	Kaplan-Meier	No	No	No
Proportion of patients without CSME at week 48, 60, and 96	FAS	HDq12 vs 2q8 and HDq16 vs 2q8	CMH test with LOCF	No	No	No
Proportion of patients with a ≥ 3 step improvement in DRSS at week 48, 60, and 96	FAS	HDq12 vs 2q8 and HDq16 vs 2q8	CMH test with LOCF	OC	No	No
Proportions of patients gaining and losing ≥ 5 or ≥ 10 letters at week 48, 60, and 96	FAS	HDq12 vs 2q8 and HDq16 vs 2q8	CMH test with LOCF	OC	No	No
Proportion of patients losing ≥ 15 letters at week 48, 60, and 96	FAS	HDq12 vs 2q8 and HDq16 vs 2q8	CMH test with LOCF	OC	No	No
Proportion of patients randomized to HDq16 maintaining q16 dosing interval or longer through weeks 48, 60, and 96	FAS	Descriptive	Descriptive statistics	No	No	No

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Proportion of patients randomized to HDq12 maintaining q12 dosing interval or longer through weeks 48, 60 and 96	FAS	Descriptive	Descriptive statistics	No	No	No
Proportion of patients with an assigned injection interval of ≥16 or ≥20 weeks based on assessment at the last injection visit	FAS	Descriptive	Descriptive statistics	No	No	No

Safety Analyses:

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse events	SAF	Percent of patients by SOC and PT: Up to Week 48 Up to Week 60 Up to Week 96	Descriptive statistics	No	Yes, for subgroups sex, age, race, ethnicity, geographic region (Note: only for Ocular TEAEs in study eye, non-ocular TEAEs, Serious ocular TEAEs in study eye, Serious non-ocular TEAEs) Subset analysis in those patients who receive bilateral aflibercept treatment	Overall summary, ocular TEAE in study eye, ocular TEAE in fellow eye, non-ocular TEAE, drug-related AE, injection-procedure-related TEAE, study-conduct-related TEAE, 2mg-aflibercept-in-the-fellow-eye-related TEAE, TEAE leading to discontinuation, SAEs, drug-related SAEs, injection-procedure-related SAE, study-conduct-related SAE, 2mg-aflibercept-in-the-fellow-eye-related SAE, Deaths, APTC events, intraocular inflammation events, hypertension events, and nasal mucosa events

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Clinical laboratory measurements (chemistry, hematology, urinalysis, HbA1c)	SAF	Summary by visit including changes from baseline	Descriptive statistics	No	No	Shift tables, PCSV summary
Vital signs (temperature, pulse, and blood pressure)	SAF	Summary by visit including changes from baseline	Descriptive statistics	No	No	No
12-Lead ECG	SAF	Summary by visit including changes from baseline	Descriptive statistics	No	No	ECG status (normal/abnormal) by visit, shift tables of ECG status
Intraocular pressure	SAF	Summary by visit including changes from baseline	Descriptive statistics	No	No	Proportions of patients with ≥ 10 mmHg increase in IOP measurement from baseline to any pre-dose measurement, > 21 mmHg for any pre-dose measurement, ≥ 25 mmHg for any pre-dose measurement, ≥ 35 mmHg at any time
Surgical procedures	SAF	Ocular surgeries in the study eye, percent of patients by PT	Descriptive statistics	No	No	Ocular surgeries in the fellow eye, non-ocular surgeries

10.2. Schedule of Time and Events

10.2.1. Schedule of Time and Events (Main study)

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

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

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, UWFA = ultra-widefield fluorescein angiography.

Footnotes for the Schedule of Events

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 timepoints 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 in protocol shows additional measurements for patients enrolled in the dense PK substudy.

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 in protocol. 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.

10.2.2. Schedule of Time and 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]

10.3. NEI-VFQ-25 Sub-scale Scores and Total Score

The calculation for NEI-VFQ-25 sub-scale scores and total score will be performed according to The National Eye Institute (2000). The algorithm is then: As a preparation of the VFQ-25 calculation, the items of the questionnaire will be recoded according to Table 3 . In the further calculations, only the recoded item values will be used. For the recoded values, they generally represent the best possible result as "100" and the worst possible result as "0".

Table 3: Recoding of NEI-VFQ 25 items

Item no.	Original response to	Recoded item
1, 3, 4, 15c[(a)]	1	100
	2	75
	3	50
	4	25
	5	0
2	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 16a	1	100
	2	75
	3	50
	4	25
	5	0
	6	*
17, 18, 19, 20, 21, 22, 23, 24, 25	1	0
	2	25
	3	50
	4	75
	5	100

[(a)] Item 15c has four-response levels but is expanded to a five-levels using item 15b: if 15b="1", then 15c="0" / if 15b=("2" or "3"), then 15c="missing"

* Here, Response choice "6" indicates that the person does not perform the activity because of non-vision-related problems. If this choice is selected, the item is coded as "missing".

For the VFQ questionnaire, 12 sub-scal. es will be evaluated (see Table 4), and 11 of these sub-scales will be included in the total VFQ score.

Table 4: Sub-scales of the NEI-VFQ 25 score

Sub-scale no.	Sub-scale	Number of items	(Recoded) items to be averaged	Sub-scale included in total scale
1	General Health	1	1	No
2	General Vision	1	2	Yes
3	Ocular Pain	2	4, 19	Yes
4	Near Activities	3	5, 6, 7	Yes
5	Distance Activities	3	8, 9, 14	Yes
	Vision specific:			
6	Social Functioning	2	11, 13	Yes
7	Mental Health	4	3, 21, 22, 25	Yes
8	Role Difficulties	2	17, 18	Yes
9	Dependency	3	20, 23, 24	Yes
10	Driving	3	15c, 16, 16a	Yes
11	Color vision	1	12	Yes
12	Peripheral Vision	1	10	Yes

For a single sub-scale, the value will be determined as the average of the non-missing recoded item values assigned to this sub-scale. A sub-scale value will only be assessed as missing if all items for this sub-scale have "missing" as a result.

The total score is calculated as the arithmetic mean of all non-missing sub-scales (except General Health):

$$total\ result = \frac{(sum\ of\ non\ -missing\ sub-\ scale\ values)}{Total\ number\ of\ sub-\ scales\ with\ non\ -missing\ result}$$

Due to this calculation approach, the total result will be non-missing if at least one sub-scale result is non-missing.

10.4. Detailed Definitions of Special AE Categories and Medical History Subgroups

Prior to database lock these preferred terms will be updated as necessary based on the current MedDRA version.

10.4.1. Medical history and AE grouping of hypertension

Preferred term
Accelerated hypertension
Blood pressure ambulatory increased
Blood pressure diastolic increased
Blood pressure inadequately controlled
Blood pressure increased
Blood pressure systolic increased

Preferred term
Diastolic hypertension
Endocrine hypertension
Essential hypertension
Hypertension
Hypertension neonatal
Hypertensive angiopathy
Hypertensive cardiomegaly
Hypertensive cardiomyopathy
Hypertensive cerebrovascular disease
Hypertensive crisis
Hypertensive emergency
Hypertensive encephalopathy
Hypertensive end-organ damage
Hypertensive heart disease
Hypertensive nephropathy
Hypertensive urgency
Labile hypertension
Malignant hypertension
Malignant hypertensive heart disease
Malignant renal hypertension
Maternal hypertension affecting foetus
Mean arterial pressure increased
Neurogenic hypertension
Orthostatic hypertension
Page kidney
Prehypertension
Renal hypertension
Renovascular hypertension
Retinopathy hypertensive
Supine hypertension
Systolic hypertension
White coat hypertension

10.4.2. AE grouping of intraocular inflammation

Preferred term
Anterior chamber cell
Anterior chamber fibrin
Anterior chamber flare
Anterior chamber inflammation
Aqueous fibrin
Autoimmune uveitis
Candida endophthalmitis
Chorioretinitis
Choroiditis
Cyclitis
Endophthalmitis
Eye infection
Eye infection bacterial
Eye infection chlamydial
Eye infection fungal
Eye infection intraocular
Eye infection staphylococcal
Eye inflammation
Hypopyon
Infectious iridocyclitis
Infective iritis
Infective uveitis
Iridocyclitis
Iritis
Mycotic endophthalmitis
Necrotising retinitis
Non-infectious endophthalmitis
Noninfective chorioretinitis
Pseudoendophthalmitis
Uveitis
Vitreal cells
Vitreous fibrin
Vitritis

10.4.3. AE grouping of nasal mucosal events

Preferred term
Epistaxis
Nasal inflammation
Nasal mucosal erosion
Nasal mucosal ulcer
Nasal ulcer

10.4.4. Medical history of renal impairment

Renal impairment is defined by CRCL values.

Categories for renal impairment:

- CLCR >80ml/min (normal),
- CLCR >50-80ml/min (mild),
- CLCR >30-50 ml/min (moderate),
- CLCR <=30ml/min or 'requiring dialysis' (severe)

CLCR will be calculated using baseline values (creatinine, age, weight, sex) using the Cockcroft-Gault equation:

Males: CLCR = (140-age)*body weight / (72*creatinine in mg/dL)

Females: CLCR = (140-age)*body weight*0.85 / (72*creatinine in mg/dL)

'Requiring dialysis' is defined by PT in medical history

Preferred Term
Continuous haemodiafiltration
Dialysis
Dialysis device insertion
Haemodialysis
Haemofiltration
Peritoneal dialysis
Removal of renal transplant
Renal replacement therapy
Renal transplant

10.4.5. Medical history of hepatic impairment

Preferred term
5'nucleotidase increased
AST to platelet ratio index increased
AST/ALT ratio abnormal
Accessory liver lobe
Acquired antithrombin III deficiency
Acquired factor IX deficiency
Acquired factor V deficiency
Acquired factor VIII deficiency
Acquired factor XI deficiency
Acquired hepatocerebral degeneration
Acquired protein S deficiency
Acute graft versus host disease in liver
Acute hepatic failure
Acute hepatitis B
Acute hepatitis C
Acute on chronic liver failure
Acute yellow liver atrophy
Adenoviral hepatitis
Alagille syndrome
Alanine aminotransferase abnormal
Alanine aminotransferase increased
Alcoholic encephalopathy
Alcoholic liver disease
Allergic hepatitis
Alloimmune hepatitis
Ammonia abnormal
Ammonia increased
Anorectal varices
Anorectal varices haemorrhage
Anti factor X activity abnormal
Anti factor X activity decreased
Anti factor X activity increased
Anti-liver cytosol antibody type 1 positive
Antithrombin III decreased
Ascites
Aspartate aminotransferase abnormal
Aspartate aminotransferase increased
Asterixis
Asymptomatic viral hepatitis
Autoimmune hepatitis

Preferred term
Bacterascites
Benign hepatic neoplasm
Benign hepatobiliary neoplasm
Benign recurrent intrahepatic cholestasis
Bile output abnormal
Bile output decreased
Biliary ascites
Biliary cirrhosis
Biliary fibrosis
Bilirubin conjugated abnormal
Bilirubin conjugated increased
Bilirubin excretion disorder
Bilirubin urine present
Biopsy liver abnormal
Blood alkaline phosphatase abnormal
Blood alkaline phosphatase increased
Blood bilirubin abnormal
Blood bilirubin increased
Blood bilirubin unconjugated increased
Blood cholinesterase abnormal
Blood cholinesterase decreased
Blood fibrinogen abnormal
Blood fibrinogen decreased
Blood thrombin abnormal
Blood thrombin decreased
Blood thromboplastin abnormal
Blood thromboplastin decreased
Bromosulphthalein test abnormal
Cardiohepatic syndrome
Cerebrohepatorenal syndrome
Child-Pugh-Turcotte score abnormal
Child-Pugh-Turcotte score increased
Cholaemia
Cholangiosarcoma
Cholestasis
Cholestatic liver injury
Cholestatic pruritus
Chronic graft versus host disease in liver
Chronic hepatic failure
Chronic hepatitis
Chronic hepatitis B

Preferred term
Chronic hepatitis C
Cirrhosis alcoholic
Coagulation factor IX level abnormal
Coagulation factor IX level decreased
Coagulation factor V level abnormal
Coagulation factor V level decreased
Coagulation factor VII level abnormal
Coagulation factor VII level decreased
Coagulation factor X level abnormal
Coagulation factor X level decreased
Coagulation factor decreased
Coma hepatic
Complications of transplanted liver
Computerised tomogram liver abnormal
Congenital absence of bile ducts
Congenital hepatic fibrosis
Congenital hepatitis B infection
Congenital hepatitis C infection
Congenital hepatobiliary anomaly
Congenital hepatomegaly
Congenital viral hepatitis
Congestive hepatopathy
Cryptogenic cirrhosis
Cystic fibrosis hepatic disease
Cytokeratin 18 increased
Cytomegalovirus hepatitis
Deficiency of bile secretion
Diabetic hepatopathy
Dilatation intrahepatic duct congenital
Drug-induced liver injury
Duodenal varices
Fatty liver alcoholic
Flood syndrome
Focal nodular hyperplasia
Foetor hepaticus
Galactose elimination capacity test abnormal
Galactose elimination capacity test decreased
Gallbladder varices
Gamma-glutamyltransferase abnormal
Gamma-glutamyltransferase increased
Gastric variceal injection

Preferred term
Gastric variceal ligation
Gastric varices
Gastric varices haemorrhage
Gastrooesophageal variceal haemorrhage prophylaxis
Gianotti-Crosti syndrome
Glutamate dehydrogenase increased
Glycocholic acid increased
Glycogen storage disease type I
Glycogen storage disease type III
Glycogen storage disease type IV
Glycogen storage disease type VI
Graft versus host disease in liver
Granulomatous liver disease
Guanase increased
HBV-DNA polymerase increased
Haemangioma of liver
Haemorrhagic ascites
Haemorrhagic hepatic cyst
Hepaplastin abnormal
Hepaplastin decreased
Hepatectomy
Hepatic adenoma
Hepatic amoebiasis
Hepatic angiosarcoma
Hepatic artery flow decreased
Hepatic atrophy
Hepatic calcification
Hepatic cancer
Hepatic cancer metastatic
Hepatic cancer recurrent
Hepatic cancer stage I
Hepatic cancer stage II
Hepatic cancer stage III
Hepatic cancer stage IV
Hepatic candidiasis
Hepatic cirrhosis
Hepatic cyst
Hepatic cyst infection
Hepatic cyst ruptured
Hepatic cytolysis
Hepatic echinococciasis

Preferred term
Hepatic encephalopathy
Hepatic encephalopathy prophylaxis
Hepatic enzyme abnormal
Hepatic enzyme decreased
Hepatic enzyme increased
Hepatic failure
Hepatic fibrosis
Hepatic fibrosis marker abnormal
Hepatic fibrosis marker increased
Hepatic function abnormal
Hepatic gas gangrene
Hepatic haemangioma rupture
Hepatic hamartoma
Hepatic hydrothorax
Hepatic hypertrophy
Hepatic hypoperfusion
Hepatic infection
Hepatic infection bacterial
Hepatic infection fungal
Hepatic infection helminthic
Hepatic infiltration eosinophilic
Hepatic lesion
Hepatic lipoma
Hepatic lymphocytic infiltration
Hepatic mass
Hepatic necrosis
Hepatic neoplasm
Hepatic neuroendocrine tumour
Hepatic pain
Hepatic perfusion disorder
Hepatic sarcoma
Hepatic sequestration
Hepatic steato-fibrosis
Hepatic steatosis
Hepatic vascular resistance increased
Hepatic venous pressure gradient abnormal
Hepatic venous pressure gradient increased
Hepatitis
Hepatitis A
Hepatitis A antibody abnormal
Hepatitis A antibody positive

Preferred term
Hepatitis A antigen positive
Hepatitis A immunity confirmed
Hepatitis A virus test positive
Hepatitis B
Hepatitis B DNA assay positive
Hepatitis B DNA increased
Hepatitis B antibody abnormal
Hepatitis B antibody positive
Hepatitis B antigen positive
Hepatitis B core antibody positive
Hepatitis B core antigen positive
Hepatitis B e antibody positive
Hepatitis B e antigen positive
Hepatitis B immunity confirmed
Hepatitis B reactivation
Hepatitis B surface antibody positive
Hepatitis B surface antigen positive
Hepatitis B virus test positive
Hepatitis C
Hepatitis C RNA increased
Hepatitis C RNA positive
Hepatitis C antibody positive
Hepatitis C core antibody positive
Hepatitis C virus test positive
Hepatitis D
Hepatitis D RNA positive
Hepatitis D antibody positive
Hepatitis D antigen positive
Hepatitis D virus test positive
Hepatitis E
Hepatitis E RNA positive
Hepatitis E antibody abnormal
Hepatitis E antibody positive
Hepatitis E antigen positive
Hepatitis E immunity confirmed
Hepatitis E virus test positive
Hepatitis F
Hepatitis G
Hepatitis H
Hepatitis acute
Hepatitis alcoholic

Preferred term
Hepatitis cholestatic
Hepatitis chronic active
Hepatitis chronic persistent
Hepatitis fulminant
Hepatitis infectious mononucleosis
Hepatitis mumps
Hepatitis neonatal
Hepatitis non-A non-B
Hepatitis non-A non-B non-C
Hepatitis post transfusion
Hepatitis syphilitic
Hepatitis toxic
Hepatitis toxoplasmal
Hepatitis viral
Hepatitis viral test positive
Hepato-lenticular degeneration
Hepatobiliary cancer
Hepatobiliary cancer in situ
Hepatobiliary cyst
Hepatobiliary disease
Hepatobiliary infection
Hepatobiliary neoplasm
Hepatobiliary scan abnormal
Hepatoblastoma
Hepatoblastoma recurrent
Hepatocellular carcinoma
Hepatocellular damage neonatal
Hepatocellular foamy cell syndrome
Hepatocellular injury
Hepatomegaly
Hepatopulmonary syndrome
Hepatorenal failure
Hepatorenal syndrome
Hepatosplenic abscess
Hepatosplenic candidiasis
Hepatosplenomegaly
Hepatosplenomegaly neonatal
Hepatotoxicity
Hereditary haemochromatosis
Herpes simplex hepatitis
Hyperammonaemia

Preferred term
Hyperbilirubinaemia
Hyperbilirubinaemia neonatal
Hypercholia
Hyperfibrinolysis
Hypertransaminasaemia
Hypoalbuminaemia
Hypocoagulable state
Hypofibrinogenaemia
Hypoprothrombinaemia
Hypothrombinaemia
Hypothromboplastinaemia
Icterus index increased
Immune-mediated cholangitis
Immune-mediated hepatic disorder
Immune-mediated hepatitis
Increased liver stiffness
International normalised ratio abnormal
International normalised ratio increased
Intestinal varices
Intestinal varices haemorrhage
Intrahepatic portal hepatic venous fistula
Ischaemic hepatitis
Jaundice
Jaundice cholestatic
Jaundice hepatocellular
Jaundice neonatal
Kayser-Fleischer ring
Kernicterus
Leucine aminopeptidase increased
Liver abscess
Liver and pancreas transplant rejection
Liver carcinoma ruptured
Liver dialysis
Liver disorder
Liver function test abnormal
Liver function test decreased
Liver function test increased
Liver induration
Liver injury
Liver iron concentration abnormal
Liver iron concentration increased

Preferred term
Liver opacity
Liver operation
Liver palpable
Liver sarcoidosis
Liver scan abnormal
Liver tenderness
Liver transplant
Liver transplant failure
Liver transplant rejection
Liver-kidney microsomal antibody positive
Lupoid hepatic cirrhosis
Lupus hepatitis
Magnetic resonance imaging hepatobiliary abnormal
Magnetic resonance proton density fat fraction measurement
Mitochondrial aspartate aminotransferase increased
Mixed hepatocellular cholangiocarcinoma
Mixed liver injury
Model for end stage liver disease score abnormal
Model for end stage liver disease score increased
Molar ratio of total branched-chain amino acid to tyrosine
Multivisceral transplantation
Necrolytic acral erythema
Neonatal cholestasis
Neonatal hepatomegaly
Nodular regenerative hyperplasia
Non-alcoholic fatty liver
Non-alcoholic steatohepatitis
Non-cirrhotic portal hypertension
Ocular icterus
Oedema due to hepatic disease
Oesophageal varices haemorrhage
Omental oedema
Osteopontin increased
Parenteral nutrition associated liver disease
Perihepatic discomfort
Perinatal HBV infection
Peripancreatic varices
Periportal oedema
Peritoneal fluid protein abnormal
Peritoneal fluid protein decreased
Peritoneal fluid protein increased

Preferred term
Peritoneovenous shunt
Pneumobilia
Polycystic liver disease
Porphyria acute
Porphyria non-acute
Portal fibrosis
Portal hypertension
Portal hypertensive colopathy
Portal hypertensive enteropathy
Portal hypertensive gastropathy
Portal pyaemia
Portal shunt
Portal shunt procedure
Portal tract inflammation
Portal vein cavernous transformation
Portal vein dilatation
Portal vein flow decreased
Portal vein pressure increased
Portal venous system anomaly
Portopulmonary hypertension
Primary biliary cholangitis
Progressive familial intrahepatic cholestasis
Protein C decreased
Protein S abnormal
Protein S decreased
Prothrombin level abnormal
Prothrombin level decreased
Prothrombin time abnormal
Prothrombin time prolonged
Prothrombin time ratio abnormal
Prothrombin time ratio increased
Radiation hepatitis
Regenerative siderotic hepatic nodule
Renal and liver transplant
Retinol binding protein decreased
Retrograde portal vein flow
Reye's syndrome
Reynold's syndrome
Schistosomiasis liver
Small-for-size liver syndrome
Spider naevus

Preferred term
Splenic artery embolisation
Splenic varices
Splenic varices haemorrhage
Splenorenal shunt
Splenorenal shunt procedure
Spontaneous bacterial peritonitis
Spontaneous intrahepatic portosystemic venous shunt
Steatohepatitis
Stomal varices
Subacute hepatic failure
Sugiura procedure
Sustained viral response
Thrombin time abnormal
Thrombin time prolonged
Total bile acids increased
Transaminases abnormal
Transaminases increased
Ultrasound liver abnormal
Urine bilirubin increased
Urobilinogen urine decreased
Urobilinogen urine increased
Varices oesophageal
Varicose veins of abdominal wall
Viral hepatitis carrier
Weil's disease
White nipple sign
Withdrawal hepatitis
X-ray hepatobiliary abnormal
Yellow skin
Zieve syndrome

10.4.6. Medical history of cerebrovascular disease

Preferred term
Agnosia
Amaurosis fugax
Amyloid related imaging abnormalities
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits
Amyloid related imaging abnormality-oedema/effusion
Angiogram cerebral abnormal
Aphasia
Balint's syndrome
Basal ganglia haematoma
Basal ganglia haemorrhage
Basal ganglia infarction
Basal ganglia stroke
Basilar artery aneurysm
Basilar artery occlusion
Basilar artery perforation
Basilar artery stenosis
Basilar artery thrombosis
Benedikt's syndrome
Blood brain barrier defect
Brachiocephalic arteriosclerosis
Brachiocephalic artery occlusion
Brachiocephalic artery stenosis
Brain hypoxia
Brain injury
Brain stem embolism
Brain stem haematoma
Brain stem haemorrhage
Brain stem infarction
Brain stem ischaemia
Brain stem microhaemorrhage
Brain stem stroke
Brain stem thrombosis
Brain stent insertion
CADASIL
CARASIL syndrome
CSF bilirubin positive
CSF red blood cell count positive
Capsular warning syndrome
Carotid aneurysm rupture

Preferred term
Carotid angioplasty
Carotid arterial embolus
Carotid arteriosclerosis
Carotid artery aneurysm
Carotid artery bypass
Carotid artery disease
Carotid artery dissection
Carotid artery dolichoectasia
Carotid artery insufficiency
Carotid artery occlusion
Carotid artery perforation
Carotid artery restenosis
Carotid artery stenosis
Carotid artery stent insertion
Carotid artery stent removal
Carotid artery thrombosis
Carotid endarterectomy
Carotid revascularisation
Central nervous system haemorrhage
Central nervous system vasculitis
Central pain syndrome
Cerebellar artery occlusion
Cerebellar artery thrombosis
Cerebellar atherosclerosis
Cerebellar embolism
Cerebellar haematoma
Cerebellar haemorrhage
Cerebellar infarction
Cerebellar ischaemia
Cerebellar microhaemorrhage
Cerebellar stroke
Cerebral amyloid angiopathy
Cerebral aneurysm perforation
Cerebral aneurysm ruptured syphilitic
Cerebral arteriosclerosis
Cerebral arteriovenous malformation haemorrhagic
Cerebral arteritis
Cerebral artery embolism
Cerebral artery occlusion
Cerebral artery perforation
Cerebral artery restenosis
Cerebral artery stenosis

Preferred term
Cerebral artery stent insertion
Cerebral artery thrombosis
Cerebral capillary telangiectasia
Cerebral cavernous malformation
Cerebral circulatory failure
Cerebral congestion
Cerebral cyst haemorrhage
Cerebral endovascular aneurysm repair
Cerebral gas embolism
Cerebral haematoma
Cerebral haemorrhage
Cerebral haemorrhage foetal
Cerebral haemorrhage neonatal
Cerebral haemosiderin deposition
Cerebral hypoperfusion
Cerebral infarction
Cerebral infarction foetal
Cerebral ischaemia
Cerebral microangiopathy
Cerebral microembolism
Cerebral microhaemorrhage
Cerebral microinfarction
Cerebral reperfusion injury
Cerebral revascularisation
Cerebral septic infarct
Cerebral small vessel ischaemic disease
Cerebral thrombosis
Cerebral vascular occlusion
Cerebral vasoconstriction
Cerebral venous sinus thrombosis
Cerebral venous thrombosis
Cerebral ventricular rupture
Cerebrovascular accident
Cerebrovascular accident prophylaxis
Cerebrovascular arteriovenous malformation
Cerebrovascular disorder
Cerebrovascular insufficiency
Cerebrovascular pseudoaneurysm
Cerebrovascular stenosis
Charcot-Bouchard microaneurysms
Chronic cerebrospinal venous insufficiency
Claude's syndrome

Preferred term
Congenital cerebrovascular anomaly
Congenital hemiparesis
Delayed ischaemic neurological deficit
Diplegia
Dural arteriovenous fistula
Dysarthria
Embolic cerebellar infarction
Embolic cerebral infarction
Embolic stroke
Epidural haemorrhage
Extra-axial haemorrhage
Extradural haematoma
Extradural haematoma evacuation
Extraischaemic cerebral haematoma
Foetal cerebrovascular disorder
Foville syndrome
Haemorrhage intracranial
Haemorrhagic cerebellar infarction
Haemorrhagic cerebral infarction
Haemorrhagic stroke
Haemorrhagic transformation stroke
Heidelberg classification
Hemianaesthesia
Hemiasomatognosia
Hemiataxia
Hemidysaesthesia
Hemihyperaesthesia
Hemihypoaesthesia
Hemiparaesthesia
Hemiparesis
Hemiplegia
Hunt and Hess scale
Hypertensive cerebrovascular disease
Hypoxic-ischaemic encephalopathy
Inner ear infarction
Internal capsule infarction
Internal carotid artery deformity
Intra-cerebral aneurysm operation
Intracerebral haematoma evacuation
Intracranial aneurysm
Intracranial artery dissection
Intracranial haematoma

Preferred term
Intracranial haemorrhage neonatal
Intracranial tumour haemorrhage
Intraventricular haemorrhage
Intraventricular haemorrhage neonatal
Ischaemic cerebral infarction
Ischaemic stroke
Lacunar infarction
Lacunar stroke
Lateral medullary syndrome
Lateropulsion
Malignant middle cerebral artery syndrome
Medullary compression syndrome
Meningorrhagia
Metabolic stroke
Migrainous infarction
Millard-Gubler syndrome
Modified Rankin score decreased
Modified Rankin score increased
Monoparesis
Monoplegia
Moyamoya disease
NIH stroke scale abnormal
NIH stroke scale score decreased
NIH stroke scale score increased
Paralysis
Paraparesis
Paraplegia
Paresis
Perinatal stroke
Periventricular haemorrhage neonatal
Pituitary apoplexy
Pituitary haemorrhage
Post cardiac arrest syndrome
Post procedural stroke
Post stroke depression
Posthaemorrhagic hydrocephalus
Precerebral arteriosclerosis
Precerebral artery aneurysm
Precerebral artery dissection
Precerebral artery embolism
Precerebral artery occlusion
Precerebral artery thrombosis

Preferred term
Primary familial brain calcification
Pseudo-occlusion of internal carotid artery
Putamen haemorrhage
Quadriparesis
Quadriplegia
Reversible cerebral vasoconstriction syndrome
Reversible ischaemic neurological deficit
Right hemisphere deficit syndrome
Ruptured cerebral aneurysm
Septic cerebral embolism
Sigmoid sinus thrombosis
Sneddon's syndrome
Spinal artery embolism
Spinal artery thrombosis
Spinal cord haematoma
Spinal cord haemorrhage
Spinal cord infarction
Spinal cord ischaemia
Spinal epidural haematoma
Spinal epidural haemorrhage
Spinal stroke
Spinal subarachnoid haemorrhage
Spinal subdural haematoma
Spinal subdural haemorrhage
Spinal vascular disorder
Spinal vessel congenital anomaly
Stroke in evolution
Subarachnoid haematoma
Subarachnoid haemorrhage
Subarachnoid haemorrhage neonatal
Subclavian steal syndrome
Subdural haematoma
Subdural haematoma evacuation
Subdural haemorrhage
Subdural haemorrhage neonatal
Superficial siderosis of central nervous system
Superior sagittal sinus thrombosis
Susac's syndrome
Thalamic infarction
Thalamus haemorrhage
Thrombotic cerebral infarction
Thrombotic stroke

Preferred term
Transient ischaemic attack
Transverse sinus thrombosis
Vascular encephalopathy
Vascular stent occlusion
Vascular stent stenosis
Vein of Galen aneurysmal malformation
Vertebral artery aneurysm
Vertebral artery arteriosclerosis
Vertebral artery dissection
Vertebral artery occlusion
Vertebral artery perforation
Vertebral artery stenosis
Vertebral artery thrombosis
Vertebrobasilar dolichoectasia
Vertebrobasilar insufficiency
Vertebrobasilar stroke
Visual agnosia
Visual midline shift syndrome
Weber's syndrome

10.4.7. Medical history of ischemic heart disease

Preferred term
Acute coronary syndrome
Acute myocardial infarction
Angina pectoris
Angina unstable
Anginal equivalent
Arterial revascularisation
Arteriogram coronary abnormal
Arteriosclerosis coronary artery
Arteriospasm coronary
Cardiac perfusion defect
Cardiac ventricular scarring
Chronic coronary syndrome
Computerised tomogram coronary artery abnormal
Coronary angioplasty
Coronary arterial stent insertion
Coronary artery bypass
Coronary artery compression
Coronary artery disease
Coronary artery dissection
Coronary artery embolism
Coronary artery insufficiency
Coronary artery occlusion
Coronary artery reocclusion
Coronary artery restenosis
Coronary artery stenosis
Coronary artery surgery
Coronary artery thrombosis
Coronary brachytherapy
Coronary bypass stenosis
Coronary bypass thrombosis
Coronary endarterectomy
Coronary no-reflow phenomenon
Coronary ostial stenosis
Coronary revascularisation
Coronary steal syndrome
Coronary vascular graft occlusion
Coronary vascular graft stenosis
ECG electrically inactive area
ECG signs of myocardial infarction
ECG signs of myocardial ischaemia

Preferred term
Electrocardiogram PR segment depression
Electrocardiogram PR segment elevation
Electrocardiogram ST segment abnormal
Electrocardiogram ST segment depression
Electrocardiogram ST segment elevation
Electrocardiogram ST-T segment abnormal
Electrocardiogram ST-T segment depression
Electrocardiogram ST-T segment elevation
External counterpulsation
Haemorrhage coronary artery
Infarction
Ischaemic cardiomyopathy
Ischaemic contracture of the left ventricle
Kounis syndrome
Myocardial hypoperfusion
Myocardial hypoxia
Myocardial infarction
Myocardial ischaemia
Myocardial necrosis
Myocardial reperfusion injury
Myocardial stunning
Papillary muscle infarction
Percutaneous coronary intervention
Periprocedural myocardial infarction
Positive vessel remodelling
Post angioplasty restenosis
Post procedural myocardial infarction
Postinfarction angina
Prinzmetal angina
Scan myocardial perfusion abnormal
Silent myocardial infarction
Stent patency maintenance
Stress cardiomyopathy
Subclavian coronary steal syndrome
Subendocardial ischaemia
Vascular device occlusion
Vascular graft occlusion
Vascular graft restenosis
Vascular graft stenosis
Vascular graft thrombosis
Vascular stent occlusion
Vascular stent stenosis

Preferred term
Ventricular compliance decreased
Wellens' syndrome

10.5. Criteria for Potentially Clinically Significant Values (PCSV)

Table 5: Criteria for Potentially Clinically Significant Values

Parameter	Potentially clinically significant value (PCSV)
Clinical Chemistry	
ALT	> 3 ULN
AST	> 3 ULN
Alkaline Phosphatase	> 1.5 ULN
Total Bilirubin	> 1.5 ULN
Conjugated Bilirubin	> 35% Total Bilirubin (when Total Bilirubin >1.5 ULN)
ALT and Total Bilirubin	ALT > 3 ULN and Total Bilirubin > 2 ULN
CPK	> 3 ULN
Creatinine	≥ 150 µmol/L (Adults) ≥ 30% from baseline
Uric Acid	Hyperuricemia: >408 µmol/L Hypouricemia: <120 µmol/L
Blood Urea Nitrogen	≥ 17 mmol/L
Chloride	< 80 mmol/L > 115 mmol/L
Sodium	≤ 129 mmol/L ≥ 160 mmol/L
Potassium	< 3 mmol/L ≥ 5.5 mmol/L
Total Cholesterol	≥ 7.74 mmol/L (3 g/L)
Triglycerides	≥ 4.6 mmol/L (4 g/L)
Glucose - Hypoglycaemia - Hyperglycaemia	 ≤ 3.9 mmol/L and < LLN ≥ 11.1 mmol/L (unfasted), ≥ 7 mmol/L (fasted)
HbA1c	> 8 %
Albumin	≤ 25 g/L
Hematology	
WBC	< 3.0 GIGA/L (non-Black), < 2.0 GIGA/L (Black), ≥ 16.0 GIGA/L
Lymphocytes	> 4.0 GIGA/L

Parameter	**Potentially clinically significant value (PCSV)**
Neutrophils	< 1.5 GIGA/L (non-Black) < 1.0 GIGA/L (Black)
Monocytes	> 0.7 GIGA/L
Basophils	> 0.1 GIGA/L
Eosinophils	> 0.5 GIGA/L or > ULN if ULN ≥ 0.5 GIGA /L
Hemoglobin	Males : ≤115 g/L (≤ 7.14 mmol/L), ≥ 185 g/L (11.48 mmol/L) Females : ≤ 95 g/L (5.9 mmol/L), ≥ 165 g/L (10.24 mmol/L) Decrease from Baseline ≥ 20 g/L (1.24 mmol/L)
Hematocrit	Males : ≤ 0.37 v/v, ≥ 0.55 v/v Females : ≤ 0.32 v/v, ≥ 0.5 v/v
RBC	≥ 6 TERA/L
Platelets	< 100 GIGA/L
Blood pressure	
Systolic BP	≤ 95 mmHg and decrease from baseline ≥ 20 mmHg ≥160 mmHg and increase from baseline ≥ 20 mmHg
Diastolic BP	≤ 45 mmHg and decrease from baseline ≥ 10 mmHg ≥110 mmHg and increase from baseline ≥ 10 mmHg

10.6. Process to Derive Week 48 Data Cut-off

For week 48 evaluations, a strategy for performing the data cut-off for the clinical database was developed, as described in the following:

10.6.1. Visit Independent Data

Visit independent data (or event-based data) include adverse events, concomitant/prior medication, and surgeries.

Patients that discontinued study prematurely before or at week 48 (Visit 14)

These patients are defined as having their end of study CRF page filled, and have either:

- a dropout date earlier or equal to date of first injection + 336 days + 5 days (to account for the visit window) or
- a dropout date equal to week 48 visit date

For such patients, all event-based records are kept in the clinical database for week 48 analysis without any change.

Patients who stayed longer than week 48 (visit 14) in the study

These patients are the patients who did not discontinue study prematurely at/before week 48 (visit 14). Therefore, these patients are either:

- still ongoing after week 48 (visit 14)
- discontinued the study prematurely, but were in the study for longer than week 48 (visit 14)

For such patients, the following will be applied:

All event records with a start date later than the date of the week 48 (visit 14) will be censored. This includes the case where the incomplete date is without any doubt later than the week 48 visit date, eg, week 48 (visit 14) is 10 April 2020 and the incomplete date is May 2020 or only 2021. If the week 48 visit date is missing, then the date of first injection + 336 days will be used instead.

Records with a start date earlier or equal to the date of week 48 (first injection + 336 days if date of week 48 visit is missing) will be kept. This includes records with incomplete dates when the incomplete date is earlier than the week 48 date or in cases where it is not clear if the record occurred before or after week 48 (eg, week 48 [visit 14] is 10 April 2020 and the incomplete date is March 2020, April 2020 or only 2020 or even a missing date). If the date is incomplete, the following adaptions to the data will be made.

Concomitant medication:

If a stop date is reported which is earlier than the date of week 48 (visit 14) (first injection + 336 days if date of week 48 is missing), the record will not be changed.

If a stop date is reported which is later than the date of week 48 (visit 14) (first injection + 336 days if date of week 48 is missing), the stop date will be set to missing and the variable CMONG will be set to 1 (yes).

Adverse Events:

AEs with a start date on or after the date of the week 48 (visit 14) will be censored. Cut-off date will be first injection + 336 days if date of week 48 is missing.

If a stop date of adverse event is specified and earlier or equal to date of week 48 (visit 14) (first injection + 336 days if date of week 48 missing), then the record will not be changed.

If a stop date of adverse event is specified and later than the date of week 48 (visit 14) (first injection + 336 days if date of week 48 is missing), then the stop date will be set to missing and the outcome of the adverse event (SAS variable AEOUT) will be set to missing.

If no stop date is specified and the outcome is either not yet reported (AEOUT is blank) or is reported (AEOUT is 3 - recovering/resolving, 4 - not recovered/not resolved, 6 - unknown), then the outcome will be set to missing (AEOUT is blank).

Surgeries:

All surgeries with a date of surgery later than week 48 (visit 14) date will not be included in the analysis. Cut-off date will be first injection + 336 days if date of week 48 is missing.

10.6.2. Study Medication Data

Study medication data in the study eye up to week 44 (visit 13) will be kept for the week 48 analysis. Study medication data in the fellow eye prior to week 48 (week 14) will be included for the week 48 analysis.

10.6.3. Visit Dependent Data

All visit dependent data up to week 48 (visit 14) will be kept for the week 48 analysis except for post-dose IOP at the week 48 visit. All visit dependent data later than week 48 (visit 14) will not be included for the week 48 analysis. Unscheduled visits with a date prior to the week 48 (visit 14) visit date will be kept for the week 48 analysis. If a patient did not have a week 48 (visit 14) visit, unscheduled visit will be kept up to date of first injection + 336 days for the week 48 analysis.

10.7. Process to Derive Week 60 Data Cut-off

For week 60 evaluations, the same strategy for performing the data cut-off for the clinical database as described in Appendix 10.6 will be followed. Instead of "first injection + 336 days" for week 48, missing dates for week 60 will be imputed by first injection + 420 days.

10.8. SAS Procedures

10.8.1. MMRM

```
PROC MIXED DATA = <data at Week48>;
       CLASS subjid trtpn avisitn basecrt pdme region;
       MODEL chg = base basecrt pdme region trtpn avisitn base*avisitn trtpn*avisitn /DDFM=kr;
       REPEATED avisitn / SUBJECT=subjid TYPE=un GROUP=trtpn;
       LSMESTIMATE trtpn*avisitn "HDq12 - 2q8 " XXX /  cl upper testvalue=-4;
        *for non-inferiority test with margin = 4;
       LSMESTIMATE trtpn*avisitn "HDq16 - 2q8 " XXX /  cl upper testvalue=-4;
        *for non-inferiority test with margin = 4;
       LSMESTIMATE trtpn*avisitn "HDq12 - 2q8 " XXX /  cl upper testvalue=0;
        *for superiority test;
       LSMESTIMATE trtpn*avisitn "HDq16 - 2q8 " XXX /  cl upper testvalue=0;
        *for superiority test;
RUN;
```

10.8.2. ANCOVA

```
PROC MIXED DATA = <data until Week48>;
       CLASS trtpn basecrt pdme region ;
       MODEL chg = base basecrt pdme region trtpn;
       LSMESTIMATE trtpn "HDq12 - 2q8" xxx /cl upper testvalue=-4;
       *for non-inferiority test with margin = 4;
       LSMESTIMATE trtpn "HDq16 - 2q8" xxx /cl upper testvalue=-4;
       *for non-inferiority test with margin = 4;
RUN;
```

10.8.3. Multiple Imputation

Step 1. Imputation: Impute missing value using MCMC method and subsequently impute missing data by a regression model.

```
PROC MI DATA=<indata> SEED=01934 OUT=mi01 NIMPUTE=50; * seed = 01934;minimum = 0 0 0 0 0
       maximum = 100 100 100 100 100; * BCVA feasible range is 0 to 100;
       mcmc impute=monotone;
       VAR base v2 v3 v4 v5;
RUN;

PROC MI DATA=mi01 SEED=01934 out = full NIMPUTE=1; * seed = 01934;
       minimum = . . . . 0 0 0 0 0 0
       maximum = . . . . 100 100 100 100 100;
      CLASS basecrt pdme region trtpn
       BY _imputation_;
       MONOTONE REG;
       VAR basecrt pdme region trtpn base v2 v3 v4 v5;
RUN;
```

Step 2. Analysis: Each complete dataset is analyzed by ANCOVA model.

```
PROC MIXED DATA = full;
       by _imputation_;
       CLASS trtpn basecrt pdme region;
       MODEL chg = base basecrt pdme region trtpn;
       LSMESTIMATE trtpn "HDq12 - 2q8" xxx /cl upper testvalue=-4;
       LSMESTIMATE trtpn "HDq16 - 2q8" xxx /cl upper testvalue=-4;
       ods output lsmestimates=lsme;
RUN;
```

Step 3. Pooling: The MIANALYZE procedure is used to combine results.

```
PROC MIANALYZE DATA=lsme theta0=-4;
       by label;
       modeleffects estimate;
       stderr stderr;
       ods output parameterestimates=parameterest1 VarianceInfo=varinfo1;
       run;
```

10.8.4. Tipping Point Analysis

Step 1 to Step 3 below are repeated for a range of feasible **&delta** values. The tipping point will be determined as the &delta value for which the conclusion under MAR is reversed.

Step 1. Imputation: Impute missing value using MCMC method and subsequently impute missing data by a regression model with MNAR adjustment.

```
PROC MI DATA=<indata> SEED=01934 OUT=mi01 NIMPUTE=50; * seed = 01934;minimum = 0 0 0 0 0
       maximum = 100 100 100 100 100; * BCVA feasible range is 0 to 100;
       mcmc impute=monotone;
       VAR base v2 v3 v4 v5;
RUN;

PROC MI DATA=mi01 SEED=01934 out = full NIMPUTE=1; * seed = 01934;
       minimum = . . . . 0 0 0 0 0 0
       maximum = . . . . 100 100 100 100 100;
       CLASS basecrt pdme region trtpn
      BY _imputation_;
       MONOTONE REG;
       MNAR ADJUST( v5 / SHIFT= &delta ADJUSTOBS=(TRT01PN ='HDq12') );* v5 is the outcome at the
visits of interest, e.g. BCVA at week 48;
       MNAR ADJUST( v5 / SHIFT= &delta ADJUSTOBS=(TRT01PN ='HDq16') );
       VAR basecrt pdme region trtpn base v2 v3 v4 v5;
RUN;
```

Step 2. Analysis: Each complete dataset with MNAR adjustment is analyzed by ANCOVA model.

```
PROC MIXED DATA = full;
       by _imputation_;
       CLASS trtpn basecrt pdme region;
       MODEL chg = base basecrt pdme region trtpn;
        LSMESTIMATE trtpn "HDq12 - 2q8" xxx /cl upper testvalue=-4;
        LSMESTIMATE trtpn "HDq16 - 2q8" xxx /cl upper testvalue=-4;
       ods output lsmestimates=lsme;
RUN;
```

Step 3. Pooling: The MIANALYZE procedure is used to combine results.

```
PROC MIANALYZE DATA=lsme theta0=-4;
       by label;
       modeleffects estimate;
       stderr stderr;
       ods output parameterestimates=parameterest1 VarianceInfo=varinfo1;
       run;
```

10.9. Additional Secondary Efficacy Variables and Analyses

This section pre-specifies the statistical approaches for defining and analyzing additional secondary efficacy variables at week 48, for submission to the US FDA (based on the G-SAP that constitutes the primary analysis for the study).

10.9.1. Analysis Populations

The following populations of analysis will be used for the additional secondary efficacy analyses.

10.9.1.1. Full Analysis Set (FAS)

Refer to Section 3.1

10.9.1.2. Modified Full Analysis Set (mFAS)

The modified full analysis set 1 (mFAS1) includes all randomized patients who completed initial treatment phase and maintained their dosing interval (i.e.,

- maintained post 3-dose loading on a q12 interval for HDq12 group and never having their dosing interval shortened to less than q12w;
- maintained post 3-dose loading on a q16 interval for the HDq16 group and never having their dosing interval shortened to less than q16w; and
- all patients in the 2q8 group receive fixed q8 dosing).

The modified full analysis set 2 (mFAS2) includes all randomized patients who completed initial treatment phase and maintained their dosing interval (i.e.,

- maintained post 3-dose loading for All HD group (pooled HDq12 and HDq16 groups) on either q12 or q16 interval and never having their dosing interval shortened to less than q12w; and
- all patients in the 2q8 group receive fixed q8 dosing).

Both analysis sets, mFAS1 and mFAS2, are based on the treatment assigned to the patient at baseline (as randomized).

10.9.2. Additional Secondary Efficacy Variable(s)

Additional secondary efficacy analyses will be conducted for the following variables:

- Change from baseline in BCVA (as measured by ETDRS letter score) at week 48 (previously defined primary efficacy variable; see Section 4.5.1)
- Change from 8-weeks post initial treatment phase in BCVA (as measured by ETDRS letter score) at week 48 (additional secondary efficacy variable).

Note that per the dosing schedule shown in Figure 2, the initial treatment phase is through week 8 (3 doses) for both HDq12 and HDq16 treatment groups, and through week 16 (5 doses) for the 2q8 treatment group. Hence 8-weeks post initial treatment phase is Week 16 for both HDq12 and HDq16 treatment groups and Week 24 for the 2q8 treatment group.

10.9.3. Additional Secondary Efficacy Analyses

The additional secondary efficacy analyses will be an alternative tipping point analysis on the efficacy variables in Section 10.9.2.

For analysis set (FAS and mFAS) and each variable, the following algorithm will be applied:

1. Within each treatment group, for patients with data at both week 48 and at the designated baseline for the analysis, sort the patient level data for change in BCVA at week 48 from smallest to largest, e.g., ranging from -60, -59, …, -1, 0, +1, …to +50 ETDRS letter score. Patients without data at both week 48 and designated baseline are removed from numerator and denominator calculations described below.
2. For the analysis (sub)set, compare mean change in BCVA at week 48 between HDq12 with the mean change in BCVA at week 48 for the 2q8 control group.
3. If the mean change in BCVA for HDq12 group ≥ [mean change in BCVA for 2q8 group + Δ] where Δ=0 or -2, then
   a. report the number, percentage of patients in the (sub)set relative to the original analysis set, and 2-sided 95% CI (continuity-corrected Wilson (score) method) for HDq12 group,
   b. report the tipping point value in the HDq12 group analysis subset that is the lowest letter change in BCVA, and
   c. stop.
4. Otherwise, exclude patients with the next worst score in HDq12 group to obtain a new subset. Retain original analysis set in 2q8 control group. Repeat steps 2 and 3, until stopping condition is reached or all patient level data is used in the HDq12 group.

Repeat the above algorithm for HDq16 group and the All HD group.

The above analyses specified for completers may also be repeated using the estimand framework (see Section 5.6).

The reported results from these additional analyses will be as follows (see Table 6).

Table 6: Additional Secondary Efficacy Analyses – Alternative Tipping Point Analyses

	Population	Variable	Analysis Results	Δ	Tipping Point in HD group
1a	FAS[a]	Change from baseline in BCVA at week 48	• Number and Percentage of patients in the HDq12 analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	0	x_1 letters
			• Number and Percentage of patients in the HDq16 analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	0	y_1 letters
			• Number and Percentage of patients in the All HD analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	0	z_1 letters
1b	FAS[a]	Change from baseline in BCVA at week 48	• Number and Percentage of patients in the HDq12 analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	-2	x_2 letters
			• Number and Percentage of patients in the HDq16 analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	-2	y_2 letters
			• Number and Percentage of patients in the All HD analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	-2	z_2 letters
2a	FAS[a]	Change from 8-weeks post initial treatment in BCVA at week 48	• Number and Percentage of patients in the HDq12 analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	0	x_3 letters
			• Number and Percentage of patients in the HDq16 analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	0	y_3 letters
			• Number and Percentage of patients in the All HD analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	0	z_3 letters

	Population	Variable	Analysis Results	Δ	Tipping Point in HD group
2b	FAS[a]	Change from 8-weeks post initial treatment in BCVA at week 48	• Number and Percentage of patients in the HDq12 analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	-2	x_4 letters
			• Number and Percentage of patients in the HDq16 analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	-2	y_4 letters
			• Number and Percentage of patients in the All HD analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	-2	z_4 letters
3a	mFAS1[b]; mFAS2[c]	Change from baseline in BCVA at week 48	• Number and Percentage of patients in the HDq12 analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	0	x_5 letters
			• Number and Percentage of patients in the HDq16 analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	0	y_5 letters
3b	mFAS1[b]; mFAS2[c]	Change from baseline in BCVA at week 48	• Number and Percentage of patients in the HDq12 analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	-2	x_6 letters
			• Number and Percentage of patients in the HDq16 analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	-2	y_6 letters
			• Number and Percentage of patients in the All HD analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	-2	z_6 letters

	Population	Variable	Analysis Results	Δ	Tipping Point in HD group
4a	mFAS1[b]; mFAS2[c]	Change from 8-weeks post initial treatment in BCVA at week 48	• Number and Percentage of patients in the HDq12 analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	0	x_7 letters
			• Number and Percentage of patients in the HDq16 analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	0	y_7 letters
			• Number and Percentage of patients in the All HD analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	0	z_7 letters
4b	mFAS1[b]; mFAS2[c]	Change from 8-weeks post initial treatment in BCVA at week 48	• Number and Percentage of patients in the HDq12 analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	-2	x_8 letters
			• Number and Percentage of patients in the HDq16 analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	-2	y_8 letters
			• Number and Percentage of patients in the All HD analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	-2	z_8 letters

[a] FAS = Full Analysis Set, which includes all randomized patients who received at least 1 dose of study medication.
[b] mFAS1 = Modified Full Analysis Set 1, which includes all randomized patients who completed the initial treatment phase and maintained dosing interval (HDq12, HDq16, and 2q8 groups).
[c] mFAS2 = Modified Full Analysis Set 2, which includes all randomized patients who completed the initial treatment phase and maintained dosing interval (All HD group and 2q8 group).

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