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PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, VISUAL ASSESSOR–MASKED, ACTIVE-COMPARATOR STUDY OF THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF THE PORT DELIVERY SYSTEM WITH RANIBIZUMAB IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION**
PROTOCOL NUMBER:	GR40548
VERSION NUMBER:	4
EUDRACT NUMBER:	Not applicable
IND NUMBER:	113,552
NCT NUMBER	NCT03677934
TEST PRODUCT:	Port Delivery System with ranibizumab
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd.
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
16-Jun-2020 23:16:37	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
3	18 December 2019
2	29 July 2019
1	31 May 2018

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol GR40548 (Archway) has been amended in response to the COVID-19 public health emergency to provide flexibility due to extenuating circumstances.

- Several alternate final study visit scenarios have been provided to allow patients to remain in the study and receive treatment at regular intervals until consenting patients can enroll into an open-label safety extension study per-protocol (Section 3.1, Figure 1, Appendices 1 and 2).
- Schedules of activities and assessment timepoints have been provided for these alternate final study visit scenarios (Appendix 1, Table 3 and Appendix 2, Table 3).

Additional changes to the protocol, along with a rationale for each change, are summarized below:

- Central subfield thickness (CST) has been defined further to describe which retinal layers are included in the measurement (average thickness of the central 1 mm circle of the ETDRS grid centered on the fovea measured between the internal limiting membrane and the Bruch's membrane) (Section 4.5.6).
- Instructions for use of self-administered antimicrobial and anti-inflammatory ophthalmic drops before and after the PDS implant insertion, implant refill-exchange procedure, and explantation have been added (Section 5.1.1 and Appendix 17).
- Rhegmatogenous retinal detachment and endophthalmitis have been added to the list of anticipated risks associated with the Port Delivery System with ranibizumab (PDS) implant and/or implant insertion procedure (Sections 5.1.3.5 and 5.1.3.6).
- Study treatment dose interruption criteria for local or systemic infection have been updated with the latest guidance (Section 5.1.5.2 , Table 4).
- Instructions on the management of conjunctival bleb have been added (Section 5.1.5.6, Table 7).
- The PDS-related adverse events of special interest terminology has been updated to ocular adverse event of special interest per Protocol Clarification Letter #4 (3 March 2020) (Section 5.2.3).
- The name and contact information of the secondary Medical Monitor has been updated (Section 5.4.1).
- The statistical considerations and analysis plan has been updated to align with the Statistical Analysis Plan (SAP v2, 21-Apr-2020) (Section 6). These updates include, but are not limited to, the following
  - The Primary Efficacy Endpoint has been clarified to modify the estimand of the primary analysis (change in best-corrected visual acuity [BCVA] score from baseline averaged over Weeks 36 and 40) to a treatment policy estimand. A supplemental analysis was added in which assessments at any timepoint after 2 or more supplemental treatments or after prohibited treatments in the study

eye will be imputed using the last post-baseline observation prior to such intercurrent event. (Section 6.4.1).

  - Changes to the secondary efficacy endpoints were made to remove the key secondary endpoint of proportion of patients who lose <15 letters in BCVA from baseline to the average over Week 36 and Week 40. (Sections 2 and 6.42).

- The schedules of activities have been updated with minor clarifications regarding final study visit assessments (Appendices 1 and 2).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, VISUAL ASSESSOR–MASKED, ACTIVE-COMPARATOR STUDY OF THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF THE PORT DELIVERY SYSTEM WITH RANIBIZUMAB IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION**
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MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form to your local study monitor.

PROTOCOL SYNOPSIS

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

Objectives and Endpoints

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

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

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

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

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

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

Study Design

Description of Study

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

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

Patients who are randomly allocated to the implant arm will have the implant (pre-filled with ranibizumab 100 mg/mL) surgically inserted on Day 1, which must occur 1–7 days (inclusive) after randomization (i.e., randomization and Day 1 visit assessments cannot be performed on the same day) and no later than 28 days from the last intravitreal ranibizumab 0.5 mg injection. If the implant insertion surgery (Day 1) cannot be completed within the visit window after randomization, the randomization visit assessments may be repeated and an additional intravitreal ranibizumab 0.5 mg injection may be required after discussion with the Sponsor. After Day 1, patients in the implant arm will have scheduled safety visit assessments on Days 2 and 7 (±2 days) and will receive implant refill-exchanges with ranibizumab 100 mg/mL Q24W at Week 24 (±7 days), Week 48 (±7 days), and Week 72 (±7 days).

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

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

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

Number of Patients

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

Target Population

Inclusion Criteria

General Inclusion Criteria

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

- Ability and willingness to provide signed informed consent

  Additionally, patients must provide Health Insurance Portability and Accountability Act (HIPAA) authorization.
- Age ≥50 years, at time of signing Informed Consent Form
- Ability and willingness to undertake all scheduled visits and assessments
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 28 days after the last intravitreal injection of ranibizumab or 1 year after the last implant refill-exchange of ranibizumab.

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

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

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

Ocular Inclusion Criteria

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

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

  If a patient did not receive at least three anti-VEGF injections as described above but is otherwise eligible for the study, the patient can be treated in a run-in phase to meet this specific criterion.
- Demonstrated response to prior anti-VEGF intravitreal treatment since diagnosis, as evidenced at screening by the following:

  Overall decrease in nAMD disease activity detected on SD-OCT, as assessed by the investigator and confirmed by the central reading center

  and

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

  nAMD lesions at the time of diagnosis must involve the macula (6-mm diameter centered at the fovea).
- Sufficiently clear ocular media and adequate pupillary dilation to allow for analysis and grading by the central reading center of FP, FA, FAF, and SD-OCT images

Exclusion Criteria

Prior Ocular Treatment

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

Study Eye

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

Either Eye

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

CNV Lesion Characteristics

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

Study Eye

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

Either Eye

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

Concurrent Ocular Conditions

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

Study Eye

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

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

Either Eye

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

Concurrent Systemic Conditions

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

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

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

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

End of Study

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

Length of Study

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

Investigational Medicinal Products

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

Test Product (Investigational Drug)

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

of the implant with ranibizumab, patients will receive implant refill-exchanges at fixed 24-week intervals.

At each refill-exchange, a volume of approximately 100 µL ranibizumab will be injected in situ into the implant through the septum to exchange the remaining contents of the implant with newly introduced ranibizumab. The volume of newly introduced ranibizumab remaining in the implant after the refill-exchange procedure will be approximately 20 µL. Missed implant refill-exchanges should be made up no later than the next scheduled study visit. If at the next scheduled study visit the implant refill-exchange cannot be performed, the investigator must contact the Sponsor for further discussion prior to administering future implant refill-exchanges. Subsequent refill-exchanges will be administered according to the study treatment schedule relative to Day 1 until patients complete the study.

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

Comparator

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

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

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

Statistical Methods

Primary Analysis

The primary efficacy endpoint is the change in BCVA score from baseline averaged over Weeks 36 and 40 with BCVA assessed using the ETDRS chart at a distance of 4 meters. The primary objective is to determine the NI and equivalence between the two treatment arms, as measured by the primary efficacy endpoint with an NI margin of 4.5 letters and equivalence margin of ±4.5 letters. To control the overall type I error, a fixed sequence testing procedure (Westfall and Krishen 2001) will be used. If the implant arm is shown to be non-inferior to the intravitreal arm at the one-sided 0.025 level, then the clinical equivalence test will be conducted using two one-sided 0.025 tests.

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

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

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

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

Determination of Sample Size

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

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

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

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
ATE	arterial thromboembolic event
BCVA	best-corrected visual acuity
CNV	choroidal neovascularization
CPT	center point thickness
CST	central subfield thickness
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FAF	fundus autofluorescence
FDA	Food and Drug Administration
FP	fundus photography
FSV4	ForSight VISION4, Inc.
GA	geographical atrophy
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IFU	instructions for use
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IOP	intraocular pressure
IRB	Institutional Review Board
IxRS	interactive voice or web-based response system
MacTSQ	Macular Degeneration Treatment Satisfaction Questionnaire
mITT	modified intent-to-treat (population)
MMRM	mixed-effect model for repeated measures
MRI	magnetic resonance imaging
nAMD	neovascular AMD
NI	non-inferiority
NSAID	nonsteroidal anti-inflammatory drug
OCT	optical coherence tomography

Abbreviation	Definition
PD	pharmacodynamics
PDS	Port Delivery System with ranibizumab
PK	Pharmacokinetic
PPPQ	PDS Patient Preference Questionnaire
PRO	patient-reported outcome
Q4W	every 4 weeks
Q24W	every 24 weeks
RBR	Research Biosample Repository
RPE	retinal pigment epithelium
SAP	Statistical Analysis Plan
SD-OCT	spectral-domain optical coherence tomography
WES	whole exome sequencing
VA	visual acuity
VEGF (-A)	vascular endothelial growth factor (–A)
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON AGE-RELATED MACULAR DEGENERATION

Neovascular age-related macular degeneration (nAMD) (also known as choroidal neovascularization [CNV] secondary to age-related macular degeneration [AMD] is a form of advanced AMD that causes rapid and severe visual loss, and remains a leading cause of visual impairment in the elderly (Bourne et al. 2013; Wong et al. 2014). The prevalence of nAMD increases exponentially with age, with estimates in the United States in 2011 ranging from 0.5% among people 65–69 years old to 14.6% among those 90 years old or older (Rudnicka et al. 2012). In the next 40 years, the global population aged 60 and older is projected to increase dramatically, translating into an increase in the prevalence of nAMD from 23 million in 2010 to 80 million by 2050 (Smith 2010). The precise causes of AMD remain unknown, although numerous risk factors have been identified, including genetic (e.g., complement factor H polymorphisms), demographic (e.g., ethnicity), nutritional (e.g., lack of antioxidant vitamins, dietary fats, or fish), lifestyle (e.g., smoking), medical (e.g., cardiovascular risk factors), environmental (e.g., sun exposure), and ocular factors (Chakravarthy et al. 2010).

1.1.1 Pathophysiology of Age-Related Macular Degeneration

AMD is categorized into early, intermediate, and advanced forms, based on clinical examination, ocular imaging, and pathologic findings. In approximately 10% of early or intermediate AMD cases, a conversion to nAMD occurs over time. Although nAMD is comparatively uncommon, it accounted for the majority of severe vision loss from AMD prior to the development of anti-vascular endothelial growth factor (VEGF) therapy. nAMD is typically characterized by the development of CNV in the macula. Abnormal capillary vessels and fibrovascular membranes proliferate in regions of Bruch's membrane damage. The new vessels are abnormally permeable and result in accumulation of exudative fluid and hemorrhage beneath the retinal pigment epithelium (RPE) and/or neurosensory retina. The fluid and hemorrhage can cause acute and, historically, permanent loss of central vision. At the end stage, fibrous metaplasia can occur, resulting in a chronic subretinal scar (disciform scar) (Jager et al. 2008).

The stimuli that result in the development of CNV remain unclear. However, there is significant experimental and clinical evidence implicating VEGF-A in the pathogenesis of nAMD, as discussed in the Port Delivery System with Ranibizumab (PDS) Investigator's Brochure.

1.1.2 Treatment for Neovascular Age-Related Macular Degeneration

Treatment of nAMD was significantly impacted by the introduction of anti-VEGF therapy. Prior to the availability of anti-VEGF therapy, vision loss could be slowed but not reversed. Ranibizumab, a recombinant, humanized monoclonal antibody fragment,

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.

A key challenge with currently available anti-VEGF treatments is the requirement for frequent and long-term administration to maintain vision gains (Heier et al. 2012; the Comparison of Age-Related Macular Degeneration Treatment Trials [CATT] Research Group 2016). Real-world data suggest that many patients with nAMD do not receive treatment according to the approved prescribing information and this under-treatment in clinical practice is associated with lower visual acuity (VA) gains compared with those observed in controlled clinical trials (Cohen et al. 2013; Finger et al. 2013; Holz et al. 2015). For example, a retrospective chart review of patients with newly diagnosed nAMD in multiple countries outside of the United States showed that patients received a mean of 5.0 and 2.2 injections in the first and second years, respectively and although an initial improvement in VA was observed, the gain was not maintained over time (mean change in VA score from baseline of only +2.4 and +0.6 letters, respectively, at Years 1 and 2) (Holz et al. 2015).

Under-treatment of nAMD in clinical practice reflects the burden of frequent therapy on patients, caregivers, and the healthcare system (Gohil et al. 2015; Prenner et al. 2015; Varano et al. 2015; CATT Research Group et al. 2016; Vukicevic et al. 2016).

This difference in outcomes between patients treated in the real-world setting and those treated in the controlled environment of a clinical trial demonstrates the clear clinical need for therapies with a more durable effect which would thus require less frequent dosing, while still being able to provide VA outcomes comparable to those observed in the pivotal clinical trials of licensed anti-VEGF monotherapies.

1.2 BACKGROUND ON RANIBIZUMAB

Ranibizumab is a recombinant humanized IgG1 κ isotype monoclonal antibody fragment administered by intravitreal administration. It binds to and inhibits the biologic activity of VEGF-A. Ranibizumab is produced by standard recombinant technology methods in an *Escherichia coli* expression vector and bacterial fermentation. Ranibizumab is not glycosylated and has a molecular mass of approximately 48,000 daltons.

Current U.S. prescribing information supports monthly intravitreal injection of ranibizumab 0.5 mg for treatment of nAMD and also provides information on results that may be expected following less frequent than monthly dosing after an initial loading phase.

Refer to the PDS Investigator's Brochure for details about nonclinical and clinical ranibizumab studies.

1.3 BACKGROUND ON THE PORT DELIVERY SYSTEM WITH RANIBIZUMAB

The PDS is a drug delivery technology that allows physicians to use ranibizumab with a continuous drug delivery profile without altering its chemistry and consists of an intraocular implant (hereafter referred to as the implant), four ancillary devices (insertion tool, initial fill needle, refill needle, and explant tool), and a customized formulation of ranibizumab tailored for continuous delivery (see Appendix 16).

The implant is an intraocular refillable device that is surgically implanted through the pars plana to allow for a continuous delivery of ranibizumab into the vitreous. After insertion of the implant, the proximal end of the implant *(flange) sits on top of the sclera, under the conjunctiva and Tenon's capsule*, with the body of the implant extending into the vitreous. The implant is used in conjunction with *the customized formulation of* ranibizumab to precisely control the rate and duration of drug delivery and is refillable through the implant septum in situ.

For additional PDS details (e.g., fill, insertion, refill-exchange, and explantation of the implant), consult the PDS instructions for use (IFU) document and the PDS Investigator's Brochure.

Prior to this current study, the implant has been investigated in prospective Phase I and II studies. A prospective Phase I, open-label study in patients with nAMD was conducted by the device developer, ForSight VISION4, Inc. (FSV4), at a single site in Latvia. The study investigated the safety, tolerability, and duration of ranibizumab exposure delivered with the implant. The implant used in Phase I was composed of biocompatible materials (polymethyl methacrylate, silicone, and 316L stainless steel; see Appendix 16).

For additional details about the Phase I study, see Section 1.4 and the PDS Investigator's Brochure. The implant evaluated in Phase II was composed of biocompatible materials (polysulfone, silicone, and titanium; see Appendix 16).

1.3.1 Phase I Port Delivery System with Ranibizumab Study: FH-1.2

The safety, tolerability, and duration of ranibizumab (10 mg/mL) exposure delivered through the implant were investigated in a Phase I prospective, open-label study (FH-1.2) in a patient population with nAMD and conducted by FSV4 at a single site in Latvia. Patient enrollment was initiated in August 2010, and the study assessed the safety of the PDS in 20 eyes through the collection and analysis of adverse events and complications, including procedure-related adverse events, device-related adverse events, ranibizumab-related adverse events, and all general health and patient-reported adverse events.

All 20 patients completed the planned 12-month treatment phase of the Phase I study. No patients were treated via the implant after the first 12 months of the study. At

Month 12, 6 patients underwent per-protocol planned implant removal and discontinued from the study after completion of the Month 13 visit. Of the 14 remaining patients eligible for an additional 24-month safety-monitoring phase (quarterly safety visits), 1 patient was lost to follow-up after 12 months. The remaining 13 patients continued in the safety-monitoring phase; and 1 of the 13 patients was subsequently lost to follow-up after 21 months. Follow-up data out to 36 months are available for the remaining 12 patients.

A total of 95 adverse events were reported in all 20 patients (100%) in this study: 87 adverse events during the 12-month treatment phase and 8 adverse events during the safety-monitoring phase. Of the 87 adverse events reported during treatment, 76 events were considered by the investigator to be related (possibly, probably, or definitely) to the implant insertion procedure, the refill-exchange procedure, the implant removal procedure, or study drug treatment.

The most common study-related adverse events were conjunctival hyperemia (59%), vitreous hemorrhage (7%), hyphema (7%), VA decrease (5%), eye dryness (4%), and conjunctival edema (3%). Conjunctival hyperemia occurred in 19 of 20 patients (95%), for a total of 45 events; 44 of those events (98%) were mild in severity and 1 event was of moderate severity. Conjunctival hyperemia was typically observed following the implant insertion or refill-exchange procedures, and the average duration of these events was 8 days, with all resolving over a range from 3 to 48 days from onset.

A total of 96 implant refill-exchange procedures were performed in the study. The most frequently reported adverse events considered by the investigator to be related to the implant refill-exchange on a per-procedure basis were conjunctival hyperemia (33%), eye dryness (2%), vitreous haze (2%), increased lacrimation (1%), and ocular discomfort (1%). The adverse event rate per implant refill-exchange procedure was 38%. The adverse events were of mild severity, and the average duration to resolution was 7 days.

Please refer to the PDS Investigator's Brochure for further details.

1.3.2 Phase II Port Delivery System with Ranibizumab: Study GX28228 (Ladder)

Subsequent to Study FH-1.2, a Phase II, dose-ranging, randomized, active treatment–controlled, multicenter study (GX28228 [Ladder]) was initiated to evaluate the safety, efficacy, and pharmacokinetics of three different doses of ranibizumab (10 mg/mL, 40 mg/mL, and 100 mg/mL) delivered via the PDS versus monthly intravitreal ranibizumab 0.5 mg injections in patients with nAMD and a history of positive response to any anti-VEGF therapy. The study, which was U.S. based, was approximately 43 months in duration. The last patient, last visit occurred on 28 March 2019 *and the final study analysis was then conducted (snapshot date of 2 May 2019).*

The primary analysis, performed when all enrolled patients had been followed up for 9 months, measured the time at which a patient first required an implant refill-exchange according to protocol-defined refill-exchange criteria. In the PDS 100 mg/mL, PDS 40 mg/mL, and PDS 10 mg/mL arms, the median time to first refill-exchange was 15.0, 13.0, and 8.7 months, respectively. In addition, 79.8%, 71.3%, and 63.5% of patients went ≥ 6 months without requiring a refill-exchange in PDS 100 mg/mL, PDS 40 mg/mL, and PDS 10 mg/mL, respectively. BCVA and anatomic outcomes were comparable between the PDS 100 mg/mL arm and the monthly intravitreal ranibizumab 0.5 mg arm. The overall safety profile from the primary analysis revealed a favorable benefit–risk assessment. The optimized implant insertion surgery and refill-exchange procedures were generally well tolerated. Systemic safety profile of PDS treatment was well characterized and comparable with monthly intravitreal ranibizumab 0.5 mg treatment (Campochiaro et al. 2019). *Results from the final analysis were consistent with the results from the primary analysis.* Please refer to the PDS Investigator's Brochure for further details.

Patients from Study GX28228 who completed the study and consented to *the* open-label extension study (GR40549 [Portal*]) have now enrolled.*

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

As a result of the chronic, progressive nature of nAMD, frequent intravitreal ranibizumab 0.5 mg injections continue for extended periods for many patients. The pivotal Phase III studies (MARINA [FVF2598g] and ANCHOR [FVF2587g]) in nAMD demonstrated significant and well-maintained VA outcomes with monthly intravitreal ranibizumab 0.5 mg injections for 2 years.

The study HARBOR (FVF4579g), which compared monthly with PRN ranibizumab administration, showed comparable efficacy and maintenance of visual and anatomic improvements for 2 years between the two regimens. However, all patients were evaluated monthly to determine the need for retreatment and still required frequent injections. The mean number of intravitreal ranibizumab 0.5 mg injections through Month 24 was 21.4 injections for the monthly treatment arm and 13.3 injections for the PRN treatment arm. In clinical practice, frequent office monitoring visits are required and regular injections are necessary to maintain optimal vision gains; however, this places a significant burden on patients and their caregivers, treating physicians, and the healthcare system.

Such requirements present a substantial barrier to maintenance of desired efficacy outcomes. Indeed, in clinical practice, many patients are treated less frequently than per the approved prescribing information and as a consequence experience suboptimal efficacy (Holz et al. 2015; Maguire et al. 2016; Egan et al. 2017; Rao et al. 2018). As such, there remains a substantial unmet need for an optimized treatment and dosing regimen that could alleviate the current treatment burden on patients, caregivers, and healthcare providers and consequently improve vision outcomes in clinical practice.

Continuous delivery of ranibizumab from the implant, with a prolonged fixed period between refill-exchanges, is a novel approach that may result in less-frequent need for retreatment than monthly dosing and patient monitoring. The decrease in treatment burden may reduce the risk of intravitreal injection–related adverse events, increase compliance, and reduce the burden to patients, their caregivers, and the healthcare system, while maintaining optimal visual outcomes.

The primary analysis of the results of the Phase II GX28228 (Ladder) study revealed a favorable benefit–risk assessment for the PDS, which was well tolerated, with no evidence of dose dependency on the frequency or severity of the reported adverse events. The overall safety profile of the PDS from available study data is generally consistent with the known safety profile of both ranibizumab administered by intravitreal injection (Lucentis® U.S. Package Insert [USPI]) and similar surgical procedures involving intraocular implants (Dunn et al. 2004; Gedde et al. 2012; Buys 2013; Retisert® U.S. Package Insert; Vitrasert® Implant U.S. Package Insert). See Section 5.1.3 for anticipated risks associated with the PDS or implant insertion procedure. For a complete summary of safety information, refer to the PDS Investigator's Brochure.

The Phase I and II studies provide evidence of the safety and tolerability of the PDS and support the evaluation of the PDS in a Phase III study.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of ranibizumab delivered via the PDS implant compared with ranibizumab 0.5 mg delivered as a monthly intravitreal injection in patients with nAMD. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 Objectives and Corresponding Endpoints

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

Table 1 Objectives and Corresponding Endpoints (cont.)

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

Table 1 Objectives and Corresponding Endpoints (cont.)

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

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Pharmacokinetic Objectives	Corresponding Endpoints
• To evaluate potential relationships between drug exposure and the efficacy of the PDS	• Relationship between serum concentration or PK parameters for ranibizumab delivered via the PDS and efficacy endpoints
• To characterize ranibizumab aqueous humor concentration over time	• Observed aqueous humor ranibizumab concentrations over time
Immunogenicity Objective	**Corresponding Endpoint**
• To investigate the formation of serum anti-ranibizumab antibodies	The incidence of ADAs during the study, grouped in the following manner: • Patients who were ADA negative at baseline and became positive only after dosing • Patients who were ADA positive at randomization and ADA titer increased after dosing • Patients who were ADA positive at randomization and ADA titer did not increase after dosing
Exploratory Biomarker Objectives	**Corresponding Endpoints**
• To explore relationships between aqueous humor free-VEGF concentrations over time and the efficacy of ranibizumab, delivered via the PDS Q24W with the 100-mg/mL formulation	• Comparison of patients with and without aqueous humor free-VEGF present between refill-exchanges and needing supplemental treatment • Comparison of patients with and without aqueous humor free-VEGF present between refill-exchanges and CST change from baseline over time • Comparison of patients with and without aqueous humor free-VEGF present between refill-exchanges and BCVA score change from baseline over time
• To identify biomarkers that are prognostic of response to ranibizumab, are associated with acquired resistance to ranibizumab, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of ranibizumab activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of AMD-related disease biology	• Relationship between biomarkers in blood and aqueous humor with disease characteristics and response to ranibizumab • Relationship between genetic variants (such as AMD risk alleles, polymorphisms within the complement pathway, and polymorphisms within the VEGF-A genetic locus) with the disease characteristics and/or response to treatment with ranibizumab • Relationship between imaging features with disease characteristics and/or response to treatment with ranibizumab

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Patient Experience Objectives	Corresponding Endpoints
• To evaluate the preference of patients for ranibizumab delivered via the PDS for 40 weeks compared to intravitreal anti-VEGF treatment received in the 6 months prior to Day 1	• Proportion of patients who report preferring ranibizumab treatment via the PDS compared with intravitreal anti-VEGF treatment, as assessed by the PPPQ, at Week 40 among patients in the implant arm
• To evaluate patient-reported treatment satisfaction with ranibizumab delivered via the PDS for 40 weeks compared with that of Q4W intravitreal ranibizumab injections, as assessed by the MacTSQ	• MacTSQ total score at Week 40

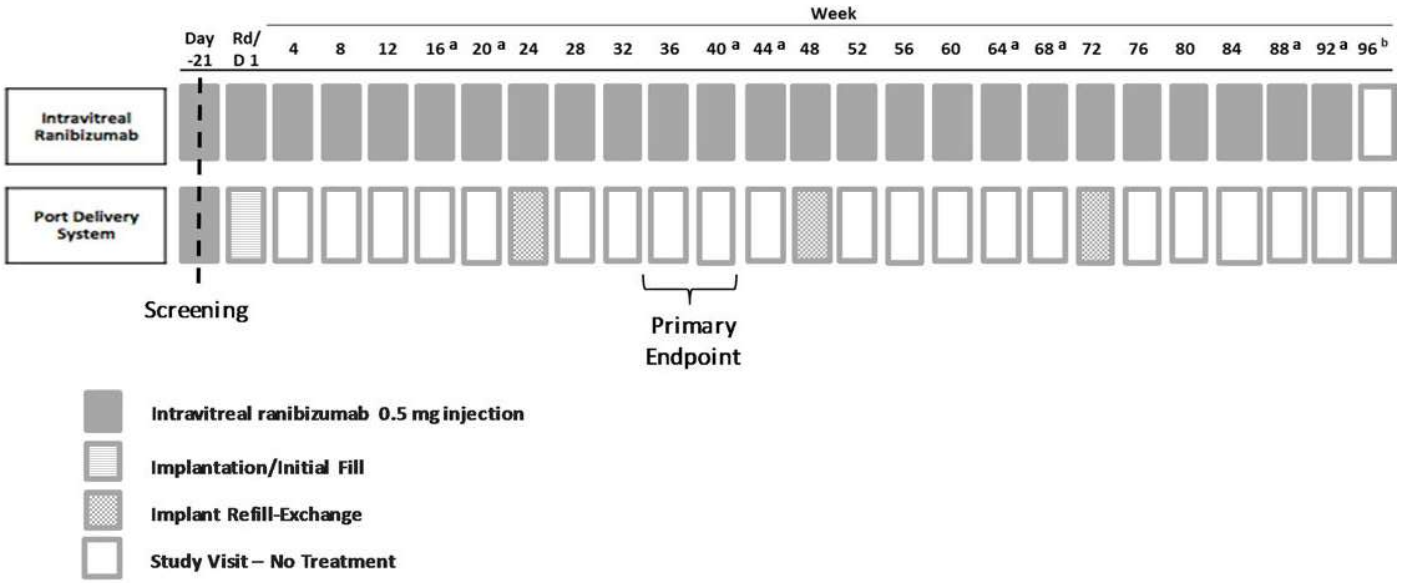
ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; AMD = age-related macular degeneration; $AUC_{0\text{-}6M}$ = area under the concentration–time curve from 0 to 6 months; BCVA = best-corrected visual acuity; C_{max} = maximum serum concentration; C_{min} = minimum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

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Study GR40548 (Archway) is a Phase III, randomized, multicenter, open-label (visual assessor [VA]–masked), active-comparator study designed to assess the efficacy, safety, and pharmacokinetics of ranibizumab 100 mg/mL every 24 weeks (Q24W) delivered via the PDS compared with ranibizumab intravitreal 0.5 mg injections every 4 weeks (Q4W) in patients with nAMD. Approximately 360 patients were planned to be enrolled at approximately 90 sites; a total of 418 were recruited. For the study schema, see Figure 1.

Figure 1 Study Schema



D = day; Rd = randomization.

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

[b] *At Week 96, patients may consent to enter the open-label extension study GR40549 (Portal). In the event a patient is unable to complete Archway at Week 96 and enroll in Portal on the same day, follow the alternate scenarios presented in Table 3 and the schedules of activities in Appendix 1, Table 3 and Appendix 2, Table 3.*

Patients must satisfy all eligibility criteria at both the screening and the randomization visits, including receipt of all screening visit images by the central reading center. Historical optical coherence tomography (OCT) images taken around the time of diagnosis of nAMD will be evaluated by the central reading center to support determination of a patient's eligibility.

If available, fluorescein angiography (FA) images taken around the time of diagnosis of nAMD in the study eye should be submitted to the central reading center but will not be required to determine eligibility at the screening visit.

As part of the screening process, the central reading center will evaluate the patient's FA, fundus photography (FP), fundus autofluorescence (FAF), and spectral-domain optical coherence tomography (SD-OCT) images obtained at the screening visit, as well as the patient's historical OCT (mandatory) and historical FA images (if available) taken around the time of nAMD diagnosis to provide an objective, masked assessment of patient eligibility regarding CNV lesion details (including macular atrophy). Screening visit assessments may be performed on multiple days but must be completed within 7 days of obtaining informed consent.

Patients who do not meet eligibility criteria (screen-failed patients) may be eligible to repeat screening up to two times if deemed appropriate by the investigator. At rescreening, a new screening number will be assigned to the patient through an interactive voice or web-based response system (IxRS) and all screening visit assessments will be performed except for FA image collection if reading center–accepted images were taken within 12 weeks from the rescreening visit.

After all eligibility requirements are confirmed, patients will be randomly allocated in a 3:2 ratio so that approximately 216 patients will receive the PDS implant filled with ranibizumab 100 mg/mL Q24W (implant arm) and approximately 144 patients will receive intravitreal injections of ranibizumab 10 mg/mL Q4W (intravitreal arm; see Figure 1). On the day of a patient's randomization visit, best-corrected visual acuity (BCVA) will be measured based upon the Early Treatment Diabetic Retinopathy Study (ETDRS) chart assessment at a starting test distance of 4 meters, and randomization will be stratified by the BCVA score (<74 letters vs. ≥ 74 letters). Randomization will be performed by the IxRS.

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

There are five eligibility scenarios based on prior intravitreal anti-VEGF treatment history (see also Table 2):

1. **Patients newly diagnosed with nAMD who are anti-VEGF treatment-naive**

   If patients in this group satisfy all other eligibility criteria (other than prior anti-VEGF treatment criteria in the study eye, see Section 4.1.1) and sign the Informed Consent Form, patients will:

   - Receive three monthly (28 [±7] days) intravitreal ranibizumab 0.5 mg injections in the run-in period to determine if they demonstrate response to anti-VEGF treatment as outlined per the eligibility criteria (see Appendix 3).
   - After the third run-in intravitreal ranibizumab 0.5 mg injection, patients will proceed to screening, scheduled 28 (±7) days from the last administered intravitreal ranibizumab 0.5 mg injection, and will receive an additional intravitreal ranibizumab 0.5 mg injection at the end of the screening visit.
   - If all eligibility criteria are then met, patients will proceed to the randomization visit.

2. **Patients diagnosed with nAMD in the study eye within 9 months prior to screening who have been treated with one or two intravitreal anti-VEGF injections within the last 6 months**

   If patients in this group satisfy all other eligibility criteria (other than prior anti-VEGF treatment criteria in the study eye, see Section 4.1.1) and sign the Informed Consent Form, patients will:

   - Receive up to three intravitreal ranibizumab 0.5 mg injections in the run-in period to meet the required three anti-VEGF intravitreal injections within 6 months prior to screening (see Appendix 3).
   - After completing the required run-in treatments, patients will proceed to screening, scheduled 28 (±7) days from the last administered intravitreal ranibizumab 0.5 mg injection, and will receive an additional intravitreal ranibizumab 0.5 mg injection at the end of the screening visit.
   - If all eligibility criteria are then met, patients will proceed to the randomization visit.

3. **Patients diagnosed with nAMD in the study eye within 9 months prior to screening who have been treated with three intravitreal anti-VEGF injections within 6 months prior to screening**

   If patients in this group satisfy all other eligibility criteria (see Section 4.1.1) and sign the Informed Consent Form, patients will:

   - Proceed directly to screening, scheduled ≥21 days from the last intravitreal anti-VEGF injection administered per standard of care, and will receive an additional intravitreal ranibizumab 0.5 mg injection at the end of the screening visit.

- If all eligibility criteria are then met, patients will proceed to the randomization visit.

4. **Patients diagnosed with nAMD in the study eye within 9 months prior to screening who have been treated with at least four intravitreal anti-VEGF injections within 6 months prior to screening and with the most recent dose being aflibercept or bevacizumab**

   If patients from this group satisfy all other eligibility criteria (see Section 4.1.1) and sign the Informed Consent Form, patients will:

   - Proceed directly to screening, scheduled ≥21 days from the last intravitreal anti-VEGF injection, and will receive an intravitreal ranibizumab 0.5 mg injection at the end of the screening visit.
   - If all eligibility criteria are then met, patients will proceed to the randomization visit.

5. **Patients diagnosed with nAMD in the study eye within 9 months prior to screening who have been treated with at least four intravitreal anti-VEGF injections within 6 months prior to screening, with the most recent dose being ranibizumab**

   If patients from this group satisfy all other eligibility criteria (see Section 4.1.1) and sign the Informed Consent Form, patients will:

   - Proceed directly to the screening visit, which should be scheduled ≥7 days from the last administered ranibizumab dose, and will not receive another intravitreal ranibizumab 0.5 mg injection at the screening visit, provided that the randomization and Day 1 visits can be completed within 21–28 days after the last ranibizumab dose administered in the study eye prior to screening.

     If the randomization and Day 1 visit cannot be completed within the allotted time window, the patient should be scheduled for a screening visit at ≥21 days from the last ranibizumab dose and will receive an additional intravitreal ranibizumab 0.5 mg injection at the end of the screening visit.
   - If all eligibility criteria are then met, patients will proceed to the randomization visit.

All patients must maintain the 9-month cap on the time from initial nAMD diagnosis to the screening visit and must meet the minimum number of required anti-VEGF treatments within the last 6 months prior to screening (see Section 4.1.1).

Table 2 Dosing Guidelines during Run-in Period and at Screening Visit

Eligibility Scenario	Historical Anti-VEGF Use in the Study Eye within the Last 6 Months prior to Screening	Ranibizumab Dose(s) Required prior to Screening (Run-In Period)	Ranibizumab at Screening Visit
1	Anti-VEGF treatment-naive	3 doses	Yes
2	1–2 previous anti-VEGF doses within the last 6 months	Up to 3 doses	Yes
3	3 previous anti-VEGF doses within 6 months prior to screening	0	Yes
4	≥4 previous anti-VEGF doses within 6 months prior to screening and the most recent dose was aflibercept or bevacizumab	0	Yes
5	≥4 prior previous anti-VEGF doses within 6 months prior to screening and the most recent dose was ranibizumab	0	No (If randomization and Day 1 visits can be completed in required timeframe) [a]
			Yes (If randomization and Day 1 visits cannot be completed in required timeframe) [a]

Anti-VEGF = anti–vascular endothelial growth factor.

[a] Randomization and the Day 1 visits should be completed within 21–28 days (inclusive) after last ranibizumab dose in the study eye.

All patients will return for a randomization visit and the Day 1 visit within 21–28 days (inclusive) after their last ranibizumab dose.

Patients who are randomly allocated to the implant arm will have the implant (pre-filled with ranibizumab 100 mg/mL) surgically inserted on Day 1, which must occur 1–7 days (inclusive) after randomization (i.e., randomization and Day 1 visit assessments cannot be performed on the same day) and no later than 28 days from the last intravitreal ranibizumab 0.5 mg injection. If the implant insertion surgery (Day 1) cannot be completed within the visit window after randomization, the randomization visit assessments may be repeated and an additional intravitreal ranibizumab 0.5 mg injection may be required after discussion with the Sponsor. After Day 1, patients in the implant arm will have scheduled safety visit assessments on Days 2 and 7 (±2 days) and will receive implant refill-exchanges with ranibizumab 100 mg/mL Q24W at Week 24 (±7 days), Week 48 (±7 days), and Week 72 (±7 days).

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

Study visits will occur according to the schedule of activities in Appendix 1 and Appendix 2 relative to Day 1 (first study treatment) and will continue until the patient completes the study. Patients are not expected to attend their scheduled visits if there are extenuating circumstances justifying their inability to come to the clinic.Patients will be contacted by site personnel 3 (±1) days after each intravitreal ranibizumab injection or implant refill-exchange procedure to elicit reports of eye pain, decrease in vision, unusual redness, or any other new ocular symptoms in the study eye. Patients in the implant arm will also be asked to verify whether they have taken the prescribed, self-administered, post-treatment antimicrobial therapy. Patients in the intravitreal arm will be prescribed self-administered antimicrobial treatments at the investigator's discretion.

In the event a patient's non-study (fellow) eye requires treatment for nAMD, treatment with any FDA-approved intravitreal anti-VEGF treatment for nAMD may be administered. The Sponsor will provide intravitreal ranibizumab 0.5 mg starting from the screening visit, if the investigator chooses to treat the fellow eye with ranibizumab. Study eye treatment and fellow eye treatment with anti-VEGF agents may be done at the same study visit; however, the study eye should receive study treatment per protocol prior to intravitreal anti-VEGF treatment in the fellow eye.

Study investigators will be qualified ophthalmologists, trained in the management of retinal diseases and ocular surgery, and will be trained by the Sponsor to perform study-specific implant initial filling, insertion, refill-exchange, and explantation procedures. The surgical procedures involved in the use of the investigational devices are also detailed in the IFU document. It is strongly preferred that a site has at least one investigator who evaluates and treats all patients, with backup investigators selected. The site may opt to have more than one investigator, but to maintain consistency in the evaluation and treatment of patients, it is strongly suggested that the same physician conduct the evaluation and treatment of each individual patient throughout the trial.

Study patients and all study site personnel with the exception of VA examiners will be unmasked to the study eye and study treatment assignment.

The Sponsor recognizes that it may be difficult to fully mask site staff in an open label surgical study.

The Sponsor will require that the following steps be implemented as a best attempt to mask VA examiners in order to minimize biases in VA assessments.

- The VA examiner will only conduct refraction and VA assessments and will be masked as best as possible to patient study eye assignment, study visit type, and patient treatment assignment.
- The VA examiner will have no access to a patient's BCVA scores from previous visits and will be aware only of the patient's refraction data from previous visits.
- The VA examiner may provide no other direct or indirect patient care.
- Patients and unmasked site personnel will be asked not to discuss the study eye assignment, study visit type, and patient treatment assignment with the VA examiner.

At the Archway Week 96, eligible patients may *consent* to enter the open-label extension study GR40549 (Portal*), designed to evaluate the long-term safety and tolerability of PDS,* and receive treatment according to the extension study protocol. *The Portal enrollment visit will occur the same day as Archway Week 96 visit for both arms (Table 3). Eligible patients who do not consent to enter the Portal study should complete the Archway Week 96 procedures as described in Appendix 1 or Appendix 2, as applicable.* In the event that *an eligible* patient in the implant arm decides not to enter *Portal*, the patient will be instructed to contact their study physician or the Sponsor's adverse event reporting line if they experience an adverse event related to the implant. Patients must contact their study physician if they elect to remove the implant.

In order to provide flexibility due to extenuating circumstances and assure appropriate patient care, if the patient is unable to complete Archway at Week 96 and enroll into Portal during the same visit, several alternate final study visit scenarios are available (Table 3). In general, Archway patients should be provided the opportunity to remain on study and receive treatment at regular intervals until consenting patients can enroll into Portal per-protocol.

Table 3 Scenarios for Archway Week 96 and Portal Enrollment Visits

IMPLANT ARM [a]			
Scenario	**Week 96 (± 7 days)**	**Monthly Week (X) (± 7 days)**	**Portal Enrollment Visit**
Week 96 and Portal enrollment visits can be conducted within window.	*Conduct the Week 96 visit.*	*Not Applicable*	*Conduct the Portal enrollment visit on the same day as the Week 96 visit. Administer the PDS refill-exchange (per Portal protocol).*
IMPLANT ARM / Alternate Scenarios [b]			
1. *Week 96 visit can be conducted within window; Portal enrollment can only be conducted 21-28 days post-Week 96 visit.*	*Conduct the Week 96 visit; however do not administer a PDS-refill-exchange.*	*Conduct one Week (X) visit after Week 96 (i.e., Week 100).*	*Conduct the Portal Enrollment visit on the same day as Week 100 visit. Administer the PDS refill-exchange (per Portal protocol).*
2. *Week 96 visit can be conducted within window; Portal enrollment visit is NOT expected to be conducted 21-28 days post-Week 96 visit.*	*Conduct the Week 96 visit and administer a PDS refill-exchange.*	*Conduct monthly Week (X) visits after Week 96 until the Portal Enrollment visit can be scheduled within the required window.*	*Conduct the Portal Enrollment on the same day as the final Week (X) visit. Administer the PDS refill-exchange (per Portal protocol).*
3. *Week 96 visit is missed.*	*Not applicable*	*Conduct a Week (X) visit and administer a PDS refill-exchange [c].* *Conduct monthly Week (X) visits until the Portal Enrollment visit can be scheduled within the required window.*	*Conduct the Portal Enrollment visit on the same day as the final Week (X) visit. Administer the PDS refill-exchange (per Portal protocol).*

[a] *See Appendix 1, Table 2 for Schedule of Activities.*

[b] *See Appendix 1, Table 3 for Schedule of Activities.*

[c] *If the first Week (X) is also missed, the investigator must contact the Sponsor for further discussion prior to scheduling the next visit.*

Table 3 Scenarios for Archway Week 96 and Portal Enrollment Visits (cont.)

INTRAVITREAL ARM [a]			
Scenario	**Week 96 (± 7 days)**	**Monthly Week (X) (± 7 days)**	**Portal Enrollment Visit**
Week 96 visit and Portal enrollment visit can be conducted within window.	*Conduct the Week 96 visit.*	*Not Applicable*	*Conduct the Portal enrollment visit on the same day as the Week 96 visit.* *Perform the implant surgery no later than 28 days after the last intravitreal ranibizumab injection (per Portal protocol).*
INTRAVITREAL ARM / Alternate Scenario [b]			
1. *Week 96 visit can be conducted within window; Portal enrollment can only be conducted 21-28 days post-Week 96 visit.*	*Conduct the Week 96 visit and administer an intravitreal ranibizumab injection.*	*Conduct one Week (X) visit after Week 96 (i.e, Week 100); however do not administer an intravitreal ranibizumab injection.*	*Conduct the Portal Enrollment visit on the same day as the Week 100 visit.* *Perform the implant surgery no later than 28 days after the last intravitreal ranibizumab injection (per Portal protocol).*
2. *Week 96 visit can be conducted within window; Portal enrollment is NOT expected to be conducted 21-28 days post-Week 96 visit.*	*Conduct the Week 96 visit and administer an intravitreal ranibizumab injection.*	*Conduct monthly Week (X) visits after Week 96 and administer intravitreal ranibizumab injections until the Portal Enrollment visit can be scheduled within the required window. At the final Week (X) visit, do not administer an intravitreal ranibizumab injection.*	*Conduct the Portal Enrollment visit on the same day as the final Week (X) visit.* *Perform the implant surgery no later than 28 days after the last intravitreal ranibizumab injection.*

Table 3 Scenarios for Archway Week 96 and Portal Enrollment Visits (cont.)

INTRAVITREAL ARM / Alternate Scenario [b] (cont.)			
3. Week 96 visit is missed.	*Not applicable*	*Conduct monthly Week (X) visits [c] and administer intravitreal ranibizumab injections until the Portal Enrollment visit can be scheduled within the required window. At the final Week (X) visit, do not administer an intravitreal ranibizumab injection.*	*Conduct the Portal Enrollment visit on the same day as the final Week (X) visit.* *Perform the implant surgery no later than 28 days after the last intravitreal ranibizumab injection.*

[a] *See Appendix 2, Table 2 for Schedule of Activities.*

[b] *See Appendix 2, Table 3 for Schedule of Activities.*

[c] *If the first planned Week (X) is also missed, the investigator must contact the Sponsor for further discussion prior to scheduling the next visit.*

3.2 INTERNAL SAFETY MONITORING

A safety team will closely monitor patient safety throughout the study to ensure early identification and corrective action of procedure- and operator-associated adverse events for individual patients.

Unmasked safety data will be reviewed on a routine basis by the Sponsor's safety team in order to expeditiously identify and manage risks. The efficacy data will not be reviewed during internal safety monitoring.

3.3 INDEPENDENT DATA MONITORING COMMITTEE

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

3.4 END OF STUDY AND LENGTH OF STUDY

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

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

3.5 RATIONALE FOR STUDY DESIGN

The PDS is being investigated as an alternate means of delivering ranibizumab in patients with nAMD. Providing ranibizumab treatment through a device designed to provide continuous drug delivery for up to 6 months may reduce the number of required office visits and the frequency of drug administration necessary in clinical practice, while achieving efficacy similar to that observed in pivotal ranibizumab trials. In addition, improved compliance that may result from such a regimen might lead to enhanced long-term vision outcomes for patients.

3.5.1 Rationale for Ranibizumab Dose and Schedule

The ranibizumab 100 mg/mL administered to patients via the PDS implant and the 24-week refill-exchange interval were selected on the basis of:

- Observed efficacy and safety data from Study GX28228 (Ladder), which evaluated a range of ranibizumab formulations (10 mg/mL, 40 mg/mL, and 100 mg/mL) and a refill-exchange dosing regimen based on pre-specified criteria
- Pharmacokinetic (PK)-efficacy modeling and simulation for the 100-mg/mL formulation

Taken together, the above data and analyses support that ranibizumab 100 mg/mL will deliver pharmacologically efficacious concentrations of ranibizumab in the majority of patients over the entire dosing interval of 24 weeks.

Based on the implant fill volume of 20 μL, the maximum amount of ranibizumab that can be initially filled and subsequently refilled is approximately 2 mg for the 100-mg/mL formulation. Total local (i.e., vitreal) and systemic drug exposures with the 100-mg/mL formulation Q24W are estimated to be below the drug exposures from the intravitreal ranibizumab 0.5 mg injections and the highest ranibizumab dose tested (monthly intravitreal ranibizumab 2 mg injections).

3.5.2 Rationale for Patient Population

Ranibizumab has been shown to be effective in improving and maintaining vision in patients with nAMD; therefore, this patient population was selected to evaluate the PDS with ranibizumab 100 mg/mL. This study will enroll only patients with nAMD who have received multiple anti-VEGF treatments to control a recently active CNV lesion and who demonstrated a response to those injections. This approach aims to limit the number of patients who would potentially not respond to continuous delivery of ranibizumab, thus minimizing the chance for an individual anti-VEGF non-responder to undergo surgery and receive the PDS implant.

The goal of exposing patients with nAMD to the PDS is to demonstrate a treatment approach that maintains the efficacy seen with monthly anti-VEGF intravitreal injections, while offering the potential for reduced monitoring, more sustained disease control, and better long-term visual outcomes than currently observed in clinical practice, in which many patients are treated less frequently than monthly and experience suboptimal efficacy as a consequence.

3.5.3 Rationale for Control Group

Ranibizumab administered via intravitreal injection is an approved, standard-of-care treatment for nAMD in the United States, the European Union, and many other countries worldwide. The monthly dosing of intravitreal ranibizumab 0.5 mg is the most effective approved regimen based on United States product labeling for ranibizumab and was therefore selected as the most appropriate control group.

3.5.4 Rationale for Pharmacokinetic Sample Collection Schedule

The objective of the serum PK sampling is to characterize the serum pharmacokinetics of ranibizumab delivered via the PDS in the implant arm and to assess the potential impact of immunogenicity on pharmacokinetics. The serum pharmacokinetics of ranibizumab following intravitreal administration has been well characterized; however, the PK profile for continuous delivery is expected to be markedly different (by design).

In this study, PK serum samples will be collected from all patients at all sites at the randomization visit and at Weeks 4, 24, 36, and 96 to align with anti-drug antibody (ADA) sample collection timepoints. At selected sites, additional PK samples will be collected from patients in the implant arm on Days 2 and 7 and Weeks 12, 48, and 72. The sampling timepoints through Week 24 are expected to be sufficient to estimate the half-life for ranibizumab delivery from the implant, and sampling timepoints at Weeks 36–96 will be assessed to ensure consistent drug delivery over time. Limited PK sampling will occur in the intravitreal arm (control) because the serum pharmacokinetics of ranibizumab following intravitreal administration has been well characterized, as presented in the PDS Investigator's Brochure. In addition, at selected sites, a PK sample will be collected in patients in the intravitreal arm 1 to 5 days after an intravitreal ranibizumab 0.5 mg injection in order to collect a sample near C_{max}.

See Appendix 1 and Appendix 2 for sample collection timepoints.

3.5.5 Rationale for Immunogenicity Sample Collection

The objective of serum sampling for ADA testing is to characterize the immunogenicity of ranibizumab delivered via the PDS in the implant arm compared with patients receiving ranibizumab by intravitreal administration. The immunogenicity of ranibizumab following intravitreal administration has been well characterized, and the incidence of ADAs in the context of the delivery system is not expected to be markedly different. The sampling timepoints for ADA assessment will ensure that the anti-ranibizumab immunogenicity profile of patients in the study is monitored throughout the study.

Serum ADA samples will be collected from all patients at the randomization visit and at Weeks 4, 24, 36, and 96 (see Appendix 1 and Appendix 2).

3.5.6 Rationale for Biomarker Assessments

Previous studies have demonstrated a broad range of treatment needs across patients (Ho et al. 2014); thus, some patients in the implant arm may require additional treatment(s) with ranibizumab outside of the fixed 24-week dosing interval. To better understand the cause of their increased treatment needs, aqueous humor samples from patients who require supplemental treatment will be collected (just prior to the supplemental treatment and at the next subsequent visit) and analyzed for drug and/or free-VEGF concentrations and correlated with retreatment need. In addition, aqueous humor, plasma, and serum samples will be collected from patients who terminate study

treatment early or who undergo explantation. Information obtained from these analyses will be used in an effort to better understand variability in treatment need and to identify patients best suited for continuous delivery of ranibizumab.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 360 patients with CNV secondary to AMD, diagnosed within 9 months prior to screening and treated with at least three injections with any anti-VEGF agent within the last 6 months prior to screening, were planned to be enrolled in this study; a total of 418 patients were ultimately recruited.

4.1.1 Inclusion Criteria

4.1.1.1 General Inclusion Criteria

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

- Ability and willingness to provide signed informed consent

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

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

  Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 28 days after the last intravitreal injection of ranibizumab or 1 year after the last implant refill-exchange of ranibizumab.

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

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

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

4.1.1.2 Ocular Inclusion Criteria

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

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

  If a patient did not receive at least three anti-VEGF injections as described above but is otherwise eligible for the study, the patient can be treated in a run-in phase to meet this specific criterion.
- Demonstrated response to prior anti-VEGF intravitreal treatment since diagnosis, as evidenced at screening by the following:

  Overall decrease in nAMD disease activity detected on SD-OCT, as assessed by the investigator and confirmed by the central reading center

  and

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

  nAMD lesions at the time of diagnosis must involve the macula (6-mm diameter centered at the fovea).
- Sufficiently clear ocular media and adequate pupillary dilation to allow for analysis and grading by the central reading center of FP, FA, FAF, and SD-OCT images

4.1.2 Exclusion Criteria

4.1.2.1 Prior Ocular Treatment

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

Study Eye

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

Either Eye

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

4.1.2.2 CNV Lesion Characteristics

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

Study Eye

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

Either Eye

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

4.1.2.3 Concurrent Ocular Conditions

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

Study Eye

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

  Previous violation of the posterior capsule is also an exclusion criterion unless it occurred as a result of yttrium-aluminum garnet (YAG) laser posterior capsulotomy in association with prior, posterior chamber intraocular lens implantation.
- Spherical equivalent of the refractive error demonstrating more than 8 diopters of myopia
- Preoperative refractive error that exceeds 8 diopters of myopia, for patients who have undergone prior refractive or cataract surgery in the study eye

- Intraocular surgery (including cataract surgery) within 3 months preceding the randomization visit
- Uncontrolled ocular hypertension or glaucoma (defined as intraocular pressure [IOP] >25 mmHg or a cup to disc ratio >0.8, despite treatment with antiglaucoma medication) and any such condition the investigator determines may require a glaucoma-filtering surgery during a patient's participation in the study
- History of glaucoma-filtering surgery, tube shunts, or microinvasive glaucoma surgery
- History of corneal transplant
- History of prior vitrectomy surgery and absence of posterior capsule

Either Eye

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

4.1.2.4 Concurrent Systemic Conditions

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

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

  If a patient's initial measurement exceeds these values, a second reading may be taken 30 or more minutes later. If the patient's blood pressure must be controlled by antihypertensive medication, the patient may become eligible if medication is taken continuously for at least 30 days prior to Day 1.
- History of stroke within the last 3 months prior to informed consent
- Uncontrolled atrial fibrillation within 3 months of informed consent
- History of myocardial infarction within the last 3 months prior to informed consent
- History of other disease, metabolic dysfunction, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of ranibizumab or placement of the implant and that might affect interpretation of the results of the study or renders the patient at high risk of treatment complications in the opinion of the investigator
- Current systemic treatment for a confirmed active systemic infection
- Use of any systemic anti-VEGF agents
- Chronic use of oral corticosteroids (>10 mg/day of prednisone or equivalent)
- Active cancer within 12 months of randomization except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of <6 and a stable prostate-specific antigen for >12 months

- Previous participation in any non-ocular (systemic) disease studies of investigational drugs within 1 month preceding the informed consent (excluding vitamins and minerals)
- Use of antimitotic or antimetabolite therapy within 30 days or 5 elimination half-lives of the randomization visit
- Requirement for continuous use of any medications or treatments indicated in Section 4.4.2, "Prohibited Therapy"
- Pregnant or breastfeeding, or intending to become pregnant during the treatment period and for at least 28 days after the last intravitreal injection of ranibizumab or 1 year after the last implant refill-exchange of ranibizumab

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

4.2 METHOD OF TREATMENT ASSIGNMENT AND MASKING

4.2.1 Randomization and Masking

Patients will be randomly allocated in a 3:2 ratio so that approximately 216 patients will receive the PDS implant with ranibizumab 100 mg/mL Q24W and approximately 144 patients will receive Q4W intravitreal ranibizumab 0.5 mg injections. On the day of a patient's randomization visit, BCVA will be measured based upon the ETDRS chart assessment at a starting test distance of 4 meters and randomization will be stratified by the BCVA score ($<$74 letters vs. $\geq$74 letters). Randomization will be performed through an IxRS.

The Sponsor recognizes that it may be difficult to fully mask site staff in an open label surgical study.

The Sponsor will require that the following steps be implemented as a best attempt to mask VA examiners in order to minimize biases in VA assessments.

- The VA examiner will only conduct refraction and VA assessments and will be masked as best as possible to patient study eye assignment, study visit type, and patient treatment assignment.
- The VA examiner will have no access to a patient's BCVA scores from previous visits and will be aware only of the patient's refraction data from previous visits.
- The VA examiner may provide no other direct or indirect patient care.
- Patients and unmasked site personnel will be asked not to discuss the study eye assignment, study visit type, and patient treatment assignment with the VA examiner.

Patients and study site personnel (except VA examiner) will not be masked with regard to patient assignment to the intravitreal arm or the implant arm because of the difficulties

of maintaining masking following the surgical procedure. Additional safety visits will be applicable only to the implant arms, and implant visualization will occur during ophthalmic examinations.

Ocular images obtained from patients will be forwarded to the central reading center for masked analysis and/or storage.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

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

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Port Delivery System with Ranibizumab

The PDS, described in Section 1.3 and Appendix 16, will be supplied by the Sponsor. For detailed information on the PDS components and the initial implant filling, insertion, refill-exchange, and explantation procedures, as well as contraindicated uses, consult the PDS IFU and PDS Investigator's Brochure.

The implant, insertion tool, initial fill needle, refill needle, and explant tool should be maintained at a room temperature below 25°C (77°F). The storage location at the clinical site must have restricted access and be available only to study personnel. The implant and insertion tool are supplied sterilized by exposure to ethylene oxide. The initial fill needle, refill needle, and explant tool are sterilized by electron-beam processing.

The PDS components must not be re-sterilized because of the possibility of damaging the mechanical integrity of the implant and ancillary devices.

The packages should be opened only immediately prior to use.

Do not use if the package is damaged, punctured, or broken as sterility may be compromised. Do not use beyond the expiration date.

Note: Unless otherwise directed by the Sponsor, only ranibizumab (100 mg/mL) will be injected into the implant.

4.3.1.2 Formulation of Ranibizumab 100 mg/mL Used to Fill or Refill-Exchange the Implant

Ranibizumab 100 mg/mL for the PDS will be supplied by the Sponsor for the initial fill and refill-exchange of the implant.

Contents should not be frozen or shaken and should be protected from direct light. Ranibizumab must be refrigerated at 2°C–8°C (36°F–46°F) upon receipt until used. Sites must monitor and record refrigerator temperature at all times (24 hours per day,

7 days per week). **Store in original carton before and after use.** Ranibizumab will be labeled as required by the relevant regulatory agencies.

For further details, see the pharmacy manual.

4.3.1.3 Formulation of Intravitreal Ranibizumab 10 mg/mL

Ranibizumab for intravitreal injection will be supplied by the Sponsor and is formulated as a sterile, colorless to pale yellow solution. Ranibizumab is supplied as a preservative-free, sterile solution in a single-use container designed to deliver 0.05 mL of ranibizumab 10 mg/mL solution with 10 mM histidine hydrochloride, 10% α,α-trehalose dihydrate, 0.01% polysorbate 20, pH 5.5. Ranibizumab contents should not be frozen or shaken and should be protected from direct light. Ranibizumab contents must be refrigerated at 2°C–8°C (36°F–46°F) upon receipt until used.

For further details, see the pharmacy manual.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12).

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.5.

4.3.2.1 Port Delivery System with Ranibizumab

Study investigators must adhere to study-specific implant initial filling, insertion, refill-exchange, and explantation procedures as outlined in the PDS IFU document.

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

At each refill-exchange, a volume of approximately 100 µL ranibizumab will be injected in situ into the implant through the septum to exchange the remaining contents of the implant with newly introduced ranibizumab. The volume of newly introduced ranibizumab remaining in the implant after the refill-exchange procedure will be approximately 20 µL. Missed implant refill-exchanges should be made up no later than the next scheduled study visit. If at the next scheduled study visit the implant refill-exchange cannot be performed, the investigator must contact the Sponsor for further discussion prior to administering future implant refill-exchanges. Subsequent refill-

exchanges will be administered according to the study treatment schedule relative to Day 1 as outlined in Appendix 1 until patients complete the study.

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

4.3.2.2 Ranibizumab Intravitreal Injection

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

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

Patients in the intravitreal arm will receive their first intravitreal injection of 50 µL of the ranibizumab 10 mg/mL (0.5-mg dose) at the Day 1 visit, which will occur at the conclusion of the randomization visit. Afterward, patients will receive intravitreal ranibizumab injections of 50 µL of the 10-mg/mL formulation Q4W at each scheduled study visit until Week 92 *(see Appendix 2, Table 3 for guidance on additional intravitreal injections post-Week 92 due to extenuating circumstances)*. Missed treatments will not be made up. Study visits for the intravitreal arm will be scheduled to occur according to the schedule of activities in Appendix 2 and are relative to the Day 1 visit.

Guidelines for treatment interruption or discontinuation are provided in Section 5.1.5.2 and Table 4.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (PDS with ranibizumab and intravitreal ranibizumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

Prior to site closure, IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation, except all unused PDS components that should be returned to the Sponsor. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log and should provide a complete accounting of all IMPs provided by the Sponsor.

4.3.4 Continued Access to Port Delivery System with Ranibizumab

The Sponsor will offer continued access to Roche IMP (PDS with ranibizumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMP (PDS with ranibizumab) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A patient will not be eligible to receive Roche IMP (PDS with ranibizumab) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for nAMD
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for nAMD
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

Patients may be eligible to receive PDS with ranibizumab as part of an extension study, as described in Section 3.1.

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to the randomization visit until conclusion of the patient's study participation or early termination visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF except for ranibizumab treatment of either eye (if applicable), which will be recorded on a separate eCRF log.

4.4.1 Permitted Therapy

Patients who use other maintenance therapy should continue its use unless prohibited as indicated in Section 4.4.2. All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF.

Patients are permitted to use the following therapies during the study:

- Intravitreal administration of FDA-approved anti-VEGF agents, including Sponsor-provided ranibizumab 0.5 mg, at the discretion of the evaluating investigator if a patient's fellow eye requires treatment for nAMD

  If the fellow eye is to receive an FDA-approved intravitreal anti-VEGF agent, treatment may be administered at the same visit as the study eye treatment. All study assessments and study eye treatment per protocol should be completed prior to anti-VEGF administration in the fellow eye. Individual trays and sterile preparation must be separately prepared for each eye treatment.

- Continuous use of aspirin or nonsteroidal anti-inflammatory drug (NSAID) treatment, except as outlined below

  All patients randomized to the implant arm and receiving ongoing aspirin or NSAID treatment must interrupt aspirin or NSAID treatment for 7 days prior to implant surgery. Interruption of these medications must be pre-planned at the screening visit to avoid delay in implant surgery. These medications can be restarted, if appropriate, after the Day 2 safety visit occurs. One-time use of aspirin or NSAIDs for pain management after implantation is allowed.

- Ongoing anticoagulant or antiplatelet therapy (other than aspirin or other NSAIDs), as outlined below

  Patients randomized to the implant arm who are receiving ongoing anticoagulant or antiplatelet therapy (other than aspirin or other NSAIDs) could be enrolled if they can safely and are willing to temporarily interrupt these medications prior to Day 1, after discussion with their prescribing physician. 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 ticlopidine. The duration of the treatment interruption period should be deferred to the investigator in consultation with prescribing physician and should be made on the basis of the risks of oral anticoagulant or antiplatelet therapy weighed against potential benefits and in consideration of the medication's prescribing information. Interruption of these medications must be pre-planned at the screening visit to avoid delay in implant surgery. These medications can be restarted after the Day 2 safety visit occurs.

- Cataract surgery in the study eye, if clinically indicated and occurring 7 or more days after the last study treatment, with the next study treatment held for 7 or more days following the surgery
- Treatment, as clinically indicated, for the onset of increased IOP and/or glaucoma in the study eye during a patient's study participation
- Use of topical steroids post-implant insertion or post-explantation surgery in the study eye
- Conditional use of magnetic resonance imaging (MRI) scans for patients in the implant arm

  Note that a patient with the PDS implant can be safely scanned in an MR system meeting the following conditions:

  – Static magnetic field of 1.5-Tesla (1.5 T) or 3-Tesla (3 T)
  – Maximum spatial field gradient of 3,000 G/cm (30 T/m)
  – Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 4.0 W/kg (First Level Controlled Operating Mode)

  For additional information refer to the current PDS IFU document.

4.4.2 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Concurrent use of any systemic anti-VEGF agents
- Concurrent study eye treatment for nAMD with anti-VEGF agents other than the study-assigned treatment
- Concurrent fellow eye treatment for nAMD with unapproved anti-VEGF therapy
- Concurrent treatment with laser photocoagulation (any type) for nAMD in the study eye
- Concurrent treatment with Visudyne® for nAMD in study eye
- Concurrent use of intravitreal corticosteroids in the study eye
- Concurrent use of subtenon corticosteroids in the study eye (except at the conclusion of PDS implantation or explantation surgery)

- Concurrent use of and participation in other experimental therapies (except those with minerals and vitamins)

Note: If patients receive any of the above listed treatments at any time during the study, the Sponsor will determine if discontinuation of the study treatment is required.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1 and Appendix 2. All activities should be performed and documented for each patient.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening and randomization visit evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) other than protocol-specified procedural medications (e.g., dilating drops, fluorescein dyes, cefazolin or vancomycin, implant insertion, refill-exchange and explantation procedures medications, and pre- and post-treatment medications [e.g., proparacaine, antimicrobials, steroids]) used by the patient within 7 days prior to initiation of study treatment will be recorded.

All intravitreal anti-VEGF medications administered to the patient within 9 months prior to the screening visit will also be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Height and Weight

A patient's height and weight will be recorded.

4.5.4 Vital Signs

Vital signs will include measurements of pulse and systolic and diastolic blood pressure while the patient in a seated position after resting for 5 minutes.

4.5.5 Ocular Assessments

Except where noted, all of the following ocular assessments should be performed for both eyes:

- BCVA, as assessed on an ETDRS chart at a starting distance of 4 meters (performed prior to dilating eyes)
- IOP measurement
  - At each visit, perform IOP measurement prior to dilating eyes or refill-exchange procedure; the method used for a patient must remain consistent throughout the study for visits in the office.
  - Before implant insertion or explantation surgery, the treating physician must check IOP for the study eye using indentation tonometry
  - Upon completion of the implant insertion or explantation surgery, the treating physician will check IOP for the study eye only by digital palpation before patching the eye.
- Slitlamp examination (for grading scales for anterior and vitreous flare/cells and vitreous hemorrhage density; see Appendix 7)
- Dilated binocular indirect high-magnification ophthalmoscopy

  In addition, examinations will be performed for patients in the implant arm after implant insertion in the study eye and on Days 2 and 7 (±2 days); afterward, dilated ophthalmoscopy examinations will be performed at each visit to monitor the implant placement, and to evaluate other implant problems.
- Finger-counting test, followed by hand motion and light perception tests (as applicable) performed by the treating physician within 15 minutes following implant refill-exchange or intravitreal ranibizumab treatment for the study eye only

Patients will remain at the surgical center after implant insertion and in the office after implant refill-exchange until the designated physician has assessed that there are no safety concerns following treatment, at which point the patient will be allowed to leave. If any safety concerns or immediate toxicity is noted, the patient will remain and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event and the adverse event treatment must be reported on the appropriate eCRF page.

Additional non-invasive ocular assessments may be performed by the investigator to explore patient factors related to the implant surgical procedures, regardless of whether a safety event occurred in a particular patient or not. Results of the additional ocular assessments will be forwarded to the Sponsor for evaluation and/or storage.

4.5.6 Ocular Imaging

The central reading center will provide a central reading center manual and training material to sites for specified study ocular images. Before any study images are obtained, site personnel, test images, room, systems, and software (where applicable)

will be certified and validated by the reading center as specified in the central reading center manual. All ocular imaging assessments will be obtained by trained site personnel at the study sites and forwarded to the central reading center for analysis and/or storage. Ocular images obtained from patients will be retained by the reading center and will later be transferred to Roche. They may also be included in future exploratory analysis.

Note: After randomization, if a patient misses a study visit when ocular images are scheduled (see Appendix 1 and Appendix 2), images should be obtained at the next scheduled visit the patient attends.

The following ocular images of both eyes will be collected from all study patients:

- Fundus photographs (see Appendix 10)
- Lens photographs (fundus reflex photographs)
- FA images (to be performed after laboratory samples are obtained; see Appendix 11)
- Fundus autofluorescence images (Appendix 9)
- SD-OCT scans (see Appendix 12)

  Note: Center point thickness (CPT) is *defined as the* retinal thickness in the center point of the fovea measured between the internal limiting membrane and the inner third of the retinal pigment epithelium layer. Central subfield thickness (CST) is defined as the average thickness of the central 1 mm circle of the ETDRS grid centered on the fovea *measured between the internal limiting membrane and the Bruch's membrane* (see central reading center manual).

The following ocular images will be collected only from the study eye of patients in the implant arm and forwarded to the reading center for evaluation and/or storage and will later be transferred to Roche:

- Implant photographs (high-magnification of the implant in the eye through dilated pupil and outside the eye; see Appendix 13)

The following ocular images of both eyes will be collected from all study patients at selected sites that have OCT angiography equipment and forwarded to the reading center for evaluation and/or storage and will later be transferred to Roche:

- OCT-angiography images (see Appendix 10)

Additional non-invasive ocular assessments (e.g., ocular B-scan ultrasonography or ultrasound biomicroscopy) may be performed by the investigator to explore patient factors related to the implant surgical procedures, regardless of whether a safety event occurred in a particular patient or not.

Ocular images collected from study patients may be evaluated using advanced analytics tools (e.g., artificial intelligence-based tools) to assess clinically relevant features.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Samples for the laboratory tests listed below should be obtained prior to study eye treatment and FA (if applicable) for all study patients. Patients are not required to fast prior to sample collection. Samples will be shipped to a central laboratory and/or the Sponsor or a selected designee for analysis and/or storage. All instructions for obtaining, processing, storing, and shipping specimens are provided in the laboratory manual. Laboratory supply kits will be provided to the sites by the central laboratory. Please refer to Appendix 1, Appendix 2, and Appendix 5, for sample collection timepoints and Appendix 15 for biological sample collection and shipping instructions.

The following assessments will be performed:

- Hematology: hemoglobin, hematocrit, quantitative platelet count, RBCs, WBCs, and differentials, including neutrophils, bands, lymphocytes, basophils, eosinophils, and monocytes (absolute and percent)
- Serum chemistry: bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN, creatinine, calcium, phosphorus, total and direct bilirubin, total protein, albumin, AST, ALT, lactic dehydrogenase, ALP, and uric acid
- Urinalysis: specific gravity, pH, blood, protein, ketones, glucose, bilirubin, urobilinogen, and microscopic examination (if any of the preceding urinalysis tests, other than glucose and ketones, are abnormal)
- Coagulation: aPTT and PT
- Serum pregnancy test (if required)
- Serum samples for measurement of anti-drug antibodies (ADA)
- Serum samples for measurement of ranibizumab concentration
- Aqueous humor, serum, and plasma samples (from supplemental treatment and the subsequent study visit, early termination, and implant explantation visits) for exploratory biomarker research (including free-VEGF) and/or PK analysis
- At selected sites, additional serum PK samples will be collected from the patients in the intravitreal arm 1-5 days after an intravitreal ranibizumab 0.5 mg injection (see Appendix 2).

  Every attempt should be made to collect all samples prior to the primary analysis time point, which will occur when all patients have completed their Week 40 visit.

  The sample collection may be performed at the study site or by a mobile nursing (MN) professional at the patient's home or another suitable location. The Sponsor will select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed.

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Pregnancy test

  All women of childbearing potential, including those who have had tubal ligation, will have a urine pregnancy test at screening and at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test, which will be sent to a central laboratory.

The following samples will be obtained from patients in the implant arm only and may be analyzed in the future:

- Explanted implant with contents (explanted implant containing a mixture of ranibizumab drug product and vitreal components diffused into the implant), preserved for potential analysis upon explantation procedure

Exploratory biomarker research may include, but will not be limited to, analysis of growth factors and cytokines associated with angiogenesis and genes associated with AMD risk.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.10), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Aqueous, plasma, and serum samples collected during supplemental treatment and the subsequent study visit, early termination, and implant explantation visits will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.8 Patient Preference and Treatment Satisfaction

Patient preference and treatment satisfaction will be assessed using the PDS Patient Preference Questionnaire (PPPQ) and Macular Degeneration Treatment Satisfaction Questionnaire (MacTSQ). Patient preference and treatment satisfaction questionnaires will be administered by an interviewer prior to any other visit assessments being performed. Interviews will be conducted using versions of the questionnaire translated into the spoken language of the patient. Patients may be excluded from completing these assessments if a translation is not available in their spoken language.

4.5.8.1 Port Delivery System Patient Preference Questionnaire

The PPPQ is a 3-item questionnaire that captures a patient's preference for treatment, the strength of their preference, and the reasons for their preference. The PPPQ will be administered only to patients in the implant arm, who will have received intravitreal anti-VEGF treatment prior to Day 1. The PPPQ was developed from patient preference questionnaires in the literature, modified for use with the PDS (Pivot et al. 2013; Rummel et al. 2017).

Refer to Patient Questionnaire Booklet for copy of the PPPQ.

4.5.8.2 Macular Degeneration Treatment Satisfaction Questionnaire

The MacTSQ is a 12-item questionnaire designed to assess treatment satisfaction in patients with macular degeneration. Scoring of the MacTSQ results in two subscale scores: 1) convenience, information, and satisfaction; and 2) safety, efficacy, and discomfort. A total score may also be computed. Subscale scores range from 0 to 36, and the total score ranges from 0 to 72. A higher score indicates greater satisfaction (Mitchell and Bradley 2017).

Refer to Patient Questionnaire Booklet for copy of the MacTSQ.

4.5.9 Video Recording of Implant Insertion, Refill-Exchange, and Explantation Procedures

The implant insertion, explantation, refill-exchange, and any other ocular surgical procedures (e.g., conjunctival erosion or retinal detachment repair) performed in the study eye will be captured on video unless the study center has policies in place that prohibit these procedures from being video captured. Recordings may be used for, but are not limited to, physician training or product characterization and may be forwarded to a central reading center for analysis and/or storage.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new

pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to ranibizumab, AMD and other conditions, or drug safety:

- Whole blood samples collected at randomization
- Aqueous humor samples collected at randomization and at Weeks 24, 28, 48, 52, 72, 76, 96*, and X (for patients who follow an alternate final study visit scenario, as applicable)*
- Plasma and serum samples collected (if aqueous humor samples are collected) at randomization and at Weeks 24, 28, 48, 52, 72, 76, 96*, and X (for patients who follow an alternate final study visit scenario, as applicable)*
- Leftover serum, plasma, and aqueous humor samples collected during supplemental treatment and at the subsequent study visit, early termination, and implant explantation visits
- Leftover blood, serum, plasma, and aqueous humor samples, and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.10.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.10.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

[redacted]

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.10.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed

Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Any treatment for nAMD not specified in the protocol

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Upon study treatment discontinuation, patients in the implant arm will no longer receive implant refill-exchanges and patients in the intravitreal arm will no longer receive ranibizumab injections.

All patients who discontinue study treatment will be strongly encouraged to attend as many scheduled study visits as possible, with an emphasis on visits at Weeks 36, 40, and 96 (see Appendix 4 for the minimum required assessments to be performed). Per investigator judgment, patients may start an FDA-approved intravitreal anti-VEGF treatment for nAMD in the study eye after the decision to discontinue study treatment is made. Study-sponsored intravitreal ranibizumab 0.5 mg treatment will be provided for patients who discontinue from the implant arm only, if the anti-VEGF treatment chosen by the investigator is ranibizumab and until the patient completes the study.

The investigator must notify the Medical Monitor if the decision to perform explantation is made after study treatment discontinuation. Explanted patients will return for safety assessments at 1, 7 (±2), 30 (±7), and 60 (±7) days post-explantation (see Appendix 4). All patients will be strongly encouraged to remain in the study after their last post-explantation safety visit. They can return for as many scheduled study visits as possible (with an emphasis on completing the Week 36, Week 40, and Week 96 visits). Patients may start an FDA-approved intravitreal anti-VEGF treatment in the study eye, including Sponsor-provided intravitreal ranibizumab 0.5 mg if chosen by the investigator once the need for explantation is confirmed and preferably after explantation is completed.

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

  If a patient misses more than two consecutive monthly visits within any 6-month treatment period, the investigator and the Sponsor may consider withdrawing the patient from the study.

- Investigator or Sponsor determines it is in the best interest of the patient

Patients in the implant arm who withdraw from the study prematurely will be scheduled for an early termination evaluation visit 90 (+7) days after the implant insertion procedure or 30 (+7) days following the last implant refill-exchange for monitoring of all adverse events (serious and non-serious) (see Appendix 1).

The investigator must notify the Medical Monitor if the decision to perform explantation is made. Explanted patients will return for safety assessments at 1, 7 (±2), 30 (±7), and 60 (±7) days post-explantation (see Appendix 4), and for an early termination visit 90 (+7) days post-explantation. As per investigator judgment, patients may start an intravitreal FDA-approved anti-VEGF treatment for nAMD in the study eye once the need for explantation is confirmed, and preferably after explantation is completed if possible. Patients may receive Sponsor-provided intravitreal ranibizumab 0.5 mg, if chosen by the investigator, until the early termination visit is completed and patients withdraw from the study.

Patients in the intravitreal arm who withdraw from the study prematurely should return for an early termination evaluation visit 30 (+7) days following the last intravitreal ranibizumab 0.5 mg injection for monitoring of all adverse events (serious and non-serious) and early termination assessments (see Appendix 2).

Every effort should be made to obtain information on patients who withdraw from the study but have not withdrawn consent. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Data recording is inaccurate or incomplete

The Sponsor will notify the investigator if the study is placed on hold or if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The PDS is not approved for commercial distribution, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with the PDS in completed and ongoing studies. Please refer to the PDS Investigator's Brochure for a complete summary of safety information.

The safety and tolerability of intravitreal ranibizumab 0.5 mg injections have been investigated in previous Phase I, I/II, III, and IIIb studies in patients with nAMD. Potential safety issues associated with the route of administration or the pharmacology of ranibizumab in the study population include VA reduction, intraocular inflammation, transient and/or sustained elevation of IOP, cataract development or progression, retinal hemorrhage, vitreous hemorrhage, macular edema, endophthalmitis, retinal tear or detachment, hypersensitivity reactions, and arterial thromboembolic events (ATEs). Adverse events that should be considered ATEs include, but are not limited to, myocardial infarction and cerebrovascular accident (ischemic and/or hemorrhagic). See the PDS Investigator's Brochure for further details.

5.1.1 Safety Assessments

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for treatment-related complications. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit (see Appendix 4) and will be instructed to contact the investigator at any time should they have any health-related concerns.

Upon completion of implant insertion procedure on Day 1, patients will have indirect ophthalmoscopy performed to monitor the implant placement and to evaluate any potential implant problems. The treating physician will check IOP by digital palpation for the study eye only as clinically indicated. These assessments must be performed prior to placing a patch on the eye after implant insertion. Patients will remain in the surgical center until the designated physician has assessed that there are no safety concerns following treatment, at which point the patient will be allowed to leave. If any safety concerns or immediate toxicity is noted, the patient will remain in the surgical center and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event and treatment of adverse event will be reported on the appropriate eCRFs.

Patients in the implant arm will return after the implant insertion procedure for safety evaluation visits on Day 2, Day 7 (±2), and at study visits every 4 weeks (±7 days). See Appendix 1 for assessments conducted at safety evaluation visits following implant insertion.

Following each implant refill-exchange, patients will undergo a finger-counting test, followed by hand motion and light perception tests (when necessary) performed by the designated physician within 15 minutes post-treatment for the study eye only; indirect ophthalmoscopy will be performed after each implant refill-exchange to monitor the implant.

The use of self-administered antimicrobial ophthalmic drops is required before and after PDS implant insertion, and is optional per investigator's discretion prior to the implant refill-exchange procedure but required after the PDS implant refill-exchange procedure. Anti-inflammatory ophthalmic drops are required after implant insertion and explantation (see Appendix 17).

For the study eye only, following each intravitreal ranibizumab 0.5 mg injection, patients will undergo a finger-counting test, followed by hand motion and light perception tests

(when necessary) performed by the designated physician within 15 minutes post-treatment.

All patients will remain at the office until the designated physician has assessed that there are no safety concerns following treatment, at which point the patient will be allowed to leave. If any safety concerns or immediate toxicity is noted, the patient will remain at the office and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event and treatment of adverse event (if applicable) will be reported on the appropriate eCRFs.

All patients will be contacted by study site personnel 3 (±1) days after each treatment (implant refill-exchange or intravitreal injection) to elicit reports of any decrease in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. Patients will also be asked whether they have taken the prescribed, self-administered, post-treatment antimicrobials (if applicable) for their study eye as directed by the investigator.

Detailed ocular examinations, including indirect ophthalmoscopy and slitlamp examination, will be performed throughout the study. All patients will undergo dilated binocular indirect high-magnification ophthalmoscopic examination at each visit, which will include visual monitoring of the implant placement and evaluation of any other implant-related problems, as well as data collection on the associated eCRF and/or Medical Device Complaint Form. The sample content retrieved during explantation procedures will be collected and forwarded to the Sponsor's designee and may be analyzed in the future.

Implant refill-exchange will be interrupted or discontinued as per the dose-interruption criteria listed in Table 4 and at the investigator's discretion if he or she suspects any safety or other treatment-related issues. If the investigator decides to interrupt a dose, the reason will be recorded on the corresponding eCRF and, if appropriate, on the Adverse Event eCRF. In the event a patient experiences an adverse event in the study eye that is considered by the investigator to be severe in intensity or serious in nature, consideration should be given to interrupting the treatment or discontinuing the patient from study drug treatment or the study. The decision will be at the investigator's discretion and should be recorded on the eCRF. See Section 4.3 for information of study drug and patient discontinuation.

The incidence of all adverse events (serious and non-serious) will be recorded on eCRFs for the duration of this study. Serious adverse events will be collected and reported to the Sponsor in compliance with Good Clinical Practice guidelines.

5.1.2 Risks Associated with Intravitreal Ranibizumab Injection

5.1.2.1 Increased Intraocular Pressure

Transient increases in IOP have been seen within 60 minutes of injection of ranibizumab. Sustained IOP increases have also been reported. Both IOP and perfusion of the optic nerve head must be monitored and managed appropriately.

5.1.2.2 Cataract

Cataract may be a clinically relevant event with possible outcome of visual loss. Patients receiving intravitreal injections are at risk for the development of traumatic cataract. During the intravitreal injection, any direct trauma to the lens by the needle touching the lens could result in traumatic cataract.

5.1.2.3 Vitreous Hemorrhage

Vitreous hemorrhage is generally a clinically relevant event with a possible outcome of vision loss. Vitreous hemorrhage usually occurs from a disruption of the retinal vessels, or bleeding from diseased or abnormal retinal vessels. Perivascular tractional forces along any of the vitreous attachments, whether traumatic or from pathologic vascularization of the retina, may result in hemorrhage into or behind the vitreous. Hemorrhage may occur due to a diseased retina (nAMD) or proliferative diabetic retinopathy, or a traumatic insult (injection or surgical intervention). Sufficient traction along a vessel can lead to a vessel tear, resulting in a vitreous hemorrhage.

5.1.2.4 Intraocular Inflammation

Intraocular inflammation can range from a mild to severe inflammation of the eye with sequelae that may lead to vision loss. Inflammation can occur due to potential immunogenicity, in reaction to the active substance or its excipients, or in response to the invasive nature of the procedure. It is also hypothesized that intravitreal antibody formation may contribute to the development of intraocular inflammation; however, there is currently no evidence either from the published literature or from the postmarketing data to support this assertion. There is potential introduction of microorganisms during the injection procedure as described below in Section 5.1.2.6 (endophthalmitis).

5.1.2.5 Retinal Detachment and Retinal Tear

Retinal detachment and retinal tear are considered clinically relevant events with a possible outcome of permanent vision loss. A tear or hole in the retina, typically in the periphery, leads to fluid accumulation and separation of the neurosensory retina from the underlying RPE. Vitreoretinal traction is responsible for most of the rhegmatogenous retinal detachments. With age, the vitreous becomes more liquefied, and a posterior vitreous detachment (PVD) can occur. In some eyes, strong vitreoretinal adhesions are present and the occurrence of a PVD can lead to the formation of a retinal tear. The liquefied vitreous can then seep through the tear and under the retina, leading to a retinal detachment.

5.1.2.6 Endophthalmitis

Intravitreal injections, including those with ranibizumab, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering ranibizumab. In addition, patients should be monitored following the injection to permit early treatment should an infection occur.

5.1.2.7 Retinal Pigment Epithelial Tear

Retinal pigment epithelium tears may be considered clinically relevant events, with the possibility of severe permanent vision loss, especially in tears that are greater than 1-disk diameter and involve the fovea. RPE tear can be part of the natural course of nAMD or can occur as a complication following intravitreal injections.

Please refer to the PDS Investigator's Brochure for further information.

5.1.3 Anticipated Risks Associated with Port Delivery System with Ranibizumab Implant and/or Implant Insertion Procedure

5.1.3.1 Vitreous Hemorrhage

The implant insertion procedure has been associated with vitreous hemorrhage. These events may be clinically relevant and in some cases may result in vision loss. Visual recovery is expected in the case of spontaneously clearing vitreous hemorrhage. However, surgical intervention (i.e., vitrectomy) may be needed in the case of a non-clearing vitreous hemorrhage. Close adherence to the most up-to-date PDS IFU document is required to minimize risks of surgery and implant insertion–related vitreous hemorrhage.

5.1.3.2 Conjunctival Bleb

The implant and implant insertion procedure have been associated with adverse events of conjunctival bleb (encapsulated elevation of the *conjunctival tissue* above the implant flange). These events may be clinically relevant. Surgical intervention (i.e., conjunctival repair) may be needed. Close adherence to the most up-to-date PDS IFU is required to minimize risks of surgical or implant insertion-related conjunctival disorder.

5.1.3.3 Conjunctival Erosion

The implant and implant insertion procedure have been associated with conjunctival erosion (defined as a *partial or full thickness* thinning of the conjunctiva). The conjunctival erosion events have included early onset erosion, secondary to improper suturing and generally subsequent to conjunctival retraction in close temporal relationship to the surgery, and late onset erosion not associated with retraction but secondary to the long-term presence of a foreign body under the conjunctiva. These events may be clinically relevant. Surgical intervention (i.e., conjunctival repair) may be needed in case of full-thickness conjunctival erosion, or evidence of progression. Close adherence to the most up-to-date PDS IFU is required to minimize risks of surgery/implant insertion-related conjunctival erosion.

5.1.3.4 Conjunctival Retraction

The implant and implant insertion procedure have been associated with adverse events of conjunctival retraction (defined as the opening of the sutured conjunctival flap). These events may be clinically relevant. Surgical intervention (i.e., conjunctival repair) may be needed. Close adherence to the most up-to-date PDS IFU is required to minimize risks of surgical or implant insertion-related conjunctival disorder.

5.1.3.5 *Rhegmatogenous Retinal Detachment*

Rhegmatogenous retinal detachment has been observed with the implant insertion procedure. These events are clinically relevant and may result in vision loss if not promptly treated with an intervention (e.g., pneumatic retinopexy, vitrectomy, or scleral buckle surgery). Careful evaluation of the retinal periphery by scleral indentation before inserting the implant in the eye, and close adherence to the current PDS IFU, are required to minimize risks of rhegmatogenous retinal detachment.

5.1.3.6 *Endophthalmitis*

Endophthalmitis has been observed with the PDS implant and/or implant insertion procedure. These events are clinically relevant and require prompt treatment as per standard of care to reduce risk of vision loss and maximize recovery (e.g., intravitreal vancomycin and ceftazidime, as well as antibiotic drops, for bacterial endophthalmitis). Saline flush of the implant content using the refill needle, followed by implant fill with vancomycin may also be performed as additional treatment on top of intravitreal and topical antibiotics. Close adherence to the current PDS IFU is required to minimize risks of implant procedures-related endophthalmitis.

Please refer to the PDS Investigator's Brochure for further information.

5.1.4 Potential Risks Associated with Ranibizumab Administered as an Intravitreal Injection or via the Port Delivery System

5.1.4.1 Glaucoma

Sustained IOP increase can be associated with the development of glaucoma, which in turn can lead to permanent vision loss. Although sustained increases in IOP have been reported following administration of VEGF inhibitors, there is no conclusive evidence to date that these IOP increases develop into glaucoma.

5.1.4.2 Venous Thromboembolic Events

Venous thromboembolic events are generally clinically relevant, ranging from superficial phlebitis to a potentially fatal pulmonary embolism. VEGF inhibition, especially systemically, could contribute to the development of this event.

5.1.4.3 Non-Myocardial Arterial Thromboembolic Events

ATEs may be associated with VEGF inhibition in the vascular system, as well as with underlying abnormal blood vessels due to medical conditions, such as hypertension, atherosclerosis, or diabetes.

5.1.4.4 Myocardial Infarction

Myocardial infarction is a clinically relevant event, ranging from an asymptomatic event to a fatal outcome.

5.1.4.5 Non-Ocular Hemorrhage

Non-ocular hemorrhage is a heterogeneous risk, ranging from events such as mild nose bleed to fatal gastrointestinal hemorrhage. These events may be related to the systemic effects of anti-VEGF treatment.

5.1.4.6 Hypertension

Hypertension may be caused by VEGF inhibition, especially when anti-VEGF agents are used systemically.

Please refer to the PDS Investigator's Brochure for further information.

5.1.5 Management of Patients Who Experience Adverse Events

5.1.5.1 Dose Modifications

No dose modifications will be permitted in this study.

5.1.5.2 Treatment Interruption

Study treatment dose interruption and/or study treatment discontinuation or study discontinuation following an adverse event will be determined according to the criteria in Table 4. The reason for interrupting the treatment should be recorded on the associated eCRF and, if applicable, on the Adverse Event eCRF.

Table 4 Dose Interruption, Study Treatment Discontinuation, or Study Discontinuation Criteria

Event	Dose Interruption Criteria
Intraocular inflammation	Interrupt dose if intraocular inflammation is ≥2+ in the study eye (see the definitions of intraocular inflammation in Section 5.1.2.4).
BCVA decrease	Interrupt dose if there is a study drug–related decrease of ≥30 letters in BCVA in the study eye compared with the last assessment of BCVA.
Elevated IOP	Interrupt ranibizumab study treatment via intravitreal injection if pre-treatment IOP in the study eye is ≥30 mmHg. Treatment will be permitted when IOP has been lowered to <30 mmHg, either spontaneously or by treatment, as determined by the investigator. Note: In the implant arm, if IOP in the study eye is ≥30 mmHg at an implant refill-exchange visit, study treatment may proceed if the implant is seated in correct position.
Rhegmatogenous retinal break or detachment and macular hole Stages 3 or 4	Interrupt dose if a retinal break is present in the study eye. Treatment may be resumed ≥28 days after the retinal break has been successfully treated. Patients with a rhegmatogenous retinal detachment or Stage 3 or 4 macular holes may require discontinuation from study treatment after consultation with the Medical Monitor.
Local or systemic infection	Interrupt dose if any of the following are present: infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye. Dose *should* be interrupted if the patient is currently *under observation or* receiving treatment for a *suspected or confirmed* severe systemic infection per clinical judgment *(including COVID-19).*
IV corticosteroids	Dose may be interrupted after consultation with the Medical Monitor if patients need to receive IV corticosteroids. Study treatment may be resumed when the patient has finished IV corticosteroid course.
Intraocular surgery	Dose may be interrupted after consultation with the Medical Monitor if intraocular surgery (except cataract, see Section 4.4.1) has been performed in the study eye within the previous 28 days.
Observed damage to the implant	If damage to the implant is observed by the investigator, the implant may be explanted even if it did not cause any adverse event to the patient. The patient may be discontinued from the study treatment.
Pregnancy	Discontinue patient's study treatment in the case of positive serum pregnancy test during the study. For patients in the implant arm, a saline flush of implant content may be performed.

BCVA = best-corrected visual acuity; IOP = intraocular pressure.

5.1.5.3 Supplemental Treatment with Intravitreal Ranibizumab for Implant Patients

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

- Decrease of ≥15 letters from the best-recorded BCVA in the study, due to nAMD disease activity
- OR
- Increase of ≥150 μm in central subfield thickness (CST) on SD-OCT from the lowest CST measurement in the study, due to nAMD disease activity

OR

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

At each visit in which supplemental treatment is possible, the study eye BCVA score and CST value must be entered into IxRS to assess the need for supplemental treatment. If any of the criteria above are met, the supplemental treatment must be administered at the end of the visit. If treatment cannot be administered at the end of the visit, patients will be asked to return within 7 days to receive supplemental treatment.

Following supplemental treatment with intravitreal ranibizumab 0.5 mg, patients will continue with scheduled implant refill-exchanges at Weeks 24, 48, and 72 relative to the Day 1 visit.

Note: Supplemental treatment is allowed at Weeks 16 and 20 (after implant insertion) and at Weeks 40, 44, 64, 68, 88 and 92 only if any of the criteria above are met. Supplemental treatment is not allowed at any other study visits. Patients with progressive worsening of nAMD disease activity (e.g., BCVA or CST worsening, new macular hemorrhage) who, in the investigator's judgment, require any treatment for nAMD in the study eye outside of protocol (e.g., ranibizumab intravitreal injection treatment at Week 8) will be discontinued from study treatment (i.e., no additional refill-exchanges) after discussion with the Medical Monitor. Patients discontinuing study treatment will be encouraged to attend as many scheduled study visits as possible, with an emphasis on completing the Week 36, Week 40, and Week 96 visits (see Appendix 4 for the minimum required assessments to be performed).

5.1.5.4 Recommended Management of Cases of Vitreous Hemorrhage

Cases of vitreous hemorrhage secondary to implant-related procedures throughout the study should be managed following the recommendations in Table 5.

Table 5 Recommended Management of Cases of Vitreous Hemorrhage

Timing	Patient's Examination and Management Guidelines
Day of vitreous hemorrhage diagnosis	• If the diagnosis of vitreous hemorrhage is made during a scheduled visit, perform ocular B-scan ultrasonography if possible in addition to the assessments scheduled for that specific visit. • If the diagnosis of vitreous hemorrhage is made during an unscheduled visit, perform ocular B-scan ultrasonography if possible in addition to the assessments listed in Appendix 4. • A safety assessment visit (scheduled or unscheduled) should be performed approximately 2 weeks after occurrence of vitreous hemorrhage (see Appendix 4). If possible, perform ocular B-scan ultrasonography.
Approximately 4 weeks after occurrence (scheduled visit)	• If possible, perform ocular B-scan ultrasonography in addition to the assessments scheduled for that specific visit. • An unscheduled safety assessment visit should be performed between 4 and 8 weeks after occurrence of vitreous hemorrhage (Appendix 4).
Approximately 8 weeks after occurrence (scheduled visit)	• If possible, perform ocular B-scan ultrasonography • If vitreous hemorrhage causes loss in BCVA and neither assessment of the macula nor SD-OCT can be performed successfully: – Discuss a pars plana vitrectomy with the patient as a possibility to remove the vitreous hemorrhage. Consultation with the Medical Monitor is advised prior to performing pars plana vitrectomy.

BCVA = best-corrected visual acuity; SD-OCT = spectral-domain optical coherence tomography.

If a pars plana vitrectomy is clinically necessary to resolve vitreous hemorrhage, the implant must be refilled at the end of the vitrectomy procedure.

5.1.5.5 Recommended Management of Conjunctival Retraction or Conjunctival Erosion Cases

The recommended management of patients with conjunctival retraction or conjunctival erosion is presented in Table 6.

Table 6 Recommended Management of Patients with Conjunctival Retraction or Conjunctival Erosion

Event	Patient's Examination and Management Guidelines
Conjunctival Retraction	• Prescribe antibiotic drops as per standard of care. • Schedule for surgery as soon as possible. – Perform conjunctival flap with undermining of the conjunctiva and release of any traction from previous surgery. – Suture the flap with multiple interrupted sutures. • In case of recurrent retraction or thin conjunctiva, a split corneal graft can be performed.
Conjunctival Erosion	• Prescribe antibiotic drops as per standard of care. • Consult the Medical Monitor for management. • Watch and wait in case of small localized erosion without flange exposure. • Schedule for surgery in case of full-thickness erosion (i.e., exposing the flange) or evidence of progression. – Perform conjunctival flap with undermining of the conjunctiva and release of any traction from previous surgery. – Suture the flap with multiple interrupted sutures. • In case of recurrent retraction or thin conjunctiva, a split corneal graft can be performed.

5.1.5.6 *Recommended Management of Conjunctival Bleb*

The recommended management of patients with conjunctival bleb is presented in Table 7.

Table 7 Recommended Management of Patients with Conjunctival Bleb

Timing of Occurrence	*Patient's Examination and Management Guidelines*
Post implant insertion surgery	• *Perform Seidel test* – *If positive, discuss with the Medical Monitor about potential surgery to revise the scleral wound.* – *If negative, continue with post-operative topical medications (Appendix 17), and follow regular visit schedule.*
During a refill-exchange attempt	• *If the implant septum becomes no longer visible, consider delaying the refill-exchange. Reattempt the refill-exchange after approximately 7 days once the bleb is resolved.*
A month before a scheduled refill-exchange	• *If the bleb has not resolved and the implant septum is not fully visible, perform retroillumination by shining a light towards the implant body through the dilated pupil* – *If the implant septum becomes illuminated with clear margins, consider observation.* – *If the implant septum does not illuminate or its margins do not appear sufficiently defined, discuss with the Medical Monitor about potential surgery to revise the conjunctiva and excise the bleb, potentially in conjunction with the refill-exchange procedure.*

5.1.5.7 Recommended Management of Endophthalmitis Cases

The recommended management of patients with endophthalmitis is presented in Table 8.

Table 8 Recommended Management of Patients with Endophthalmitis

Event	Patient's Examination and Management Guidelines
Endophthalmitis (implant arm)	• Perform anterior chamber/vitreous tap. The aqueous humor should be collected with needle directed toward the exudates/hypopyon to enhance the possibility of microbial isolation and identification. Send aqueous humor sample to local laboratory or out for microbiology cultures. • Treat with intravitreal vancomycin and ceftazidime per standard of care. • Perform saline flush of implant contents using refill needle. • Fill implant using 100 µL of vancomycin (1.0 mg) using refill needle. • Start antibiotic drop coverage per standard of care. • Perform a safety assessment visit (unscheduled; see Appendix 4) daily after occurrence of endophthalmitis until eye posterior segment improves with clearance of the vitreous debris. If possible, perform ocular B-scan ultrasonography. • Refill implant (ranibizumab 100 mg/mL) after endophthalmitis resolves as determined by the investigator and after discussion with Medical Monitor.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.8 and 5.3.5.9 for more information)

- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe according to the adverse event severity scale; see Section 5.3.3, Table 9); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Sight-threatening adverse events: an adverse event is considered to be sight threatening if it is a serious adverse event (as defined in Section 5.2.2) and it meets one or more of the following criteria:
  - The adverse event causes a decrease of ≥30 letters in BCVA (compared with the last assessment of VA prior to the most recent treatment) lasting more than 1 hour.
  - The adverse event requires surgical intervention (i.e., conventional surgery, vitrectomy, vitreous tap, or biopsy with intravitreal injection of anti-infective medications, or laser or retinal cryopexy with gas) to prevent permanent loss of sight.
  - The adverse event is associated with severe intraocular inflammation (e.g., endophthalmitis, 4+ anterior chamber cell/flare or 4+ cells in the vitreous; see Appendix 7 for intraocular inflammation grading scales).

    Note: Adverse events should be reported, listing the underlying cause (if known) of the event as the primary event term (see Section 5.3.5.2).
- *Ocular adverse events of special interest, defined as any of the events listed below, regardless of whether they occur in the study eye or the fellow eye, in a patient randomized to the PDS arm or the intravitreal arm, or the AE causality:*
  - Vitreous hemorrhage
  - Endophthalmitis
  - Retinal detachment
  - Conjunctival retraction
  - Conjunctival erosion
  - Conjunctival bleb or conjunctival filtering bleb leak

- Hyphema
- Cataract

Please refer to the PDS Investigator's Brochure for further information.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events whether associated with the drug, with the implant or one of the ancillary devices, with any of the study procedures, and all adverse events not associated with any of these elements (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4–5.6.

The investigator is also responsible for reporting medical device complaints (see Section 5.4.4). For a device defect with an associated adverse event this means that the investigator must report both an adverse event and a Medical Device Complaint (Section 5.4.4).

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study treatment (Day 1), only serious adverse events caused by a protocol-mandated intervention (e.g., discontinuation of medications or intravitreal ranibizumab administered at screening or during run-in period) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events, regardless of relationship to study drug, implant, or ancillary devices, or study procedures, will be reported until the patient's final study visit. For patients who terminate study treatment and discontinue from the study prematurely, all adverse events will be reported up to the early termination visit. For patients who discontinue study treatment early but continue to participate in the study, adverse events will be reported until their last or final study visit.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 9 provides guidance for assessing adverse event severity.

Table 9 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine causality of an adverse event. Investigators will assess any relationship between the adverse event and each component separately, indicating “yes” or “no” as applicable on Adverse Event eCRF.

Patients in the Implant Arm: The investigator will assess whether there is a potential association with each of the following “components” of the study intervention:

- Implant, insertion tool, or implant procedure
- Refill-exchange or refill needle
- Explant or explant tool
- Ranibizumab (study drug)

Patients in the Intravitreal Arm: The investigator will assess whether there is a potential association with each of the following “components” of the study intervention:

- The intravitreal injection procedure
- Ranibizumab (study drug)

The following guidance should be taken into consideration when assessing causality:

- Temporal relationship of event onset to the initiation of study drug, implant and its insertion, refill-exchange, or explantation procedures or due to other PDS components (see Table 10) or due to intravitreal injection procedure.

- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with study drug, implant or other PDS components/procedures, or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 10 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

For the purposes of reporting events of infection and inflammation, the following terms and definitions should be used (see also Appendix 7 and Appendix 8):

- Iritis: the presence of inflammatory cells in the anterior chamber (trace or greater)

  The presence of aqueous humor flare alone will not constitute iritis but should be documented as an anterior chamber flare for adverse event reporting purposes.
- Iridocyclitis: the presence of inflammatory cells in both the aqueous humor and vitreous (trace or greater)

- Vitritis: the presence of active inflammation in the vitreous, demonstrated by the presence of inflammatory cells (trace or greater)

  Active inflammation in the vitreous should be clinically differentiated from cellular debris from prior episodes of inflammation, hemorrhage, or other causes.

- Endophthalmitis: diffuse intraocular inflammation predominantly involving the vitreous cavity but possibly also involving the anterior chamber, implying a suspected underlying infectious cause

  A culture is required prior to initiating antibiotic treatment for presumed infectious endophthalmitis.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases; record only endophthalmitis that resulted in ≥30 letters loss rather than the decrease of ≥30 letters in BCVA). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of nAMD.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of nAMD, "neovascular age-related macular degeneration progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Worsening of Neovascular Age-Related Macular Degeneration

Study eye medical occurrences or symptoms of deterioration in the study eye that are anticipated as part of nAMD should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of nAMD on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of neovascular age-related macular degeneration").

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse

event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.11 Patient-Reported Questionnaire and Outcomes Data

Adverse event reports will not be derived from patient-reported questionnaire data by the Sponsor, and safety analyses will not be performed using patient questionnaire data. Sites are not expected to review the patient questionnaire data for adverse events.

5.3.5.12 Reporting Requirements for Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For ranibizumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with ranibizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list

of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Medical device complaints (see Section 5.4.4 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor: [redacted], M.D. (Primary)

Mobile Telephone No.: [redacted]

Medical Monitor: [redacted], M.D. (Secondary)

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.

The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until the final study visit. For patients who terminate from study treatment and study early, all adverse events will be collected up to the early termination visit. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study serious adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 28 days after the last intravitreal ranibizumab injection or 1 year after the last implant ranibizumab refill-exchange. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. If medically necessary, as per investigator's judgment and after discussion with the Medical Monitor, a saline flush of implant content may be performed for patients in the implant arm. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Medical Device Complaints

The investigator must report all complaints associated with medical device and their packaging to the Sponsor no more than 24 hours after learning of the event.

In this study, the PDS implant, the PDS ancillary devices, and the intravitreal ranibizumab 0.5 mg single-use container are considered medical devices.

To report a medical device complaint, the investigator should follow the guidance outlined in the Device Complaints and Return Instructions for the Clinical Sites document and provide as much information as possible to the Sponsor, including the product batch number.

If the medical device results in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system by the investigator. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2. If a medical device causes an adverse event to an individual other than the study patient (e.g., study site personnel), the event should be reported to the Sponsor (refer to the Device Complaints and Return Instructions for the Clinical Sites for further details).

For further information on returning the PDS implant and the ancillary devices associated with a complaint, refer to the Device Complaints and Return Instructions for the Clinical Sites document.

5.4.4.1 Device Defects or Deficiencies That Could Have Led to Medical Occurrence

Device deficiencies (inadequacy with respect to labeling, identity, quality, durability, reliability, safety, or performance, including malfunctions) that did not lead to an adverse event but could have led to a medical occurrence if suitable action had not been taken, must be reported immediately (i.e., no more than 24 hours after learning of the event). Refer to the Device Complaints and Return Instructions for the Clinical Sites for further details.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 30 [+7] days after the last dose of study drug for intravitreal arm; the final study visit for patients in the implant arm; and 90 [+7] days after explantation for patients who undergo implant explantation), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper

Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- PDS Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

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

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

The final analysis will be performed *after* all patients have either completed the 2-year study *treatment* period *including their final study visit,* or discontinued early from the study, all data from the study are in the database, and the database is locked.

The primary analysis, summarized by treatment group, may be reported to the public before completion of the study.

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

Detailed specifications of the statistical methods will be described in the Statistical Analysis Plan (SAP).

6.1 DETERMINATION OF SAMPLE SIZE

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

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

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

An independent statistician was employed to conduct a masked evaluation of the variance of the primary efficacy endpoint, but not the proportion of patients who receive supplemental treatment during the study or the study dropout rate before the end of enrollment because the enrollment was too rapid for these evaluations to be of value. The variance comparison to the assumptions used in planning the study did not suggest the initial assumption for the variance of the primary efficacy endpoint was substantially lower. However, independent of this assessment, due to a high speed of enrollment combined with a lower screen failure rate than expected, the number of patients enrolled was unintentionally increased to 418. Details of the masked assessment, findings, and actions will be documented in the SAP.

6.2 SUMMARIES OF CONDUCT OF STUDY

Patient disposition (the number of patients randomized, treated, and completing each study period) will be tabulated by treatment *received*. Reasons for premature study treatment discontinuation and study discontinuation, any eligibility criteria deviation, and other major protocol deviations will also be tabulated.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics such as age, sex, race, baseline disease characteristics (such as baseline CPT, baseline BCVA), and number of prior anti-VEGF injections will be summarized in the efficacy population by treatment group using

descriptive statistics. Exposure to study treatment (number of study treatments and duration of treatment) will be summarized by treatment *received*.

6.4 EFFICACY ANALYSES

Efficacy data will be summarized on the efficacy population comprising all patients who are randomized and receive the study treatment, with patients grouped according to treatment actually received. Patients who received the PDS implant will be included in the implant arm.

Unless otherwise noted, analyses of efficacy outcome measures will be stratified by baseline BCVA (<74 letters vs. ≥74 letters). *The stratification factor as recorded in IxRS will be used. The* estimates and *confidence intervals (*CIs*)* will be provided for the mean (for continuous variables) or proportion (for binary variables) for each treatment group and the difference in means or proportions between two treatment groups. All CIs will be two-sided and at the 95.*03*% level. Details of the calculation of the estimates and CIs will be provided in the SAP.

6.4.1 Primary Efficacy Endpoint

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

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

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

The primary objective is to determine the NI and equivalence between the two treatment arms, as measured by the primary efficacy endpoint with an NI margin of 4.5 letters and equivalence margin of ±4.5 letters. To control the overall type I error, a fixed sequence testing procedure (Westfall and Krishen 2001) will be used. If the implant arm is shown to be non-inferior to the intravitreal arm at the one-sided 0.*02485* level, then the equivalence test will be conducted using two one-sided 0.*02485* tests.

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

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

For the primary efficacy endpoint, if a lower bound of a two-sided 95.*03*% CI for the difference of two treatments is greater than –4.5 letters (the NI margin), then treatment via PDS is considered non-inferior to monthly intravitreal ranibizumab treatment. If the two-sided 95% CI is within –4.5 letters and +4.5 letters, then the two treatment regimens are considered clinically equivalent.

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

Supplemental Analyses for the Primary Endpoint

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

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

The estimand is defined as follows:

- *Population: Adult patients with nAMD diagnosed within 9 months and receiving at least 4 anti-VEGF intravitreal injections (with the last injection being ranibizumab) responsive to prior anti-VEGF treatment*
- *Variable: Change in BCVA score from baseline averaged over Weeks 36 and 40*

- *Intercurrent events: Assume patients have the worst outcome after the following intercurrent events prior to Week 40:*
  - *Receives more than 1 supplemental treatment*
  - *Receives any prohibited systemic treatment or prohibited therapy in the Study eye (Section 4.4.2 of the Protocol)*
  - *Discontinues study treatment due to AEs*
  - *Discontinues study treatment due to lack of efficacy as per investigator's clinical judgment*
- *Population-level summary: Difference in adjusted trimmed mean between PDS 100 mg/mL and intravitreal groups.*

The trimmed mean analysis (Permutt and Li 2017) will be performed using an analysis of covariance (ANCOVA) model *with* adjustment for covariates. The dependent variable in the ANOVA model is the average of non-missing values of Weeks 36 and 40 assessments in change from baseline in BCVA score (if one of the two assessments is missing, the non-missing assessment will be used), and the independent variables are the treatment group, baseline BCVA score (continuous), and the randomization stratification factor of baseline ($<$74 letters vs. $\geq$74 letters).

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

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

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

For the remaining patients, if they have Week 36 and/or Week 40 BCVA assessments, they will be considered "completers"; if they have missing *both* Week 36 and Week 40 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.*03*% CI) for the trimmed mean will be based on the permutation test. The treatment assignments will be permuted in a sufficiently large random sample of possible ways (~30,000 random samples will be generated).

The *method* can be stated in the following four steps:

1. Remove patients whose missing *BCVA* assessments are considered missing at random (see definition above) from the analysis.
2. The percentage of patients to be trimmed will be based on a masked evaluation of percentage of patients meeting the trimming criteria by Week 36 and will be documented in the SAP. The analysis will be used to assess the difference in BVCA between two treatments excluding the true or assumed worst outcomes. Order the data based on adjusted values from the ANCOVA model, and trim equal fractions (*20.3% in the PDS 100 mg/mL arm and 20.2% in the intravitreal ranibizumab arm*) 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 36 and 40 weeks, X is the matrix for the covariates—baseline BCVA score (continuous) and the baseline BCVA category ($<$ 74 letters vs. $\geq$ 74 letters), and 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 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) $\times$ 100% in each group will be used for the analysis specified in Step 3. *If multiple patients have the same adjusted values, they will be ranked randomly relative to each other prior to trimming.*

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

When the proportion of the "must 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 "*must be trimmed patients*" in the two treatment groups.

Other supportive analyses may be performed and details will be provided in the SAP.

6.4.2 Secondary Efficacy Endpoints

The continuous secondary endpoints will be *summarized using descriptive statistics based on all observed data. These continuous endpoints will also be* analyzed *following* the same *method as the* analysis *of the* primary endpoint *(see Section* 6.4.1*) with the independent variable,* baseline BCVA score (continuous*),* in the model replaced with the baseline value of the corresponding endpoint (e.g., *baseline CPT). The intercurrent events and data handling rules for the primary endpoint will apply here. Descriptive*

summaries will be provided for all secondary endpoints based on all observed data. Baseline is defined as the last available measurement prior to first treatment.

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

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

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

6.4.3 Exploratory Endpoints

Details regarding the exploratory endpoints will be provided in the SAP.

6.5 SAFETY ANALYSES

Safety data will be summarized on the safety population comprising all patients who receive study treatment, with patients grouped according to treatment actually received (patients who receive PDS implant will be included in the implant arm).

Safety will be assessed through descriptive summaries of adverse events, ocular assessments, and ADAs to ranibizumab. Clinically significant laboratory abnormalities and clinically significant vital sign abnormalities will be reported as adverse events and evaluated as part of the adverse event assessments.

At the time of the primary analysis, safety summaries will be summarized based on the complete Week 40 data in the safety population. In addition, ongoing safety data (*from first treatment* up to a single specified clinical cutoff date) in the safety population will also be summarized. At the time of the final analysis, safety summaries will be produced based on cumulative data in the safety population.

6.5.1 Adverse Events

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and their incidence will be summarized by treatment arm.

Treatment-emergent adverse events will be defined as events beginning at the surgical insertion of the implant or at the first intravitreal ranibizumab 0.5 mg injection through the completion of the study or until a patient discontinues prematurely. Adverse events will be tabulated by body system and preferred term. All adverse events, serious adverse events, deaths, adverse events leading to discontinuation of study treatment, adverse events of special interest, and adverse events judged to be related to study treatment or procedure will be summarized overall and by the adverse event onset day ($\leq$37 days vs. $>$37 days). Separate summaries will be prepared for non-ocular and ocular adverse events, with events in the study eye and fellow eye summarized separately.

6.5.2 Ocular Assessments

Results of the following ocular assessments will be summarized by treatment group, by timepoint and by eye (study vs. fellow) as applicable, using descriptive summaries: IOP, slitlamp examination, and indirect ophthalmoscopy. Changes from baseline for selected ocular assessments will be tabulated. The presence of intraocular inflammation and vitreous hemorrhage, as determined on slitlamp examination, will be tabulated by grade (according to grading scales for flares and cells and vitreous hemorrhage grading scale and density in Appendix 7 and Appendix 8, respectively). The presence of retinal break or detachment as determined from ophthalmoscopy will be tabulated.

6.6 PHARMACOKINETIC ANALYSES

The PK Population will consist of patients who receive study treatment *grouped according to treatment received* and have *at least one post study treatment PK sample available and* key parameters *will be estimated* (e.g., area under the concentration–time curve [AUC], maximum serum concentration [C_{max}], minimum serum concentration [C_{min}], and half-life) Sensitivity analysis may be performed with the *PK-Evaluable Population: PK Population excluding patients receiving intravitreal injections of ranibizumab in the study eye post PDS implant (including supplemental treatment),* patients with *fellow eye ranibizumab or* bevacizumab *treatment,* or *prior bevacizumab* treatment *in either eye.*

Individual and mean serum ranibizumab concentration versus time data will be tabulated and plotted by treatment arm for all patients *in the PK Population and PK-Evaluable Population.* In a subset of patients in the implant arm with more intensive sampling (at selected sites), the serum pharmacokinetics of ranibizumab will be summarized by estimating total exposure (AUC), C_{max}, and half-life of drug delivered from the implant after PDS implant insertion. Estimates for these parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, and minimum and maximum). Inter-patient variability will be evaluated.

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

6.7 IMMUNOGENICITY ANALYSES

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

The immunogenicity analyses will group patients according to treatment received. The analyses on incidence of immunogenicity will include all patients with at least one ADA sample collected at the randomization visit and *at least* one postdose ADA sample. ADA samples will be collected prior to dosing during the randomization visit and at Weeks 4, 24, 36, and 96. To account for pre-study exposure to ranibizumab, ADA incidence will be summarized as follows:

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

The combined rates described in (a) and (b) above will provide the incidence of treatment-emergent ADAs in the study. Patients are considered to be negative for ADAs if they are ADA negative at all timepoints.

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

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported using descriptive statistics.

6.8 EXPLORATORY BIOMARKER ANALYSES

The pharmacodynamic (PD) biomarker analysis population will consist of patients who are in the safety population and have sufficient data to enable assessment of potential

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

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

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and reading center data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures. The Sponsor will supply eCRF specifications for this study. For additional details of the data quality assurance please see the Data Quality Review Plan.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, images, laboratory notes, memoranda, patient-reported outcomes (PROs), questionnaires, treatment experience questionnaires, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial -related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Mobile Nursing Informed Consent Form, if applicable) will be provided

to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. HIPAA of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not

participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.3).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor has implemented a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor identified potential risks associated with critical trial processes and data and implemented plans for evaluating and controlling these risks. Risk evaluation and control included the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations

from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits are provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This study is sponsored by F. Hoffmann-La Roche Ltd.

The Sponsor and/or its designee will perform study management, oversight of data management, statistical programming, project management, monitoring, vendor management, and data management (quality checking of the data).

Procedures used for data review, database cleaning, issuing and resolving data queries, verification and validation are detailed in the Data Management Plan and in the Internal Data Review Plan documents.

Approximately 90 sites will participate with original plans to enroll approximately 360 patients; 418 patients were ultimately enrolled. An IxRS will be used for patient enrollment and for management of study drug/device requests and shipments.

A central laboratory will be used for most laboratory assessments (e.g., safety laboratory assessments) and for storage of other laboratory samples (e.g., serum samples for PK assessments) prior to being shipped to the Sponsor or a Sponsor-selected designee for analysis.

Data will be recorded by an EDC system using eCRFs (see Section 5.4.2).

A central reading center will be used for ocular imaging analyses and storage (e.g., FA, FP, and SD-OCT).

An iDMC will be employed to monitor and evaluate patient safety throughout the study.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and

redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities: Implant Arm

Table 1: Implant Arm, Year 1

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

Appendix 1: Schedule of Activities: Implant Arm (cont.)

Table 1: Implant Arm, Year 1 (cont.)

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

Appendix 1: Schedule of Activities: Implant Arm (cont.)

Table 1: Implant Arm, Year 1 (cont.)

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

Appendix 1: Schedule of Activities: Implant Arm (cont.)

Table 1: Implant Arm, Year 1 (cont.)

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

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

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

[a] Refer to Section 3.1 and Table 2 for patient eligibility scenario.

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

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

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

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

Appendix 1: Schedule of Activities: Implant Arm (cont.)

Table 1: Implant Arm, Year 1, Footnotes (cont.)

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

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

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

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

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

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

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

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

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

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

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

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

Appendix 1: Schedule of Activities: Implant Arm (cont.)

Table 1: Implant Arm, Year 1, Footnotes (cont.)

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

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

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

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

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

[w] At sites that permit video recording.

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

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

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

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

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

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

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

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

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

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

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

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

Appendix 1: Schedule of Activities: Implant Arm (cont.)

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

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

Appendix 1: Schedule of Activities: Implant Arm (cont.)

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

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

Appendix 1: Schedule of Activities: Implant Arm (cont.)

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

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

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

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

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

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

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

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

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

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

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

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

Appendix 1: Schedule of Activities: Implant Arm (cont.)

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

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

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

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

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

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

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

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

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

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

[r] For sites that permit video recording.

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

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

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

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

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

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

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

Appendix 1: Schedule of Activities: Implant Arm (cont.)

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

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

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

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

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

Appendix 1: Schedule of Activities: Implant Arm (cont.)

Table 3: Alternate Scenarios for Implant Arm: Week 96 and Week (X) (Q4W)

Assessment	Visit	
	Week 96	Week (X) (Q4W)
Visit window (days)	±7	
Contact IxRS [a]	x	x
Vital signs [b]	x	x [c]
Concomitant medications [d]	x	x
Adverse events [e]	x	x
Concurrent ocular procedures [f]	x	x
Pregnancy test [g]	x	x
Serum PK sample [h]	x	x
Serum ADA sample [h]	x	x
BCVA	x	x
IOP [i]	x	x
Slitlamp examination	x	x
Dilated binocular Indirect ophthalmoscopy [j]	x	x
SD-OCT [k]	x	x
Fundus photography [k]	x	x [l, m]
Fluorescein angiograph [k]	x	x [l, m]
Fundus autofluorescence [k]	x	x [l, m]
Lens photograph (fundus reflex photograph) [k]	x	x [l, m]
OCT-A (at selected sites) [n]	x	x [l, m]
Implant refill-exchange and video	x [o]	x [p]
Pre-and post-study treatment antimicrobials [q]	x	x
Post-treatment finger-counting test [r]	x	x
Implant photographs [s]	x	x [t]
Supplemental ranibizumab (if supplemental treatment criteria are met)		x [u]
Follow-up call [v]	x	x
Aqueous humor sample for biomarkers and ranibizumab conc. (optional)	x [w]	x [w, x]
Plasma and serum sample for biomarkers (if aqueous humor sample collected) (optional)	x [w]	x [w,x]

ADA =anti-drug antibody; BCVA =best-corrected visual acuity; conc. =concentration; IOP =intraocular pressure; IxRS =interactive voice or web-based response system; OCT-A =optical coherence tomography–angiography; PK =pharmacokinetics; PDS =Port Delivery System with ranibizumab; (Q4W)=optional every 4 weeks; SD-OCT =spectral-domain optical coherence tomography; VA =visual acuity

Notes: All ocular assessments are to be performed for both eyes prior to study treatment unless noted otherwise.

Table 3: Alternate Scenarios for Implant Arm: Week 96 and Week (X) (Q4W), Footnotes (cont.)

[a] *The IxRS will be contacted if visit is conducted and study treatment is required.*

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

[c] *Vital signs will be measured only at the last Week (X) of the study.*

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

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

[f] *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.*

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

[h] *If implant refill-exchange is administered, collect sample, prior to implant refill-exchange, and/or fluorescein angiography (if applicable). If sample collection is missed, collect at the earliest visit scheduled after the refill-exchange is performed.*

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

[j] *Dilated ophthalmoscopy examinations will be performed at each visit to monitor the implant for any potential implant problems.*

[k] *Refer to the reading center manual for details.*

[l] *If fundus photography, fluorescein angiography, fundus autofluorescence, lens photograph, OCT-A and implant photographs were missed at Week 96 visit or if Week 96 visit was not conducted (per scenario 3, Table 3), perform assessments at first conducted Week (X).*

[m] *Fundus photography, fluorescein angiography, fundus autofluorescence, lens photograph, OCT-A, and implant photographs should be repeated if more than 3 months have passed since the last assessments were conducted.*

[n] *Only at selected sites.*

[o] *If Week 96 visit is within window, but the patient will not be able to complete the Portal enrollment visit within 21-28 days post-Week 96, administer a refill-exchange at Week 96. If Portal enrollment is expected to occur within 21-28 days after the Week 96 visit, do not administer a refill-exchange at Week 96. For sites that permit video recording.*

[p] *If Week 96 is missed, administer a refill-exchange at the first conducted Week (X) visit. If both Week 96 and the first Week (X) are missed, the investigator must contact the Sponsor for further discussion prior to scheduling the next visit. For sites that permit video recording.*

[q] *If Implant refill-exchange is administered. The pre-implant refill-exchange use of self-administered antimicrobials is per the investigator's discretion. The post-implant refill-exchange use of self-administered antimicrobials is required.*

Appendix 1: Schedule of Activities: Implant Arm (cont.)

Table 3: Alternate Scenarios for Implant Arm: Week 96 and Week (X) (Q4W), Footnotes (cont.)

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

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

[t] *If Implant refill-exchange is administered and at the last Week (X) of the study.*

[u] *Only for patients who will reach Week 112 and 116. For additional required assessments if supplemental treatment criteria are met see Appendix 5.*

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

[w] *If a patient has consented to this optional sample collection, collect if implant refill-exchange is performed at the visit (prior to or immediately after procedure, and prior to fluorescein angiography if applicable)*

[x] *Collect at the last Week (X) of the study as required per scenarios 2 and 3, Table 3.*

Appendix 2 Schedule of Activities: Intravitreal Arm

Table 1: Intravitreal Arm, Year 1

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

Appendix 2: Schedule of Activities: Intravitreal Arm (cont.)

Table 1: Intravitreal Arm, Year 1 (cont.)

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

Appendix 2: Schedule of Activities: Intravitreal Arm (cont.)

Table 1: Intravitreal Arm, Year 1 (cont.)

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

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

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

[a] Refer to Section 3.1 and Table 2 for patient eligibility scenario.

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

[c] Day 1 study treatment visit should occur on the same day as randomization visit.

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

Appendix 2: Schedule of Activities: Intravitreal Arm (cont.)

Table 1: Intravitreal Arm, Year 1, Footnotes (cont.)

[e] Vital signs consist of blood pressure and pulse measurement while patient is in a seated position after resting for 5 minutes. Vital signs will be measured pre-treatment (as applicable).

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

[g] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events related to a protocol-mandated intervention (e.g., procedures such as fluorescein angiography or medication interruption) should be reported. Adverse events will be recorded starting on Day 1 through the last study visit.

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

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

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

[k] Obtain from all study patients pre-treatment and prior to fluorescein angiography, if applicable. For a description of the laboratory assessments to be performed see Section 4.5.7 or the laboratory manual.

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

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

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

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

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

[q] As required, depending on patient eligibility category. Refer to Section 3.1 and Table 2 for patient eligibility scenario.

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

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

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

[u] If treatment is given.

Appendix 2: Schedule of Activities: Intravitreal Arm (cont.)

Table 1: Intravitreal Arm, Year 1, Footnotes (cont.)

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

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

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

Appendix 2: Schedule of Activities: Intravitreal Arm (cont.)

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

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

Appendix 2: Schedule of Activities: Intravitreal Arm (cont.)

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

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

Appendix 2: Schedule of Activities: Intravitreal Arm (cont.)

Table 2: Intravitreal Arm, Year 2 and Early Study Termination Visit, Footnotes

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Appendix 2: Schedule of Activities: Intravitreal Arm (cont.)

Table 3: Alternate Scenarios for Intravitreal Arm: Week 96 and Week (X) (Q4W)

Assessment	Week Visit	
	Week 96	Week (X) (Q4W)
Visit window (days)	±7	
Contact IxRS [a]	x	x
Vital signs [b]	x	x [c]
Concomitant medications [d]	x	x
Adverse events [e]	x	x
Concurrent ocular procedures [f]	x	x
Pregnancy test [g]	x	x
Serum PK sample	x [h]	x [i]
Serum ADA sample	x [h]	x [i]
BCVA	x	x
IOP [j]	x	x
Slitlamp examination	x	x
Dilated binocular Indirect ophthalmoscopy [k]	x	x
SD-OCT [l]	x	x
Fundus photography [l]	x	x [m, n]
Fluorescein angiography [l]	x	x [m, n]
Fundus autofluorescence [l]	x	x [m, n]
Lens photograph (fundus reflex photograph) [l]	x	x [m, n]
OCT-A (at selected sites) [o]	x	x [m, n]
Pre-and post-study treatment antimicrobials	x	x
Administration of study treatment (intravitreal ranibizumab 0.5 mg)	x	x [p]
Post-treatment finger-counting test [q]	x	x
Follow-up call [r]	x	x
Aqueous humor sample for biomarkers and ranibizumab conc. (optional) [s]	x	x [t]
Plasma and serum sample for biomarkers (if aqueous humor sample collected) (optional) [s]	x	x [t]

ADA =anti-drug antibody; BCVA =best-corrected visual acuity; conc. =concentration; IOP =intraocular pressure; IxRS =interactive voice or web-based response system; OCT-A =optical coherence tomography–angiography; PK =pharmacokinetics; PDS =Port Delivery System with ranibizumab; (Q4W)=optional every 4 weeks; SD-OCT =spectral-domain optical coherence tomography; VA =visual acuity

Notes: All ocular assessments are to be performed for both eyes prior to study treatment unless noted otherwise.

Appendix 2: Schedule of Activities: Intravitreal Arm (cont.)

Table 3: Alternate Scenarios for Intravitreal Arm: Week 96 and Week (X) (Q4W) Footnotes

[a] *The IxRS will be contacted if visit is conducted and study treatment is required.*

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

[c] *Vital signs will be measured only at the last Week (X) of the study.*

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

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

[f] *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.*

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

[h] *If intravitreal ranibizumab is administered, collect sample prior to study treatment and prior to fluorescein angiography (if applicable). If sample collection is missed, collect at the earliest visit scheduled after the treatment is administered.*

[i] *If Week 96 visit is not conducted (per scenario 3, Table 3), collect sample prior to study treatment only at the first conducted Week (X) visit (and prior to fluorescein angiography if applicable). If sample collection is missed, it should be collected at the earliest visit scheduled after the treatment is administered.*

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

[k] *Dilated ophthalmoscopy examinations will be performed at each visit to monitor the implant for any potential implant problems.*

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

[m] *If fundus photography, fluorescein angiography, fundus autofluorescence, lens photograph, OCT-A were missed at Week 96 visit or if Week 96 visit was not conducted (per scenario 3, Table 3), perform assessments at first conducted Week (X).*

[n] *Fundus photography, fluorescein angiography, fundus autofluorescence, lens photograph and OCT-A should be repeated if more than 3 months have passed since the last assessments were conducted.*

[o] *Only at selected sites.*

[p] *If required, conduct monthly Week (X) visits and administer intravitreal ranibizumab injection until Portal enrollment visit can be scheduled within the required window; at the final planned Week (X), do not administer an intravitreal ranibizumab injection*

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

[r] *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.*

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

[t] *Only if Week 96 visit is not conducted (per scenario 3, Table 3), sample collection should be performed once at first conducted Week (X) when the study treatment is administered.*

Appendix 3
Run-In Visits (If Applicable)

The following assessments will be performed on patients who enter the run-in period of the study. In the run-in period, after patients have reached the required number of anti-vascular endothelial growth factor (anti-VEGF) treatments prior to screening (see Section 4.1.1.2), they will be scheduled for screening 28 (± 7) days after the last run-in visit is completed.

Assessments [a]	Run-In Visit 1	Run-In Visit 2	Run-In Visit 3
Window (days)	≥21 days from last intravitreal anti-VEGF	28 (± 7) days from Run-In Visit 1	28 (± 7) days from Run-In Visit 2
Informed consent	x [b]	x [b]	x [b]
Review of run-in inclusion and exclusion criteria [c]	x		
Demographic data	x		
BCVA (assessed on ETDRS chart at a 4-meter starting distance)	x	x	x
Pregnancy test [d]	x	x	x
FA [e]	x		
SD-OCT [e]	x	x	x
Site to contact IxRS	x	x	x
Optional pre and post-study treatment antimicrobials	x	x	x
Administration of intravitreal ranibizumab 0.5 mg	x	x	x
Post-treatment finger-counting test [f]	x	x	x
Adverse events [g]	x	x	x
Follow-up call [h]	x	x	x

BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluorescein angiography; IxRS = interactive voice/web-based response system; nAMD = neovascular age-related macular degeneration; SD-OCT = spectral-domain optical coherence tomography.

[a] A run-in period will be available for patients with newly diagnosed nAMD who are treatment naïve or who have had previous treatment with one or two intravitreal anti-VEGF injections within the previous 6 months.

[b] Patients must satisfy all eligibility criteria and sign the Informed Consent Form only once, at their initial run-in visit.

[c] Run-in evaluations for inclusion/exclusion criteria will only be performed and evaluated locally by the investigator.

[d] Perform locally the urine pregnancy test prior to FA (if applicable) and study treatment 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 FA or intravitreal ranibizumab treatment until the final results are available. If the serum pregnancy test is positive, do not administer intravitreal ranibizumab treatment.

[e] Refer to the reading center manual for details. These images, if taken around the time of diagnosis of nAMD, will be used as historical images for patient's eligibility at the screening visit (both SD-OCT and FA images will be submitted to the reading center; only SD-OCT images are required for eligibility determination).

[f] 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. Patients will be allowed to leave the office after the designated physician has assessed that there are no safety concerns. If any safety concerns or immediate toxicity are noted, the patient will remain at the office and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event and treatment of adverse event (if applicable) will be reported.

[g] During the run-in, only serious adverse events related to a protocol-mandated intervention (e.g., intravitreal injection procedure, or intravitreal ranibizumab) should be reported. Adverse events assessed by the qualified ophthalmologist as related to ranibizumab and intravitreal 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.

[h] Patients will be contacted 3 (± 1) days following intravitreal ranibizumab 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.

ELIGIBILITY CRITERIA FOR RUN-IN (IF APPLICABLE)

Patients must meet the following ocular inclusion criteria in the study eye for entry in the run-in period in addition to the general inclusion criteria (Section 4.1.1.1) and exclusion criteria (Section 4.1.2):

- Patients with neovascular age-related macular degeneration (nAMD) who are treatment-naive or who have had previous treatment with one or two intravitreal anti-VEGF injection within the previous 6 months
- Best-corrected visual acuity (BCVA) of 34 letters or better (20/200 or better Snellen equivalent) using ETDRS chart at a starting distance of 4 meters (see the BCVA manual for additional details)
- All subtypes of nAMD lesions are permissible (i.e., type I, type II, type III, or mixed forms according to optical coherence tomography classification)
    - Active primary choroidal neovascularization lesions at the time of diagnosis of nAMD must involve the macula (6mm in diameter centered at the fovea)
- Sufficiently clear ocular media and adequate pupillary dilation to allow for analysis and grading by the central reading center of fluorescein angiography and spectral-domain optical coherence tomography images

Appendix 4
Unscheduled Safety Assessment Visits, Post-Study Treatment Discontinuation Visits, or Post-Explantation Safety Visits

The assessments listed below will be performed at:

- Unscheduled safety assessment visits
- Study visits for patients who discontinued study treatment but remain in the study. Other assessments, listed in Appendix 1 and Appendix 2 for specific study visits, may be performed at discretion of the investigator.
- Safety visits following explantation (at 1, 7 [± 2], 30 [± 7], and 60 [± 7] days post-explantation).

Assessments [a,b]	
Vital signs (blood pressure and pulse)	x
BCVA (assessed on ETDRS chart at a 4-meter starting distance) [c]	x
Slitlamp examination	x
Dilated binocular indirect high-magnification ophthalmoscopy	x
IOP [d]	x
SD-OCT [e]	x
Adverse events [f]	x
Concurrent ocular procedures	x
Concomitant medications	x

BCVA = best-corrected visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; SD-OCT = spectral-domain optical coherence tomography.

[a] An unscheduled safety assessment visit is applicable to any randomized study patients. If an unscheduled safety assessment visit is determined to be necessary by the physician, perform all listed assessments. Ocular assessments may be performed on one eye only, except for BCVA that must be performed on both eyes.

[b] At a post-study treatment discontinuation visit or a post-explantation safety visit, perform all listed assessments. Ocular assessments may be performed on the study eye only, except for BCVA which must be performed on both eyes.

[c] BCVA assessment must be performed in both eyes by masked visual acuity examiner. Perform finger-counting test followed by hand motion and light perception tests when necessary.

[d] The method used for the IOP measurement for a patient must remain consistent throughout the study.

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

[f] Adverse event causality to be evaluated by the qualified ophthalmologist.

Appendix 5
Additional Assessments if Supplemental Treatment Criteria Are Met

If a patient in the implant arm meets the supplemental treatment criteria (see Section 5.1.5.3 at any of the following weeks (Weeks 16, 20, 40, 44, 64, 68, 88, and 92 *and Weeks 112 and 116 for patients who follow an alternate final study visit scenario*), the following assessments must be performed in addition to assessments listed in Appendix 1.

Assessments	
Pregnancy test [a]	x
Serum PK sample [b]	x [c]
Aqueous humor PD sample [b]	x [c]
Plasma and serum PD sample	x [c]
Optional pre- and post-study treatment antimicrobials	x
Supplemental intravitreal ranibizumab 0.5 mg	x
Post-treatment finger-counting test [d]	x
Follow-up call [e]	x

IxRS = interactive voice or web-based response system; PD = pharmacodynamic; PK = pharmacokinetic.

[a] For women of childbearing potential, including those who have had tubal ligation, urine pregnancy test will be performed locally prior to supplemental treatment . If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Do not administer the supplemental treatment until the final results are available. If the serum pregnancy test is positive, do not administer the supplemental treatment.

[b] Collect sample prior to supplemental intravitreal injection.

[c] Sample should be collected at the supplemental treatment visit and at the subsequent study visit.

[d] 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. Patients will be allowed to leave the office after the designated physician has assessed that there are no safety concerns. If any safety concerns or immediate toxicity are noted, the patient will remain at the office and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event and treatment of adverse event (if applicable) will be reported.

[e] Patients will be contacted 3 (± 1) days following supplemental 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.

Appendix 6
Best-Corrected Visual Acuity Testing

SCOPE

Best-corrected visual acuity (BCVA) will be measured by trained and certified personnel at the study sites.

The Sponsor recognizes that it may be difficult to fully mask site staff in an open label surgical study.

The Sponsor will require that the following steps be implemented as a best attempt to mask VA examiners in order to minimize biases in VA assessments.

- The VA examiner will only conduct refraction and VA assessments and will be masked as best as possible to patient study eye assignment, study visit type, and patient treatment assignment.
- The VA examiner will have no access to a patient's BCVA scores from previous visits and will be aware only of the patient's refraction data from previous visits.
- The VA examiner may provide no other direct or indirect patient care.
- Patients and unmasked site personnel will be asked not to discuss the study eye assignment, study visit type, and patient treatment assignment with the VA examiner.

VA will be measured at the intervals specified in the protocol (see Section 4.5.5, Appendix 1, and Appendix 2).

EQUIPMENT

The following is needed at minimum to conduct the examination:

- Examination lane of adequate dimensions to allow testing at required distances
- Standard chair with a firm back
- Set of three Precision Vision™ or Lighthouse distance acuity charts (modified ETDRS Charts 1, 2, and R)
- Retro-illuminated box
- Trial frame
- Trial lens set

TRAINING AND CERTIFICATION

A VA specifications document, procedure manual, and training materials will be provided to the investigational sites, and VA examiner certification will be obtained. The VA examination room also must be certified before any VA examinations are performed. If new VA personnel or VA rooms are added to the study, certification must be obtained prior to performing study assessments.

Appendix 7
Grading Scales for Anterior Chamber Flare or Cells and Vitreous Cells

GRADING SCALE FOR ANTERIOR CHAMBER FLARE OR CELLS

Flare	
0	No protein is visible in the anterior chamber when viewed by an experienced observer using slitlamp biomicroscopy; a small, bright, focal slit-beam of white light; and high magnification.
Trace	Trace amount of protein is detectable in the anterior chamber: This protein is visible only with careful scrutiny by an experienced observer using slitlamp biomicroscopy; a small, bright, focal slit-beam of white light; and high magnification.
1+	Slight amount of protein is detectable in the anterior chamber: The presence of protein in the anterior chamber is immediately apparent to an experienced observer using slitlamp biomicroscopy and high magnification, but such protein is detected only with careful observation with the naked eye and a small, bright, focal slit-beam of white light.
2–3+	Moderate amount of protein is detectable in the anterior chamber. These grades are similar to 1+ but the opacity would be readily visible to the naked eye of an observer using any source of a focused beam of white light. This is a continuum of moderate opacification, with 2+ being less apparent than 3+.
4+	A large amount of protein is detectable in the anterior chamber. This grade is similar to 3+, but the density of the protein approaches that of the lens. Additionally, frank fibrin deposition is frequently seen in acute circumstances. It should be noted that because fibrin may persist for a period of time after partial or complete restoration of the blood–aqueous humor barrier, it is possible to have resorbing fibrin present with lower numeric assignations for flare (e.g., 1+ flare with fibrin).
Cells	
0	No cells are seen in any optical section when a large slitlamp beam is swept across the anterior chamber.
Trace	Few (1–3) cells are observed when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, not every optical section contains circulating cells.
1+	3–10 cells/optical section are seen when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells.
2+	10–25 cells are seen when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells.

Modified from: Hogan MJ, Kimura SJ, Thygeson P. Signs and symptoms of uveitis. I. Anterior uveitis. Am J Ophthalmol 1959;47(Part 2):155–70.

Appendix 7
Grading Scales for Anterior Chamber Flare or Cells and Vitreous Cells (cont.)

GRADING SCALE FOR ANTERIOR CHAMBER FLARE OR CELLS

Cells (cont.)	
3+	25–50 cells are seen when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells. Keratic precipitates or cellular deposits on the anterior lens capsule may be present.
4+	More than 50 cells are seen when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains cells, or hypopyon is noted. As for fibrin deposition, hypopyon may persist for some period of time after the active exudation of cells into the anterior chamber has diminished or ceased entirely, making it possible to have 1+ circulating cells in the anterior chamber with a resolving hypopyon.

Modified from: Hogan MJ, Kimura SJ, Thygeson P. Signs and symptoms of uveitis. I. Anterior uveitis. Am J Ophthalmol 1959;47(Part 2):155–70.

GRADING SCALE FOR VITREOUS CELLS

Number of Cells in Retro Illuminated Field	Description	Grade
0	Clear	0
1–20	Few opacities	Trace
21–50	Scattered opacities	1
51–100	Moderate opacities	2
101–250	Many opacities	3
>251	Dense opacities	4

Modified from: Nussenblatt RB, Whitcup SM, Palestine AG. Uveitis: fundamentals and clinical practice. 2nd rev. ed. St. Louis: Mosby, 1996, p. 64.

Appendix 8
Grading Scales for Vitreous Hemorrhage

GRADING SCALE FOR VITREOUS HEMORRHAGE DENSITY

Grade	Description
None (0)	Retina is visible.
Trace	Retina is visible and red blood cells are visible only on slitlamp examination.
1+	Retinal detail is visible; some hemorrhage is visible by ophthalmoscopy.
2+	Large retinal vessels are visible, but central retinal detail is not visible by ophthalmoscopy.
3+	Red reflex is visible, but no central retinal detail is seen posterior to the equator by ophthalmoscopy.
4+	No red reflex by ophthalmoscopy.

VITREOUS HEMORRHAGE FUNCTIONAL GRADING SCALE

Grade	Description
1	≤ 15 letter BCVA loss from the previous visit
2	16–30 letter BCVA loss from the previous visit
3	>30 letter BCVA loss from the previous visit to hand motion
4	Light Perception or worse

Appendix 9
Fundus Autofluorescence

SCOPE

Fundus autofluorescence (FAF) will be performed at the study sites by trained personnel who are certified by the central reading center. FAF imaging will be performed for each patient at the intervals specified in the protocol (see Section 4.5.6, Appendix 1, and Appendix 2) and will be forwarded to the central reading center for analysis and/or storage. Analysis (if applicable) of FAF images will be performed by the central reading center. The list of timepoints at which images will be analyzed are recorded in the reading center manual.

EQUIPMENT

Equipment utilized during this trial is described in the central reading center manual. The ability to transfer images to electronically export digital files is required (i.e., no printed FAF images will be sent to the central reading center).

PROCEDURES AND CERTIFICATION

The central reading center will provide the study manual and training materials. FAF operators, systems, and software will be certified prior to any evaluation of patients.

Appendix 10
Fundus Photography

SCOPE

Fundus photography (FP) will be taken by trained personnel at the study sites at the intervals specified in the protocol.

FP imaging will be performed for each patient at the intervals specified in the protocol (see Section 4.5.6, Appendix 1, and Appendix 2) and will be forwarded to the central reading center for analysis and/or storage. Analysis (if applicable) of fundus photographs will be performed by the central reading center.

The list of timepoints at which images will be analyzed are recorded in the reading center manual.

EQUIPMENT

See the central reading center manual.

PROCEDURE

The central reading center will provide a study manual and training material.
The photographer and equipment will be certified by the reading center before any study images are taken.

Appendix 11
Fluorescein Angiography

SCOPE

Fluorescein angiography (FA) will be performed at the study sites by trained personnel who are certified by the central reading center. The FA images will be obtained at the intervals specified in the protocol (see Section 4.5.5, Appendix 1, and Appendix 2) and will be forwarded to the central reading center for analysis and/or storage.

The list of timepoints at which images will be analyzed are recorded in the reading center manual.

EQUIPMENT

Digitally based angiograms must be used while conducting an angiographic evaluation for the study.

FILM-BASED ANGIOGRAPHY AND CERTIFICATION

Film-based angiography is not acceptable.

DIGITAL IMAGING SYSTEMS AND CERTIFICATION

Digital imaging systems are required. The system and software at the site will be certified by the central reading center prior to obtaining any study angiograms. This certification and validation process will ensure that the central reading center will be able to correctly calculate the required measurements.

PROCEDURES

The central reading center will provide a study manual and training material. Photographers, systems, and software will be certified prior to obtaining patient angiograms.

Appendix 12
Spectral Domain Optical Coherence Tomography

SCOPE

Spectral-domain optical coherence tomography (SD-OCT) will be performed on both eyes at the study sites by trained personnel who are certified by the central reading center. SD-OCT imaging will be performed for each patient at the intervals specified in the protocol (see Section 4.5.6, Appendix 1, and Appendix 2) and will be forwarded to the central reading center for analysis and/or storage.

The list of timepoints at which images will be analyzed are recorded in the reading center manual.

EQUIPMENT

Equipment utilized during this trial is described in the central reading center manual. The ability to transfer images to electronically export digital files is required (i.e., no printed SD-OCT images will be sent to the central reading center).

PROCEDURES AND CERTIFICATION

The central reading center will provide the study manual and training materials. SD-OCT operators, systems, and software will be certified prior to any evaluation of patients.

Appendix 13
Implant Photographs

SCOPE

Implant photographs will be taken by trained personnel at the study sites at the intervals specified in the protocol.

Implant imaging will be performed for implant patients only at Day 2 after Day 1 visit and at each study visit as specified in the protocol (see Section 4.5.6 and Appendix 1) and will be forwarded to the central reading center for analysis and/or storage. Analysis (if applicable) of implant photographs will be performed by the central reading center.

The list of timepoints at which images will be analyzed are recorded in the reading center manual.

EQUIPMENT

See the central reading center manual.

PROCEDURE

The central reading center will provide a study manual and training material. The photographer and equipment will be certified by the reading center before any study images are taken.

Appendix 14
Optical Coherence Tomography Angiography (at Selected Sites)

SCOPE

Optical coherence tomography (OCT) angiography will be performed on both eyes only at selected study sites that have OCT angiography equipment by trained personnel who are certified by the central reading center. OCT angiography imaging will be performed for each patient at the intervals specified in the protocol (see Section 4.5.6, Appendix 1, and Appendix 2) and will be forwarded to the central reading center for analysis and/or storage.

The list of timepoints at which images will be analyzed are recorded in the central reading center manual.

EQUIPMENT

Equipment utilized during this trial is described in the central reading center manual. The ability to transfer images to electronically export digital files is required (i.e., no printed OCT angiography images will be sent to the central reading center).

PROCEDURES AND CERTIFICATION

The central reading center will provide the study manual and training materials. OCT angiography operators, systems, and software will be certified prior to any evaluation of patients.

Appendix 15
Sample Collection and Shipping

Refer to the laboratory study manual for detailed sample collection, storage, and shipping instructions. All necessary transfer tubes, Vacutainers™, labels, shipping boxes, and forms will be provided by the central laboratory, except when indicated.

BIOLOGICAL SAMPLES

Samples for assessment of laboratory safety (hematology, serum chemistry, coagulation) and urinalysis will be collected at screening visit.

Urine pregnancy test will be collected and performed prior to each treatment for women of childbearing potential, including those who have had tubal ligation. If positive, serum pregnancy test will be performed. If the serum pregnancy test is positive, the study treatment will be discontinued.

Serum for assessment of ranibizumab concentrations (pharmacokinetics) and anti-ranibizumab antibodies will be collected at the timepoints specified in Section 4.5.7 of the protocol and the schedule of activities (see Appendix 1and Appendix 2).

Aqueous humor (see below for sample collection), plasma, and serum PD samples will be collected if patient requires a supplemental treatment and at the subsequent study visit, terminates early, or undergoes an explantation.

In addition, optional aqueous humor, plasma, and serum samples prior to refill-exchanges and at the subsequent scheduled study visit post-refill-exchange will be collected in the implant arm (see Appendix 1). Sampling in the intravitreal arm will also be performed following the same schedule (see Appendix 2).

The laboratory safety (hematology, serum chemistry, coagulation, and urinalysis) and serum pregnancy (as required) will be shipped and analyzed by the central laboratory.

The rest of the collected samples will be shipped to the central laboratory and analyzed by Sponsor or selected designee, except for the urine pregnancy test which will be analyzed at study site's local laboratory. All necessary transfer tubes, labels, forms, and shipping supplies will be provided by the central laboratory.

ANTERIOR CHAMBER (AQUEOUS HUMOR) SAMPLE COLLECTION

Aqueous humor samples will be required to be collected if a patient in the implant arm receives a supplemental intravitreal injection and at the subsequent study visit, terminates early, or undergoes an explantation. A patient, in either study arm, may also consent to optional aqueous humor sampling, which would occur at the timepoints listed in Appendix 1. Unscheduled sampling may be performed at other or additional planned visits at the discretion of the investigator in agreement with the participating patient.

Appendix 15
Sample Collection and Shipping (cont.)

The optional aqueous humor paracentesis samples will be collected from patients who consent to the procedure and sample acquisition. The aqueous humor sample collection consists of an anterior chamber paracentesis (removing 0.05 to 0.1 mL of fluid from the anterior chamber of the eye).

The anterior chamber paracentesis will be performed by a qualified physician by placing a drop of topical anesthetic on the cornea, passing a 30-gauge needle through the limbus into the anterior chamber and removing 0.05 to 0.1 mL of aqueous humor fluid.

Samples will be collected with the kit provided by central laboratory and shipped on dry ice to the central laboratory as soon as possible after the draw.

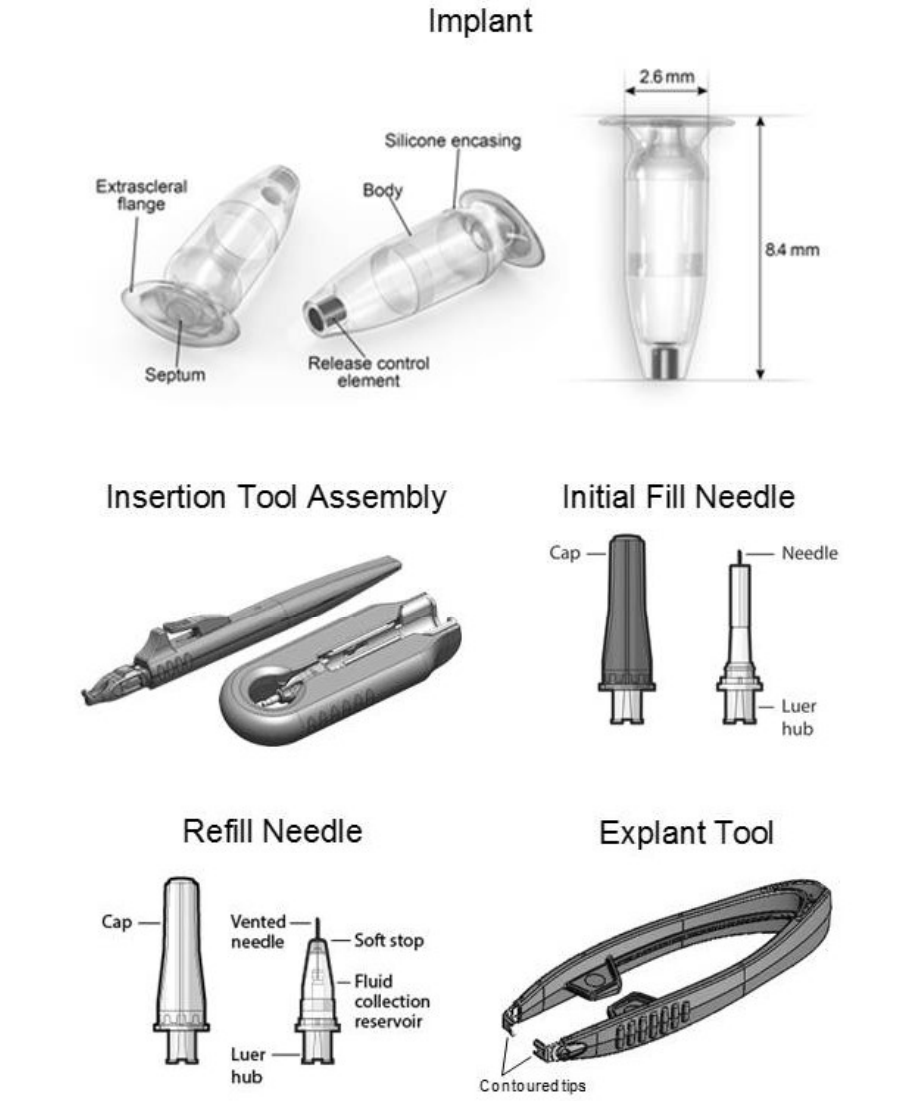
For administration of intravitreal injection (intravitreal arm or supplemental treatment in the implant arm) following the collection of the aqueous humor sample, *if the investigator chooses to use* subconjunctival lidocaine anesthetic*, it* must be injected subconjunctivally prior to study treatment.

EXPLANTED IMPLANTS WITH CONTENTS

Explanted implants containing ranibizumab drug product will be preserved for potential analysis upon explantation procedure. A method to retrieve the contents from explanted implants is in place and protocols to characterize drug product are under development. In addition, the explanted implants may undergo physical inspection and/or functional testing. All necessary materials to return explanted implants will be provided to each site. Please refer to the Device Complaints and Return Instructions for the Clinical Sites document.

Appendix 16
Port Delivery System with Ranibizumab

Figure 1 Port Delivery System Components



The following are the intended uses of the Port Delivery System (PDS) components:

- Implant: The implant is designed to be inserted through the pars plana of the eye to deliver ranibizumab in a controlled and continuous manner into the vitreous humor. The physician will both initially fill and subsequently refill-exchange the reservoir with the ranibizumab and will refill-exchange it in accordance with the instructions for use.
- Insertion tool: The insertion tool is a component designed to a) hold the implant, b) assist with filling of the implant before insertion, and c) enable insertion of the implant through a sclera-pars plana incision.

- Initial fill needle: The initial fill needle is a 34G Luer-Lock needle designed to perform the initial fill of the implant while the implant is held in the insertion tool.
- Refill needle: The refill needle is a 34G Luer-Lock needle designed to simultaneously exchange (in situ) the fluid in the implant reservoir, including any remaining ranibizumab, with new ranibizumab.
- Explant tool: The explant tool is a component designed to enable the removal of the implant from the eye after resection of the conjunctiva and removal of any scar tissue.

The implant used in a Phase I study conducted by the device developer, ForSight VISION4, was composed of biocompatible materials (polymethyl methacrylate, silicone, 316L stainless steel). The implant in the Phase II (GX28228/Ladder) study conducted by Roche was composed of biocompatible materials (polysulfone, silicone, titanium). The implant in this Phase III study conducted by Roche is composed of the identical biocompatible materials (polysulfone, silicone, titanium) as in the Phase II study. The implant remains unchanged in its exterior shape and size between the Phase II and Phase III designs; however, some processing changes were made to improve the overall manufacturability of the Phase III implant. These changes include the semi-automation of critical alignments and bonds. The Phase III release control element is identical to the Phase II titanium design. Details and terminology are shown in the table below.

Table 1 Components of the Port Delivery System with Corresponding Terminology

Terminology	PDS Components
PDS with ranibizumab	Ranibizumab, implant, and ancillary devices
Implant	Port delivery implant
Phase I implant	Port delivery implant with stainless steel RCE used in Phase I FSV4 (FH-1.2) study
Phase II and III implant	Port delivery implant with titanium RCE used in the Phase II and to be used in the Phase III studies
Ancillary devices	Insertion tool, initial fill needle, refill *needle*, and explant tool

FSV4 = ForSight VISION4; PDS = Port Delivery System with ranibizumab; RCE = release control element.

The PDS (implant and ancillary components) is manufactured by [redacted].

Appendix 17
Topical Antimicrobial and Anti-Inflammatory Ophthalmic Drops Administration Schedule

		Prior to Procedure	*After Procedure*
Implant Insertion	*Antimicrobial ophthalmic drops*	*Required – 4 times within 24 hours (every 6 hours) prior to Implant insertion*	*Required – dosing per standard of care*
	Anti-inflammatory ophthalmic drops	*Not required*	*Required – dosing per standard of care*
Refill-exchange procedure	*Antimicrobial ophthalmic drops*	*Optional – 4 times within 24 hours (every 6 hours) prior to Implant refill-exchange procedure*	*Required – dosing per standard of care*
Explantation	*Antimicrobial ophthalmic drops*	*Required – 4 times within 24 hours (every 6 hours) prior to explantation*	*Required – dosing per standard of care*
	Anti-inflammatory ophthalmic drops	*Not required*	*Required – dosing per standard of care*
Intravitreal Injection	*Antimicrobial ophthalmic drops*	*Optional – dosing per standard of care*	*Optional – dosing per standard of care*

Suggested topical broad spectrum antimicrobial ophthalmic drops: Ofloxacin ophthalmic solution (Ocuflox®), gatifloxacin ophthalmic solution (Zymar®), moxifloxacin ophthalmic solution (Vigamox®), or trimethoprim-polymyxin B ophthalmic solution [Polytrim®]).
Topical anti-inflammatory ophthalmic drops: Per physician discretion.