Official Title: A Phase II, Multicenter, Randomized, Active Treatment-Controlled Study of the Efficacy and Safety of the Ranibizumab Port Delivery System for Sustained Delivery of Ranibizumab in Patients With Subfoveal Neovascular Age-Related Macular Degeneration

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STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE II, MULTICENTER, RANDOMIZED, ACTIVE TREATMENT–CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF THE RANIBIZUMAB PORT DELIVERY SYSTEM FOR SUSTAINED DELIVERY OF RANIBIZUMAB IN PATIENTS WITH SUBFOVEAL NEOVASCULAR AGE-RELATED MACULAR DEGENERATION**

PROTOCOL NUMBER: GX28228

STUDY DRUG: Ranibizumab Port Delivery System for Sustained Delivery of Ranibizumab (RO4893594)

VERSION NUMBER: 2

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STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

Name	Reason for Signing	Date and Time (UTC)
[redacted]	Company Signatory	21-Jun-2018 09:06:58

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

The following changes to the Statistical Analysis Plan (SAP), Version 2, are being made subsequent to the end of Phase II meeting held with the U.S. Food and Drug Administration (FDA) on 23 March 2018.

- Added details of two unplanned interim efficacy analyses conducted per allowance of the protocol: the first interim was performed after ~50% of patients completed the 6-month follow-up in October 2017, and the second interim was performed after ~70% of patients completed the 9-month follow-up in April 2018.
- Added supportive preliminary assessments on the differences in best corrected visual acuity (BCVA) and anatomical outcomes between the Port Delivery System with ranibizumab (PDS) arms and ranibizumab monthly intravitreal injection arm. Statistical methods and the endpoints used for the preliminary assessments are provided. Formal hypothesis testing will not be performed because the study is not powered for such assessments.
- Modified data handling rules for primary, secondary, and exploratory endpoints. The last observation carried forward approach will not be used as the primary method for imputation of missing data.
- Updated the analysis population definitions with regard to the handling of sites with Good Clinical Practice (GCP) non-compliance issues.
- Added additional safety analyses for comprehensive safety assessment.
- Added information pertaining to the oral antithrombotic therapy (OAT) substudy.

  Analysis plan for the OAT substudy is provided in the substudy protocol and is not repeated in this SAP.

Additional minor changes have been made to improve clarity and consistency.

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1. BACKGROUND

Age-related macular degeneration (AMD) is one of the major causes of legal blindness in elderly persons in the developed world (Bressler et al. 2011). Advanced AMD includes two sub-types: neovascular AMD (nAMD) and geographic atrophy (GA). The prevalence of nAMD increases exponentially with age, with prevalence estimates in the United States in 2011 ranging from 0.5% among those 65–69 years of age to 14.6% among those 90 years of age or greater (Rudnicka et al. 2012).

The treatment of nAMD was significantly impacted by the introduction of anti-vascular endothelial growth factor (VEGF) therapy because prior to the availability of anti-VEGF therapy, vision loss could be slowed but not reversed. Ranibizumab, a recombinant, humanized monoclonal antibody fragment (Fab), which binds to all known isoforms of VEGF-A, was approved by the U.S. Food and Drug Administration (FDA) for use in nAMD in June 2006. In November 2011, a second anti-VEGF therapy, aflibercept, was approved for nAMD in the United States with a similar safety and efficacy profile to ranibizumab. Both ranibizumab and aflibercept therapies require frequent intravitreal injections and physician monitoring.

As a result of the chronic, progressive nature of nAMD, frequent ranibizumab intravitreal injections continue for extended periods for many patients. Pivotal studies of ranibizumab in nAMD (Studies FVF2598g and FVF2587g) demonstrated significant and well-maintained visual acuity (VA) outcomes with monthly 0.5-mg intravitreal injections for 2 years. Trials that investigated less frequent than monthly dosing (Study FVF3192g and Lalwani et al. 2009) showed that visual outcomes were not as well maintained with more intermittent dosing schedules.

The Port Delivery System with ranibizumab (PDS), previously called ranibizumab Port Delivery System (RPDS), 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 port delivery implant (referred to as the Implant), ancillary devices (Insertion Tool, Initial Fill Needle, Refill Needle, and Explant Tool), and ranibizumab. 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.

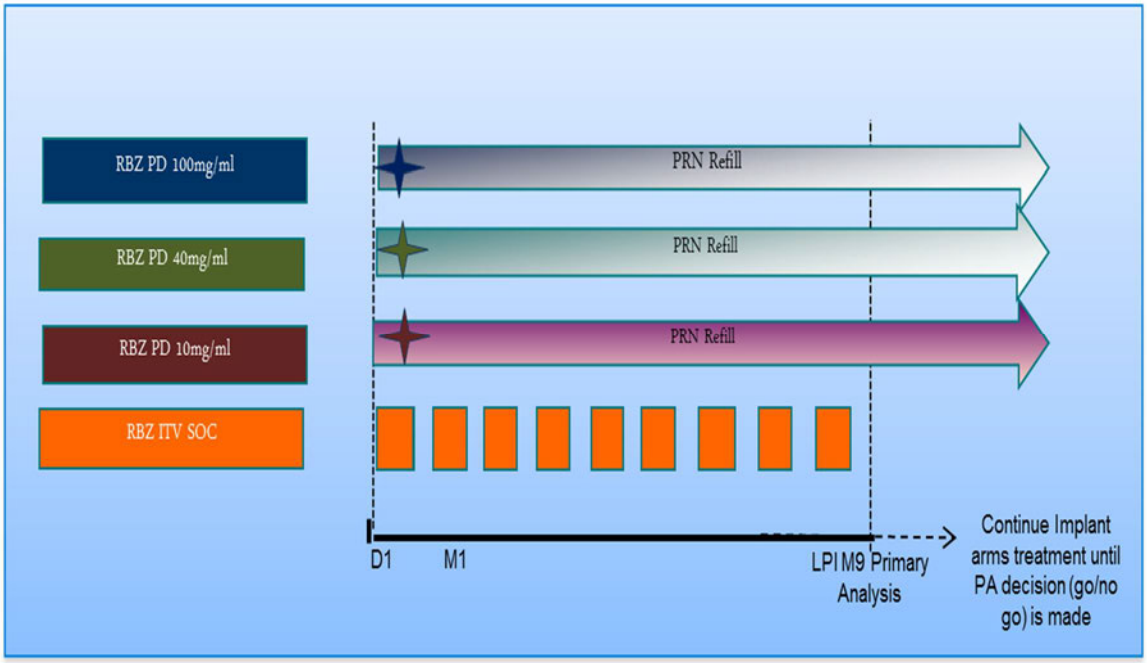
The analyses specified in this document supersede the analysis plan described in the Study GX28228 Protocol, Version 8. Additional supportive analyses were added in this amendment to provide further evaluation of the treatment benefits.

2. STUDY DESIGN

Study GX28228 is a Phase II, multicenter, dose-ranging, randomized, active treatment (monthly intravitreal injection)–controlled study to evaluate the efficacy, safety, and pharmacokinetics (PK) of ranibizumab delivered through the Implant using three ranibizumab formulation arms (10 mg/mL, 40 mg/mL, and 100 mg/mL) compared with

the control arm (0.5-mg monthly intravitreal injections of 10 mg/mL formulation) in patients with nAMD. Approximately 220 patients at up to 60 sites in the United States will be randomized in a 3:3:3:2 ratio to the PDS 10 mg/mL, PDS 40 mg/mL, PDS 100 mg/mL, and the control arms, respectively (Figure 1).

Figure 1 Study Schema



D1 = Day 1; ITV = intravitreal; LPI = last patient in; M1 = Month 1; M9 = Month 9; PA = primary analysis; PD = ranibizumab port delivery; PRN = as needed (as per the refill criteria); RBZ = ranibizumab; SOC = standard-of-care.
Note: Ranibizumab filled Implant inserted (Day 1).

The study will include screening and randomization visits followed by a treatment period. Baseline measurements will be taken at the randomization visit. The patients will then be randomized to a treatment arm using a permuted block randomization scheme stratifying by best corrected visual acuity (BCVA) score (≤65 letters vs. ≥66 letters) and number of prior anti-VEGF intravitreal injections (≤3 vs. ≥4).

Patients randomized to the Implant treatment arms will have the Implant (prefilled with ranibizumab) surgically inserted in the study eye at their Day 1 visit, after which they will be evaluated monthly for the need for an Implant refill based upon protocol-specified-refill criteria for the remainder of the study treatment duration. Patients randomized to the intravitreal injection treatment arm (control) will be treated monthly with intravitreal injections of ranibizumab, starting at their Day 1 visit and continuing for the remainder of the study treatment duration.

The study had specific criteria for refill, rescue, and lack of clinical efficacy (LCE), which are provided below.

Refill Criteria: The patients randomized to the Implant treatment arms will have their Implant refilled only if any of the following criteria is met, as automatically determined by contacting interactive voice/Web response system (IxRS):

- Increase in central foveal thickness (CFT) of ≥75 μm on spectral domain optical coherence tomography (SD-OCT) at the current visit compared with the average CFT over the last 2 available measurements, due to nAMD disease activity

  OR

- Increase in CFT of ≥100 μm from the lowest CFT measurement on study, due to nAMD disease activity

  OR

- Decrease of ≥5 letters in BCVA at the current visit compared with the average BCVA over the last two available measurements, due to nAMD disease activity

  OR

- Decrease of ≥10 letters from best recorded BCVA on study, due to nAMD disease activity

  OR

- Presence of new macular hemorrhage, due to nAMD disease activity.

Rescue Criteria: Rescue treatment with open-label ranibizumab (0.5 mg intravitreal injections of 10 mg/mL formulation) for patients in the Implant arm is allowed only under the following circumstances:

- Approximately 1 month and/or 2 months after occurrence of vitreous hemorrhage, if vitreous hemorrhage causes loss in BCVA, and neither assessment of the macula nor SD-OCT can be performed successfully.
- At the time a patient meets criteria for LCE (see below).
- In the case of progressive worsening of BCVA and/or CFT due to wet AMD activity across two consecutive scheduled visits, only if the patient does not meet refill criteria. If a treatment is clinically necessary due to the progressive clinical worsening per the investigator's judgment, rescue treatment must be discussed and agreed upon by the Medical Monitor prior to being introduced.

Lack of Clinical Efficacy Criteria: If a study patient randomized to the Implant treatment arm meeting criteria for LCE, he or she will receive a rescue injection with open-label ranibizumab at the time of meeting LCE. In addition, he or she will receive a mandatory refill at the 100 mg/mL formulation one month after the rescue intravitreal injection. After that, the 100 mg/mL formulation will be used for all future refills, whenever the patient meets refill criteria. The LCE criteria are as follows:

- Loss in BCVA of ≥15 letters from the best recorded BCVA on study following two consecutive ranibizumab Implant refills (as per protocol-specified refill criteria)

occurring 1 month apart due to nAMD disease activity and not attributable to a change in the ocular media (i.e., cornea, lens, aqueous or vitreous humor, epiretinal membrane development, etc.) unless there is at least a five-letter increase in BCVA, in which case a refill will occur.

and/or

- Increase in CFT ≥150 μm from the lowest CFT measurement on study following two consecutive ranibizumab Implant refills (as per protocol-specified refill criteria) occurring 1 month apart due to nAMD disease activity and not attributable to a change in the ocular media (i.e., cornea, lens, aqueous or vitreous humor, epiretinal membrane development, etc.) unless there is a decrease in CFT ≥75 microns from the last refill, in which case a refill will occur.

See the protocol synopsis (Appendix 1) for further study design features, including screening, inclusion details, and randomization. The schedule of assessments is in Appendix 2.

An oral antithrombotic therapy (OAT) substudy is being conducted as a substudy of the main Study GX28228. This substudy is a non-randomized, uncontrolled, open-label study to evaluate the safety, efficacy, and PK of ranibizumab delivered through an implant using the 100-mg/mL formulation of ranibizumab in patients with nAMD who required ongoing OAT for a preexisting medical condition, and such subjects were not eligible to participate to the main study. Subjects for the substudy are enrolled separately from the main study and the analyses for the substudy will also be conducted separately. Please refer to Section 6 in the substudy protocol for details regarding statistical considerations and analysis plan.

2.1 PROTOCOL SYNOPSIS

The protocol synopsis is in Appendix 1. The schedule of assessments is provided in Appendix 2. Of note, the analyses specified in this SAP supersede the analysis plan described in the Protocol.

2.2 OUTCOME MEASURES

2.2.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure for this study is the time until a patient first requires the Implant refill according to protocol-defined refill criteria.

2.2.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures are as follows:

- Change from baseline in BCVA at Month 9
- Average change from baseline in BCVA over time
- Change from baseline in BCVA over time

- Change from baseline in CFT over time, as assessed on SD-OCT by the central reading center
- Occurrence of Implant clogging

2.2.3 Safety Outcome Measures

The safety outcome measures are as follows:

- Incidence of adverse events of special interest (AESIs): Adverse events (AEs) associated with ranibizumab, the Implant, Implant-associated procedures, and/or ancillary devices
- Incidence of "pre-specified PDS-associated AEs"
- Incidence of ocular and non-ocular AEs and serious adverse events (SAEs)
- Incidence of positive serum antibodies to ranibizumab

2.2.4 Pharmacokinetic Efficacy Outcome Measures

The PK outcome measures related to ranibizumab serum concentration-time data following the Implant insertion and refills are as follows:

- Observed maximum serum concentration (C_{max}) and selected postdose-serum concentrations after Implant insertion and all subsequent refills
- Additional estimated PK parameter values including area under the concentration time curve (AUC), time to maximum concentration (t_{max}), and half-life ($t_{1/2}$) after Implant insertion, and all subsequent refills
- Observed serum concentrations (C_t) over time from monthly serum sampling when no refills are administered
- Observed steady-state serum concentration (C_{trough}) prior to refills

In addition, optional anterior chamber (aqueous humor) samples will be collected to assess ocular drug concentration.

2.2.5 Exploratory Efficacy Outcome Measures

The exploratory outcome measures are as follows:

- Treatment emergent macular atrophy in all treatment arms
- The Macular Degeneration Treatment Satisfaction Questionnaire (MacTSQ) score at randomization and at Months 1, 6, 9, and the final or early termination visit for patients who speak English or Spanish
- Time to subsequent Implant refills according to protocol-defined refill criteria
- Number of times a patient meets protocol-specified refill criteria
- Proportion of patients in each Implant arm who first meet the protocol-defined refill criteria prior to and at Months 4, 5, and 6
- Proportion of patients with an improvement of BCVA from baseline of $\geq$15 letters over time

- Proportion of patients losing ≥15 letters in BCVA from baseline over time
- Change from baseline in BCVA over time measured under low luminance conditions
- Changes from screening in total lesion area, area of choroidal neovascularization (CNV) lesion, and CNV leakage over time, as assessed by fluorescein angiography
- Proportion of patients meeting LCE criteria
- Proportion of patients requiring explantation
- Changes in CNV perfusion over time, as assessed by optical coherence tomography (OCT) angiography

2.3 DETERMINATION OF SAMPLE SIZE

This study is exploratory in nature and designed to estimate the time to first refill (TTFR) for each of the PDS treatment arms (10 mg/mL, 40 mg/mL, and 100 mg/mL) enrolling 60 patients in each of the PDS treatment arms. The sample size of approximately 220 randomized patients will be adequate to evaluate the primary objective of the study (see the protocol synopsis in Appendix 1). Pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation were performed to inform key assumptions used in sample size calculation. Given the simulation results, the hazard ratio (HR) for comparing the 100 mg/mL arm with the 10 mg/mL arm was estimated to be 0.66 for TTFR. Assuming this HR, a total of at least 125 events from all three Implant arms is expected at the primary analysis time (approximately 85 events in the 10 mg/mL arm and a higher dose arm). With 85 events, this study will have approximately 80% power to detect an HR=0.66 between the two Implant arms using a log-rank test at a one-sided significance level of 15%. No multiplicity adjustment is planned for this Phase II study.

Forty patients in the intravitreal arm are considered sufficient to compare each device arm versus the intravitreal arm in change in BCVA from baseline through Month 9 (assuming an estimated SD=10 letters, a two-sided 80% CI will extend approximately 2.62 letters from the observed mean).

2.4 ANALYSIS TIMING

The planned primary analysis will be conducted after the last patient's Month 9 visit occurs. The final analysis will be conducted following the conclusion of the study. The analysis timing for interim analyses can be found in Section 4.8.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Stratified permutated block randomization was used to assign patients to one of the study treatment arms. The randomization stratification factors are BCVA score (≤65 letters vs. ≥66 letters) and number of prior anti-VEGF intravitreal injections (≤ 3 vs. ≥4). Randomization was performed by the IxRS. Outcomes of the stratification factors used in randomization and outcomes of stratification factors as recorded in Case

Report Forms (CRF) will be compared to examine whether there are mis-stratifications. For analyses, the stratification factors as recorded in IxRS will be used.

3.2 INDEPENDENT IMAGE REVIEW FACILITY

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 analyses and storage. The staff at the central reading center is masked for the treatment assignment and the location (left vs. right) of the study eye.

3.3 DATA MONITORING

Ongoing review of aggregate safety (including AESIs, SAEs, and adverse device effects [ADEs]) along with key efficacy data (BCVA and refills for benefit-risk assessments) was performed by the Internal Monitoring Committee (IMC). The IMC is composed of two subcommittees: a masked IMC that will meet regularly to review study safety data, study conduct, and operation and an unmasked IMC that will meet as needed to review unmasked safety and/or efficacy data and operational issues. The masked IMC members were granted access to the unmasked interim efficacy analysis results for the purpose of planning future Phase III studies, and continued to review only the aggregate cumulative safety summary in an attempt to provide unbiased assessment. The IMC roles and responsibilities are outlined in the IMC Agreement.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

Any site with serious Good Clinical Practice (GCP) non-compliance issues will impact the efficacy and safety assessments for this study. In case of any data falsification or other deviations from GCP, data will be handled as follows:

- Exclude data for summaries of patient disposition, summaries of demographic and baseline characteristics, PK/PD analyses, and all efficacy analyses
- Exclude data for all safety analyses for a clean overall summary
- Additionally, include data for ocular adverse event summaries as sensitivity analyses
- Provide a separate listing of all safety adverse events for non-compliance sites for full disclosure

A directed Roche Quality Assurance audit conducted in November 2017 confirmed serious GCP non-compliance involving fraudulent data collection on the part of multiple staff members (study coordinators) was established at Site [redacted], and the FDA was notified of the alleged misconduct on 21 December 2017. Due to the findings identified to date (data falsification), the data for this site will be handled as described above since the Sponsor concluded that the integrity of the data produced at this specific site did not meet requirements for GCP.

4.1.1 Modified Intent-to-Treat Population

Efficacy analyses will be based on the modified intent-to-treat (ITT) population, which will comprise all patients who were randomly assigned to study treatment and receive at least one study treatment. Patients will be summarized by treatment arm and analyzed according to the treatment actually received and not according to the treatment they were randomized to receive, in the event of a discrepancy. Patients who received an Implant will be considered a PDS patient.

4.1.2 Safety Population

The safety population will be composed of all patients who received at least one study treatment. Patients will be summarized by treatment arm and analyzed according to the treatment actually received and not according to the treatment they were randomized to receive, in the event of a discrepancy. This population will be used for safety summaries and analyses.

4.1.3 Pharmacokinetic-Evaluable Population

Pharmacokinetic-evaluable patients will include randomized patients who have received at least one study drug administration and have provided at least one serum and/or aqueous PK sample for determination of ranibizumab concentration. Patients may be excluded from the PK analyses if they have AEs that will interfere with the interpretation of the results. Treatment arms for this population will be defined according to the actual treatment received.

4.2 ANALYSIS OF STUDY CONDUCT

A summary of patient disposition will be presented in the all randomized patient population excluding patients from site [redacted] and will include the number of patients randomized, and the number and percentage of patients who completed the study, who received study drug, who discontinued study drug, and who discontinued study participation. The reasons for study/study drug discontinuation will also be summarized. A summary of the number and percentage of patient's eligibility criteria deviations and other major protocol deviations will also be tabulated.

4.3 ANALYSIS OF TREATMENT ARM COMPARABILITY

Demographic and baseline characteristics such as age, sex, race/ethnicity, and baseline disease characteristics (i.e., BCVA and OCT parameters) will be summarized by treatment arm in the modified ITT population using means, standard deviation, medians, and ranges for continuous variables, and counts and proportions for categorical variables, as appropriate.

4.4 EFFICACY ANALYSIS

Efficacy analyses will be done using the modified ITT population. Although this study is powered based on the log-rank test at a one-sided significance level of 15% for the primary outcome measure, there is no prespecified alpha level for other outcome

measures. 95% CIs will be reported for estimation purposes and for treatment arm differences unless stated otherwise. No adjustments will be made for multiplicity. Except for the primary endpoint, no statistical tests will be conducted. All analyses will be based on observed results unless imputation of missing data is specified. For the analysis purpose, the stratification factors as recorded in IxRS will be used if there is a discrepancy between the CRF and the IxRS data.

Unless otherwise specified, continuous variables will be summaries using descriptive statistics including mean, standard deviation, median, and range. Categorical variables will be summarized using counts and percentages.

4.4.1.1 Primary Efficacy Endpoint

The primary endpoint for this analysis is the time from the day of device implantation until a patient first requires the Implant refill according to protocol-defined refill criteria (TTFR). For patients without any refills prior to or on the cutoff date, TTFR will be censored. The censoring date will be defined as the date of a patient's last visit before the cutoff date or the date when the patient discontinues from the study, whichever occurs first. Observed data will be used for these analyses.

Time to first refill will also be censored for the following patients:

- At the time of an intravitreal anti-VEGF injection in the study eye if administered before the first refill
- At the time the refill criteria cannot be assessed, which is defined as at least two refill variables (BCVA, CFT, or new macular hemorrhage) cannot be evaluated for any reason, or are affected by a clinical reason different from nAMD activity, before the first refill
- At the time of explant

Kaplan-Meier plots will be provided by PDS treatment arm. Median TTFR and corresponding 80% CIs will be calculated for each treatment arm using the Kaplan-Meier method.

To support the dose level selection among the Implant groups, the primary analysis for TTFR will include the following pairwise group comparisons, each with a stratified log-rank test at a one-sided significance level of 15%. The stratification factors to be included are baseline BCVA score ($\leq$65 letters vs.$\geq$66 letters) and number of anti-VEGF-intravitreal injections ($\leq$3 vs.$\geq$4).

- Implant with 100 mg/mL versus Implant with 10 mg/mL
- Implant with 100 mg/mL versus Implant with 40 mg/mL
- Implant with 40 mg/mL versus Implant with 10 mg/mL

In addition, the HR for each pairwise comparison of the treatment arms will be estimated using a Cox proportional hazards regression model stratified by baseline BCVA score

(≤65 letters vs. ≥66 letters) and number of prior anti-VEGF-intravitreal injections (≤3 vs. ≥4) with main effects for treatment. Estimated HRs for each pairwise comparison will be presented with the corresponding 70% CIs.

Using the above methods, two sensitivity analyses will be performed. One sensitivity analysis will be done where TTFR will be additionally censored for patients with dosing errors. The other sensitivity analysis will be done where TTFR is defined as the time from day of device implantation until a patient actually received the first Implant refill, regardless whether there is an intravitreal anti-VEGF injection, a visit where refill criteria cannot be adequately assessed, or patients have dosing errors. For patients without any refills prior to or on the cutoff date, TTFR will be censored on the date of a patient's last visit before the cutoff date or the date when the patient discontinues from the study, whichever occurs first.

To assist in the interpretation of TTFR and change from baseline in BCVA, the following figures will be generated:

- Swimmer plots by patient time from first dose of study treatment (ranibizumab filled Implant insertion) to the end of study with a mark for each refill time will be provided by Implant arm to explore the refill pattern.
- Spaghetti plots of change in BCVA and change in CFT over time for each Implant arm showing refill times will be provided to explore the association of refill frequency with BCVA and CFT.

4.4.1.2 Additional Efficacy Analyses Focused on Refill Times

The following endpoints will be summarized using descriptive statistics and 80% CIs. These analyses will be done using the modified ITT population observed data.

- Time to subsequent Implant refills according to protocol-defined refill criteria will be estimated using the Kaplan-Meier method.

  Time from first refill to the second refill will be analyzed for patients who have undergone the first refill, do not receive an intravitreal anti-VEGF injection in the study eye prior to the first refill, and do not have visits prior to the first refill where refill criteria cannot be adequately assessed.

  Time from the first refill to the second refill is defined as time from the date of the first refill to the date of the second refill. For patients who do not have the second refill prior to or on the cutoff date, time to second Implant refill will be censored on the date of a patient's last visit before the cutoff date or the date when the patient discontinues from the study, whichever occurs first.

  Time to second Implant refill will also be censored for the following patients:

  – At the time of an intravitreal anti-VEGF injection in the study eye if administered before the second refill

  – At the time the refill criteria cannot be adequately assessed, which is defined as at least two refill variables (BCVA, CFT, or new macular

hemorrhage) cannot be evaluated for any reason, or are affected by a clinical reason different from nAMD activity, before the second refill

  - At the time of explant

  Similar approach will be used to define time from the second refill to the third refill, etc.

- Total number of times a patient meets protocol-specified refill criteria and is refilled will be provided over the following time intervals first 5 months, from Month 6 to Month 10, greater than 10 months
- Patient listing of dosing errors and refill time errors
- Percentage of patients not meeting the protocol-defined first refill criteria over time, derived from Kaplan-Meier estimates

4.4.2 Additional Efficacy Endpoints

This section describes the analysis methods for the secondary and exploratory efficacy endpoints listed in Section 2.2.2 and Section 2.2.5.

Descriptive summaries will be provided for all secondary and exploratory endpoints for the 3 Implant arms (10 mg/mL, 40 mg/mL, and 10 mg/mL) and the monthly intravitreal arm. Figures based on the descriptive summaries over time may be provided when appropriate to support the interpretation of the study results.

Additional supportive analyses are provided for preliminary assessments of differences in visual acuity and anatomical outcomes between each of the Implant arms and the intravitreal arm. Descriptions of the statistical methods and the endpoints used for the preliminary assessments are grouped into the following subsections: BCVA, anatomical outcomes, patient reported outcomes, and other exploratory efficacy endpoints. Formal hypothesis testing will not be performed because the study is not powered for such assessments. The difference in outcome measure between each of the Implant arms and the intravitreal arm will be provided along with a 95% CI.

4.4.2.1 Visual Acuity

Change in Best Corrected Visual Acuity (BCVA)

For change in BCVA from baseline, several supportive preliminary analyses will be performed as described below:

- Change from baseline in BCVA score averaged over Month 9 and Month 10 analyzed with an mixed effects repeated measures (MMRM) model
- Change from baseline in BCVA score averaged over Month 9 and Month 10 analyzed with a trimmed mean approach
- Change from baseline in BCVA score through Month 10 analyzed with an analysis of covariance (ANCOVA) model with missing data imputed by the last observation carry forward (LOCF) approach

- Change from baseline in BCVA score over time through Month 10 for patients treated after surgical Instruction for Use Version 10 (IFU v10) analyzed with descriptive statistics

The details for these analyses are provided as follows:

- Mixed effects with repeated measures (MMRM) analysis for change in BCVA score from baseline averaged over Month 9 and Month 10:

  The change from baseline in BCVA score averaged over Month 9 and Month 10 will be compared between each PDS arm and the comparator intravitreal arm using a MMRM model. The model will include the change from baseline at Months 1 to 10 as the response variables and will include the categorical covariates of treatment group, visit, visit-by-treatment group interaction, the continuous baseline value for the response variable (in this case, baseline BCVA), as well as randomization stratification factors as fixed effects. Comparisons between each PDS and the intravitreal arm will be made using a composite contrast over Months 9 and 10. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, then a heterogeneous compound symmetry or a first order autoregressive (AR [1]) covariance structure may be fitted.

  Best corrected visual acuity (BCVA) assessments will be censored after the time of rescue intravitreal anti-VEGF injection in the study eye and after the time of explant. Missing data will be implicitly imputed by the MMRM model, assuming a missing at random missing data mechanism (i.e., missing data are dependent on other observed variables but not on the missing data).

  An additional MMRM analysis will be performed including all observed measurements. That is, all observed BCVA data will be included regardless of whether patients received rescue treatment or discontinued study treatment due to AE or LCE. Best corrected visual acuity (BCVA) assessments at the time of explant will be censored. This analysis evaluates the treatment policy of PDS with rescue therapy versus the monthly intravitreal ranibizumab.

  From the recent end of Phase II meeting with the US FDA on 23 March 2018, the Agency agreed that the change in BCVA from baseline averaged over Month 9 and Month 10 is an appropriate primary endpoint for the Phase III study to assess the non-inferiority (NI) in visual acuity between the Implant and intravitreal arms with an NI margin of 4.5 letters. This NI margin will be used as a reference to assist data interpretation in this preliminary assessment.

  To support the interpretation of BCVA change from baseline over time, figures for the adjusted mean change from baseline over time through Month 10 will be provided.

- Trimmed mean analysis for change in BCVA score from baseline averaged over Month 9 and Month 10:

  A trimmed mean analysis (Permutt and Li 2016) will be performed using an analysis of covariance (ANCOVA model) for adjustment for covariates. The dependent variable in the ANCOVA model is the average of Month 9 and Month 10

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 (≤65 letters vs. ≥66 letters) and number of anti-VEGF-intravitreal injections (≤3 vs. ≥4).

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

- Patients in the PDS arm receive a rescue treatment (intravitreal injection) or undergo explantation prior to Month 9
- Patients in all treatment arms discontinue study treatment due to LCE or AE prior to Month 9
- Patients in all treatment arms have a missing Month 9 assessment and discontinue study treatment due to LCE or AE at Month 9
- Patients in all treatment arms have missing Month 9 and Month 10 assessments and discontinue study treatment due to LCE or AE at Month 10

Such patients will be referred to as "must be trimmed patients." For the remaining patients, if they have Month 9 and/or Month 10 BCVA assessments, they will be considered "completers"; if they have missing Month 9 and Month 10 assessments, the missing data will be considered missing at random, and these patients will be removed from the analysis.

The inferential statistics (i.e., 95% 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 algorithm can be stated in the following four steps:

1. Remove patients whose missing 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 (i.e., a pre-specified fraction for fixed trimming) from both treatment arms

   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 - b' X for each patient, for which Y is the change in BCVA score averaged over Month 9 and Month 10, X is the matrix for the covariates—baseline BCVA score (continuous) and the baseline BCVA score (≤65 letters vs. ≥66 letters) and number of anti-VEGF-intravitreal injections (≤3 vs. ≥4), and b 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-trimming fraction)*100% in each group will be used for the analysis specified in Step 3.

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 on each permuted data to construct a reference distribution for confidence interval estimation for the difference in trimmed mean.

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.

The percentage of patients to be trimmed will be based on an evaluation of percentage of patients meeting the trimming criteria by Month 9 rounded up to the nearest 5% to avoid many permutation tests from reverting to an adaptive approach. The analysis will be used to assess the difference in BCVA between two treatments excluding the true or assumed worst outcomes. Sensitivity analyses with different choices of trimming percentage may also be conducted.

- Change from baseline in BCVA score through Month 10 analyzed with an ANCOVA model:

  The ANCOVA model will include the categorical covariates of treatment group, baseline BCVA score (continuous), and the randomization stratification factors as fixed effects. Separate models will be fit for each pairwise comparison and each study visit. Missing BCVA data, prior to or at Month 10 for each patient, will be imputed using the LOCF approach.

  BCVA assessments will be censored after the time of rescue intravitreal anti-VEGF injection in the study eye and after the time of explant. These assessments after initiation of rescue treatment will be imputed using the LOCF approach.

- Descriptive summaries and figures will be provided for change from baseline in BCVA over time through Month 10 for patients treated after IFU Version 10. Observed data will be used. BCVA assessments will be censored after the time of rescue intravitreal anti-VEGF injection in the study eye and after the time of explant.

In addition, a descriptive summary for change from baseline in BCVA over time through the end of the study will be provided. This summary will include all observed data without censoring observations after use of rescue treatment or after explant.

Proportion of Patients Who Lose <15 Letters in BCVA score from Baseline

For proportion of patients who lose $<$15 letters in BCVA score from baseline to the average over Month 9 and Month 10, 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 factors using the Cochran-Mantel-Haenszel weights (Cochran 1954; Mantel and Haenszel 1959). 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). Data for patients who receive rescue treatment or undergo explantation prior to Month 9 will be censored for binary endpoints. For all other patients, the analysis will be based on the available data at each visit, with no imputation for missing data.

In addition, figures for proportion of patients who lose <15 letters in BCVA score from baseline over time will be provided.

Additional Efficacy Analyses Focused on BCVA Parameters

- The mean average change from baseline through Month 9 (AUC-like endpoint) in BCVA and 95% CIs will be generated for each treatment arm.
- Summary statistics and figures by treatment arm showing the proportion of patients losing <15 letters, <10 letters, <5 letters, and <0 letters over time through Month 10 will be provided.
- Change from baseline in BCVA over time through Month 10 measured under low luminance conditions will be summarized by treatment arm using descriptive statistics.

Data for patients who receive rescue treatment or undergo explantation prior to Month 9 will be censored. Missing data will not be imputed.

4.4.2.2 Anatomical Outcomes

The change in CFT (with and without inclusion of pigment epithelium thickness and its elevation in the foveal center, as assessed by the Reading Center) from baseline at Month 9 will be compared between each PDS arm and the intravitreal arm using the same analysis method (MMRM) and data handling rules that are used for the change from baseline in BCVA score at the average of Month 9 and Month 10. Comparisons between the Implant arms and the intravitreal arm will be made using a contrast at Month 9. Figures for adjusted mean change from baseline in CFT over time through Month 9 will be provided. Descriptive summaries for change from baseline in CFT through Month 9 will also be provided. Data for patients who receive rescue treatment or undergo explantation prior to Month 9 will be censored.

In addition, a descriptive summary for change from baseline in CFT over time through the end of the study will be provided. This summary will include all observed data without censoring observations after use of rescue treatment or after explant.

Changes from screening in total lesion area, area of CNV lesion, and CNV leakage over time through Month 9, as assessed by fluorescein angiography, as well as changes in CNV perfusion over time through Month 9, as assessed by OCT angiography will be summarized using descriptive statistics. Data for patients who receive rescue treatment or undergo explantation prior to Month 9 will be censored. Missing data will not be imputed.

4.4.2.3 Patient-Reported Outcomes (MacTSQ)

The MacTSQ was developed to provide a means of evaluating satisfaction with therapies for macular disease. The MacTSQ provides 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 descriptive statistics based on the observed data. 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 items in the subscale is missing.
- Subscale 2 (impact of treatment score): Set the subscale 2 value to missing if two or more 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 items are missing. If three or less items are missing, impute the missing item values based on the average of the other available items.

Data for patients who receive rescue treatment or undergo explantation prior to Month 9 will be censored.

4.4.2.4 Other Exploratory Efficacy Endpoints

Other exploratory efficacy endpoints listed in Section 2.2.5 will be summarized using descriptive statistics. Observed data will be used.

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Analyses were performed using a PK-PD model, and this model was used to run clinical trial simulations to inform Phase III clinical study design (RPDS EOP2 PMP, February 2018).

Individual and mean serum ranibizumab concentrations over time will be tabulated and plotted by refill number. The serum PK of ranibizumab will be characterized by estimating the AUC, C_{max}, t_{max}, $t_{1/2}$, and C_{trough} between dose intervals. Estimates for these parameters will be tabulated and summarized by descriptive statistics. Additional PK analyses may be conducted as appropriate.

4.6 SAFETY ANALYSES

The safety analyses will use the safety population as described in Section 4.1 and 4.1.2. Missing data will not be imputed.

Adverse events (AEs) are coded using the current MedDRA version. Rates will be provided for intravitreal patients and PDS patients by dose arm and pooled across PDS arms.

For safety analyses, unless otherwise specified, AEs after the start of study treatment (intravitreal injection or Implant) will be included in the analyses; AEs from patients who are explanted will be included up to a follow-up period of 90 days after explant; the post-explant ocular AEs considered related to PDS will also be included in the analyses regardless of the timing of the AE onset. To fully characterize these patients' safety, a listing will be provided for ocular AEs that occurred ≥90 days after explant.

Frequency tables including patient incidence rates will be provided for the following:

- Ocular AEs and SAEs (study and fellow eye)
- Non-ocular AEs and SAEs (study and fellow eye)
- Adverse events of special interest (study and fellow eye)
  - AEs resulting from medication errors
  - An AE considered to be sight threatening
  - Suspected transmission of an infectious agent by the study drug
  - AEs resulting from use error or from intentional misuse of the PDS
  - ADEs, that is, AEs that are considered to be related to the PDS and to the use of the PDS

- Adverse events potentially related to the PDS Implant or Implant procedures:
  - Vitreous hemorrhage
  - Endophthalmitis
  - Retinal detachment
  - Conjunctival retraction
  - Conjunctival erosion
  - Conjunctival bleb
  - Conjunctival filtering bleb leak
  - Hyphema
  - Cataract

For AEs potentially related to the PDS Implant or Implant procedures in the study eye, incidence tables will be generated using the following time windows relative to first dose or implant surgery:

- ≤ 1 month (up to the end of Month 1 visit window, 37 days)
- > 1 month
- during the entire study

In addition, ocular AEs and SAEs will be provided by causality as determined by the investigator.

Adverse events (AEs) potentially related to the PDS Implant or Implant procedures will be summarized separately for two subgroups of patients based on the IFU version in use at the time of their randomization (before IFU 10 vs. IFU 10 forward). There was a study pause to evaluate post-implantation vitreous hemorrhage and modifications were made beginning with Version 10 with the aim to reduce the risk of vitreous hemorrhages.

Non-ocular AEs and SAEs will be tabulated using the following time windows relative to first ranibizumab injection or device implant following randomization:

- Cumulative rates through 10-month follow-up for each patient
- Cumulative rates for through the end of the study (expected Month 38)

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

The number and percentage of patients with positive serum anti-drug antibodies (ADA) at baseline and post-baseline during the study period will be tabulated. Impact of positive serum ADA on efficacy and safety will be explored. A listing of patients with positive serum antibodies to ranibizumab will be provided.

4.6.1 Exposure of Study Medication

Patient exposure to ranibizumab will be summarized in the intravitreal arm and the PDS arms for the study eye.

4.6.2 Laboratory Data

Laboratory data will be collected at baseline only (see Section 4.3). This data can be used for interpretation of some adverse events, no general summary is planned.

4.6.3 Vital Signs

Summary statistics for worst change from baseline in vital signs will be tabulated. If an imbalance between treatment arms is observed, the summaries of the corresponding vital signs over the course of the study will be provided.

4.6.4 Ocular Assessments

Results of the following ocular assessments will be summarized by timepoint and by eye (study vs. fellow), as applicable, using descriptive summaries: intra-ocular pressure, fluorescein angiography, and fundus photography. Changes from baseline for selected ocular assessments will be tabulated. The presence of intra-ocular inflammation and vitreous hemorrhage, as determined from the slit-lamp examination, will be tabulated by grade (according to grading scales for flare/cells and vitreous hemorrhage density in the appendix of the study protocol). The presence of retinal break or detachment as determined from ophthalmoscopy will be tabulated.

4.7 MISSING DATA

Refer to the relevant sections above for further details.

4.8 INTERIM ANALYSES

Given the exploratory nature of this study, the Sponsor decided to conduct two interim efficacy analyses per allowance of the protocol: the first interim was performed after ~50% of patients completed the 6-month follow-up in October 2017 and the second interim was performed after ~70% of patients completed the 9-month follow-up in April 2018. The decision to conduct an optional interim analysis and the timing of the analysis was documented in the IMC Agreement prior to the conduct of the interim analysis.

The interim efficacy analyses were performed by members of the Sponsor's unmasked study team and were interpreted by the unmasked IMC and senior management personnel from the Sponsor. The details of the timing and scope of the interim analyses and the communication of the interim results were specified in the IMC Agreement, data analysis plan, and a statistical note to file (in the Sponsor's trial master file).

5. REFERENCES

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Pre-meeting Package (RO4893594)—Type B (End of Phase II) Meeting—Ranibizumab port delivery system (implant, ancillary devices, and ranibizumab). February 2018.

Appendix 1
Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, MULTICENTER, RANDOMIZED, ACTIVE TREATMENT–CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF THE RANIBIZUMAB PORT DELIVERY SYSTEM FOR SUSTAINED DELIVERY OF RANIBIZUMAB IN PATIENTS WITH SUBFOVEAL NEOVASCULAR AGE-RELATED MACULAR DEGENERATION**
PROTOCOL NUMBER:	GX28228
VERSION NUMBER:	8
EUDRACT NUMBER:	Not applicable
IND NUMBER:	113,552
TEST PRODUCT:	Ranibizumab Port Delivery System for Sustained Delivery of Ranibizumab (RO4893594)
PHASE:	II
INDICATION:	Subfoveal neovascular age-related macular degeneration
SPONSOR:	Genentech, Inc.

Objectives

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To evaluate the relative efficacy of 10-mg/mL, 40-mg/mL, and 100-mg/mL formulations of ranibizumab, delivered via the Implant, as measured by the time a patient first requires Implant refill according to protocol-defined refill criteria

The secondary efficacy objectives for this study are as follows:

- To evaluate and compare the relative efficacy of 10-mg/mL, 40-mg/mL, and 100-mg/mL formulations of ranibizumab, delivered via the Implant, to that of 10-mg/mL (0.5-mg dose) monthly ITV ranibizumab injections, as measured by the change in BCVA from baseline at Month 9
- To evaluate the efficacy of 10-mg/mL, 40-mg/mL, and 100-mg/mL formulations of ranibizumab, delivered via the Implant, with that of 10-mg/mL (0.5-mg dose) monthly ITV ranibizumab injections over time, as measured by the change in BCVA from baseline over time
- To evaluate the efficacy of 10-mg/mL, 40-mg/mL, and 100-mg/mL formulations of ranibizumab, delivered via the Implant, with that of 10-mg/mL (0.5-mg dose) monthly ITV ranibizumab injections over time, as measured by the change in central foveal thickness (CFT, defined as the retinal thickness in the center of the fovea) from baseline over time

- To evaluate the functionality of the Implant by assessing that there is no evidence of Implant clogging in more than 10% of patients in the Implant arms at Month 9.

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety of ranibizumab delivered via the Implant, compared with that of monthly ITV injection, as measured by ocular and non-ocular adverse events and serious adverse events
- To evaluate the safety of the Ranibizumab Port Delivery System (RPDS), as measured by "Prespecified RPDS-associated adverse events"
- To evaluate the proportion of patients with positive serum antibodies to ranibizumab

Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives for this study are as follows:

- To characterize the serum pharmacokinetics of ranibizumab in patients after the initial fill and subsequent refills in the Implant treatment arms

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the development of macular atrophy in all three Implant treatment arms relative to one another and to the monthly ITV arm
- To examine the impact of ranibizumab treatment on patient-reported treatment satisfaction as assessed by the Macular Degeneration Treatment Satisfaction Questionnaire (MacTSQ) at Months 1, 6, 9, and the final or early termination visit for patients who speak English or Spanish
- To explore time to subsequent Implant refills according to protocol-defined refill criteria
- To describe the number of times patients meet protocol-specified refill criteria
- To evaluate the proportion of patients in each Implant arm who first meet the protocol-defined refill criteria prior to and at Months 4, 5, and 6
- To evaluate the proportion of patients with an improvement of $\geq$ 15 letters in BCVA from baseline
- To evaluate the proportion of patients with a loss of $\geq$ 15 letters in BCVA from baseline over time
- To explore the utility of BCVA measured under low luminance as a predictor of treatment benefit over time
- To evaluate the changes in total lesion area, area of CNV lesion, and CNV leakage over time, as assessed by fluorescein angiography
- To explore the serum ranibizumab concentration data with a PK model in an attempt to infer the concentration–time pattern in the vitreous or aqueous humor and, if possible, derive information on the rate of ranibizumab release from the Implant
- To characterize ranibizumab aqueous humor concentration over time (optional)
- To characterize ranibizumab vitreous or aqueous humor concentration after Implant explantation (if applicable)
- To evaluate the potential association of circulating biomarkers with disease characteristics and response to ranibizumab (optional)
- To evaluate the relationship of 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 (optional)
- To evaluate the potential association of vitreous or aqueous humor biomarkers with disease characteristics and/or response to ranibizumab
- To evaluate the proportion of patients meeting lack of clinical efficacy criteria

- To evaluate the proportion of patients requiring explantation
- To evaluate the changes in CNV perfusion over time as assessed by OCT Angiography (at selected sites that have OCT angiography equipment)

Study Design

Description of Study

Study GX28228 is a Phase II, multicenter, dose-ranging, randomized, active treatment (monthly ITV injection)-controlled study to evaluate the efficacy, safety, and pharmacokinetics of ranibizumab delivered through the Implant using three ranibizumab formulation arms (10 mg/mL, 40 mg/mL, and 100 mg/mL) compared with the control arm (0.5-mg monthly ITV injections of 10-mg/mL formulation) in patients with subfoveal neovascular age-related macular degeneration (nAMD). The study will also evaluate the safety of the RPDS combination product. The study will include pre-screening, screening, and randomization visits followed by a treatment period. Treatment and safety assessment schedules are set.

Number of Patients

Approximately 220 patients at up to 60 sites in the United States will be randomized in a 3:3:3:2 ratio to four treatment arms (60 per each of three Implant treatment arms and 40 to the ITV injection arm) within an approximate 24-month period of time.

Target Population

Patients with subfoveal neovascularization secondary to age-related macular degeneration (AMD) diagnosed within 9 months and treated with ITV anti-VEGF agents will be enrolled in the study.

Inclusion Criteria

Patients must meet the following criteria for study entry:

General Inclusion Criteria

- Age $\geq$ 50 years
- Willingness and ability to provide signed informed consent and Health Insurance Portability and Accountability Act (HIPPA) authorization
- Willingness and ability to undertake all scheduled visits and assessments
- For sexually active women of childbearing potential, agreement to the use of an appropriate form of contraception (or abstinence) for the duration of the study. A woman is considered not to be of childbearing potential if she is postmenopausal or has undergone hysterectomy and/or bilateral oophorectomy.

  For women who are not postmenopausal ($\geq$ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 30 days after the last dose of study treatment

  Abstinence is only acceptable if it is in line with 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.
- Sexually active men are recommended to use a barrier contraceptive method (condom), even if they have been surgically sterilized, for the duration of the treatment period and for at least 30 days after the last dose of study treatment.

Appendix 1
Protocol Synopsis (cont.)

Ocular Inclusion Criteria (Study Eye)

- Newly diagnosed with nAMD within 9 months prior to screening visit
- Patient must have received at least 2 prior anti-VEGF injections (including ranibizumab, bevacizumab, or aflibercept). However, the most recent anti-VEGF injection must have been ranibizumab and must have occurred at least 7 days prior to the screening visit.
- Demonstrated response to prior ITV anti-VEGF treatment, as evidenced by the following:

  Decrease in CFT of >50 μm since commencing ITV anti-VEGF treatment

  OR

  Stable or improved BCVA since commencing ITV anti-VEGF treatment
- BCVA using ETDRS charts of 20/20-20/200 Snellen equivalent
- All subtypes of nAMD choroidal neovascularization (CNV) lesions are permissible (i.e., classic CNV, occult CNV, or with some classic CNV component, or retinal angiomatous proliferation lesions).

  Active primary CNV lesions at the time of diagnosis of nAMD must be subfoveal or juxtafoveal with a subfoveal component related to the CNV activity (such as subretinal hemorrhage, subretinal fluid, or retinal pigment epithelium [RPE] detachment)

Ocular Inclusion Criteria for Pre-Screening (Study Eye) (If Applicable)

- Treatment naïve nAMD patients
- BCVA using ETDRS charts of 20/20 to 20/200 Snellen equivalent
- All subtypes of nAMD choroidal neovascularization (CNV) lesions are permissible (i.e., classic CNV, occult CNV, or with some classic CNV component, or retinal angiomatous proliferation lesions).

  Active primary CNV lesions must be subfoveal or juxtafoveal with a subfoveal component related to the CNV activity (such as subretinal hemorrhage, subretinal fluid, or RPE detachment)

Ocular Inclusion Criteria for Run-In (Study Eye) (If Applicable)

- Previous treatment with a single anti-VEGF ITV injection or no more than eight anti-VEGF ITV injections, with aflibercept or bevacizumab being the most recent injection
- BCVA using ETDRS charts of 20/20 to 20/200 Snellen equivalent
- All subtypes of nAMD CNV lesions are permissible (i.e., classic CNV, occult CNV, or with some classic CNV component or retinal angiomatous proliferation lesions)

  Active primary CNV lesions at the time of diagnosis of nAMD must be subfoveal or juxtafoveal with a subfoveal component related to the CNV activity (such as subretinal hemorrhage, subretinal fluid, or RPE detachment)

<u>Exclusion Criteria</u>

Patients who meet any of the following criteria will be excluded from study entry:

Prior Ocular Treatment

- Treatment with ITV anti-VEGF agents other than ranibizumab within 1 month prior to the randomization visit in either eye
- History of vitrectomy surgery, submacular surgery, or other surgical intervention for AMD in the study eye
- Prior treatment with Visudyne®, external-beam radiation therapy, or transpupillary thermotherapy in the study eye
- Previous treatment with ITV corticosteroid injection or device implantation in the study eye
- Previous focal laser photocoagulation used for AMD treatment in the study eye

Appendix 1
Protocol Synopsis (cont.)

- Prior participation in a clinical trial involving anti-angiogenic drugs, other than ranibizumab, in either eye within 2 months prior to the randomization visit
- Treatment with Visudyne® in the fellow eye $<$ 7 days preceding screening visit

CNV Lesion Characteristics

- Subretinal hemorrhage in the study eye that involves the center of the fovea, if the size of the hemorrhage is either $>$50% of the total area of the lesion or $>$ 1 disc area (2.54 mm^2) in size at screening
- Subfoveal fibrosis or atrophy in the study eye
- CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia

Concurrent Ocular Conditions

- BCVA using ETDRS charts lower than 20/200 Snellen equivalent in the fellow eye
- Retinal pigment epithelial tear involving the macula in the study eye
- Any concurrent intraocular condition in the study eye (e.g., cataract, glaucoma, or diabetic retinopathy) that, in the opinion of the investigator, 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) in the study eye
- History of vitreous hemorrhage in the study eye within 3 months prior to the randomization visit
- History of rhegmatogenous retinal detachment or macular hole (Stage 3 or 4) in the study eye
- History of idiopathic or autoimmune-associated uveitis in either eye
- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye
- Aphakia or absence of the posterior capsule in the study eye

  Previous violation of the posterior capsule break in the study eye is also excluded unless it occurred as a result of yttrium aluminium garnet laser posterior capsulotomy in association with prior, posterior chamber intraocular lens implantation.
- Spherical equivalent of the refractive error in the study eye demonstrating more than 8 diopters of myopia
- For patients who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye does not exceed 8 diopters of myopia
- Intraocular surgery (including cataract surgery) in the study eye within 3 months preceding the randomization visit
- Uncontrolled ocular hypertension or glaucoma in the study eye (defined as intraocular pressure [IOP] $>$25 mmHg or a Cup to Disc ratio $>$0.8, despite treatment with anti-glaucoma medication) and any such condition for which the investigator feels may require a glaucoma filtering surgery while in the study
- History of glaucoma-filtering surgery in the study eye, tube shunts, or microinvasive glaucoma surgery in the study eye
- History of corneal transplant in the study eye

Concurrent Systemic Conditions

- Uncontrolled blood pressure (defined as systolic $>$ 155 mmHg and/or diastolic $>$ 95 mmHg, based on the average of 3 readings taken with the patient in a resting state [i.e., supine or sitting, but consistent across readings] over a period of up to 15 minutes at screening)

If the average of 3 readings exceeds these values, patient's blood pressure must to be controlled by antihypertensive medication. The patient can become eligible for rescreening if medication is taken continuously for at least 30 days prior to the randomization visit.

- Uncontrolled atrial fibrillation within 3 months of informed consent
- History of stroke within the last 3 months prior to informed consent
- History of myocardial infarction within the last 3 months prior to informed consent
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of ranibizumab or placement of the Implant, that might affect interpretation of the results of the study or renders the patient at high risk of treatment complications
- Current treatment for any active systemic infection
- Use of any systemic anti-VEGF agents
- Use of oral corticosteroids (prednisone $>$10mg/day or equivalent)
- Use of anticoagulants, antiplatelets (other than aspirin), or medications known to exert similar effects at the time of study entry for a pre-existing condition. Oral anticoagulants include vitamin K antagonists (e.g. warfarin), direct factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban, fondaparinux) and direct thrombin inhibitors (e.g., dabigatran). Antiplatelet therapies include clopidogrel, prasugrel, dipyridamole, ticagrelor and ticlodipine.
- Bleeding disorders, including platelet disorders, acquired or hereditary coagulations disorders, and acquired or hereditary vascular disorders.
- Active malignancy 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.
- History of allergy to fluorescein, not amenable to treatment
- Inability to obtain fundus photographs, fluorescein angiograms, fundus autofluorescence, or spectral domain optical coherence tomography (SD-OCT) images of sufficient quality to be analyzed and graded by the central reading center
- Inability to comply with study or follow-up procedures
- 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
- Intolerance or hypersensitivity to topical anesthetics, mydriatic medications, any of the excipients in ranibizumab, fluorescein, or components of the Implant
- Requirement for continuous use of any medications or treatments indicated in the "Prohibited Therapy" section.
- Women who are pregnant or lactating or intending to become pregnant during the study
- Women who are of childbearing potential, including those who have had tubal ligation, must have a negative serum pregnancy test result within 21 days prior to Day 1. A woman is considered not to be of childbearing potential if she is postmenopausal or has undergone hysterectomy and/or bilateral oophorectomy.
- No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients

Length of Study

The estimated study duration is 38 months.

Patients randomized to the Implant treatment arms will have the Implant (pre-filled with ranibizumab) surgically inserted in the study eye at their Day 1 visit, after which they will be evaluated monthly for the need for an Implant refill, based upon protocol-specified refill criteria, until the Sponsor decides, based on the primary analysis results, to either terminate the study and discontinue study treatment, or offer patients entry into the RPDS *Extension* Study. The duration of their participation in the study is expected to last approximately 13–38 months dependent on the date of their randomization to the study.

Patients randomized to the ITV injection treatment arm (control) will be treated monthly with ITV injections of ranibizumab *until the Sponsor decides, based on the primary analysis results, to either terminate the study and discontinue study treatment, or offer patients entry into the RPDS Extension Study.* The duration of their participation in the study is expected to last approximately *13–38* months dependent on the date of their randomization to the study.

End of Study

The end of the study is defined as the date when the last patient, last study visit occurs.

Outcome Measures

Efficacy Outcome Measures

The primary efficacy outcome measure for this study is the time until a patient first requires the Implant refill according to protocol-defined refill criteria.

The secondary efficacy outcome measures for this study are as follows:

- Change in BCVA from baseline at Month 9
- Average change in BCVA from baseline over time
- Change in BCVA from baseline over time
- Change in CFT over time, as assessed on SD-OCT by the Central Reading Center
- Occurrence of implant clogging

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence of adverse events of Special Interest: Adverse events associated with ranibizumab, the Implant, implant-associated procedures, and/or ancillary devices
- Incidence of "Prespecified RPDS-associated adverse events"
- Incidence of ocular and non-ocular adverse events and serious adverse events
- Incidence of positive serum antibodies to ranibizumab

Pharmacokinetic Outcome Measures

The PK outcome measures related to ranibizumab serum concentration-time data following the Implant insertion and refills are as follows:

- Observed maximum serum concentrations (C_{max}) and selected post dose serum concentrations after Implant insertion and all subsequent refills
- Additional estimated PK parameter values including AUC, t_{max}, and $t_{1/2}$ after Implant insertion and all subsequent refills
- Observed serum concentrations (C_t) over time from monthly serum sampling when no refills are administered
- Observed trough serum concentrations (C_{trough}) prior to refills

In addition, optional anterior chamber (aqueous humor) will be collected to assess ocular drug concentration.

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Treatment emergent macular atrophy in all treatment arms
- The MacTSQ score at randomization and at Months 1, 6, 9, and the final or early termination visit for patients who speak English or Spanish
- Time to subsequent Implant refills according to protocol-defined refill criteria
- Number of times a patient meets protocol-specified refill criteria
- Proportion of patients in each Implant arm who first meet the protocol-defined refill criteria prior to and at Months 4, 5,and 6
- Proportion of patients with an improvement of BCVA from baseline of $\geq$15 letters over time
- Proportion of patients losing $\geq$15 letters in BCVA from baseline over time
- Change in BCVA from baseline over time measured under low luminance conditions
- Changes from screening in total lesion area, area of CNV lesion, and CNV leakage over time, as assessed by fluorescein angiography
- Proportion of patients meeting lack of clinical efficacy criteria
- Proportion of patients requiring explantation
- Changes in CNV perfusion over time, as assessed by OCT Angiography

In addition, vitreous samples from the Refill Needle (if applicable), optional aqueous humor samples, and optional serum and plasma samples may be collected to assess the relationship between biomarkers and the disease characteristics and/or response to treatment with ranibizumab. Optional whole blood samples will be collected for DNA extraction (genetic analysis) to assess the relationship between genetic variants and the disease characteristics and/or response to treatment with ranibizumab.

In addition, vitreous or aqueous humor samples before Implant explantation, and optional aqueous humor samples prior to or immediately following one or more refills and at the Day 7 safety visit post refill will be collected to characterize ranibizumab vitreous and aqueous humor concentration.

Investigational Medicinal Products

Test Product (Investigational Drug)

The Implant initially filled and then refilled as per protocol specified refill criteria, with either 10-mg/mL, 40-mg/mL, or 100-mg/mL ranibizumab formulations.

Non-Investigational Medicinal Products

Comparator

Ranibizumab 0.5-mg monthly intravitreal (ITV) injections of 10-mg/mL formulation

Statistical Methods

Detailed specifications of the statistical methods will be described in the statistical analysis plan (SAP).

Primary Analysis

The primary endpoint for this analysis will be time to first meeting refill criteria. The primary analyses will be based on data as of 9 months after last patient's entry into the study. For patients without any refills prior to or on the cut-off date of 9 months after LPI, the time of refill will be censored. The censoring date will be defined as the date of a patient's last visit before the cut-off date of 9 months after LPI, or the date when the patient discontinues from the study, whichever occurs first.

The primary analysis population for efficacy is the modified intent-to-treat population defined as all randomized patients who were randomly assigned to study treatment receive study treatment. Patients will be summarized by treatment arm and analyzed according to the treatment actually received and not according to the treatment they were randomized to receive, in the event of a discrepancy.

Appendix 1
Protocol Synopsis (cont.)

To support the dose level selection among the Implant groups, the primary analysis for TTFR will include the following pair-wise group comparisons, each with a stratified log-rank test at a one-sided significance level of 15%. The stratification factors to be included are baseline BCVA score (≤65 letters vs. ≥66 letters) and number of anti-VEGF ITV injections (≤3 vs. ≥4).

- Implant with 100 mg/mL versus Implant with 10 mg/mL
- Implant with 100 mg/mL versus Implant with 40 mg/mL
- Implant with 40 mg/mL versus Implant with 10 mg/mL

In addition, the HR for each pair-wise comparison of the treatment arms will be estimated using a Cox proportional hazards regression model stratified by baseline BCVA score (≤65 letters vs. ≥66 letters) and number of prior anti-VEGF ITV injections (≤3 vs. ≥4) with main effects for treatment. Estimated HRs for each pair-wise comparison will be presented with the corresponding 80% CIs.

Kaplan–Meier plots will be provided showing TTFR by implant group. Median time to first meeting refill criteria will be calculated for each treatment arm with the Kaplan Meier method, and the corresponding 80% confidence intervals will also be reported.

- Moreover, for each treatment group, percentage of patients not meeting the protocol-defined first refill criteria by Months 4, 5, 6, 7, 8, and 9, derived from Kaplan-Meier estimates will be provided.

Determination of Sample Size

This study is exploratory in nature and designed to estimate the time to first refill (TTFR) for each of the RPDS treatment arms (10 mg/mL, 40 mg/mL, and 100 mg/mL) enrolling 60 patients in each of the RPDS treatment arms. The sample size of approximately 220 randomized patients will be adequate to evaluate the primary objective of the study. PK/PD modeling and simulation was performed to inform key assumptions used in sample size calculation. Given the simulation results, the HR for comparing the 100-mg/mL arm with the 10-mg/mL arm was estimated to be 0.66 for TTFR. Assuming this HR, a total of at least 125 events from all three Implant groups is expected at the primary analysis time (approximately 85 events in the 10-mg/mL group and a higher dose group). With 85 events, this study will have approximately 80% power to detect an HR=0.66 between the two Implant arms using a log-rank test at a one-sided significance level of 15%. No multiplicity adjustment is planned for this Phase II study.

Forty patients in the ITV arm are considered sufficient to compare each device arm versus the ITV arm in change in BCVA from baseline through Month 9 (assuming an estimated SD=10 letters, a two-sided 80% CI will extend approximately 2.62 letters from the observed mean).

Appendix 2
Schedule of Assessments

Schedule of Assessments for Implant Arms: Screening, Randomization, Day 1, Month 1 through Month 9, Month X, Safety Visits, and Final/Early Termination Visits

Assessment	Screen [a] ≥7 days after RBZ tx	Rand [b] ≥28 and ≤37 days after RBZ tx	Day				Month									Month X Visit [d]	Safety Visit [c]	Final/ ET[e]
			1 [b]	2 [c]	7 [c]	14 [c]	1	2	3	4	5	6	7	8	9			
Window (Days)				±0	±2	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	See footnote c	See footnote e
Written informed consent	x																	
Review of inclusion and exclusion criteria	x	x																
Medical and surgical history, tobacco and alcohol use	x																	
Demographic Information	x																	
Physical Examination	x														x			x
MacTSQ [f]		x					x					x			x			x

Appendix 2
Schedule of Assessments (cont.)

Assessment	Screen [a] ≥7 days after RBZ tx	Rand [b] ≥28 and ≤37 days after RBZ tx	Day				Month									Month X Visit [d]	Safety Visit [c]	Final/ ET[e]
			1 [b]	2 [c]	7 [c]	14 [c]	1	2	3	4	5	6	7	8	9			
Window (Days)				±0	±2	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	See footnote c	See footnote e
Site to contact IxRS (as applicable) [g]	x	x	x				x	x	x	x	x	x	x	x	x	x	x	x
Vital signs [h]	x	x	x				x	x	x	x	x	x	x	x	x	x	x	x
Central laboratory samples (hematology, coagulation, serum chemistry, and urinalysis) [i]	x																	
Serum pregnancy sample [j]	x						If urine pregnancy test is positive, collect serum pregnancy sample and do not perform study treatment until the final results are available.											x
Urine pregnancy test [k]			x[l]				If a patient meets criteria for Implant refill, collect urine pregnancy test prior to the refill. If urine pregnancy test is positive, collect serum pregnancy sample and do not perform study treatment until the final results are available.											
Serum PK sample for ranibizumab concentration																	x[m]	

Appendix 2
Schedule of Assessments (cont.)

Assessment	Screen [a] ≥7 days after RBZ tx	Rand [b] ≥28 and ≤37 days after RBZ tx	Day				Month									Month X Visit [d]	Safety Visit [c]	Final/ ET[e]
			1 [b]	2 [c]	7 [c]	14 [c]	1	2	3	4	5	6	7	8	9			
Window (Days)				±0	±2	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	See footnote c	See footnote e
Serum PK sample for ranibizumab concentration PRIOR to treatment [n]		x					Collect serum PK sample for ranibizumab concentration at each monthly visit PRIOR to the treatment, even if treatment is not subsequently given.											x
Serum PK sample for ranibizumab concentration POST treatment [o]			x[p]	x	x	x	If Implant refill is performed, collect PK sample 1 to 2 days after refill, and 7 days after refill										x	
Serum anti-ranibizumab antibody sample [q]		x				x	x		x			x			x			x
Optional whole blood for DNA (RCR Sample)		x																
Optional serum sample for candidate biomarkers		x								x					x			

Appendix 2
Schedule of Assessments (cont.)

Assessment	Screen [a] ≥7 days after RBZ tx	Rand [b] ≥28 and ≤37 days after RBZ tx	Day				Month									Month X Visit [d]	Safety Visit [c]	Final/ ET[e]
			1 [b]	2 [c]	7 [c]	14 [c]	1	2	3	4	5	6	7	8	9			
Window (Days)				±0	±2	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	See footnote c	See footnote e
Optional plasma (EDTA) sample for candidate biomarkers		x								x					x			
Optional aqueous humor sample [r]							Obtain prior to or immediately following one or more refills and at the safety visit 7 days post refill											
BCVA testing (starting at 4 m)	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Low luminance BCVA testing [s]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Visual Field testing (Humphrey 24-2)[t]		x[u]													x			x
Axial Length Measurement (ultrasound or optical biometry)[v]		x[u]																
Intraocular pressure (IOP) [w]	x	x	x [x]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Slit-lamp examination	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 2
Schedule of Assessments (cont.)

Assessment	Screen [a] ≥7 days after RBZ tx	Rand [b] ≥28 and ≤37 days after RBZ tx	Day				Month									Month X Visit [d]	Safety Visit [c]	Final/ ET[e]
			1 [b]	2 [c]	7 [c]	14 [c]	1	2	3	4	5	6	7	8	9			
Window (Days)				±0	±2	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	See footnote c	See footnote e
Dilated binocular indirect ophthalmoscopy [y]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Historical OCT images collection [z]	x																	
SD-OCT [w, aa]	x	x			x		x	x	x	x	x	x	x	x	x	x		x
Fundus photography [w, aa]	x														x			x
Fluorescein angiography [w, aa]	x									x		x			x			x
Fundus Autofluorescence [w, aa]	x									x					x			x
OCT Angiography (at selected sites) [ab]		x			x	x	x	x	x	x	x	x	x	x	x	x		x

Appendix 2
Schedule of Assessments (cont.)

Assessment	Screen [a] ≥7 days after RBZ tx	Rand [b] ≥28 and ≤37 days after RBZ tx	Day				Month									Month X Visit [d]	Safety Visit [c]	Final/ ET[e]
			1 [b]	2 [c]	7 [c]	14 [c]	1	2	3	4	5	6	7	8	9			
Window (Days)				±0	±2	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	See footnote c	See footnote e
External Photo - study eye only (High magnification Implant and conjunctiva, scleral surface)				x	x		x	x	x	x	x	x	x	x	x	x		x
Lens Photo (fundus reflex photo)	x			x	x		x	x	x	x	x	x	x	x	x	x		x
Implant Photo - study eye only (High magnification Implant in eye, through dilated pupil) [ac]				x	x		x	x	x	x	x	x	x	x	x	x		x
Pre-study treatment antimicrobials (as applicable) [ad]			x				x	x	x	x	x	x	x	x	x	x		

Appendix 2
Schedule of Assessments (cont.)

Assessment	Screen [a] ≥7 days after RBZ tx	Rand [b] ≥28 and ≤37 days after RBZ tx	Day				Month									Month X Visit [d]	Safety Visit [c]	Final/ ET[e]
			1 [b]	2 [c]	7 [c]	14 [c]	1	2	3	4	5	6	7	8	9			
Window (Days)				±0	±2	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	See footnote c	See footnote e
Post-study treatment antimicrobials [ad]			x				x	x	x	x	x	x	x	x	x	x		
Video of Implant insertion and explantation and, if feasible, video of refill [ae]			x				Video of Implant insertion and explantation and, if feasible, video of refill (if applicable)											
Ranibizumab filled Implant insertion			x															
Implant refill with ranibizumab [af]							Refill if refill criteria are met (see Section 3.1.1)											
Post-treatment finger counting (as applicable) [ag]							As applicable per treatment											
Post-treatment IOP measurement			x[ah]															

Appendix 2
Schedule of Assessments (cont.)

Assessment	Screen [a] ≥7 days after RBZ tx	Rand [b] ≥28 and ≤37 days after RBZ tx	Day				Month									Month X Visit [d]	Safety Visit [c]	Final/ ET [e]
			1 [b]	2 [c]	7 [c]	14 [c]	1	2	3	4	5	6	7	8	9			
Window (Days)				±0	±2	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	See footnote c	See footnote e
Refill Needle collection after Implant refill for vitreous biomarkers [ai]							Collect Refill Needle with its content if Implant refill is performed, if applicable											
Implant insertion evaluation [aj]			x															
Concomitant medications [ak]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse event [al]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures or additional assessments [am]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Follow-up call (if applicable) [an]			x				As applicable per treatment									x		
Eye fluid sample collection [ao]							Collect vitreous or aqueous humor sample at the start of explantation for patients undergoing an explantation procedure											

Appendix 2
Schedule of Assessments (cont.)

AMD = age-related macular degeneration; AREDS = Age-Related Eye Disease Study; BCVA = best corrected visual acuity; ET = end of treatment; IOP = intraocular pressure; ITV = intravitreal; IxRS = interactive Voice/Web response system; MacTSQ = Macular Degeneration Treatment Satisfaction Questionnaire; NA = not applicable; PK = pharmacokinetic; Rand = randomization; RBZ = ranibizumab; SA = safety visit; SD-OCT = spectral domain optical coherence tomography; tx = treatment.

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] Screening cannot occur earlier than 7 days after the last standard-of-care of ITV ranibizumab treatment in the study eye.

[b] Patients randomized to Implant treatment arms will be scheduled at the conclusion of their randomization visit for their Implant insertion surgery (Day 1) on such a date that no less than 28 days and no more than 37 days have lapsed between the surgery and their the last standard-of-care ITV ranibizumab treatment in the study eye, unless a patient needs more time to interrupt aspirin or NSAID usage 7 days before Day 1 (see Section 4.3.2.3). For these patients, Day 1 study treatment visit must occur no later than 45 days after the patient's last ITV ranibizumab treatment. In the case of a pause of enrollment and implant insertion surgeries, patients who have been randomized but have not yet received the study drug must repeat all randomization assessments (except for the randomization transaction in IxRS) after enrollment and implant insertion surgeries recommence, before receiving the study drug.

[c] Implant treatment arms safety assessment visits will be scheduled on Days 2, 7 (± 2 days), and 14 (± 2 days) after Implant insertion; 7 (± 2) days after each Implant refill; 1 and 7 (± 2) days post-explantation if a patient is continuously followed in the study (prior to study Last Patient In Month 9 visit); and 1, 7(±2), 30 (± 7), and 60 (± 7) days post-explantation if a patient is exiting the study, after which a patient will be scheduled for the early termination visit 30 (+ 7) days later.

[d] After completion of the Month 9 visit, the Implant arms study patients will continue monthly study visits according to Month X (i.e., Month 10, Month 11, Month 12, etc.) schedule of assessments until the Sponsor decides, based on the primary analysis results, to either terminate the study and discontinue study treatment, or offer patients entry into the RPDS *Extension* Study.

[e] For patients who are completing the study or withdrawing early, perform 90 (+7) days after the Implant explantation.

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

[g] Refer to the IxRS Manual for further details.

[h] Vital signs consist of blood pressure and pulse measurement. Height and weight will also be performed at the screening visit. On the visits when a patient receives treatment, including Day 1 visit, perform vital signs measurements pre-treatment. On the day of implant insertion and explantation of procedure, blood pressure must also be recorded during surgery and upon completion of the surgery.

[i] 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 4.6.6 or the separate laboratory manual.

Appendix 2
Schedule of Assessments (cont.)

[j] Perform urine pregnancy test prior to fluorescein angiography (if applicable) for women of childbearing potential, including those who have had tubal ligation. If the urine pregnancy test is positive, collect serum pregnancy sample and do not perform fluorescein angiography or study treatment until the final results are available. If the serum pregnancy test is positive, do not administer the study treatment.

[k] Collect and perform locally the urine pregnancy test prior to fluorescein angiography and/or study treatment (if applicable) for women of childbearing potential, including those who have had tubal ligation. If urine pregnancy test is positive, collect serum pregnancy sample and do not perform study treatment until the final results are available. If the serum pregnancy test is positive, do not administer the study treatment.

[l] May be collected up to 1 day prior to day 1.

[m] Collect serum PK sample from Implant arms patients at each post explantation safety visit (see protocol Section 4.7.2 and Section 4.7.3).

[n] Collect serum PK sample for ranibizumab concentration from Implant treatment arms patients at the Randomization visit and then at each monthly visit PRIOR to the treatment, even if treatment is not subsequently given.

[o] Collect serum PK sample for ranibizumab concentration from Implant treatment arms patients ≥ 60 minutes post treatment on Day 1 visit (if possible) and then on Days 2, 7(±2 days), and 14 (±2 days) after Day 1 visit; afterwards collect serum PK sample 1 and 7 (±2) days after each refill. Collect a serum PK sample at the early termination visit if applicable. Note: for patients who are unable to visit the clinic for the PK sample collection 1 day after each Implant refill, provision will be made for this timepoint sample collection to be collected at their home. Alternatively, the sample may be collected 2 days after the refill. Training will be provided to site staff on how to perform this task. The sample will be sent to a central laboratory.

[p] Perform only if possible.

[q] Obtain serum anti-ranibizumab antibody sample from the Implant treatment arms patients prior to the study treatment and prior to fluorescein angiography (if applicable) on the Randomization visit, Visits Day 14, Month 1, 3, 6, and 9 and at the early termination visit if applicable.

[r] If a patient has consented to this optional sample collection, obtain the aqueous humor sample prior to or immediately following one or more refills and at the Day 7 safety visit post refill.

[s] Perform low luminance BCVA testing after standard BCVA testing.

[t] Perform only if you have the Humphrey Visual Field machine at your site. In addition to the listed timepoints, this testing will be performed any time the patient reports a new defect of the peripheral vision.

[u] If it cannot be performed during Randomization, this testing must be performed on a subsequent day but before Day 1.

[v] Perform only if you have ultrasound or optical biometry capability at your site.

[w] Perform pre-treatment.

[x] Should be performed in the surgical center using Tono-Pen tomometry prior to the Implant insertion surgery.

[y] Dilated ophthalmoscopy examinations will be performed for patients in the Implant treatment arms after Implant insertion in the study eye at the Day 1 visit, and then on Days 2, 7 (± 2 days), and 14 (± 2 days) after the Day 1 visit; afterward, perform dilated ophthalmoscopy examinations at each monthly visit to monitor the Implant and its release control element for visible clogging and other Implant problems.

Appendix 2
Schedule of Assessments (cont.)

[z] Historical OCT taken at the time of diagnosis of nAMD will also be required to determine patient's eligibility at the screening visit. If fluorescein angiograms were taken at the time of diagnosis of nAMD, they must be submitted to the reading center as well. If available, historical fluorescein angiograms will be evaluated by the reading center, but are not required to determine patient's eligibility. Refer to the Reading Center Manuals for details.

[aa] The central reading center will evaluate fundus photography, fluorescein angiograms, and SD-OCT taken at the screening visit for determination of a patient's eligibility, together with the historical OCT taken at the time of diagnosis of nAMD. Refer to the Reading Center Manual for details.

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

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

[ad] The pre-Implant insertion or explantation use of self-administered antimicrobials is required. The pre-Implant refill use of self-administered antimicrobials is per the investigator's discretion. The post-Implant insertion, explantation, or refill use of self-administered antimicrobials is required.

[ae] The video of the implant/explant procedure (if applicable) should be recorded. The video of the refill is optional.

[af] Initially fill the Implant with IxRS assigned kit of ranibizumab prior to its insertion into the study eye. Afterwards, starting at Month 1 visit, if refill criteria are met (see Section 3.1.1), refill the Implant with IxRS assigned ranibizumab kit.

[ag] Following each Implant refill, patients will have a 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 patients will remain at the clinic for approximately 40 minutes. If there are no safety concerns 40 ($\pm$ 10) minutes following treatment, the patient will be allowed to leave the clinic. If any safety concerns or immediate toxicity is noted, the patient will remain at the clinic and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event will be reported on the appropriate eCRF page.

[ah] Upon completion of the Implant insertion or explantation procedure, patients will have indirect ophthalmoscopy performed to monitor the Implant placement and to evaluate any potential Implant problems. Intraocular pressure will be checked for the study eye only by the treating physician by digital palpation. These assessments must be performed prior to placing a patch on the eye. If any safety concerns or immediate toxicity is 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 on the appropriate eCRF page.

[ai] Follow Refill Needle return instructions from the laboratory manual if Implant refill has been performed (if applicable).

[aj] 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 on the appropriate eCRF page.

[ak] Record any concomitant medications (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications, and pre-treatment and post-treatment medications, such as proparacaine, antimicrobials) 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.

Appendix 2
Schedule of Assessments (cont.)

[al] 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, medication wash-out, etc.) 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/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.

[am] 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.

[an] 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.

[ao] Aqueous humor or vitreous sample collection must be performed at the start of explantation for all patients undergoing an explantation procedure. The choice between aqueous humor collection or vitreous collection is per investigator's discretion (see Appendix 19).

Appendix 2
Schedule of Assessments (cont.)
Schedule of Assessments for ITV Arm: Screening, Randomization/Day 1, Month 1 through Month 9, Month X, and Final/Early Termination Visits

Assessment	Screen [a] ≥ 7 days after RBZ tx	Rand/ Day 1 [b] ≥28 and ≤37 days after RBZ tx	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month X visit [c]	Final/ ET [d]
Window (Days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Written informed consent	x												
Review of inclusion and exclusion criteria	x	x											
Medical and surgical history, tobacco and alcohol use	x												
Demographic Information	x												
Physical Examination	x										x		x
MacTSQ [e]		x	x					x			x		x
Site to contact IxRS (as applicable) [f]	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs [g]	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 2
Schedule of Assessments (cont.)

Assessment	Screen [a] ≥ 7 days after RBZ tx	Rand/ Day 1 [b] ≥ 28 and ≤ 37 days after RBZ tx	Month 1	2	3	4	5	6	7	8	9	Month X visit [c]	Final/ ET [d]
Window (Days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Central laboratory samples (hematology, coagulation, serum chemistry, and urinalysis) [h]	x												
Serum PK sample for ranibizumab [i]		x	x		x			x			x		x
Serum anti-ranibizumab antibody sample [i]		x	x		x			x			x		x
Serum pregnancy sample [j]	x		If urine pregnancy test is positive, collect serum pregnancy sample and do not perform study treatment until the final results are available										x
Urine pregnancy test [k]		x	Collect urine pregnancy test prior to treatment. If urine pregnancy test is positive, collect serum pregnancy sample and do not perform study treatment until the final results are available										
BCVA testing (starting at 4 m)	x	x	x	x	x	x	x	x	x	x	x	x	x
Low luminance BCVA testing [l]	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 2
Schedule of Assessments (cont.)

Assessment	Screen [a] ≥ 7 days after RBZ tx	Rand/ Day 1 [b] ≥28 and ≤37 days after RBZ tx	Month 1	2	3	4	5	6	7	8	9	Month X visit [c]	Final/ ET [d]
Window (Days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Intraocular pressure (IOP) [m]	x	x	x	x	x	x	x	x	x	x	x	x	x
Slit-lamp examination	x	x	x	x	x	x	x	x	x	x	x	x	x
Dilated binocular indirect ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x	x
Historical fundus images collection [n]	x												
SD-OCT [m,o]	x	x	x	x	x	x	x	x	x	x	x	x	x
Fundus photography [m,o]	x										x		x
Fluorescein angiography [m,o]	x					x		x			x		x
Fundus autofluorescence [m,o]	x					x					x		x
OCT Angiography [p]		x	x	x	x	x	x	x	x	x	x	x	x
Lens Photo (fundus reflex photos)	x					x					x		x
Optional whole blood for DNA (RCR Sample)		x											

Appendix 2
Schedule of Assessments (cont.)

Assessment	Screen [a] ≥ 7 days after RBZ tx	Rand/ Day 1 [b] ≥ 28 and ≤ 37 days after RBZ tx	Month 1	2	3	4	5	6	7	8	9	Month X visit [c]	Final/ ET [d]
Window (Days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Optional serum sample for candidate biomarkers		x				x					x		
Optional plasma (EDTA) sample for candidate biomarkers		x				x					x		
Pre- and post- study treatment antimicrobials (as applicable) [q]		x	x	x	x	x	x	x	x	x	x	x	
Administration of ranibizumab to ITV injection arm		x	x	x	x	x	x	x	x	x	x	x	
Post-treatment finger counting (as applicable) [r]		x	x	x	x	x	x	x	x	x	x	x	
Concomitant medications [s]	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse event [t]		x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [u]		x	x	x	x	x	x	x	x	x	x	x	x

Appendix 2
Schedule of Assessments (cont.)

Assessment	Screen [a] ≥ 7 days after RBZ tx	Rand/ Day 1 [b] ≥ 28 and ≤ 37 days after RBZ tx	Month 1	2	3	4	5	6	7	8	9	Month X visit [c]	Final/ ET [d]
Window (Days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Follow-up call (if applicable) [v]		x	x	x	x	x	x	x	x	x	x	x	

AMD = age-related macular degeneration; AREDS = Age-Related Eye Disease Study; BCVA = best corrected visual acuity; ET = end of treatment; IOP = intraocular pressure; ITV = intravitreal; IxRS = interactive Voice/Web response system; MacTSQ = Macular Degeneration Treatment Satisfaction Questionnaire; NA = not applicable; PK = pharmacokinetic; Rand = randomization; RBZ = ranibizumab; SA = safety visit; SD-OCT = spectral domain optical coherence tomography; tx = treatment.

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] Screening cannot occur earlier than 7 days after the last standard-of-care of ITV ranibizumab treatment in the study eye.

[b] Patients randomized to the ITV injection treatment arm may receive their first study treatment (Day 1) at the conclusion of the randomization visit or later; however no less than 28 days and no more than 37 days should have lapsed between the first study treatment and their last standard-of-care ITV ranibizumab treatment in the study eye.

[c] After completion of the Month 9 visit, the ITV *arm* patients will continue monthly study visits according to Month X (i.e., Month 10, Month 11, Month 12, etc.) schedule of assessments *until the Sponsor decides, based on the primary analysis results, to either terminate the study and discontinue study treatment, or offer patients entry into the RPDS Extension Study.*

[d] Patients final study visit or early termination visit will be scheduled 30 (+7) days following the last study treatment.

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

[f] Refer to the IxRS Manual for details.

[g] Vital signs consist of blood pressure and pulse measurement. Height and weight will also be performed at the screening visit. On the visits when a patient receives treatment, perform vital signs measurements pre-treatment.

Appendix 2
Schedule of Assessments (cont.)

[h] Obtain from all study patients pre-treatment and prior to fluorescein angiography, if applicable, except early termination (no time requirement). For a description of the laboratory assessments to be performed, see Section 4.6.6 or the separate laboratory manual.

i Obtain sample prior to the study treatment and prior to fluorescein angiography (if applicable).

[j] Collect serum pregnancy sample prior to fluorescein angiography (if applicable) for women of childbearing potential, including those who have had tubal ligation. If the serum pregnancy test is positive, do not administer the study treatment.

[k] Collect and perform locally the urine pregnancy test prior to fluorescein angiography and study treatment for women of childbearing potential, including those who have had tubal ligation. If urine pregnancy test is positive, collect serum pregnancy sample and do not perform study treatment until the final results are available. If the serum pregnancy test is positive, do not administer the study treatment.

[l] Perform low luminance BCVA testing after standard BCVA testing.

[m] Perform pre-treatment.

[n] Historical OCT taken at the time of diagnosis of nAMD will also be required to determine patient's eligibility at the screening visit. If fluorescein angiograms were taken at the time of diagnosis of nAMD, they must be submitted to the reading center as well. If available, historical fluorescein angiograms will be evaluated by the reading center, but are not required to determine patient's eligibility. Refer to the Reading Center Manuals for details.

[o] The central reading center will evaluate fundus photography, fluorescein angiograms, and SD-OCT taken at the screening visit for determination of a patient's eligibility, together with the historical OCT 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] The pre- and post-treatment use of self-administered antimicrobials for the ITV injection arm is per the investigator discretion.

[r] Following each ITV treatment with ranibizumab, patients will have a 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 patients will remain at the clinic for approximately 40 minutes. If there are no safety concerns 40 ($\pm$10) minutes following treatment, the patient will be allowed to leave the clinic. If any safety concerns or immediate toxicity is noted, the patient will remain at the clinic and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event will be reported on the appropriate eCRF page.

[s] Record any concomitant medications (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications, and pre-treatment and post-treatment medications, such as proparacaine, antimicrobials) 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.

Appendix 2
Schedule of Assessments (cont.)

[t] 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 etc.) 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 ranibizumab and ITV injections 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.

[u] Record all concurrent ocular procedures performed on the study or fellow eye.

[v] All study patients will be contacted 3 ($\pm$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 (if applicable).