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Title page

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

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

Bayer study drug	BAY 86-5321 / aflibercept		
Study purpose	Efficacy		
Clinical study phase:	3	**Date:**	22 AUG 2022
Study No.:	20968	**Version:**	3.0
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This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

Table of Contents

Table of Tables

Abbreviations

2q8	aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals
AAS	ADA Analysis Set
ADA	Anti-drug Antibodies
AE	Adverse event
ANCOVA	Analysis of covariance
APTC	Anti-Platelet Trialists Collaboration
AUCinf	Area under the curve from time zero to infinity
AUClast	Area under the curve to the last quantifiable concentration
BCVA	Best corrected visual acuity
BLOQ	Below limit of quantification
BMI	Body mass index
CI	Confidence interval
Cmax	Maximum concentration
CNV	Choroidal neovascularization
CRF	Case Report Form
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
CST	Central subfield retinal thickness
Ctrough	Trough concentration
DB	Database
DPKS	Dense Pharmacokinetic analysis set
DRSS	diabetic retinopathy severity scale
DMC	Data Monitoring Committee
DRM	Dose regimen modification
ECG	Electrocardiogram
ED	Early Discontinuation
EMA	European Medicines Agency
EOS	end of study
EP-SAP	EMA/PMDA Statistical Analysis Plan
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FAS	Full Analysis Set
FCS	Fully Conditional Specification
FDA	U.S. Food and Drug Administration
FP	fundus photography
GA	Geographic atrophy
G-SAP	Global Statistical Analysis Plan
HD	High dose (aflibercept 8 mg)
HDq12	high dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals
HDq16	high dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals
HLT	MedDRA High level term
ICE	Intercurrent event
ICGA	Indocyanine green angiography
IOP	Intraocular pressure
IRF	Intraretinal fluid
IVT	Intravitreal
IXRS	Interactive Response System
LL	Lower limit
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LOQ	Limit of quantification
LS	Least squared
LSmeans	Least-square means

MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed model for repeated measurements
MNAR	Missing not at random
NAb	Neutralizing antibody data
nAMD	Neovascular (wet) age-related macular degeneration
NAbAS	NAb Analysis Set
NEI-VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
OC	Observed case
OCT-A	optical coherence tomography angiography
PCSV	Potentially clinically significant value
PCV	Polypoidal choroidal vascularization
PD	Protocol deviation
PK	Pharmacokinetics
PKS	Pharmacokinetic analysis set
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PPS	Per protocol set
PT	Preferred Term
q12	every 12 weeks
q16	every 16 weeks
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard deviation
SD-OCT	Spectral domain optical coherence tomography
SOC	Primary system organ class
SRF	Subretinal fluid
subRPE	Subretinal pigment epithelium
t1/2	Half-life
tlast	Last time point
tmax	Time of Cmax
TEAE	Treatment-emergent adverse event
TFLs	Tables, figures and listings
UA	Unscheduled Assessment
ULN	Upper limit of normal
VEGF	Anti-vascular endothelial growth factor

1. Introduction

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

Although many patients benefit from treatment with currently available anti-vascular endothelial growth factor (VEGF) agents, a sizable proportion of patients still need intravitreal (IVT) injections as frequently as every 4 to 8 weeks, specifically in the first year of treatment. A continued need for treatment in intervals as short as 4 to 8 weeks poses significant treatment burden to patients, physicians, and to healthcare systems. In addition, long-term data in patients with nAMD suggest that visual benefits achieved in the first year of treatment may be lost if regular dosing is not maintained.

EYLEA (also known as aflibercept 2 mg) is a VEGF antagonist approved as of 07 OCT 2019 in over 109 countries for the treatment of nAMD at a dosage level of 2 mg (administered at a concentration of 40 mg/mL injected IVT) administered every 8 (q8) weeks.

This study will investigate the efficacy and safety of a high dose aflibercept 8 mg (HD; provided at a concentration of 114.3 mg/mL) with the intent of achieving non-inferior best corrected visual acuity (BCVA), while extending the dosing interval and potentially improving visual and/or anatomic outcomes for HD versus the currently approved aflibercept 2 mg dose regimen.

This statistical analysis plan (SAP) describes all details of the required statistical analyses to be conducted at Week 48, Week 60 and Week 96 (end of study [EOS]). The summary tables, figures and listings (TFLs) to be included in the Clinical Study Report (CSR) will be defined in a separate document. This SAP is based on the integrated clinical study protocol version 3.0 (dated 26 APR 2022), which includes Amendment 2. All references to study protocol hereafter refer to that version of the protocol.

2. Study Objectives

Table 2–1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine if treatment with aflibercept 8 mg (HD) at intervals of 12 or 16 weeks provides non-inferior BCVA change compared to aflibercept 2 mg every 8 weeks in participants with nAMD	Primary Endpoint • Change from baseline in BCVA measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at Week 48
Secondary - Efficacy	
To determine the effect of HD versus 2 mg aflibercept on other visual and anatomic measures of response To assess the efficacy of HD compared to 2 mg aflibercept on vision-related quality of life	Key Secondary Efficacy Endpoints • Change from baseline in BCVA measured by the ETDRS letter score at Week 60 (for regulatory submissions to European Medicines Agency/Pharmaceuticals and Medical Devices Agency [EMA/PMDA] Analysis Plan only, see Section 6.2 • Proportion of participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in central subfield at Week 16 Additional Secondary Efficacy Endpoints • Proportion of participants gaining at least 15 letters in BCVA from baseline at Week 48 • Proportion of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Week 48 • Change in choroidal neovascularization (CNV) size from baseline to Week 48 • Change in total lesion area from baseline to Week 48 • Proportion of participants with no IRF and no SRF in the central subfield at Week 48 • Change from baseline in central subfield retinal thickness (CST) at Week 48 • Change from baseline in National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) total score at Week 48
Secondary - Safety	
To evaluate the safety of aflibercept	• Treatment-emergent adverse events (AEs) and serious AEs (SAEs) through Week 48, 60, and 96
Secondary - Other	
To evaluate the pharmacokinetics (PK) and immunogenicity of aflibercept	• Systemic exposure to aflibercept as assessed by plasma concentrations of free, bound, adjusted bound and total aflibercept from baseline through Week 48 • Assessment of immunogenicity to aflibercept through end of study (Week 96)

Table 2–1: Objectives and Endpoints

Objectives	Endpoints
Exploratory	
To determine the effect of HD versus 2 mg aflibercept on functional and anatomic measures of response as well as on vision-related quality of life	• Change from baseline in BCVA measured by the ETDRS letter score at Week 96 • Change from baseline in BCVA averaged over the period from Week 36 to Week 48 and from Week 48 to Week 60 • Proportion of participants gaining at least 15 letters in BCVA from baseline at Week 60 and Week 96 • Proportion of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Week 60 and Week 96 • Proportions of participants gaining and losing at least 5 or at least 10 letters in BCVA from baseline at Week 48, Week 60, and Week 96 • Proportion of participants losing at least 15 letters in BCVA from baseline at Week 48, Week 60, and Week 96 • Change in CNV size from baseline to Week 60 and Week 96 • Change in total lesion area from baseline to Week 60 and Week 96 • Change from baseline in CST at Week 60 and Week 96 • Proportion of participants with no IRF and no SRF in the central subfield at Week 96 • Proportion of participants without retinal fluid (total fluid, IRF, and/or SRF) and subretinal pigment epithelium (subRPE) fluid in central 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, and/or SRF in the central subfield) • Proportion of participants with sustained fluid-free retina over 48 weeks, 60 weeks, and 96 weeks (total fluid, IRF, and/or SRF in the central subfield) • Change from baseline in NEI-VFQ-25 total score at Week 60 and Week 96 • Proportion of participants without leakage on fluorescein angiography (FA) at Week 48, Week 60, and Week 96
To evaluate the duration of effect of HD after 3 initial doses at 4-week intervals followed by dosing q12 or q16	• Proportion of participants with q16 or longer treatment interval through Week 48, Week 60, and Week 96 in HDq16 group • Proportion of participants with q12 or longer interval through Week 48, Week 60, and Week 96 in the HDq12 and HDq16 groups • Proportion of participants with q12 or q16 or longer treatment interval as the last treatment interval at Week 48, Week 60, and Week 96 in HDq12 and HDq16 groups, respectively
Based on dense PK sampling, characterize the concentrations in plasma over time, and corresponding PK parameters	• Concentrations of free, bound, adjusted bound and total aflibercept over time, and PK parameters

Table 2–1: Objectives and Endpoints

Objectives	Endpoints
for aflibercept	
For all participants, explore the relationship between PK and selected systemic and ocular response variables	• Relationship of free aflibercept concentrations and blood pressure • Dose and/or exposure-response analyses for select safety and efficacy endpoints, as appropriate
Other Pre-specified Objectives	These objectives will be reported outside of the CSR.
To study molecular drivers of nAMD or related diseases, clinical efficacy of aflibercept, and affected molecular pathways	• Evaluation of clinical efficacy parameters by repertoire or frequency of genetic alterations (genomics substudy) • Treatment related changes in circulating biomarkers (future biomedical research [FBR])

Additional pre-specified exploratory efficacy endpoints and 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 9.7 for details.

3. Study Design

This is a randomized, double-masked (participant and investigator masked), active-controlled, multi-center study with 3 parallel groups.

The study consists of a screening/baseline period, a treatment period with duration of 92 weeks, and an end of study visit at Week 96 (and a safety follow-up visit at Week 100 for French participants only). No study intervention will be administered at the end of study visit at Week 96 (or Week 100).

Approximately 960 eligible participants with nAMD will be randomly assigned to receive IVT injections of HD or 2 mg in a 1:1:1 ratio to 3 parallel treatment groups (320 in each group):

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

Participants will be centrally assigned to randomized study intervention using an Interactive Response System (IXRS). Before the study is initiated, the directions for the IXRS will be provided to each site.

Study intervention will be dispensed at the study visits summarized in the schedule of activities in the study protocol.

Participants will be stratified based on baseline BCVA (<60 vs. ≥60) and geographical region (Japan vs. Rest of World), to ensure balanced distribution of the treatment groups within each stratum. A Dense PK Substudy is planned to be conducted in 24 participants (refer to Section 6.3.2).

Only one eye can be treated within the study. Sham procedures will be done on visits when an active injection is not planned. No sham procedures will be done at the non-treatment visits 5

(Day 60-64) and 6 (Week 12). At all subsequent visits, all participants will receive either active study treatment injection or sham procedure (for masking purposes), depending on their assigned treatment schedule (including any changes to the interval based on the dose regimen modification (DRM) assessments).

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

Based on these assessments, participants in the HD groups may have their treatment intervals shortened or extended. The minimum interval between injections will be 8 weeks, which is considered a rescue regimen for participants randomized to HD aflibercept who are unable to tolerate a dosing interval greater than every 8 weeks. Participants in the aflibercept 2 mg group will remain on fixed q8 dosing throughout the study (i.e., will not have modifications of their treatment intervals regardless of the outcomes of the DRM assessments).

Beginning at Week 16, participants in the HD groups may have the dosing interval shortened based on meeting pre-specified DRM criteria.

Starting at Week 52, all participants randomized to HDq12 or HDq16 will be eligible for adjustments of their treatment intervals (shortening or extension) based on pre-specified DRM criteria, with the dose interval adjustments (shortening or extension) becoming effective at or after Week 60. All participants will be followed every 4 weeks through Week 96 (Week 100 for French participants only).

Due to differing requirements for the submission to regulatory authorities, 2 different testing strategies will be applied, which will be detailed in this SAP document: a Global plan (G-SAP) and an European Medicines Agency [EMA] and Pharmaceuticals and Medical Devices Agency [PMDA] plan (EP-SAP). The G-SAP will constitute the main analysis for the study. The EP-SAP has been specifically planned for submission to the EMA/PMDA regulatory authorities.

An analysis of data up to Week 48 (including the primary efficacy analysis according to the G-SAP) will take place once all participants have completed Week 48 (or prematurely discontinued). A further analysis of data up to Week 60 (including a confirmatory analysis at this time point according to the EP-SAP) will take place once all participants have completed Week 60 (or prematurely discontinued). Furthermore, a descriptive analysis of all data will be conducted after all participants have completed the study at Week 96 (or prematurely discontinued). This SAP covers all three planned analyses.

The databases and analyses at Week 48 and Week 60 will only include study intervention information up to the visit prior to Week 48 and Week 60, respectively. For these visits (Week 48 and Week 60, respectively), only data assessed prior to the study intervention will be part of the database/analyses. Further details are provided in a separate document “Data Cut-Off Specifications”.

Masking of the study site personnel will continue until the end of the study. Masking/unmasking of the study team is described in the study protocol and will further be detailed in the blinding maintenance plan.

4. General Statistical Considerations

4.1 General Principles

Continuous data will be summarized in terms of the number of observations, mean, standard deviation (SD), median, quartiles, minimum, and maximum. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database (DB). All other statistics (mean, median, quartiles, arithmetic SD, confidence intervals [CI]) will have one additional decimal place more than the raw data recorded in the database.

Categorical data will be summarized in terms of the number of participants providing data at the relevant time point (n), frequency counts and percentages. Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n (the number of observations with non-missing values) as the denominator, except for outputs where the denominator is already specified differently. Change from baseline will be calculated as the visit value of interest minus the baseline value.

All p-values should have 4 decimal digits; in case of p-values less than 0.0001, the documentation should be <.0001.

The statistical evaluation will be performed by using the software package SAS release 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

4.1.1 Determination of Sample Size

The sample size calculation is based on the primary endpoint analysis, “change from baseline in BCVA measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score to Week 48” in 2 comparisons to assess non-inferiority: HDq12 versus 2q8, and HDq16 versus 2q8.

The sample size has been calculated under the following assumptions:

- The changes in BCVA letter score from baseline are normally distributed.
- The true difference in the mean change in BCVA between HDq12 and 2q8, and between HDq16 and 2q8 is 0 letters.
- The SD of the residuals is CCI (derived from the residuals of an analysis of covariance (ANCOVA) analysis of the VIEW1/VIEW2 studies).

Under the hierarchical testing strategy, a sample size of 288 evaluable participants per group provides 94% power for rejecting the initial null hypothesis (HDq12 vs 2q8) for the primary endpoint assessing non-inferiority with a 1-sided t-test at significance level of 0.025. The power to reject both primary null hypotheses (HDq12 vs 2q8 and HDq16 vs 2q8) is 88%. Under the prior testing strategy that was planned originally (before Protocol version 3.0, Global Amendment 2), a sample size of 288 evaluable participants per group provides 90% power for rejecting each of the null hypotheses for the primary endpoints assessing non-inferiority (HDq12 vs 2q8 and HDq16 vs 2q8) with a 1-sided t-test at significance level of 1.25% (=2.5%/2 Bonferroni correction).

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

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

Justification of Japanese sample size

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

For superiority trials, the PMDA guidance (1) proposes to determine the number of Japanese participants so that $D_{Japan} / D_{all} > \pi$ will occur with a probability of 80 % or higher, whereas D_{all} is the treatment difference in the entire study population across regions, and D_{Japan} is the treatment difference within the Japanese sub-population. Furthermore, $\pi = 0.5$ is generally recommended.

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

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

- the probability to show a consistent result in at least one of the 2 hypothesis tests for the primary endpoints assessing non-inferiority (HDq12 vs. 2q8 and HDq16 vs. 2q8)) described in Section 6.2.2 is 81%.
- the probability to show a consistent result in one particular hypothesis test for the primary endpoints is 71%.

4.2 Handling of Dropouts

Dropouts will be defined as participants who prematurely discontinue from the study and study intervention at the same time for any reason. This includes also participants who are lost to follow-up. Possible reasons for premature discontinuation from the study can be found in the protocol, Section 7.2. Additionally, participants might prematurely discontinue from the study and study intervention due to the COVID-19 pandemic. It may be also necessary for a participant to permanently discontinue study intervention, while remaining in the study to be evaluated for safety evaluation as described in the protocol, Section 7.1.

In the case of such premature discontinuation of the study intervention, all assessments, as described in the protocol for the end of study/early discontinuation (ED) visit, should be completed (ED assessments). If the discontinuation from the study and from the study intervention is happening at the same time, an ED visit should be completed (see Section 4.5.3) while for participants who prematurely discontinued study intervention at the timing of one of their regular study intervention visits (i.e. Visits 3-26) but remained in the study afterwards, all ED assessments that were not planned at the respective visit, should be entered as unscheduled assessments and need to be re-mapped to the regular visit, since some assessments are not scheduled to be conducted at each visit.

Data assessed after the time period as described in Table 9–12 below, but prior to study completion or discontinuation will not be used in the main confirmatory analysis of primary and key secondary endpoints.

Handling of missing data due to dropouts is described in Section 6.2 for efficacy variables. No action for missing data due to dropouts is taken for other variables. Participants who dropped out will not be excluded from any summaries except where clearly stated.

4.3 Handling of Missing Data

All missing or partial data will be presented in the participant data listing as they are recorded on the Case Report Form (CRF).

4.3.1 Additional Descriptive Analyses in the Presence of Missing Data

The number of participants who prematurely discontinued from the study and/or study intervention for any reason, as well as the reasons for premature discontinuation from the study and/or study intervention, will be reported. Kaplan-Meier plots for "Time to end of study" and "Time to end of study intervention" will be provided.

4.3.2 General Rules

Where appropriate, the following rules will be implemented so as not to exclude participants from statistical analyses due to missing or incomplete data:

- **Efficacy Variables**
  Statistical methods for missing data due to dropouts in efficacy variables is described in Section 6.2.
- **Concomitant medication and adverse events**
  For AEs and medications the complete start and stop date must be available to determine if the AE or medication is occurring during the study intervention period. When only partial dates are available, the following rules will be used:
  If only month and year of the start date are available and the end date is after the date of first study intervention, impute with the first day of the month or with the date of the first study intervention (i.e. first injection in the study eye), whichever occurs later.
  If only the year of the start date is available and the end date is after the date of first study intervention, impute with month and day of first study intervention or with the first day of the year, whichever occurs later.
  Imputed dates will only be used for summary tables, listings will contain the original (partial) entries.

4.4 Interim Analyses and Data Monitoring

No interim analyses in the sense of a group-sequential or adaptive design are planned.

An analysis of data up to Week 48 (including the primary efficacy analysis) will take place once all participants have completed Week 48 (or prematurely discontinued). A further analysis of data up to Week 60 (including a confirmatory analysis at this time point for regulatory submission to EMA and PMDA) will take place once all participants have completed Week 60 (or prematurely discontinued). A final analysis of all data will be conducted after all participants have completed the study at Week 96 (or prematurely discontinued).

An independent Data Monitoring Committee (DMC) will meet periodically to review the ongoing masked and unmasked safety data of participants in the study and to provide recommendations to continue or terminate the study depending upon these reviews. The operation of the DMC is governed by a charter that describes the group's frequency of meeting, procedures (including but not limited to periodic safety monitoring), and requirements for reporting its observations to the sponsor. No early stopping for overwhelming efficacy is foreseen (consequently no alpha level adjustment will be done with regards to DMC analyses).

A Steering Committee will have close communication with the DMC, but only masked data will be shared or discussed. The study protocol provides more details on this.

Furthermore, potential arterial thromboembolic events (ATEs) will be evaluated by a masked adjudication committee prior to database unmasking. ATEs as defined by the Anti-Platelet Trialists' Collaboration (APTC) criteria include nonfatal myocardial infarction, nonfatal ischaemic stroke, nonfatal haemorrhagic stroke, or death resulting from vascular or unknown causes.

4.5 Data Rules

4.5.1 Determination of Baseline Values

Baseline values are defined as the last valid non-missing measurement at or prior to randomization (including scheduled and unscheduled assessments). This may be the measurement at screening (Visit 1) or the measurement at baseline (Visit 2) depending on the planned timing of procedures for each study visit. The study protocol provides more details on the timing of study procedures.

For systolic and diastolic blood pressure the baseline value is defined as the average of all measurements at or prior to randomization (for participants who failed the initial screening, measurements taken at the initial screening visit will not be included).

4.5.2 Unscheduled Assessments

Any measurements taken at unscheduled visits will be shown in subject data listings but will not be included in any summary tables in general. If more than one measurement of a variable is taken at an unscheduled visit, all measurements will be shown in listings.

4.5.3 End of Study / Early Discontinuation Visit

Participants may discontinue prematurely from study intervention. At the same time or later participants may discontinue prematurely from study. In case of premature discontinuation of the study and/or study intervention, all assessments should be completed, as described in the protocol for the end of study (EOS)/ED visit.

For participants who discontinue prematurely from the study and/or study intervention, visit-based information recorded in the EOS/ED visit folder might be re-mapped to the regular study visit, if the EOS/ED visit was performed within the relevant regular visit window and the corresponding regular study visit was not perfomed (see detailed rules below). Visit-based information recorded in the EOS/ED visit folder which cannot be re-mapped to the regular study visit will be mapped to "ED Visit" and handled like unscheduled assessments, described in the section above.

For participants who completed the study and study intervention, no re-mapping is necessary, but visit-based information recorded in the EOS/ED visit folder will be mapped to "Visit 27 / Week 96" and displayed in summary tables as such.

For some variables this can result in data for visits at which this variable was not scheduled to be collected. This data will nevertheless be included into the LOCF analyses. In descriptive by visit summary tables and also in repeated measurement analysis, only the pre-planned scheduled visits should be shown/included.

Mapping of selected assessments to regular study visits

The following assessments will be mapped:

- BCVA (ETDRS) and Refraction (24)
- IOP
- Slit Lamp Examination
- Indirect Ophthalmoscopy
- SD-OCT
- Vital signs
- Pregnancy test

The following rule will be used:

- If EOS/ED visit performed within visit window of a regular study visit (as specified in the "Schedule of Activities" in the protocol), then re-mapping to regular study visit

For example, if a participant discontinued prematurely (study and/or study intervention) at the timing of Visit 3 / Week 4 (i.e. EOS/ED visit date = study day 29±5 days), then any of the assessments listed above recorded in the EOS/ED visit folder will be re-mapped to regular study Visit 3, unless a regular study Visit 3 was already perfomed.

No remapping to Visit 5 will be done (i.e. PK collection visit only).

4.5.4 Imaging data assessed by the reading center

If imaging data have been assessed by the reading center, but were also captured in the eCRF, only the data assessed by the reading center will be used for the analysis.

In summary tables the following parameters will be evaluated and classified as follows:

From spectral domain optical coherence tomography (SD-OCT) assessment:

- Intraretinal fluid (IRF) in central subfield (Reading center variable: IRF presence [IRF], Testname in OE domain: IRTFLVIS):
    - IRF=No (if any of them is ticked):
        - Absent
        - Definite, outside center subfield only
        - Questionable
    - IRF=Yes (if any of them is ticked):
        - Definite, only non-cystoid, center subfield involved
        - Definite, cystoid, center subfield involved
    - IRF=Undetermined (if any of them is ticked):
        - Cannot Grade
        - Not Applicable
- Subretinal fluid (SRF) in central subfield (Reading center variable: SRF presence [SRF], Testname in OE domain: SRFVIS):
    - SRF=No (if any of them is ticked):
        - Absent

- Definite, outside center subfield only
- Questionable

- SRF=Yes:
  - Definite, center subfield involved
- SRF=Undetermined (if any of them is ticked):
  - Cannot Grade
  - Not Applicable

- Subretinal pigment epithelium (subRPE) fluid in central subfield (Reading center variable: SubRPE fluid [SRPEFP], Testname in OE domain: SRPEFP):
  - SubRPE fluid =No (if any of them is ticked):
    - Absent
    - Definite, outside center subfield only
    - Questionable
  - SubRPE fluid =Yes:
    - Definite, center subfield involved
  - SubRPE fluid = Undetermined (if any of them is ticked):
    - Cannot Grade
    - Not Applicable
- IRF in foveal center (Reading center variable: IRF presence at center point [IRFPCP], Testname in OE domain: PRIRFCP):
  - IRF in foveal center = No (if any of them is ticked):
    - IRF presence = Absent
    - IRF presence = Questionable
    - IRF presence = Definite, outside center subfield only
    - IRF presence = Definite, only non-cystoid, center subfield involved AND IRF presence at center point = Absent
    - IRF presence = Definite, only non-cystoid, center subfield involved AND IRF presence at center point = Questionable
    - IRF presence = Definite, cystoid, center subfield involved AND IRF presence at center point = Absent
    - IRF presence = Definite, cystoid, center subfield involved AND IRF presence at center point = Questionable
  - IRF in foveal center=Yes (if any of them is ticked):
    - IRF presence = Definite, only non-cystoid, center subfield involved AND IRF presence at center point = Definite
    - IRF presence = Definite, cystoid, center subfield involved AND IRF presence at center point = Definite

- IRF in foveal center=Undetermined (if any of them is ticked):
  - IRF presence = Cannot Grade
  - IRF presence = Not Applicable
  - IRF presence = Definite, only non-cystoid, center subfield involved AND IRF presence at center point = Cannot Grade
  - IRF presence = Definite, only non-cystoid, center subfield involved AND IRF presence at center point = Not Applicable
  - IRF presence = Definite, cystoid, center subfield involved AND IRF presence at center point = Cannot Grade
  - IRF presence = Definite, cystoid, center subfield involved AND IRF presence at center point = Not Applicable

- SRF in foveal center (Reading center variable: SRF presence at center point [SRFPCP], Testname in OE domain: SRFPCP):
  - SRF in foveal center=No (if any of them is ticked):
    - SRF presence = Absent
    - SRF presence = Questionable
    - SRF presence = Definite, outside center subfield only
    - SRF presence = Definite, center subfield involved AND SRF presence at center point = Absent
    - SRF presence = Definite, center subfield involved AND SRF presence at center point = Questionable
  - SRF in foveal center=Yes:
    - SRF presence = Definite, center subfield involved AND SRF presence at center point = Definite
  - SRF in foveal center=Undetermined (if any of them is ticked):
    - SRF presence = Cannot Grade
    - SRF presence = Not Applicable
    - SRF presence = Definite, center subfield involved AND SRF presence at center point = Cannot Grade
    - SRF presence = Definite, center subfield involved AND SRF presence at center point = Not Applicable

- Central subfield retinal thickness (CST) (Reading center variable: SECTORC, Testname in OE domain: RETHKSEC, note: it is recorded in mm but needs to be summarized in µm)

From fluorescein angiography (FA)/ fundus photography (FP) assessment:

- Geographic atrophy (GA) (Reading center variable: GA, Testname in OE domain: GAVIS):
  - GA=No (if any of them is ticked):

        - Absent
        - Questionable
    - GA=Yes:
        - Definite
    - GA=Not available (if any of them is ticked):
        - Cannot Grade
        - Not Applicable
- Choroidal neovascularization (CNV) size (Reading center variable: CNVCLSZ [Total CNV area – AreaSize], Testname in OE domain: CNVSIZE, note: it is recorded in mm^2)
- CNV type (Reading center variable: CNVTYPE, Testname in OE domain: CNVTYPE):
    - CNVTYPE= Type 1 – occult or PCV:
        - Type 1
    - CNVTYPE= Type 2 – classic CNV:
        - Type 2
    - CNVTYPE= Type 1 and Type 2 – both classic and occult are present:
        - Type 1 and Type 2
    - CNVTYPE= Type 3 – RAP:
        - Type 3
    - CNVTYPE= Cannot grade:
        - Cannot grade
    - CNVTYPE= Not applicable – no CNV present:
        - Not applicable
- CNV classification (Reading center variable: CNVCLASS, Testname in OE domain: CNVCLASS)
    - CNVCLASS:
        - CNV less than 50% of lesion
        - Predominantly classic
        - Minimally classic
        - Occult only
        - RAP
        - PCV
        - Cannot grade
        - Not applicable

- Total lesion area (Reading center variable: TLEAREA [Total lesion area within ETDRS grid – AreaSize], Testname in OE domain: TLESAREA, note: it is recorded in mm^2)
- Leakage on fluorescein angiography (based on reading center variables LEAAREA [Leakage Area], LEASIZE [Area Size - Total Leakage Area], RPERIPTE [Presence of RPE Rip Tear (Macular)], Testnames in OE domain: LEAKAREA, LEAKSIZE, RPERIPTE)
    - Leakage = No (when the following is fulfilled):
        - LEAAREA = "Not Applicable" and RPERIPTE is not "Definite"
    - Leakage = Yes (when the following is fulfilled):
        - LEAAREA is not "Not Applicable" and is not "Cannot grade" and LEASIZE > 0
    - Leakage = Undetermined (when any of the following is fulfilled):
        - LEAAREA = "Not Applicable" and RPERIPTE=" Definite"
        - LEAAREA = "Cannot grade"

From indocyanine green angiography (ICGA) assessment:

- Polypoidal choroidal vascularization (PCV) (Reading center variable: PCV, Testname in OE domain: PCV)
    - PCV=No (if any of them is ticked):
        - Absent
        - Questionable
    - PCV=Yes:
        - Definite
    - PCV=Not available (if any of them is ticked):
        - Cannot Grade
        - Not Applicable

The subgroup of participants with PCV is defined as participants with "Definite" PCV in the ICGA assessment (Reading center variable: PCV, Testname in OE domain: PCV) or "PCV" as CNV classification in the FA/FP assessment (Reading center variable: CNVCLASS, Testname in OE domain: CNVCLASS).

4.5.5 Definition of Fellow Eye Treatment

Fellow eye treatment will be identified from the prior and concomitant medication page by

- selecting for any of the following medications:
    - Aflibercept (trade name: Eylea)
    - Bevacizumab (trade name: Avastin)
    - Brolucizumab (trade name: Beovu)
    - Ranibizumab (trade name: Lucentis)

- Faricimab (trade name: Vabysmo)
- Conbercept (trade name Lumitin)
- Pegaptanib sodium (trade name: Macugen)

- and selecting for the laterality of the fellow eye.

Medication that was administered prior to the first dose of study treatment will be considered prior fellow eye treatment, whereas medication that was administered at the first dose of study treatment or later will be considered concomitant fellow eye treatment (i.e. bilateral treatment).

4.5.6 Definition of Prohibited Medications

Prohibited medications as identified from the prior and concomitant medication page are

- any of the following anti-VEGF medications administered in the study eye:
  - Aflibercept (trade name: Eylea), unless administered as study intervention
  - Bevacizumab (trade name: Avastin)
  - Brolucizumab (trade name: Beovu)
  - Ranibizumab (trade name: Lucentis)
  - Faricimab (trade name: Vabysmo)
  - Conbercept (trade name Lumitin)
  - Pegaptanib sodium (trade name: Macugen)
- as well as those following medications administered systemically with the intent of treating AMD in the study or fellow eye:
  - Verteporfin (trade name Visudyne)

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

4.6 Masked Review

Upon each database release (Week 48, Week 60 and Week 96), listings of masked protocol deviations (PDs) and validity findings, as well as the analysis datasets will be produced after release of the final pre-freeze/pre-lock clinical eCRF DB and discussed in Data Review Meetings, where for Week 48 database release it will be decided which participants will be excluded from the per protocol set. The validity for the different analysis sets for the analysis at Week 48, Week 60 and Week 96, respectively, and especially the decision at Week 48 database release regarding the exclusion of participants from the per protocol analysis will be determined. Note, the PPS should not change throughout the analysis at Week 48, Week 60 and Week 96, respectively, since exclusion of subjects is mainly based on screening/baseline data which will not change over time.

For determining the validity for the different analysis sets, all participants of these meetings are masked to the treatment assignment and to the detailed results. The results of these meetings may comprise decisions and details relevant for statistical evaluation. Any changes

to the statistical analysis prompted by the results of the Data Review Meetings will be documented in an amendment to this SAP.

After unmasking of the frozen/locked clinical eCRF DB the analysis datasets will be created again and will be compared with the pre-freeze/pre-lock analysis datasets to verify if there were changes to the clinical eCRF DB and/or to the relevant PDs and also to identify those PDs that can only be assessed after unmasking. Those evaluations for the analyses at Week 48 and Week 60 will be done by an unmasked statistician, while the main study team will remain masked until the final analysis at Week 96 as described in the blinding maintenance plan.

4.7 Outputs/Procedures related to COVID-19

This study started after the onset of the COVID-19 pandemic. A separate listing will display all participants affected by the COVID-19 related study disruption by unique participant identifier and by investigational site, and a description of how the participant's study participation was altered. Other listings will display all participants with protocol deviations associated with the COVID-19 pandemic and with COVID-19 adverse events. Furthermore, tables for participant validity status and disposition will contain COVID-19 pandemic associated findings and reasons.

Additionally, the following summary tables will be displayed:

- Study sample sizes by trial unit: Participants affected by COVID-19 pandemic related study disruption for all enrolled participants
- Number of participants by country / region for all participants affected by COVID-19 pandemic related study disruption
- Number of participants affected by COVID-19 pandemic related study disruption.

Additional analyses may be added due to regulatory requirements or requests.

4.8 Outputs/Procedures related to the Ukraine/Russia crisis

This study started prior to the onset of the 2022 crisis between Russia and Ukraine and includes study sites located in Ukraine and in Russia. A separate listing will display all participants affected by the crisis related findings and deviations by unique participant identifier and by investigational site, and a description of the finding or deviation.

Additional analyses may be added due to regulatory requirements or requests.

5. Analysis Sets

Primary and the key secondary efficacy variables will be evaluated on both the Full Analysis Set (FAS) and the Per Protocol Set (PPS), all other efficacy variables will be evaluated on the FAS only. Safety variables will be analyzed using the Safety Analysis Set (SAF). Sparse pharmacokinetic data will be analyzed using the Pharmacokinetic analysis set (PKS), while dense pharmacokinetic data will be analyzed using the Dense Pharmacokinetic Analysis Set (DPKS). Anti-drug antibody (ADA) data will be analyzed using the ADA Analysis Set (AAS) and neutralizing antibody (NAb) data will be analyzed using the NAb Analysis Set (NAbAS).

5.1 Assignment of Analysis Sets

Final decisions regarding the assignment of participants to analysis sets will be made during the Data Review Meetings prior to unmasking at Week 48, Week 60 and Week 96 and the list of important deviations and validity findings leading to exclusion from analysis sets as well as assignment to analysis sets will be documented in the Data Review Meeting minutes (see Section 4.6).

Full analysis set (FAS)

The FAS will include all participants who have been randomly assigned to study intervention and who received at least 1 dose of study intervention. Participants will be analyzed within their original randomized group (regardless of any changes to dose interval; as randomized).

Per protocol set (PPS)

As defined in the protocol, the PPS will include all participants in the FAS who did not have an important deviation from the protocol affecting the primary efficacy variable or a validity finding as listed below.

More concretely this means, the PPS will include all participants in the FAS that

- did not have any violation of relevant inclusion / exclusion criteria
- had a baseline BCVA value available
- had at least one post-baseline BCVA value available
- had any IRF or SRF affecting the central subfield at baseline according to the definitions described in Section 4.5.4.

Other relevant deviations from the protocol affecting efficacy will be considered as intercurrent events in the context of the Estimands strategy described in Section 9.5.

The final determination on the exclusion of participants from the PPS will be made during the Data Review Meeting (on masked data) held in accordance with ICH E9 prior to database freeze on Week 48 data.

Analysis of the PPS will be performed according to the treatment the participant actually received (as treated).

Safety analysis set (SAF)

The SAF will include all participants who were randomly assigned to study intervention and who received at least 1 dose of study intervention. Analysis of the SAF will be performed according to the treatment the participant actually received (as treated).

PK analysis sets

The PKS will include all participants who received any study intervention and who had at least 1 non-missing drug concentration measurement following the first dose of study intervention. Analysis of the PKS will be performed according to the treatment the participant actually received (as treated).

The DPKS will include all participants who did not meet any of the additional exclusion criteria for the Dense PK Substudy, who gave their written consent to participate in the Dense PK Substudy and who had a at least 1 non-missing drug concentration measurement (dense PK result) following the first dose of study intervention. Analysis of the DPKS will be performed according to the treatment the participant actually received (as treated).

Immunogenicity analysis sets

The AAS will include all participants who received study intervention and had at least 1 non-missing result in the ADA assay following the first study dose.

The NAbAS will include all participants who received any study intervention 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).

Analysis of both immunogenicity analysis sets will be performed according to the treatment the participant actually received (as treated).

As randomized versus as treated

Since the only systematic deviation from the randomized treatment could occur due to a systematic error in the IXRS system set up, it is assumed that, in general, participants are treated as randomized (i.e. the randomized treatment group will be considered the actual treatment group, unless the participant has not been treated at all after randomization). Isolated incorrect treatments at particular timepoints will not constitute a change in the "as treated" assignment, but will be considered as intercurrent events (refer to Section 9.5).

Participants whose "as treated" assignment differs from their "as randomized" assignment will be listed.

5.2 Definition of Subgroups

The following subgroups will be considered for efficacy analyses:

- Age at enrollment: < 65 years, ≥ 65 to < 75 years, ≥ 75 years to < 80 years, ≥ 80 years to < 85 years, ≥ 85 years
- Sex: male, female
- Geographic region: Japan, Rest of the world
- Ethnicity: Not Hispanic or Latino, Hispanic or Latino
- Race (only subgroups with sufficient sample size): White, Asian
- Baseline BCVA: ≤ 73 letters, > 73 letters
- Baseline PCV: yes, no (as defined in Section 4.5.4)

All subgroup analyses will be descriptive only, i.e. any statistical testing / calculation of p-values were done for exploratory purpose.

The following subgroups will be considered for safety analyses:

- Age at enrollment: < 65 years, ≥ 65 to < 75 years, ≥ 75 years to < 80 years, ≥ 80 years to < 85 years, ≥ 85 years
- Sex: male, female
- Geographic region: Japan, Rest of the world
- Ethnicity: Not Hispanic or Latino, Hispanic or Latino
- Race (only subgroups with sufficient sample size): White, Asian
- Medical history of hypertension: No, Yes
- Medical history of cerebrovascular disease: No, Yes

  - Medical history of ischaemic heart disease: No, Yes
- Medical history of renal impairment: Normal, Mild, Moderate, Severe
  - Medical history of hepatic impairment: No, Yes

These subgroups are defined in more detail in Appendix 9.4.

6. Statistical Methodology

All summaries will be presented by study intervention. All variables shown in summaries will also be included in subject data listings.

The analysis of the primary and key secondary efficacy endpoints will be done for FAS and also for PPS. Pharmacokinetic analysis will be presented for PKS and DPKS. Safety analyses will be presented for SAF and immunogenicity analyses also for AAS or NAbAS.

6.1 Population Characteristics

6.1.1 Demographics and Disease Characteristics

Demographics and baseline assessments of vital signs to be summarized for FAS, DPKS and PPS will include:

- Age (as entered in CRF)
- Age categorized (< 65 years, ≥ 65 to < 75 years, ≥ 75 years to < 80 years, ≥ 80 years to < 85 years, ≥ 85 years)
- Sex
- Race (incl. further subgroupings for Asians) and ethnicity
- Weight (kg)
- Height (cm)
- Body mass index (BMI in kg/m²)
- BMI (≤ 25 kg/m², 25 kg/m² < BMI ≤ 30 kg/m², 30 kg/m² < BMI ≤ 35 kg/m², BMI > 35 kg/m²)
- Systolic blood pressure
- Diastolic blood pressure
- Heart rate
- Body temperature (°C)
- Fellow eye with history of wet AMD (YES/NO)
- Prior fellow eye treatment (as defined in Section 4.5.6) (YES/NO)
    - Aflibercept
    - Bevacizumab
    - Brolucizumab
    - Ranibizumab
    - Faricimab
    - Conbercept
    - Pegaptanib sodium

- Hypertension: yes, no
- Medical history of cerebrovascular disease: yes, no
- Medical history of ischaemic heart disease: yes, no
- Medical history of renal impairment: normal, mild, moderate, severe
- Medical history of hepatic impairment: yes, no

Baseline assessments of disease characteristics to be summarized for FAS, DPKS and PPS will include:

- Baseline BCVA (ETDRS letters score)
- Categorized baseline BCVA: ≤ 73 letters, > 73 letters
- Categorized baseline BCVA: < 60, ≥ 60 letters
- Baseline intraocular pressure (IOP in mmHg)
- Baseline GA (YES/NO/not available as defined in Section 4.5.4)
- Baseline PCV (YES/NO/not available as defined in Section 4.5.4)
- Baseline CST (in µm as defined in Section 4.5.4)
- Baseline CNV size (in mm^2 as defined in Section 4.5.4)
- Baseline total lesion area (in mm^2 as defined in Section 4.5.4)
- CNV type (as defined in Section 4.5.4)
- CNV classification (as defined in Section 4.5.4)
- Baseline National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25, total score)

Demographic data and baseline characteristics variables will be summarized using descriptive statistics for all three analysis sets (i.e. FAS, DPKS and PPS). Disease characteristics will be presented in a separate table. Only data of the study eye will be shown although most examinations are done bilateral.

6.1.2 Medical History

Medical history will be coded according to the version of Medical Dictionary for Regulatory Activities (MedDRA) available at database lock. Medical history is evaluated by a frequency table, showing number of participants with medical history findings by primary system organ class (SOC) and preferred term (PT). Ocular medical or surgical history of the study eye, ocular medical or surgical history of the fellow eye and non-ocular medical or surgical history will be summarize, respectively. All summaries will be presented for the SAF. Additionally, a listing including medical history records will be provided.

6.1.3 Disposition of Study Participants

The following categories for disposition of participants will be summarized descriptively:

The total number of participants who signed informed consent, were randomized, treated, completed study intervention and completed study for the respective analysis (Week 48, Week 60 and Week 96). The summary will include all participants who gave informed consent. Participants prematurely discontinuing the study/ study intervention will be summarized by reason for discontinuation.

The total number and percentage of participants who qualified as FAS, SAF, PPS, PKS, DPKS, AAS and NAbAS (as defined in Section 5.1) including the reasons for exclusion from the respective analysis set will be included in a summary table. Participants who were excluded from PPS will also be listed.

The disposition of participants who signed the informed consent will be summarized overall and by study site including the date of first consent, date of last visit and the number of participants with informed consent and in each analysis set.

The disposition of participants and the number of sites in regions and countries will be presented for the FAS. Totals of all regions and within a country will be added.

The number of participants with important protocol deviations by country and study site will be presented for all participants with signed informed consent. Number of screen failures will be included. A second summary will show the number and percentage of participants in each protocol deviation category for the FAS. Important protocol deviations will be listed for FAS.

6.1.4 Exposure and Compliance to Study Intervention

Compliance and exposure to the study intervention will be analyzed for SAF and PPS. Descriptive statistics will be used for analysis. For the analyses at Week 48 only study intervention data prior to Week 48 will be used and for the analyses at Week 60 only study intervention data prior to Week 60 will be used (as described in a separate document "Data Cut-Off Specifications").

6.1.4.1 Compliance

Compliance with study intervention during the first 48 weeks (60 weeks, 96 weeks, respectively) or up to premature discontinuation, respectively, will be calculated per participant as follows:

Compliance = (Number of actual study interventions received during period [before Week 48/ Week 60/ Week 96 or up to premature discontinuation, respectively])/ (Number of planned study interventions during period [before Week 48/ Week 60/ Week 96 or up to premature discontinuation, respectively]) x 100%.

For example, if a participant will prematurely discontinue the study after Week 20 but before or at the Week 24, the denominator will be 5 (i.e. the number of planned injections until before Week 24). For the calculation of compliance all injections (regardless if sham or active or from scheduled or unscheduled study interventions) will be used.

Compliance will be summarized for all periods and a listing will be prepared.

6.1.4.2 Exposure

For each participant, the following variables for the study eye will be used to summarize exposure to study intervention (including scheduled and unscheduled study interventions):

Based on actual injections:

- Total number of active injections
- Total number of sham injections
- Total amount of active study treatment (mg)
- Duration of study intervention calculated in weeks as: [(date of last study intervention prior to Week 48/ Week 60/ Week 96) – (date of first study intervention) +28]/7; 28 days are added because of the minimum 4-week dosing interval in the study

Based on assigned intervals as determined through IVRS, in accordance with DRM criteria (assessed at Week 16, Week 20 and at visits with active injections planned):

- Proportion of participants with q16 or longer treatment interval through Week 48, Week 60, and Week 96 in HDq16 group (i.e. all participants on q16 interval for whom it was not planned to have their interval shortened to q12 or q8 interval [according to DRM criteria] prior to Week 48, prior to Week 60, and prior to Week 96 [i.e. including only DRM criteria through Week 44, through Week 56, and through Week 92]) – exploratory endpoint
- Proportion of participants with q12 or longer interval through Week 48, Week 60, and Week 96 in the HDq12 and HDq16 groups (i.e. all participants on q12 or q16 interval for whom it was not planned to have their interval shortened to q8 interval [according to DRM criteria] prior to Week 48, prior to Week 60, and prior to Week 96 [i.e. including only DRM criteria through Week 44, through Week 56, and through Week 92]) – exploratory endpoint
- Proportion of participants with q12 or q16 or longer treatment interval as the last intended treatment interval at Week 48, Week 60, and Week 96 in HDq12 and HDq16 groups, respectively (based on DRM criteria assessed at the last visit with active injection before Week 48, Week 60, and Week 96 [i.e. including DRM criteria until Week 44, through Week 56, and through Week 92]) – exploratory endpoint
- Proportion of participants shortening treatment interval to q8 at Week 16 in HDq12 and HDq16 groups, respectively (i.e. immediately / never tolerated intervals longer than q8)
- Proportion of participants shortening treatment interval to q8 at Week 20 in HDq12 and HDq16 groups, respectively (i.e. immediately / never tolerated intervals longer than q8)
- Proportion of participants shortening treatment interval at anytime through Week 48, Week 60, and Week 96 in HDq12 and HDq16 groups, respectively
    - Proportion of participants shortening treatment interval to q8 at anytime through Week 48, Week 60, and Week 96 in HDq12 and HDq16 groups, respectively
    - Proportion of participants shortening treatment interval to q12 at anytime through Week 48, Week 60, and Week 96 in HDq12 and HDq16 groups, respectively
- Proportion of participants never extending treatment interval through Week 60, and Week 96 in HDq12 and HDq16 groups, respectively
- Proportion of participants extending treatment interval at anytime through Week 60, and Week 96 in HDq12 and HDq16 groups, respectively

These exposure variables do not consider if the study intervention is temporarily interrupted.

Exposure to study intervention will be summarized for the following periods:

- from Baseline to Week 48 (excluding intervention data at Week 48) – summary to be displayed at Week 48 and Week 60 analysis,
- from Baseline to Week 48 (excluding intervention data at Week 48, only participants considered as completer for Week 48) – summary to be displayed at Week 48 and Week 60 analysis,
- from Baseline to Week 60 (excluding intervention data at Week 60),

- from Baseline to Week 60 (excluding intervention data at Week 60, only participants considered as completer for Week 60),
- from Baseline to end of study (Week 96),
- from Week 48 to end of study (Week 96).

For each participant who received concomitant fellow eye treatment (as defined in Section 4.5.6), the following variables will be shown for SAF only:

- Total number of injections in fellow eye
- Participants without concomitant fellow eye treatment
- Participants with concomitant fellow eye treatment
    - Aflibercept (trade name: Eylea)
    - Bevacizumab (trade name: Avastin)
    - Brolucizumab (trade name: Beovu)
    - Ranibizumab (trade name: Lucentis)
    - Faricimab (trade name: Vabysmo)
    - Conbercept (trade name: Lumitin)
    - Pegaptanib sodium (trade name: Macugen)

Listings will show the participants' exposure duration, the number of sham and active injections. All participants who met DRM criteria will be listed separately.

6.1.5 Prior and Concomitant Medication

Prior and concomitant medication or therapy will be coded to Anatomical Therapeutic Chemical (ATC) classification codes according to the version of World Health Organization Drug Dictionary (WHO Drug Dictionary) available at database lock.

Prior and concomitant medication will be presented for the number and percentage of participants who took at least one prior and (new) concomitant medication and by ATC class (level 1) and subclass (level 2) for the SAF. Participants with prior and concomitant medication will be summarized for all medications. All medication will be included in a listing including reason for use, start and end dates and dosage information for the SAF. The following definitions will be used:

- Concomitant medications are defined as medications that are ongoing at or began after the start and prior to the stop of study intervention.
- Prior medications are defined as medications that began before the start of study intervention regardless of when they ended.

Treatment of the fellow eye (as defined in Section 4.5.6) will be collected as concomitant medication.

All prior and concomitant medication will be listed.

6.2 Efficacy

Due to differing requirements for the submission to regulatory authorities, 2 different testing strategies for the analysis at Week 48 and the analysis at Week 60 will be applied and described in detail in this section.

Furthermore, a descriptive analysis of all data will be conducted after all participants have completed the study at Week 96 (or prematurely discontinued).

All efficacy analyses will be evaluated based on the FAS, which is considered the primary analysis set for all efficacy endpoints. As a supplementary analysis the primary endpoint and the key secondary endpoint "dryness at Week 16" will also be evaluated based on the PPS. The key secondary endpoint "BCVA change at Week 60" will also be evaluated based on the PPS.

All efficacy analyses will be using the injection visits (i.e., multiples of 4 weeks) and not the calendar time as unit.

The main confirmatory analysis of the primary and key secondary endpoints will only contain data up to the time period which has been described in Table 9–12 and Table 9–13 below.

6.2.1 Confirmatory Hypothesis Testing

For the G-SAP, statistical hypotheses of the primary endpoint (BCVA at Week 48) and the key secondary endpoint (dryness at Week 16) will be assessed together, after all participants completed Week 48 (or discontinued prematurely) using the below described methods.

For the EP-SAP, statistical hypotheses of primary endpoint (BCVA at Week 48) and the key secondary endpoints (BCVA at Week 60, dryness at Week 16) will be assessed together, after all participants completed Week 60 (or prematurely discontinued) using the below described methods. For this EP-SAP a repetition of the analysis of the primary endpoint (BCVA at Week 48) and the key secondary endpoint (dryness at Week 16) as well as all additional secondary and exploratory endpoints at Week 48 will not be done, but reference will be made to the analyses performed after all participants completed Week 48 (or discontinued prematurely) using the below described methods (i.e. Week 48 database).

The overall family-wise type 1 error will be controlled at 0.025 (one-sided tests) for testing the primary and key secondary endpoints. Adjustment for multiple comparisons in the primary and key secondary endpoints will be made with a hierarchical testing procedure (see Table 6–1). This approach allows the confirmatory testing of a hypothesis at the full alpha level of 0.025 after successful rejection of the hypotheses which are ranked higher in the hierarchy.

Table 6–1: Testing Order of Hierarchical Testing Procedure in G-SAP and EP-SAP

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

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

6.2.2 Primary Efficacy Endpoint

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

All main analyses described below for the primary efficacy variable will be analyzed for the FAS and the PPS, where the analysis for the FAS is considered as the primary one.

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

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

Target population: Defined by the inclusion/exclusion criteria.

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

Treatment condition:	HD aflibercept administered HDq12 with option for DRM/rescue regimen, or HDq16 with option for DRM/rescue regimen, versus aflibercept 2 mg administered 2q8.
Intercurrent events (ICE):	Premature discontinuation from treatment (handled by hypothetical strategy). Details for other potential ICEs are given in the Table 9–12 in Appendix 9.5. Shortening/extension of the dosing interval (DRM/rescue regimen) will not be considered an ICE, but as part of the randomized treatment regimen.
Population-level summary:	Difference in least squares (LS) mean change from baseline to Week 48 in BCVA between HDq12 and 2q8 (HDq16 and 2q8, respectively).

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

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

A justification of the non-inferiority margin and a description of the DRM are given in the protocol.

6.2.2.1 Primary Analysis

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), visit and the stratification variables (geographic region [Japan vs. Rest of World] and baseline BCVA [<60 vs. ≥60]) as fixed factors 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 to model the within-subject error, assuming different covariance parameters per treatment group. If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: Toeplitz with heterogeneity, autoregressive with heterogeneity, Toeplitz, autoregressive and compound symmetry.

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

with

- Y_{ijk} being the change from baseline to visit j for the ith participant receiving treatment k
- β_0 being the intercept

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

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

$$D_{HDq12} = \left[\beta_{treat}^{(HDq12)} + \beta_{treat*visit}^{(HDq12,w48)}\right] - \left[\beta_{treat}^{(2q8)} + \beta_{treat*visit}^{(2q8,w48)}\right]$$

and

$$D_{HDq16} = \left[\beta_{treat}^{(HDq16)} + \beta_{treat*visit}^{(HDq16,w48)}\right] - \left[\beta_{treat}^{(2q8)} + \beta_{treat*visit}^{(2q8,w48)}\right].$$

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

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

Furthermore, the following 2 hypotheses will be tested (within the pre-defined testing strategy, see Section 6.2.1), using the MMRM described above, to assess also superiority in the primary endpoint, only if non-inferiority could be concluded before:

- HDq12 is superior to 2q8 regarding the mean change in BCVA from baseline to Week 48:
  H_{60}: $\mu_1 \leq \mu_0$ vs. H_{61}: $\mu_1 > \mu_0$ (i.e., HDq12 vs. 2q8),
  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_{80}: $\mu_2 \leq \mu_0$ vs. H_{81}: $\mu_2 > \mu_0$ (i.e., HDq16 vs. 2q8),
  where μ_0, μ_2 are the mean change from baseline in BCVA at Week 48 for 2q8, and HDq16, respectively.

To control the overall family-wise type I error rate of 0.025, a hierarchical testing procedure will be applied (Section 6.2.1) that also includes the confirmatory testing of the key secondary endpoints described in Section 6.2.3.1 and the confirmatory testing of change from baseline in BCVA at Week 48 (and Week 60, only for EP-SAP) for superiority at the end of the confirmatory testing hierarchy.

Summary tables will include number of participants, least-square mean (LSmean) change, (unadjusted) mean change and SD and baseline means of each treatment group. For non-inferiority testing the one-sided adjusted α (as described in Section 6.2.1) for the population-level estimates comparing HDq16 vs. 2q8 (D_{HDq16}) and HDq12 vs. 2q8 (D_{HDq12}), respectively, the estimates expressed as LSmean change, the test statistics, the degrees of freedom and corresponding p-values will be presented. Two-sided 95% confidence intervals will be provided as well.

The MMRM assumes missing at random (MAR) for participants who discontinue the study prematurely, i.e. missingness only depends on observed data. Alternative assumptions (not MAR) will be included in the sensitivity analyses.

Descriptive summary tables will be provided by treatment group and visit for:

- All observed cases until the occurrence of an ICE (primary estimand strategy for continuous endpoints) in the FAS population
- All observed cases until the occurrence of an ICE (primary estimand strategy for continuous endpoints) in the PPS population
- All observed cases until the occurrence of an ICE with imputation of missing values with LOCF (sensitivity analysis strategy for continuous endpoints) in the FAS population

6.2.2.2 Sensitivity Analyses

Last observation carried forward (LOCF) will be conducted for participants who have at least one post-baseline value but have any further missing post-baseline BCVA values until 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.

6.2.2.2.1 ANCOVA using LOCF

The sensitivity analysis of the primary efficacy endpoint using an ANCOVA with LOCF follows the same estimand strategy as the primary analysis.

For this sensitivity analysis of the primary efficacy variable, an 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 (geographic region [Japan vs. Rest of World] and baseline BCVA [<60 vs. ≥60]) as fixed factors. A separate variance term will be estimated for the three treatment groups.

The observation at Week 48 of participant i receiving treatment t can be written as follows:

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

with

- Y_{itrb} being the change from baseline to Week 48 for the ith participant,
- μ_t being the treatment effect,
- γ_r being the geographic region effect (as recorded on the eCRF),
- η_b being the categorical baseline BCVA (<60 vs. ≥60; as recorded on the eCRF),
- x_i being the baseline BCVA of participant i,
- ϵ_{itrb} the residual error with $\epsilon_{itrb} \sim N(0, \sigma_t^2)$ being the residual error for treatment arm *t*.

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

$$D_{HDq12} = \left[\beta_{treat}^{(HDq12)}\right] - \left[\beta_{treat}^{(2q8)}\right]$$

and

$$D_{HDq16} = \left[\beta_{treat}^{(HDq16)}\right] - \left[\beta_{treat}^{(2q8)}\right].$$

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 will be carried forward up to Week 48.

Summary tables will include number of participants, least-square mean (LSmean) change, (unadjusted) mean change and SD and baseline means of each treatment group. For non-inferiority testing the one-sided α of 2.5% for the population-level estimates comparing HDq16 vs. 2q8 and HDq12 vs. 2q8, the estimates expressed as LSmean change, the test statistics, the degrees of freedom and corresponding p-values will be presented. Two-sided 95% confidence intervals will be provided as well.

This sensitivity analysis will be analyzed for the FAS.

6.2.2.2.2 Multiple Imputation

The sensitivity analysis of the primary efficacy endpoint using an ANCOVA after applying multiple imputation follows the same estimand strategy as the primary analysis. Multiple imputation (MI) methods involve three steps:

I. Imputation

Imputation is the generation of multiple copies of the original dataset by replacing missing values by using an appropriate stochastic model. The missing data will be imputed using the Fully Conditional Specification (FCS) method. The FCS method is based on an iterative algorithm; at each iteration and for each variable of the prediction model, there is a prediction step and an imputation step. The models used for prediction and imputation will be linear regression models. A total of 10 imputations will be performed using a seed of 12345.

The imputation model will include treatment groups, geographic region (Japan, Rest of World) and categorical baseline BCVA (<60, ≥60), baseline BCVA, and the BCVA at each previous post-baseline visit.

Final imputed values will be rounded to integer values and cut-offs will be applied to imputed values outside of the normal range of 0 to 100.

II. Analysis

The analysis step is performed for each of the imputed datasets. Since all imputed datasets are complete there is no need to bother with any missing data.

The statistical method for analysis will be ANCOVA and is specified in Section 6.2.2.2.1.

III. Pooling

Pooling is the combination of the different parameter estimates across the multiple imputed datasets based on Rubin's rules (Rubin, 1987 (6)) to produce a unique point estimate and standard error taking into account the uncertainty of the imputation process.

This sensitivity analysis will be analyzed for the FAS.

6.2.2.2.3 Tipping-point analysis

In order to check the assumption that the missing data is not MAR, also a tipping point analysis will be conducted based on the multiple imputation analysis in Section 6.2.2.2.2. 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 can show non-inferiority of the high dose groups compared to the low dose group.

If the non-inferiority could be 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 participants, least-square mean (LSmean) 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 for α of 5%, the test statistics, the degrees of freedom and corresponding p-values. This sensitivity analysis will be analyzed for the FAS.

6.2.3 Secondary Efficacy Endpoints

6.2.3.1 Key Secondary Endpoints

The key secondary efficacy endpoints are described below.

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

This key secondary efficacy endpoint (for regulatory submissions to EMA/PMDA according to the EP-SAP only) has a similar underlying estimand that follows the same strategies as for the primary efficacy endpoint

The following 2 non-inferiority hypotheses will be tested for this key secondary endpoint:

- 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 (EP-SAP, see Section 6.2.1). The change from baseline in BCVA at Week 60 will be analyzed with the same methodology and main and sensitivity summaries as for the primary endpoint assessing non-inferiority described in Section 6.2.2 in this SAP.

Also for the key secondary endpoint of change from baseline in BCVA at Week 60, the following 2 hypotheses will be tested, using the MMRM described above, to assess superiority, only if non-inferiority could be concluded before:

- HDq12 is superior to 2q8 regarding the mean change in BCVA from baseline to Week 60:
  H_{70}: $\mu_1 \leq \mu_0$ vs. H_{71}: $\mu_1 > \mu_0$ (i.e., HDq12 vs. 2q8),
  where μ_0, μ_1, are the mean change from baseline in BCVA at Week 60 for 2q8 and HDq12, respectively.
- HDq16 is superior to 2q8 regarding the mean change in BCVA from baseline to Week 60:
  H_{90}: $\mu_2 \leq \mu_0$ vs. H_{91}: $\mu_2 > \mu_0$ (i.e., HDq16 vs. 2q8),
  where μ_0, μ_2, are the mean change from baseline in BCVA at Week 60 for 2q8 and HDq16, respectively.

6.2.3.1.2 Proportion of Participants with no IRF and no SRF in Central Subfield at Week 16

The underlying estimand for the primary analysis of the binary key secondary endpoint using a Cochran-Mantel-Haenszel test with LOCF, mainly follows the hypothetical strategy. It describes the proportion of all participants with no IRF and no SRF in central subfield at Week 16 that started treatment assuming all participants have stayed on treatment until Week 16.

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

Target population:	Defined by the inclusion/exclusion criteria.
Variable:	Absence of IRF and SRF in Central Subfield at Week 16.
Treatment condition:	HD aflibercept versus aflibercept 2 mg.
Intercurrent events:	Premature discontinuation from treatment (handled by hypothetical strategy). Details for other potential ICEs are given in the Table 9–13 in Appendix 9.5.
Population-level summary:	Difference in proportion of participants with no IRF and no SRF in Central Subfield at Week 16 between pooled high dose groups (HDq12 and HDq16) and 2q8.

The existence of IRF or SRF are abnormal findings of the SD-OCT and will be classified based on data assessed by a reading center as described in Section 4.5.4.

For the calculation of the endpoint dryness, absence of IRF and SRF (or “Dryness at Week 16”) in Central Subfield is achieved, when the definitions for IRF=NO and SRF=NO are achieved at Week 16.

The opposite “Not dry” will be achieved when the definitions for either

- IRF=YES or
- SRF=YES or
- IRF=YES and SRF=YES

are achieved at Week 16 (including cases when [IRF=YES and SRF=missing/undetermined] or [IRF=missing/undetermined and SRF=YES]).

In case of IRF and SRF as Missing or Undetermined or [IRF=NO and SRF=missing/undetermined] or [IRF=missing/undetermined and SRF=NO] the whole endpoint will be missing/undetermined. These cases will not be included in the denominator when calculating proportions.

The following superiority hypothesis will be tested for this key secondary endpoint on the FAS and repeated as supplementary analysis on the PPS:

- H_{50}: $p_{HD} \leq p_{2q8}$ vs. H_{51}: $p_{HD} > p_{2q8}$ (i.e., pooled high dose vs. 2q8),
- where p_{2q8}, p_{HD} are the proportion of participants with no IRF and no SRF in central subfield at Week 16 for 2q8, and the pooled high dose groups (HDq12 and HDq16), respectively. HDq12 and HDq16 high dose groups have same dosing regimen up to Week 16.

This endpoint will be analyzed by a Cochran-Mantel-Haenszel test stratified by geographic region (Japan vs. Rest of World) and baseline BCVA (<60 vs. ≥60).

The number of prematurely discontinued participants before Week 16 is assumed to be rather small. LOCF will be applied for participants not having a Week 16 SD-OCT performed (carrying forward the last non-missing [not missing/undetermined] post-baseline measurement).

Additionally, 95% two-sided CIs for the Mantel-Haenszel weighted treatment difference between pooled high dose groups and 2q8 will be calculated using normal approximation. The following methodology (Koch et al, 1990 (4)) is used:

$d = (\sum_{hk} w_{hk}(\hat{p}_{hkt} - \hat{p}_{hkc}))/\sum_{hk} w_{hk})$, where $w_{hk} = n_{hkt}n_{hkc}/(n_{hkt} + n_{hkc})$.

Then $\widehat{\mathrm{var}}(\hat{d}) = \left(\sum_{hk} w_{hk}^2(\hat{p}_{hkc}(1 - \hat{p}_{hkc})/(n_{hkc} - 1) + \hat{p}_{hkt}(1 - \hat{p}_{hkt})/(n_{hkt} - 1))\right)/(\sum_{hk} w_{hk})^2$.

With this, the 95% CI can be given as: $\hat{d} \pm z_{\alpha/2}\sqrt{\widehat{var}(\hat{d})}$ ($z_{\alpha/2}$ being the lower $\alpha/2$ quantile of the standard normal distribution).

In the formulae,

- h: number of strata for the geographic region, which ranges from 1 to 2 (Japan, Rest of World; as recorded on the eCRF),
- k: number of strata for the baseline BCVA, which ranges from 1 to 2 (<60, ≥60; as recorded on the eCRF),
- p_{hkt}: proportion of participants with no IRF and no SRF in central subfield at Week 16 in the pooled high dose treatment group in stratum$_1$ h and stratum$_2$ k,
- p_{hkc}: proportion of participants with no IRF and no SRF in central subfield at Week 16 in the 2q8 treatment group in stratum$_1$ h and stratum$_2$ k,
- n_{hkt}: number of participants in the pooled high dose treatment group in stratum$_1$ h and stratum$_2$ k,
- n_{hkc}: number of participants in the 2q8 dose treatment group in stratum$_1$ h and stratum$_2$ k.

The number and percentage of participants with no IRF and no SRF in central subfield at Week 16 for each treatment group and the pooled HD group, the p-value of the one-sided Cochran-Mantel-Haenszel test and the weighted treatment difference including the two-sided 95%-CI as percentage (multiplied by 100) will be included in a summary table.

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

Descriptive summary tables will be provided by treatment group and visit for:

- All observed cases until the occurrence of an ICE with imputation of missing values with LOCF (primary estimand strategy for binary endpoints) in the FAS population
- All observed cases until the occurrence of an ICE with imputation of missing values with LOCF (primary estimand strategy for binary endpoints) in the PPS population
- All observed cases until the occurrence of an ICE in the FAS population

Descriptive summary tables will be provided by treatment group and visit for IRF in central subfield and SRF in central subfield (LOCF as well as OC for the FAS population).

In addition, descriptive summary tables will be provided by treatment group and visit for IRF in foveal center, SRF in foveal center and corresponding dryness status (LOCF as well as OC for the FAS population).

6.2.3.1.2.1 Sensitivity Analyses

A sensitivity analysis will be performed for the proportion of participants with no IRF and no SRF in central subfield at Week 16 for the FAS. In case of any participants prematurely discontinuing before Week 16 or having any occurrence of another ICE, a Cochran-Mantel-Haenszel test will be calculated based on observed case (OC) only. The number and percentage of participants with no IRF and no SRF in central subfield at Week 16 for each treatment group and the pooled HD group, the p-value of the one-sided Cochran-Mantel-Haenszel test and the weighted treatment difference including the two-sided 95%-CI will be included in a summary table.

6.2.3.2 Additional Secondary Efficacy Endpoints

The additional secondary efficacy endpoints are

- Proportion of participants gaining at least 15 letters in BCVA from baseline at Week 48
- Proportion of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Week 48
- Change in CNV size from baseline to Week 48
- Change in total lesion area from baseline to Week 48
- Proportion of participants with no IRF and no SRF in the central subfield at Week 48
- Change from baseline in CST at Week 48
- Change from baseline in NEI-VFQ-25 total score at Week 48

All analyses will be done for the FAS.

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

6.2.3.2.1 Proportion of Participants Gaining at least 15 Letters in BCVA from Baseline at Week 48

The proportion of participants gaining at least 15 letters in BCVA from baseline at Week 48 will be summarized descriptively by treatment group for:

- All observed cases until the occurrence of an ICE (primary estimand strategy for continuous endpoints) in the FAS population
- All observed cases until the occurrence of an ICE with imputation of missing values with LOCF (sensitivity analysis strategy for continuous endpoints) in the FAS population

Missing cases will not be included in the denominator when calculating proportions. Additionally, the Cochran-Mantel-Haenszel test stratified by geographic region (Japan vs. Rest of World) and baseline BCVA (<60 vs. ≥60) will be applied for the comparison of the treatment groups HDq12 vs. 2q8 and HDq16 vs. 2q8. Two-sided 95% CIs and p-values will be provided for descriptive purposes. The main analysis will be done for the LOCF imputation of missing BCVA measurements in the FAS as described in Section 6.2.3.1.2 and an additional sensitivity analysis will be done for the OC only case in the FAS.

6.2.3.2.2 Proportion of Participants Achieving an ETDRS Letter Score of at least 69 (Approximate 20/40 Snellen Equivalent) at Week 48

The proportion of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Week 48 will be summarized descriptively by treatment group for:

- All observed cases until the occurrence of an ICE (primary estimand strategy for continuous endpoints) in the FAS population
- All observed cases until the occurrence of an ICE with imputation of missing values with LOCF (sensitivity analysis strategy for continuous endpoints) in the FAS population

Missing cases will not be included in the denominator when calculating proportions. Additionally, the Cochran-Mantel-Haenszel test stratified by geographic region (Japan vs. Rest of World) and baseline BCVA (<60 vs. ≥60) will be applied for the comparison of the treatment groups HDq12 vs. 2q8 and HDq16 vs. 2q8. Two-sided 95% CIs and p-values will be provided for descriptive purposes. The main analysis will be done for the LOCF imputation of missing BCVA measurements in the FAS as described in Section 6.2.3.1.2 and an additional sensitivity analysis will be done for the OC only case in the FAS.

6.2.3.2.3 Change in CNV Size from Baseline to Week 48

CNV size will be evaluated using FA/FP (see Section 4.5.4) and will be collected at screening, week 12 (visit 6), week 24 (visit 9), week 36 (visit 12), week 48 (visit 15), week 60 (visit 18) and week 96 (visit 27). The change in CNV size from baseline to Week 48 will be summarized descriptively by treatment group for:

- All observed cases until the occurrence of an ICE (primary analysis strategy for continuous endpoints) in the FAS population

- All observed cases until the occurrence of an ICE with imputation of missing values with LOCF (sensitivity analysis strategy for continuous endpoints) in the FAS population

Additionally, a MMRM will be used with baseline CNV size as a covariate and treatment group (HDq16 vs. 2q8 and HD12 vs. 2q8), visit and the stratification variables (geographic region (Japan vs. Rest of World) and baseline BCVA (<60 vs. ≥60)) as fixed factors as well as terms for the interaction between baseline CNV size and the visit and for the interaction between treatment and visit. This model is similar to the model described in Section 6.2.2.1 and will be provided for FAS. Two-sided 95% CIs for LSmeans, coefficient estimates and p-values will be provided for descriptive purposes. As additional sensitivity analysis an ANCOVA will be calculated as described in Section 6.2.2.2.1 using the LOCF method for imputation of missing values for participants discontinuing before Week 48.

Visit-based information recorded in the EOS/ED visit folder which will not be re-mapped to a regular study visit will nevertheless be included into the LOCF analysis.

6.2.3.2.4 Change in Total Lesion Area from Baseline to Week 48

Lesion characteristics will be evaluated using FA/FP (see Section 4.5.4) and will be collected at screening, week 12 (visit 6), week 24 (visit 9), week 36 (visit 12), week 48 (visit 15), week 60 (visit 18) and week 96 (visit 27). The change in total lesion area from baseline to Week 48 will be summarized descriptively by treatment group for:

- All observed cases until the occurrence of an ICE (primary estimand strategy for continuous endpoints) in the FAS population
- All observed cases until the occurrence of an ICE with imputation of missing values with LOCF (sensitivity analysis strategy for continuous endpoints) in the FAS population

Additionally, a MMRM will be used with baseline total lesion area as a covariate and treatment group (HDq16 vs. 2q8 and HD12 vs. 2q8), visit and the stratification variables (geographic region (Japan vs. Rest of World) and baseline BCVA (<60 vs. ≥60)) as fixed factors as well as terms for the interaction between baseline total lesion area and the visit and for the interaction between treatment and visit. This model is similar to the model described in Section 6.2.2.1 and will be provided for FAS. Two-sided 95% CIs for LSmeans, coefficient estimates and p-values will be provided for descriptive purposes. As additional sensitivity analysis an ANCOVA will be calculated as described in Section 6.2.2.2.1 using the LOCF method for imputation of missing values for participants discontinuing before Week 48.

Visit-based information recorded in the EOS/ED visit folder which will not be re-mapped to a regular study visit will nevertheless be included into the LOCF analysis.

6.2.3.2.5 Proportion of Participants with no IRF and no SRF in the Central Subfield at Week 48

The proportion of participants with no IRF and no SRF (according to the definitions in Section 4.5.4 and Section 6.2.3.1.2) in the central subfield at Week 48 will be summarized descriptively by treatment group for:

- All observed cases until the occurrence of an ICE with imputation of missing values with LOCF (primary estimand strategy for binary endpoints) in the FAS population
- All observed cases until the occurrence of an ICE in the FAS population

Missing cases will not be included in the denominator when calculating proportions. Additionally, the Cochran-Mantel-Haenszel test stratified by geographic region (Japan vs. Rest of World) and baseline BCVA (<60 vs. ≥60) will be applied for the comparison of the treatment groups HDq12 vs. 2q8 and HDq16 vs. 2q8. Two-sided 95% CIs and p-values will be provided for descriptive purposes. The main analysis will be done for the LOCF imputation for participants with missing SD-OCT assessment in the FAS as described in Section 6.2.3.1.2 and an additional sensitivity analysis will be done for the OC only case in the FAS.

6.2.3.2.6 Change from Baseline in CST at Week 48

CST will be evaluated using SD-OCT (see Section 4.5.4) and will be collected at each visit. The change from baseline in CST at Week 48 will be summarized descriptively by treatment group for:

- All observed cases until the occurrence of an ICE (primary estimand strategy for continuous endpoints) in the FAS population
- All observed cases until the occurrence of an ICE with imputation of missing values with LOCF (sensitivity analysis strategy for continuous endpoints) in the FAS population

Additionally, a MMRM will be used with baseline CST as a covariate and treatment group (HDq16 vs. 2q8 and HD12 vs. 2q8), visit and the stratification variables (geographic region (Japan vs. Rest of World) and baseline BCVA (<60 vs. ≥60)) as fixed factors as well as terms for the interaction between baseline CST and the visit and for the interaction between treatment and visit. This model is similar to the model described in Section 6.2.2.1 and will be provided for FAS. Two-sided 95% CIs for LSmeans, coefficient estimates and p-values will be provided for descriptive purposes. As additional sensitivity analysis an ANCOVA will be calculated as described in Section 6.2.2.2.1 using the LOCF method for imputation of missing values for participants discontinuing before Week 48.

6.2.3.2.7 Change from Baseline in NEI-VFQ-25 Total Score at Week 48

The change from baseline in NEI-VFQ-25 total score (for calculation details see Section 9.1.1) at Week 48 will be summarized descriptively by treatment group for:

- All observed cases until the occurrence of an ICE (primary estimand strategy for continuous endpoints) in the FAS population
- All observed cases until the occurrence of an ICE with imputation of missing values with LOCF (sensitivity analysis strategy for continuous endpoints) in the FAS population

Additionally, a MMRM will be calculated with baseline NEI-VFQ-25 total score as a covariate and treatment group (HDq16 vs. 2q8 and HD12 vs. 2q8), visit and the stratification variables (geographic region (Japan vs. Rest of World) and baseline BCVA (<60 vs. ≥60)) as fixed factors as well as terms for the interaction between baseline NEI-VFQ-25 total score and the visit and for the interaction between treatment and visit. This model is similar to the model described in Section 6.2.2.1 and will be provided for FAS. Two-sided 95% CIs for LSmeans, coefficient estimates and p-values will be provided for descriptive purposes. As additional sensitivity analysis an ANCOVA will be calculated as described in Section 6.2.2.2.1 using the LOCF method for imputation of missing values for participants discontinuing before Week 48.

Visit-based information recorded in the EOS/ED visit folder which will not be re-mapped to a regular study visit will nevertheless be included into the LOCF analysis.

6.2.4 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints will be analyzed descriptively for the FAS and will include the following:

- Change from baseline in BCVA measured by the ETDRS letter score at Week 96
- Change from baseline in BCVA averaged over the period from Week 36 to Week 48 and from Week 48 to Week 60
- Proportion of participants gaining at least 15 letters in BCVA from baseline at Week 60 and Week 96
- Proportion of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Week 60 and Week 96
- Proportions of participants gaining and losing at least 5 or at least 10 letters in BCVA from baseline at Week 48, Week 60, and Week 96
- Proportion of participants losing at least 15 letters in BCVA from baseline at Week 48, Week 60, and Week 96
- Change in CNV size from baseline to Week 60 and Week 96
- Change in total lesion area from baseline to Week 60 and Week 96
- Change from baseline in CST at Week 60 and Week 96
- Proportion of participants with no IRF and no SRF in the central subfield at Week 60 and Week 96
- Proportion of participants without retinal fluid (total fluid, IRF, and/or SRF) and subRPE fluid in central 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, and/or SRF in the central subfield)
- Proportion of participants with sustained fluid-free retina over 48 weeks, 60 weeks, and 96 weeks (total fluid, IRF, and/or SRF in the central subfield)
- Change from baseline in NEI-VFQ-25 total score at Week 60 and Week 96
- Proportion of participants without leakage on FA at Week 48, Week 60, and Week 96

6.2.4.1 Change from Baseline in BCVA Measured by the ETDRS Letter Score at Week 96

The change from baseline in BCVA measured by the ETDRS letter score at Week 96 will be summarized descriptively by treatment group for:

- All observed cases until the occurrence of an ICE (primary estimand strategy for continuous endpoints) in the FAS population
- All observed cases until the occurrence of an ICE with imputation of missing values with LOCF (sensitivity analysis strategy for continuous endpoints) in the FAS population

6.2.4.2 Change from Baseline in BCVA Averaged over the Period from Week 36 to Week 48 and from Week 48 to Week 60

BCVA will be averaged over all non-missing visits between Week 36 to Week 48 (Week 36, Week 40, Week 44, Week 48) and between Week 48 to Week 60 (Week 48, Week 52, Week 56, Week 60), respectively. Then the change from baseline BCVA will be calculated for both averages. The change from baseline in BCVA to the average periods will be analyzed descriptively and displayed by treatment group for:

- All observed cases until the occurrence of an ICE (primary estimand strategy for continuous endpoints) in the FAS population
- All observed cases until the occurrence of an ICE with imputation of missing values during the periods from Week 36 to Week 48 and from Week 48 to Week 60 with LOCF (sensitivity analysis strategy for continuous endpoints) in the FAS population

6.2.4.3 Proportion of Participants Gaining at least 15 Letters in BCVA from Baseline at Week 60 and Week 96

The proportion of participants gaining at least 15 letters in BCVA from baseline at Week 60 and Week 96 will be analyzed descriptively by treatment group. Missing cases will not be included in the denominator when calculating proportions.

6.2.4.4 Proportion of Participants Achieving an ETDRS Letter Score of at least 69 (Approximate 20/40 Snellen Equivalent) at Week 60 and Week 96

The proportion of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Week 60 and Week 96 will be analyzed descriptively by treatment group. Missing cases will not be included in the denominator when calculating proportions.

6.2.4.5 Proportions of Participants Gaining and Losing at least 5 or at least 10 Letters in BCVA from Baseline at Week 48, Week 60, and Week 96

For each week (Week 48, Week 60 and Week 96) five proportions will be calculated

- Proportion of participants gaining more than 0 letters in BCVA from baseline (any gain)
- Proportion of participants gaining at least 5 letters in BCVA from baseline
- Proportion of participants losing at least 5 letters in BCVA from baseline
- Proportion of participants gaining at least 10 letters in BCVA from baseline
- Proportion of participants losing at least 10 letters in BCVA from baseline

Missing cases will not be included in the denominator when calculating proportions. The proportions will be analyzed descriptively and displayed by treatment group for:

- All observed cases until the occurrence of an ICE (primary estimand strategy for continuous endpoints) in the FAS population
- All observed cases until the occurrence of an ICE with imputation of missing values with LOCF (sensitivity analysis strategy for continuous endpoints) in the FAS population

6.2.4.6 Proportion of Participants Losing at least 15 Letters in BCVA from Baseline at Week 48, Week 60, and Week 96

The proportion of participants gaining or losing at least 15 letters in BCVA from baseline will be analyzed descriptively and displayed by treatment group for:

- All observed cases until the occurrence of an ICE (primary estimand strategy for continuous endpoints) in the FAS population
- All observed cases until the occurrence of an ICE with imputation of missing values with LOCF (sensitivity analysis strategy for continuous endpoints) in the FAS population

Missing cases will not be included in the denominator when calculating proportions.

6.2.4.7 Change in CNV Size from Baseline to Week 60 and Week 96

The change in CNV size from baseline to Week 60 and Week 96 will be analyzed descriptively by treatment group. Visit-based information recorded in the EOS/ED visit folder which will not be re-mapped to a regular study visit will nevertheless be included into the LOCF analysis.

6.2.4.8 Change in Total Lesion Area from Baseline to Week 60 and Week 96

The change in total lesion area from baseline to Week 60 and Week 96 will be analyzed descriptively by treatment group. Visit-based information recorded in the EOS/ED visit folder which will not be re-mapped to a regular study visit will nevertheless be included into the LOCF analysis.

6.2.4.9 Change from Baseline in CST at Week 60 and Week 96

The change from baseline in CST at Week 60 and Week 96 will be analyzed descriptively by treatment group.

6.2.4.10 Proportion of Participants with no IRF and no SRF in the Central Subfield at Week 60 and Week 96

The proportion of participants with no IRF and no SRF (according to the definitions in Section 4.5.4 and Section 6.2.3.1.2) in the central subfield at Week 60 and Week 96 will be analyzed descriptively by treatment group. Missing/undetermined cases will not be included in the denominator when calculating proportions.

6.2.4.11 Proportion of Participants without Retinal Fluid (Total Fluid, IRF, and/or SRF) and subRPE Fluid in Central Subfield at Week 48, Week 60, and Week 96

IRF, SRF and subRPE will be classified as defined in Section 4.5.4.

The proportion of participants without retinal fluid (no IRF and no SRF), with retinal fluid (IRF and/or SRF) or IRF and SRF missing/undetermined will be analyzed descriptively in the subgroups of participants with and without subRPE fluid in central subfield at Week 48, Week 60, and Week 96 and displayed by treatment group for:

- All observed cases until the occurrence of an ICE with imputation of missing values with LOCF (primary estimand strategy for binary endpoints) in the FAS population
- All observed cases until the occurrence of an ICE in the FAS population

Missing/undetermined cases will not be included in the denominator when calculating proportions.

6.2.4.12 Time to Fluid-Free Retina over 48 Weeks, 60 Weeks, and 96 Weeks (Total Fluid, IRF, and/or SRF in the Central Subfield)

Total fluid-free retina (no IRF and no SRF in central subfield) is defined as the absence of total fluid, i.e. no IRF and no SRF in the central subfield as found in the SD-OCT, regardless of whether any retinal fluid was found again after that.

Time to total fluid-free retina (no IRF and no SRF in central subfield) will be analyzed by Kaplan-Meier analysis and shown in Kaplan-Meier plots and descriptive summaries. Time to total fluid-free retina is defined as the duration from randomization to the timepoint when total fluid was absent for the first time whereas intercurrent events are handled according to Table 9–13. The analysis will be using the study visits (i.e. multiples of 4 weeks) and not the calendar time as unit. Participants without total fluid-free retina will be censored at the time of their last SD-OCT assessment.

Each of the HD groups will be compared with the 2q8 group using a stratified log-rank test and a stratified Cox proportional hazards model, including baseline BCVA (<60 vs. ≥60) and geographical region (Japan vs. Rest of World) as strata.

Time to IRF-free retina (no IRF in central subfield) and time to SRF-free retina (no SRF in central subfield) will be analysed in the similar way.

6.2.4.13 Proportion of Participants with Sustained Fluid-Free Retina over 48 Weeks, 60 Weeks, and 96 Weeks (Total Fluid, IRF, and/or SRF in the Central Subfield)

Sustained total fluid-free retina (no IRF and no SRF in central subfield) is defined as the absence of total fluid for at least 2 consecutive visits and all subsequent visits, i.e. no IRF and no SRF in the central subfield as found in the SD-OCT.

The proportion of participants with sustained total fluid-free retina (no IRF and no SRF in central subfield) over 48 weeks, 60 weeks and 96 weeks will be analyzed descriptively by treatment group for:

- All observed cases until the occurrence of an ICE in the FAS population

Missing cases will not be included in the denominator when calculating proportions.

Additionally, time to sustained total fluid-free retina (no IRF and no SRF in central subfield) over 48 weeks, 60 weeks and 96 weeks will be analyzed by Kaplan-Meier analysis and shown in Kaplan-Meier plots and descriptive summaries. Time to total sustained fluid-free retina is defined as the duration from randomization to the timepoint when total fluid was absent for the first time at 2 consecutive visits and for all subsequent study visits whereas intercurrent events are handled according to Table 9–13. The analysis will be using the study visits (i.e. multiples of 4 weeks) and not the calendar time as unit. Participants without sustained total fluid-free retina will be censored at the time of their last SD-OCT assessment.

Each of the HD groups will be compared with the 2q8 group using a stratified log-rank test and a stratified Cox proportional hazards model, including baseline BCVA (<60 vs. ≥60) and geographical region (Japan vs. Rest of World) as strata.

Time to sustained IRF-free retina (no IRF in central subfield) and time to sustained SRF-free retina (no SRF in central subfield) will be analysed in the similar way.

6.2.4.14 Change from Baseline in NEI-VFQ-25 Total Score at Week 60 and Week 96

The change from baseline in NEI-VFQ-25 total score at Week 60 and Week 96 will be analyzed descriptively by treatment group. Visit-based information recorded in the EOS/ED visit folder which will not be re-mapped to a regular study visit will nevertheless be included into the LOCF analysis.

6.2.4.15 Proportion of Participants Without Leakage on FA at Week 48, Week 60, and Week 96

The proportion of participants without leakage on FA (as defined in Section 4.5.4) will be analyzed descriptively and displayed by treatment group for:

- All observed cases until the occurrence of an ICE with imputation of missing values with LOCF (primary estimand strategy for binary endpoints) in the FAS population
- All observed cases until the occurrence of an ICE in the FAS population.

Missing cases will not be included in the denominator when calculating proportions. Visit-based information recorded in the EOS/ED visit folder which will not be re-mapped to a regular study visit will nevertheless be included into the LOCF analysis.

6.2.5 Subgroup Analyses

Statistical analyses for primary and key secondary efficacy endpoints will be conducted for the FAS by each subgroup defined in Section 5.2 for efficacy analyses. For the subgroup analysis by geographic region the corresponding variable will be removed from the statistical models. The subgroup analyses are only descriptive and 95% CIs will be presented in tables. Subgroups for continuous endpoints are done using the MMRM without imputation of missing values and subgroups for categorical endpoints are done using Cochran-Mantel-Haenszel test with imputation by LOCF.

6.3 Pharmacokinetics/Pharmacodynamics

All analysis done for sparse PK samples will be done by treatment group on the PKS. Analysis of the data from the dense PK substudy will be analyzed by treatment group for the DPKS. Pharmacodynamic parameters are not evaluated in this study.

6.3.1 Main Study

PK samples for sparse PK are collected during Year 1 only at baseline (Visit 2), Week 4 (Visit 3), Visit 5, Week 12 (Visit 6), Week 28 (Visit 10) and Week 48 (Visit 15) for all participants (optional for participants in China). The individual concentrations of free, adjusted bound, and total aflibercept over time will be summarized and listed by descriptive statistics by visit. As far as possible, the increase of concentrations will be described.

Individual concentrations of adjusted bound aflibercept will be calculated as 0.717 x individual concentrations of bound aflibercept.

Individual concentrations of total aflibercept will be calculated as the sum of individual concentrations of free and adjusted bound aflibercept.

The following LLOQs were used by the laboratory:

- For free aflibercept assay: LLOQ = 15.6ng/mL

- For bound aflibercept assay: LLOQ = 31.3ng/mL

Drug concentrations will be further grouped by the following baseline factors:

- age categories as defined in 5.2,
- medical history of renal impairment as determined by baseline serum creatinine values as defined in 9.4.6,
- hepatic impairment based on medical history as defined in 9.4.7,
- BMI categories as defined in 6.1.1,
- ethnicity as defined in 5.2,
- race as defined in 5.2

and evaluated by means of descriptive statistics.Dose and/or exposure-response analyses may be performed for select safety and efficacy endpoints, as appropriate.

No formal statistical hypothesis testing will be performed.

6.3.2 Dense PK Substudy

The Dense PK Substudy is planned to include approximately 24 participants (at least 12 Japanese participants from Japan sites and at least 12 non-Asian participants from Europe or U.S. sites). For each region a minimum of 6 participants should be randomized to the HDq12 group or the HDq16 group combined. The stratification factors for randomization in the study (geographic region [Japan vs. Rest of World], and baseline BCVA [<60 vs. ≥60]) will also apply for the Dense PK Substudy as part of the overall population.

All participants in the Dense PK Substudy will participate in the main study for 96 weeks but will have additional visits for the substudy as outlined in the protocol. Samples for Dense PK will be collected at a screening visit, at baseline visit pre-injection and then 4 h (within ±30 minutes) and 8 h (within ±2 hours) after injection, as well as on post-baseline day 2, 3, 5, 8, 15 and 22 (all within ±2 hours of the clock time of dosing at baseline).

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

- Maximum concentration (Cmax)
- Cmax/Dose
- Time of Cmax (tmax)
- Last time point (tlast)
- Last concentration (Clast)
- Area under the curve to the last quantifiable concentration (AUClast)
- Area under the curve from time zero to infinity (AUCinf)
- AUCinf/Dose
- Half-life (t1/2)
- Trough concentration (Ctrough)

After repeat dosing, PK parameters to be determined, if possible, may include, but are not limited to C_{trough}, time to reach steady-state, and accumulation ratio. PK parameters will be summarized by descriptive statistics by treatment group, and geographical region as appropriate. This descriptive statistical assessment will include number of observations, the geometric mean, 95% CI of the geometric mean, geometric coefficient of variation, arithmetic

mean, SD, CV%, median, Q1,Q3, minimum and maximum values. No formal statistical hypothesis testing will be performed. If there are any values below limit of quantification (BLOQ) they will be substituted by 1/2 of the lower limit of quantification (LLOQ) for the calculation of geometric statistics and 0 for arithmetic statistics.

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

6.4 Safety

The analysis of safety variables will be conducted descriptively on the SAF population for the data up to Week 48, up to Week 60 and up to Week 96 (Week 100 for French participants only).

6.4.1 Adverse Events and Serious Adverse Events

An AE is any untoward medical occurrence in a clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention. All reported AEs will be coded using the version of MedDRA available at database lock. Coding will be to lowest level terms according to Bayer global standards.

AEs will be collected from the time of informed consent signature and at each visit until the end of the study. If the participant withdraws from the study during the screening, AEs will be collected up until the participant withdraws. If the participant is withdrawn after receiving the first dose of study medication, AEs will be collected up until 30 days after the last dose of study intervention or the termination visit, whichever is later.

Adverse events will be summarized as:

- **Pre-treatment AE:** Pre-treatment AEs are defined as AEs that started after the participant has signed the informed consent, but prior to the first injection at baseline (Visit 2, date of the participant's first dose of study intervention).
- **Post-treatment AE:** Post-treatment AEs are defined as AEs that started more than 30 days after the last injection (active or sham) in the study. For the participants who have not discontinued study treatment prematurely (i.e. are "ongoing") at the Week 48 analysis and at the Week 60 analysis, respectively, no AEs will be considered post-treatment, even if they started more than 30 days after the latest injection.
- **Treatment-emergent adverse event (TEAE):** TEAEs are defined as AEs that started in the time frame from first injection to the last injection (active or sham) in the study plus 30 days. For the participants who have not discontinued study treatment prematurely (i.e. are "ongoing") at the Week 48 analysis and at the Week 60 analysis, respectively, all AEs that started at first injection or later will be considered treatment-emergent.

The data cut-off rules for Week 48 and Week 60 AE reporting are described in a separate document "Data Cut-Off Specifications").

The proportions of participants with AEs will be used as safety variables for AE summary.

Other variables for AE description and analysis will include AE Verbatim Term, AE start date/ time and end date/time/ongoing and corresponding study day, AE Duration, relationship of AE to study drug, relationship of AE to commercial aflibercept (2 mg), relationship of AE

to intravitreal injection, relationship of AE to protocol-required procedure, seriousness, intensity, action due to AE, treatment of AE and outcome.

Summaries that include frequencies and proportions of participants reporting AEs will include the PTs and the SOCs.

Evaluations for TEAE will be mainly done for the following categories, which will be identified from the information of the CRF:

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

AE summaries will be provided displaying AEs within each SOC in alphabetical order.

For overall characterization of the AE profile for aflibercept in this study, an AE summary will include AEs within each SOC listed in alphabetical order with columns for treatment group, including a column “All HD” for the pooled HD group.

TEAEs in the study eye assessed by the investigator as being related to the injection procedure, related to protocol-required procedures and those related to the study medication will be summarized separately.

TEAEs in the fellow eye assessed by the investigator as being related to the injection procedure, related to protocol-required procedures, related to the study medication and those related to commercial aflibercept (2 mg) will be summarized separately.

A listing will be constructed that includes the participant identification, the treatment group, category of AE (ocular study eye, non-ocular), AE, MedDRA term, seriousness, severity, causality, elapsed time to onset, duration, and outcome.

Serious Adverse Events (SAEs) will be summarized in the same way as described for TEAEs.

A frequency table of TEAEs of **intraocular inflammation** terms, cross-tabulated with related MedDRA PT and SOC, will be displayed by treatment arm (see Section 9.4 for definition of terms).

A frequency table of adjudicated treatment-emergent APTC events terms, cross-tabulated with related MedDRA PT and SOC, will be displayed by treatment arms. The adjudication of AE is described in the “APTC adjudication committee charter”.

A frequency table of TEAEs of **hypertension** terms, cross-tabulated with related MedDRA PT and SOC, will be displayed by treatment arm (see Section 9.4 for definition of terms).

A frequency table of TEAEs of **nasal mucosal finding** terms, cross-tabulated with related MedDRA PT and SOC, will be displayed by treatment arm (see Section 9.4 for definition of terms).

6.4.1.1 Subgroup Analyses

Subgroup analyses for TEAEs will be performed for the safety analysis subgroups described in Section 5.2, for each of the following types of TEAE:

Number of participants with

- ocular TEAEs in the study eye

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

6.4.2 Immunogenicity

Antibodies to aflibercept will be evaluated in serum samples collected from all participants (optional for participants in China) at baseline (Visit 2), at Week 48 (Visit 15) and at Week 96 (EOS) or ED visit.

The number and proportion of participants developing a treatment-emergent ADA response will be summarized for the AAS by treatment group, by visit and overall (for definitions, see Appendix 9.2). ADA titers will be summarized descriptively by treatment arm and visit.

ADA titer will additionally be summarized with number and percentage of sujects for categories:

- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤ 10,000)
- High (titer >10,000).

The number and proportion of participants positive in the NAb assay will be summarized for the NAbAS by treatment group and visit and overall.

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. Participants 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. Participants 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. Plots of drug concentrations will be examined and the influence of ADAs and NAbs on individual PK profiles evaluated.

6.4.3 Surgeries

All surgeries after informed consent are collected on the CRF. All surgeries and diagnostic procedures will be displayed in listings.

6.4.4 Clinical Laboratory Variables

Chemistry, hematology and urinalysis will be collected at screening (Visit 1), Week 48 (Visit 15) and at Week 96 (EOS) or ED. Only pregnancy testing is done at each visit. The tests detailed in Table 6–2 will be performed by the central laboratory.

Table 6–2: Pre-defined laboratory abnormalities

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

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

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

Laboratory test results will be summarized by baseline and change from baseline at each scheduled assessment using descriptive statistics.

If there are any values below LOQ they will be substituted by 1/2 LLOQ for the calculation of statistics.

Number and percentage of participants with a treatment-emergent potentially clinically significant value (PCSV, any value fulfilling pre-defined criteria for abnormal laboratory parameters as described in Table 9–4 in the Appendix 9.3) at any time point will be summarized for selected clinical laboratory test for all participants.

Shift tables based on baseline normal/abnormal will be used to present the results for laboratory tests.

Laboratory values out of normal range will be summarized in tables and also flagged in laboratory value listings.

6.4.5 Electrocardiogram

A standard digital 12-lead Electrocardiogram (ECG) will be performed at screening (Visit 1), Week 48 (Visit 15) and at Week 96 (EOS) or ED. ECG variables will include the heart rate recorded from the ventricular rate and the PR interval, QRS duration, RR interval, QT interval and overall interpretation of ECG (normal/abnormal) . QTc with Bazett and Fridericia correction will be used.

All ECG variables as described above will be analyzed for the SAF by appropriate descriptive methods and change from baseline or frequency tables and/or cross-tabulation of baseline vs. post-baseline status for categorical variables (overall interpretation of ECG normal/abnormal) by visit and treatment arms.

6.4.6 Vital Signs

Vital signs will be collected pre-injection, and before any blood draws at each visit during the study. When possible, timing of all blood pressure assessments should be within ±2 hours of clock time of dosing at the baseline visit. Variables of analysis for vital signs include body temperature, heart rate, systolic blood pressure and diastolic blood pressure. Vital signs will be summarized by baseline and change from baseline to each scheduled visit by treatment group for the SAF.

Additionally, summaries will be provided for participants with at least one systolic blood pressure treatment emergent PCSV of

- ≤ 95 mmHg and decrease from baseline ≥ 20 mmHg
- ≥160 mmHg and increase from baseline ≥ 20 mmHg

As well as for participants with diastolic blood pressure treatment emergent PCSV of

- ≤ 45 mmHg and decrease from baseline ≥ 10 mmHg
- ≥110 mmHg and increase from baseline ≥ 10 mmHg.

Heart rate and blood pressure assessments will also be displayed as figures with mean change from baseline for SAF.

6.4.7 Other Safety Measures

Variables of analysis for ocular safety measures include:

- Proportion of participants with increased IOP
    - ≥ 10 mmHg increase in IOP measurement from baseline to any pre-dose measurement
    - > 21 mmHg for any pre-dose measurement at any time during the study
    - ≥ 25 mmHg for any pre-dose measurement at any time during the study
    - ≥ 35 mmHg for any pre-dose or post-dose measurement at any time during the study,

where the post-dose IOP measurement will be the final measurement before the participant leaves the site.

Summary statistics will also be displayed by visit for:

- change from baseline for pre-dose IOP values

- Proportion of participants with Anterior Chamber Cells (only pre-dose assessment for study eye)
    - 0: no cells
    - Trace: less than 5 cells
    - 1+: 5 to 10 cells
    - 2+: 10 to 20 cells
    - 3+: 20 to 30 cells
    - 4+: cells too numerous to count.
- Proportion of participants with Anterior Chamber Flare (only pre-dose assessment for study eye)
    - 0: no protein
    - Trace: trace amount of protein
    - 1+: mild amount of protein
    - 2+ and 3+: moderate amount of protein (continuum)
    - 4+: severe amount of protein.
- Proportion of participants with Vitreous cells (only pre-dose assessment for study eye)
    - 0: clear (0-1 cells)
    - Trace: few opacities (2-20 cells)
    - 1+: scattered opacities (21-50 cells)
    - 2+: moderate opacities (51-100 cells)
    - 3+: many opacities (101-250 cells)
    - 4+: dense opacities (>251 cells).

Frequency tables will be provided for each of the above categories at each visit where data is available. Shift tables will be provided for the gradings (only pre-dose assessment for study eye).

- Proportion of participants with PCV (YES/NO/not available)
- Proportion of participants with GA development (YES/NO/not available)

Frequency tables will be provided for each of the above categories at each visit where data is available.

7. Document History and Changes in the Planned Statistical Analysis

This Statistical Analysis Plan is based on the integrated clinical study protocol version 3.0 (dated 26 APR 2022), which includes Amendment 2.

Table 7–1: Document history

SAP Version	Date	Change	Rationale
V 0.8	14/AUG/2020		Stable draft
V 1.0	27/SEP/2021	- Safety follow-up at Week 100 for French participants added (sections 3, 4.5.4, 6.4) - Section 4.5.5 regarding imaging data added - Additional COVID-related outputs added (section 4.7) - Only one per protocol set kept (section 5.1) - Analysis timepoints for exposure analysis updated (section 6.1.4.2) - Section 6.2.1.3 for adjusted confidence limits added - Section 6.2.2.2.2.1 Tipping point analysis added - Further information for analysis regarding different intercurrent events added (sections 6.2.2.1, 6.2.3.1.2, 6.2.3.2.1 – 6.2.3.2.7, 6.2.4.1, 6.2.4.2, 6.2.4.5, 6.2.4.6, 6.2.4.11, 6.2.4.14) - Estimand description for sensitivity analysis of primary endpoint added (section 6.2.2.2.1) - Estimand description for binary key secondary endpoint added (section 6.2.3.1.2) - PK plots added (section 6.3.1) - Analysis timepoints for safety analysis updated (section 6.4.1) - AE relationship summaries added (section 6.4.1) - Surgery summaries removed (section 6.4.3) - Lab section updated according to required summaries (section 6.4.4) - Heart rate and blood pressure pots added (section 6.4.6) - IOP summaries updated (section 6.4.7) - ADA definitions updated (appendix 9.2) - Pre-defined abnormalities removed for parameter that are not collected (appendix 9.3) - Table 9-12 with Strategies for occurrence of intercurrent events for analysis of continous variables added - Table 9-13 with Strategies for occurrence of intercurrent events for analysis of binary variables added - Table 9-14 with regions and countries added - Minor wording updates and clarifications added	More details added; Updates made to align with Regeneron and after Bayer review of TLF shells

V2.0	13 JUL 2022	- Section 2, Table 1: Exploratory endpoint "Change from baseline in BCVA at each visit in relation to fluid outcomes" removed (as well as corresponding analysis in section 6.2.4) - Section 2, Table 1: Exploratory endpoint "Proportion of participants without leakage on fluorescein angiography (FA) at Week 48, Week 60, and Week 96" added (as well as corresponding analysis in section 6.2.4.15 and definition in section 4.5.5) - Section 2, Table 1: Exploratory endpoints updated to "Proportion of participants with q16 or longer treatment interval through Week 48, Week 60, and Week 96 in HDq16 group", "Proportion of participants with q12 or longer interval through Week 48, Week 60, and Week 96 in the HDq12 and HDq16 groups", and "Proportion of participants with q12 or q16 or longer treatment interval as the last treatment interval at Week 48, Week 60, and Week 96 in HDq12 and HDq16 groups, respectively" (as well as corresponding analysis in section 6.1.4.2) - Section 3: Clarification added that the two statistical analysis strategies (G-SAP and EP-SAP) will be described in one SAP document instead of two separate SAP documents - Section 4.1.1 Sample Size Determination: Text was added to describe the power, based on the revised confirmatory testing hierarchy. - Section 5.1: FAS definition updated to include "and who received at least 1 dose of study intervention" - Section 6.2.1 Statistical Hypotheses - Control of Multiplicity: Replaced the 2 figures showing: Global SAP (G-SAP), EMA/PMDA SAP(EP-SAP) and related explanations by a strictly sequential confirmatory testing hierarchy, and including the superiority hypotheses at the end of the confirmatory testing hierarchy, all related sections updated consistently - Section 6.2.1.3 for adjusted confidence intervals removed and related sections updated consistently - Section 6.2.2: Minor updates in wording and re-numbering of hypotheses according to section 6.2.1 - Section 6.2.2.1 Primary Efficacy Endpoint: MMRM updated to remove random effect b_i to avoid over parametrization, to add index k to Y and ϵ; clarification of ϵ updated. - Section 6.2.2.1 PPS analysis renamed from sensitivity to supplementary analysis and added to this section - Section 6.2.2.2 Sensitivity Analysis: PPS moved into section 6.2.2.1 - Section 6.2.2.2.1 updated for consistency with Primary Efficacy Endpoint section - Section 6.2.3.1.: Re-numbering of hypotheses	To reflect the changes introduced in the clinical study protocol v3.0 (amendment 2)

Table 7–1: Document history

SAP Version	Date	Change	Rationale
		according to section 6.2.1 - Section 6.2.3.1.2 updated for consistency with Primary Efficacy Endpoint section, PPS analysis renamed from sensitivity to supplementary analysis and added to this section - Section 6.2.3.1.2.1 PPS moved into section 6.2.3.1.2 - Section 6.3.1 PK analysis main study: bound concentrations removed and further minor text updates - Section 6.3.2 Dense PK analysis: minor text updates - Section 6.4.1: Frequency tables, cross-tabulated with related MedDRA PT, added for intraocular inflammation, hypertension and nasal mucosal finding	

Table 7–1: Document history

SAP Version	Date	Change	Rationale
		- Section 4.5.1: Definition of baseline for blood pressure clarified (to describe that average over all visits at or prior to randomization will be calculated) - Section 4.6: Clarifying text added that only one PPS will be defined for all analyses - Section 5.1: PPS definition updated to remove “received at least one dose of study treatment” (because this condition was added to the FAS) and to include “had a baseline BCVA value available” and “had at least one post-baseline BCVA value available”. NAbAS definition updated to add that the participants must also be in the ADA analysis set, test negative at all ADA sampline times or test positive at one or more post-dose ADA sampling times, and must have at least one post-dose NAb result. - Section 6.2.4.5: Proportion of participants with any gain in BCVA added - Section 6.4.7: Proportion of participants with increased IOP changed from “≥10 mmHg increase in IOP measurement from pre-dose to post-dose” to “≥10 mmHg increase in IOP measurement from baseline to pre-dose”; Proportion of participants with increased IOP changed from “≥21 mmHg for any pre-dose and post-dose measurement at any time during the study” to “>21 mmHg for any pre-dose measurement at any time during the study”; Remove post-dose summaries for IOP “≥10 mmHg, “>21 mmHg and “≥25 mmHg - Sections 6.2.4.12 and 6.2.4.13: Addition of separate analysis on IRF and SRF for “time to fluid-free retina” and “time to sustained fluid-free retina”. Addition of stratified log-rank test and addition of Cox proportional hazards model to compare each HD group with the 2q8 group using the study visits, not calendar days, as units. - Section 6.2.4.13: Definition of sustained fluid-free retina clarified and analysis of time to sustained fluid-free retina added. - Section 6.3.1: Subgroup analysis by body weight changed to by BMI categories. - Section 9.4: Subsections and their PTs updated using MedDRA version 25.0.	To align with PHOTON study

Table 7–1: Document history

SAP Version	Date	Change	Rationale
		- Section 5 / Section 6 / Section 6.2: Remove PPS analysis for additional secondary efficacy variables - Section 6.1.2: General summary for all medical history events removed, MH listings for drop-out participants removed - Section 6.2.2 / Section 6.2.3 (and subsections) / Section 6.2.4 (and subsections): Remove summary tables for observed cases ignoring the occurrence of ICEs for all efficacy endpoints; Remove MI analysis for all binary additional secondary and exploratory efficacy variables - Section 6.2.3.1.2.1: Remove logistic regressions for dryness endpoint - Section 6.2.5: Remove subgroup analysis for all additional secondary endpoints; Removed forrest plots - Remove analysis of Bilateral Treatment Experience with Aflibercept Treatment (prior Section 6.4.1.2) - Section 6.3.1: Removal of summaries for PK concentration and BP relationship, Removal of summaries for PK concentration by ADA subgroups. Removal of PK listings by subgroup. - Section 6.3.2: Removal of summaries for PK concentration and BP relationship - Section 6.4.2: Removed immunogenecity subgroup for analysis of TEAEs. - Sections 6.2.2.2.1 and 9.5: Definition of the Sensitibity Estimand and “Strategy” column removed from “Sensitivity Estimand” section in Table 16 as it follows the same strategy as the primary estimand but using a different analysis approach.	To remove analyses that are not necessary for the clinical study report

Table 7–1: Document history

SAP Version	Date	Change	Rationale
		- Section 4.5.3: Clarification added for re-mapping of early discontinuation visit data - Section 4.5.4: Clarification added how to classify and summarize imaging data assesses by the reading center - Section 4.5.5: Definition of fellow eye treatment added and subsequent sections updated accordingly - Section 4.5.6: Definition of prohibited medication added - Section 4.8: Listing added for participants affected by Ukraine/Russia crisis related findings and deviations - Section 6.2.2.1: Proposal added for convergence issues with unstructured covariance matrix. Additional text to clarify that different covariance parameters are assumed per treatment group. This information was already illustrated in the equation. - Section 6.2.2.2.1 / 6.2.2.2.2.1 / 6.2.3.1.2.1: Clarification added that unadjusted two-sided 95% CIs will be presented as well for the primary and key secondary efficacy endpoints - Section 6.2.2.2.2: Clarification added for the method to be used in the MI procedure - Section 6.2.3.1.2: Clarification added how to derive the dryness endpoint - Section 6.2.3.2.5: Previously removed text added back - Section 6.4.1: Clarification added that all AEs that started at first injection or later will be considered treatment-emergent for participants who are “ongoing” at the Week 48 analysis and at the Week 60 analysis, respectively - Section 6.4.7: Clarification added that slit lamp summaries will only include pre-dose assessments for the study eye - Section 9.4.3: List of PTs added to identify nasal mucosal events - Section 9.5: Footnotes added for clarification of missing loading dose injections and reference to section 4.5.6 added for prohibited medication ICE	To provide additional details

Table 7–1: Document history

SAP Version	Date	Change	Rationale
		- Section 4.5.1: Definition of baseline based on date of randomization instead of date of first study intervention - Section 4.5.2: Removal of re-mapping of unscheduled assessment data - Section 4.5.3: Removal of re-mapping of unscheduled assessment data - Section 4.5.3: The “last visit” will not be summarized on a visit level - Section 5.2: Age, ethnicity, race and baseline BCVA subgroups updated - Section 6.1.1: Age and baseline BCVA categories updated; menarch and childbearing potential, IRF, SRF and dryness status removed; medical history of hypertension, medical history of cerebrovascular disease, medical history of ischaemic heart disease, medical history of renal impairment, hepatic impairment added - Section 6.1.2: Separate summaries for medical history of hypertension, medical history of cerebrovascular disease, medical history of ischaemic heart disease, medical history of renal impairment, hepatic impairment removed - Section 6.1.4.2: Following added: Proportion of participants with q12 or q16 or longer treatment interval as the last completed treatment interval at Week 48, Week 60, and Week 96 in HDq12 and HDq16 groups, respectively (based on the 2 last active injections received before Week 48, Week 60, and Week 96); Proportion of participants maintained with q16 treatment interval through through Week 60 in HDq16 group; Proportion of participants maintained with q12 or longer interval through Week 60 in the HDq12 and HDq16 groups added; Proportion of participants dropping out during loading phase; Proportion of participants shortening treatment interval to q8 at Week 16 or Week 20 in HDq12 and HDq16 groups; Proportion of participants shortening treatment interval due to DRM criterion in HDq12 and HDq16 groups; Proportion of participants never extending treatment interval in HDq12 and HDq16 groups; Proportion of participants extending treatment interval due to DRM criteria in HDq12 and HDq16 groups - Section 9.5: clarifying text added, minor mistakes corrected	Minor updates

Table 7–1: Document history

SAP Version	Date	Change	Rationale
		- Section 4.5.4: IRF presence in center point and SRF presence in center point added - Section 5.2: Statement added that any statistical testing / calculation of p-values for subgroups will only be done for exploratory purpose - Section 6.1.4.2: Sequence of exposure variables updated and additional treatment summaries for patients with bilateral treatment added - Section 6.2.1: Statement for re-production of week 48 summaries for week 60 delivery removed - Section 6.2.3.1.2: Clarification for denominator for proportion calculation added and additional summaries for IRF/SRF at central subfield and IRF/SRF/Dryness status at center point added - Section 6.2.3.2.1, 6.2.3.2.2, 6.2.3.2.5, 6.2.4.3, 6.2.4.4, 6.2.4.5, 6.2.4.6, 6.2.4.10, 6.2.4.11, 6.2.4.13, 6.2.4.15: Clarification for denominator for proportion calculation added - Section 6.2.3.2.3, 6.2.3.2.4, 6.2.3.2.7, 6.2.4.7, 6.2.4.8, 6.2.4.14, 6.2.4.15: Clarification added that also data from early termination visits, that could not be re-mapped to a regular visit will be considered for LOCF summaries - Section 6.2.4.13: descriptive LOCF summary removed - Section 6.4.1: Sorting changed to alphabetical order, summaries for pooled HD group added, SOC summaries added for separate intraocular inflammation, APTC, hypertension and nasal mucosal finding event tables, further minor text updates - Section 6.4.2: Titer summaries added - Section 6.4.4: Clarification added for summaries of treatment-emergent pre-defined lab abnormalities, Statement about SI units removed - Section 6.4.6: Summaries for treatment emergent PCSV added, Figures for DPKS removed - Section 9.4.3: PT terms updated	Updates based on dry run and mock CSR review comments
V 3.0	Date of last signature	- Additional pre-specified exploratory efficacy endpoints and analyses mentioned in Section 2 and details added in Appendix 9.7	Additional pre-specified exploratory efficacy endpoints and analyses added for submission to US FDA

8. References

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9. Appendix

9.1 Handling of Questionnaires

9.1.1 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 9–1. 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 9–1: 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-scales will be evaluated (see Table 9–2), and 11 of these sub-scales will be included in the total VFQ score.

Table 9–2: 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.

9.2 Development of Anti-drug Antibodies

The measurements of antibody assays (screening and confirmatory assay) at baseline, Week 48 and Week 96 will be used to classify the respective antibody status at the respective visit in the following Table 9–3

Table 9–3: Classification of the respective antibody status

Screening test	Confirmatory test	Antibody status at respective visit
Negative	ND	Negative
Negative	Negative	Negative
Negative	Positive	Positive
Positive	ND	ND
Positive	Negative	Negative
Positive	Positive	Positive
ND	ND	ND
ND	Negative	Negative
ND	Positive	Positive

The antibody status for the overall study course until Week 96 will be defined according to the following definition.

- **ADA Negative:** defined as negative response in the ADA assay at all time points and those that exhibit a pre-existing response, regardless of any missing samples
- **ADA positive:** defined as those that exhibit a treatment-emergent or treatment-boosted ADA response, regardless of any missing sample

  Pre-existing immunoreactivity: defined as either a positive response in the ADA assay at baseline with all post first dose ADA results negative OR a positive response at baseline with all post first dose ADA responses less than 4-fold of baseline titer levels.

  Treatment-boosted ADA response: defined as a positive response post first dose that is greater than or equal to 4-fold over baseline titer level, when baseline results are positive.

  Treatment-emergent positive: defined as an ADA positive response post first dose when baseline results are negative or missing, or ADA positive response more than 4-fold of a positive baseline titer. The treatment-emergent responses will be further characterized as Persistent, Indeterminate or Transient.

  - - Persistent Response – Treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points, with no ADA

negative samples in between, regardless of any missing samples.

- Indeterminate Response –Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay, regardless of any missing samples.

- Transient Response –Treatment-emergent ADA positive response that is not considered persistent or indeterminate, regardless of any missing samples.

9.3 Pre-defined Laboratory Abnormalities

Table 9–4: Pre-defined laboratory abnormalities

Parameter	Pre-defined laboratory abnormalities for phase 2/3 studies
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	≤ 3.9 mmol/L and < LLN
- Hyperglycaemia	≥ 11.1 mmol/L (unfasted), ≥ 7 mmol/L (fasted)
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
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

LLN: lower limit of normal, ULN: upper limit of normal

9.4 Definition of safety subgroups

In the following the definitions for subgroups based on medical history and adverse events are given.

9.4.1 Hypertension

Hypertension will be selected based on the PTs as described in Table 9–5 below, following the PBMQ 1275. All PTs given are based on MedDRA version 25.0 and might be subject to change in future MedDRA version.

Table 9–5: PTs for selection of "Hypertension"

Preferred term (MedDRA version 25.0)
Accelerated hypertension
Blood pressure ambulatory increased
Blood pressure diastolic increased
Blood pressure inadequately controlled
Blood pressure increased
Blood pressure systolic increased
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

9.4.2 Intraocular inflammation

Intraocular inflammation will be selected based on the PTs as described in Table 9–6 below. All PTs given are based on MedDRA version 25.0 and might be subject to change in future MedDRA version.

Table 9–6: PTs for selection of "Intraocular Inflammation"

Preferred term (MedDRA version 25.0)
Anterior chamber fibrin
Anterior chamber cell
Anterior chamber flare
Anterior chamber inflammation
Aqueous fibrin
Autoimmune uveitis
Candida endophthalmitis
Chorioretinitis
Choroiditis
Cyclitis
Endophthalmitis
Eye infection bacterial
Eye infection chlamydial
Eye infection fungal
Eye infection intraocular
Eye infection staphylococcal
Eye infection
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

9.4.3 Nasal mucosal events

Nasal mucosal events will be selected based on the PTs as described in Table 9–7 below. All PTs given are based on MedDRA version 25.0 and might be subject to change in future MedDRA version.

Table 9–7: PTs for selection of "Nasal mucosal events"

Preferred term (MedDRA version 25.0)
Epistaxis
Nasal inflammation
Nasal mucosal erosion
Nasal mucosal ulcer
Nasal ulcer

9.4.4 Medical history of cerebrovascular disease (e.g. CVA / Stroke)

Defined by MSSO SMQ 20000060 ‘Central nervous system vascular disorders’as described in Table 9–8 below. All PTs given are based on MedDRA version 25.0 and might be subject to change in future MedDRA version.

Table 9–8: PTs for selection of medical history of “Cerebrovascular Disease”

Preferred Term (MedDRA version 25.0)
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

Table 9–8: PTs for selection of medical history of "Cerebrovascular Disease"

Preferred Term (MedDRA version 25.0)
Carotid aneurysm rupture
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

Table 9–8: PTs for selection of medical history of "Cerebrovascular Disease"

Preferred Term (MedDRA version 25.0)
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
Congenital cerebrovascular anomaly

Table 9–8: PTs for selection of medical history of "Cerebrovascular Disease"

Preferred Term (MedDRA version 25.0)
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
Intracranial haemorrhage neonatal
Intracranial tumour haemorrhage

Table 9–8: PTs for selection of medical history of "Cerebrovascular Disease"

Preferred Term (MedDRA version 25.0)
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
Primary familial brain calcification
Pseudo-occlusion of internal carotid artery
Putamen haemorrhage

Table 9–8: PTs for selection of medical history of "Cerebrovascular Disease"

Preferred Term (MedDRA version 25.0)
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
Transient ischaemic attack
Transverse sinus thrombosis
Vascular encephalopathy
Vascular stent occlusion

Table 9–8: PTs for selection of medical history of "Cerebrovascular Disease"

Preferred Term (MedDRA version 25.0)
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

9.4.5 Medical history of ischaemic heart disease (e.g., myocardial infarction)

PBMQ 'Myocardial Infarction' is defined by selected PTs only (from MSSO SMQs below):

- 20000043: Ischaemic heart disease (MSSO SMQ)
- 20000047: Myocardial infarction (MSSO SMQ)

as described in Table 9–9 below. All PTs given are based on MedDRA version 25.0 and might be subject to change in future MedDRA version.

Table 9–9: PTs for selection of medical history of "Ischaemic Heart Disease"

Preferred Term (MedDRA version 25.0)
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

Table 9–9: PTs for selection of medical history of "Ischaemic Heart Disease"

Preferred Term (MedDRA version 25.0)
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
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

Table 9–9: PTs for selection of medical history of "Ischaemic Heart Disease"

Preferred Term (MedDRA version 25.0)
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
Ventricular compliance decreased
Wellens' syndrome

9.4.6 Medical history of renal impairment

Renal impairment is defined by creatinine clearance (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)

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

'Requiring dialysis' is defined by PT from Table 9–10. All PTs given are based on MedDRA version 25.0 and might be subject to change in future MedDRA version.

Table 9–10: PTs for selection of medical history of "Requiring dialysis"

Preferred Term (MedDRA version 25.0)
Continuous haemodiafiltration
Dialysis
Dialysis device insertion
Haemodialysis
Haemofiltration
Peritoneal dialysis
Removal of renal transplant
Renal replacement therapy
Renal transplant

9.4.7 Medical history of hepatic impairment

Defined by MSSO SMQ: Hepatic disorders 20000005 excluding sub-SMQ 20000018: Pregnancy-related hepatic disorders as described in Table 9–11 below. All PTs given are based on MedDRA version 25.0 and might be subject to change in future MedDRA version.

Table 9–11: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 25.0)
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

Table 9–11: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 25.0)
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
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

Table 9–11: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 25.0)
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
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

Table 9–11: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 25.0)
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
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

Table 9–11: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 25.0)
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
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

Table 9–11: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 25.0)
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
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

Table 9–11: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 25.0)
Hepatitis E antigen positive
Hepatitis E immunity confirmed
Hepatitis E virus test positive
Hepatitis F
Hepatitis G
Hepatitis H
Hepatitis acute
Hepatitis alcoholic
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

Table 9–11: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 25.0)
Hepatosplenomegaly
Hepatosplenomegaly neonatal
Hepatotoxicity
Hereditary haemochromatosis
Herpes simplex hepatitis
Hyperammonaemia
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

Table 9–11: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 25.0)
Liver induration
Liver injury
Liver iron concentration abnormal
Liver iron concentration increased
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

Table 9–11: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 25.0)
Peritoneal fluid protein decreased
Peritoneal fluid protein increased
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

Table 9–11: PTs for selection of medical history of "Hepatic Impairment"

Preferred term (MedDRA version 25.0)
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

9.5 Strategies for occurrence of intercurrent events

Analysis strategies for intercurrent events occurring through week 48 are described in Table 9–12 below for BCVA and other continuous efficacy endpoint variables. Intercurrent events for the analysis of BCVA and other continuous efficacy endpoint variables (or binary endpoints which are based on continuous variables) at week 60 and later will be handled analogously.

Table 9–12: Strategies for occurrence of intercurrent events for analysis at week 48 for BCVA and other continuous endpoint variables

Potential post-randomization event	Intercurrent event (yes/no)	Strategy	Primary Estimand Primary Analysis	Sensitivity Analysis
Premature discontinuation of study intervention for any reason before week 48 (and discontinuation of study) (a)	Yes	Hypothetical	Non-observed data beyond discontinuation of study intervention will be covered implicitly in the MMRM	Non-observed data beyond discontinuation of study intervention will be imputed by LOCF
Premature discontinuation of study intervention for any reason before week 48 (but continuation of study) (b)	Yes	Hypothetical	Observed data beyond last active injection (that was administered before the premature discontinuation of study intervention) + current treatment interval +5 days will be excluded from analysis and resulting missing data will be covered implicitly in the MMRM	Observed data beyond last active injection (that was administered before the premature discontinuation of study intervention) + current treatment interval +5 days will be excluded from analysis and resulting missing data will be imputed by LOCF

Table 9–12: Strategies for occurrence of intercurrent events for analysis at week 48 for BCVA and other continuous endpoint variables

Potential post-randomization event	Intercurrent event (yes/no)	Primary Estimand Strategy	Primary Analysis	Sensitivity Analysis
Missed (skipped) study intervention for any reason before week 48:				
- Missed study intervention was planned to be a *sham* injection	Yes, but no impact since no active treatment was missed	Not applicable	Observed data beyond missed sham injection will be included in the analysis and the MMRM	Observed data beyond missed sham injection will be included in the analysis
- Missed study intervention was planned to be an *active* injection, but at the next scheduled visit a make-up injection was given to compensate for the missed active injection (c)	Yes	Treatment policy	All observed data will be included in the analysis and the MMRM	All observed data will be included in the analysis
- Missed study intervention was planned to be an *active* injection, but at the next scheduled visit make-up injection was *not* given to compensate for the missed active injection (d)	Yes	Hypothetical	Observed data beyond last active injection (that was administered before the first missed active injection) + current treatment interval +5 days will be excluded from analysis and resulting missing data will be covered implicitly in the MMRM	Observed data beyond last active injection (that was administered before the the first missed active injection) + current treatment interval +5 days will be excluded from analysis and resulting missing data will be imputed by LOCF

Table 9–12: Strategies for occurrence of intercurrent events for analysis at week 48 for BCVA and other continuous endpoint variables

Potential post-randomization event	Intercurrent event (yes/no)	Primary Estimand		
		Strategy	Primary Analysis	Sensitivity Analysis
Wrong study intervention before week 48:				
- *Active* injection instead of a *sham* injection (note, this does not refer to potential make-up injections which should be given at the next scheduled visit in case of any missed active injection)	Yes	Treatment policy	Observed data beyond the wrong active injection will be included in the analysis and the MMRM	Observed data beyond the wrong active injection will be included in the analysis
- *Sham* injection instead of an *active* injection	Yes	Hypothetical	Observed data beyond last active injection (that was administered before the wrong sham injection) + current treatment interval +5 days will be excluded from analysis and resulting missing data will be covered implicitly in the MMRM	Observed data beyond last active injection (that was administered before the wrong sham injection) + current treatment interval +5 days will be excluded from analysis and resulting missing data will be imputed by LOCF
- Wrong dose (for participants randomized to the 2q8 group): *High dose 8 mg* injection instead of *2 mg* injection	Yes	Treatment policy	Observed data beyond the wrong high dose 8 mg injection will be included in the analysis and the MMRM	Observed data beyond the wrong high dose 8 mg injection will be included in the analysis
- Wrong dose (for participants randomized to the HDq12 or HDq16 group): *2 mg* injection instead of *high dose 8 mg* injection	Yes	Treatment policy	Observed data beyond the wrong high dose 2 mg injection will be included in the analysis and the MMRM	Observed data beyond the wrong high dose 2 mg injection will be included in the analysis

Table 9–12: Strategies for occurrence of intercurrent events for analysis at week 48 for BCVA and other continuous endpoint variables

Potential post-randomization event	Intercurrent event (yes/no)	Strategy	Primary Estimand	
			Primary Analysis	Sensitivity Analysis
Use of a prohibited medication (as defined in section 4.5.6) before week 48	Yes	Hypothetical	Observed data beyond first administration of the prohibited medication in study eye will be excluded from analysis and resulting missing data will be covered implicitly in the MMRM	Observed data beyond first administration of the prohibited medication in study eye will be excluded from analysis and resulting missing data will be imputed by LOCF
Shortening of dosing interval according to DRM criteria before week 48	No, since DRM is considered part of the randomized treatment regimen	Not applicable	Observed data beyond shortening of dosing interval will be included in the analysis and the MMRM	Observed data beyond shortening of dosing interval will be included in the analysis

Any missing assessment of BCVA at a certain visit is not considered an intercurrent event per se but is considered missing at random and covered implicitly in the MMRM.

It is assumed that a COVID-19 illness does not affect the treatment effect but at most the treatment schedule. Therefore, any deviations from the treatment schedule due to a COVID-19 illness (i.e. missed study intervention due to the COVID-19 illness) will be handled as described in the table above. Any other study disruption related to the COVID-19 pandemic (discontinuations or missed study intervention, e.g. due to site closed, local travel restrictions, participant not willing to go to the site) will also be handled as described in the table above.

(a) This ICE covers the situation when the treatment intervention and the study was discontinued early (prior to Week 48) at the same time

(b) This ICE covers the situation when the treatment intervention was discontinued early (prior to Week 48) and the participant either remained in the study or discontinued from the study, but at a later time.

(c) This ICE covers situation when an injection during the loading dose was missed but an injection was given at the next visit (i.e. Baseline injection was missed but Week 4 injection was given, Week 4 injection was missed but Week 8 injection was given, Week 8 injection was missed but make-up injection was given at Week 12).

(d) This ICE covers situation when an injection during the loading dose was missed and no injection was given at the next visit (i.e. Baseline injection was missed and Week 4 injection was missed, Week 4 injection was missed and Week 8 injection was missed, Week 8 injection was missed and no make-up injection was given at Week 12).

Analysis strategies for intercurrent events occurring post-baseline are described in Table 9–13 below for the analysis of participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in central subfield. Other binary efficacy endpoint summaries will handled analogously.

Table 9–13: Strategies for occurrence of intercurrent events for analysis of proportions of participants with no IRF and no SRF in central subfield and other binary endpoint variables

Potential post-randomization event*	Intercurrent event (yes/no)	Primary Estimand Strategy	Primary Estimand Analysis
Premature discontinuation of study intervention for any reason (and discontinuation of study) (a)	Yes	Hypothetical	Non-observed data beyond discontinuation of study intervention will be imputed using LOCF
Premature discontinuation of study intervention for any reason (but continuation of study) (b)	Yes	Hypothetical	Observed data beyond last active injection (that was administered before the premature discontinuation of study intervention) + current treatment interval +5 days will be excluded from analysis and resulting missing data will be imputed using LOCF
Missed (skipped) study intervention for any reason:			
- Missed study intervention was planned to be a *sham* injection	Yes, but no impact since no active treatment was missed	Not applicable	Observed data beyond missed sham injection will be included in the analysis
- Missed study intervention was planned to be an *active* injection, but at the next scheduled visit a make-up injection was given to compensate for the missed active injection (c)	Yes	Treatment policy	All observed data will be included in the analysis
- Missed study intervention was planned to be an *active* injection, but at the next scheduled visit make-up injection was *not* given to compensate for the missed active injection (d)	Yes	Hypothetical	Observed data beyond last active injection (that was administered before the the first missed active injection) + current treatment interval +5 days will be excluded from analysis and resulting missing data will be imputed by LOCF

Table 9–13: Strategies for occurrence of intercurrent events for analysis of proportions of participants with no IRF and no SRF in central subfield and other binary endpoint variables

Potential post-randomization event*	Intercurrent event (yes/no)	Primary Estimand Strategy	Primary Estimand Analysis
Wrong study intervention			
- *Active* injection instead of a *sham* injection (note, this does not refer to potential make-up injections which should be given at the next scheduled visit in case of any missed active injection)	Yes	Treatment policy	Observed data beyond the wrong active injection will be included in the analysis
- *Sham* injection instead of an *active* injection	Yes	Hypothetical	Observed data beyond last active injection (that was administered before the wrong sham injection) + current treatment interval +5 days will be excluded from analysis and resulting missing data will be imputed by LOCF
- Wrong dose (for participants randomized to the 2q8 group): *High dose 8 mg* injection instead of *2 mg* injection	Yes	Treatment policy	Observed data beyond the wrong high dose 8 mg injection will be included in the analysis
- Wrong dose (for participants randomized to the HDq12 or HDq16 group): *2 mg* injection instead of *high dose 8 mg* injection	Yes	Treatment policy	Observed data beyond the wrong high dose 2 mg injection will be included in the analysis
Use of a prohibited medication (as defined in section 4.5.6)	Yes	Hypothetical	Observed data beyond first administration of the prohibited medication in study eye will be excluded from analysis and resulting missing data will be imputed by LOCF
Shortening of dosing interval according to DRM criteria	No, since DRM is considered part of the randomized treatment regimen	Not applicable	Observed data beyond shortening of dosing interval will be included in the analysis

Table 9–13: Strategies for occurrence of intercurrent events for analysis of proportions of participants with no IRF and no SRF in central subfield and other binary endpoint variables

Potential post-randomization event*	Intercurrent event (yes/no)	Primary Estimand Strategy	Primary Estimand Analysis

* Not all intercurrent events are applicable for all endpoints and visits.

Any missing assessment of SD-OCT data at a certain visit is not considered an intercurrent event per se but is considered missing at random.

It is assumed that a COVID-19 illness does not affect the treatment effect but at most the treatment schedule. Therefore, any deviations from the treatment schedule due to a COVID-19 illness (i.e. missed study intervention due to the COVID-19 illness) will be handled as described in the table above. Any other study disruption related to the COVID-19 pandemic (discontinuations or missed study intervention, e.g. due to site closed, local travel restrictions, participant not willing to go to the site) will also be handled as described in the table above.

(a) This ICE covers the situation when the treatment intervention and the study was discontinued early at the same time

(b) This ICE covers the situation when the treatment intervention was discontinued early and the participant either remained in the study or discontinued from the study, but at a later time.

(c) This ICE covers situation when an injection during the loading dose was missed but an injection was given at the next visit (i.e. Baseline injection was missed but Week 4 injection was given, Week 4 injection was missed but Week 8 injection was given, Week 8 injection was missed but make-up injection was given at Week 12).

(d) This ICE covers situation when an injection during the loading dose was missed and no injection was given at the next visit (i.e. Baseline injection was missed and Week 4 injection was missed, Week 4 injection was missed and Week 8 injection was missed, Week 8 injection was missed and no make-up injection was given at Week 12).

9.6 Participating Regions and Countries

The following regions and countries are participating in this study and are shown in Table 9–14.

Table 9–14: Participating Regions and Countries

Region	Country
APAC	AUSTRALIA
	CHINA
	JAPAN
	KOREA, REPUBLIC OF
	SINGAPORE
	TAIWAN
Europe	AUSTRIA
	BULGARIA
	CZECH REPUBLIC
	ESTONIA
	FRANCE
	GEORGIA
	HUNGARY
	ISRAEL
	ITALY
	LATVIA
	LITHUANIA
	PORTUGAL
	RUSSIAN FEDERATION
	SERBIA
	SLOVAKIA
	SPAIN
	SWITZERLAND
	UKRAINE
	UNITED KINGDOM
Latin America	ARGENTINA
North America	CANADA
	UNITED STATES

9.7 Additional Pre-Specified Exploratory Efficacy Variables and Analyses

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

9.7.1 Analysis Populations

The following populations of analysis will be used for the additional pre-specified exploratory efficacy analyses.

9.7.1.1 Full Analysis Set (FAS)

Refer to Section 5.1.

9.7.1.2 Modified Full Analysis Set (mFAS)

The modified full analysis set 1 (mFAS1) includes all randomized patients who completed the 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 participants in the 2q8 group receive fixed q8 dosing).

The modified full analysis set 2 (mFAS2) includes all randomized participants who completed the 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 participants in the 2q8 group receive fixed q8 dosing).

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

9.7.2 Additional Pre-Specified Exploratory Efficacy Variable(s)

Additional pre-specified exploratory 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 6.2.2)
- Change from 8-weeks post initial treatment phase in BCVA (as measured by ETDRS letter score) at week 48 (additional pre-specified exploratory efficacy variable)

Note that per the dosing schedule shown in Figure 1–2 of the protocol, the initial treatment phase is through week 8 (3 doses) for all treatment groups (i.e. HDq12, HDq16, 2q8). Hence 8-weeks post initial treatment phase is Week 16 for all treatment groups.

9.7.3 Additional Pre-Specified Exploratory Efficacy Analyses

The additional pre-specified exploratory efficacy analyses will be an alternative tipping point analysis on the efficacy variables in Section 9.7.2.

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

1. Within each treatment group, for participants with data at both week 48 and at the designated baseline for the analysis, sort the participant 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. Participants 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 participants 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 participants 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 participant 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 6.2.2).

The reported results from these additional analyses will be as follows (see Table 9–15).

Table 9–15: Additional Pre-Specified Exploratory 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 participants 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 participants 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 participants 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 participants 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 participants 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 participants in the All HD analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	-2	z_2 letters

	Population	**Variable**	**Analysis Results**	**Δ**	**Tipping Point in HD group**
2a	FAS[a]	Change from 8-weeks post initial treatment in BCVA at week 48	• Number and Percentage of participants 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 participants 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 participants in the All HD analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	0	z_3 letters
2b	FAS[a]	Change from 8-weeks post initial treatment in BCVA at week 48	• Number and Percentage of participants 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 participants 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 participants in the All HD analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	-2	z_4 letters

	Population	**Variable**	**Analysis Results**	**Δ**	**Tipping Point in HD group**
3a	mFAS1[b]; mFAS2[c]	Change from baseline in BCVA at week 48	• Number and Percentage of participants 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 participants in the HDq16 analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	0	y_5 letters
			• Number and Percentage of participants in the All HD analysis subset for whom mean change in BCVA ≥ [mean change in BCVA for 2q8 group – Δ]	0	z_5 letters
3b	mFAS1[b]; mFAS2[c]	Change from baseline in BCVA at week 48	• Number and Percentage of participants 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 participants 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 participants 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 participants 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 participants 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 participants 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 participants 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 participants 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 participants 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 participants who received at least 1 dose of study intervention.

[b] mFAS1 = Modified Full Analysis Set 1, which includes all randomized participants 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 participants who completed the initial treatment phase and maintained dosing interval (All HD group and 2q8 group).

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