Official Title: A Phase III, Multicenter, Randomized, Visual Assessor-Masked, Active-Comparator Study of the Efficacy, Safety, and Pharmacokinetics of the Port Delivery System With Ranibizumab in Patients With Neovascular Age-Related Macular Degeneration (Archway)

NCT Number: NCT03677934

Document Date: SAP Version 3: 09 April 2021

STATISTICAL ANALYSIS PLAN

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, VISUAL ASSESSOR–MASKED, ACTIVE-COMPARATOR STUDY OF THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF THE PORT DELIVERY SYSTEM WITH RANIBIZUMAB IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (ARCHWAY)**
PROTOCOL NUMBER:	GR40548
STUDY DRUG:	Port Delivery System with Ranibizumab
VERSION NUMBER:	3
IND NUMBER:	113,552
EUDRACT NUMBER:	Not applicable
SPONSOR:	F. Hoffmann-La Roche Ltd
PLAN PREPARED BY:	[redacted], Ph.D. [redacted], Ph.D. [redacted], Ph.D.
DATE FINAL:	Version 1: 29 March 2019 Version 2: 21 April 2020
DATE AMENDED:	See electronic date stamp below.

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

Date and Time(UTC)	Reason for Signing	Name
09-Apr-2021 17:44:46	Company Signatory	[redacted]

STATISTICAL ANALYSIS PLAN AMENDMENT
RATIONALE OF CHANGES

Changes from Statistical Analysis Plan (SAP) Version 2 to SAP Version 3 have been made in preparation for the Final CSR analysis. At the time of amendment, the Primary CSR and Update CSR have been completed, and the following changes to the SAP are focused on analyses of data after Study Week 48. Changes include the following:

Changes to add additional analysis to assess the impact of COVID-19

- Changes to Section 4.4.2.2 to specify additional supplemental analyses incorporating COVID-19 related intercurrent events.
- Changes to Section 4.7.2 to specify additional safety analyses performed for COVID-19.

Changes to add additional details of secondary efficacy endpoints

- Changes to Section 4.4.2 to modify the definition of the proportion used to measure the secondary efficacy objectives on supplemental treatment.
- Changes to Section 4.4.2.1 to add an additional sensitivity analysis of the per protocol complete cases population.

Additional changes include:

- Changes to Section 4.4.3 to add the Exploratory Efficacy Endpoint assessed at Weeks 88 and 92 of the proportion of patients who gain or lose 15 letters from baseline.
- Changes to Section 4.7.1 with the addition of the new Ocular AESI term “Device Dislocation”.
- Changes to Appendix 1, Appendix 2, and Appendix 3 to align with the current version of the Protocol (version 5).

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GLOSSARY OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
AUC	area under the concentration-time curve
BCVA	best-corrected visual acuity
CI	confidence interval
C_{max}	maximum serum concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CPT	center point thickness
CST	central subfield thickness
CSR	Clinical Study Report
EMA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
ILM	inner limiting membrane
IOP	intraocular pressure
IxRS	interactive voice/web based response system
MacTSQ	Macular Disease Treatment Satisfaction Questionnaire
MMRM	mixed-effect model with repeated measures
nAMD	neovascular age-related macular degeneration
NI	non-inferiority
PD	pharmacodynamic
PDS	Port Delivery System
PK	Pharmacokinetics
PPPQ	PDS Patient Preference Questionnaire
Q24W	every 24 weeks
Q4W	every 4 weeks
RPE	retinal pigment epithelium
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD-OCT	spectral domain optical coherence tomography
SMQ	Standardized MedDRA Query
$t_{1/2}$	half-life
VA	visual acuity
VEGF	vascular endothelial growth factor

1. BACKGROUND

Neovascular age-related macular degeneration (nAMD) is a form of advanced age-related macular edema (AMD) that causes rapid and severe visual loss, and remains a leading cause of visual impairment in the elderly. The prevalence of nAMD increases exponentially with age, with onset typically after 50 years of age (National Institutes of Health 2014). Prevalence of nAMD is also found to increase with age, based on a meta-analysis of 31 population-based studies of persons with European ancestry (Rudnicka et al. 2012; Owen et al. 2012). In the next 30 years, the global population aged 60 years and older is projected to increase dramatically, translating into an increase in the prevalence of nAMD from 23 million in 2010 to 80 million by 2050 (Smith AF 2010).

Ranibizumab, a recombinant, humanized monoclonal antibody fragment, which binds to all known isoforms of vascular endothelial growth factor (VEGF)-A, was approved by the US Food and Drug Administration (FDA) for use in nAMD, in June 2006 and by the European Medicine Agency (EMA) in January 2007. As a result of the chronic, progressive nature of nAMD, frequent ranibizumab intravitreal injections continue for extended periods for many patients. Pivotal studies of intravitreal ranibizumab in nAMD (Studies MARINA [FVF2598g] and ANCHOR [FVF2587g]) demonstrated significant and well-maintained visual acuity (VA) outcomes with monthly 0.5 mg intravitreal injections for 2 years.

Real-world data suggest that many patients with nAMD do not receive treatment according to the approved prescribing information and this under-treatment in clinical practice is associated with lower visual acuity gains compared with those observed in controlled clinical trials. Under-treatment of nAMD in clinical practice reflects the burden of frequent therapy on patients, caregivers, and the healthcare system.

The Port Delivery System with ranibizumab (PDS) is a drug delivery technology that allows physicians to use ranibizumab with a continuous drug delivery mechanism without altering its chemistry. It consists of the PDS implant (referred to as the implant), 4 ancillary devices (insertion tool, initial fill needle, refill needle, and explant tool), and a customized formulation of ranibizumab 100 mg/mL tailored for continuous delivery. The implant is an intra-ocular refillable device that is surgically placed through the pars plana to allow for continuous delivery of ranibizumab into the vitreous.

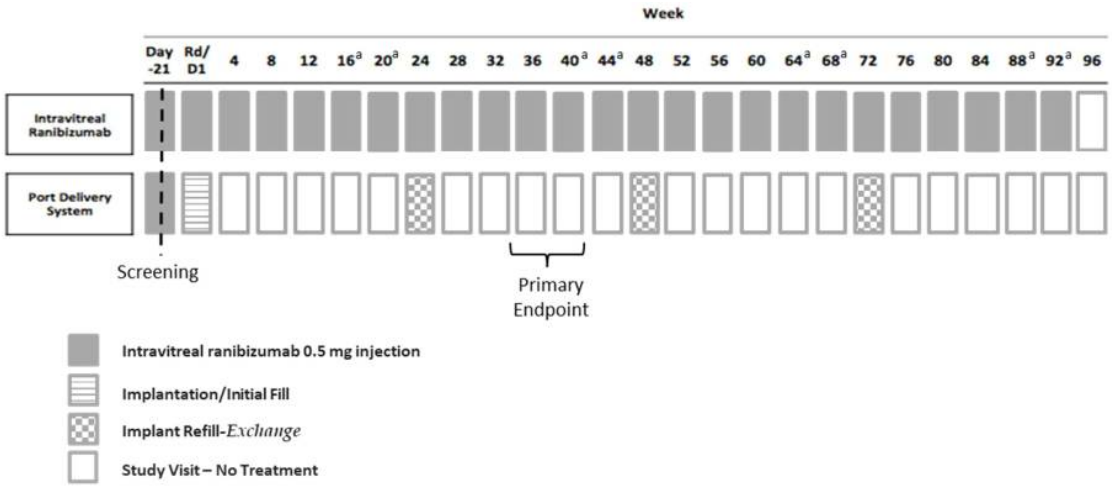
Continuous delivery of ranibizumab from the implant, with a prolonged fixed period between refill-exchange intervals, is a novel approach that may result in less-frequent need for treatment than monthly dosing and patient monitoring, while maintaining optimal visual outcomes. The Phases I and II PDS studies provided evidence of the safety and tolerability of the PDS and support the evaluation of the PDS in a Phase III study.

The purpose of this document is to provide details of the planned analyses for Study GR40548 (Archway). The analyses and endpoints specified in this document supersede the analysis plan described in the study protocol and the previous version of the Statistical Analysis Plan (SAP).

2. STUDY DESIGN

Study GR40548 is a Phase III, randomized, multicenter, open-label (visual assessor-masked), active-comparator study, designed to assess the efficacy, safety, and pharmacokinetics (PK) of PDS with ranibizumab 100 mg/mL every 24 weeks (Q24W) compared with ranibizumab intravitreal injections every 4 weeks (Q4W) at 0.5 mg (10 mg/mL) in patients with nAMD. Approximately 360 patients will be enrolled at approximately 90 sites. For the study schema, see Figure 1.

Figure 1 Study Schema



D = day; Rd = randomization.

[a] Patients in the implant arm may be eligible for supplemental treatment with intravitreal ranibizumab 0.5mg at Weeks 16, 20, 40, 44, 64, 68, 88, and 92.

Patients must satisfy all eligibility criteria at both the screening and the randomization visits, including receipt of all screening visit images by the central reading center. Patients who do not meet eligibility criteria (screen-failed patients) may be eligible to repeat screening up to two times if deemed appropriate by the investigator.

After all eligibility requirements are confirmed, patients are to be randomly allocated in a 3:2 ratio so that approximately 216 patients receive the PDS implant filled with 100 mg/mL ranibizumab Q24W (implant arm) and approximately 144 patients will receive monthly intravitreal ranibizumab 0.5 mg injections Q4W (intravitreal arm). On the day of a patient's randomization visit, best-corrected visual acuity (BCVA) is measured based upon the Early Treatment Diabetic Retinopathy Study (ETDRS) chart assessment at a starting test distance of 4 meters, and randomization is stratified by the

BCVA score (<74 letters vs. ≥74 letters). Randomization will be performed by the interactive voice/web based response system (IxRS).

Only one eye will be chosen as the study eye. If both eyes are eligible, the investigator will determine which eye will be selected for study treatment.

Patients who are randomly allocated to the PDS 100 mg/ml arm will have the implant (pre-filled with 100 mg/mL ranibizumab) surgically inserted on Day 1, which must occur 1-7 days (inclusive) after randomization (i.e., randomization and Day 1 visit assessments cannot be performed on the same day) and no later than 28 days from the last intravitreal ranibizumab injection. After Day 1, patients in the implant arm will have scheduled safety visit assessments on Days 2 and 7 (±2 days) and will receive implant refill-exchanges with 100 mg/mL ranibizumab Q24W at Week 24 (±7 days), Week 48 (±7 days), and Week 72 (±7 days).

Patients who are randomly allocated to the intravitreal arm will receive 0.5 mg of ranibizumab intravitreal injections starting on Day 1, which is to be administered at the conclusion of the randomization visit (i.e., randomization and Day 1 visit assessments are performed on the same day). Patients will receive 0.5 mg ranibizumab, injected intravitreally Q4W (±7 days) from Day 1 until Week 92.

Patients randomized to the implant arm will be eligible for supplemental treatment with intravitreal ranibizumab (0.5 mg intravitreal injections of 10 mg/mL formulation) at Weeks 16 and 20 (after implant insertion) and at Weeks 40, 44, 64, 68, 88, and 92 if any of the following criteria are met in the study eye:

- Decrease of ≥15 letters from the best-recorded BCVA in the study, due to nAMD disease activity.

OR

- Increase of ≥150 μm in central subfield thickness (CST) on spectral domain optical coherence tomography (SD-OCT) from the lowest CST measurement in the study, due to nAMD disease activity.

OR

- Increase of ≥100 μm in CST on SD-OCT from the lowest CST measurement in the study associated with a decrease of ≥10 letters from the best recorded BCVA during the study, due to nAMD disease activity.

Note: CST is assessed by central reading center with boundaries of the inner limiting membrane (ILM) to Bruch's Membrane, which includes the pigment epithelial detachment (PED) thickness.

In the event a patient's non-study (fellow) eye requires treatment for nAMD after randomization, treatment with any FDA-approved intravitreal anti-VEGF treatment for nAMD may be administered. The Sponsor will provide intravitreal ranibizumab 0.5 mg

starting from the screening visit, if the Investigator chooses to treat the fellow eye with ranibizumab.

All study assessments and study eye treatment should be completed per protocol prior to anti-VEGF administration in the fellow eye.

Refer to Section 3 of the Study GR40548 Protocol for the further details of the study design and Appendix 2 and Appendix 3 for the Schedule of Activities.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1.

2.2 DETERMINATION OF SAMPLE SIZE

Patients will be randomly allocated in a 3:2 ratio to the implant arm or intravitreal arm.

The primary endpoint is the change in BCVA score from baseline averaged over Weeks 36 and 40. The study is sized to achieve adequate power to show non-inferiority (NI) and equivalence of the implant arm to the intravitreal arm in the change in BCVA score from baseline averaged over Week 36 and Week 40 using an NI margin of 4.5 letters and equivalence margins of $\pm$4.5 letters.

Assuming a standard deviation of 9.5 letters for the change from baseline in BCVA score averaged over 36 and 40 weeks, up to a true mean change from baseline in BCVA of 0.75 letters worse for the PDS 100 mg/ml arm, compared with the monthly intravitreal arm, 216 patients in the implant arm and 144 patients in the intravitreal arm will provide at least 90% power to demonstrate NI and equivalence between the two treatment groups. Calculations were based on a one-sided *t*-test at $\alpha = 0.025$ level for the NI test and two one-sided *t*-tests at the $\alpha = 0.025$ level for the equivalence test with the assumption of a 10% dropout rate by Week 40 and a 10% increase for the trimmed mean analysis. Note, the original sample size did not account for the type I error adjustment specified in Section 3.2, however the study will still have at least 90% power with this adjustment.

An independent statistician from the Independent Data Coordinating Center (iDCC) was employed to conduct a masked evaluation of the variance of the primary efficacy endpoint, but not the proportion of patients who receive supplemental treatment during the study or the study dropout rate before the end of enrollment because the enrollment was too rapid for these evaluations to be of value. The variance comparison to the assumptions used in planning the study did not suggest the initial assumption for the variance of the primary efficacy endpoint was substantially lower. Therefore, no change to the planned sample size was required. However, independent of this assessment, due to a high speed of enrollment combined with a lower screen failure rate than expected, there were a total of 418 patients enrolled. Details of the masked assessment and findings are provided in the memorandum from the iDCC in Appendix 4.

2.3 ANALYSIS TIMING

The primary analysis will be performed when all patients have completed the Week 40 visit or have discontinued from the study prior to Week 40, all data collected through Week 40 are in the database, and the data have been cleaned and verified. At the time of the primary analysis, the study will be ongoing. An analysis of the available data post Week 40 (after Week 40 and up to a specified clinical cutoff date) will also be performed. Such results will be reported with, but separate from, the 40-week study results to provide additional information.

Additional analyses may be performed to support the requirements of health authorities relative to marketing applications, as appropriate.

The final analysis will be performed when all patients have either completed the 2-year study period (i.e., Week 96) or discontinued early from the study, all data from the study are in the database, and the database is locked.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Patients will be randomly allocated in a 3:2 ratio so that approximately 216 patients will receive the PDS implant with 100 mg/mL ranibizumab Q24W and approximately 144 patients will receive Q4W intravitreal injections of 10 mg/mL ranibizumab. On the day of a patient's randomization visit, BCVA will be measured based upon the ETDRS chart assessment at a starting test distance of 4 meters and randomization will be stratified by the BCVA score (<74 letters vs. ≥ 74 letters). Randomization will be performed through an IxRS.

3.2 INDEPENDENT IMAGE READING CENTER

All ocular images will be obtained by trained and certified site personnel at the study sites and forwarded to the central reading center for independent, masked, analyses and storage.

3.3 DATA MONITORING

An independent Data Monitoring Committee (iDMC) will monitor safety and study conduct on an ongoing basis. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines the iDMC's roles and responsibilities. The iDMC will meet approximately every 6 months (frequency adjustable as required) to evaluate unmasked ocular and systemic (non-ocular) safety events. After reviewing the data, the iDMC will provide a recommendation to the Sponsor as described in the iDMC Charter. Final decisions will rest with the Sponsor. Any outcomes of these data reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards (IRBs).

A nominal type I error penalty of 0.0001 will be taken for each time the iDMC reviews unmasked data prior to the formal analysis of the primary efficacy endpoint. At the time of the primary analysis, it is estimated that 3 interim data reviews will have been conducted by the iDMC; therefore, efficacy analyses will be performed with a family-wise significance level of 0.0497.

4. STATISTICAL METHODS

Descriptive summaries will include the mean, standard deviation, median, and range for continuous variables, and counts and percentages for categorical variables.

4.1 ANALYSIS POPULATIONS

4.1.1 Efficacy Population

Efficacy data will be summarized for the Efficacy Population comprising all patients who are randomized and receive the study treatment, with patients grouped according to treatment actually received (patients who receive PDS implant will be included in the PDS 100 mg/ml group).

4.1.2 Per-Protocol Population

A per protocol analysis is planned as a sensitivity analysis for the primary endpoint and the key secondary endpoint. Prior to study unblinding, protocol deviations will be reviewed and a determination of the definition of the population for per protocol analysis will be made.

The Per-Protocol Population is defined as all patients in the Efficacy Population who do not have a major protocol deviation that impact the efficacy evaluation. For analyses based on this patient population, patients will be grouped according to the treatment actually received.

4.1.3 Pharmacokinetic Population

The PK population will be based on the subset of patients in the Safety Population with at least one post study treatment PK sample available.

4.1.4 Pharmacokinetic-Evaluable Population

The PK-Evaluable Population will consist of patients in the PK Population excluding patients receiving intravitreal injections of ranibizumab in the study eye post PDS implant (including supplemental treatment), patients with fellow eye ranibizumab or bevacizumab treatment, or prior bevacizumab treatment in either eye.

4.1.5 Aqueous Humor Pharmacokinetic-Evaluable Population

The Aqueous Humor PK-Evaluable Population is the subset of patients in the PK-Evaluable Population with at least one optional aqueous-humor sample.

4.1.6 Safety Population

Safety data will be summarized on the Safety Population comprising all patients who receive the study treatment, with patients grouped according to treatment actually received.

4.1.7 Biomarker Analysis Population

The Biomarker Analysis Population will consist of patients who are in the Safety Population and have sufficient data to enable assessment of potential changes in biomarkers in response to treatment during the conduct of this study. The analysis will group patients according to treatment actually received.

4.2 ANALYSIS OF STUDY CONDUCT

Patient disposition (the number of patients randomized, treated, and completing each study period) will be tabulated by treatment actually received in Efficacy Population. Reasons for premature study treatment discontinuation and study discontinuation will be tabulated and a listing will be provided. Detailed, free text reasons are collected for discontinuations due to physician decision and 'other' reasons. This information will be included in the listing.

Eligibility criteria deviation and other major protocol deviations will be tabulated and a listing will be provided.

Exposure to study treatment (number of study treatments [PDS refill-exchanges, intravitreal ranibizumab injection, supplemental intravitreal ranibizumab injection] and duration of treatment) will be summarized by treatment group for the study eye in the Safety Population.

Duration of treatment is the time from first study treatment (implant or intravitreal ranibizumab injection) to the earlier of:

- The date of treatment discontinuation or date of study completion
- The analysis cutoff date

Pre-treatment and concomitant systemic medications, ocular medications for the fellow eye and, ocular medications for the study eye will be summarized separately by treatment group. Measures were implemented to mitigate the risk to data integrity posed by coronavirus disease 2019 (COVID-19). The impact of COVID-19 will be assessed in the COVID-19 Clinical Study Report (CSR) Annex in terms of the following criteria:

- Early study treatment discontinuation due to COVID-19
- Missed treatments due to COVID-19 or related precautions
- Use of prohibited therapy due to COVID-19
- Missing BCVA or BCVA not performed per protocol due to COVID-19 or related precautions

- Major protocol deviations associated with COVID-19 directly or indirectly
- Missed visits reported as due to COVID-19 or related precautions
- Early study discontinuation due to COVID-19
- Death due to COVID-19
- Confirmed or suspected cases of COVID-19 and adverse events (AEs) associated with COVID-19

Additional details on the analysis to address the impact of COVID-19 are provided in Section 4.4. The impact of COVID-19 on safety analysis is expected to be low since physicians will retrospectively collect safety events following missed visits; hence, the safety analysis plan is not amended except that additional summaries/listings will be provided for confirmed or suspected COVID-19 infection and AEs associated with COVID-19, as described in Section 4.7.2.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics, such as age, sex, race, baseline disease characteristics (such as baseline center point thickness [CPT], and baseline BCVA), and number of prior anti-VEGF injections, will be summarized in the Efficacy Population by treatment group using descriptive statistics.

Baseline is defined as the last available measurement prior to first study treatment (PDS implant or post-randomization intravitreal injection).

4.4 EFFICACY ANALYSIS

The efficacy analyses will be based on the Efficacy Population.

Patients in the PDS 100 mg/mL arm can receive intravitreal ranibizumab injection as supplemental treatment if they meet the criteria described in Section 2.

Unless otherwise noted, analyses of efficacy outcome measures will be stratified by baseline BCVA ($<$74 letters vs. $\geq$74 letters). The stratification factor as recorded in IxRS will be used. The estimates and confidence intervals (CIs) will be provided for the mean (for continuous variables) or proportion (for binary variables) for each treatment group and the difference in means or proportions between two treatment groups. All CIs will be two-sided and at the 95.03% level (see Section 3.3).

4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change in BCVA score from baseline averaged over Weeks 36 and 40 with BCVA assessed using the ETDRS chart at a starting distance of 4 meters. The primary estimand is defined as follows:

- Population: Adult patients with nAMD diagnosed within 9 months and receiving at least 4 anti-VEGF intravitreal injections (with the last injection being ranibizumab), responsive to prior anti-VEGF treatment
- Variable: Change in BCVA score from baseline averaged over Weeks 36 and 40
- Intercurrent events: Regardless whether or not a patient has the following intercurrent event prior to Week 40:
  - Receives more than 1 supplemental treatment
  - Receives any prohibited systemic treatment or prohibited therapy in the Study eye (Section 4.4.2 of the Protocol)
  - Discontinues study treatment due to AEs
  - Discontinues study treatment due to lack of efficacy as per investigator's clinical judgment
- Population-level summary: Difference in adjusted mean between PDS 100 mg/mL and intravitreal groups

Of note, lack of efficacy includes investigators choices for reason for discontinuation from treatment of lack of efficacy, progressive disease, disease relapse, and symptomatic deterioration.

The primary objectives are to determine the NI and equivalence between the two treatment groups, as measured by the primary efficacy endpoint with a NI margin of 4.5 letters and equivalence margins of $\pm$4.5 letters. To control the overall type I error, a fixed sequence testing procedure (Westfall and Krishen 2001) will be used. If the PDS 100 mg/mL arm is shown to be non-inferior to the intravitreal arm at the one-sided 0.02485 level, then the equivalence test will be conducted using two one-sided 0.02485 tests.

The primary analysis will be performed using the mixed-effect model with repeated measures (MMRM) based on all available data up to Week 40. All observed measurements will be included in the analysis regardless whether or not a patient has an intercurrent event. Missing data will be implicitly imputed by the MMRM model, assuming a missing at random mechanism.

The dependent variable in the MMRM model is the change from baseline in BCVA score at post-baseline visits, up to 40 weeks, and the independent variables are the treatment group, time, treatment-by-time interaction, baseline BCVA score (continuous), and the randomization stratification factor of baseline BCVA ($<$74 letters vs. $\geq$74 letters) as fixed

effects. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, then a compound symmetry covariance or a first order autoregressive order (AR [1]) covariance structure will be used. Comparisons between the two treatment groups will be made using a composite contrast over Weeks 36 and 40.

For the primary efficacy endpoint, if a lower bound of a two-sided 95.03% CI for the difference of two treatments is greater than −4.5 letters (the NI margin), then treatment via PDS is considered non-inferior to monthly intravitreal ranibizumab treatment. If the two-sided 95.03% CI is within −4.5L and +4.5L, then the two treatment regimens are considered clinically equivalent.

As a sensitivity analysis the per-protocol analysis will follow the same methods as the primary analysis except the Per-Protocol Population will be used.

4.4.1.1 Supplemental Analyses

The following supplemental analyses will be performed for the primary efficacy endpoint to evaluate the robustness of the primary analysis finding:

a) Trimmed Mean Analysis: The analysis will be used to assess the difference in BVCA between two treatments using a truncated distribution, truncating patients with the worst outcome, with the assumption that patients have the worst outcome after intercurrent events.

The estimand is defined as follows:

- Population: Adult patients with nAMD diagnosed within 9 months and receiving at least 4 anti-VEGF intravitreal injections (with the last injection being ranibizumab) responsive to prior anti-VEGF treatment
- Variable: Change in BCVA score from baseline averaged over Weeks 36 and 40
- Intercurrent events: Assume patients have the worst outcome after the following intercurrent events prior to Week 40:
    - Receives more than 1 supplemental treatment
    - Receives any prohibited systemic treatment or prohibited therapy in the Study eye (Section 4.4.2 of the Protocol)
    - Discontinues study treatment due to AEs
    - Discontinues study treatment due to lack of efficacy as per investigator's clinical judgment
- Population-level summary: Difference in adjusted trimmed mean between PDS 100 mg/mL and intravitreal groups

The trimmed mean analysis (Permutt and Li 2017) will be performed using an analysis of covariance (ANCOVA) model with adjustment for covariates. The dependent variable in the ANCOVA model is the average of non-missing values of Weeks 36 and 40

assessments in change from baseline in BCVA score (if one of the two assessments is missing, the non-missing assessment will be used), and the independent variables are the treatment group, baseline BCVA score (continuous), and the randomization stratification factor of baseline BCVA (<74 letters vs. ≥ 74 letters).

Patients will be considered to have the worst outcomes and will be trimmed from analysis if any of the following occurs:

- They have an intercurrent event prior to Week 36.
- They have a missing Week 36 assessment and have an intercurrent event at Week 36.
- They have missing assessments at both Week 36 and Week 40, and have an intercurrent event in either of these two visits.

Such patients will be referred to as "must be trimmed patients". Of note, if a patient has a non-missing Week 36 assessment and has an intercurrent event at Week 36, then the change in BCVA from baseline to Week 36 for this patient will be used for the analysis, the Week 40 data would not be used.

For the remaining patients, if they have Week 36 and/or Week 40 BCVA assessments, they will be considered "completers"; if they have missing assessments at both Week 36 and Week 40, the missing data will be considered missing at random and these patients will be removed from the analysis.

The inferential statistics (i.e., 95.03% CI) for the trimmed mean will be based on the permutation test. The treatment assignments will be permuted in a sufficiently large random sample of possible ways (~30,000 random samples will be generated).

The method can be stated in the following four steps:

1. Remove patients whose missing BCVA assessments are considered missing at random (see definition above) from the analysis.
2. Order the data based on adjusted values from the ANCOVA model, and trim equal fractions (approximately 20%, the trimming fraction will be finalized based on a masked assessment prior to the primary analysis) from both treatment groups.
    - The adjusted values are determined as follows. An ANCOVA model as specified above will be fitted for all completers. The estimated treatment effect will be discarded and the coefficients for the covariates will be kept to calculate the adjusted value $Y - \beta' X$ for each patient, for which Y is the change in BCVA score averaged over 36 and 40 weeks, X is the matrix for the covariates-baseline BCVA score (continuous) and the baseline BCVA category (<74 letters vs. $\geq$ 74 letters), and β is the estimated coefficient matrix for the covariates.
    - These adjusted values will be used to rank the data within each treatment group. The "must be trimmed" patients will always be ranked the lowest

(regardless of whether their adjusted values are available) and trimmed from the analyses. The best $(1-0.2)\times 100$ (=80%) in each group will be used for the analysis specified in Step 3. If multiple patients have the same adjusted values, they will be ranked randomly relative to each other prior to trimming.

3. Refit the ANCOVA model (as specified above) to the trimmed data set, and compute the difference in trimmed mean between two treatment groups.
4. Repeat steps 2 and 3 30,000 times based on augmented datasets with the treatment assignment randomly permuted according to the original randomization procedures (blocked randomization stratified by baseline BCVA category).

When the proportion of the "must be trimmed patients" in either treatment group in the permuted data exceeds the planned trimmed fraction, the trimming fraction will be chosen adaptively as the greater of the proportions of the "must be trimmed patients" in the two treatment groups.

b) Analyses using different handling rules for intercurrent event

The estimand is defined as follows:

- Population: Adult patients with nAMD diagnosed within 9 months and receiving at least 4 anti-VEGF intravitreal injections (with the last injection being ranibizumab), responsive to prior anti-VEGF treatment
- Variable: Change in BCVA score from baseline averaged over Weeks 36 and 40
- Intercurrent events prior to Week 40:
  - Had more than 1 supplemental treatment not been made available
  - Had any prohibited systemic treatment or prohibited therapy in the Study eye (Section 4.4.2 of the Protocol) not been made available
  - Regardless whether a patient discontinues study treatment due to AEs
  - Regardless whether a patient discontinues study treatment due to lack of efficacy as per investigator's clinical judgment
- Population-level summary: Difference in adjusted mean between PDS 100 mg/ml and intravitreal groups

Two analyses will be performed using the same analysis method as the primary endpoint with the exception that data handling methods for intercurrent events and missing data:

- Method 1: Assessments at any timepoint after 2 or more supplemental treatments or after prohibited treatments in the study eye will be imputed using the last post-baseline observation prior to such intercurrent event. This means for example that if a patient has their first intercurrent event at Week 36 or between the Week 36 and Week 40, the Week 36 assessment will be used for Week 40 (BCVA assessment will be performed before any treatment). Other missing assessments

not preceded by an intercurrent event will be imputed using the last post-baseline observation carried forward method.

– Method 2: Assessments after 2 or more supplemental treatments or after prohibited treatment will be excluded. All missing data will be implicitly imputed by the MMRM model, assuming a missing at random mechanism.

4.4.2 Secondary Efficacy Endpoints

Descriptive summaries will be provided for all secondary endpoints based on all observed data. The secondary endpoints are:

1. Change from baseline in BCVA score averaged over Week 60 and Week 64.
2. Change from baseline in BCVA score over time.
3. Proportion of patients with BCVA score of 38 letters (20/200 approximate Snellen equivalent) or worse at the average over Week 36 and Week 40.
4. Proportion of patients with BCVA score of 38 letters (20/200 approximate Snellen equivalent) or worse over time.
5. Proportion of patients with BCVA score of 69 letters (20/40 approximate Snellen equivalent) or better at the average over Week 36 and Week 40.
6. Proportion of patients with BCVA score of 69 letters (20/40 approximate Snellen equivalent) or better over time.
7. Proportion of patients who lose < 10 or < 5 letters in BCVA score from baseline to the average over Week 36 and Week 40.
8. Proportion of patients who lose < 10 or < 5 letters in BCVA score from baseline over time.
9. Proportion of patients who gain ≥0 letters in BCVA score from baseline to the average over Week 36 and Week 40.
10. Proportion of patients who gain ≥0 letters in BCVA score from baseline over time.
11. Change from baseline in CPT assessed by central imaging vendor with boundaries ILM to inner third of the retinal pigment epithelium (RPE) at Week 36.
12. Change from baseline in CPT assessed by central imaging vendor with boundaries ILM to inner third of the RPE over time.
13. Proportion of patients in the PDS 100 mg/ml group who undergo supplemental treatment of intravitreal ranibizumab before the first, second, third, and fourth fixed refill-exchange intervals.
14. Proportion of patients in the PDS 100 mg/ml group that undergo a supplemental treatment that requires at least one additional supplemental treatments during the study.

The estimand for the binary secondary endpoints are defined as follows:

- Population: Adult patients with nAMD diagnosed within 9 months and receiving at least 4 anti-VEGF intravitreal injections (with the last injection being ranibizumab), responsive to prior anti-VEGF treatment.
- Variable: Proportion of patients for event of interest
- Intercurrent events: Regardless whether or not a patient has the following intercurrent event prior to visit for endpoint:
    - Receives more than 1 supplemental treatments
    - Receives any prohibited systemic treatment or prohibited therapy in the Study eye (Section 4.4.2 of the Protocol)
    - Discontinuation study treatment due to AEs
    - Discontinuation study treatment due to lack of efficacy as per investigator's clinical judgment.
- Population-level summary: Difference in proportions between PDS 100 mg/ml and intravitreal groups

The proportion of patients in each treatment group and the overall difference in proportions between treatment groups will be estimated using the weighted average of the observed proportions and the differences in observed proportions over the strata defined by randomization stratification factor of baseline BCVA ($<$ 74 letters vs. $\geq$ 74 letters) using the Cochran-Mantel-Haenszel (CMH) weights (Cochran 1954; Mantel and Haenszel 1959). All observed measurements will be included in the analysis regardless whether or not a patient has an intercurrent event. Confidence intervals of the proportion of patients in each treatment group and the overall difference in proportions between treatment groups will be calculated using the normal approximation to the weighted proportions (Mehrotra and Railkar 2000). If the response rate is low, an unstratified analysis may also be performed.

In addition, the binary secondary endpoints through Week 40 will also be summarized using the same approach with missing assessments imputed with the last post-baseline observation carried forward (continuous BCVA values are carried forward and then the binary endpoint is derived).

Different strata will be used for the CMH analyses of the following binary endpoint:

- Proportion of subjects with a BCVA score of 69 letters (approximate 20/40 Snellen equivalent) or better at the average over Weeks 36 and 40: the difference between the two treatment groups will be estimated using the same approach stratified by baseline BCVA (Snellen equivalent of 20/40 or better vs. worse than 20/40).

The continuous secondary endpoints will be summarized using descriptive statistics based on all observed data. These continuous endpoints will also be analyzed following

the same method as the analysis of the primary endpoint (see Section 4.4.1) with the independent variable, baseline BCVA score (continuous), in the model replaced with the baseline value of the corresponding endpoint (e.g., baseline CPT). The intercurrent events and data handling rules for the primary endpoint will apply here.

The proportion of patients in the PDS 100 mg/ml group who undergo supplemental treatment of intravitreal ranibizumab and who do not undergo supplemental treatment will be summarized descriptively during the entire study period and between each refill-exchange. The proportion of patients in the PDS 100 mg/ml group who undergo a supplemental treatment and require subsequent additional supplemental treatments during the study will also be summarized descriptively. The proportion of patients who undergo supplemental treatment will be evaluated using only the patients who were able to be assessed for the need for supplemental treatment. This is the subset of patients who were assessed for supplemental treatment at least once at eligible weeks within a given interval (at 4 and 8 weeks prior to the scheduled refill visit), which does not include those who missed both visits within a given interval or discontinued the study prior to these 2 visits within a given interval, as these patients are not able to be assessed for the need for supplemental treatment. The proportion of patients who undergo supplemental treatment during the entire study period will be evaluated using the subset of patients who were assessed for supplemental treatment at least once during the entire study period.

For the Final CSR analysis, the following secondary efficacy endpoints occurring after Week 48 will be analyzed using the same MMRM model as specified in Section 4.1.1, with the dependent variables of changes in BCVA at Weeks 4-96: change in BCVA averaged over Week 60 and Week 64, change in BCVA averaged over Week 88 and Week 92, and change in BCVA over time through Week 96. Composite contrasts will be used to estimate each endpoint. These endpoints will also be analyzed on the Per Protocol Population using the same MMRM approach. No data collected after Week 96 will be used to evaluate these efficacy endpoints. In addition, a small number of BCVA assessments were not assessed per protocol (e.g., completed by uncertified staff or by unmasked staff), and these records will be removed from the efficacy analyses, as these records may not be reliable assessments of BCVA.

4.4.2.1 Key Secondary Endpoints for EMA

The following endpoints are considered key secondary endpoints for purpose of the marketing authorization application for EMA:

- Change from baseline in BCVA score averaged over Week 36 and Week 40
- Change from baseline in BCVA score averaged over Week 44 and Week 48
- Change from baseline in BCVA score averaged over Week 88 and Week 92

The hypothesis testing for these endpoint will be gated on achieving NI for the primary endpoint test at a 4.5 letter margin as per Section 4.4.1. A fixed sequence testing

procedure will be used to control the type I error rate. The NI tests for the key secondary endpoints will be performed in the order shown above with a NI margin of 3.9 letters, proceeding sequentially and testing each after achieving NI on the previous endpoint. Analysis of these key secondary endpoints will follow the same method as the analysis of the primary endpoint (see Section 4.4.1) in all respects except for the NI margin and timepoints included in the analysis. The two supplementary analyses for using different handling rules for intercurrent events (Section 4.4.1.1) and the per protocol sensitivity analysis (Section 4.4.1) used in the analysis of the primary endpoint will also be conducted for the key secondary endpoints.

Additionally, to address feedback from the EMA, sensitivity analyses will be conducted for each of the above 3 endpoints based on the complete cases in the Per Protocol Population. These analyses include only patients in the Per Protocol Population with BCVA assessments available at both study visits for a particular endpoint (e.g., patients needed to have BCVA assessments at both Weeks 36 and 40 for change in BCVA averaged over Weeks 36 and 40). The analyses will be conducted using the MMRM model as specified in Section 4.4.1, , and using the ANCOVA models with adjustment of treatment group, baseline BCVA score (continuous), and the randomization stratification factor of baseline BCVA (< 74 letters vs. ≥ 74 letters).

4.4.2.2 Supplemental Analysis to Assess COVID-19 Impact

Additional supplemental analyses incorporating intercurrent events related to COVID-19 will be used to assess the impact of COVID-19. Previous assessments of the impact of COVID-19 in the Primary and Update CSRs concluded that the impact of COVID-19 on the efficacy findings through Week 48 was minimal; therefore, the additional analyses will only be performed on the following endpoints after Week 48: change in BCVA averaged over Week 60 and Week 64, change in BCVA averaged over Week 88 and Week 92, and change in BCVA over time through Week 96.

The estimand for the additional supplemental analyses is defined as follows:

- Population: Adult patients with nAMD diagnosed within 9 months and receiving at least 4 anti-VEGF intravitreal injections (with the last injection being ranibizumab), responsive to prior anti-VEGF treatment
- Variable: Change in BCVA score from baseline averaged over Week 60 and Week 64, Change in BCVA averaged over Week 88 and Week 92, and Change in BCVA over time through Week 96
- Intercurrent events:
  - Discontinuation of study treatment due to adverse events (AEs) or lack of efficacy not due to COVID-19: A treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event
  - Use of any prohibited systemic treatment or prohibited therapy in the study eye (Section 4.4.2 of Protocol) not due to COVID-19: A treatment policy strategy will

be applied where all observed values will be used regardless of the occurrence of the intercurrent event

- Discontinuation of study treatment due to COVID-19: A hypothetical strategy will be applied where all values will be censored after the intercurrent event
- Use of any prohibited systemic treatment or prohibited therapy in the study eye due to COVID-19: A hypothetical strategy will be applied where all values will be censored after the intercurrent event
- Missed dose(s) with potentially major impact on efficacy due to COVID-19, defined according to the treatment arm:
  - Intravitreal arm: two or more consecutive missed visits due to COVID-19 (reported as an intercurrent event at the second consecutive missed visit), or three or more total missed visits due to COVID-19 (reported as an intercurrent event at the third missed visit)
  - PDS arm: any missed refill-exchange due to COVID-19 (reported as an intercurrent event at the missed refill-exchange visit), or missed both supplemental treatment evaluation visits during the refill-exchange interval due to COVID-19

    A hypothetical strategy will be applied where all values will be censored after the intercurrent event

  - COVID-19 death: A hypothetical strategy will be applied

– Population-level summary: Difference in adjusted mean between PDS 100 mg/mL and intravitreal groups

The analyses will be performed using the same analysis method as the primary endpoint (see Section 4.4.1).

In addition, the COVID-19 related intercurrent events will be summarized by treatment arm.

4.4.3 Exploratory Efficacy Endpoints

Exploratory endpoints are:

– BCVA and CST results over time relative to supplemental treatment
– Change from baseline in CST at Week 36
– Change from baseline in CST over time
– Proportion of patients with macular atrophy at baseline, Weeks 36, 48, and 96
– Change from baseline in macular atrophy area at Weeks 36, 48 and 96
– Proportion of patients who gain ≥5 letters in BCVA score from baseline over time.
– Proportion of patients who lose < 15 letters in BCVA score from baseline to the average over Week 88 and Week 92

– Proportion of patients who gain > 15 letters in BCVA score from baseline to the average over Week 88 and Week 92

To evaluate the impact of supplemental treatment with intravitreal ranibizumab on efficacy endpoints for the PDS 100 mg/ml group patients receiving supplemental treatment, graphs by patient showing BCVA and CST over time and indicating times of refill-exchange or supplemental treatments will be provided.

Change from baseline in CST at Week 36 and over time will be analyzed using the same analysis method and data handling rules as the primary endpoint.

Proportion of patients with macular atrophy and macular atrophy area will be analyzed by descriptive summaries including confidence intervals at each timepoint.

The other binary endpoints will be analyzed using the same method as the binary secondary endpoints (see Section 4.4.2).

4.4.4 Patient-Reported Experiences

Patient preference will be assessed using the PDS Patient Preference Questionnaire (PPPQ). The PPPQ is a 3-item questionnaire that captures a patient's preference for treatment, the strength of their preference, and the reasons for their preference. The PPPQ will be administered only to patients in the PDS 100 mg/ml arm, who received intravitreal anti-VEGF treatment prior to Day 1. The PPPQ specifically assesses patient preference for treatment and could demonstrate a benefit of PDS over monthly intravitreal ranibizumab 0.5 mg due to less frequent treatments and the advantage of a refill-exchange over injection. However, due to the nature of the clinical trial, monthly visits are required so study participants will not experience the advantage of less frequent visits. The strength of preference and reasons for preference will be summarized descriptively.

The Macular Disease Treatment Satisfaction Questionnaire (MacTSQ) was developed to provide a means of evaluating satisfaction with therapies for macular disease. The MacTSQ provides a total score and two subscale scores: impact of treatment, and information provision and convenience. Higher scores for the total scale and the subscales represent increased satisfaction with treatment.

The MacTSQ score, including both total score and subscale scores at scheduled visits, will be summarized using appropriate descriptive statistics based on the observed data. The MacTSQ will be scored per the instructions in the “Summary of the MacTSQ rev11.8.15.” Subscale 1 (Information provision and convenience) contains six items (1, 9, 10 to 13). Item scores are summed to give a subscale score between 0 and 36. Subscale 2 (Impact of treatment) contains six items (items 2 to 6, 8). After recoding item 2 and 3 per the instructions, item scores are summed to create a subscale score

between 0 and 36. The total score is calculated by combining the 12 items from the two subscales, and ranges from 0 to 72.

Data will be specifically imputed using the rules as follows:

- Subscale 1 (information provision and convenience): Set the subscale 1 value to missing if any of the 6 items in the subscale are missing.
- Subscale 2 (impact of treatment score): Set the subscale 2 value to missing if two or more of the 6 items in the subscale 2 are missing. If only one item is missing, impute the item value based on the average of the other five items.
- Single scale (overall score): Set the single scale value to missing if four or more of the 12 items are missing. If three or less items are missing, impute the missing item values based on the average of the other available items.

4.4.5 Subgroup Analyses

Subgroup analyses will be provided in forest plots for the following endpoints:

- Change from baseline in BCVA score averaged over Week 36 and Week 40
- Change from baseline in CPT at Week 36

Subgroups will be Age (< 65 years, 65 to <75 years, ≥ 75 years) and Sex (male, female). In addition subgroups may be analyzed according to number of anti-VEGF injections performed before randomization (<5, ≥5), baseline BCVA (< 74 letters vs. ≥ 74 letters). The analyses will follow the same methods (except in the case of baseline BCVA subgroup the baseline covariate consisting of the BCVA stratification factor will be removed) as for these endpoints in the overall analysis but will be done for each subgroup separately.

4.5 PHARMACOKINETIC ANALYSES

Individual and mean serum ranibizumab concentration versus time data will be tabulated and plotted by treatment group for all patients in the Pharmacokinetic Population and Pharmacokinetic-Evaluable Population. In a subset of patients in the PDS 100 mg/mL group with more intensive sampling (at selected sites), the serum pharmacokinetics of ranibizumab will be summarized by estimating total exposure (area under the concentration-time curve [AUC]), maximum serum concentration (C_{max}), and half-life ($t_{1/2}$) of drug delivered from the implant after PDS implant insertion. Estimates for these parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, and minimum and maximum). Inter-patient variability will be evaluated.

Exploratory PK analyses to evaluate potential relationships between drug exposure and efficacy of the PDS will be performed. Additional PK analyses will be conducted as appropriate.

4.6 EXPLORATORY BIOMARKER ANALYSES

Pharmacodynamic (PD) biomarker analyses will be focused primarily on, but not limited to, the change in free-VEGF or other angiogenesis-related biomarker concentrations (absolute or percent change as appropriate) over time and analyzed based on the Biomarker Analysis Population. The data will be analyzed in the context of ranibizumab pharmacokinetics, using a longitudinal model approach, to gain an understanding of the relationship between ranibizumab concentrations and target modulation. Results will be summarized descriptively.

Additional analyses will be performed, as deemed appropriate, to explore biomarkers that are associated with progression to a more severe disease, acquired resistance to ranibizumab, and susceptibility to developing AEs, can provide evidence of ranibizumab activity, or can increase the knowledge and understanding of disease biology. Prognostic biomarker analyses will include all patients for which biomarker assessments were made during randomization ("baseline"). Baseline values will be used to evaluate prognostic biomarkers in the context of efficacy, PK, safety, and/or immunogenicity endpoints. Results will be summarized descriptively.

4.7 SAFETY ANALYSES

The safety analyses will be performed on the Safety Population (described in Section 4.1.6).

Safety will mainly be assessed through descriptive summaries of AEs, ocular assessments, and anti-drug antibodies (ADAs) to ranibizumab. Clinically significant laboratory abnormalities and clinically significant vital sign abnormalities will be reported as AEs and evaluated as part of the AE assessments.

At the time of the primary analysis, safety data will be summarized based on the complete Week 40 data in the Safety Population. In addition, ongoing safety data (from first treatment up to a single specified clinical cutoff date) in the Safety Population will also be summarized. Such results will be reported with, but separate from, the 40-week study results to provide additional safety information.

At the time of the final analysis, safety summaries will be produced based on cumulative Week 96 data in the Safety Population. Due to the addition of several final study visit scenarios specified in the Protocol Version 4 in order to provide flexibility and assure appropriate patient care in response to the COVID-19 public health emergency, safety data will be available for some patients beyond Week 96. Post-Week 96 data will not be included in the safety summaries and will be provided separately in a listing.

4.7.1 Adverse Events

All verbatim AE terms will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

For safety analyses, unless otherwise specified, only treatment-emergent AEs will be included in the analyses. Treatment-emergent AEs will be defined as any new AEs reported or any worsening of an existing condition on or after the surgical insertion of the implant or the first intravitreal ranibizumab injection post randomization through the completion of the study or until a patient discontinues prematurely. Adverse events with missing onset date will be considered to be treatment emergent. Adverse events with partially missing onset date will also be included as treatment emergent when the month (if it was recorded) and the year occur on or later than the month and year of the study treatment start date.

Frequency tables, including patient incidence rates by treatment group, will be provided for the events listed below. For ocular AEs, events in the study eye and fellow eye will be summarized separately.

- Ocular AEs and serious adverse events (SAEs)
- Non-ocular AEs and SAEs
- Adverse events of special interest (AESI) defined as follows:
  - An AE considered to be sight threatening (see Section 5.2.3 of the Protocol)
  - Cases of potential drug-induced liver injury that include elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6 of the Protocol)
  - Suspected transmission of an infectious agent by the study drug
  - Ocular AESIs (formerly adverse events potentially related to PDS) defined as:
    - Vitreous hemorrhage
    - Endophthalmitis
    - Retinal detachment
    - Conjunctival retraction
    - Conjunctival erosion
    - Conjunctival bleb or conjunctival filtering bleb leak
    - Hyphema
    - Cataract (includes Preferred Terms cataract, cataract nuclear, cataract cortical, and cataract subcapsular)
    - Device dislocation (added in Protocol v 5)
- AEs leading to discontinuation of study treatment
- Treatment related Ocular AEs and SAEs as determined by the Investigator
- Anti-Platelet Trialists Collaboration Events (APTCs) defined as:
  - non-fatal stroke AEs defined by terms from the conditions associated with central nervous system haemorrhages and cerebrovascular accidents Standardized

MedDRA Query (SMQ) (Narrow), ischaemic cerebrovascular conditions SMQ (Narrow), and haemorrhagic cerebrovascular conditions SMQ (Narrow) or

- non-fatal myocardial infarction AEs defined by terms from the myocardial infarction SMQ (Narrow) or
- vascular death (including deaths of unknown cause)

Of note, vitreous hemorrhage data will be presented by the functional grading scale for vitreous hemorrhage (see Study GR40458 Study Protocol Appendix 8) which incorporates impact of vitreous hemorrhage on patient's BCVA. All vitreous hemorrhage data will be presented however for key analyses the focus will be on Grades 3 and 4 as these are clinically relevant when discussing vitreous hemorrhage.

A subgroup analysis of cataract incidence will be performed by baseline lens status subgroup (phakic vs pseudophakic), as in the Primary CSR Section 3.11.8.

In addition, the rates of intraocular inflammation AEs will be analyzed as in the Primary CSR Section 6.3.5.2.1, based on selected PTs according to the Standardization of Uveitis Nomenclature (SUN) (Jabs et al. 2005). Intraocular inflammation will be defined as anterior uveitis (included iritis, iridocycltis, anterior cyclytis, anterior channel cell, flare, and inflammation); intermediate uveitis (included pars planitis, posterior cyclitis, hyalitis, vitritis, and vitreous haze); posterior uveitis (included choroiditis, chorioretinitis, retinochoroiditis, retinitis, neuroretinitis, and retinal vasculitis); and events which were not otherwise specified (included eye inflammation, uveitis, post procedural inflammation, incision site inflammation, inflammation of wound, and ocular vasculitis). Endophthalmitis, while included in the SUN criteria for intraocular inflammation, will be analyzed separately as an AESI.

Adverse events (AEs) of endophthalmitis will additionally be summarized as incidence rates by treatment group on a per study treatment intervention basis (total number of endophthalmitis AEs divided by the total number of interventions in the study eye. Interventions in the intravitreal group include intravitreal ranibizumab injections. Interventions in the PDS 100 mg/ml group include implantation, PDS refill-exchange procedure, and supplementary ranibizumab treatment in the study eye.

Frequency tables including patient incidence rates will also be generated by treatment group and by onset of events using the following time windows relative to first dose or implant surgery:

- $\leq$Week 4 (up to the end of Week 4 visit window, $\leq$37 days) (post-operative period)
- $>$Week 4 ($>$37 days) (follow-up period)

for the following AEs:

- Ocular AEs and SAEs in the study eye
- Ocular AESIs.

A listing of patients who died during the study will be provided.

4.7.2 Additional Safety Analyses Performed for COVID-19

Based on the first reports of COVID-19 infection globally, the Sponsor determined that the window for all analyses of COVID-19 associated events would start from 01 December 2019, until CCOD for the study. At the time of the Update CSR, the Sponsor developed a narrow search strategy to identify AEs of confirmed or suspected COVID-19 infection, a Roche Adverse Event Grouped Term (AEGT) that included 19 terms identified by Maintenance and Support Services Organization (MSSO) as relevant to the COVID-19 infection. These AEGT terms were used to assess the impact of COVID-19 in the Update CSR.

Following the MedDRA 23.1 release, a COVID-19 SMQ (narrow) is now available. This SMQ includes 18 terms relevant to COVID-19 infection (see Table 1), and these terms will be used to assess the impact of COVID-19 in the Final CSR. Patients with AEs from this COVID-19 SMQ (narrow) will be considered to have a confirmed or suspected COVID-19 infection.

A listing or table of confirmed and suspected COVID-19 AEs will be produced from the patients identified from the search as having confirmed or suspected COVID-19 infection (Table 1).

Table 1 Roche COVID-19 SMQ (narrow) Preferred Terms for all Cases (Confirmed and Suspected)

Asymptomatic COVID-19
Coronavirus infection
Coronavirus test positive
COVID-19
COVID-19 immunisation
COVID-19 pneumonia
COVID-19 prophylaxis
COVID-19 treatment
Exposure to SARS-CoV-2
Multisystem inflammatory syndrome in children
Occupational exposure to SARS-CoV-2
SARS-CoV-2 antibody test positive
SARS-CoV-2 carrier
SARS-CoV-2 sepsis
SARS-CoV-2 test false negative
SARS-CoV-2 test positive
SARS-CoV-2 viraemia
Suspected COVID-19

In addition to presenting the suspected/confirmed COVID-19 infections, the Sponsor developed a broad search strategy for AEs associated with COVID-19 infection to further evaluate the confirmed events of COVID-19 and reported AEs that could be considered complications of the disease. This search strategy includes both the AEs of a confirmed or suspected COVID-19 infection (PTs in Table 1) and any AEs considered associated with COVID-19 (temporally reported around PTs in Table 2). As causality to COVID-19 was not collected on the standard eCRF, the Sponsor identified associated AEs as those reported ≤7 days before and ≤30 days after any reported AE suggesting a confirmed COVID-19 infection (PTs listed in Table 2). The COVID-19 associated AEs for patients with confirmed COVID-19 infection will be provided in a summary table or a listing.

Table 2 Roche COVID-19 SMQ (narrow) Preferred Terms for Confirmed Cases

Coronavirus Infection
Coronavirus Test Positive
COVID-19
COVID -19 Pneumonia
Sars-Cov-2 Test Positive
SARS-CoV-2 sepsis
SARS-CoV-2 viraemia
COVID-19 Treatment
Multisystem Inflammatory Syndrome in Children

4.7.3 Laboratory Data

Laboratory data will be collected at baseline only (see Study GR40548 Protocol Section 4.5.7). These data can be used for interpretation of some AEs, no general summary is planned.

4.7.4 Vital Signs

Vital signs will be collected at screening, randomization and Week 96 or early termination visit only. These data can be used for interpretation of some AEs, no general summary is planned.

4.7.5 Ocular Assessments

Results of the following ocular assessments will be summarized by treatment group, by timepoint and by eye (study vs. non-study) as applicable, using descriptive summaries:

- intraocular pressure (IOP)
- slit lamp examination
- indirect ophthalmoscopy

Changes from baseline for IOP assessments will be tabulated. The presence of intraocular inflammation and vitreous hemorrhage, as determined on slit lamp examination, will be tabulated by grade (according to grading scales for flares and cells in Study GR40548 Protocol Appendix 7, and vitreous hemorrhage density and functional scales in Study GR40548 Protocol Appendix 8). The presence of retinal break or detachment as determined from ophthalmoscopy will be tabulated.

4.7.6 Immunogenicity Analyses

Because patients will have been exposed to ranibizumab prior to entry into study, the ADA status of patients at the randomization visit may not reflect pretreatment ADA prevalence in the study. Thus, the ADA incidence will be analyzed.

The immunogenicity analyses will group patients according to treatment received. Anti-drug antibody samples will be collected prior to dosing during the randomization

visit and at Weeks 4, 24, 36, and 96. To account for pre-study exposure to ranibizumab, ADA incidence (number and percentage) will be summarized as follows:

- ADA incidence at the time of entry into the study (randomization visit) based on the Safety Population
- ADA incidence at any time after randomization visit, grouped in the following manner, based on patients in the Safety Population who have ADA samples at randomization and after dosing:
    a) Patients who were ADA negative at randomization and became positive only after dosing, during the study.
    b) Patients who were ADA positive at randomization and ADA titer increased after dosing during the study; in this case, the titer of one or more samples collected after randomization must be at least 4-fold greater (i.e., >0.60 titer units) than the titer of the randomization visit sample. These patients are considered to have treatment-enhanced ADA responses.
    c) Patients who were ADA positive at randomization and ADA titer did not increase after dosing during the study.

The combined rates described in (a) and (b) above will provide the incidence of treatment-emergent ADAs in the study. Patients are considered to be negative for ADAs if they are ADA negative at all timepoints. Patients are also considered to be negative for ADAs if they are ADA positive at randomization and ADA negative at all post-randomization timepoints. A listing of patients with positive serum antibodies to ranibizumab will be provided.

The immunogenicity assessment will also include testing for the presence of neutralizing antibodies in samples confirmed to be positive for anti-ranibizumab antibodies. The incidence of neutralizing antibodies will be grouped and reported in a similar fashion to that described above.

In addition, subgroup analyses will be performed summarizing ADA and neutralizing antibody incidences based on pre-screening anti-VEGF intravitreal treatment.

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be explored.

4.8 MISSING DATA

In efficacy analyses, the handling of missing data is specified for analysis in the efficacy analysis section.

4.9 INTERIM ANALYSES

No interim efficacy or futility analyses are planned. The iDMC will review the interim safety analyses approximately every 6 months

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Appendix 1 Protocol Synopsis

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, VISUAL ASSESSOR–MASKED, ACTIVE-COMPARATOR STUDY OF THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF THE PORT DELIVERY SYSTEM WITH RANIBIZUMAB IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION *(ARCHWAY)***
PROTOCOL NUMBER:	GR40548
VERSION NUMBER:	*5*
EUDRACT NUMBER:	Not applicable
IND NUMBER:	113,552
NCT NUMBER:	NCT03677934
TEST PRODUCT:	Port Delivery System with ranibizumab
PHASE:	Phase III
INDICATION:	Neovascular age-related macular degeneration
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of ranibizumab delivered via the Port Delivery System with ranibizumab (PDS) implant compared with ranibizumab 0.5 mg delivered as a monthly intravitreal injection in patients with neovascular age-related macular degeneration (nAMD). Specific objectives and corresponding endpoints for the study are outlined below.

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the non-inferiority and equivalence in efficacy of ranibizumab delivered via the PDS Q24W with the 100-mg/mL formulation compared with that of 10-mg/mL (0.5-mg dose) Q4W intravitreal ranibizumab injections	• Change from baseline in BCVA score at the average of Week 36 and Week 40, as assessed using the ETDRS visual acuity chart at a starting distance of 4 meters

Secondary Efficacy Objectives	Corresponding Endpoints
• To evaluate the relative efficacy of ranibizumab delivered via the PDS Q24W with the 100-mg/mL formulation compared with that of 10-mg/mL (0.5-mg dose) Q4W intravitreal ranibizumab injections, as assessed by visual acuity	• Change from baseline in BCVA score averaged over Week 60 and Week 64 • Change from baseline in BCVA score over time • Proportion of patients with BCVA score of 38 letters (20/200 approximate Snellen equivalent) or worse at the average over Week 36 and Week 40 • Proportion of patients with BCVA score of 38 letters (20/200 approximate Snellen equivalent) or worse over time • Proportion of patients with BCVA score of 69 letters (20/40 approximate Snellen equivalent) or better at the average over Week 36 and Week 40 • Proportion of patients with BCVA score of 69 letters (20/40 approximate Snellen equivalent) or better over time • Proportion of patients who lose < 10 or < 5 letters in BCVA score from baseline to the average over Week 36 and Week 40 • Proportion of patients who lose < 10 or < 5 letters in BCVA score from baseline over time • Proportion of patients who gain ≥ 0 letters in BCVA score from baseline to the average over Week 36 and Week 40 • Proportion of patients who gain ≥ 0 letters in BCVA score from baseline over time
• To evaluate the relative efficacy of ranibizumab delivered via the PDS Q24W with the 100-mg/mL formulation compared with that of 10-mg/mL (0.5-mg dose) Q4W intravitreal ranibizumab injections, as assessed by CPT on SD-OCT	• Change from baseline in CPT at Week 36 • Change from baseline in CPT over time
• To evaluate the proportion of patients who undergo supplemental treatment with intravitreal ranibizumab 0.5 mg	• Proportion of patients in the implant arm who undergo supplemental treatment with intravitreal ranibizumab 0.5 mg before the first, second, third, and fourth fixed refill-exchange intervals • Proportion of patients in the implant arm that undergo a supplemental treatment that requires subsequent additional supplemental treatments during the study
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the impact of supplemental treatment with intravitreal ranibizumab 0.5 mg	• Endpoints will be results-dependent based on number of supplemental treatment

Exploratory Efficacy Objectives (cont.)	Corresponding Endpoints (cont.)
• To evaluate the relative efficacy of ranibizumab delivered via the PDS Q24W with the 100-mg/mL formulation compared with that of 10-mg/mL (0.5-mg dose) Q4W intravitreal ranibizumab injections, as assessed by central subfield thickness on SD-OCT	• Change from baseline in CST at Week 36 • Change from baseline in CST over time
• To assess clinically relevant features using advanced analytics tools (including artificial intelligence-based tools) on multimodal images and clinical data	• Clinically relevant features over time
• To evaluate the development of macular atrophy in patients treated with the PDS Q24W with the 100-mg/mL formulation compared with those with 10-mg/mL (0.5-mg dose) Q4W intravitreal ranibizumab injections.	• Proportion of patients with macular atrophy at baseline, Weeks 36, 48, and 96 • Change from baseline in macular atrophy area at Weeks 36, 48 and 96
• To evaluate the relative efficacy of ranibizumab delivered via the PDS Q24W with the 100-mg/mL formulation compared with that of 10-mg/mL (0.5-mg dose) Q4W intravitreal ranibizumab injections, as assessed by visual acuity	• Proportion of patients who gain ≥5 letters in BCVA score from baseline over time.
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety and tolerability of ranibizumab, delivered via the PDS Q24W with the 100-mg/mL formulation compared with that of 10-mg/mL (0.5-mg dose) Q4W intravitreal ranibizumab injections	• Incidence and severity of ocular and systemic (non-ocular) AEs • Incidence, severity, and duration of AESIs, including PDS-associated AEs • Incidence, severity, and duration of ocular AESIs during the postoperative period (up to 37 days of initial implantation) and follow-up period (>37 days after implantation surgery)
Pharmacokinetic Objective	**Corresponding Endpoints**
• To characterize the serum pharmacokinetics of ranibizumab in patients after the initial fill and subsequent refill-exchanges in patients with the PDS	• Observed serum ranibizumab concentrations at specified timepoints • Additional estimated PK parameter values, including $AUC_{0\text{-}6M}$, C_{max}, C_{min}, and $t_{1/2}$ after PDS implant insertion
Exploratory Pharmacokinetic Objectives	**Corresponding Endpoints**
• To evaluate potential relationships between drug exposure and the efficacy of the PDS	• Relationship between serum concentration or PK parameters for ranibizumab delivered via the PDS and efficacy endpoints
• To characterize ranibizumab aqueous humor concentration over time	• Observed aqueous humor ranibizumab concentrations over time

Immunogenicity Objective	Corresponding Endpoint
• To investigate the formation of serum anti-ranibizumab antibodies	The incidence of ADAs during the study, grouped in the following manner: • Patients who were ADA negative at baseline and became positive only after dosing • Patients who were ADA positive at randomization and ADA titer increased after dosing • Patients who were ADA positive at randomization and ADA titer did not increase after dosing
Exploratory Biomarker Objectives	**Corresponding Endpoints**
• To explore relationships between aqueous humor free-VEGF concentrations over time and the efficacy of ranibizumab, delivered via the PDS Q24W with the 100-mg/mL formulation	• Comparison of patients with and without aqueous humor free-VEGF present between refill-exchanges and needing supplemental treatment • Comparison of patients with and without aqueous humor free-VEGF present between refill-exchanges and CST change from baseline over time • Comparison of patients with and without aqueous humor free-VEGF present between refill-exchanges and BCVA score change from baseline over time
• To identify biomarkers that are prognostic of response to ranibizumab, are associated with acquired resistance to ranibizumab, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of ranibizumab activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of AMD-related disease biology	• Relationship between biomarkers in blood and aqueous humor with disease characteristics and response to ranibizumab • Relationship between genetic variants (such as AMD risk alleles, polymorphisms within the complement pathway, and polymorphisms within the VEGF-A genetic locus) with the disease characteristics and/or response to treatment with ranibizumab • Relationship between imaging features with disease characteristics and/or response to treatment with ranibizumab
Exploratory Patient Experience Objectives	**Corresponding Endpoints**
• To evaluate the preference of patients for ranibizumab delivered via the PDS for 40 weeks compared to intravitreal anti-VEGF treatment received in the 6 months prior to Day 1	• Proportion of patients who report preferring ranibizumab treatment via the PDS compared with intravitreal anti-VEGF treatment, as assessed by the PPPQ, at Week 40 among patients in the implant arm
• To evaluate patient-reported treatment satisfaction with ranibizumab delivered via the PDS for 40 weeks compared with that of Q4W intravitreal ranibizumab injections, as assessed by the MacTSQ	• MacTSQ total score at Week 40

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; AMD = age-related macular degeneration; AUC_{0-6M} = area under the concentration–time curve from 0 to 6 months;
BCVA = best-corrected visual acuity; C_{max} = maximum serum concentration; C_{min} = minimum serum concentration; CPT = center point thickness; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; MacTSQ = Macular Degeneration Treatment Satisfaction Questionnaire; PDS = Port Delivery System with ranibizumab; PK = pharmacokinetic; PPPQ = PDS Patient Preference Questionnaire; Q4W = every 4 weeks; Q24W = every 24 weeks; SD-OCT = spectral domain optical coherence tomography; $t_{1/2}$ = half-life; VEGF = vascular endothelial growth factor.

Study Design

Description of Study

Study GR40548 (Archway) is a Phase III, randomized, multicenter, open-label (visual assessor
[VA]–masked), active-comparator study designed to assess the efficacy, safety, and pharmacokinetics of 100 mg/mL ranibizumab every 24 weeks (Q24W) delivered via the PDS compared with ranibizumab intravitreal injections every 4 weeks (Q4W) at 0.5 mg (10 mg/mL) in patients with nAMD.

Patients will be randomly allocated in a 3:2 ratio so that approximately 216 patients will receive the PDS implant filled with 100 mg/mL ranibizumab Q24W (implant arm) and approximately 144 patients will receive monthly intravitreal injections of 10 mg/mL ranibizumab intravitreal injections Q4W (intravitreal arm).

Patients who are randomly allocated to the implant arm will have the implant (pre-filled with ranibizumab 100 mg/mL) surgically inserted on Day 1, which must occur 1–7 days (inclusive) after randomization (i.e., randomization and Day 1 visit assessments cannot be performed on the same day) and no later than 28 days from the last intravitreal ranibizumab 0.5 mg injection. If the implant insertion surgery (Day 1) cannot be completed within the visit window after randomization, the randomization visit assessments may be repeated and an additional intravitreal ranibizumab 0.5 mg injection may be required after discussion with the Sponsor.

After Day 1, patients in the implant arm will have scheduled safety visit assessments on Days 2 and 7 (±2 days) and will receive implant refill-exchanges with ranibizumab 100 mg/mL Q24W at Week 24 (±7 days), Week 48 (±7 days), and Week 72 (±7 days).

Patients who are randomly allocated to the intravitreal arm will receive intravitreal ranibizumab
0.5 mg injections starting on Day 1, which is to be administered at the conclusion of the randomization visit (i.e., randomization and Day 1 visit assessments are performed on the same day). Patients will receive ranibizumab 0.5 mg, injected intravitreally Q4W (± 7 days) from Day 1 until Week 92.

In order to provide flexibility due to extenuating circumstances, it is possible that patients may receive additional study treatments until they are able to enroll into the long-term safety study.

Study visits will occur according to the schedule of activities relative to Day 1 (first study treatment). Study patients and all study site personnel with the exception of VA examiners will be unmasked to the study eye and study treatment assignment. To minimize bias, VA examiners will only conduct refraction and VA assessments and will be masked as best as possible to patient study eye assignment, study visit type, and patient treatment assignment.

Number of Patients

Approximately 360 patients were planned to be enrolled in this study; a total of 418 patients were ultimately recruited.

Target Population

Inclusion on Criteria

General Inclusion Criteria

Patients must meet the following general inclusion criteria at screening and randomization for study entry:

- Ability and willingness to provide signed informed consent

  Additionally, patients must provide Health Insurance Portability and Accountability Act (HIPAA) authorization.

- Age ≥50 years, at time of signing Informed Consent Form
- Ability and willingness to undertake all scheduled visits and assessments
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of

  < 1% per year during the treatment period and for at least 28 days after the last intravitreal injection of ranibizumab or 1 year after the last implant refill-exchange of ranibizumab.

  A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone- releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Ocular Inclusion Criteria

Patients must meet the following ocular inclusion criteria for the study eye for study entry:

- Initial diagnosis of exudative nAMD within 9 months prior to the screening visit
- Previous treatment with at least three anti-*vascular endothelial growth factor* (VEGF) intravitreal injections (e.g., ranibizumab, bevacizumab, or aflibercept) for nAMD per standard of care within 6 months prior to the screening visit

  If a patient did not receive at least three anti-VEGF injections as described above but is otherwise eligible for the study, the patient can be treated in a run-in phase to meet this specific criterion.

- Demonstrated response to prior anti-VEGF intravitreal treatment since diagnosis, asevidenced at screening by the following:

  Overall decrease in nAMD disease activity detected on *spectral-domain optical coherence tomography* (SD-OCT), as assessed by the investigator and confirmed by the central reading center

and

Stable or improved *best-corrected visual acuity* (BCVA)

- BCVA of 34 letters or better (20/200 or better approximate Snellen equivalent), using *Early Treatment Diabetic Retinopathy Study* (ETDRS) chart at a starting distance of 4 meters (see the BCVA manual for additional details) at screening and randomization visits
- All subtypes of nAMD lesions are permissible (i.e., type I, type II, type III, or mixed forms per OCT classification)

  nAMD lesions at the time of diagnosis must involve the macula (6-mm diameter centered at the fovea).

- Sufficiently clear ocular media and adequate pupillary dilation to allow for analysis and grading by the central reading center of *fundus photography* FP, *fluorescein angiography* FA, *fundus autofluorescence* FAF, and SD-OCT images

Exclusion Criteria

Prior Ocular Treatment

Patients who meet any of the following prior ocular treatment exclusion criteria will be excluded from study entry.

Study Eye

- History of vitrectomy surgery, submacular surgery, or other surgical intervention for
  age-related macular degeneration (AMD)
- Prior treatment with Visudyne®, external-beam radiation therapy, or transpupillary thermotherapy
- Previous treatment with corticosteroid intravitreal injection
- Previous intraocular device implantation
- Previous laser (any type) used for AMD treatment

Either Eye

- Treatment with anti-VEGF agents other than ranibizumab within 1 month prior to the randomization visit
- Prior participation in a clinical trial involving anti-VEGF drugs within 6 months prior to the randomization visit, other than ranibizumab

Choroidal Neovascularization (CNV) Lesion Characteristics

Patients who meet any of the following exclusion criteria related to CNV lesion characteristics will be excluded from study entry.

Study Eye

- Subretinal hemorrhage that involves the center of the fovea, if the hemorrhage is greater than 0.5-disc area (1.27 mm^2) in size at screening
- Subfoveal fibrosis or subfoveal atrophy

Either Eye

- CNV due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia

Concurrent Ocular Conditions

Patients who meet any of the following exclusion criteria related to concurrent ocular conditions will be excluded from study entry.

Study Eye

- Retinal pigment epithelial tear
- Any concurrent intraocular condition (e.g., cataract, glaucoma, diabetic retinopathy, or epiretinal membrane) that would either require surgical intervention during the study to prevent or treat visual loss that might result from that condition or affect interpretation of study results
- Active intraocular inflammation (grade trace or above)
- History of vitreous hemorrhage
- History of rhegmatogenous retinal detachment
- History of rhegmatogenous retinal tears or peripheral retinal breaks within 3 months prior to the randomization visit
- Aphakia or absence of the posterior capsule

  Previous violation of the posterior capsule is also an exclusion criterion unless it occurred as a result of yttrium-aluminum garnet (YAG) laser posterior capsulotomy in association with prior, posterior chamber intraocular lens implantation.
- Spherical equivalent of the refractive error demonstrating more than 8 diopters of myopia
- Preoperative refractive error that exceeds 8 diopters of myopia, for patients who have undergone prior refractive or cataract surgery in the study eye
- Intraocular surgery (including cataract surgery) within 3 months preceding the randomization visitUncontrolled ocular hypertension or glaucoma (defined as intraocular pressure [IOP] $>$ 25 mmHg or a cup to disc ratio $>$ 0.8, despite treatment with antiglaucoma medication) and anysuch condition the investigator determines may require a glaucoma-filtering surgery during a patient's participation in the study
- History of glaucoma-filtering surgery, tube shunts, or microinvasive glaucoma surgery
- History of corneal transplant
- History of prior vitrectomy surgery and absence of posterior capsule

Either Eye

- History of idiopathic or autoimmune-associated uveitis
- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis

Concurrent Systemic Conditions

Patients who meet any of the following exclusion criteria related to concurrent systemic conditions will be excluded from study entry:

- Inability to comply with study schedule or procedures as described in the study protocol
- Uncontrolled blood pressure (defined as systolic blood pressure $>$ 180 mmHg and/or diastolic blood pressure $>$ 110 mmHg, while a patient is at rest)

  If a patient's initial measurement exceeds these values, a second reading may be taken 30 or more minutes later. If the patient's blood pressure must be controlled by antihypertensive medication, the patient may become eligible if medication is taken continuously for at least 30 days prior to Day 1.
- History of stroke within the last 3 months prior to informed consent
- Uncontrolled atrial fibrillation within 3 months of informed consent

- History of myocardial infarction within the last 3 months prior to informed consent
- History of other disease, metabolic dysfunction, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of ranibizumab or placement of the implant and that might affect interpretation of the results of the study or renders the patient at high risk of treatment complications in the opinion of the investigator
- Current systemic treatment for a confirmed active systemic infection
- Use of any systemic anti-VEGF agents
- Chronic use of oral corticosteroids (> 10 mg/day of prednisone or equivalent)
- Active cancer within 12 months of randomization except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of < 6 and a stable prostate-specific antigen for > 12 months
- Previous participation in any non-ocular (systemic) disease studies of investigational drugs within 1 month preceding the informed consent (excluding vitamins and minerals)
- Use of antimitotic or antimetabolite therapy within 30 days or 5 elimination half-lives of the randomization visit
- Requirement for continuous use of any medications or treatments indicated in "Prohibited Therapy"
- Pregnant or breastfeeding, or intending to become pregnant during the treatment period and for at least 28 days after the last intravitreal injection of ranibizumab or 1 year after the last implant refill-exchange of ranibizumab

  Women of childbearing potential, including those who have had tubal ligation, must have a urine pregnancy test at screening and at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

End of Study

The end of this study is defined as the date when the last patient, last visit occurs. The end of study is expected to occur approximately 96 weeks after the last patient is enrolled.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 34 months.

Investigational Medicinal Products

The investigational medicinal products (IMPs) for this study are the PDS with ranibizumab (100 mg/mL) and the monthly intravitreal ranibizumab 0.5 mg.

Test Product (Investigational Drug)

Patients will have the implant (filled prior to implantation with approximately 20 μL of the
100-mg/mL formulation of ranibizumab [approximately 2-mg dose of ranibizumab]) surgically inserted in the study eye at the Day 1 visit following their randomization visit. After the initial fill of the implant with ranibizumab, patients will receive implant refill-exchanges at fixed 24-week intervals.

At each refill-exchange, a volume of approximately 100 μL ranibizumab will be injected in situ into the implant through the septum to exchange the remaining contents of the implant with newly introduced ranibizumab. The volume of newly introduced ranibizumab remaining in the implant after the refill-exchange procedure will be approximately 20 μL. Missed implant refill-

exchanges should be made up no later than the next scheduled study visit. If at the next scheduled study visit the implant refill-exchange cannot be performed, the investigator must contact the Sponsor for further discussion prior to administering future implant refill-exchanges. Subsequent refill-exchanges will be administered according to the study treatment schedule relative to Day 1 until patients complete the study.

A representative from the Sponsor or an affiliate of the Sponsor may be present during the study-specific PDS surgeries or procedures (initial filling, insertion, refill-exchanging, and/or explantation) and/or other PDS-related surgeries or procedures to provide technical support to investigators during the use of the PDS and/or to observe the procedures related to the PDS.

Comparator

Ranibizumab (10 mg/mL) will be provided by the Sponsor and used in the study eye during the run-in period and at the screening visit for applicable patients; as study treatment for patients in the intravitreal arm; as supplemental treatment for the implant arm; if delaying surgery is required; as nAMD treatment in the fellow eye for patients, per investigator's discretion; and if a patient in the PDS arm discontinues study treatment and starts receiving ranibizumab intravitreal injections in study eye, per investigator's discretion.

Commercially available intravitreal ranibizumab 0.5 mg supply may be used only if an intravitreal ranibizumab injection is necessary per protocol and study supply is not available at the site. Prior to administering commercial supply ranibizumab, the site will need to obtain Sponsor's approval.

Patients in the intravitreal arm will receive their first intravitreal injection of 50 μL of the ranibizumab10 mg/mL (0.5-mg dose) at the Day 1 visit, which will occur at the conclusion of the randomization visit. Afterward, patients will receive intravitreal ranibizumab injections of 50 μL of the 10-mg/mL formulation Q4W at each scheduled study visit until Week 92. Missed treatments will not be made up.

Statistical Methods

Primary Analysis

The primary efficacy endpoint is the change in BCVA score from baseline averaged over
Weeks 36 and 40 with BCVA assessed using the ETDRS chart at a distance of 4 meters. The primary objective is to determine the *non-inferiority* (NI) and equivalence between the two treatment arms, as measured by the primary efficacy endpoint with an NI margin of 4.5 letters and equivalence margin of ±4.5 letters. To control the overall type I error, a fixed sequence testing procedure will be used. If the implant arm is shown to be non-inferior to the intravitreal arm at the one-sided 0.025 level, then the clinical equivalence test will be conducted using two one-sided 0.025 tests.

The primary analysis will be performed using the mixed-effect model with repeated measures (MMRM) based on all available data up to Week 40. All observed measurements will be included in the analysis regardless whether or not a patient has an intercurrent event. Missing data will be implicitly imputed by the MMRM model, assuming a missing at random mechanism.

The dependent variable in the MMRM model is the change from baseline in BCVA score at
post-baseline visits, from 4 to 40 weeks, and the independent variables are the treatment group, time, treatment-by-time interaction, baseline BCVA score (continuous), and the randomization stratification factor of baseline BCVA (< 74 letters vs. ≥ 74 letters) as fixed effects. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, then a compound symmetry covariance or an AR(1) covariance structure will be used. Comparisons between the two treatment arms will be made using a composite contrast over Weeks 36 and 40.

For the primary efficacy endpoint, if a lower bound of a two-sided 95.03% CI for the difference of two treatments is greater than -4.5 letters (the NI margin), then treatment via PDS is considered non-inferior to monthly intravitreal ranibizumab treatment. If the two-sided 95% CI is within -4.5 letters and $+4.5$ letters, then the two treatment regimens are considered clinically equivalent.

As a sensitivity analysis, the per-protocol analysis will follow the same methods as the primary analysis except the **Per-Protocol Population** will be used.

Determination of Sample Size

Patients will be randomly allocated in a 3:2 ratio to the implant arm or intravitreal arm.

The primary endpoint is the change in BCVA score from baseline averaged over Weeks 36 and
40. The study is sized to achieve adequate power to show NI and equivalence of the implant arm to the intravitreal arm in the change in BCVA score from baseline averaged over Week 36 and Week 40 using an NI margin of 4.5 letters and equivalence margins of ± 4.5 letters.

Assuming a standard deviation of 9.5 letters for the change from baseline in BCVA score averaged over 36 and 40 weeks, up to a true mean change from baseline in BCVA of 0.75 letters worse for the implant arm, compared with the monthly intravitreal arm, 216 patients in the implant arm and 144 patients in the intravitreal arm will provide $>90\%$ power to demonstrate NI and equivalence between the two treatment groups. Calculations were based on a one-sided *t*-test at $\alpha = 0.025$ level for the NI test and two one-sided *t*-tests at the $\alpha = 0.025$ level for the equivalence test with the assumption of a 10% dropout rate by Week 40 and a 10% increase for the trimmed mean analysis.

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Appendix 2 Schedule of Activities: Implant Arm, Year 1 and Year 2

Table 1: Schedule of Activities: Implant Arm, Year 1

Assessment	Screening [a]	Rand. [b]	Week 1			Week Visit											
			D1 [b, c]	D2	D7	4	8	12	16	20	24	28	32	36	40	44	48
Visit window (days)	≥ 21 days from prior ITV Anti-VEGF	21–28 days from last ITV RBZ Tx		NA	±2	±7											
Informed consent	x [d]																
Review of inclusion and exclusion criteria	x	x															
Medical and surgical history	x																
Demographic data	x																
Height and Weight	x																
Contact IxRS [e]	x	x							x	x	x				x	x	*x*
Vital signs [f]	x	x	x														
Concomitant medications [g]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	*x*
Adverse events [h]	x			x	x	x	x	x	x	x	x	x	x	x	x	x	*x*
Concurrent ocular procedures[i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	*x*
MacTSQ [j]		x													x		
PPPQ [j]															x		
Pregnancy test [k]	x	x							x	x	x				x	x	*x*
Urinalysis [l]	x																
Hematology [l]	x																

Appendix 2 Schedule of Activities: Implant Arm, Year 1 and Year 2 (cont.)

Table 1: Schedule of Activities: Implant Arm, Year 1 (cont.)

Assessment	Screening [a]	Rand. [b]	Week 1			Week Visit											
			D1 [b, c]	D2	D7	4	8	12	16	20	24	28	32	36	40	44	48
Visit window (days)	≥ 21 days from prior ITV Anti-VEGF	21–28 days from last ITV RBZ Tx		NA	±2	±7											
Chemistry [l]	x																
Coagulation [l]	x																
Serum PK sample [m]		x				x					x			x			
Serum PK sample (at selected sites) [m]				x	x			x									x
Serum ADA sample [m]		x				x					x			x			
BCVA	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
IOP [n]	x	x	x [o]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Slitlamp examination	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dilated binocular indirect ophthalmoscopy [p]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Historical images collection: OCT and FA [q]	x																
SD-OCT [r]	x	x			x	x	x	x	x	x	x	x	x	x	x	x	x
Fundus photography [r]	x													x			x
Fluorescein angiography [r]	x													x			x
Fundus autofluorescence [r]	x													x			x
Lens photo (fundus reflex photograph)	x													x			x
OCT-A (at selected sites) [s]		x			x	x		x			x	x		x			x

Appendix 2 Schedule of Activities: Implant Arm, Year 1 and Year 2 (cont.)

Table 1: Schedule of Activities: Implant Arm, Year 1 (cont.)

Assessment	Screening [a]	Rand. [b]	Week 1			Week Visit											
			D1 [b, c]	D2	D7	4	8	12	16	20	24	28	32	36	40	44	48
Visit window (days)	≥ 21 days from prior ITV Anti-VEGF	21–28 days from last ITV RBZ Tx		NA	±2	±7											
Pre- and post-study treatment antimicrobials [t]			x								x						x
Intravitreal ranibizumab 0.5 mg injection [u]	x																
Ranibizumab filled implant insertion [v]			x														
Implant insertion and refill-exchange video [w]			x								x						x
Post-implantation IOP measurement [x]			x														
Implant insertion evaluation [y]			x														
Implant photographs [z]				x	x	x	x		x		x		x		x		x
Implant refill-exchange [aa]											x						x
Post-treatment finger-counting test [bb]	x [ii]										x						x
Supplemental ranibizumab (if supplemental treatment criteria are met) [cc]									x	x					x	x	
Follow-up call [dd]	x [ee]										x						x
Whole blood sample for genotyping (optional) [ff]		x															

Appendix 2 Schedule of Activities: Implant Arm, Year 1 and Year 2 (cont.)

Table 1: Schedule of Activities: Implant Arm, Year 1 (cont.)

Assessment	Screening [a]	Rand. [b]	Week 1			Week Visit											
			D1 [b, c]	D2	D7	4	8	12	16	20	24	28	32	36	40	44	48
Visit window (days)	≥ 21 days from prior ITV Anti-VEGF	21–28 days from last ITV RBZ Tx		NA	±2	±7											
Aqueous humor sample for biomarkers and ranibizumab conc. (optional) [gg]		x									x	x					x
Serum and plasma samples for biomarkers (if aqueous humor sample collected) (optional) [hh]		x									x	x					x
Serum sample for PK (if aqueous humor sample collected) (optional) [hh]												x					x

ADA = anti-drug antibody; anti-VEGF = anti–vascular endothelial growth factor; BCVA = best-corrected visual acuity; conc. = concentration; D = day; FA = fluorescein angiography; FAF = fundus autofluorescence; FP = fundus photography; IOP = intraocular pressure; ITV = intravitreal; IxRS = interactive voice or web-based response system; MacTSQ = Macular Degeneration Treatment Satisfaction Questionnaire; NA = not applicable; nAMD = neovascular age-related macular degeneration; OCT = optical coherence tomography; OCT-A = optical coherence tomography–angiography; PDS = Port Delivery System with ranibizumab; PK = pharmacokinetics; PPPQ = PDS Patient Preference Questionnaire; Rand = randomization; RBZ = ranibizumab; SD-OCT = spectral-domain optical coherence tomography; Tx = treatment; VA = visual acuity.

Notes: All ocular assessments are to be performed for both eyes prior to study treatment unless noted otherwise. All assessments for a visit are to be performed on the same day, except those at screening.

[a] Refer to Section 3.1 and Table 2 (Protocol v3) for patient eligibility scenario.

[b] Randomization and implant insertion surgery (Day 1) should be scheduled 21–28 days (inclusive) from the last intravitreal ranibizumab treatment in the study eye.

[c] Implant insertion surgery (Day 1) should occur within 1–7 days from randomization and no later than 28 days from the last intravitreal ranibizumab treatment in the study eye.

[d] Patients who participate in the run-in must sign the Informed Consent Form prior to performing protocol-mandated assessments.

Appendix 2 Schedule of Activities: Implant Arm, Year 1 and Year 2 (cont.)

[e] The IxRS will be contacted at Weeks 16, 20, 40, and 44 for supplemental treatment evaluation (for additional assessments if supplemental treatment criteria are met, see Appendix 5 of Protocol v3).

[f] Vital signs consist of blood pressure and pulse measurement while patient is in a seated position after resting for 5 minutes. Vital signs will be measured pre-treatment (as applicable). On the day of implant insertion procedure (Day 1 visit), vital signs will be recorded before the surgery and only blood pressure will be recorded during surgery and after surgery.

[g] Record any concomitant medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) other than protocol-specified procedural medications, and pretreatment and post-treatment medications (e.g., proparacaine, antimicrobials, steroids) used by the patient within 7 days preceding the randomization visit date and through the conclusion of the patient's study participation or early termination visit.

[h] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events related to a protocol-mandated intervention (e.g., procedures such as fluorescein angiography or medication interruption) should be reported. Adverse events will be recorded starting on Day 1 through the last study visit. Adverse events assessed by the qualified ophthalmologist as related to implant insertion, refill-*exchange*, and explantation should be followed until the event resolves or the event is assessed as irreversible, chronic, or stable, even if the patient's participation in the study is over.

[i] Record all concurrent ocular procedures or additional assessments performed on the study or fellow eye. Results of the additional ocular assessments must be forwarded to the Sponsor for evaluation and/or storage.

[j] Must be interviewer-administered by site personnel (other than VA examiner) prior to any other study procedures.

[k] Urine pregnancy test will be performed locally prior to fluorescein angiography and study treatment (if applicable) at screening and subsequent specified visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Do not perform fluorescein angiography or administer study treatment until the final results are available. If the serum pregnancy test is positive, do not administer the study treatment.

[l] Obtain from all study patients pre-treatment and prior to fluorescein angiography, if applicable. Hematology includes hemoglobin, hematocrit, quantitative platelet count, RBCs, WBCs, and differentials, including neutrophils, bands, lymphocytes, basophils, eosinophils, and monocytes (absolute and percent). Chemistry includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN, creatinine, calcium, phosphorus, total and direct bilirubin, total protein, albumin, AST, ALT, lactic dehydrogenase, ALP, and uric acid. Urinalysis includes specific gravity, pH, blood, protein, ketones, glucose, bilirubin, urobilinogen, and microscopic examination (if any of the preceding urinalysis tests, other than glucose and ketones, are abnormal). Coagulation includes aPTT and PT.

[m] Collect prior to implant refill-*exchange* and prior to fluorescein angiography (if applicable).

[n] Perform IOP measurement prior to dilating eyes or procedure; the method used for a patient must remain consistent throughout the study for visits in the office. When performed at implant refill-*exchange* visit, IOP needs to be measured prior to implant refill-*exchange*.

[o] Should be performed in the surgical center using indentation tonometry (e.g. Tono-Pen) for the study eye only prior to the implant insertion surgery.

[p] Upon completion of the implant insertion surgery, patients will have dilated indirect ophthalmoscopy performed to monitor the implant placement and to evaluate any potential implant problems (capturing the results of the indirect ophthalmoscopy findings on EDC is not needed at Day 1). Dilated ophthalmoscopy examinations will also be performed in the study eye at Day 2 and Day 7 (±2 days); afterward, perform dilated ophthalmoscopy examinations at each visit to monitor the implant placement and to evaluate other implant problems.

[q] Historical OCT images taken around the time of diagnosis of nAMD (and before the start of anti-VEGF treatment) will be required to determine patient's eligibility at the screening visit. FAs if taken around the time of diagnosis of nAMD (and before the start of anti-VEGF treatment) must be submitted to the reading center as well and will be evaluated, but are not required to determine patient's eligibility. Refer to the reading center manuals for details.

Appendix 2 Schedule of Activities: Implant Arm, Year 1 and Year 2 (cont.)

[r] The central reading center will evaluate FP, FA, FAF and SD-OCT images taken at the screening visit for determination of a patient's eligibility, together with the historical OCT images taken at the time of diagnosis of nAMD. Refer to the reading center manual for details.

[s] Only at selected sites. Perform pre-treatment.

[t] The pre-implant insertion use of self-administered antimicrobials is required. The pre-implant refill-*exchange* use of self-administered antimicrobials is per the investigator's discretion. The post-implant insertion or refill-*exchange* use of self-administered antimicrobials is required. Anti-inflammatory drops post-implant insertion may be administered as well, per standard of care.

[u] As required, depending on patient eligibility category. Refer to Section 3.1 and Table 2 (Protocol v3) for patient eligibility scenario.

[v] Initially fill the implant with IxRS-assigned kit of ranibizumab 100 mg/mL prior to its insertion into the study eye.

[w] At sites that permit video recording.

[x] IOP will be checked for the study eye only by the treating physician by digital palpation as clinically indicated. These assessments must be performed prior to placing a patch on the eye. Patients will be allowed to leave the surgical center after the designated physician has assessed that there are no safety concerns. If any safety concerns or immediate toxicity are noted, the patient will remain at the surgical center and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event will be reported.

[y] Upon completion of the implant insertion procedure, complete the implant insertion evaluation to indicate surgical details of the insertion procedure. Information captured in the evaluation will be reported.

[z] In addition to the timepoints listed, the photographs will also be taken at any visit if there are concerns with implant function.

[aa] Refill the implant with IxRS-assigned kit of ranibizumab 100 mg/mL.

[bb] Finger-counting test, followed by hand motion and light perception tests (when necessary) performed by the physician within 15 minutes post-treatment for the study eye only. The patient will be allowed to leave the office after the designated physician has assessed that there are no safety concerns. If any safety concerns or immediate toxicity are noted, the patient will remain at the office and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event will be reported.

[cc] Implant arm patients are eligible for supplemental treatment with intravitreal ranibizumab 0.5 mg if the supplemental treatment criteria are met (Section 5.1.5.3 of Protocol v3). Following supplemental treatment, patients will continue with implant *refill-exchanges* per protocol.

[dd] All study patients will be contacted 3 (±1) days following study treatment to elicit reports of any decreases in vision, occurrence of eye pain, unusual redness, or any other new ocular symptoms. Patients will also be asked whether they have taken the prescribed, self-administered, post-treatment antimicrobials.

[ee] If intravitreal ranibizumab 0.5 mg injection is given.

[ff] If a patient has consented to this optional sample collection.

[gg] If a patient has consented to this optional sample collection. At implant refill-*exchange* visit, the aqueous humor sample should be obtained prior to or immediately after implant refill-*exchange*.

[hh] If a patient has consented to this optional sample collection, obtain the sample prior to study treatment and prior to fluorescein angiography (if applicable).

[ii] Only if patient receives intravitreal ranibizumab 0.5 mg injection.

Appendix 2 Schedule of Activities: Implant Arm, Year 1 and Year 2 (cont.)

Table 2: Schedule of Activities: Implant Arm, Year 2, Early Study Termination and Explantation Visits

Assessment	Week Visit												Early Study Term. Visit [y]	Explant. Visit [z]
	52	56	60	64	68	72	76	80	84	88	92	96 [cc]		
Visit window (days)	±7													
Contact IxRS [a]				x	x	x				x	x	x	x	x
Vital signs [b]												x	x	x
Concomitant medications [c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
MacTSQ [f]													x	
PPPQ [f]													x	
Pregnancy test [g]				x	x	x				x	x	x	x	
Serum PK sample [h]												x	x	
Serum PK sample (at selected sites) [h]						x								
Serum ADA sample [h]												x	x	
BCVA	x	x	x	x	x	x	x	x	x	x	x	x	x	
IOP [i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x [j]
Slitlamp examination	x	x	x	x	x	x	x	x	x	x	x	x	x	
Dilated binocular Indirect ophthalmoscopy [k]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SD-OCT [l]	x	x	x	x	x	x	x	x	x	x	x	x	x	
Fundus photography [l]												x	x	
Fluorescein angiography [l]												x	x	
Fundus autofluorescence [l]												x	x	

Appendix 2 Schedule of Activities: Implant Arm, Year 1 and Year 2 (cont.)

Table 2: Schedule of Activities: Implant Arm, Year 2, Early Study Termination and Explantation Visits (cont.)

Assessment	Week Visit												Early Study Term. Visit [y]	Explant. Visit [z]
	52	56	60	64	68	72	76	80	84	88	92	96 [cc]		
Visit window (days)	±7													
Lens photograph (fundus reflex photograph)												x	x	
OCT-A (at selected sites) [m]	x		x			x	x		x			x	x	
Pre-and post-study treatment antimicrobials [n]						x								x
Implant refill-exchange [o]						x								
Post-treatment finger-counting test [p]						x								
Implant explantation [q]														x
Implant refill-exchange and explantation video [r]						x								x
Implant photographs [s]		x		x		x		x		x		x	x	x [aa]
Supplemental ranibizumab (if supplemental treatment criteria are met) [t]				x	x					x	x			
Aqueous humor sample for PD and ranibizumab conc. [u]													x	x [bb]
Plasma and serum samples for PD [u]													x	x [bb]
Follow-up call [v]						x								
Aqueous humor sample for biomarkers and ranibizumab conc. (optional) [w]	x					x	x					x		

Appendix 2 Schedule of Activities: Implant Arm, Year 1 and Year 2 (cont.)

Table 2: Schedule of Activities: Implant Arm, Year 2, Early Study Termination and Explantation Visits (cont.)

Assessment	Week Visit												Early Study Term. Visit [y]	Explant. Visit [z]
	52	56	60	64	68	72	76	80	84	88	92	96 [cc]		
Visit window (days)	±7													
Plasma and serum sample for biomarkers (if aqueous humor sample collected) (optional) [x]	x					x	x					x		
Serum sample for PK (if aqueous humor sample collected) (optional) [x]	x					x	x							

ADA = anti-drug antibody; BCVA = best-corrected visual acuity; conc. = concentration; Explant. = explantation; IOP = intraocular pressure; IxRS = interactive voice or web-based response system; MacTSQ = Macular Degeneration Treatment Satisfaction Questionnaire; OCT-A = optical coherence tomography–angiography; PD=pharmacodynamic; PK = pharmacokinetics; PDS = Port Delivery System with ranibizumab; PPPQ = PDS Patient Preference Questionnaire; SD-OCT = spectral-domain optical coherence tomography; Term. = termination; VA = visual acuity.

Notes: All ocular assessments are to be performed for both eyes prior to study treatment unless noted otherwise. All assessments for a visit are to be performed on the same day, except those at screening.

[a] The IxRS will be contacted at Weeks 64, 68, 88, and 92 for supplemental treatment evaluation (for additional assessments if supplemental treatment criteria are met, see Appendix 5 of Protocol v3).

[b] Vital signs consist of blood pressure and pulse measurement while patient is in a seated position after resting for 5 minutes. If implant explantation is required, vital signs will be recorded before the surgery and only blood pressure will be recorded during surgery and after surgery.

[c] Record any concomitant medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) other than protocol-specified procedural medications, and pretreatment and post-treatment medications (such as proparacaine, antimicrobials, steriods) used by the patient within 7 days preceding the randomization visit date and through the conclusion of the patient's study participation or early termination visit.

[d] Adverse events will be recorded starting on Day 1 through the last study visit. Adverse events assessed by the qualified ophthalmologist as related to implant refill-*exchange*, and explantation should be followed until the event resolves or the event is assessed as irreversible, chronic, or stable, even if the patient's participation in the study is over.

[e] Record all concurrent ocular procedures or additional assessments performed on the study or fellow eye. Results of the additional ocular assessments must be forwarded to the Sponsor for evaluation and/or storage.

[f] Must be interviewer-administered by site personnel (other than VA examiner) prior to any other study procedures.

[g] Urine pregnancy test will be performed locally prior to fluorescein angiography and study treatment (if applicable) at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Do not perform fluorescein angiography or administer the study treatment until the final results are available. If the serum pregnancy test is positive, do not administer the study treatment.

[h] Collect sample prior to implant refill-*exchange*, and/or fluorescein angiography (if applicable).

Appendix 2 Schedule of Activities: Implant Arm, Year 1 and Year 2 (cont.)

[i] Perform IOP measurement prior to dilating eyes or procedure; the method used for a patient must remain consistent throughout the study for visits in the office. When performed at implant refill-*exchange* visit, IOP needs to be measured prior to implant refill-*exchange*.

[j] Should be performed in the surgical center using indentation tonometry (e.g. Tono-Pen) prior to the implant explantation surgery.

[k] Dilated ophthalmoscopy examinations will be performed at each visit to monitor the implant for any potential implant problems. Upon completion of the explantation procedure, patients will also have indirect ophthalmoscopy of the study eye.

[l] Refer to the reading center manual for details.

[m] Only at selected sites. Perform pre-treatment.

[n] The pre-implant refill-*exchange* use of self-administered antimicrobials is per the investigator's discretion. The pre-explantation use of self-administered antimicrobials is required. The post-implant refill-*exchange* or explantation use of self-administered antimicrobials is required. Anti-inflammatory drops post-implant explantation may administered as well, per standard of care.

[o] Refill the implant with IxRS-assigned kit of ranibizumab 100 mg/mL.

[p] Finger-counting test, followed by hand motion and light perception tests (when necessary) performed by the physician within 15 minutes post-treatment for the study eye only. The patient will be allowed to leave the office after the designated physician has assessed that there are no safety concerns. If any safety concerns or immediate toxicity are noted, the patient will remain at the office and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event will be reported.

[q] IOP will be checked after explantation for the study eye only by the treating physician by digital palpation as clinically indicated. These assessments must be performed prior to placing a patch on the eye. Patients will be allowed to leave the surgical center after the designated physician has assessed that there are no safety concerns. If any safety concerns or immediate toxicity are noted, the patient will remain at the surgical center and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event will be reported.

[r] For sites that permit video recording.

[s] In addition to the timepoints listed, the photograph will also be taken at any visit if there are concerns with Implant function.

[t] Implant arm patients are eligible for supplemental treatment with intravitreal ranibizumab 0.5 mg if supplemental treatment criteria are met (see Section 5.1.5.3 of Protocol v3). Following supplemental treatment, patients will continue with implant *refill-exchanges* per protocol.

[u] At the explantation visit, collect aqueous sample prior or immediately after explantation. At the early study termination visit, plasma/serum samples should be obtained prior to fluorescein angiography.

[v] All study patients will be contacted 3 (± 1) days following study treatment to elicit reports of any decreases in vision, occurrence of eye pain, unusual redness, or any other new ocular symptoms. Patients will also be asked whether they have taken the prescribed, self-administered, post-treatment antimicrobials.

[w] If a patient has consented to this optional sample collection. At implant refill-*exchange* visit, the sample should be obtained prior to or immediately after implant refill-*exchange*.

[x] If a patient has consented to this optional sample collection, obtain the sample prior to study treatment and prior to fluorescein angiography (if applicable).

[y] Patients will be scheduled for an early termination evaluation visit 90 (+ 7) days after the implant insertion procedure or 30 (+ 7) days following the last implant refill-*exchange* for monitoring of all adverse events (serious and non-serious).

[z] Patients will be scheduled for safety visits at 1, 7 (± 2), 30 (± 7), and 60 (± 7) days post-explantation (refer to Appendix 4 [Protocol v3] for visit assessments).

[aa] Implant photographs can be taken either the day of the explantation surgery (if possible) or within days leading to the explantation surgery.

[bb] Samples can be taken either the day of the explantation surgery (if possible) or within days leading to the explantation surgery. Aqueous humor, plasma, and serum samples for biomarkers should all be taken at the same visit.

[cc] If a patient is unable to complete Archway at Week 96 and enroll in Portal on the same day, follow the alternate schedule of activities in Protocol Appendix 1, Table 3.

Appendix 3 Schedule of Activities: Intravitreal Arm

Table 1: Schedule of Activities: Intravitreal Arm, Year 1

Assessment	Screening [a]	Rand. [b]	D1 [c]	Week Visit											
				4	8	12	16	20	24	28	32	36	40	44	48
Visit window (days)	≥ 21 days from prior ITV Anti-VEGF Tx	21–27 days from last ITV RBZ Tx	NA	±7											
Informed consent	x [d]														
Review of inclusion and exclusion criteria	x														
Medical and surgical history	x														
Demographic data	x														
Height and Weight	x														
Contact IxRS	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Vital signs [e]	x	x													
Concomitant medications [f]	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Adverse event [g]			x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
MacTSQ [i]		x											x		
Pregnancy test [j]	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Urinalysis [k]	x														
Hematology [k]	x														
Chemistry [k]	x														
Coagulation [k]	x														
Serum PK sample [l]		x		x					x			x			

Appendix 3 Schedule of Activities: Intravitreal Arm (cont.)

Table 1: Schedule of Activities: Intravitreal Arm, Year 1 (cont.)

Assessment	Screening [a]	Rand. [b]	D1 [c]	Week Visit											
				4	8	12	16	20	24	28	32	36	40	44	48
Visit window (days)	≥ 21 days from prior ITV Anti-VEGF Tx	21–27 days from last ITV RBZ Tx	NA	±7											
Serum ADA sample [l]		x		x					x			x			
BCVA	x	x		x	x	x	x	x	x	x	x	x	x	x	x
IOP [m]	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Slitlamp examination	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Dilated binocular Indirect ophthalmoscopy	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Historical images collection: OCT and FA [n]	x														
SD-OCT [o]	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Fundus photography [o]	x											x			x
Fluorescein angiography [o]	x											x			x
Fundus autofluorescence [o]	x											x			x
Lens photograph (fundus reflex photograph)	x											x			x
OCT-A (at selected sites only) [p]		x		x		x			x	x		x			x
Optional pre- and post-study treatment antimicrobials			x	x	x	x	x	x	x	x	x	x	x	x	x
Administration of study treatment (0.5 mg intravitreal RBZ)	x [q]		x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 3 Schedule of Activities: Intravitreal Arm (cont.)

Table 1: Schedule of Activities: Intravitreal Arm, Year 1 (cont.)

Assessment	Screening [a]	Rand. [b]	D1 [c]	Week Visit											
				4	8	12	16	20	24	28	32	36	40	44	48
Visit window (days)	≥ 21 days from prior ITV Anti-VEGF Tx	21–27 days from last ITV RBZ Tx	NA	±7											
Post-treatment finger-counting test [r]	x [s]		x	x	x	x	x	x	x	x	x	x	x	x	x
Follow-up call [t]	x [u]		x	x	x	x	x	x	x	x	x	x	x	x	x
Serum sample for PK (at selected sites) [v]				Collect serum PK sample 1-5 days post intravitreal ranibizumab injection (collect only once per patient)											
Whole blood sample for genotyping (optional) [w]		x													
Aqueous humor sample for biomarkers and ranibizumab conc. (optional) [w]		x							x	x					x
Plasma and serum samples for biomarkers (if aqueous humor sample collected) (optional) [x]		x							x	x					x
Serum sample for PK (if aqueous humor sample collected) (optional) [x]										x					x

ADA = anti-drug antibody; anti-VEGF = anti–vascular endothelial growth factor; BCVA = best-corrected visual acuity; conc. = concentration; D = day; FA = fluorescein angiography; FAF = fundus autofluorescence; FP = fundus photography; IOP = intraocular pressure; ITV = intravitreal; IxRS = interactive voice or web-based response system; MacTSQ = Macular Degeneration Treatment Satisfaction Questionnaire; NA = not applicable; nAMD = neovascular age-related macular degeneration; OCT = optical coherence tomography; OCT-A = optical coherence tomography–angiography; PK = pharmacokinetic; Rand. = randomization; RBZ = ranibizumab; SD-OCT = spectral-domain optical coherence tomography; Tx = treatment; VA = visual acuity.

Notes: All ocular assessments are to be performed for both eyes prior to study treatment unless noted otherwise. All assessments for a visit are to be performed on the same day, except those at screening.

[a] Refer to Section 3.1 and Table 2 (see Protocol v3) for patient eligibility scenario.

[b] Randomization should occur no later than 27 days from the last intravitreal ranibizumab treatment in the study eye.

Appendix 3 Schedule of Activities: Intravitreal Arm (cont.)

[c] Day 1 study treatment visit should occur on the same day as randomization visit.
[d] Patients who participate in the run-in must sign the Informed Consent Form prior to performing protocol-mandated assessments.
[e] Vital signs consist of blood pressure and pulse measurement while patient is in a seated position after resting for 5 minutes. Vital signs will be measured pre-treatment (as applicable).
[f] Record any concomitant medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) other than protocol-specified procedural medications, and pre-treatment and post-treatment medications (such as proparacaine, antimicrobials, steroids) used by the patient within 7 days preceding the randomization visit date and through the conclusion of the patient's study participation or early termination visit.
[g] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events related to a protocol-mandated intervention (e.g., procedures such as fluorescein angiography or medication interruption) should be reported. Adverse events will be recorded starting on Day 1 through the last study visit.
[h] Record all concurrent ocular procedures or additional assessments performed on the study or fellow eye. Results of the additional ocular assessments must be forwarded to the Sponsor for evaluation and/or storage.
[i] Must be interviewer-administered by site personnel (other than VA examiner) prior to any other study procedures.
[j] Urine pregnancy test will be performed locally prior to fluorescein angiography and each study treatment (if applicable) at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Do not perform fluorescein angiography or administer the study treatment until the final results are available. If the serum pregnancy test is positive, do not administer the study treatment.
[k] Obtain from all study patients pre-treatment and prior to fluorescein angiography, if applicable. For a description of the laboratory assessments to be performed see Section 4.5.7 (see Protocol v3) or the laboratory manual.
[l] Collect prior to study treatment and prior to fluorescein angiography (if applicable).
[m] Perform IOP measurement prior to dilating eyes or study treatment; the method used for a patient must remain consistent throughout the study.
[n] Historical OCT images taken around the time of diagnosis of nAMD (and before the start of anti-VEGF treatment) will be required to determine patient's eligibility at the screening visit. FAs if taken around the time of diagnosis of nAMD (and before the start of anti-VEGF treatment) must be submitted to the reading center as well and will be evaluated, but are not required to determine patient's eligibility. Refer to the reading center manuals for details.
[o] The central reading center will evaluate FP, FA, FAF and SD-OCT images taken at the screening visit for determination of a patient's eligibility, together with the historical OCT images taken at the time of diagnosis of nAMD. Refer to the reading center manual for details.
[p] Only at selected sites. Perform pre-treatment.
[q] As required, depending on patient eligibility category. Refer to Section 3.1 and Table 2 (see Protocol v3) for patient eligibility scenario.
[r] Finger-counting test, followed by hand motion and light perception tests (when necessary) performed by the physician within 15 minutes post-treatment for the study eye. Patients will be allowed to leave the office after the designated physician has assessed that there are no safety concerns. If any safety concerns or immediate toxicity are noted, the patient will remain at the office and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event will be reported.
[s] Only if patient receives intravitreal ranibizumab 0.5 mg injection.
[t] All study patients will be contacted 3 (± 1) days following study treatment to elicit reports of any decreases in vision, occurrence of eye pain, unusual redness, or any other new ocular symptoms.
[u] If treatment is given.
[v] *One time serum PK collection only. Sample will be collected from patients in the intravitreal arm 1-5 days after an intravitreal ranibizumab 0.5 mg injection once per patient during the study (selected study visit will be at the discretion of the investigator and site). This sample collection may be performed at the study site or by a trained mobile nursing professional at the patient's home or another suitable location.*
[w] If a patient has consented to this optional sample collection.
[x] If a patient has consented to this optional sample collection, obtain the sample prior to study treatment and prior to fluorescein angiography (if applicable).

Appendix 3 Schedule of Activities: Intravitreal Arm (cont.)

Table 2: Schedule of Activities: Intravitreal Arm, Year 2 and Early Study Termination Visit

Assessment	Week Visit												Early Study Term Visit [a]
	52	56	60	64	68	72	76	80	84	88	92	96 [r]	
Visit window (days)	±7												
Contact IxRS	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs [b]												x	x
Concomitant medications [c]	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [d]	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [e]	x	x	x	x	x	x	x	x	x	x	x	x	x
MacTSQ [f]													x
Pregnancy test [g]	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum PK sample [h]												x	x
Serum ADA sample [h]												x	x
BCVA	x	x	x	x	x	x	x	x	x	x	x	x	x
IOP [i]	x	x	x	x	x	x	x	x	x	x	x	x	x
Slitlamp examination	x	x	x	x	x	x	x	x	x	x	x	x	x
Dilated binocular indirect ophthalm oscopy	x	x	x	x	x	x	x	x	x	x	x	x	x
SD-OCT [j]	x	x	x	x	x	x	x	x	x	x	x	x	x
Fundus photography [j]												x	x
Fluorescein angiography [j]												x	x
Fundus autofluorescence [j]												x	x
Lens photograph (fundus reflex photograph)												x	x
OCT-A (at selected sites) [k]	x		x			x	x		x			x	x

Appendix 3 Schedule of Activities: Intravitreal Arm (cont.)

Table 2: Schedule of Activities: Intravitreal Arm, Year 2 and Early Study Termination Visit (cont.)

Assessment	Week Visit												Early Study Term Visit [a]
	52	56	60	64	68	72	76	80	84	88	92	96 [r]	
Visit window (days)	±7												
Optional pre- and post-study treatment antimicrobials	x	x	x	x	x	x	x	x	x	x	x		
Administration of study treatment (intravitreal ranibizumab 0.5 mg)	x	x	x	x	x	x	x	x	x	x	x		
Post-treatment finger-counting test [l]	x	x	x	x	x	x	x	x	x	x	x		
Aqueous humor sample for biomarkers and ranibizumab concentration													x
Plasma and serum samples for biomarkers [m]													x
Follow-up call [n]	x	x	x	x	x	x	x	x	x	x	x		
Serum sample for PK (at selected sites) [o]	Collect serum PK sample 1-5 days post intravitreal ranibizumab injection (collect only once per patient)												
Aqueous humor sample for biomarkers and ranibizumab conc. (optional) [p]	x					x	x					x [q]	
Plasma and serum samples for biomarkers (if aqueous humor sample collected) (optional) [p]	x					x	x					x [q]	
Serum sample for PK (if aqueous humor sample collected) (optional) [p]	x					x	x						

Appendix 3 Schedule of Activities: Intravitreal Arm (cont.)

ADA = anti-drug antibody; BCVA = best-corrected visual acuity; conc. = concentration; IOP = intraocular pressure; IxRS = interactive voice or web-based response system; MacTSQ = Macular Degeneration Treatment Satisfaction Questionnaire; OCT-A = optical coherence tomography–angiography; PK = pharmacokinetics; SD-OCT = spectral-domain optical coherence tomography; Term. = termination; VA = visual acuity.

Notes: All ocular assessments are to be performed for both eyes prior to study treatment unless noted otherwise. All assessments for a visit are to be performed on the same day, except those at screening.

[a] Patients will be scheduled for an early termination evaluation 30 (+7) days following the last study drug treatment for monitoring of all adverse events (serious and non-serious).

[b] Vital signs consist of blood pressure and pulse measurement while patient is in a seated position after resting for 5 minutes.

[c] Record any concomitant medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) other than protocol-specified procedural medications, and pre-treatment and post-treatment medications (such as proparacaine, antimicrobials, steroids) used by the patient within 7 days preceding the randomization visit date and through the conclusion of the patient's study participation or early termination visit.

[d] Adverse events will be recorded starting on Day 1 through the last study visit.

[e] Record all concurrent ocular procedures or additional assessments performed on the study or fellow eye. Results of the additional ocular assessments must be forwarded to the Sponsor for evaluation and/or storage.

[f] Must be interviewer-administered by site personnel (other than VA examiner) prior to any other study procedures.

[g] Urine pregnancy test will be performed locally prior to fluorescein angiography and study treatment (if applicable) at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Do not perform fluorescein angiography or administer the study treatment until the final results are available. If the serum pregnancy test is positive, do not administer the study treatment.

[h] Collect prior to study treatment and prior to fluorescein angiography (if applicable).

[i] Perform IOP measurement prior to dilating eyes or study treatment; the method used for a patient must remain consistent throughout the study.

[j] Refer to the reading center manual for details.

[k] Only at selected sites. Perform pre-treatment.

[l] Finger-counting test, followed by hand motion and light perception tests (when necessary) should be performed by the physician within 15 minutes post-treatment for the study eye only. Patients will be allowed to leave the office after the designated physician has assessed that there are no safety concerns. If any safety concerns or immediate toxicity are noted, the patient will remain at the office and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event will be reported.

[m] Samples should be obtained prior to fluorescein angiography.

[n] All study patients will be contacted 3 (± 1) days following study treatment to elicit reports of any decreases in vision, occurrence of eye pain, unusual redness, or any other new ocular symptoms.

[o] *One time serum PK collection only. Sample will be collected from patients in the intravitreal arm 1-5 days after an intravitreal ranibizumab 0.5 mg injection once per patient during the study (selected study visit will be at the discretion of the investigator and site).This sample collection may be performed at the study site or by a trained mobile nursing professional at the patient's home or another suitable location.*

[p] If a patient has consented to this optional sample collection. For plasma/serum samples, obtain the sample prior to study treatment and prior to fluorescein angiography (if applicable).

[q] Only collect if the patient is not enrolling in Portal.

[r] If a patient is unable to complete Archway at Week 96 and enroll in Portal on the same day, follow the alternate schedule of activities in Protocol Appendix 2 Table 3.

Appendix 4 Memorandum on the Variability In Change From Baseline Best-Corrected Visual Acuity Through Week 16 In Pooled Treatment Arms

Statistics•Collaborative
design and analysis for biomedical research

MEMORANDUM

To: [redacted]
From: [redacted]
Subject: Variability in change from baseline BCVA through Week 16 in pooled treatment arms
cc: [redacted]
Date: March 20, 2019

The Archway protocol's sample size section includes a provision for an independent statistician to provide a masked (i.e., pooled over treatment group) evaluation of the variability in change from baseline best corrected visual acuity (BCVA) over time. This assessment is to ensure that the assumed standard deviation of 9.5 letters is consistent with that observed thus far in the event that the trial's sample size needs to be increased before the close of enrollment. On March 6, PPD from Genentech requested that Statistics Collaborative (SCI) perform this evaluation. On March 13, SCI and Dr. [redacted] met by phone to review the request and the sample table shell that Dr. [redacted] provided.

The table below summarizes the variability in change from baseline BCVA at each four-week visit through Week 16 using the March 7, 2019 SDTM data that SCI received for its first safety monitoring report. SCI calculated 4-meter BCVA in the study eye using the number of letters correctly read for each line of the ETDRS chart as recorded in the SDTM data.

Masked Standard Deviation of Change in BCVA over time

	Change in BCVA			
Visit	N	SD	Interquartile range	Min, Max
Week 4	124	7.3	8	-32, 12
Week 8	73	8.4	8	-29, 45
Week 12	51	6.7	6	-31, 12
Week 16	19	8.8	9	-21, 13

Produced by E:\Proj\GNE Archway\Programs\adhoc_BCVAvar.sas v.001
Data received: SDTM 07MAR2019

C:\Users\[redacted]\Downloads\2019-03-20 BCVA change variability [redacted].pwd.docx[redacted]

1625 Massachusetts Avenue NW, Suite 600, Washington, DC 20036
tel: 202•247•9700 | fax: 202•247•9701 | e-mail: office@statcollab.com
www.statcollab.com