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

NCT Number: NCT02510794

Document Date: Protocol Version 8: 07-February-2018

PROTOCOL

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

PROTOCOL NUMBER: GX28228

VERSION NUMBER: 8

EUDRACT NUMBER: Not applicable

IND NUMBER: 113,552

TEST PRODUCT: Ranibizumab Port Delivery System for Sustained Delivery of Ranibizumab (RO4893594)

MEDICAL MONITOR: [redacted], M.D.

SPONSOR: Genentech, Inc.

DATE FINAL: Version 1: 02 January 2015

DATES AMENDED: Version 2: 03 April 2015
Version 3: 13 July 2015
Version 4: 08 December 2015
Version 5: 18 February 2016
Version 6: 30 August 2016
Version 7: 04 May 2017
Version 8: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	07-Feb-2018 05:07:28

PROTOCOL AMENDMENT, VERSION 8:
RATIONALE

Protocol GX28228, Version 8 has been amended primarily to reflect the extension of study duration for patients in the intravitreal ranibizumab control arm. Changes to the protocol, along with a rationale for each change, are summarized below.

- Study duration for patients in the intravitreal ranibizumab control arm has been extended by approximately 4 months to align with the other treatment arms and to allow for continued monthly evaluation and study treatment until the Sponsor decides, based on the primary analysis results, to either terminate the study and discontinue study treatment, or offer patients entry into the Ranibizumab Port Delivery System (RPDS) Extension Study. Primary analysis data is expected to be available approximately 4 months after the Month 9 visit of the last patient randomly assigned in the study. The study duration extension for this control arm aligns the duration of patient participation for all study treatment arms at approximately 13–38 months ,dependent on the date of the patient's randomization to the study (Sections 3.1 and 4.6.10.5, Figure 2, and Table 3).
- "RPDS Extended Use Life Study" has been replaced with "RPDS Extension Study" (Sections 3.1, 3.2, 4.4.2, and 4.6.10.5, and Appendix 1).
- The Secondary Medical Monitor information has been updated (Section 5.4.1).

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.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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

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 this form to your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, MULTICENTER, RANDOMIZED, ACTIVE TREATMENT–CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF THE RANIBIZUMAB PORT DELIVERY SYSTEM FOR SUSTAINED DELIVERY OF RANIBIZUMAB IN PATIENTS WITH SUBFOVEAL NEOVASCULAR AGE-RELATED MACULAR DEGENERATION**
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PHASE:	II
INDICATION:	Subfoveal neovascular age-related macular degeneration
SPONSOR:	Genentech, Inc.

Objectives

Efficacy Objectives

The primary efficacy objective for this study is as follows:

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

The secondary efficacy objectives for this study are as follows:

- To evaluate and compare the relative efficacy of 10-mg/mL, 40-mg/mL, and 100-mg/mL formulations of ranibizumab, delivered via the Implant, to that of 10-mg/mL (0.5-mg dose) monthly ITV ranibizumab injections, as measured by the change in BCVA from baseline at Month 9
- To evaluate the efficacy of 10-mg/mL, 40-mg/mL, and 100-mg/mL formulations of ranibizumab, delivered via the Implant, with that of 10-mg/mL (0.5-mg dose) monthly ITV ranibizumab injections over time, as measured by the change in BCVA from baseline over time
- To evaluate the efficacy of 10-mg/mL, 40-mg/mL, and 100-mg/mL formulations of ranibizumab, delivered via the Implant, with that of 10-mg/mL (0.5-mg dose) monthly ITV ranibizumab injections over time, as measured by the change in central foveal thickness (CFT, defined as the retinal thickness in the center of the fovea) from baseline over time
- To evaluate the functionality of the Implant by assessing that there is no evidence of Implant clogging in more than 10% of patients in the Implant arms at Month 9

Safety Objectives

The safety objectives for this study are as follows:

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

Pharmacokinetic Objectives

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

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

Exploratory Objectives

The exploratory objectives for this study are as follows:

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

Study Design

Description of Study

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

Number of Patients

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

Target Population

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

Inclusion Criteria

Patients must meet the following criteria for study entry:

General Inclusion Criteria

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

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

  Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- Sexually active men are recommended to use a barrier contraceptive method (condom), even if they have been surgically sterilized, for the duration of the treatment period and for at least 30 days after the last dose of study treatment.

Ocular Inclusion Criteria (Study Eye)

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

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

  OR

  Stable or improved BCVA since commencing ITV anti-VEGF treatment
- BCVA using ETDRS charts of 20/20-20/200 Snellen equivalent

- All subtypes of nAMD choroidal neovascularization (CNV) lesions are permissible (i.e., classic CNV, occult CNV, or with some classic CNV component, or retinal angiomatous proliferation lesions).

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

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

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

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

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

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

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

<u>Exclusion Criteria</u>

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

Prior Ocular Treatment

- Treatment with ITV anti-VEGF agents other than ranibizumab within 1 month prior to the randomization visit in either eye
- History of vitrectomy surgery, submacular surgery, or other surgical intervention for AMD in the study eye
- Prior treatment with Visudyne®, external-beam radiation therapy, or transpupillary thermotherapy in the study eye
- Previous treatment with ITV corticosteroid injection or device implantation in the study eye
- Previous focal laser photocoagulation used for AMD treatment in the study eye
- Prior participation in a clinical trial involving anti-angiogenic drugs, other than ranibizumab, in either eye within 2 months prior to the randomization visit
- Treatment with Visudyne® in the fellow eye <7 days preceding screening visit

CNV Lesion Characteristics

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

Concurrent Ocular Conditions

- BCVA using ETDRS charts lower than 20/200 Snellen equivalent in the fellow eye
- Retinal pigment epithelial tear involving the macula in the study eye

- Any concurrent intraocular condition in the study eye (e.g., cataract, glaucoma, or diabetic retinopathy) that, in the opinion of the investigator, would either require surgical intervention during the study to prevent or treat visual loss that might result from that condition or affect interpretation of study results
- Active intraocular inflammation (grade trace or above) in the study eye
- History of vitreous hemorrhage in the study eye within 3 months prior to the randomization visit
- History of rhegmatogenous retinal detachment or macular hole (Stage 3 or 4) in the study eye
- History of idiopathic or autoimmune-associated uveitis in either eye
- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye
- Aphakia or absence of the posterior capsule in the study eye

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

Concurrent Systemic Conditions

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

  If the average of 3 readings exceeds these values, patient's blood pressure must to be controlled by antihypertensive medication. The patient can become eligible for rescreening if medication is taken continuously for at least 30 days prior to the randomization visit.
- Uncontrolled atrial fibrillation within 3 months of informed consent
- History of stroke within the last 3 months prior to informed consent
- History of myocardial infarction within the last 3 months prior to informed consent
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of ranibizumab or placement of the Implant, that might affect interpretation of the results of the study or renders the patient at high risk of treatment complications
- Current treatment for any active systemic infection
- Use of any systemic anti-VEGF agents
- Use of oral corticosteroids (prednisone $>$10mg/day or equivalent)

- Use of anticoagulants, antiplatelets (other than aspirin), or medications known to exert similar effects at the time of study entry for a pre-existing condition. Oral anticoagulants include vitamin K antagonists (e.g. warfarin), direct factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban, fondaparinux) and direct thrombin inhibitors (e.g., dabigatran). Antiplatelet therapies include clopidogrel, prasugrel, dipyridamole, ticagrelor and ticlodipine.
- Bleeding disorders, including platelet disorders, acquired or hereditary coagulations disorders, and acquired or hereditary vascular disorders.
- Active malignancy within 12 months of randomization except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of <6 and a stable prostate-specific antigen for >12 months.
- History of allergy to fluorescein, not amenable to treatment
- Inability to obtain fundus photographs, fluorescein angiograms, fundus autofluorescence, or spectral domain optical coherence tomography (SD-OCT) images of sufficient quality to be analyzed and graded by the central reading center
- Inability to comply with study or follow-up procedures
- Previous participation in any non-ocular (systemic) disease studies of investigational drugs within 1 month preceding the informed consent (excluding vitamins and minerals)
- Use of antimitotic or antimetabolite therapy within 30 days or 5 elimination half-lives of the Randomization visit
- Intolerance or hypersensitivity to topical anesthetics, mydriatic medications, any of the excipients in ranibizumab, fluorescein, or components of the Implant
- Requirement for continuous use of any medications or treatments indicated in the "Prohibited Therapy" section.
- Women who are pregnant or lactating or intending to become pregnant during the study
- Women who are of childbearing potential, including those who have had tubal ligation, must have a negative serum pregnancy test result within 21 days prior to Day 1. A woman is considered not to be of childbearing potential if she is postmenopausal or has undergone hysterectomy and/or bilateral oophorectomy.
- No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients

Length of Study

The estimated study duration is 38 months.

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

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

End of Study

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

Outcome Measures

Efficacy Outcome Measures

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

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

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

Safety Outcome Measures

The safety outcome measures for this study are as follows:

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

Pharmacokinetic Outcome Measures

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

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

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

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

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

- Changes from screening in total lesion area, area of CNV lesion, and CNV leakage over time, as assessed by fluorescein angiography
- Proportion of patients meeting lack of clinical efficacy criteria
- Proportion of patients requiring explantation
- Changes in CNV perfusion over time, as assessed by OCT Angiography

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

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

Investigational Medicinal Products

Test Product (Investigational Drug)

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

Non-Investigational Medicinal Products

Comparator

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

Statistical Methods

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

Primary Analysis

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

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

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

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

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

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

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

Determination of Sample Size

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

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

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
AREDS	Age-Related Eye Disease Study
ATE	arterial thromboembolic event
AUC	area under the concentration–time curve
BCVA	best corrected visual acuity
BLQ	below the lower limit of quantification
CFT	central foveal thickness
C_{max}	maximum serum concentration
CNV	choroidal neovascularization
C_{trough}	steady-state serum concentration at the end of a dosing interval
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiogram
FAF	fundus autofluorescence
FDA	(U.S.) Food and Drug Administration
FSV4	ForSight VISION 4, Inc.
HA	health authority
HCl	hydrochloride
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFU	instruction for use
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IOP	intraocular pressure
IRB	Institutional Review Board

Abbreviation	Definition
ITV	intravitreal
IxRS	interactive voice/Web response system
LPI	Last Patient In
MacTSQ	Macular Degeneration Treatment Satisfaction Questionnaire
MRI	magnetic resonance imaging
nAMD	neovascular age-related macular degeneration
PK	pharmacokinetic
PRO	patient-reported outcome
OCT	optical coherence tomography
RCE	release control element
RCR	Roche Clinical Repository
RPDS	Ranibizumab Port Delivery System
RPE	retinal pigment epithelium
SAP	Statistical Analysis Plan
SD-OCT	spectral domain optical coherence tomography
SOC	standard of care
$t_{1/2}$	half-life
t_{max}	time to maximum concentration
TMP	Trial Monitoring Plan
ULN	upper limit of normal
VA	visual acuity
VEGF	vascular endothelial growth factor

1. BACKGROUND

1.1 BACKGROUND ON AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration (AMD) is one of the major causes of legal blindness in elderly persons in the developed world (Bressler et al. 2011). Late stage AMD includes two morphological subtypes: neovascular AMD and geographic atrophy. The prevalence of neovascular AMD increases exponentially with age, with prevalence estimates in the United States in 2011 ranging from 0.5% among those 65 to 69 years of age to 14.6% among those 90 years of age or greater (Rudnicka et al. 2012). In the next 40 years, the global population aged 60 years and older is projected to increase dramatically translating into an increase in the prevalence of neovascular AMD 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 two subtypes, dry and neovascular, based on clinical examination, ocular imaging, and pathologic findings. In dry AMD, which represents approximately 80%–90% of AMD cases, damage occurs at the level of the retinal pigment epithelium (RPE) and Bruch's membrane, the basement membrane between the RPE and the underlying choriocapillaris. The most notable early change in dry AMD is the accumulation of drusen within the macula and posterior pole of the retina. Drusen are focal deposits of extracellular debris located between the basal lamina of the RPE and the inner collagenous layer of Bruch's membrane. Drusen compositional studies have revealed carbohydrates, zinc, nearly 150 proteins, and numerous components of the complement system. The largest single component of drusen is lipid, thought to be derived from a large lipoprotein of intra-ocular origin (Spaide and Curcio 2010). Early dry AMD may not produce symptoms for many years. However, as drusen continue to accumulate, the patient's central vision can become impaired, sometimes significantly. At its most extreme, dry AMD results in widespread loss of the RPE, a condition called geographic atrophy that can cause severe central vision loss and legal blindness.

In approximately 10% of dry AMD cases, a conversion to neovascular AMD (nAMD) occurs over time. Although nAMD is comparatively rare, prior to the development of anti-VEGF therapy, it accounted for the majority of severe vision loss from AMD. nAMD is typically characterized by the development of choroidal neovascularization (CNV) beneath 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 RPE and/or neurosensory retina. This 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 vascular endothelial growth factor (VEGF)-A in the pathogenesis of nAMD, as discussed in the Ranibizumab Port Delivery System (RPDS) Investigator's Brochure (IB).

1.1.2 Treatment for Age-Related Macular Degeneration

No specific treatment yet exists for dry macular degeneration, although numerous therapies have and are being investigated. The Age-Related Eye Disease Study (AREDS), conducted by the National Eye Institute, demonstrated that the rate of progression of dry AMD could be decreased by a specific vitamin and mineral supplement (AREDS Research Group 2001).

The 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 (Fab), which binds to all known isoforms of VEGF-A, was approved by the U.S. Food and Drug Administration (FDA) for use in neovascular AMD, in June 2006. In November 2011, a second anti-VEGF therapy, aflibercept, was approved for nAMD in the United States, with a similar safety and efficacy profile to ranibizumab. Both ranibizumab and aflibercept therapies require frequent intravitreal (ITV) injections and physician monitoring.

1.2 BACKGROUND ON RANIBIZUMAB

Ranibizumab is a recombinant humanized immunoglobulin (Ig) G1 kappa isotype monoclonal Fab developed by Genentech, Inc. as a therapeutic agent for treating ocular vascular diseases by ITV injection. It binds to and inhibits the biologic activity of human 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.

Monthly ITV injection of 0.5 mg of ranibizumab was approved for treatment of nAMD by the FDA on 30 June 2006. Current U.S. prescribing information also provides information on results that may be expected following less frequent than monthly dosing (after 3 to 4 monthly injections).

See the RPDS Investigator Brochure (IB) for details on relevant nonclinical and clinical ranibizumab information.

1.3 BACKGROUND ON THE RANIBIZUMAB PORT DELIVERY SYSTEM

The RPDS is a drug delivery technology that allows physicians to use ranibizumab with a sustained drug delivery profile without altering its chemistry and consists of the port delivery implant (referred to as the Implant), ancillary devices (Insertion Tool, Initial Fill Needle, Refill Needle, and Explant Tool), and ranibizumab (see Figure 1).

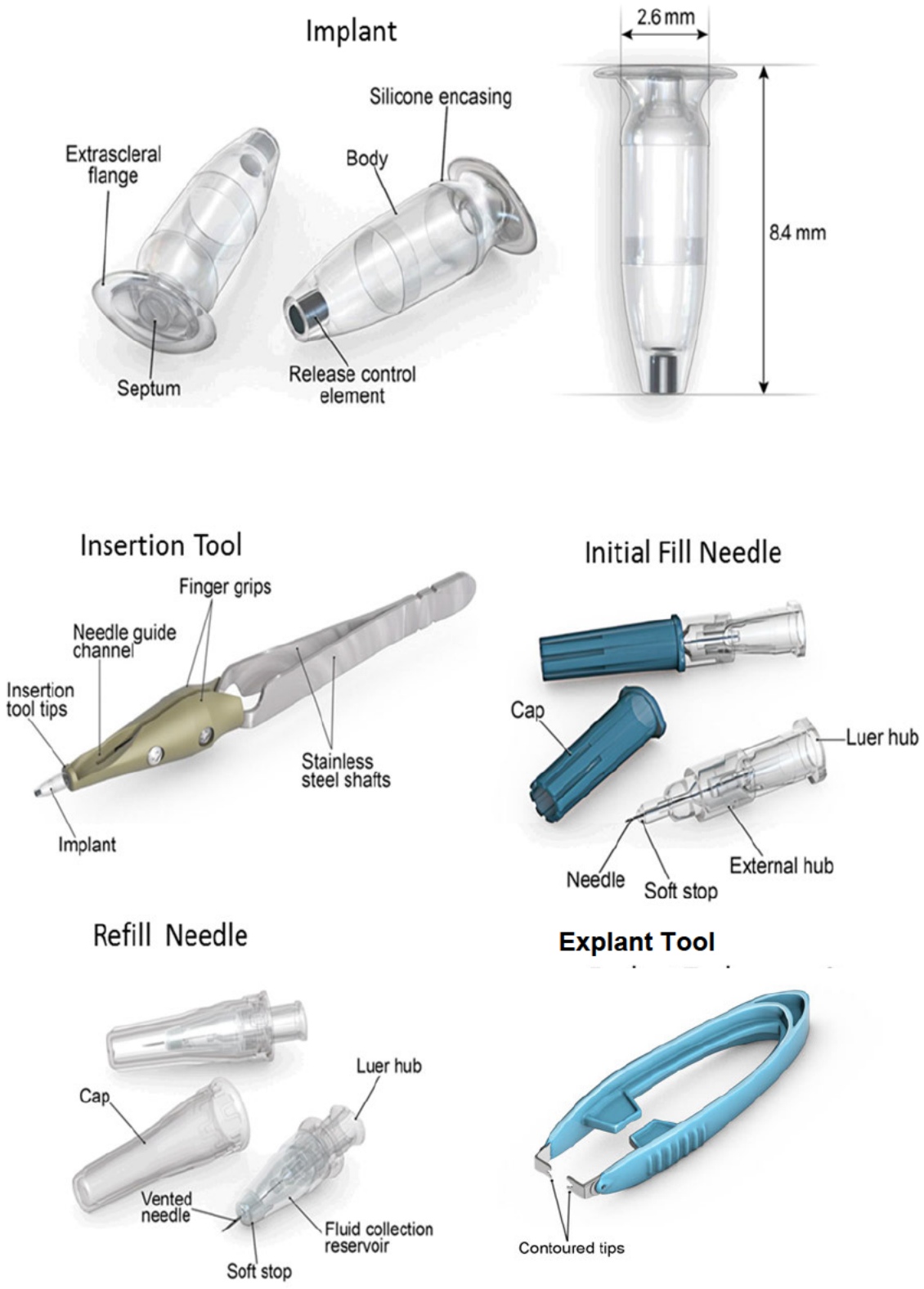
The Implant is an intra-ocular refillable device that is surgically placed through the pars plana (similar to other surgically implanted ophthalmic devices such as Retisert [Bausch and Lomb, FDA approved in 2005]) to allow for a sustained delivery of ranibizumab into the vitreous. After insertion of the Implant, the proximal end of the Implant is subconjunctival but external to the sclera, with the body of the Implant extending into the vitreous. The Implant is designed to be used in conjunction with ranibizumab to precisely control the rate and duration of drug delivery and is refillable through the Implant septum in situ.

The following are the intended uses of the RPDS components:

- Implant: The Implant is intended to be inserted through the pars plana of the eye to deliver ranibizumab in a controlled manner into the vitreous humor. The physician will initially fill the reservoir with the drug and will refill it in accordance with the instructions for use. Contraindication: the RPDS is contraindicated for use with medications other than ranibizumab.
- Insertion Tool: The Insertion Tool is a component designed to a) hold the Implant during sterilization and insertion, b) assist with filling of the Implant before insertion, and c) enable insertion of the Implant through a pars plana sclerotomy.
- Initial Fill Needle: The Initial Fill Needle is a custom 33G Luer-Lock needle designed to perform the initial fill of the Implant while the Implant is held in the Insertion Tool.
- Refill needles: The Refill Needle is a custom Luer-Lock needle designed to simultaneously exchange (in situ) any remaining old drug product in the Implant reservoir with new drug product.
- Explant Tool: The Explant Tool is a component designed to enable the removal of the Implant from the posterior segment of the eye after resection of the conjunctiva and removal of any scar tissue.

For additional RPDS details (e.g., fill, insertion, refill, and explantation of the Implant), consult the RPDS instructions for use (IFU) document and the RPDS IB.

Figure 1 RPDS Components



The Implant has been investigated in a prospective, Phase I, open-label study in patients with nAMD, conducted by the device developer, ForSight VISION 4, Inc. (FSV4), at a single site in Latvia. The study investigated the safety, tolerability, and duration of ranibizumab exposure delivered with the Implant. This Phase I Implant was composed of biocompatible materials (polymethyl methacrylate, silicone, 316L stainless steel, see Table 1). For further Phase I study details, see Section 1.4 and the RPDS IB.

Table 1 Components of the Ranibizumab Port Delivery System with Corresponding Terminology

Terminology	Ranibizumab Port Delivery System Components
Ranibizumab port delivery system	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 Implant	Port delivery Implant with Titanium RCE to be used in this Phase II study
Ancillary devices	Insertion Tool, Initial Fill Needle, Refill Needles, and Explant Tool

RCE = release control element.

The following RPDS components are manufactured by [redacted]; see Figure 1): Initial Fill Needle.

The following RPDS components are manufactured by [redacted]; see Figure 1): Implant, Insertion Tool, Refill Needles, and Explant Tool.

While the size and shape of the Implant is unchanged between the Phase I and II studies, material changes were made to improve functionality and reliability of the Phase II Implant. These changes include the use of polysulfone for the Implant body and encapsulation of the subconjunctival Implant retention features with silicone. Changes to the release control element (RCE) porosity and tortuosity were made between the Phase I and Phase II Implant designs to enable the use of higher concentrations of ranibizumab during Phase II. A change in material of the RCE from stainless steel to titanium was also implemented to take advantage of the superior physical and chemical properties of titanium.

Phase I RPDS Study

The safety, tolerability, and duration of ranibizumab exposure delivered through the Implant were investigated in a Phase I prospective, open-label study in a nAMD patient population by FSV4 at a single site in Latvia. Patient enrollment was initiated in August 2010, and the study assessed the safety of the RPDS 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. At Month 12, 6 patients underwent per-protocol planned Implant removal and exited the study after completion of the 13-month visit. The 14 remaining patients were eligible for an additional safety-monitoring phase of the protocol. One patient was lost to follow-up after 12 months. The remaining 13 patients continued in the safety-monitoring phase; one patient was subsequently lost to follow up after 21 months. Follow up data up to 36 months is available for the remaining 12 patients.

No patients were treated via the Implant after the first 12 months of the study, with the remaining 14 implanted patients returning for quarterly safety visits.

A total of 95 adverse events have been reported in this study as of 26 February 2015: 87 during the 12-month treatment phase and 8 during the additional 2-year safety monitoring phase. Of the 87 adverse events during the 12-month treatment phase, 76 were considered related (possibly, probably, or definitely) to the Implant insertion procedure, the refill procedure, the Implant removal procedure, or drug treatment. These 87 reported adverse events occurred in 20 out of 20 (100%) enrolled patients.

Among the 76 study related adverse events, the most frequent 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. The majority of these events (44/45, 98%) were considered mild and one was considered moderate. The average duration of these events was 8 days, with all resolving over a range of 3 to 48 days from onset. This adverse event was observed typically following Implant insertion and Implant refill procedures.

Of the 76 study-related adverse events, 30 were considered by the Investigator to be possibly or definitely related to the Implant insertion procedure. These adverse events occurred in 15 patients. The most frequent adverse events related to the Implant insertion procedure were conjunctival hyperemia (55% of the patients), vitreous hemorrhage (25%), hyphema (15%), and VA decrease (15%). Single adverse events were reported as related to the Implant insertion procedure: endophthalmitis (5% of the patients) and traumatic cataract (5%). A single adverse event of retinal pigment epithelial tear (5%) was reported as possibly related to the Implant placement. The number of adverse events related to the Implant insertion procedure in the first 10 patients (Patient Group 1) was greater (63% versus 19%) than that observed in the second 10 patients (Patient Group 2), suggesting that refinements in surgical instrumentation, training, and surgical experience that occurred during the trial may have in part mitigated the risk of the device placement procedure in Patient Group 2.

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

Six patients underwent planned removal of the Implant at the 12-month visit as scheduled in the protocol. All of these patients were in Group 1. Of these 6 patients, 4 patients experienced 5 adverse events related to the Implant removal procedure: two incidents of conjunctival hyperemia (33%) and single incidences of hyphema (17%), VA decrease (17%), and conjunctival hemorrhage (17%). All adverse events related to the implant removal procedure resolved within 7 days.

There were six reported serious adverse events during the treatment phase of the study. Four study-related serious adverse events were reported: two incidents of decreased VA consequent to adverse events of vitreous hemorrhage, one incident of endophthalmitis, and one incident of decreased VA consequent to the incident of endophthalmitis. Two non-study-related serious adverse events were reported: gastric adenocarcinoma and rotavirus infection. The two incidents of vitreous hemorrhage were likely caused by post-operative bleeding and were determined to be related to the Implant insertion procedure. The single incident of endophthalmitis was observed at the 2-week post-Implant insertion visit and was considered possibly related to the Implant insertion procedure. The duration of this event was 14 days.

Of the 76 study-related adverse events, 7 were ongoing at the time of study exit. These ongoing events were vitreous haze (3), and single incidents of vitreous hemorrhage, VA decrease, foreign body sensation in the eye, and retinal pigment epithelium tear.

Thirteen patients entered the 24-month safety-monitoring phase (one patient was lost to follow-up after the 12-month follow-up); out of 13 patients, 12 completed the safety-monitoring phase and 1 was lost to follow-up after 21 months. There were a total of eight reported adverse events during the safety-monitoring phase of the study. Four adverse events were considered related (possibly, probably, or definitely) to the Implant insertion procedure, the refill procedure, or drug treatment. These related adverse events were cataract progression (3) and a single incident of mild ocular discomfort. Two additional incidents of cataract progression, one incident of blurred vision, and one incident of leg edema were not considered study-related by the investigator. No serious adverse events were reported during the safety-monitoring phase.

There were no patient deaths during the 12-month treatment phase (the status of the 2 patients lost to follow-up during the 24-month extended follow-up phase was not able to be confirmed), no adverse events led to patient withdrawal or dose reduction, and no adverse events represented a previously unsuspected important adverse effect of the device (implantation procedure or Implant).

Refer to the RPDS IB for further details.

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

As a result of the chronic, progressive nature of nAMD, frequent ranibizumab ITV injections continue for extended periods for many patients. Pivotal studies of ranibizumab in nAMD (Studies FVF2598g and FVF2587g) demonstrated significant and well-maintained visual acuity (VA) outcomes with monthly 0.5 mg ITV injections for 2 years. Trials that investigated less frequent than monthly dosing (Study FVF3192g and Lalwani et al. 2009) showed that visual outcomes were not as well maintained with more intermittent dosing schedules. A recent trial that compared monthly to PRN ranibizumab ITV administration (Study FVF4579g) 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 re-treatment and still required frequent ITV injections. The mean number of ranibizumab ITV injections through month 24, with the 0.5-mg dose, was 21.4 for the monthly treatment arm and 13.3 for the PRN treatment arm. In clinical practice, frequent office monitoring visits are required and regular injections are necessary to maintain optimal vision gains. Frequent office visits place a significant burden on patients and their caregivers, as well as treating physicians and the healthcare system. Sustained release of ranibizumab from the Implant is an alternate dosing method that may result in less frequent need of re-treatment than monthly dosing with ITV injections. This decrease in treatment burden could possibly reduce the risk of ITV injection–related adverse events, increase compliance, and reduce the burden to patients, their caregivers, and the healthcare system, while maintaining optimum visual outcomes.

The safety, tolerability, and duration of ranibizumab exposure delivered through the Implant were investigated in a Phase I prospective, open-label study in a nAMD patient population by FSV4 at a single site in Latvia. Patient enrollment was initiated in August 2010 and the study was completed in July 2013. The study assessed the safety of the RPDS 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. Secondary endpoints of VA and optical coherence tomography (OCT) change were also collected.

All 20 patients completed the 12-month treatment phase of the Phase I study. At month 12, 6 patients underwent per-protocol planned Implant removal and exited the study after completion of the 13-month visit. Complete 13-month data are available for

these 6 explanted patients. The 14 remaining patients completed an additional 2-year safety-monitoring phase, and follow-up data ranging from 27 to 36 months are available for 12 of these patients. The remaining 2 patients being monitored for ongoing safety were lost to follow-up at 12 and 21 months.

The overall safety profile of the combination product from the available study data is generally consistent with the known safety profile of ranibizumab as administered by ITV injection (ranibizumab USPI) and similar surgical procedures involving intraocular implants (Vitrasert USPI, 2013; Retisert USPI, 2013; Dunn et al. 2004; Gedde et al. 2012; Buys 2013). Procedure-related adverse events for the 20 Implant placements were not unexpected. In 96 Implant refill procedures, the refill procedure-related adverse events were comparable to adverse events related to ITV injections (see Section 5.1 for further details).

The improvement in best corrected visual acuity (BCVA) appeared comparable to monthly injections with sustained reduction in macular thickness and area of CNV leakage. The Phase I study provided evidence of the safety and tolerability of the combination product and supports the evaluation of RPDS in a Phase II study. It is expected that in the Phase II study the drug efficacy of the Implant treatment arms will be similar to the control ITV monthly injection treatment arm.

2. STUDY OBJECTIVES

2.1 EFFICACY OBJECTIVES

The primary efficacy objective for this study is as follows:

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

The secondary efficacy objectives for this study are as follows:

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

- To evaluate the efficacy of 10-mg/mL, 40-mg/mL, and 100-mg/mL formulations of ranibizumab, delivered via the Implant, with that of 10-mg/mL (0.5-mg dose) monthly ITV ranibizumab injections over time, as measured by the change in central foveal thickness (CFT, defined as the retinal thickness in the center of the fovea) from baseline over time
- To evaluate the functionality of the Implant by assessing that there is no evidence of Implant clogging in more than 10% of patients in the Implant arms at Month 9

2.2 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the safety of ranibizumab delivered via the Implant, compared with that of monthly ITV injection, as measured by ocular and non-ocular adverse events and serious adverse events
- To evaluate the safety of the RPDS, as measured by "Prespecified RPDS-associated adverse events" (see Section 6.5.1)
- To evaluate the proportion of patients with positive serum antibodies to ranibizumab

2.3 PHARMACOKINETIC OBJECTIVES

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

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

2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate the development of macular atrophy in all three Implant treatment arms relative to one another and to the monthly ITV arm
- To examine the impact of ranibizumab treatment on patient-reported treatment satisfaction as assessed by the Macular Degeneration Treatment Satisfaction Questionnaire (MacTSQ) at Months 1, 6, 9, and the final or early termination visit for patients who speak English or Spanish (see Appendix 19)
- To explore time to subsequent Implant refills according to protocol-defined refill criteria
- To describe the number of times patients meet protocol-specified refill criteria
- To evaluate the proportion of patients in each Implant arm who first meet the protocol-defined refill criteria prior to and at Months 4, 5, and 6
- To evaluate the proportion of patients with an improvement of ≥ 15 letters in BCVA from baseline
- To evaluate the proportion of patients with a loss of ≥ 15 letters in BCVA from baseline over time
- To explore the utility of BCVA measured under low luminance as a predictor of treatment benefit over time

- To evaluate the changes in total lesion area, area of CNV lesion, and CNV leakage over time, as assessed by fluorescein angiography
- To explore the serum ranibizumab concentration data with a PK model in an attempt to infer the concentration–time pattern in the vitreous or aqueous humor and, if possible, derive information on the rate of ranibizumab release from the Implant
- To characterize ranibizumab aqueous humor concentration over time (optional)
- To characterize ranibizumab vitreous or aqueous humor concentration after Implant explantation (if applicable)
- To evaluate the potential association of circulating biomarkers with disease characteristics and response to ranibizumab (optional)
- To evaluate the relationship of genetic variants (such as AMD risk alleles; polymorphisms within the complement pathway; and polymorphisms within the VEGF-A genetic locus) with the disease characteristics and/or response to treatment with ranibizumab (optional)
- To evaluate the potential association of vitreous or aqueous humor biomarkers with disease characteristics and response to ranibizumab
- To evaluate the proportion of patients meeting lack of clinical efficacy criteria (see Section 5.1.1.3)
- To evaluate the proportion of patients requiring explantation
- To evaluate the changes in CNV perfusion over time as assessed by OCT Angiography (at selected sites that have OCT angiography equipment)

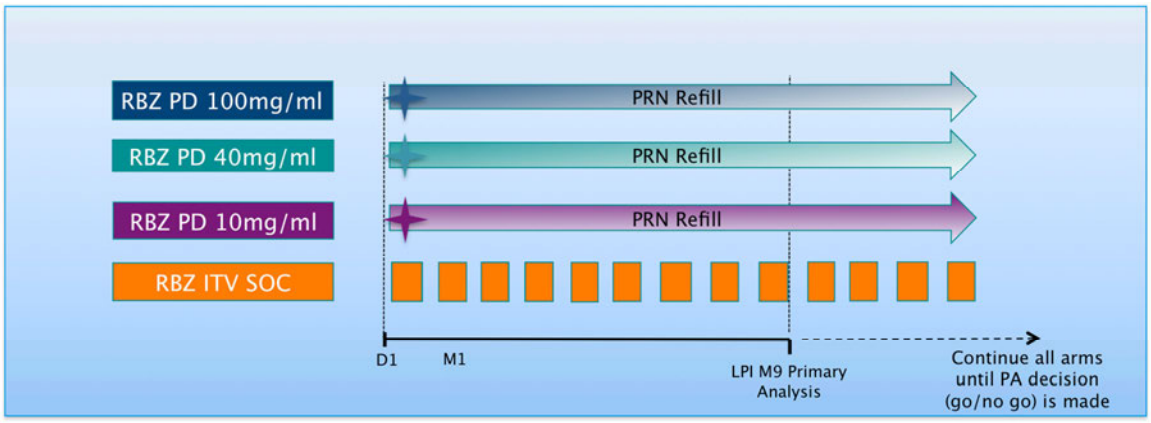
See the Device Clinical Investigation Plan (Appendix 21) for additional details of RPDS-specific data analyses to be conducted using the data generated during this study.

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

Study GX28228 is a Phase II, multicenter, dose-ranging, randomized, active treatment (monthly ITV injection)–controlled study to evaluate the efficacy, safety, and pharmacokinetics of ranibizumab delivered through the Implant using three ranibizumab formulation arms (10 mg/mL, 40 mg/mL, and 100 mg/mL) compared with the control arm (0.5-mg monthly ITV injections of 10-mg/mL formulation) in patients with nAMD. The study will also evaluate the safety of the RPDS combination product. Approximately 220 patients at up to 60 sites in the United States will be randomized in a 3:3:3:2 ratio to four treatment arms within an approximate 24-month period of time (see Figure 2).

Figure 2 Study Schema



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

Patients randomized to the Implant treatment arms will have the Implant (pre-filled with ranibizumab) surgically inserted in the study eye at their Day 1 visit, after which they will be evaluated monthly for the need for an Implant refill, based upon protocol-specified refill criteria (see Section 3.1.1), for the remainder of the study treatment duration (see Section 3.2). Patients randomized to the ITV injection treatment arm (control) will be treated monthly with ITV injections of ranibizumab, starting at their Day 1 visit and continuing for the remainder of the study treatment duration (see Section 3.2). The monthly ITV treatment arm patients will also be evaluated monthly according to the protocol-specified refill criteria (see Section 3.1.1), but will be treated monthly regardless of whether they meet the refill criteria. Study visits will be conducted every 30 ± 7 days relative to the Day 1 visit.

Following implementation of Protocol GX28228, Version 5, if warranted, enrollment and implant insertion surgeries may be paused to enable real-time review of post-implant insertion safety data by the Internal Monitoring Committee (IMC). In the case of such a pause, dosing will continue as per the protocol for patients who have already received study drug (e.g., patients who have performed Day 1 visit), while patients who have not yet received study drug will stay in Pre-Screening, Run-In, Screening, or Randomization period (as applicable) and receive monthly open-label ITV ranibizumab treatment until enrollment and implant insertion surgeries are restarted. In addition, in the case of a pause, patients who have been randomized but have not yet received the study drug must repeat the Randomization assessments after enrollment and implant insertion surgeries have recommenced and before receiving the study drug. Patients who exceed nine total anti-VEGF doses before receiving the study drug will no longer be eligible for the study.

The study will include screening and randomization visits followed by a treatment period. Baseline measurements will be taken at the randomization visit. On the day of patient

randomization, BCVA will be measured based upon the Early Treatment Diabetic Retinopathy Study (ETDRS) chart assessment at a starting test distance of 4 meters. The patients will then be randomized to a treatment arm using a stratified randomization: BCVA score (≤65 letters vs. ≥66 letters) and number of prior anti-VEGF ITV injections (≤3 vs. ≥ 4). Patients must satisfy all eligibility criteria at both the screening and the randomization visits, including receipt of all screening visit images by a central reading center. Historical OCT images taken at the time of diagnosis of nAMD will also be evaluated by the reading center to determine patient's eligibility. If fluorescein angiograms were taken at the time of diagnosis of nAMD, they must be submitted to the reading center as well. If available, historical fluorescein angiograms will be evaluated by the reading center, but are not required to determine patient's eligibility at the screening visit. As part of the screening process, the central reading center will evaluate the patient's FA, FP, and SD-OCT images taken both at the time of diagnosis of nAMD and at the screening visit to provide an objective, masked assessment of patient eligibility regarding lesion CNV, lesion classification, total lesion size, area of CNV lesion, and CNV leakage (see the Reading Center manual for details). Macular atrophy will also be evaluated at screening, using fundus autofluorescence (FAF) and SD-OCT measurements (see the reading center manual for further details). After all eligibility requirements are confirmed, patients will be randomized through an interactive voice/Web response system (IxRS) in a 3:3:3:2 ratio so that approximately 60 patients will receive the Implant filled with 10-mg/mL ranibizumab formulation, 60 patients will receive the Implant filled with 40-mg/mL ranibizumab formulation, 60 patients will receive the Implant filled with 100-mg/mL ranibizumab formulation, and 40 patients will receive monthly ITV injections of 10-mg/mL ranibizumab formulation (50 μL for the 0.5-mg dose; see Figure 2).

There are 4 patient eligibility scenarios based on prior anti-VEGF treatment history:

1. **Newly diagnosed nAMD patients who are treatment naïve**. These patients will undergo pre-screening if they satisfy eligibility criteria and sign informed consent (Table 2). During the pre-screening, patients will receive two ranibizumab ITV treatments to determine if they demonstrate response to ranibizumab treatment as outlined per the eligibility criteria (see Section 4.1.1).
2. **Patients diagnosed with nAMD in the study eye within 9 months prior to screening who have been treated with a single anti-VEGF ITV injection**. These patients may receive one "run-in" ITV ranibizumab treatment prior to screening if they satisfy eligibility criteria and sign the informed consent form (see Table 2).
3. **Patients diagnosed with nAMD in the study eye within 9 months prior to screening who have been treated with no more than eight anti-VEGF ITV injections and with the most recent dose being aflibercept or bevacizumab**. These patients may receive one "run-in" ITV ranibizumab treatment prior to screening if they satisfy eligibility criteria and sign the informed consent form (see Table 2).

4. **Patients diagnosed with nAMD in the study eye within 9 months prior to screening who have been treated with no more than nine anti-VEGF ITV injections and with the most recent dose being ranibizumab**. These patients can proceed directly to screening (see Table 2).

Table 2 Dosing Guidelines Prior to Screening

Historical anti-VEGF use in the study eye within the last 9 months prior to screening	Open-label ranibizumab dose(s) required prior to screening	Comments
Anti-VEGF treatment naive	2	The Sponsor will provide 2 ranibizumab doses prior to screening[a]
Single previous anti-VEGF dose	1	The Sponsor will provide 1 ranibizumab dose prior to screening[a]
2–8 prior anti-VEGF dose AND most recent dose was aflibercept or bevacizumab	1	The Sponsor will provide 1 ranibizumab dose prior to screening[a]
2–9 prior anti-VEGF dose AND most recent dose was ranibizumab	0	Patients can proceed directly to screening

VEGF = vascular endothelial growth factor.

[a] In the case of a pause of patient enrollment, additional ITV ranibizumab doses will be provided before receiving study drug, until enrollment and implant insertion surgeries recommence. Patients who exceed 9 total anti-VEGF doses before receiving the study drug will be excluded from the study.

A patient's screening visit should occur no sooner than 7 days following administration of the last ITV ranibizumab treatment in the study eye. All patients will be enrolled in the study on the day of their randomization visit and receive their Day 1 study treatment after conclusion of the Randomization visit. If necessary, the Day 1 study treatment may be scheduled at a later date.

Randomization visit cannot occur earlier than 28 days and no later than 37 days after the patient's last ITV ranibizumab treatment.

Day 1 study treatment visit cannot occur earlier than 28 days after and no later than 37 days after the patient's last ITV ranibizumab treatment, unless a patient randomized to the Implant arm needs more time to interrupt aspirin or NSAID usage 7 days before Day 1 (see Section 4.3.2.3). For these patients, Day 1 study treatment visit must occur no later than 45 days after the patient's last ITV ranibizumab treatment.

Patients who are randomized to the Implant treatment arms will have scheduled safety visit assessments on Day 2 (±0), Day 7 (±2 days), and Day 14 (±2 days) after their Day 1 visit. Starting at the Month 1 visit, the patients in the Implant treatment arms will be assessed monthly for the need for Implant refill with ranibizumab according to the

protocol-specified refill criteria (see Section 3.1.1). Their Implant will be refilled only if they meet re-treatment criteria. The safety visits will be scheduled 7 (±2) days after each refill (see Appendix 1). After the Day 1 visit treatment, patients randomized to the monthly ITV injection treatment arm will also be assessed monthly using the same re-treatment criteria as those for the Implant treatment arms (see Section 3.1.1) but will receive monthly ranibizumab injection treatment regardless of whether they meet the criteria (see Appendix 2 and Table 3).

Table 3 Ranibizumab Dosing and Safety Assessment Schema

Visit	Day				Month									Month X [b]	Final/ ET visit
	1 [a]	2	7	14	1	2	3	4	5	6	7	8	9		
Implant insertion/refill [c]	x				Refill Implant if refill criteria are met										NA
Safety assessment visits [d]		x	x	x	7 Days after each Implant refill										NA
ITV injection [e]	x				x	x	x	x	X	x	x	x	x	x	NA

ET = end of treatment; ITV = intravitreal; NA = not applicable.

[a] The Day 1 treatment in all treatment arms (Implant and ITV injection) will occur on such date so that no fewer than 28 days and no more than 37 days have elapsed from patient's last study eye ranibizumab ITV treatment.

[b] Month X visits: After completion of the Month 9 visit, the study patients in the Implant arms will continue monthly evaluation for refill according to the Month X schedule of assessments (see Appendix 1) until the Sponsor decides, based on the primary analysis results, to either terminate the study and discontinue study treatment or offer patients entry into the RPDS *Extension* Study. The ITV arm patients will continue to be treated monthly *according to the Month X schedule of assessments (see Appendix 2) until the Sponsor decides, based on the primary analysis results, to either terminate the study and discontinue study treatment, or offer patients entry into the RPDS Extension Study.*

[c] Starting at the Month 1 visit, Implant treatment arms will receive a refill with ranibizumab only if protocol refill criteria are met (see Section 3.1.1).

[d] There will be safety assessment visits on Days 2, 7, and 14 after the Implant insertion and then 7 days after each Implant refill. These safety assessment visits are not applicable to the ITV injections treatment arm.

[e] ITV injection arm patients will be treated monthly regardless of meeting the re-treatment criteria.

Starting at the Day 1 visit (ITV treatment arm) or starting at the Month 1 visit (Implant arms), all patients will be contacted by site personnel 3 (±1) days after each ITV injection or Implant refill to elicit reports of decrease in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. Patients in the Implant treatment arms will also be asked to verify whether they have taken the prescribed, self-administered, post-injection antimicrobial treatments. The ITV arm patients' self-administered antimicrobial treatments will be prescribed at the investigator's discretion.

Only one eye will be selected as the study eye during the screening period. If both eyes are eligible, the investigator will determine, during the screening, which eye will be selected for study treatment (study eye).

- Should a non-study (fellow) eye require treatment for nAMD after randomization, treatment with ranibizumab is not recommended within 7 days of the study eye scheduled visit. For patients in the Implant arms, if the fellow eye will be treated 7 days after study eye treatment, ranibizumab should be administered after serum PK sample collection.
- The drug for the fellow eye during the study will be open-label ranibizumab and will be supplied by Genentech (see Section 4.3.1.4 for the drug formulation for the non-study eye). If a change in therapy is clinically indicated for the fellow eye per investigator judgment, the change must be discussed and agreed by the Medical Monitor prior to being made.

All study patients will have scheduled monthly visits during the study. After the Day 1 visit, patients randomized to the Implant treatment arms will be evaluated for their Implant refill at each monthly visit. Patients randomized to the ITV injection arm will be treated at each monthly visit. Study visits will be scheduled to occur according to the schedule of assessments in Appendix 1 and Appendix 2 and have to be relative to the Day 1 (first study treatment) visit date until the patient completes the study.

Each potential study patient can be randomized into the study only once.

Please see Section 5.1.1.1 for the criteria to be used for dose interruption and treatment/study discontinuation. Missed ranibizumab doses will not be replaced.

The ITV treatment arm patients who are discontinued from study treatment prematurely will be asked to undergo the scheduled monthly assessments until Last Patient In (LPI) Month 9 visit, after which they will be scheduled 30 (+7) days later for their final study visit. The patients who are discontinuing study treatment from the Implant treatment arms will be scheduled, within 7 days after the treatment discontinuation decision is made, for Implant explantation followed by safety visits 1 and 7 (±2) days post-explantation. Afterwards, they will be followed in the study, attending their monthly scheduled visits, until LPI Month 9 visit, after which they will be scheduled for the early termination visit (see Appendix 1). As per investigator judgement, these patients may start an approved anti-VEGF for their AMD once the need for Implant explantation is confirmed and, preferably, after explantation is completed. All explanted Implants with their remaining content will be returned to the designee of the Sponsor for storage and potential future exploratory analysis (see Section 4.4). A vitreous or aqueous humor sample will be collected at the start of explantation for patients undergoing an explantation procedure (see Appendix 19).

Patients who withdraw from the study prior to scheduled study completion will be asked to return for an early termination evaluation 30 (+7) days following their last study treatment for monitoring of adverse events and early termination visit assessments if they are in the ITV treatment arm. The patients who are discontinuing the study from the Implant treatment arms will be scheduled for Implant explantation within 7 days of the treatment discontinuation decision, followed by Safety Visits 1, 7 (±2), 30 (±7), and 60 (±7) days post-explantation after which they will be scheduled for the early termination visit 30 (+7) days later. As per investigator judgment, these patients may start an approved anti-VEGF treatment for their AMD once the need for Implant explantation is confirmed and, preferably, after explantation is completed. All explanted Implants with remaining content will be returned to the designee of the Sponsor for storage and potential future exploratory analysis (see Section 4.4). A vitreous or aqueous humor sample will be collected at the start of explantation for patients undergoing an explantation procedure (see Appendix 19).

Patients in the ITV injection arm *will be evaluated monthly and will* receive monthly study treatments (Day 1, Month 1 through Month *X* visit, see Appendix 2) *until the Sponsor decides, based on the primary analysis results, to either terminate the study and discontinue study treatment, or offer patients entry into the RPDS Extension Study.* Their participation (excluding screening period) in the study will last approximately *13–38* months dependent on the date of their randomization to the study.

The patients in the Implant arms will be evaluated monthly for the Implant refill (see Appendix 1) until the Sponsor decides, based on the primary analysis results, to either terminate the study and discontinue study treatment, or offer patients entry into the RPDS *Extension* Study. If a patient requires refills outside of the protocol-defined visits window, the Medical Monitor must be contacted by the investigator. Study participation for patients in the Implant arms (excluding screening period) is expected to last approximately 13–38 months dependent on the date of their randomization to the study.

Study investigators will be qualified ophthalmologists, trained in the management of retinal diseases and ocular surgery and will be certified by a Sponsor-selected vendor to perform initial Implant fill, insertion, refill, and explantation. 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 one investigator who evaluates and treats all patients with a backup investigator selected. The site may opt to have two separate investigators 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 a patient throughout the trial.

Study patients and all study site personnel will be masked to the Implant treatment arms' ranibizumab formulation assignment (10 mg/mL vs. 40 mg/mL vs. 100 mg/mL) until the study's conclusion (see Section 5.1.1.3 for more details on formulation assignment for

patients who meet lack of clinical efficacy criteria). The Sponsor's personnel directly involved in the study conduct (except prespecified IMC members) will be masked to the Implant treatment arms' ranibizumab formulation assignment (10 mg/mL vs. 40 mg/mL vs. 100 mg/mL) until the time of primary analyses (see Section 5.1.1.3 for more details on formulation assignment for patients who meet lack of clinical efficacy criteria). The IMC will closely monitor patient safety throughout the study (see Section 3.1.4).

Clinical pharmacology and PK scientists may be unmasked early for the purposes of interpreting emerging safety and efficacy data; those staff will not be part of the study team or have any interactions with sites or investigators.

In addition, the VA examiner will only conduct refraction and VA assessments and will be masked to patient study eye assignment and patient treatment assignment. The VA examiner will have no access to patient VA scores from previous visits, and will be only aware of the patient's refraction data from previous visits. The VA examiner may perform no other direct patient-care tasks. Patients will be asked not to discuss their study eye assignment (right vs. left) with the VA examiner.

3.1.1 Refill/Re-Treatment Criteria

Starting at the Month 1 visit, all randomized patients will be assessed monthly for the refill/re-treatment. The patients randomized to the ITV injection arm will be treated monthly, regardless of whether they meet re-treatment criteria. The patients randomized to the Implant treatment arms will have their Implant refilled only if **any** of the following criteria is met, as automatically determined by contacting IxRS:

- Increase in CFT of $\geq$75 µm on SD-OCT at the current visit compared with the average CFT over the last 2 available measurements, due to nAMD disease activity

  OR

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

  OR

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

  OR

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

  OR

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

Note: To assess the need for refill at 1 month after initial fill, please utilize the following criteria:

- Decrease of ≥ 10 letters in BCVA at the current visit compared with the baseline BCVA, due to nAMD disease activity

  OR

- Increase in CFT of ≥ 100 μm at the current visit compared with the baseline CFT, due to nAMD disease activity

  OR

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

Patients assigned to the Implant treatment arms will be scheduled for a safety evaluation visit 7 (±2) days after each refill.

The schedules of study assessments are provided in Appendix 1 and Appendix 2.

3.1.2 Pharmacokinetic Evaluation

The objective of the PK analysis is to characterize the Implant sustained-delivery performance by characterizing the serum and optional aqueous humor concentrations (see Appendix 1 for details) of 10-mg/mL, 40-mg/mL, and 100-mg/mL formulations of ranibizumab delivered via the Implant. PK parameters of interest will be estimated after implant and at subsequent refills using noncompartmental analysis (NCA) and/or a population PK model as appropriate; parameters will include area under the concentration–time curve (AUC), maximum serum concentration (C_{max}) observed, time to maximum concentration (t_{max}), steady-state serum concentration at the end of a dosing interval (C_{trough} [predose]), and terminal half-life ($t_{1/2}$).

The population PK model couples the in-vitro release parameters of the Implant with the population pharmacokinetics of ranibizumab in AMD patients to describe the pharmacokinetics of ranibizumab in AMD patients receiving these Implants. Inter-patient variability will be assessed. Coefficient of variation (%CV) of serum concentration at each PK sampling time point will be reported. The observed serum pharmacokinetics will be compared to the expected PK profiles as predicted by a population PK model.

3.1.3 Planned Total Sample Size

The study will randomize approximately 220 patients, 60 per each of three Implant treatment arms and 40 to the ITV injection arm (up to 60 sites). For further details see Section 6.1.

3.1.4 Internal Monitoring Committee

Ongoing review of study data (including adverse events of special interest [AESIs], serious adverse events, adverse device effects [ADEs], and laboratory abnormalities) will be performed by the IMC. The IMC roles and responsibilities will be outlined in the IMC Agreement.

3.2 LENGTH OF STUDY

The completion of study treatment for all patients is defined as the date when the Sponsor makes the decision, based on the primary analysis results, to either terminate the study and discontinue study treatment, or offer patients entry into the RPDS *Extension* Study. The primary analyses data is expected to be available approximately 4 months after the Month 9 visit of the last patient randomized.

The length of the study is approximately 38 months.

3.3 END OF STUDY

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

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Ranibizumab Dose Selection

Delivery of ranibizumab via the Implant was chosen to investigate an alternate dosing method. Sustained release of ranibizumab from the Implant is an alternate dosing method that may result in less-frequent need of re-treatment than monthly dosing with ITV injections. It has the potential to reduce the number of patient visits, as well as the burden on patients, caregivers, and healthcare providers. In addition, increased treatment compliance and optimum visual outcomes may result from the sustained delivery of ranibizumab through the Implant.

The three ranibizumab formulations administered via the Implant will be evaluated monthly to determine the efficacy and safety of each formulation. Based on the fill volume of 20 μL of the Implant, the maximum amount of ranibizumab with which the Implant can be initially filled and subsequently refilled is approximately 0.2 mg for the 10-mg/mL formulation, 0.8 mg for the 40-mg/mL formulation, and 2 mg of ranibizumab for 100-mg/mL formulation. The selection of the proposed Phase II doses was determined by several factors. The selected doses are anticipated to maintain ranibizumab vitreous trough concentrations either below (10-mg/mL), at (40-mg/mL), or above (100-mg/mL) the vitreous drug levels estimated to be correlated with efficacy (12 μg/mL), as assessed from pivotal studies that administered monthly 0.5-mg ITV injections. Thus, the three dose levels may provide a range of exposures to assess the dose- and exposure-response relationships. If the doses do not differentiate substantially on efficacy, as a result of potentially frequent refills for lower doses according to the “as needed” protocol defined refill criteria, then the treatment arms are expected to differentiate on the basis of time to first meeting refill criteria and number of

refills over the course of the study. In addition, all doses were selected taking into account prior clinical experience to ensure patient safety.

3.4.2 Rationale for Pharmacokinetic Evaluation Schedule

The serum pharmacokinetics of ranibizumab following ITV administration have been well characterized, however the PK profile for sustained delivery is expected to be markedly different. In order to characterize the PK profile and the in vivo sustained delivery of ranibizumab via the Implant, serum PK samples will be collected from patients in the Implant treatment arms at multiple timepoints (see Appendix 1) before and after refills. The sampling timepoints are expected to be sufficient to estimate key PK parameters of interest (see Section 3.1.2) following initial insertion of the ranibizumab-filled Implant and subsequent refills, and to demonstrate sustained exposure to ranibizumab. An optional aqueous humor sample (collected prior to or immediately following Implant refills), and a vitreous or aqueous humor sample (collected at the start of explantation for patients undergoing an explantation procedure), will also be collected to further characterize Implant kinetics and relate serum to vitreous ranibizumab concentrations. For additional details on ITV ranibizumab pharmacokinetics, refer to the RPDS IB.

3.4.3 Rationale for Patient Population

Ranibizumab has been shown to be effective in preventing or reducing vision loss in patients with nAMD; therefore, this patient population was selected to be the first in which the RPDS would be evaluated. The goal is to demonstrate a treatment approach that maintains the efficacy seen with monthly ITV injections while reducing the number of ITV injections and monitoring visits. Other indications (diabetic macular edema, retinal vein occlusion) may also benefit but would be considered for investigation following the Phase II study results in nAMD.

3.4.4 Rationale for Control Group

Ranibizumab is an approved treatment for nAMD in the European Union, United States, and many other countries worldwide. The monthly dosing of 0.5 mg (10-mg/mL) of ITV ranibizumab is the approved posology in the United States and was selected as the appropriate control group based on discussions with both the FDA and European Medicines Agency. Therefore, patients in the control arm in the randomized phase of the study will be treated with monthly ITV injections of 0.5-mg dose of ranibizumab.

3.5 OUTCOME MEASURES

The primary analysis of the study will take place after the LPI Month 9 visit has occurred.

3.5.1 Primary Efficacy Outcome Measure

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

3.5.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures are as follows:

- Change in BCVA from baseline at Month 9
- Average change in BCVA from baseline over time
- Change in BCVA from baseline over time
- Change from baseline in CFT over time, as assessed on SD-OCT by the central reading center
- Occurrence of Implant clogging (see Section 5.1.1.5 for details)

3.5.3 Safety Outcome Measures

The safety outcome measures are as follows:

- Incidence of adverse events of special interest (see Section 5.2.3 for details): Adverse events associated with ranibizumab, the Implant, implant-associated procedures, and/or ancillary devices (see Table 1)
- Incidence of "prespecified RPDS-associated adverse events" (see Section 6.5.1 for details)
- Incidence of ocular and non-ocular adverse events and serious adverse events
- Incidence of positive serum antibodies to ranibizumab

3.5.4 Pharmacokinetic Outcome Measures

The PK outcome measures related to ranibizumab serum concentration-time data following the Implant insertion and refills (see Appendix 1 for details):

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

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

3.5.5 Exploratory Outcome Measures

The exploratory outcome measures are as follows:

- Treatment emergent macular atrophy in all treatment arms
- The MacTSQ score at randomization and at Months 1, 6, 9, and the final or early termination visit for patients who speak English or Spanish (see Appendix 19)
- Time to subsequent Implant refills according to protocol-defined refill criteria

- Number of times a patient meets protocol-specified refill criteria
- Proportion of patients in each Implant arm who first meet the protocol-defined refill criteria prior to and at Months 4, 5, and 6
- Proportion of patients with an improvement of BCVA from baseline of ≥15 letters over time
- Proportion of patients losing ≥ 15 letters in BCVA from baseline over time
- Change in BCVA from baseline over time measured under low luminance conditions
- Changes from screening in total lesion area, area of CNV lesion, and CNV leakage over time, as assessed by fluorescein angiography
- Proportion of patients meeting lack of clinical efficacy criteria (see Section 5.1.1.3)
- Proportion of patients requiring explantation
- Changes in CNV perfusion over time, as assessed by OCT angiography

In addition, vitreous samples from the Refill Needle (if applicable), optional aqueous humor samples, and optional serum and plasma samples may be collected to assess the relationship between biomarkers and the disease characteristics and/or response to treatment with ranibizumab. Optional whole blood samples will be collected for DNA extraction (genetic analysis) to assess the relationship between genetic variants and the disease characteristics and/or response to treatment with ranibizumab (see Section 4.6.12).

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

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients with subfoveal neovascularization secondary to AMD diagnosed within 9 months and treated with ITV anti-VEGF agents will be enrolled in the study. Written informed consent will be obtained before initiation of any study-related procedures. A patient's screening visit should occur no sooner than 7 days following administration of the last ITV ranibizumab treatment to the study eye. The screening visit will be followed by the randomization visit.

The first study treatment (Day 1) may occur at the conclusion of the randomization visit for the ITV treatment arm; the Implant arm patients may have these two visits separated due to the systemic medication wash out period (see note below) and the surgery room availability. Randomization visit and Day 1 study treatment visit must occur on a date such that no less than 28 days and no more than 37 days have elapsed from the patient's last study eye ITV ranibizumab treatment.

There are 4 patient eligibility scenarios based on prior anti-VEGF treatment history.

1. **Newly diagnosed nAMD patients who are treatment naïve**. These patients will undergo pre-screening if they satisfy eligibility criteria and sign informed consent (Table 2). During the pre-screening, patients will receive two ranibizumab ITV treatments to determine if they demonstrate response to ranibizumab treatment as outlined per the eligibility criteria (see Section 4.1.1).
2. **Patients diagnosed with nAMD in the study eye within 9 months prior to screening who have been treated with a single anti-VEGF ITV injection**. These patients may receive one run-in ITV ranibizumab treatment prior to screening if they satisfy eligibility criteria and sign the informed consent form (see Table 2).
3. **Patients diagnosed with nAMD in the study eye within 9 months prior to screening who have been treated with no more than eight anti-VEGF ITV injections and with the most recent dose being aflibercept or bevacizumab**. These patients may receive one run-in ITV ranibizumab treatment prior to screening if they satisfy eligibility criteria and sign the informed consent form (see Table 2).
4. **Patients diagnosed with nAMD in the study eye within 96 months prior to screening who have been treated with no more than nine anti-VEGF ITV injections and with the most recent dose being ranibizumab**. These patients can proceed directly to screening (see Table 2).

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

General Inclusion Criteria

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

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

  Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

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

Ocular Inclusion Criteria (Study Eye)

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

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

  OR

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

  Active primary CNV lesions at the time of diagnosis of nAMD must be subfoveal or juxtafoveal with a subfoveal component (as defined in Table 4) related to the CNV activity (such as subretinal hemorrhage, subretinal fluid, or RPE detachment)

Note: Refer to Table 5 for further details on imaging requirements.

Table 4 Definition of Terms Pertaining to AMD Inclusion Criteria

Term	Definition
Primary	Newly diagnosed within 9 months of screening visit
Subfoveal	Including the center of the fovea within the boundaries of the CNV
Juxtafoveal	Confined to an area up to 199 μm from the geometric center of the fovea
Total area of lesion	A contiguous area of abnormal tissue in the macula that encompasses angiographically documented CNV with possible additional components of subretinal hemorrhage, blocked fluorescence not from hemorrhage, serous detachment of the retinal pigment epithelium, and subretinal fibrosis
AMD	Clinical and/or angiographic signs consistent with AMD (e.g., drusen, retinal pigment epithelial changes, CNV) with no other likely etiologic explanations for the degenerative changes

AMD = age-related macular degeneration; CNV = choroidal neovascularization.

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

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

    Active primary CNV lesions must be subfoveal or juxtafoveal with a subfoveal component (as defined in Table 4) related to the CNV activity (such as subretinal hemorrhage, subretinal fluid, or RPE detachment)

Note: Refer to Table 5 for further details on imaging requirements.

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

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

    Active primary CNV lesions at the time of diagnosis of nAMD must be subfoveal or juxtafoveal with a subfoveal component (as defined in Table 4) related to the CNV activity (such as subretinal hemorrhage, subretinal fluid, or RPE detachment)

Note: Refer to Table 5 for further details on imaging requirements.

Table 5 Imaging Requirements at Pre-Screening, Run-In, and Screening

Visit	Applies to	Required Ocular Imaging at the Study Visit	Required Historical OCT [a]	Imaging Evaluation
Pre-screening	Treatment-naive patients	FA, SD-OCT [b]	NA [b]	Investigator (locally)
Run-in	Patients previously treated with anti-VEGF [c]	NA	Yes	Investigator (locally)
Screening	All patients	FA, FP, FAF, SD-OCT, lens photo	Yes	Central reading center [d]

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

[b] Fluorescein angiograms and SD-OCT will be required for entry to Pre-Screening, and must be taken following the instructions on the Reading Center Manual; these images will be used as historical images for patient's eligibility at the screening visit.

[c] See Table 2 for details.

[d] The central reading center will evaluate fundus photography, fluorescein angiograms, and SD-OCT for determination of a patient's eligibility. Historical OCT taken at the time of diagnosis of nAMD is also required to determine patient's eligibility at the screening visit.

4.1.2 Exclusion Criteria

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

Prior Ocular Treatment

- Treatment with ITV anti-VEGF agents other than ranibizumab within 1 month prior to the randomization visit in either eye
- History of vitrectomy surgery, submacular surgery, or other surgical intervention for AMD in the study eye
- Prior treatment with Visudyne®, external-beam radiation therapy, or transpupillary thermotherapy in the study eye
- Previous treatment with ITV corticosteroid injection or device implantation in the study eye
- Previous focal laser photocoagulation used for AMD treatment in the study eye
- Prior participation in a clinical trial involving anti-angiogenic drugs, other than ranibizumab, in either eye within 2 months prior to the randomization visit
- Treatment with Visudyne® in the fellow eye $<$7 days preceding screening visit

CNV Lesion Characteristics

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

Note: Historical OCT taken at the time of diagnosis of nAMD will also be required to determine patient's eligibility at the screening visit. If fluorescein angiograms were taken at the time of diagnosis of nAMD, they must be submitted to the reading center as well. If available, historical fluorescein angiograms will be evaluated by the reading center, but are not required to determine patient's eligibility. If historical OCT images are not available or are not of sufficient quality to be evaluated by the Reading Center, patients would not be eligible for enrollment in the study.

Concurrent Ocular Conditions

- BCVA using ETDRS charts lower than 20/200 Snellen equivalent in the fellow eye
- Retinal pigment epithelial tear involving the macula in the study eye
- Any concurrent intraocular condition in the study eye (e.g., cataract, glaucoma, or diabetic retinopathy) that, in the opinion of the investigator, would either: require surgical intervention during the study to prevent or treat visual loss that might result from that condition or affect interpretation of study results
- Active intraocular inflammation (grade trace or above) in the study eye
- History of vitreous hemorrhage in the study eye within 3 months prior to the randomization visit
- History of rhegmatogenous retinal detachment or macular hole (Stage 3 or 4) in the study eye
- History of idiopathic or autoimmune-associated uveitis in either eye
- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye
- Aphakia or absence of the posterior capsule in the study eye

  Previous violation of the posterior capsule break in the study eye is also excluded unless it occurred as a result of yttrium aluminium garnet laser posterior capsulotomy in association with prior, posterior chamber intraocular lens implantation.
- Spherical equivalent of the refractive error in the study eye demonstrating more than 8 diopters of myopia
- For patients who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye does not exceed 8 diopters of myopia

- Intraocular surgery (including cataract surgery) in the study eye within 3 months preceding the randomization visit
- Uncontrolled ocular hypertension or glaucoma in the study eye (defined as intraocular pressure [IOP] $>$ 25 mmHg or a Cup to Disc ratio $\geq$ 0.8, despite treatment with anti-glaucoma medication) and any such condition for which the investigator feels may require a glaucoma filtering surgery while in the study
- History of glaucoma-filtering surgery, tube shunts, or microinvasive glaucoma surgery in the study eye
- History of corneal transplant in the study eye

Concurrent Systemic Conditions

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

  If the average of 3 readings exceeds these values, patient's blood pressure must be controlled by antihypertensive medication. The patient can become eligible for rescreening if medication is taken continuously for at least 30 days prior to the randomization visit.
- Uncontrolled atrial fibrillation within 3 months of informed consent
- History of stroke within the last 3 months prior to informed consent
- History of myocardial infarction within the last 3 months prior to informed consent
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of ranibizumab or placement of the Implant, that might affect interpretation of the results of the study or renders the patient at high risk of treatment complications
- Current treatment for any active systemic infection
- Use of any systemic anti-VEGF agents
- Use of oral corticosteroids (prednisone $>$ 10mg/day or equivalent)
- Use of anticoagulants, antiplatelets (other than aspirin), or medications known to exert similar effects at the time of study entry for a pre-existing condition. Oral anticoagulants include vitamin K antagonists (e.g., warfarin), direct factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban, fondaparinux) and direct thrombin inhibitors (e.g., dabigatran). Antiplatelet therapies include clopidogrel, prasugrel, dipyridamole, ticagrelor and ticlodipine (see Section 4.5.2).
- Bleeding disorders, including platelet disorders, acquired or hereditary coagulations disorders, and acquired or hereditary vascular disorders.

- Active malignancy within 12 months of randomization except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of <6 and a stable prostate-specific antigen for >12 months.
- History of allergy to fluorescein, not amenable to treatment
- Inability to obtain fundus photographs, fluorescein angiograms, fundus autofluorescence, or SD-OCT images of sufficient quality to be analyzed and graded by the central reading center
- Inability to comply with study or follow-up procedures
- Previous participation in any non-ocular (systemic) disease studies of investigational drugs within 1 month preceding the informed consent (excluding vitamins and minerals)
- Use of antimitotic or antimetabolite therapy within 30 days or 5 elimination half-lives of the randomization visit
- Intolerance or hypersensitivity to topical anesthetics, mydriatic medications, any of the excipients in ranibizumab, fluorescein, or components of the Implant
- Requirement for continuous use of any medications or treatments indicated in the "Prohibited Therapy" section (see Section 4.5.2)
- Women who are pregnant or lactating or intending to become pregnant during the study
- Women who are of childbearing potential, including those who have had tubal ligation, must have a negative serum pregnancy test result within 21 days prior to Day 1. A woman is considered not to be of childbearing potential if she is postmenopausal or has undergone hysterectomy and/or bilateral oophorectomy.
- No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

4.2 METHOD OF TREATMENT ASSIGNMENT AND MASKING

4.2.1 Randomization and Masking

Patients will be randomized through an IxRS in a 3:3:3:2 ratio so that approximately 60 patients will receive the Implant with 10-mg/mL ranibizumab formulation, 60 patients will receive the Implant with 40-mg/mL ranibizumab formulation, 60 patients will receive the Implant with 100-mg/mL ranibizumab formulation, and 40 patients will receive monthly ITV injections of 10-mg/mL ranibizumab formulation. On the day of patient 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 ($\leq$ 65 letters vs. $\geq$ 66 letters) and number of prior anti-VEGF injections ($\leq$3 vs $\geq$4).

Study patients and all study site personnel will be masked to the Implant treatment arms' ranibizumab formulation assignment (10 mg/mL vs. 40 mg/mL vs. 100 mg/mL) until the study's conclusion (see Section 5.1.1.3 for more details on formulation assignment for patients who meet lack of clinical efficacy criteria). The Sponsor's personnel directly

involved in the study conduct (except prespecified IMC members) will also be masked to the Implant treatment arms' ranibizumab formulation assignment (10 mg/mL vs. 40 mg/mL vs. 100 mg/mL) until unblinding of treatment code after database lock (see Section 5.1.1.3 for more details on formulation assignment for patients who meet lack of clinical efficacy criteria). In addition, the VA examiner will conduct only refraction, BCVA assessment, BCVA assessment under low luminance conditions, and will be masked to patient study eye assignment and patient treatment assignment. The VA examiner will have no access to the BCVA scores of a patient's previous visits, and will be only aware of the patient's refraction data from previous visits. The VA examiner may provide no other direct patient care. Patients will be asked not to discuss their study eye assignment with the VA examiner.

Patients and study site personnel will not be masked with regard to patient assignment to the ITV arm or an Implant arm because of the difficulties of maintaining masking following the surgical procedure, the additional safety visits applicable only to the Implant arms, and Implant visualization upon ophthalmic examination.

4.2.2 Unmasking Procedure

Treatment assignment should be unmasked for a patient in an Implant treatment arm in the event of a life-threatening medical emergency (if the investigator considers this necessary for treatment of the patient) that requires immediate unmasking or in the event of an unexpected serious adverse events judged by the investigator as related to study drug or RPDS, for FDA safety reporting. In such cases, unmasking will be implemented following standard procedures.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Ranibizumab Port Delivery System

For the list of the components of the RPDS, see Table 1. For detailed information on the RPDS components, initial Implant fill, insertion, refill, as well as the explantation procedure consult the RPDS IFU and RPDS IB documents.

Note: Unless otherwise directed by the Sponsor, only ranibizumab will be injected into the Implant.

4.3.1.2 Formulation of Ranibizumab Used to Fill/Refill the Implant Ranibizumab 10 mg/mL, 40 mg/mL, and 100 mg/mL

Ranibizumab is formulated as a sterile solution aseptically filled in a sterile 3-mL stoppered glass vial. Each vial contains 0.5 mL of the 10-mg/mL, 40-mg/mL, or 100-mg/mL formulations of ranibizumab aqueous humor solution (pH 5.5) with 10 mM histidine hydrochloride (HCl), 10% α,α-trehalose dihydrate, and 0.01% polysorbate 20, pH 5.5. Each vial contains no preservative and is suitable for single use only. Vial content should not be frozen or shaken and should be protected from direct light.

Ranibizumab vials must be refrigerated at 2°C to 8°C (36°F to 46°F) upon receipt until used. All vials will be labeled as required by the relevant regulatory agencies.

4.3.1.3 Formulation of Ranibizumab Used in ITV Injection Control Arm Ranibizumab 10 mg/mL

Ranibizumab is formulated as a sterile solution aseptically filled in a sterile 2-mL stoppered glass vial. Each vial contains 0.3 mL of the 10-mg/mL formulation of ranibizumab aqueous humor solution (pH 5.5) with 10 mM histidine HCl, 10% α,α-trehalose dihydrate, and 0.01% polysorbate 20, pH 5.5. The vial contains no preservative and is suitable for single use only. Vial contents should not be frozen or shaken and should be protected from direct light. Ranibizumab vials must be refrigerated at 2°C to 8°C (36°F to 46°F) upon receipt until used. Each vial will be labeled as required by the relevant regulatory agencies.

For further details, see the RPDS IB.

4.3.1.4 Formulation of Open-Label Ranibizumab Ranibizumab 10 mg/mL

Ranibizumab is formulated as a sterile solution aseptically filled in a sterile 2-mL stoppered glass vial. Each vial contains 0.3 mL of the 10-mg/mL formulation of ranibizumab aqueous humor solution (pH 5.5) with 10 mM histidine HCl, 10% α,α-trehalose dihydrate, and 0.01% polysorbate 20, pH 5.5. The vial contains no preservative and is suitable for single use only. Vial contents should not be frozen or shaken and should be protected from direct light. Ranibizumab vials must be refrigerated at 2°C to 8°C (36°F to 46°F) upon receipt until used.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Implant

Please see the RPDS IFU document for a detailed description of the Implant initial fill, insertion, refill, and explantation procedures.

4.3.2.2 Dosage

Patients in the Implant Treatment Arms

Patients will have the Implant (prefilled with approximately 20 μL of either the 10-mg/mL (approximately 0.2 mg dose), 40-mg/mL (approximately 0.8 mg dose), or 100-mg/mL formulation (approximately 2-mg dose) of ranibizumab) surgically inserted in the study eye at the Day 1 visit following their randomization visit. Starting at the Month 1 visit, patients will be evaluated monthly for the need for Implant refill with the10-mg/mL, 40-mg/mL, or 100-mg/mL formulations of ranibizumab according to their randomization as per protocol-specified refill criteria (see Section 3.1.1). If the criteria are not met, no Implant refill will be given. At each refill, a volume of approximately 100 μL of ranibizumab will be injected in situ into the Implant through the septum to exchange the remaining contents of the Implant with newly introduced ranibizumab. During the refill procedure, the contents of the Implant will be collected in the fluid collection reservoir of

the Refill Needle, if applicable (see the RPDS IFU for further details). The volume of newly introduced ranibizumab remaining in the Implant after the refill procedure will be approximately 20 μL. After the initial fill of the Implant with ranibizumab, patients will be evaluated for their Implant refill according to protocol-specified refill criteria (see Section 3.1.1) at each of their scheduled visits until the study treatment completion (see Section 3.2 for the definition). Missed treatments will not be made up.

If a study patient meets criteria for lack of clinical efficacy, he or she will receive a rescue injection with open-label ranibizumab. After that, he or she will receive the 100-mg/mL formulation for all future refills (see Section 5.1.1.3 for more details).

Study visits for the Implant treatment arms will be scheduled to occur according to the schedule in Appendix 1 and have to be relative to the Day 1 (the first study treatment) visit date until patients complete the study.

Patients in the ITV Injection Treatment (Control) Arm

Patients will receive their first ITV injection of 50 μL of the 10-mg/mL ranibizumab (0.5 mg dose) formulation at the Day 1 visit, which may occur (if feasible) at the conclusion of the randomization visit. Afterwards, patients will receive monthly ITV injections of 50 μL of 10-mg/mL formulation. Patients will be receiving the study treatment at each scheduled monthly visit until the study treatment completion (see Section 3.2 for the definition). Missed treatments will not be made up.

Study visits for the ITV treatment arm will be scheduled to occur according to the schedule in Appendix 2 and have to be relative to the Day 1 (the first study treatment) visit date until patients complete the study.

Ranibizumab dosing should not occur earlier than 22 days after the previous dosing. Guidelines for treatment interruption or discontinuation are provided in Section 5.1.1.1 and Table 6.

Pre-Screening

Pre-screening is available for newly diagnosed nAMD patients who are treatment naïve in the study eye. Patients eligible for the pre-screening will receive their first ITV injection of 50 μL of the 10-mg/mL ranibizumab (0.5 mg dose) formulation at the Pre-Screening visit 1, and their second injection 30±7 days later (Pre-Screening visit 2). A third pre-screening treatment may be allowed after consultation with the Medical Monitor. Afterwards, patients will undergo the screening visit, which will occur at least 7 days following administration of the last pre-screening ITV ranibizumab treatment to the study eye (see Appendix 3).

Run-In

Run-in is available for patients diagnosed with nAMD in the study eye within 9 months prior to screening who have been treated with a single anti-VEGF ITV injection, or with no more than eight anti-VEGF ITV injections and with the most recent dose being aflibercept or bevacizumab. Patients eligible for the run-in treatment will receive their single ITV injection of 50 μL of the 10 mg/mL ranibizumab (0.5 mg dose) formulation in the study eye at the time of consent. In exceptional cases, a second run-in treatment may be allowed after consultation with the Medical Monitor. Afterwards, patients will undergo the screening visit, which will occur at least 7 days following administration of the run-in ITV ranibizumab treatment to the study eye (see Appendix 4).

4.3.2.3 Administration

Implant Treatment Arms

Prior to Implant insertion or explantation, patients will be required to verify that they have self-administered antimicrobial eye drops to the study eye 4 times within the previous 24 hours. As per investigator's discretion, patients may also be required to have self-administered antimicrobial eye drops to the study eye 4 times within the 24 hours prior to potential Implant refills.

All patients must be instructed to self-administer antimicrobial eye drops to the study eye 4 times daily for 3 days following any refills. Antimicrobial eye drops to the study eye will also be required 4 times daily for 7 days following Implant insertion and explantation.

All patients randomized to the Implant arm and receiving ongoing aspirin or NSAID treatment must interrupt aspirin or NSAID treatment 7 days prior to Implant insertion or explantation and until at least the Day 2 safety visit following the procedure.

Prior to and during the Implant insertion procedure, blood pressure must be controlled. Before surgery, blood pressure must be checked after the patient has been in a resting state (i.e., supine or sitting) for at least 15 minutes. If blood pressure exceeds the recommended levels (i.e., between 100/60 mmHg and 155/95 mmHg), the Implant insertion surgery must be rescheduled.

Patients in the Implant treatment arms will have the Implant, prefilled with ranibizumab, surgically inserted into the study eye at the Day 1 visit and subsequently refilled at monthly visits only if the protocol-specified refill criteria are fulfilled (see Section 3.1.1). The insertion and explantation procedures must be performed in the surgery room while the refill procedure is permitted in the physician office setting. For detailed instructions on the Implant initial fill, insertion, refill, and explantation procedures, refer to the RPDS IFU.

ITV Injection Arm

Patients' self-administered antimicrobial treatments will be prescribed at the investigator's discretion. Prior to the monthly ITV injections, patients who are prescribed antimicrobials will be required to verify that they have self-administered their antimicrobials eye drops to the study eye pre- and post-injection. For detailed instructions on pre-injection preparation, administering the ITV injection, and post-ITV injection procedures for the study eye, consult Appendix 7 to Appendix 9.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.

All Treatment Arms

Adverse events associated with an overdose or incorrect administration of ranibizumab should be recorded on the Adverse Event electronic Case Report Form (eCRF).

ITV Injection of Open-Label Ranibizumab

Patients' self-administered antimicrobial treatments will be prescribed at the investigator's discretion.

4.3.2.4 Storage

4.3.2.4.1 Ranibizumab Port Delivery System

Ranibizumab. Vials of ranibizumab are for single use only. A vial used for one patient must not be used for any other patient.

Upon receipt, study drug kits must be refrigerated at 2°C to 8°C (36°F to 46°F). Sites must monitor and record refrigerator temperature at all times (24 hours per day, 7 days per week). DO NOT FREEZE. Vial content should not be frozen or shaken and should be protected from direct light. **Store in original carton before and after use.**

RPDS. Each Implant is held by an Insertion Tool and is packaged inside a sterile barrier system pouch. The Initial Fill Needle and Explant Tool are each packaged separately in a sterile barrier pouch system. The Refill Needles are packaged separately and individually in a tray. The Implant, Insertion Tool, Initial Fill Needle, Refill Needle, and Explant Tool should be maintained at a room temperature of 15°C to 30°C (59°F to 86°F). The storage location at the clinical site must have restricted access and be available only to study personnel. The Implant, Initial Fill Needle, Insertion Tool, and Explant Tool are supplied sterilized by exposure to ethylene oxide. The Refill Needles are sterilized by e-beam.

DO NOT RESTERILIZE.

The RPDS components (see Table 1) must not be resterilized 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.

4.3.2.4.2 Investigational Medicinal Product and RPDS Accountability

All investigational medicinal products (IMPs) (ranibizumab) and RPDS required for completion of this study (including all the components of the RPDS, see Table 1) will be provided by the Sponsor. The investigational site will acknowledge receipt of IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

RPDS (Initial Fill Needle, Refill Needle with its content, explanted Implant with its remaining content, Explant Tool, and Insertion Tool) must be returned to the Sponsor or Sponsor's designee with the appropriate documentation.

In order to ensure traceability, each device component of the RPDS will be identified by a batch number.

Accurate records of all IMPs and RPDS received at, dispensed from, returned to, and destroyed and/or disposed of by the study site should be recorded on the Drug and RPDS Inventory Logs. See the Study Manual for further details.

IMPs (used, damaged drug kits) will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed. IMP destruction must be documented on the appropriate form. See site Pharmacy binder for further details.

4.3.2.4.3 Ranibizumab (Non-Study Eye)

At the discretion of the evaluating investigator, study patients may receive ITV injection of ranibizumab for their fellow (non-study) eye. The drug will be open-label ranibizumab and will be supplied by the Sponsor. If a change in therapy is clinically indicated for the fellow eye per investigator judgment, the change must be discussed and agreed with the Medical Monitor prior to being made.

4.3.2.4.4 Open-Label Ranibizumab

The drug will be open-label ranibizumab and will be supplied by the Sponsor.

4.4 PRODUCT QUALITY ASSESSMENTS

4.4.1 Ranibizumab in Contents Retrieval from Implant

4.4.1.1 Explanted Implants with Contents

Following explantation, the Implants containing a mixture of ranibizumab drug product (along with the vitreous components, which may have diffused into the Implant) will be preserved and forwarded by the site to the Sponsor or Sponsor selected designee for

potential future analysis. 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.

4.4.1.2 Ancillary Devices

The Initial Fill Needle, Insertion Tool, Refill Needle, and Explant Tool must be returned to the Sponsor or Sponsor's designee for possible physical inspection and/or functional testing.

4.4.2 Continued Access to RPDS

Currently, the Sponsor does not plan to provide ranibizumab via Implant or via ITV injections or to provide other study interventions to patients after the conclusion of the study or following early patient withdrawal. The Sponsor will evaluate the appropriateness of continuing to provide ranibizumab treatment to Implant treatment arms patients after evaluating RPDS efficacy, safety, and PK data gathered in the study. Depending on the results of the study, the Sponsor may offer study patients in the Implant arms entry into a separate RPDS *Extension* Study to continue to provide ranibizumab via the Implant in an open-label manner. If the results from this trial do not warrant further investigation of the RPDS, all patients in the Implant arms will have their Implants explanted.

4.5 CONCOMITANT THERAPY

4.5.1 Permitted Therapy

Concomitant medications are any prescription drugs or over-the-counter preparations other than protocol-specified procedural medications (e.g., dilating drops, fluorescein dyes, cefazolin or vancomycin, or medications associated with Implant insertion, refill, and extraction procedures) and pre- and post–study treatment medications (e.g., proparacaine, antimicrobials, steroids) used by a patient within 7 days preceding the randomization visit until conclusion of the patient's study participation or early termination visit.

Patients who use other maintenance therapy should continue its use unless prohibited as indicated in Section 4.5.2. All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF:

- Following randomization, if a patient's fellow eye requires treatment for nAMD, treatment with ITV ranibizumab injection may be administered at the discretion of the evaluating investigator. If a change in therapy is clinically indicated for the fellow eye per investigator judgment, the change must be discussed and agreed with the Medical Monitor prior to being made.
- All patients randomized to the Implant arm and receiving ongoing aspirin or NSAID treatment must interrupt aspirin or NSAID treatment 7 days prior to implant insertion or explantation. These medications can be restarted, if appropriate, after the Day 2 safety visit.

- As per investigator discretion, the Implant arms patients who had the Implant explanted may receive ITV ranibizumab for their study eye treatment.
- Cataract surgery in the study eye may be performed if clinically indicated and should occur 7 or more days after the last study treatment; the next study treatment will be held for 28 or more days following the surgery. At least one study treatment (e.g., monthly ITV injection treatment arm) may be missed after cataract surgery is performed.
- The onset of increased IOP and/or glaucoma in the study eye during a patient's study participation should be treated as clinically indicated.
- Use of topical steroids post-implant insertion or post-explantation surgery in the study eye is permitted.
- In a limited fashion, intra-articular or intramuscular corticosteroids may be allowed after consultation with the Medical Monitor.

4.5.2 Prohibited Therapy

At the discretion of their physician, patients may continue to receive all medications and standard treatments administered for other conditions except in the following instances:

- Concurrent use of any systemic anti-VEGF agents
- Concurrent use of oral corticosteroids (prednisone $>$ 10mg/day or equivalent)
- Concurrent study eye treatment for nAMD with anti-VEGFs other than the study drug treatment
- Concurrent fellow eye treatment for nAMD with anti-VEGFs other than ranibizumab. If a change in therapy is clinically indicated for the fellow eye per investigator judgment, the change must be discussed and agreed with the Medical Monitor prior to being made.
- Concurrent treatment with focal laser photocoagulation for nAMD in the study eye
- Concurrent treatment with Visudyne® for nAMD in either eye
- Concurrent use of ITV or subtenon corticosteroids in the study eye
- Concurrent use of and participation in other experimental therapies (except those with minerals and vitamins) are not allowed.

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

- Concurrent use of anticoagulants, antiplatelets (other than aspirin), or medications known to exert similar effects are prohibited at study entry, but may be initiated after the Day 14 safety visit if medically necessary and in consultation with the Medical Monitor. Oral anticoagulants include vitamin K antagonists (e.g., warfarin), direct factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban, fondaparinux), and direct thrombin inhibitors (e.g., dabigatran). Antiplatelet therapies include clopidogrel, prasugrel, dipyridamole, ticagrelor, and ticlodipine.

- Concurrent use of aspirin or NSAID at both the time of Implant insertion and explantation procedure (see Section 4.5.1 and Section 4.3.2.3 for aspirin and NSAID interruption requirements)
- Use of magnetic resonance imaging (MRI) scans for patients in the Implant treatment arms is conditional. Investigators should discuss with the Medical Monitor if MRI use is required prior to this procedure being performed. For additional information refer to RPDS IFU.

4.6 STUDY ASSESSMENTS

4.6.1 Medical History, Concomitant Medication, and Demographic Data

Medical history includes clinically significant diseases, surgeries, smoking history, and use of alcohol.

All medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) other than protocol-specified procedural medications (e.g., dilating drops, fluorescein dyes, cefazolin or vancomycin, Implant insertion, refill and extraction procedures medications, and pre- and post-treatment medications [e.g., proparacaine, antimicrobials, steroids]) used by the patient within 7 days prior to the randomization visit until the study completion will be recorded on the eCRF concomitant medication log.

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

4.6.2 Vital Signs

Vital signs will include measurements of pulse and systolic and diastolic blood pressure obtained with the patient in a seated position after resting for 5 minutes. Height and weight will also be recorded at screening. At visits when a patient receives study treatment, vital signs will be measured pre-treatment.

4.6.3 Physical Examinations

A targeted physical examination should include an evaluation of the head, eyes, ears, nose, throat, and cranial nerves. A patient's height and weight will be recorded as well. If any abnormalities are noted during the study, the patient may be referred to another doctor.

Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.6.4 Ocular Assessments

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

- BCVA on ETDRS chart at a starting distance of 4 m (perform prior to dilating eyes; see Appendix 10)
- BCVA on ETDRS chart under low luminance conditions at a starting distance of 4 m (perform prior to dilating eyes; see Appendix 11)
- The following measurement will be performed in both eyes of the patients in the Implant treatment arms, from sites that have ultrasound or optical biometry, and will be recorded on the appropriate eCRF:
  - Axial length measurement (ultrasound or optical biometry)
- IOP measurement
  - At each monthly visit, 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
  - Before Implant insertion or explantation surgery, the treating physician must check IOP for the study eye using Tono-Pen tonometry.
  - Upon completion of the Implant insertion or explantation surgery, the treating physician must check IOP for the study eye only by digital palpation before patching the eye.
- Slit lamp examination (for grading scales for flare/cells and vitreal hemorrhage density; see Appendix 12)
- Dilated binocular indirect high-magnification ophthalmoscopy

  In addition, examinations will also be performed for patients in the Implant treatment arms after Implant insertion in the study eye, and then on Days 2, 7 (±2 days), and 14 (±2 days) after the Day 1 visit; afterward, dilated ophthalmoscopy examinations will be performed at each monthly visit to monitor the Implant placement, to evaluate visible clogging of the RCE tip, and to evaluate other Implant problems.
- Finger counting test, followed by hand motion and light perception tests (as applicable) performed within 15 minutes following Implant refill or ITV ranibizumab for the study eye only by the treating physician
- After each treatment, the patients will remain in the office or in the surgical center (as applicable) for approximately 40 minutes. If there are no safety concerns 40 (±10) minutes following treatment, 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.

4.6.5 Ocular Imaging

Note: All ocular images will be forwarded to the central reading center for grading and/or storage, starting from the screening visit. See central reading center manual for details.

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

- Fundus photographs (see Appendix 14)
- Lens photograph (fundus reflex photograph)
- Fluorescein angiograms (to be performed after laboratory samples are obtained; see Appendix 15)
- SD-OCT scans (Heidelberg; see Appendix 16)
- Fundus autofluorescence (Heidelberg; see Appendix 13)

The following ocular images of both eyes will be collected only from patients in the Implant treatment arms from sites that have a Humphrey Visual Field machine and will be forwarded to the reading center for evaluation and/or storage:

- Visual field testing (Humphrey Automated Visual Field testing using Swedish interactive threshold algorithm Fast 24-2 protocol)

The following ocular images will be collected only from the study eye of patients in the Implant treatment arms and forwarded to the reading center for evaluation and/or storage:

- External photographs (high-magnification Implant and conjunctiva, scleral surface; see Appendix 17)
- Implant photograph (high-magnification Implant in the eye, through dilated pupil; see Appendix 17)

The following ocular images of both eyes will be collected from all study patients at selected sites that have OCT angiography equipment:

- OCT angiography (Optovue; see Appendix 18)

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.

4.6.6 Laboratory Assessments

Laboratory samples for the following tests are to be performed by a central laboratory for all patients unless otherwise noted. Patients are not required to fast prior to the sample collection.

- Hematology: hemoglobin, hematocrit, quantitative platelet count, RBCs, WBCs, and differentials including neutrophils, bands, lymphocytes, basophils, eosinophils, and monocytes (absolute and percent)
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, total and direct bilirubin, total protein, albumin, AST, ALT, lactic dehydrogenase, alkaline phosphatase, 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 (β-human chorionic gonadotropin) at screening for women of childbearing potential, including those who have had tubal ligation. If positive, study treatment will not be administered.
- Urine pregnancy test at Day 1 and before each study treatment for women of childbearing potential, including those who have had tubal ligation. If urine pregnancy test is positive, a serum pregnancy sample will be collected and study treatment will not be performed until the final results are available. If the serum pregnancy test is positive, study treatment will not be administered (see Section 5.1.1).

Instructions for obtaining, processing, storing, and shipping of all specimens for central laboratory evaluations are provided in the Laboratory Manual.

The following samples will be collected from patients who consent to the Roche Clinical Repository (RCR) sampling collection (see Section 4.6.12) and will be tested by the Sponsor or a selected designee:

- Optional serum samples at the Randomization Visit and visits at Month 4 and Month 9, for the evaluation of circulating biomarkers.
- Optional plasma samples at the Randomization Visit and Visits at Month 4 and Month 9, for the evaluation of circulating biomarkers.
- Optional whole blood for DNA extraction (genetic analysis) at the Randomization Visit

The following samples will be collected from patients in the ITV arm and will be tested by the Sponsor or a selected designee:

- Serum samples will be obtained for measurement of anti-therapeutic antibodies to ranibizumab (see Appendix 2).
- Serum samples will be obtained to measure ranibizumab concentrations (see Appendix 2).

The following samples will be collected from patients in the Implant treatment arms and will be tested by the Sponsor or a selected designee:

- Serum samples will be obtained for measurement of anti-therapeutic antibodies to ranibizumab (see Appendix 1).
- Serum samples will be obtained to measure ranibizumab concentrations (see Appendix 1).

  Note: For patients who prefer not to visit the clinic for the sample collection 1 day after each Implant refill, provision will be made for this timepoint sample collection to be collected at their home. Training will be provided to site staff on how to perform this task. The sample will be sent to a central laboratory.
- Vitreous or aqueous humor samples will be obtained to measure ranibizumab concentrations at the start of explantation for patients undergoing an explantation procedure (see Appendix 1 and Appendix 21).
- Optional anterior chamber (aqueous humor) samples will be collected prior to or immediately following one or more refills and at the Day 7 safety visit post refill for the exploratory analysis for VEGF, ranibizumab concentrations, anti-therapeutic antibodies to ranibizumab and other exploratory biomarkers (see Appendix 1 and Appendix 21).

The following samples will be obtained from patients in the Implant treatment arms 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) will be preserved for potential analysis upon explant procedure.
- Residual content of the Implant present in the Refill Needle may be collected during the refill procedure (if applicable) to evaluate the possible association of vitreous or aqueous humor biomarkers with disease characteristics and response to ranibizumab.

Unless the patient gives specific consent for the leftover of their samples to be stored for optional exploratory research (see Section 4.6.12), biological samples will be destroyed when the final clinical study report has been completed, with the following exception{s}:

- Aqueous humor, vitreous, serum PK and ATA samples for assay development, validation, or for additional characterization will be stored no longer than 5 years after the final Clinical Study Report has been completed.

See Laboratory Manual for sample processing, storing, and shipping instructions.

4.6.7 Patient-Reported Outcome

The MacTSQ must be administered to patients by an interviewer (for patients who speak English or Spanish by site personnel other than the VA examiner), before the patient completes any other study visit procedures (see Appendix 19).

The MacTSQ is a 14-item questionnaire designed to assess treatment satisfaction in patients with AMD. Scoring of the MacTSQ results in two subscale scores (information provision and convenience; impact of treatment) and a total score. Subscale scores range from 0 to 36 and total scores range from 0 to 72. A higher score indicates greater satisfaction.

Two versions of the questionnaire will be used, differing only in recall period. At randomization the questionnaire will refer to “since diagnosis”. For interim assessments at Months 1, 6, and 9, and at the final/early termination visits, the questionnaire will refer to “since you enrolled in this study”.

4.6.8 Video Capturing of Implant Insertion, Refill, and Explantation Procedures

The Implant insertion and explantation procedures will be captured on video for Investigators training purposes unless the study center has policies in place that prohibit these procedures being video captured. The Implant refill procedure video capture is optional.

4.6.9 Exploratory Substudies

The Sponsor may propose exploratory substudies associated with the Study GX28228 protocol. Each substudy will be documented in a separate substudy protocol and associated ICF(s).

4.6.10 Timing of Study Assessments

4.6.10.1 Screening and Pretreatment Assessments

The study will randomize approximately 220 patients and will be performed at up to 60 sites in the United States. Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms (ICFs) for all screened patients, including those who are not subsequently randomized, will be maintained at the study site.

Screening Visit

Screening visit assessments cannot be performed sooner than 7 days following administration of the last ITV ranibizumab treatment to the study eye. After a patient has signed the ICF, the site will contact IxRS for the patient’s screening number assignment. All screening visit evaluations must be completed and reviewed to confirm that patients

meet all eligibility criteria before they are scheduled for their randomization visit. Screening visit assessments may be performed on multiple days.

Note: If a patient fails screening assessments, he or she may be re-screened once if deemed appropriate by the investigator. A new screening number will be assigned to the patient through the IxRS. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

For the schedule of screening assessments, refer to the schedule of assessments in Appendix 1 and Appendix 2.

Randomization Visit and Day 1 Treatment

The randomization visit and the Day 1 treatment can occur on the same day for ITV treatment arm patients; the Implant arm patients may have these two visits separated due to the medication washout period (see Section 4.1) and the surgery room availability.

However, for all study patients, the Randomization visit and Day 1 study treatment must occur between 28 days and 37 days after the patient's last study eye ITV ranibizumab treatment. Unless noted otherwise, all procedures and assessments should be performed prior to contacting IxRS for the patient's randomization number assignment and prior to the first study treatment administration to confirm that the patient is still eligible to be randomized to the study. All randomization study visit assessments must be performed on the same day. A patient can only be randomized to the study once.

When a patient has satisfied all eligibility criteria at both the screening and the randomization visit, including the receipt and evaluation of historical and screening visit images by the central reading center, the patient will be assigned a randomization number (a number different from the patient's screening number) by the IxRS and will be randomized to one of the treatment arms. It is recommended that the patients randomized to the ITV-injection arm receive their Day 1 study treatment on the day of randomization, while patients randomized to the Implant treatment arms may be scheduled for their Day 1, Implant surgical insertion visit later. If the Day 1 study treatment for Implant arms cannot be completed within the visit window after randomization, an additional ITV ranibizumab treatment may be required.

Please see the schedule of assessments provided in Appendix 1 and Appendix 2 for the schedule of randomization and Day 1 visit assessments.

Study visits will be scheduled to occur according to the schedule in Appendix 1 and Appendix 2 and have to be relative to the Day 1 (first study treatment) visit date until patients complete the study or the study is terminated early.

Pre-Screening (if applicable)

Pre-screening is available for newly diagnosed nAMD patients who are treatment naïve in the study eye. After a patient has signed the informed consent form, the site will contact IxRS for the patient's pre-screening number assignment. A patient may only participate once in the pre-screening. For the schedule of assessments in the pre-screening, refer to Appendix 3.

Run-In (if applicable)

"Run-in" is available for patients diagnosed with nAMD in the study eye within 9 months prior to screening who have been treated with a single anti-VEGF ITV injection, or with no more than eight anti-VEGF ITV injections and with the most recent dose being aflibercept or bevacizumab. After a patient has signed the informed consent form, the site will contact IxRS for the patient's number assignment. A PK sample will be collected prior to receipt of the "run-in" ranibizumab ITV treatment. For the schedule of assessments in the "run-in", refer to Appendix 4.

4.6.10.2 Assessments during Treatment

All assessments must be performed on the day of the specified visit, unless a time window is specified in the schedule of assessments (see Appendix 1 and Appendix 2). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the schedule of assessments. The MacTSQ assessment should be administered prior to the completion of other study assessments.

Please see Appendix 1 and Appendix 2 for the schedule of assessments performed during the treatment period.

Study visits will be scheduled according to the schedule in Appendix 1 and Appendix 2 and have to be relative to the Day 1 (first study treatment) visit date until patients complete or are early terminated from the study. Ranibizumab dosing should occur no earlier than 22 days following the previous dosing.

4.6.10.3 Assessments at Early Study Treatment Discontinuation

The ITV treatment arm patients who are discontinued from study treatment prematurely will be asked to undergo the scheduled monthly visits until the LPI Month 9 visit, after which they will be scheduled for their final study visit 30 (+7) days later. The patients who are discontinuing study treatment from the Implant treatment arms will be scheduled, within 7 days after the treatment discontinuation decision is made, for Implant explantation followed by safety visits 1 and 7 (±2) days post-explantation. Afterwards they will be followed in the study, attending their monthly scheduled visits, until LPI Month 9 visit, after which they will be scheduled for the early termination visit (see Appendix 1). As per investigator judgement, these patients may start an approved anti-VEGF for their AMD once the need for Implant explantation is confirmed and, preferably, after explantation is completed. All explanted Implants, with remaining

content, will be returned to the designee of the Sponsor for storage and potential future exploratory analysis (see Section 4.4). A vitreous or aqueous humor sample will be collected at the start of explantation for patients undergoing an explantation procedure (see Appendix 20).

4.6.10.4 Assessments at Early Study Discontinuation

Patients withdrawing from the study early should return for an early termination evaluation 30 (+7) days following the last study drug treatment for monitoring of all adverse events (serious and non-serious), as well as for early termination assessments if they are in the ITV treatment arm. The patients who are discontinuing the study from the Implant treatment arms will be scheduled for Implant explantation within 7 days of the study discontinuation decision. This will be followed by Safety Visits 1, 7 (±2), 30 (±7), and 60 (±7) days post-explantation, after which they will be scheduled for the early termination visit 30 (+7) days later. As per investigator judgment, these patients may start an approved anti-VEGF treatment for their AMD once the need for Implant explantation is confirmed and, preferably, after explantation is completed. All explanted Implants, with remaining content, will be returned to the designee of the Sponsor for storage and potential future exploratory analysis (see Section 4.4). A vitreous or aqueous humor sample will be collected at the start of explantation for patients undergoing an explantation procedure (see Appendix 20).

4.6.10.5 Assessment at Study Completion

Study completion is defined as a patient completing the final study visit assessments. Please see Appendix 1 and Appendix 2 for the schedule of assessments performed at the final/early termination visit.

Patients *in the ITV treatment arm* will return for the final study visit evaluation 30 (+7) days following the last study drug treatment for monitoring of all adverse events (serious and non-serious), as well as for final study visit assessments*, unless* they *enter into* the *RPDS Extension Study (Section 4.4.2).*

Patients in the Implant arms who complete the study will be scheduled for the Implant explantation 30 (+7) days following the last refill (if applicable), unless they enter into the RPDS *Extension* Study (Section 4.4.2). Explantation will be followed by Safety Visits 1, 7 (±2), 30 (±7), and 60 (±7) days post-explantation, after which patients will be scheduled for the final study visit 30 (+7) days later. As per investigator judgment, these patients may start an approved anti-VEGF treatment for their AMD once the need for Implant explantation is confirmed and, preferably, after explantation is completed. All explanted Implants, with remaining content, will be returned to the designee of the Sponsor for storage and potential future exploratory analysis (see Section 4.4). A vitreous or aqueous humor sample will be collected at the start of explantation for patients undergoing an explantation procedure (see Appendix 20).

4.6.10.6 Follow-Up Assessments

After the study completion/early termination visit, adverse events should be followed as outlined in Sections 5.5 and 5.6.

4.6.10.7 Assessments at Unscheduled Visits

Refer to Appendix 5 for unscheduled safety assessments that can be utilized for all study patients. All listed assessments are to be performed if determined to be necessary by the investigator.

4.6.11 Refill Needle Sample Collection

The following samples will be collected from patients in the Implant treatment arms and may be analyzed by the Sponsor or selected designee:

- Residual content of the Implant present in the Refill Needle may be collected during refill procedure (if applicable) to evaluate the possible association of vitreous or aqueous humor biomarkers with disease characteristics and response to ranibizumab.

4.6.12 Samples for Roche Clinical Repository

4.6.12.1 Overview of the Roche Clinical Repository

The Roche Clinical Repository (RCR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens 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.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop, validate, and characterize biomarker, diagnostic, pharmacokinetic, or anti-therapeutic antibody assays and establish the performance characteristics of these assays

4.6.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC)

and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.6.12) will not be applicable at that site.

4.6.12.3 Sample Collection

The following RCR samples will be collected for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers related to Ranibizumab mode of action, VEGF biology, AMD biology, and/or related diseases biology:

- Serum samples at the Randomization Visit and Visits at Month 4 and Month 9, for the evaluation of circulating biomarkers.
- Plasma samples at the Randomization Visit and Visits at Month 4 and Month 9, for the evaluation of circulating biomarkers.

The following RCR samples will be collected for research purposes, including but not limited to research on genetic (inherited) biomarkers related to Ranibizumab mode of action, VEGF biology, AMD biology and/or related diseases biology:

- Whole blood for DNA extraction at the Randomization Visit

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

4.6.12.4 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

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

Patient medical information associated with RCR specimens 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.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

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

4.6.12.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens 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 RCR specimens. 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 by completing the RCR Research Sample Informed Consent eCRF.

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

4.6.12.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study GX28228 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study GX28228.

4.6.12.7 Monitoring and Oversight

RCR specimens 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 specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. 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 RCR samples.

4.7 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Patient Discontinuation

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 at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance: 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.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

See Appendix 1 and Appendix 2 for the assessments that are to be performed for patients who discontinue early from the study. The reason for treatment discontinuation and early withdrawal from the study should be recorded on the appropriate eCRF.

Discontinued patients will not be allowed to re-enter the study.

4.7.2 Early Study Treatment Discontinuation

Patients must discontinue study treatment if they become pregnant.

The ITV treatment arm patients who are discontinued from study treatment prematurely will be asked to undergo the scheduled monthly visits until the LPI Month 9 visit, after which they will be scheduled for their final study visit 30 (+7) days later. The patients who are discontinuing study treatment from the Implant treatment arms will be scheduled, within 7 days after the treatment discontinuation decision is made, for Implant

explantation followed by safety visits 1 and 7 (±2) days post-explantation. Afterwards they will be followed in the study, attending their monthly scheduled visits, until LPI Month 9 visit, after which they will be scheduled for the early termination visit (see Appendix 1). As per investigator discretion, explanted patients may start an approved anti-VEGF agent for their nAMD once the need for Implant explantation is confirmed and, preferably, after explantation is completed. The sponsor will provide explanted patients with ranibizumab ITV treatment until the LPI Month 9 visit (if applicable). All explanted Implants with remaining content will be returned to the designee of the Sponsor for storage and potential future exploratory analysis (see Section 4.4). A vitreous or aqueous humor sample will be collected at the start of explantation for patients undergoing an explantation procedure (see Appendix 19).

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

4.7.3 Early Withdrawal from Study

Every effort should be made to obtain information on patients who are withdrawing from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

Patients withdrawing from the study early should return for an early termination evaluation 30 (+7) days following the last study drug treatment for monitoring of all adverse events (serious and non-serious), as well as for early termination assessments if they are in the ITV treatment arm. The patients who are discontinuing study from the Implant treatment arms will be scheduled for Implant explantation within 7 days of the treatment discontinuation decision, followed by Safety Visits 1, 7 (±2), 30 (±7), and 60 (±7) days post-explantation, after which they will be scheduled for the early termination visit 30 (+7) days later. As per investigator judgment, these patients may start an approved anti-VEGF treatment for their AMD once the need for Implant explantation is confirmed and, preferably, after explantation is completed. All explanted Implants, with remaining content, will be returned to the designee of the Sponsor for storage and potential future exploratory analysis (see Section 4.4). A vitreous or aqueous humor sample will be collected at the start of explantation for patients undergoing an explantation procedure (see Appendix 19).

The primary reason for premature study discontinuation (which may differ from study treatment discontinuation) should be documented on the appropriate eCRF. Patients who discontinue from the study prematurely will not be replaced and cannot re-enter the study.

4.7.4 Study and Site 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.

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 Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety and tolerability of ranibizumab ITV injections have been investigated in previous Phase I, I/II, III, and IIIb studies in patients with AMD. 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). Please see RPDS IB for further details.

In this study, GX28228, the patients in the Implant treatment arms will return after Implant insertion for safety evaluation visits on Day 2 (±0), Day 7 (±2), and Day 14 (±2); subsequently, the safety visit will be scheduled 7 (±2) days post–implant refill with ranibizumab; and safety visits on 1 (±0) and 7 (±2) days post explantation of the Implant for the patients who will continue to be followed up in the study; and for the patients who are exiting the study, safety visits on 1 (±0), 7 (±2), 30 (±7), and 60 (±7) days post-explantation of their Implant prior to being scheduled for the final/early termination visit 30 (+7) days later.

All ranibizumab-treated patients will be contacted by study site personnel 3 (±1) days after each treatment 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-injection antimicrobials (if applicable) for their study eye as directed by the investigator.

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

Upon completion of implant insertion or explantation procedure, patients will have indirect ophthalmoscopy performed to monitor the Implant placement and to evaluate any potential Implant problems. The treating physician will check IOP for the study eye only digital palpation. These assessments must be performed prior to placing a patch on the eye. The patients will remain at the surgical center for approximately 40 minutes. If there are no safety concerns following treatment, patients will be allowed to leave the surgical center after 40 (±10) minutes. If any safety concerns or immediate toxicity is noted, the patient will remain at the surgical center and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event and treatment of adverse event (if applicable) will be reported on the appropriate eCRFs.

Following each treatment with ranibizumab, administered either intravitreally or as an Implant refill, patients will undergo a finger counting test, followed by hand motion and light perception tests (when necessary) performed within 15 minutes post-treatment for the study eye only by the designated physician; the patients in the Implant treatment arms will have indirect ophthalmoscopy performed after each implant refill to monitor the Implant and its RCE end for visible clogging and other Implant problems. The patients will remain at the clinic for approximately 40 minutes. If there are no safety concerns following treatment, patients will be allowed to leave the clinic after 40 (±10) minutes. If any safety concerns or immediate toxicity is noted, the patient will remain at the clinic and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event and treatment of adverse event (if applicable) will be reported on the appropriate eCRFs.

Detailed ocular examinations, including indirect ophthalmoscopy and slit lamp examination, will be performed throughout the study. For patients in the Implant treatment arm, the monthly dilated binocular indirect high-magnification ophthalmoscopic examination will include visual monitoring of the Implant placement, evaluation of visible clogging of the RCE tip, and evaluation of any other Implant-related problems, as well as data collection on the associated eCRF and/or Medical Device Complaint Form. Routine hematologic, serum chemistry, coagulation, and urinalysis profiles will be obtained from all study patients at the screening visit. Blood samples for assessing serum ranibizumab concentrations and antibodies to ranibizumab will be obtained from all study patients throughout the study. In addition, optional aqueous humor samples will be obtained from patients in the Implant treatment arms only throughout the study. The sample content retrieved during Implant refill (if applicable) and explant procedures will be collected and forwarded to the Sponsor designee and may be analyzed in the future.

Ranibizumab administration by ITV injection or Implant refill (if applicable) will be interrupted or discontinued as per the dose-interruption criteria listed in Table 6 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. This decision will be at the investigator's discretion and should be recorded on the eCRF.

The ITV treatment arm patients who are discontinued from the study treatment prematurely will be encouraged to undergo the scheduled monthly visits until the LPI Month 9 visit, after which they will be scheduled for their final study visit 30 (+7) days later. The patients who are discontinuing study treatment from the Implant treatment arms will be scheduled, within 7 days after the treatment discontinuation decision is made, for Implant explantation followed by safety visits 1 and 7 (±2) days post-explantation. Afterwards they will be followed in the study, attending their monthly scheduled visits, until LPI Month 9 visit, after which they will be scheduled for the early termination visit (see Appendix 1). As per investigator judgement, these patients may start an approved anti-VEGF for their AMD once the need for Implant explantation is confirmed and, preferably, after explantation is completed. All explanted Implants, with remaining content, will be returned to the designee of the Sponsor for storage and potential future exploratory analysis (see Section 4.4). A vitreous or aqueous humor sample will be collected at the start of explantation for patients undergoing an explantation procedure (see Appendix 19).

Patients discontinuing the study early should return for an early termination evaluation 30 (±7) days following the last study drug treatment for monitoring of all adverse events (serious and non-serious), as well as for early termination assessments if they are in the

ITV treatment arm. The patients who are discontinuing the study from the Implant treatment arms will be scheduled for Implant explantation within 7 days of the discontinuation decision. This will be followed by safety visits 1, 7 (±2), 30 (±7), and 60 (±7) days post-explantation, after which they will be scheduled for the early termination visit 30 (+7) days later. As per investigator judgment, these patients may start an approved anti-VEGF treatment for their AMD once the need for Implant explantation is confirmed and, preferably, after explantation is completed. All explanted Implants, with remaining content, will be returned to the designee of the Sponsor for storage and potential future exploratory analysis (see Section 4.4). A vitreous or aqueous humor sample will be collected at the start of explantation for patients undergoing an explantation procedure (see Appendix 19).

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.

Ongoing review of safety data will be performed by Genentech IMC consisting of the Medical Monitor, Clinical Scientists, Drug Safety Scientist, and Biostatistician. External experts may be consulted. Following implementation of Protocol GX28228, version 5, if warranted, enrollment and Implant insertion surgeries may be paused to enable real-time review of post-implant insertion safety data by the IMC.

5.1.1 Management of Specific Adverse Events

5.1.1.1 Dosing Interruption/Study Treatment or Study Discontinuation Criteria

Study treatment dose interruption and/or study treatment or study discontinuation following an adverse event will be determined according to the criteria in Table 6. The reason for interrupting the treatment should be recorded on the associated eCRF and, if applicable, on the adverse event eCRF.

Table 6 Dose Interruption/Study Treatment 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 5.3.5 and Appendix 12)
VA loss	Interrupt dose if there is a decrease in BCVA of ≥30 letters in the study eye compared with the last assessment of VA prior to the most recent treatment.
IOP	Interrupt dose if 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 physician.
Sensory rhegmatogenous retinal break or detachment (including macular hole)	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 the study after consultation with the Medical Monitor.
Local or severe systemic infection	Interrupt dose if any of the following are present: infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye, or if the patient is currently receiving treatment for a severe systemic infection.
Oral corticosteroids (prednisone >10 mg/kg or equivalent)	Dose may be interrupted after consultation with the Medical Monitor if a patient needs to take oral corticosteroids (prednisone > 10mg/day or equivalent). Study treatment may be resumed when oral corticosteroids dosing is prednisone ≤ 10 mg/day or equivalent.
IV corticosteroids	Dose may be interrupted after consultation with the Medical Monitor if patients need to take 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 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 will be explanted even if it did not cause any AE to the patient. The patient will be discontinued from the study treatment.
Pregnancy	Explant the Implant and discontinue patient's study treatment in the case of positive serum pregnancy test during the study.
Malignancy	At the discretion of the investigator and after consultation with the Medical Monitor, patients may discontinue from the study drug treatment.

AE = adverse event; BCVA = best corrected visual acuity; CFT = central foveal thickness; IOP = intraocular pressure; VA = visual acuity.

5.1.1.2 Rescue Treatment with Open-Label Ranibizumab For Implant Patients

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

- Approximately 1 month and/or 2 months after occurrence of vitreous hemorrhage, if vitreous hemorrhage causes loss in BCVA, and neither assessment of the macula nor SD-OCT can be performed successfully (see Section 5.1.1.4)
- At the time a patient meets criteria for lack of clinical efficacy (see Section 5.1.1.3)
- In the case of progressive worsening of BCVA and/or CFT due to wet AMD activity across two consecutive scheduled visits, only if the patient does not meet refill criteria. If a treatment is clinically necessary due to the progressive clinical worsening per the investigator's judgment, rescue treatment must be discussed and agreed upon by the Medical Monitor prior to being introduced.

5.1.1.3 Management of Patients Who Meet Lack of Clinical Efficacy Criteria

Criteria for meeting lack clinical efficacy are shown in Table 7, and Table 8 describes how to manage patients who meet such criteria. Patients who meet criteria for lack of clinical efficacy will receive rescue treatment with ITV injection of open-label ranibizumab as described in Section 5.1.1.2. One month after meeting criteria for lack of clinical efficacy and receiving a rescue ITV ranibizumab injection, the patient will receive a mandatory refill with the 100-mg/mL ranibizumab formulation. At the next monthly visit and until the end of the study, the patient will receive a refill with the 100-mg/mL ranibizumab formulation if the patient meets protocol-defined refill criteria.

For information regarding patient discontinuation or early study treatment discontinuation refer to Section 4.7.

Table 7 Lack of Clinical Efficacy Criteria

Event	
Lack of clinical efficacy	Loss in BCVA of ≥ 15 letters from the best recorded BCVA on study following two consecutive ranibizumab Implant refills (as per protocol-specified refill criteria) occurring 1 month apart due to nAMD disease activity and not attributable to a change in the ocular media (i.e., cornea, lens, aqueous or vitreous humor, epiretinal membrane development, etc.) unless there is at least a five-letter increase in BCVA, in which case a refill will occur. and/or Increase in CFT ≥ 150 μm from the lowest CFT measurement on study following two consecutive ranibizumab Implant refills (as per protocol-specified refill criteria) occurring 1 month apart due to nAMD disease activity and not attributable to a change in the ocular media (i.e., cornea, lens, aqueous or vitreous humor, epiretinal membrane development, etc.) unless there is a decrease in CFT ≥ 75 microns from the last refill, in which case a refill will occur.

Table 8 Management of Patients Who Meet Lack of Clinical Efficacy Criteria

Time of event	Treatment to be performed
At the time of meeting lack of clinical efficacy criteria	Perform rescue treatment with intravitreal injection of open-label ranibizumab
At the study visit one month after meeting lack of clinical efficacy criteria	Perform a mandatory refill with the 100-mg/mL ranibizumab formulation
At subsequent study visits (from Month 2 after meeting lack of clinical efficacy criteria and onwards)	Perform a refill with 100-mg/mL ranibizumab formulation ONLY if refill criteria are met

5.1.1.4 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 9.

Table 9 Recommended Management of Cases of Vitreous Hemorrhage

Timing	Patient's examination/management/determination of refill requirements
Day of vitreous hemorrhage diagnosis	• If the diagnosis of vitreous hemorrhage is made during a scheduled visit, if possible perform ocular B-scan ultrasonography in addition to the assessments scheduled for that specific visit • If the diagnosis of vitreous hemorrhage is made during an unscheduled visit, if possible perform ocular ultrasonography in addition to the assessments listed in the Appendix 5 • A safety assessment visit (scheduled or unscheduled) should be performed approximately 2 weeks after occurrence of vitreous hemorrhage (see Appendix 5 for unscheduled visit). If possible, perform ocular B-scan ultrasonography.
Approximately 1 month after occurrence (scheduled visit)	• If possible, perform ocular B-scan ultrasonography in addition to the assessments scheduled for that specific visit • If vitreous hemorrhage causes loss in BCVA, but assessment of the macula or SD-OCT can be performed successfully, determine if Implant refill is needed according to the protocol-defined refill criteria (see Section 3.1.1) • If vitreous hemorrhage causes loss in BCVA, and neither assessment of the macula nor SD-OCT can be performed successfully, perform rescue treatment with ITV injection of open-label ranibizumab • An unscheduled safety assessment visit should be performed between month 1 and month 2 after occurrence of vitreous hemorrhage (see Appendix 5).

Approximately 2 months after occurrence (scheduled visit)	• If possible, perform ocular B-scan ultrasonography
	• If vitreous hemorrhage causes loss in BCVA, but assessment of the macula or SD-OCT can be performed successfully, determine if Implant refill is needed according to the protocol-defined refill criteria (see Section 3.1.1)
	• If vitreous hemorrhage causes loss in BCVA, and neither assessment of the macula nor SD-OCT can be performed successfully:
	  ○ perform rescue treatment with ITV injection of open-label ranibizumab
	  ○ discuss a pars plana vitrectomy with the patient as a possibility to remove the vitreous hemorrhage. Consultation with the Medical Monitor is required prior to perform pars plana vitrectomy.

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

5.1.1.5 Implant Clogging Assessment

If an Implant is explanted, it will be analyzed for possible clogging using the following assessments:

- Serum pharmacokinetics of ranibizumab will be used to help judge whether Implant clogging may have occurred. Aqueous humor or vitreous PK samples will be collected at explantation and may be used to further assess possible Implant clogging. For each individual patient, possible Implant clogging will be documented if at least one of the following conditions are met:

  At Implant insertion and prior to the first refill: serum ranibizumab concentrations are below the lower limit of quantification (BLQ) or below the baseline serum ranibizumab concentration value at all time-points prior to refills, that is, Day 1 (within 60 min of insertion), Day 2, Day 7, Day 14, and all monthly time points after Implant insertion and prior to the first refill or to the end of the study visit for this patient if no refill occurs.

  After the first refill: serum ranibizumab concentrations are BLQ or below the last pre-refill serum ranibizumab concentration value at all time-points post refills, that is, Day 7, and all monthly time points prior to the next refill for 2 consecutive refills or to the end of the study visit for this patient if no further refill occurs.

- Implants identified that meet PK criteria for possible clogging will then undergo further diagnostics if explanted. The Implant "complete clogging" failure statistics will be summarized across all Implant patients based on the first 9 months of Implant insertion.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and AESIs; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and 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 and/or medical device 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 or device, whether or not considered related to the medicinal product or the device

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9.
- 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., fluorescein angiography) 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)

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

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; see Section 5.3.3); 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)

AESIs can be serious or non-serious and are required to be reported by the investigator to the Sponsor within 24 hours after learning of the event (see Section 5.4.2 for reporting instructions). AESIs for this study include the following:

a) Adverse events resulting from medication errors

Examples of medication errors include, but are not limited to, overdose (see further details in the Section 5.3.5.11), incorrect dose, incorrect route, incorrect drug, incorrect administration, or incorrect kit.

If the medication error did result in an adverse event, the primary event term should reflect the adverse event that occurred as a result of the medication error. The "Other" suspected causes of adverse event data field on the adverse event record should be reported as a medication error.

b) Sight-threatening adverse events

An adverse event is considered to be sight threatening and should be reported expeditiously if it meets one or more of the following criteria:

- It causes a decrease of $\geq$30 letters in VA (compared with the last assessment of VA prior to the most recent assessment) lasting more than 1 hour
- It requires surgical intervention (i.e., conventional surgery, vitreous tap, or biopsy with ITV injection of anti-infective agents, or laser or retinal cryopexy with gas or explantation of Implant) to prevent permanent loss of sight
- It is associated with severe intraocular inflammation (i.e., 4+ anterior chamber cell/flare or 4+ vitritis; see the definitions for intraocular inflammation, iritis, iridocyclitis, and vitritis in Section 5.3.5 and inflammation grading scales in Appendix 12).
- In the opinion of the investigator, it may require medical intervention to prevent permanent loss of sight.

c) 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

d) ADEs; that is, adverse events that are considered to be related to the RPDS and to the use of the RPDS. They include, but are not limited to:

- Adverse events resulting from insufficient or inadequate device RPDS IFU
- Adverse events related to the Implant insertion procedure
- Adverse events related to the Implant refill procedure
- Adverse events related to the Implant explantation procedure
- Adverse events related to the presence of the Implant within the eye
- Adverse events caused by any malfunction of the RPDS including any adverse events resulting from an excessive release of ranibizumab into the eye
- Adverse events resulting from use error or from intentional misuse of the RPDS
- A lack of efficacy of ranibizumab due to inadequate release of ranibizumab from the Implant

In addition, any adverse event considered causally related to the RPDS **must** also always be reported as a Medical Device Complaint (Section 5.4.4).

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), 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 to Section 5.6.

In addition, the investigator is also responsible for reporting medical device complaints (see Section 5.4.4) associated with any of the components (see Table 1) of the RPDS.

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 (see 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 drug (Day 1)**, only serious adverse events related to a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications, or ITV ranibizumab given as part of pre-screening) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events, regardless of relationship to study drug, Implant, or ancillary devices, or study procedures, will be reported until the patient's study completion or early termination from the study. After completion or early termination from the study, the investigator should report any serious adverse events that are believed to be related to prior study treatment (study drug and/or RPDS, see 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 10 provides guidance for assessing adverse event severity.

Table 10 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.

- **Patients in the Implant arms**: The investigator will assess whether there is a potential association with each of the following "components" of the study intervention:
  - Each component of the RPDS (i.e., a separate assessment for the Implant, the Initial Fill Needle, the Insertion Tool, the Refill Needle, and the Explant Tool)
  - The study procedures (including the procedures to insert, refill, or explant the Implant)
  - Ranibizumab (study drug)

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 ITV arm**: The investigator will assess whether there is a potential association with each of the following “components” of the study intervention:
  - The ITV 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, or explantation procedures or due to other RPDS components (see Table 1) or due to ITV 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 RPDS 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

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:

- Iritis: the presence of inflammatory cells in the anterior chamber

  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
- 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 endophthalmitis.

Note: Trace benign, aqueous humor pigmented cells visible on slitlamp examination that are caused by dilation and are not RBCs or WBCs or the result of any ocular disorder should not be recorded as an adverse event.

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). 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) 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., alkaline phosphatase and bilirubin 5× the 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 if 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 Ae. 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 event).

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 ($>3\times$ the ULN) in combination with either an elevated total bilirubin ($>2\times$ the 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 a serious adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ the ULN in combination with total bilirubin $>2\times$ the ULN
- Treatment-emergent ALT or AST $>3\times$ the 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).

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).

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").

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 Medical History and Baseline Conditions eCRFs.

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 in Study Eye

Study eye medical occurrences or symptoms of deterioration that are anticipated as part of the nAMD disease state should only 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 study eye 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 nAMD").

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient 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.

There are some hospitalization scenarios that do not require reporting as a serious adverse event when there is no occurrence of an adverse event. These scenarios include a planned hospitalization or prolonged hospitalization to undergo a diagnostic or elective surgical procedure for a preexisting medical condition other than ocular that has not changed.

5.3.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events

associated with an overdose or incorrect administration of study drug should be recorded on the adverse event eCRF and should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

Defects in the device that are not associated with adverse events are captured according to Section 5.4.4.

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from patient-reported outcome (PRO) data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the adverse event eCRF.

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 (see Section 5.4.2 for further details)
- AESI (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

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 (HA) and Institutional Review Board (IRB)/Ethics Committee (EC).

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for Sponsor's Medical Responsible Contact

Medical Monitor:	[redacted], M.D. (primary)
Email:	[redacted]
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]
Medical Monitor:	[redacted], M.D., PhD. (secondary)
Email:	[redacted]
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 Monitor, 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 contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur Prior to Initiation of Study Drug (Day 1)

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events related to a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications, or ITV ranibizumab given as part of pre-screening) should be reported. The 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 any AESI will be reported until 30 (+7) days after the last study drug administration for the ITV injection treatment arm and until 90 (+7) days after the Implant explantation for the Implant treatment arms. However, if any patient continues to be followed in the study after an early discontinuation of the treatment, the adverse events will be reported until their study completion. 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 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 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 30 days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. 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. 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 the event that the EDC system is unavailable, the Clinical Trial Pregnancy 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 pregnancy), 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.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the study or within 30 days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on

the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Abortions

Any abortion should be classified as a serious adverse events (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).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male 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

In this study, the Implant and the ancillary devices are considered medical devices. The investigator must report all RPDS medical device complaints related to the Implant and ancillary devices (see Table 1) to the Sponsor.

The investigator should provide as much information as possible to the personnel completing the IMP Deviation Form, including the product batch number. The form will be forwarded to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event) (refer to the Study manual for further details).

If the device complaint is also associated with an adverse event in a study participant, then the adverse event must additionally be reported on the adverse event eCRF submitted through the EDC system. If the event is serious or an AESI, 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 the medical device causes an adverse event to an individual other than the study patient (e.g., study site personnel), the event should be reported on the Medical Device Complaint form and the adverse event to Roche Safety Risk Management via telephone (see Study Manual for more details).

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

Device deficiencies (inadequacy with respect to identity, quality, durability, reliability, safety or performance and including malfunctions, and inadequate labeling) that did not lead to an adverse event but could have led to a medical occurrence if suitable action

had not been taken, if intervention had not been made, or if circumstances had been less fortunate must be reported via the medical device complaints process immediately (i.e., no more than 24 hours after learning of the event) (refer to the Study manual 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. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious AESI, and pregnancies, the Sponsor or a designee may follow-up by telephone, fax, electronic mail, 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 POST-STUDY ADVERSE EVENTS

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 ITV treatment arm and 90 (+7) days after the Implant explantation for patients in the Implant treatment arms), if the event is believed to be related to prior study drug treatment or due to the Implant.

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 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 non-serious AESI 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:

- RPDS IB

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 analyses will take place after LPI has completed the Month 9 visit. Detailed specifications of the statistical methods will be described in the SAP.

6.1 DETERMINATION OF SAMPLE SIZE

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

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

6.2 SUMMARIES OF CONDUCT OF STUDY

The demographic and baseline characteristics, such as age, sex, race/ethnicity, baseline VA, angiographic and clinical evaluation of CNV, time since diagnosis of nAMD, and stratification factors including baseline BCVA score and number of prior anti-VEGF injections will be summarized by treatment group using descriptive statistics.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

The demographic and baseline characteristics, such as age, sex, race/ethnicity, baseline VA, angiographic and clinical evaluation of CNV, time since diagnosis of nAMD, baseline safety (patients outside the expected normal range for vital signs and laboratory test results), and baseline disease characteristics (i.e., BCVA and OCT parameters) will be summarized by treatment arm.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Analysis

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

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

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

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

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

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

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

6.4.2 Secondary Efficacy Analysis

A secondary efficacy outcome measure is the change in BCVA from baseline through Month 9 (by month). Missing BCVA data, prior to or at Month 9 for each patient, will be imputed using the last observation carry forward (LOCF). Comparison of implant arms (10 mg/mL, 40 mg/mL, and 100 mg/mL) versus the monthly ITV arm will be assessed using an analysis of covariance (ANCOVA) model with an effect for treatment and with covariate adjustments for baseline stratification factors: baseline BCVA score ($\leq$65 letters vs. $\geq$66 letters) and number of anti-VEGF ITV injections ($\leq$3 vs. $\geq$4). Separate models will be fit for each pairwise comparison and each study month. The dependent variables will be change from baseline in BCVA at each of Months 1–9. Model-based (least squares) estimates of the pairwise treatment differences will be provided and 80% CIs. Figures showing mean and median change in BCVA over time, by treatment group, will be provided.

The ANCOVA model above will be repeated using change from baseline in CFT from baseline through Month 9 (by month) as the outcome. The stratification factors and baseline CFT will be included in the model as covariates. Mean change from baseline in CFT from baseline through Month 9 (by month) will be compared between the implant arms and the monthly ITV arm.

In order to evaluate whether the Implant clogging rate exceeds 10% within the first 9 months, the proportion of clogged Implants will be estimated and the 80% CI will be calculated based on the binomial distribution. All clogging data from patients in the implant arms will be pooled for this analysis.

Additional statistical summaries will be reported for the secondary efficacy outcome measures as listed in Section 3.5.2. Detailed specifications of the statistical methods will be described in the SAP.

6.5 SAFETY ANALYSES

All patients receiving at least one study treatment will be included in the safety analysis.

Counts and incidence rates by treatment group for the following safety endpoints will be provided:

- Ocular and non-ocular adverse events and serious adverse events
- "Prespecified RPDS-associated adverse events" (see Section 6.5.1)
- Positive serum antibodies to ranibizumab

For "prespecified RPDS-associated adverse events", the incidence in all implant arms patients will also be summarized.

6.5.1 Adverse Events

Verbatim descriptions of treatment-emergent adverse events will be mapped to thesaurus terms. Treatment-emergent adverse events will be defined as events beginning during or after surgical insertion/explantation of the Implant or the first ranibizumab ITV injection through the completion of the study or until a patient discontinues prematurely. Adverse events will be tabulated by body system, high-level term, and preferred term. Separate summaries will be prepared for non-ocular and ocular adverse events, with events in the study eye and fellow eye summarized separately. Serious adverse events will be summarized similarly. Adverse events leading to discontinuation from the study or treatment will be listed and tabulated.

ADEs are adverse events that are considered to be related to the RPDS and to the use of the RPDS. Of particular interest are the following “Prespecified RPDS–associated adverse events”:

- Vitreous hemorrhage associated with a $>$30-letter decrease of BCVA on ETDRS chart compared with the last assessment of BCVA prior to the onset of vitreous hemorrhage lasting $>$1 month
- Reduced VA ($>$30 letters loss from previous scheduled visit)
- Traumatic cataract
- Endophthalmitis
- Damage to sclera
- Retinal detachment
- Interference of the Implant with visual field

In addition to the “Prespecified RPDS–associated adverse events”, any other ocular adverse events and serious adverse events attributed by the investigator to the: 1) Implant insertion procedure, 2) Implant refill procedure, 3) Implant explantation procedure, and 4) study drug, will be reported.

6.5.2 Deaths

Patient deaths and primary cause of death will be summarized.

6.5.3 Laboratory Tests

Summary statistics for the proportion of patients with laboratory values above the ULN or below the lower limits of normal at the screening visit will be provided.

The number and percentage of patients with positive serum antibodies to ranibizumab at baseline and during the treatment period will be tabulated.

6.5.4 Vital Signs

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

6.5.5 Ocular Assessments

Results of the following ocular assessments will be summarized by timepoint and by eye (study vs. non-study) as applicable, using descriptive summaries: IOP, fluorescein angiography, and fundus photography. Changes from baseline for selected ocular assessments will be tabulated. The presence of intraocular inflammation and vitreous hemorrhage, as determined from the slitlamp examination, will be tabulated by grade (according to grading scales for flare/cells and vitreal hemorrhage density in Appendix 12). The presence of retinal break or detachment as determined from ophthalmoscopy will be tabulated.

6.6 PHARMACOKINETIC ANALYSES

Individual and mean serum ranibizumab concentration over time will be tabulated and plotted by dose level and by refill number. The serum pharmacokinetics of ranibizumab will be characterized by estimating AUC, C_{max}, t_{max}, $t_{1/2}$, and C_{trough} between dose intervals. Estimates for these parameters will be tabulated and summarized by descriptive statistics. Additional PK analyses may be conducted as appropriate. More details are described in Section 3.5.4.

6.7 PATIENT-REPORTED OUTCOME ANALYSES

For each scheduled assessment, descriptive statistics will be computed for the total MacTSQ score and for the two subscales: 1) information provision and convenience and 2) impact of treatment. The scoring algorithm and rules for handling missing data will be provided in the SAP.

PRO data will be presented separately from adverse events data.

6.8 EXPLORATORY ANALYSES

Detailed specifications of the statistical methods for the exploratory analyses will be described in the SAP.

6.8.1 Time to Event Analysis with Data after Month 9

In case the required number of events (first refills) is not reached by Month 9, the primary analysis will be repeated as a follow-up analysis using all of the data collected up to the time when the required number of events is met.

In addition, the primary efficacy analysis described in Section 6.4.1 will be repeated based on the full data collected during the entire study as an exploratory analysis. This analysis is considered supportive to the primary efficacy analysis.

6.8.2 Analysis of Time to Subsequent Refills

Time from last refill to subsequent refills will be analyzed for patients in the Implant arms as appropriate. Details of the analysis will be described in the statistical analysis plan.

6.9 FLEXIBLE INTERIM ANALYSIS

Given the exploratory nature of this study, the Sponsor may choose to conduct up to two interim analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed by members of the Sponsor's unmasked study team and will be interpreted by the unmasked IMC and appropriate senior management personnel. Access to treatment assignment information will follow the Sponsor's standard procedures. The details of the timing and scope of the interim analysis, if any, will be specified in the IMC Agreement.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using 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 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. Data from PRO

questionnaires will be forwarded to the Sponsor electronically. 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 using a Sponsor-designated EDC system. Sites will receive training and have access to Help Text within EDC 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 on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 PATIENT-REPORTED OUTCOME DATA

Data from paper PRO questionnaires will be entered into the EDC system by site staff.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification 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, laboratory notes, memoranda, PROs, 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 (TMP). 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 7.6.

To facilitate source data verification, 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. Please see TMP for additional details.

7.5 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 HA 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.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), ICFs, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 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.

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 laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. It will also follow ISO 14155 for the RPDS Clinical Investigation Plan (see Appendix 21 for details). 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 FDA regulations and applicable local, state, and federal laws.

8.2 INFORMED CONSENT

The Sponsor's sample ICF 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 ICFs 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 HA submission purposes according to local requirements.

The benefit and risks associated with participation in this study is outlined and will be explained to the patient by the investigator.

The ICF will contain a separate section that addresses the collection and use of the optional aqueous humor samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the 15-year storage period. A separate, specific signature will be required to document a patient's agreement to allow the optional aqueous humor sample to be collected and used for exploratory research. Patients who decline to participate will check a “no” box in the appropriate section and will not provide a separate signature.

Patients’ compensation for costs resulting from participation in the study (e.g., transportation) may be provided if allowed by national regulations. Subject to national regulations, arrangement for additional healthcare for patients who suffer from an adverse event as a result of participation will be explained and documented in the ICF.

The Consent Forms must be signed and dated by the patient 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 and HA (if applicable)-approved Consent Forms must be provided to the Sponsor for HA 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/HA 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. 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.

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 ICFs, 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 9.6).

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 HA 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 HA 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 ICF (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.

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

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 HAs. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

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, ICFs, 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.

9.3 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 HAs, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study. 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.

9.4 ADMINISTRATIVE STRUCTURE

This study is sponsored by Genentech, Inc.

Genentech 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.

An IxRS will be used for patient enrollment and for management of study drug/device requests and shipments. Enrollment will be competitive.

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 Genentech or Genentech-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 (fluorescein angiography, fundus photography and SD-OCT).

9.5 PUBLICATION 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, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

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.

9.6 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).

10. REFERENCES

Age-Related Eye Disease Study Research Group. A randomized, placebo controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS Report 8. Arch Ophthalmol 2001;119:141 –36.

Bressler NM, Doan QV, Varma R, et al. Estimated cases of legal blindness and visual impairment avoided using ranibizumab for choroidal neovascularization: non-Hispanic white population in the United States with age-related macular degeneration. Arch Ophthalmol. 2011 Jun;129(6):709-17.

Buys YM. Trabeculectomy with ExPRESS: weighing the benefits and cost. Curr Opin Ophthalmol. 2013 Mar;24(2):111-8.

Chakravarthy U, Wong TY, Fletcher A, et al. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. BMC Ophthalmol. 2010 Dec 13;10:31.

Dunn JP, Van Natta M, Foster G, et al. Complications of ganciclovir implant surgery in patients with cytomegalovirus retinitis: the Ganciclovir Cidofovir Cytomegalovirus Retinitis Trial. Retina. 2004 Feb;24(1):41-50.

Gedde SJ, Singh K, Schiffman JC, et al. The Tube Versus Trabeculectomy Study: interpretation of results and application to clinical practice. Curr Opin Ophthalmol. 2012 Mar;23(2):118-26.

Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. N Engl J Med. 2008;358(24):2606-2617.

Lalwani GA, Rosenfeld PJ, Fung AE, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. Am J Ophthalmol. 2009 Jul;148(1):43-58

Rudnicka AR, Jarrar Z, Wormald R, et al. Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: a meta-analysis. Ophthalmology. 2012 Mar;119(3):571-80.

Smith AF. The growing importance of pharmacoeconomics: the case of age-related macular degeneration. Br J Ophthalmol. 2010 Sep;94(9):1116-7.

Spaide RF, Curcio CA. Drusen characterization with multimodal imaging. Retina. 2010 Oct;30(9):1441–1454.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Assessment	Screen [a] ≥7 days after RBZ tx	Rand [b] ≥28 and ≤37 days after RBZ tx	Day				Month									Month X Visit [d]	Safety Visit [c]	Final/ ET[e]
			1 [b]	2 [c]	7 [c]	14 [c]	1	2	3	4	5	6	7	8	9			
Window (Days)				±0	±2	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	See footnote c	See footnote e
Eye fluid sample collection [ao]							Collect vitreous or aqueous humor sample at the start of explantation for patients undergoing an explantation procedure											

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

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

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

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

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

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

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

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

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

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

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

[i] Obtain from all study patients pre-treatment and prior to fluorescein angiography, if applicable. For a description of the laboratory assessments to be performed, see Section 4.6.6 or the separate laboratory manual.

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

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

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

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

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

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

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

[p] Perform only if possible.

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

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

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

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

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

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

[w] Perform pre-treatment.

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

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

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

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

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

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

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

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

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

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

[ag] Following each Implant refill, patients will have a finger counting test, followed by hand motion and light perception tests (when necessary) performed by the physician within 15 minutes post-treatment for the study eye only; the patients will remain at the clinic for approximately 40 minutes. If there are no safety concerns 40 (± 10) minutes following treatment, the patient will be allowed to leave the clinic. If any safety concerns or immediate toxicity is noted, the patient will remain at the clinic and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event will be reported on the appropriate eCRF page.

[ah] Upon completion of the Implant insertion or explantation procedure, patients will have indirect ophthalmoscopy performed to monitor the Implant placement and to evaluate any potential Implant problems. Intraocular pressure will be checked for the study eye only by the treating physician by digital palpation. These assessments must be performed prior to placing a patch on the eye. If any safety concerns or immediate toxicity is noted, the patient will remain at the surgical center and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event will be reported on the appropriate eCRF page.

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

[aj] Upon completion of the Implant insertion procedure, complete the Implant insertion evaluation to indicate surgical details of the insertion procedure. Information captured in the evaluation will be reported on the appropriate eCRF page.

[ak] Record any concomitant medications (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications, and pre-treatment and post-treatment medications, such as proparacaine, antimicrobials) used by the patient within 7 days preceding the randomization visit date and through the conclusion of the patient's study participation or early termination visit.

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

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

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

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

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

Appendix 2
Schedule of Assessments for ITV arm: Screening, Randomization/Day 1, Month 1 through Month 9, Month X, and Final/Early Termination Visits

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[f] Refer to the IxRS Manual for details.

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

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

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

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

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

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

[m] Perform pre-treatment.

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

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

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

[q] The pre- and post-treatment use of self-administered antimicrobials for the ITV injection arm is per the investigator discretion.

[r] Following each ITV treatment with ranibizumab, patients will have a finger counting test, followed by hand motion and light perception tests (when necessary) performed by the physician within 15 minutes post-treatment for the study eye only; the patients will remain at the clinic for approximately 40 minutes. If there are no safety concerns 40 ($\pm$10) minutes following treatment, the patient will be allowed to leave the clinic. If any safety concerns or immediate toxicity is noted, the patient will remain at the clinic and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event will be reported on the appropriate eCRF page.

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

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

[t] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events related to a protocol-mandated intervention (e.g., procedures such as fluorescein angiography etc.) should be reported. Adverse events will be recorded starting on Day 1 through the last study visit. Adverse events assessed by the qualified ophthalmologist as related to ranibizumab and ITV injections should be followed until the event resolves or the event is assessed as irreversible, chronic, or stable, even if the patient's participation in the study is over.

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

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

Appendix 3
Pre-Screening Visits (if applicable)

Assessments[a]	Pre-Screening Visit 1 (Month -2)	Pre-Screening Visit 2 (Month -1)
Window (days)	+7	±7
Written informed consent	X	
Review of inclusion and exclusion criteria[b]	X	
Fluorescein Angiography[c]	X	
SD-OCT[c]	X	
Site to contact IxRS	X	X
Administration of ITV ranibizumab	X	X
Adverse events[d]	X	X

IxRS = interactive Voice/Web response system; PK = pharmacokinetic; SD-OCT = spectral domain optical coherence tomography

[a] A pre-screening will be available for newly diagnosed nAMD patients who are treatment naïve. Patients must satisfy pre-screening eligibility criteria and sign consent to study participation before entering the pre-screening.

[b] Pre-screening evaluations for inclusion/exclusion criteria will only be performed and evaluated locally by the Investigator

[c] Must be taken following the instructions on the Reading Center Manual; these images will be used as historical images for patient's eligibility at the screening visit.

[d] During the pre-screening, only serious adverse events related to a protocol-mandated intervention (e.g., ITV injection procedure, or ITV ranibizumab) should be reported. Adverse events assessed by the qualified ophthalmologist as related to ranibizumab and ITV injections should be followed until the event resolves or the event is assessed as irreversible, chronic, or stable, even if the patient's participation in the study is over.

Appendix 4
Run-In Visit (if applicable)

Assessments [a]	Run-In Treatment (Month -1)
Window (days)	+7
Written informed consent	X
Review of inclusion and exclusion criteria[b]	X
Serum PK sample for ranibizumab concentration prior to treatment [c]	X
Site to contact IxRS	X
Administration of ITV ranibizumab	X
Adverse events [d]	X

IxRS = interactive Voice/Web response system.

[a] Run-In treatment will be available for patients who have been:

- diagnosed with nAMD in the study eye within 9months prior to screening and treated with a single anti-VEGF ITV injection, OR
- diagnosed with nAMD in the study eye within 9months prior to screening and treated with no more than eight anti-VEGF ITV injections, with aflibercept or bevacizumab being the most recent injection.

Patients must satisfy run-in eligibility criteria and sign consent to study participation before completing any study procedures or receiving run-in treatment.

[b] Run-In evaluations for inclusion/exclusion criteria will only be performed and evaluated locally by the Investigator.

[c] Collect prior to administration of the run-in ITV ranibizumab treatment.

[d] Only serious adverse events related to a protocol-mandated intervention (e.g., ITV injection procedure, or ITV ranibizumab) should be reported. Adverse events assessed by the qualified ophthalmologist as related to ranibizumab and ITV injections should be followed until the event resolves or the event is assessed as irreversible, chronic, or stable, even if the patient's participation in the study is over.

Appendix 5
Unscheduled Safety Assessment Visit

Assessments[a]	
Vital signs (blood pressure, respiration rate, pulse, and temperature)	x
Best corrected visual acuity (4-m starting distance)[b]	x
Slit-lamp examination	x
Dilated binocular indirect high-magnification ophthalmoscopy	x
Intraocular pressure[c]	x
SD-OCT	x
Adverse events[d]	x
Concurrent ocular procedures	x
Concomitant medications	x

IOP = intraocular pressure; SD-OCT = spectral domain optical coherence tomography.

[a] An unscheduled safety visit is applicable to any randomized study patients. If determined to be necessary by the physician, perform the listed assessments. All ocular assessments should be performed on both eyes.

[b] Perform finger-counting test followed by hand motion and light perception tests when necessary.

[c] The method used for the IOP measurement for a patient must remain consistent throughout the study.

[d] Adverse event causality to be evaluated by the qualified ophthalmologist.

Appendix 6
Implant Treatment Arms Procedures

Please consult Instruction for Use (IFU) Manual for the Implant fill, insertion, refill, and explantation details as well as preparation of study drug (ranibizumab) for the Implant treatment arms.

Surgeons will be qualified ophthalmologists trained in the management of retinal diseases and retinal surgery who will be certified by a Roche-selected vendor prior to performing the Implant insertion, its fill, refill, and explantation.

Appendix 7
Pre-Injection Procedures for ITV Treatment Arm

The following procedures will be used to minimize the risk of potential adverse events associated with intravitreal (ITV) injections (e.g., endophthalmitis). Aseptic technique will be observed by clinic staff involved in the injection tray assembly, anesthetic preparation, and study drug preparation and administration. In addition to the procedures outlined below, any additional safety measures in adherence to specific institutional policies associated with ITV injections will be observed. Physician should wear surgical face mask and refrain from talking, coughing, or sneezing during the injection.

The following procedures (except where noted) will be conducted by the investigator performing the ITV injection of study drug.

Patients self-administered antimicrobials will be prescribed for this treatment arm at the investigator's discretion. At the discretion of the investigator, sites may use either ophthalmic drops or lidocaine injection for study eye anesthesia.

PROCEDURE FOR PROPARACAINE OR TETRACAINE-BASED ANESTHESIA

Note: Topical anesthetic gels are prohibited.

If using proparacaine or tetracaine-based ophthalmic drops for anesthesia, the injecting physician or technician (if applicable) assembles the supplies and prepares a sterile field with supplies that include the following:

- 10% povidone iodine swabs, sterile surgical gloves
- 4×4 sterile pads
- A pack of sterile cotton-tipped applicators
- Eyelid speculum
- Sterile ophthalmic drape, sterile 0.5% proparacaine hydrochloride or 0.5% tetracaine hydrochloride drops (topical ophthalmic gels for anesthesia are NOT permitted)
- 5% povidone iodine ophthalmic solution
- Injection supplies

PROCEDURE

- Instill two drops of proparacaine or tetracaine ophthalmic drops into the study eye.
- Wait 5 minutes.
- Instill two more drops of proparacaine or tetracaine ophthalmic drops into the study eye.

Appendix 7
Pre-Injection Procedures for ITV Treatment Arm (cont.)

- Disinfect the periocular skin and eyelid of the study eye in preparation for injection. Scrub the eyelid, lashes, and periorbital skin with 10% povidone iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin. Ensure that the eyelid margins and lashes are swabbed, and proceed in a systematic fashion, from medial to temporal aspects.
- The physician will glove, place sterile ophthalmic drape to isolate the field, and place the speculum underneath the eyelid of the study eye.
- Instill two drops of 5% povidone iodine ophthalmic solution in the study eye, ensuring that the drops cover the planned injection site on the conjunctiva.
- Wait 90 seconds.
- Saturate a sterile, cotton-tipped applicator with proparacaine or tetracaine ophthalmic drops and hold the swab against the planned intravitreal injection site for 10 seconds.
- Use a sterile 4 × 4 pad in a single wipe to absorb excess liquid and to dry the periocular skin.
- Instruct the patient to direct gaze away from syringe prior to study drug injection.

PROCEDURE FOR LIDOCAINE-BASED ANESTHESIA

- If using lidocaine injection for anesthesia, physician or technician (if applicable) assembles the supplies and prepares a sterile field with supplies that include the following:
- 10% povidone iodine swabs, sterile surgical gloves
- 4 x 4 sterile pads
- A pack of sterile cotton tipped applicators
- Eyelid speculum
- Sterile ophthalmic drape, sterile 0.5% proparacaine hydrochloride or 0.5% tetracaine hydrochloride
- 5% povidone iodine ophthalmic solution
- 1% or 2% lidocaine for injection
- Injection supplies

PROCEDURE

- Instill two drops of proparacaine or tetracaine ophthalmic drops into the study eye.
- Disinfect the periocular skin and eyelid of the study eye in preparation for injection. Scrub the eyelid, lashes, and periorbital skin with 10% povidone iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin. Ensure that the eyelid margins and lashes are swabbed, and proceed in a systematic fashion, from medial to temporal aspects.

Appendix 7
Pre-Injection Procedures for ITV Treatment Arm (cont.)

- The physician will glove, place sterile ophthalmic drape to isolate the field, and place the speculum underneath the eyelid of the study eye.
- Instill two drops of 5% povidone iodine ophthalmic solution in the study eye, ensuring that the drops cover the planned injection site on the conjunctiva.
- Wait 90 seconds.
- Saturate a sterile, cotton-tipped applicator with 0.5% proparacaine hydrochloride drops and hold the swab against the planned intravitreal injection site for 10 seconds in preparation for the subconjunctival injection of 1% or 2% lidocaine hydrochloride ophthalmic solution for injection (without epinephrine).
- Inject 1% or 2% lidocaine (without epinephrine) subconjunctivally.
- Use a sterile 4 x 4 pad in a single wipe to absorb excess liquid and to dry the periocular skin.
- Instruct patient to direct gaze away from syringe prior to study drug injection.

Appendix 8
Preparation and Administration of Ranibizumab ITV Injection

The physician will prepare the ranibizumab injection as outlined below.

Vials of ranibizumab in aqueous humor solution should remain refrigerated at 2°C to 8°C (36°F to 46°F) until just prior to use. DO NOT FREEZE vials. Protect from direct light. Do not use beyond the expiration date. In order to minimize the risk of microbial growth, dose solutions should be prepared immediately before dosing. Dose solutions are for single use only.

After preparing the study eye as outlined in Appendix 7, withdraw 0.2-mL ranibizumab dose solution through a 5-μm filter needle. Remove the filter needle, replace it with a 30-gauge, 1/2-inch Precision Glide® needle, and **expel excess** ranibizumab **so that the syringe contains 0.05 mL of solution**. Insert the syringe through an area 3.5 to 4.0 mm posterior to the limbus, avoiding the horizontal meridian, and aiming toward the center of the globe. **The injection volume should be delivered slowly.** The needle should then be removed slowly to ensure that all drug solution is in the eye. **The scleral site for subsequent intravitreal injections should be rotated.** Refer to Appendix 9, for detailed post-injection procedures.

All injection materials (i.e., syringes, needles) will be discarded in a sharps container immediately following each ranibizumab injection.

A patient's study eye will be monitored with a finger count test within 15 minutes of the ranibizumab injection by the physician. A measurement of IOP in the study eye will be obtained 40 (±10) minutes post-injection. If there are no safety concerns, the patient will be allowed to leave the clinic. If any safety concerns or immediate toxicity is noted, the patient will remain at the clinic and will be treated according to the designated physician's clinical judgment. The following table provides specific instructions for the preparation and administration of ranibizumab in aqueous humor solution.

Appendix 8
Preparation and Administration of Ranibizumab ITV Injection (cont.)

Step	Procedures	Materials	Methods
1.	Filter study drug. Withdraw 0.2-mL ranibizumab dose solution through a 5-μm filter needle attached to provided 1mL syringe. After withdrawing ranibizumab through the filter, remove filter needle, replace it with a 30-gauge, ½-inch Precision Glide® needle, and expel excess ranibizumab so that the syringe contains 0.05-mL ranibizumab solution.	5-μm filter needle (needle is 19-gauge, 1.5 TW) 1-mL syringe Ranibizumab dose solution in the 2-mL ranibizumab vial	To minimize contamination from skin, sterile gloves should be used before handling the study drug vial and other supplies. Use aseptic technique to maintain sterility of the surface of the rubber stopper.
2.	Administer ranibizumab. Inject 0.05 mL ranibizumab into the eye 3.5–4.0 mm posterior to the limbus.	30-gauge, 1/2-inch Precision Glide® needle Ranibizumab dose solution in the syringe	Avoid the horizontal meridian and aim toward the center of the globe. Inject slowly. Remove the needle slowly to ensure that all drug solution is in the eye.
3.	Discard the syringe and all needles on the sterile tray in the Sharps container immediately following each ranibizumab injection.	Sharps container	

Appendix 9
Post-Injection Procedures for Patients in the ITV Injection Arm

INSTRUCTIONS

Immediately following the ranibizumab injection, discard all syringes and needles in the sharps container.

As per investigator's discretion, instruct the patient to self-administer antimicrobial drops following each injection of study drug (ranibizumab).

Appendix 10
Best Corrected Visual Acuity Testing

SCOPE

Best corrected visual acuity (BCVA) will be measured by trained and certified personnel at the study sites. The visual acuity (VA) examiner will be masked to the patient study eye assignment and patient treatment assignment. The VA examiner will have no access to a patient's previous visits' VA scores; the VA examiner will only be aware of the patient's refraction data from previous visits. The VA examiner is not permitted to perform any other tasks involving direct patient care except for VA refraction and VA examination. VA will be measured at the intervals specified in the protocol (see Section 4.6 of the protocol and 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 Early Treatment Diabetic Retinopathy Study 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 11
Low Luminance Best Corrected Visual Acuity Testing

There are the same requirements as the best corrected visual acuity described in Appendix 10; however, the low luminance visual acuity will be measured by placing a 2.0-log-unit neutral density filter over the best correction for that eye and having the participant read the normally illuminated Early Treatment Diabetic Retinopathy Study chart.

Appendix 12
Grading Scales

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 slit-lamp 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 slit-lamp 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 slit-lamp 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 slit-lamp beam is swept across the anterior chamber.
Trace	Few (1–3) cells are observed when the slit-lamp 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 slit-lamp 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 slit-lamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells.
3+	25–50 cells are seen when the slit-lamp 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 slit-lamp 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 MH, Kimura SJ, Thygeson P. Signs and symptoms of uveitis. I. Anterior uveitis. Am J Ophthalmol 1959;47(5, Part 2):155–70.

Appendix 12
Grading Scales (cont.)

GRADING SCALE FOR VITREAL HEMORRHAGE DENSITY

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.

GRADING SCALE FOR VITREOUS CELLS

Cells in Retroilluminated 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. New York: Mosby, 1996, p. 64.

Appendix 13
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 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 and 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 14
Color Fundus Photographs

SCOPE

Color fundus photographs (CFP) will be taken by trained personnel at the study sites at the intervals specified in the protocol.

CFP imaging will be performed for each patient at the intervals specified in the protocol (see 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 and timepoints at which images will be analyzed are recorded in the reading center manual.

EQUIPMENT

See the reading center manual.

PROCEDURE

The central reading center will provide a study manual and training materials.
The photographer and equipment will be certified by the reading center before any study images are taken.

Appendix 15
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 FAs will be obtained at the intervals specified in the protocol (see Section 4.6 of the protocol and Appendix 1 and Appendix 2) and will be forwarded to the central reading center for analysis and/or storage.

The list and 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 materials. Photographers, systems, and software will be certified prior to obtaining patient angiograms.

Appendix 16
Spectral Domain Optical Coherence Tomography

SCOPE

Spectral domain optical coherence tomography (SD-OCT) will be performed 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 4.6 and Appendix 1 and Appendix 2) and will be forwarded to the central reading center for analysis and/or storage.

The list and 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 17
External and Implant Photographs

SCOPE

External and 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 Appendix 1) 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 and timepoints at which images will be analyzed are recorded in the reading center manual.

EQUIPMENT

See the reading center manual.

PROCEDURE

The central reading center will provide a study manual and training materials. The photographer and equipment will be certified by the reading center before any study images are taken.

Appendix 18
Optical Coherence Tomography Angiography (at Selected Sites)

SCOPE

Optical coherence tomography (OCT) angiography will be performed 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 Appendix 1 and Appendix 2) and will be forwarded to the central reading center for analysis and/or storage.

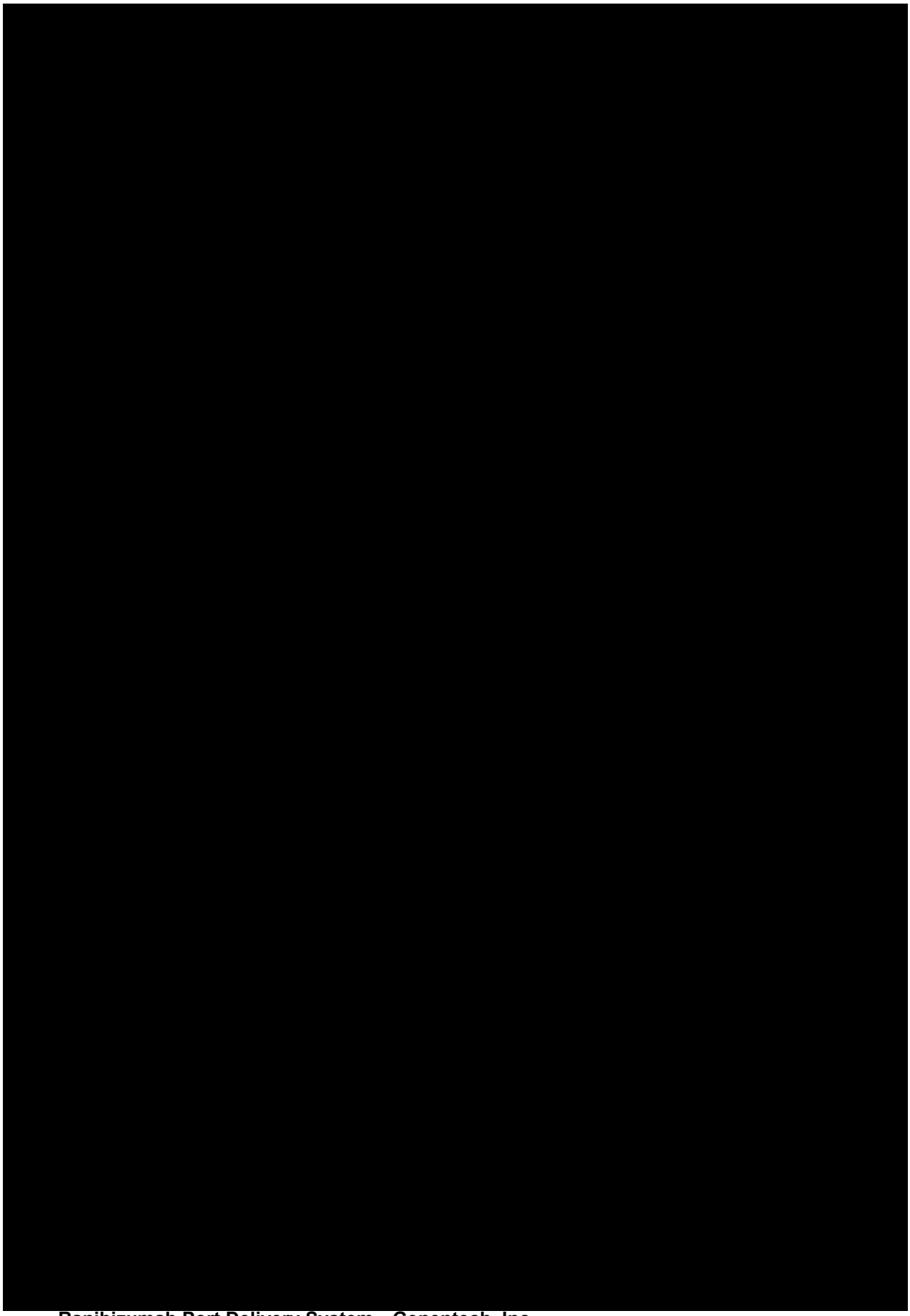
The list and timepoints at which images will be analyzed are recorded in the reading center manual.

EQUIPMENT

Equipment utilized during this trial is described in the central reading center manual. OCT angiography will be performed using Optovue AngioVue™ Imaging System only with the AngioVue™ software. 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.



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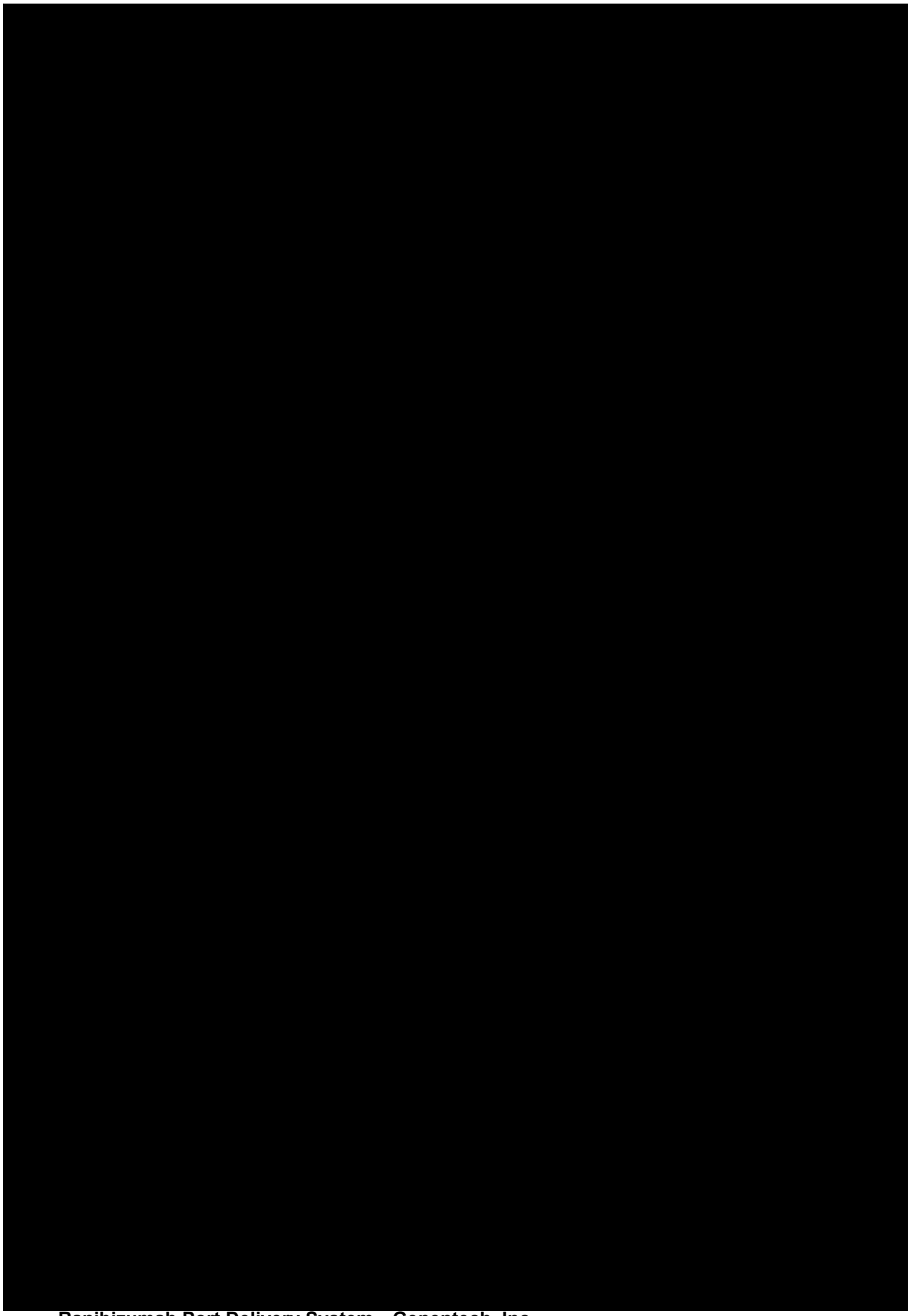

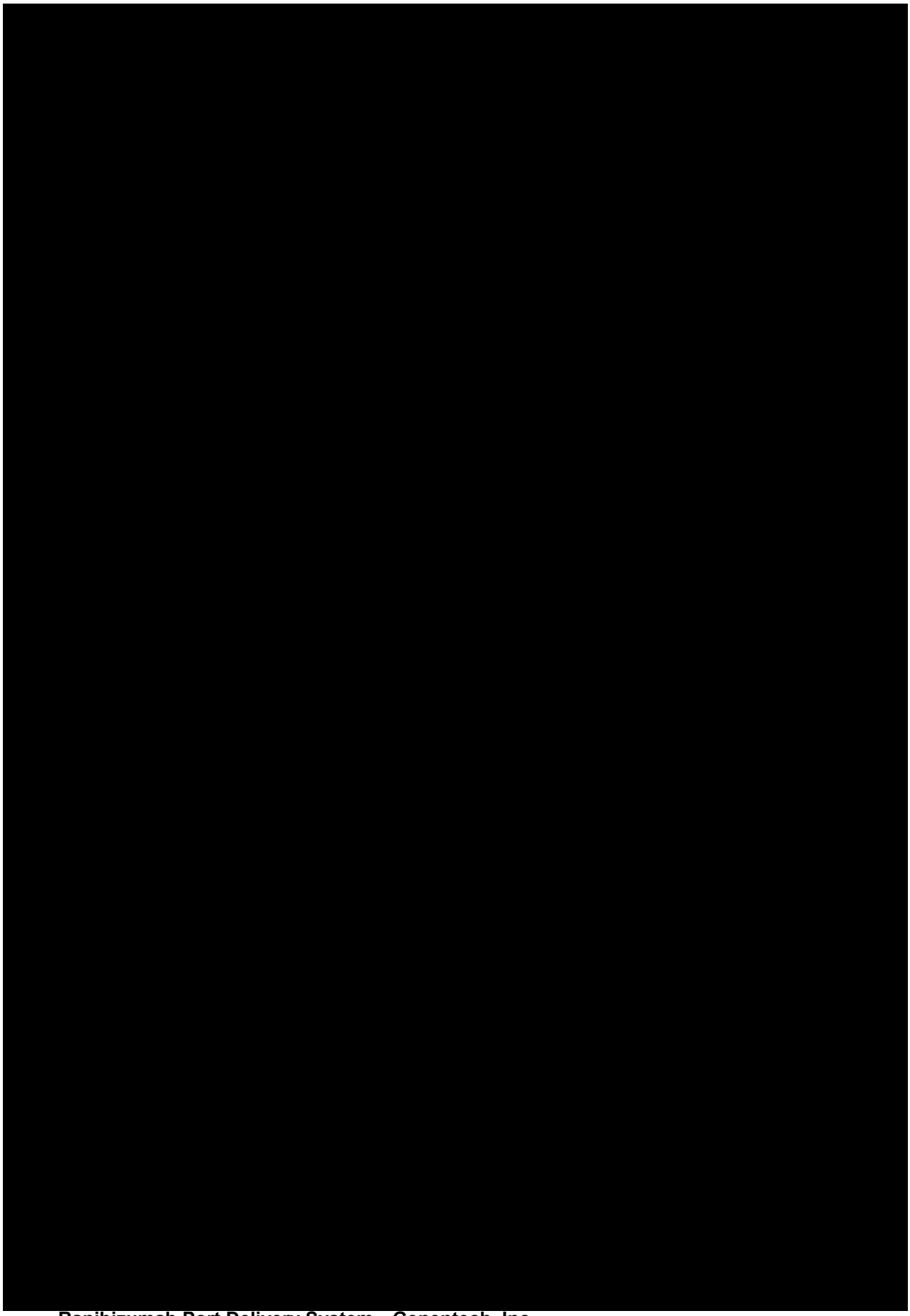

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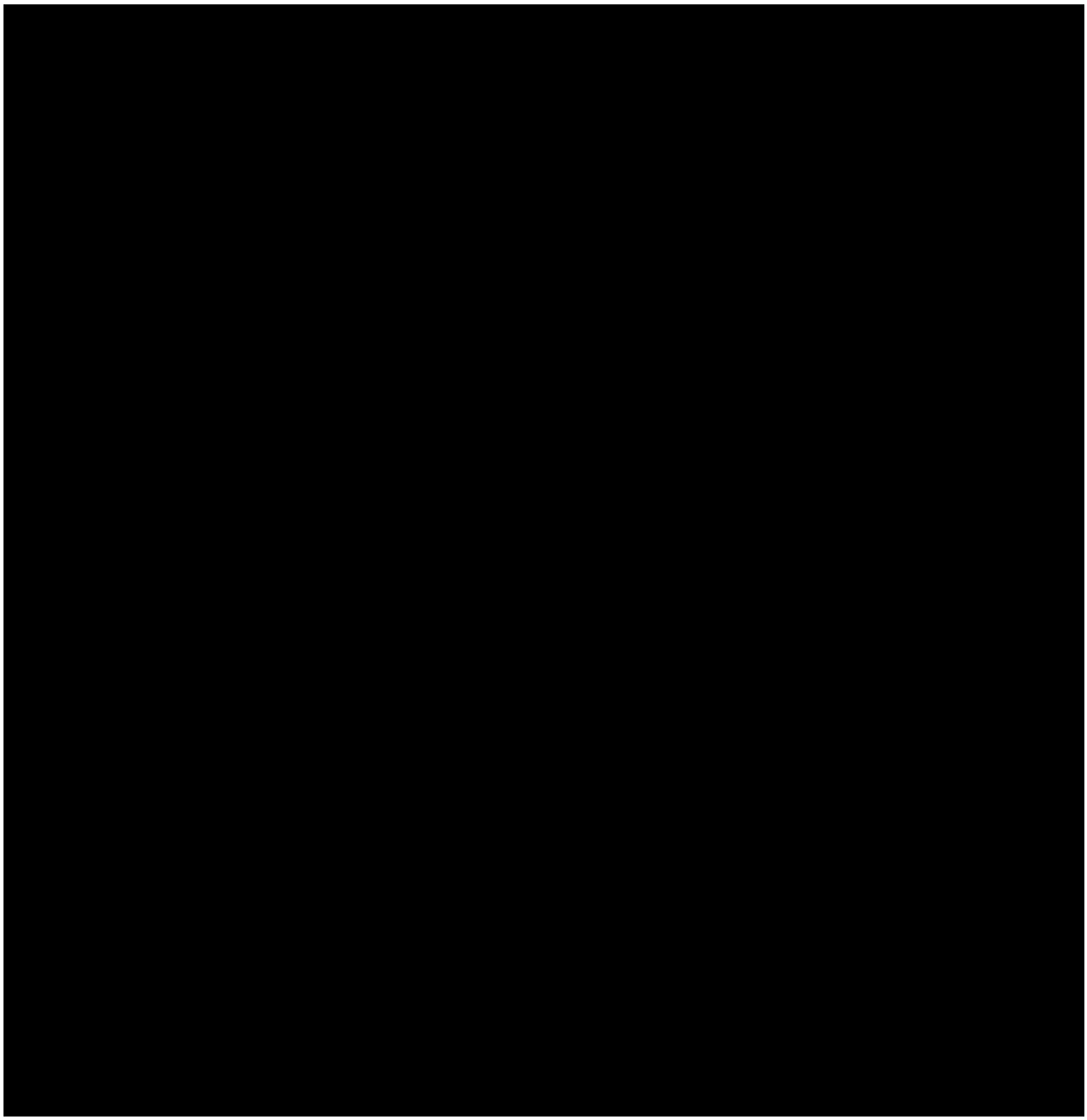

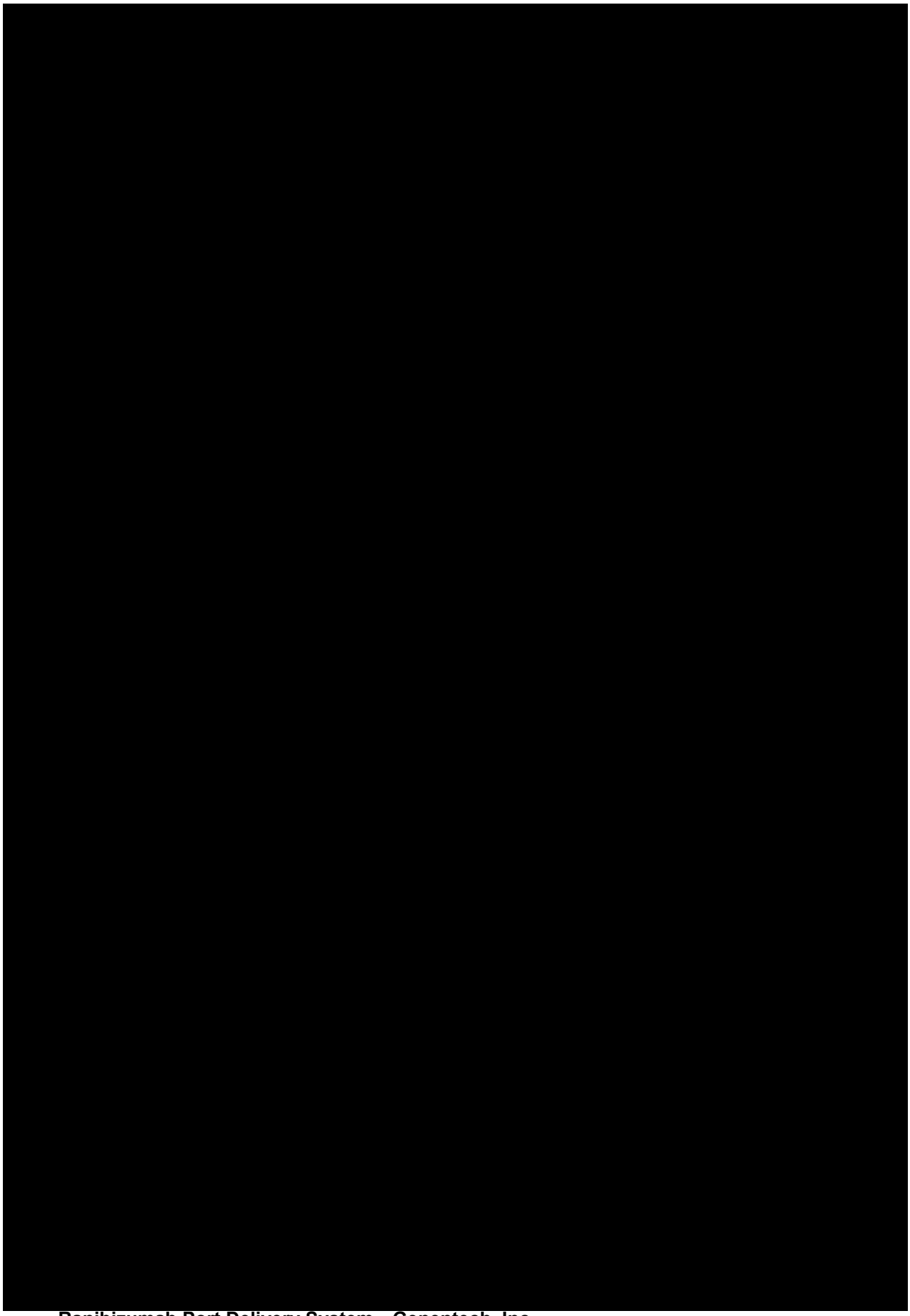

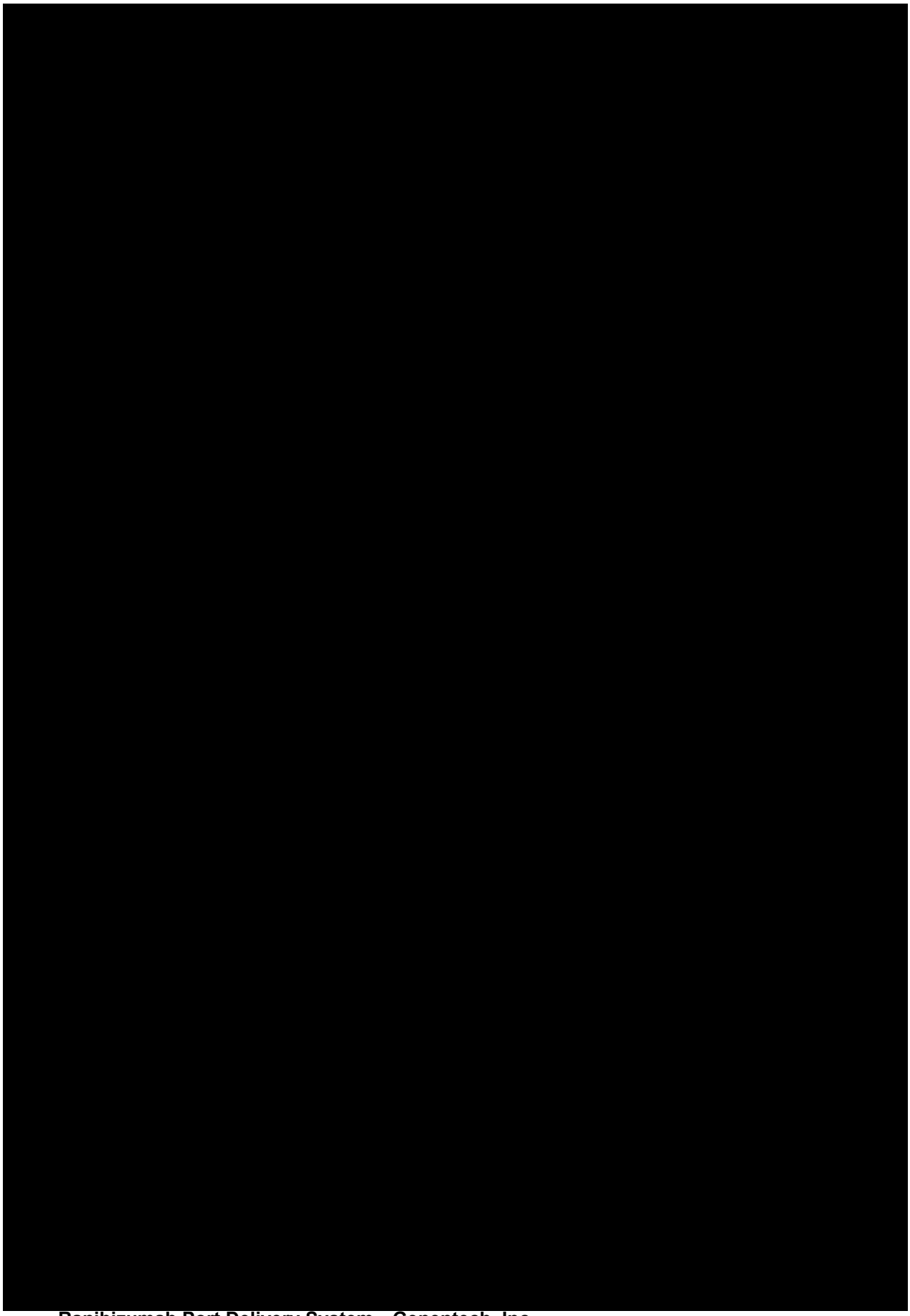

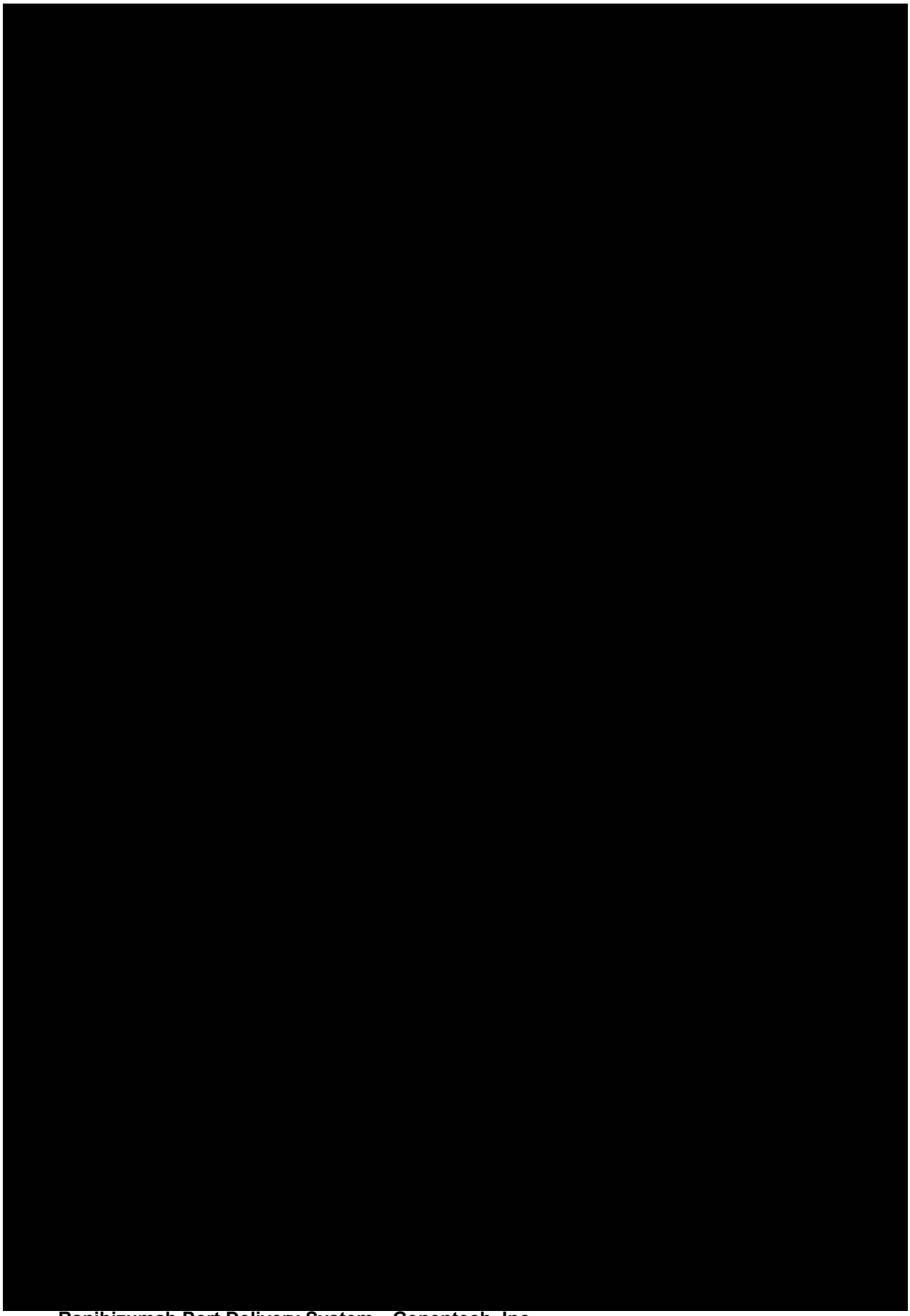

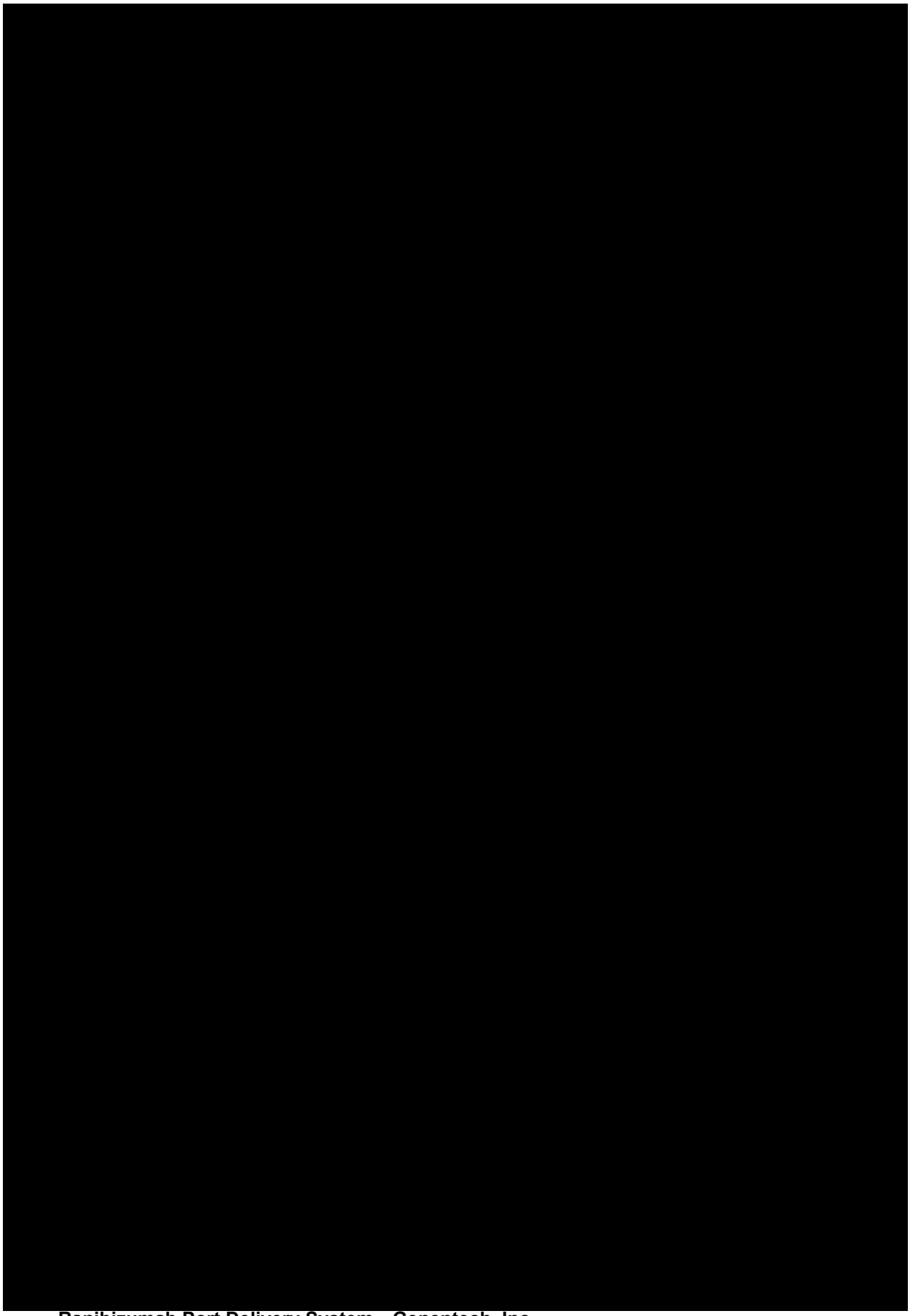

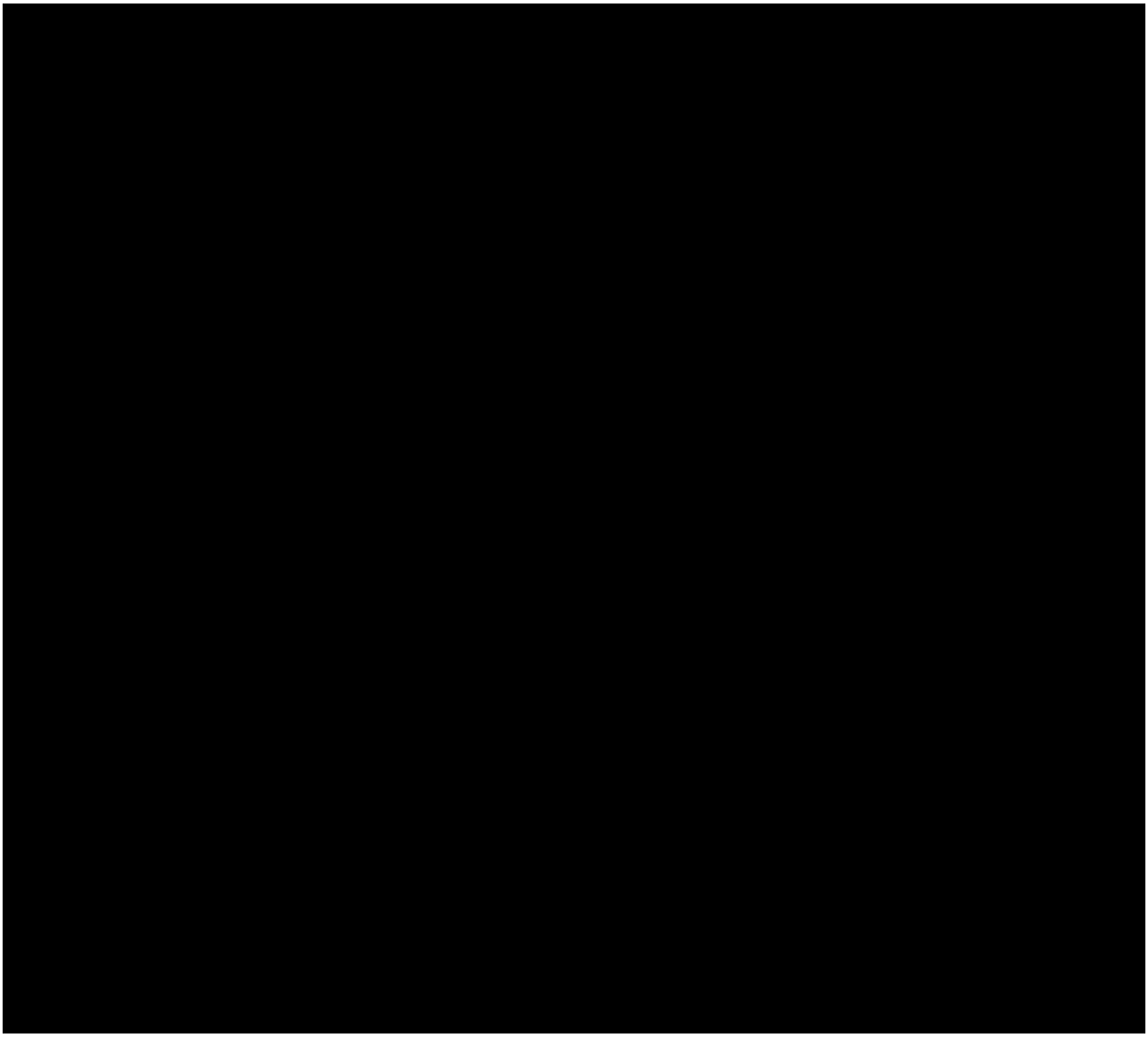

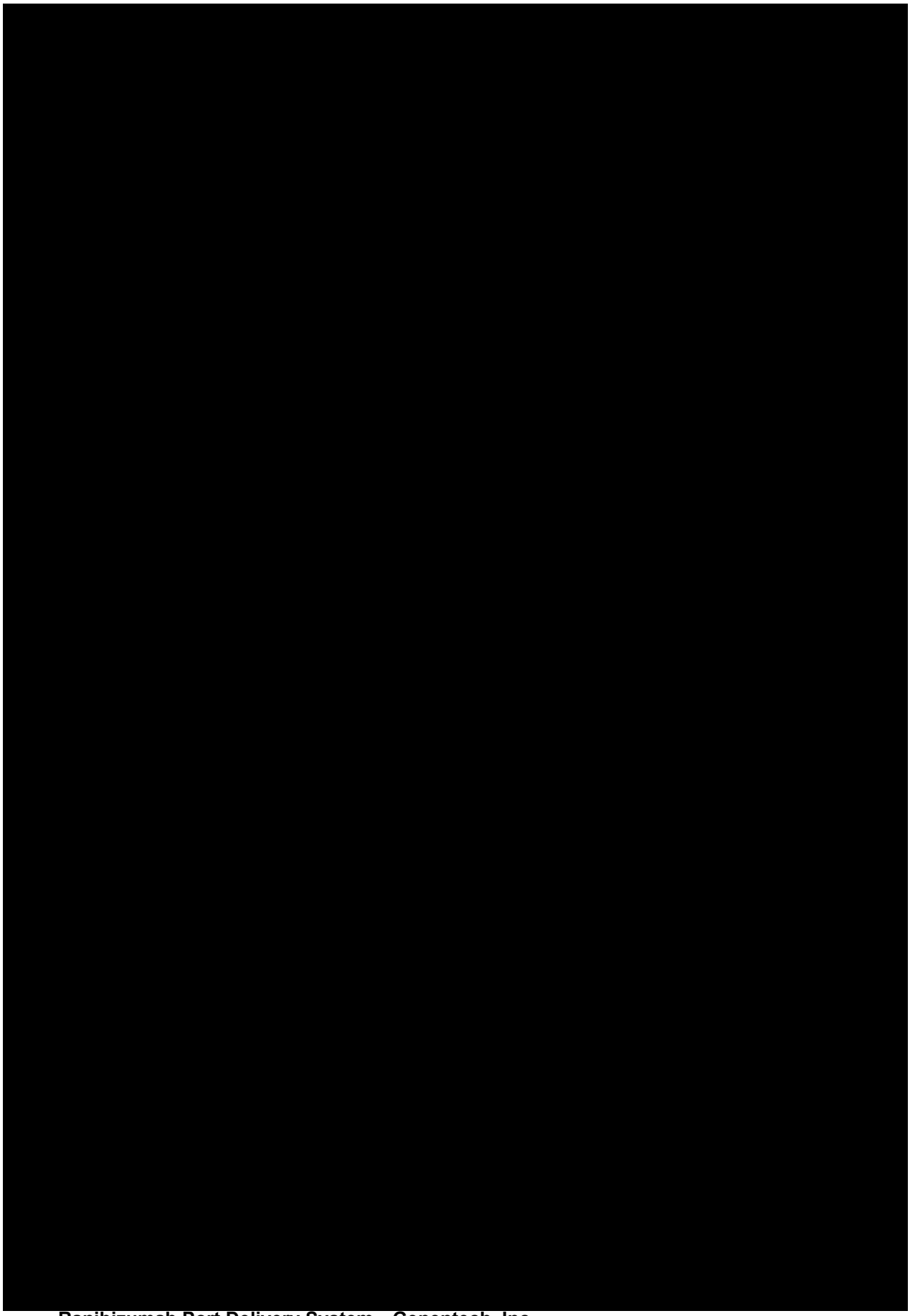

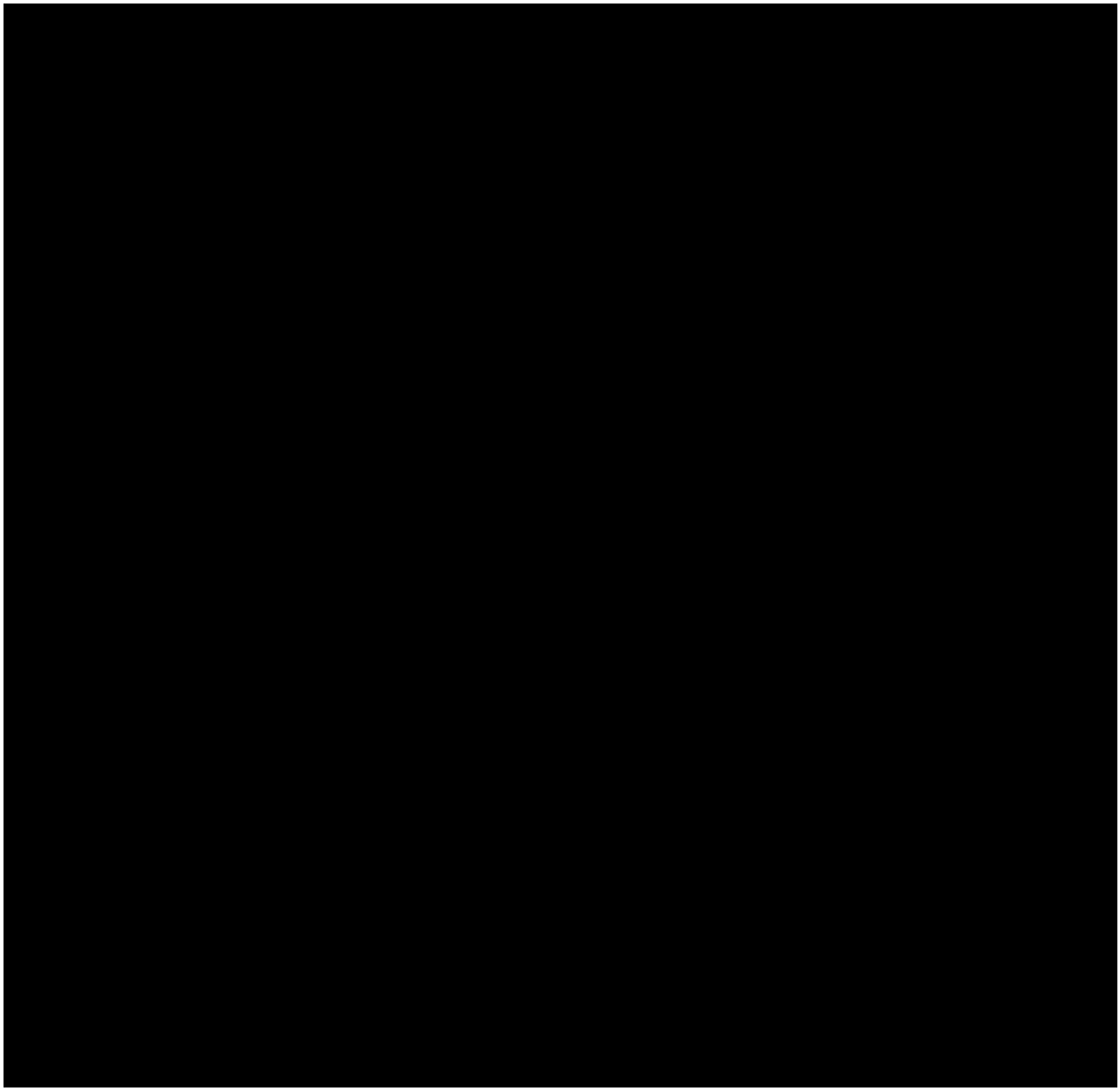

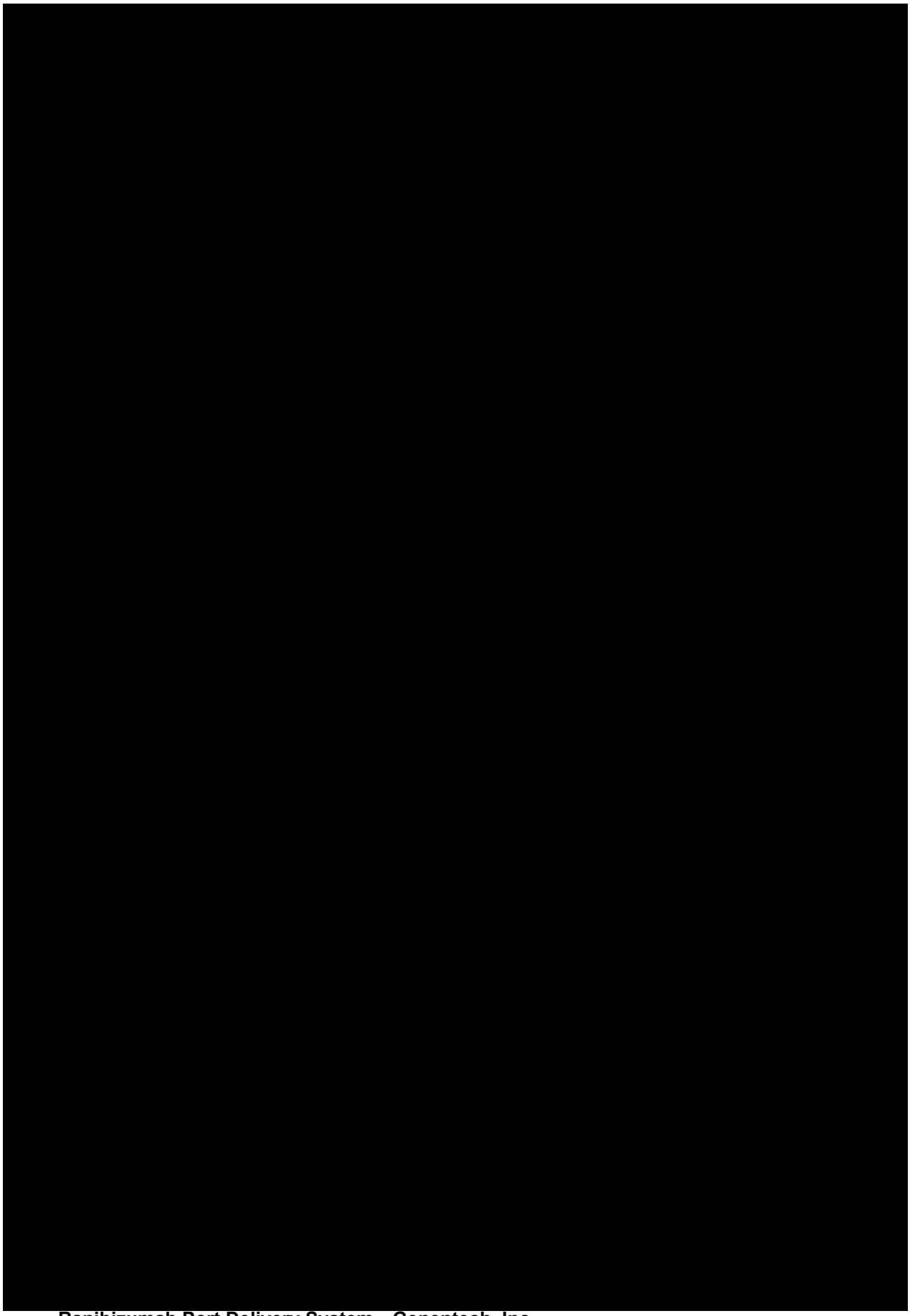

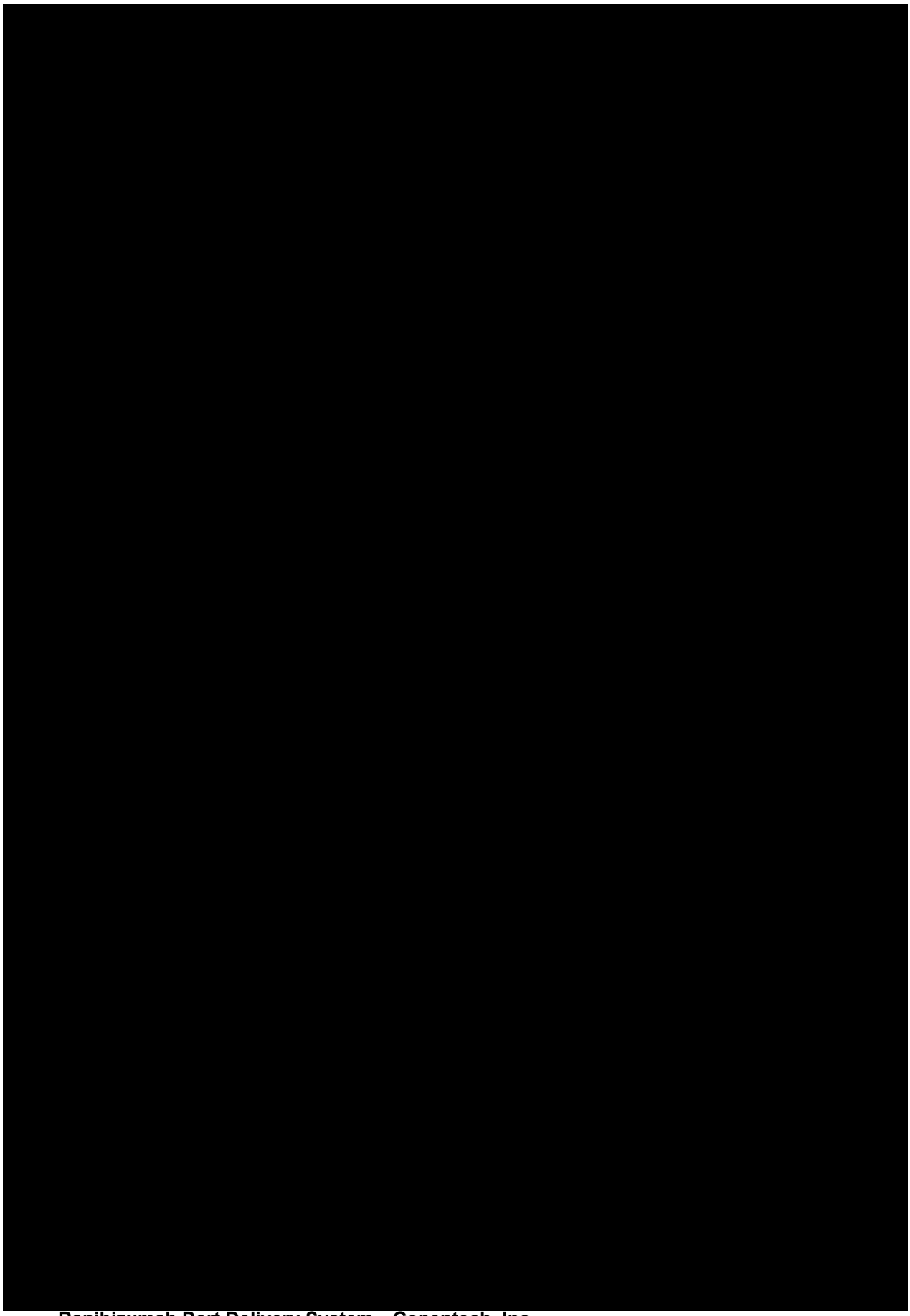

Appendix 20
Central Laboratory Sample Collection and Shipping

BIOLOGICAL SAMPLES

Serum for assessment of laboratory safety (hematology, serum chemistry, coagulation, pregnancy test) and urinalysis will be collected at screening visit. Urine pregnancy test will be collected and performed at Day 1 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, residual content of the Implant from the Refill Needle (if applicable), and aqueous humor or vitreous samples (at the start of explantation for patients undergoing an explantation procedure) will be collected at the timepoints specified in Section 4.6.6 of the protocol and the schedule of assessments (see Appendix 1 and Appendix 2). The optional aqueous humor samples prior to one or more refills and at the Day 7 safety visit post refill will be collected as well.

All samples should be collected and shipped initially to the central laboratory. The laboratory safety (hematology, serum chemistry, coagulation, and urinalysis) samples will be analyzed by the central laboratory. The rest of the collected samples will be analyzed by Sponsor or selected designee. All necessary transfer tubes, labels, forms, and shipping supplies will be provided by the central laboratory.

OPTIONAL ANTERIOR CHAMBER (AQUEOUS HUMOR) SAMPLE COLLECTION FROM IMPLANT TREATMENT ARMS

The optional aqueous humor paracentesis samples will be collected from patients who consent to the procedure and sample acquisition. An aqueous humor sample will be collected prior to or immediately following the patient's study eye treatment visits as indicated in Appendix 1. 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 study treatment to ITV arm patients following the collection of the aqueous humor sample, the subconjunctival lidocaine anesthetic must be injected into the eye prior to study treatment.

Appendix 20
Central Laboratory Sample Collection and Shipping (cont.)

EYE FLUID SAMPLE COLLECTION FROM IMPLANT TREATMENT ARMS

Vitreous or aqueous humor sample collection must be performed at the start of explantation for all patients undergoing an explantation procedure. The choice between vitreous collection or aqueous humor collection is per investigator's discretion.

- The aqueous humor sample collection consists of an anterior chamber paracentesis (removing 0.05–0.1 mL of fluid from the anterior chamber of the eye).
- The vitreous humor sample collection consists of a vitreous tap (removing 0.05–0.1 mL of undiluted vitreous from the central vitreal cavity).

The vitreous humor sample collection will be performed by a qualified physician using standard 23-gauge or 25-gauge vitrectomy procedures. The infusion cannula will be inserted through a sclerotomy in the pars plana of the infero-temporal quadrant of the eye, without opening the infusion. The vitreous humor tap will be performed by placing the vitrectome in the central vitreous through a second sclerotomy in the pars plana of the supero-nasal quadrant of the eye, and by aspirating 0.05 to 0.1 mL of undiluted vitreal sample with a 5-mL syringe while cutting vitreous actively. After collecting enough vitreous humor sample, the aspiration will be stopped and the vitrectome will be carefully removed from the eye.

After collecting the undiluted vitreous humor sample, the Implant will be removed from the eye and the scleral wound will be sutured as described in the RPDS IFU. In case of hypotony, the infusion through the cannula will be opened to restore the normal intraocular pressure. The physician will then perform a careful exploration of the retina, and a standard vitrectomy will be performed in the case of visible retinal detachment or other complications that require immediate surgical intervention.

Vitreous or aqueous humor samples will be collected with the kit provided by the central laboratory and shipped on dry ice to the central laboratory as soon as possible after the draw. Please see the RPDS IFU for further details.

EXPLANTED IMPLANTS WITH CONTENTS

Explanted Implants containing ranibizumab drug product will be preserved for potential analysis upon explant 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.

Refer to the 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.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

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Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADE	adverse device effect
AE	adverse event
AMD	age-related macular degeneration
BCVA	best corrected visual acuity
BLQ	below the lower limit of quantification
CIP	Clinical Investigational Plan
DME	diabetic macular edema
EC	Ethics Committee
eCRF	electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
FSV4	Forsight Vision4
GCP	Good Clinical Practice
HA	Health Authority
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	Informed Consent Form
IFU	instructions for use
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITV	intravitreal
PK	pharmacokinetic
RCE	Release Control Element
RPDS	Ranibizumab Port Delivery System
SAE	serious adverse event
VEGF	vascular endothelial growth factor
VA	visual acuity

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

GLOSSARY OF TERMS

Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with U.S. Code of Federal Regulations 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an Interactive Response Technology system
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Period	A subdivision of a cross-over study

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

Premature subject/patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

1. GENERAL

The Ranibizumab Port Delivery System (RPDS) Device Clinical Investigational Plan (CIP) describes the data that will be extracted from the Phase II study (GX28228) that is being conducted with the RPDS in order to assess its safety and performance. This CIP also focuses on the endpoints and analyses that will demonstrate that the RPDS works as intended. The purpose of the CIP is to comply with the International Organization for Standardization (ISO) 14155 standard "Clinical investigation of medical devices for human subjects", to assess the Implant safety and performance. The CIP will also be used to support obtaining a Conformité Européenne (CE; European Conformity) certificate, which is necessary for regulatory approval in the European Economic Area.

This CIP is intended to complement the Phase II pivotal study, which will collect the clinical information needed to fulfill the Essential Requirements of the European Medical Device Directive. Data are collected as part of the Phase II protocol. This CIP is specifically designed to investigate the functionality of the Implant while the ancillary devices' functionality will mainly be demonstrated as part of engineering/ design verification testing and human factor engineering studies.

Age-related macular degeneration (AMD) is a chronic disorder of the macula and is the most common cause of irreversible vision loss in older Americans and Europeans. AMD is categorized into two subtypes, dry and wet, based on clinical examination, ocular imaging, and pathologic findings. Dry AMD represents approximately 80% to 90% of AMD cases. In approximately 10% of dry AMD cases, a conversion to wet, or neovascular, AMD occurs over time. Although wet AMD is comparatively rare, prior to the development of anti-vascular endothelial growth factor (anti-VEGF) therapy, it accounted for the majority of severe vision loss from AMD. Central vision loss is painless and emerges gradually or suddenly (Bressler 1995; Klein et al. 1997).

Ranibizumab, a recombinant, humanized monoclonal antibody fragment (Fab), which binds to all known isoforms of VEGF-A, was first registered for use in neovascular wet AMD in the United States on 30 June 2006 and in the European Union on 22 January 2007 and has a well-established efficacy and safety profile.

Ranibizumab is approved for the treatment of wet AMD, macular edema secondary to retinal vein occlusion, diabetic macular edema (DME), and diabetic retinopathy in DME. In the European Union, ranibizumab is also approved for the treatment of choroidal neovascularization due to pathological myopia. The primary treatment modality is injection of ranibizumab into the vitreous humor of the patient's eye.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

Ranibizumab is injected directly into the vitreous humor of the eye. Intravitreal (ITV) injections of ranibizumab have shown efficacy in treating these ocular diseases, however, a drug delivery system that could reduce the burden of regular, often monthly, injections while maintaining satisfactory clinical outcomes is desired. Ranibizumab has been studied extensively to date and treatment with ITV injection has been demonstrated to be effective in preventing vision loss associated with VEGF-related retinal disorders. For many patients with VEGF-driven ocular diseases, long-term managment involving frequent, repeated ranibizumab ITV injections and monitoring visits is required.

Frequent clinic visits can place a significant burden on the patients and their caregivers as well as treating physicians and the healthcare system.

Administration of ranibizumab through an intra-ocular implant with a drug reservoir and a controlled release element may enable sustained delivery over extended periods of time, to substantially reduce the number of ITV injections while achieving similar efficacy to monthly injections. This decrease in treatment burden could reduce the risk from ITV injection-related adverse events (AE), increase treatment compliance, and reduce the burden to patients, their caregivers, and the healthcare system while maintaining optimum visual outcomes.

2. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

The RPDS is a novel, investigational intraocular drug delivery system designed to be used specifically with ranibizumab. The system consists of an intraocular Implant along with four ancillary devices.

The Implant is a refillable drug reservoir. It is filled with ranibizumab before it is inserted into the eye through the pars plana. The Implant is secured within the sclera, with an injection port that remains visible through the conjunctiva following insertion. Once filled with ranibizumab, the Implant is designed to provide sustained release of ranibizumab for the treatment of patients with neovascular wet AMD. The Implant can be refilled with ranibizumab in situ via an injection through the conjunctiva and Implant septum.

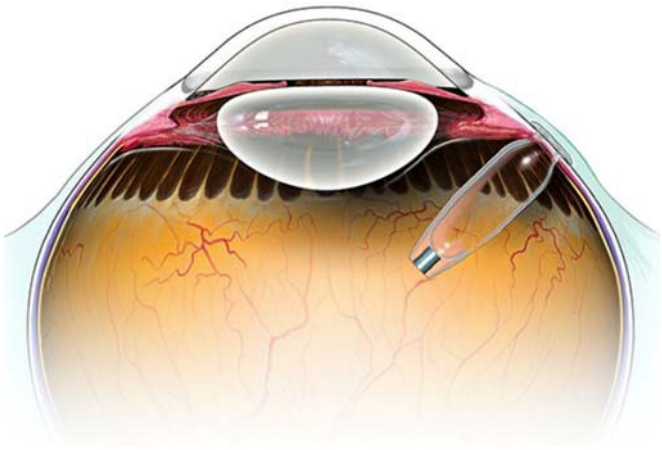
The RPDS consists of five components:

- Implant
- Insertion Tool
- Initial Fill Needle
- Refill Needle
- Explant Tool

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

Each of these components is a novel, investigational device, specifically designed as part of the RPDS.

Figure 1 Port Delivery Implant in the Eye



2.1 SUMMARY DESCRIPTION OF THE INVESTIGATIONAL DEVICE AND ITS INTENDED PURPOSE

2.1.1 Implant

The Implant is designed to deliver ITV ranibizumab via sustained release over the course of at least 4 months and is intended to be refilled multiple times through a septum in the Implant. The primary mode of action of the combination product is provided by the drug, ranibizumab.

The Implant is intended for surgical placement through the pars plana of the eye (see Figure 1). The distal end of the Implant extends into the vitreous humor with the proximal end accessible through the conjunctiva. When in place, an injection port is visible through the conjunctiva, and ranibizumab is refilled into the Implant through a septum that is in contact with the conjunctiva, thus not requiring repeat penetration of the sclera or choroid. The Implant is designed to contain approximately 20 μL of ranibizumab solution when filled.

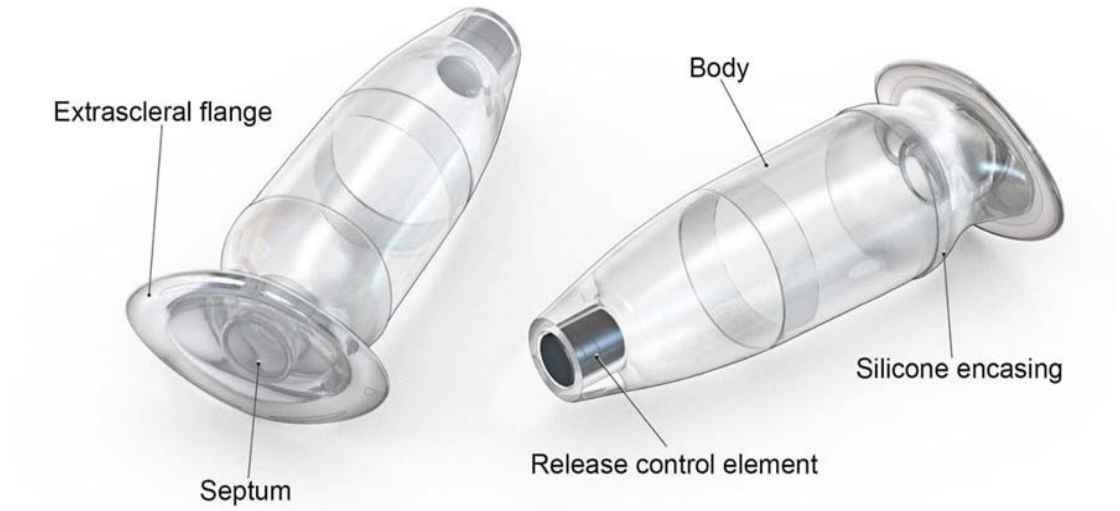
The rate of ranibizumab release from the Implant into the vitreous is controlled by passive, concentration gradient-driven molecular diffusion through the porous distal end of the Implant. This porous barrier, known as the Release Control Element (RCE), allows

molecules to diffuse at a rate dependent on the diffusivity of the molecule and the concentration gradient across the RCE.

The Implant is filled with ranibizumab solution with a custom Initial Fill Needle prior to insertion. After placement of the Implant, subsequent injections are performed with a custom Refill Needle that allows for the exchange of the contents of the Implant (residual ranibizumab, vitreal components) with the new ranibizumab solution.

The Implant is presented below in Figure 2. No material or design changes are expected after the clinical batch release of the Phase II Implant.

Figure 2 Implant



The Implant is a refillable reservoir designed for intravitreal insertion through the pars plana. The Implant consists of four primary components (Figure 2):

- Extrascleral flange
- Septum
- Body
- RCE

Once inserted in the eye, the body and the release control element of the Implant extend into the vitreous cavity, while the flange anchors the Implant within the sclera.

The extrascleral flange provides secure anchoring of the Implant within the sclera and is encased in silicone.

The septum is a self-sealing interface through which ranibizumab is injected into the Implant both prior to insertion and during subsequent refills in situ.

The body of the Implant contains the drug reservoir, which holds approximately 20 µL of drug. The Implant arrives with an empty reservoir. The reservoir is filled with ranibizumab by the surgeon immediately prior to insertion of the Implant into the eye.

The RCE controls the rate of ranibizumab diffusion from the drug reservoir into the vitreous.

The Implant is packaged in a sterile blister.

2.1.2 Initial Fill Needle

The Initial Fill Needle is a needle designed to fill the Implant with ranibizumab prior to Implant insertion. The Initial Fill Needle consists of five primary components (Figure 3):

- Needle (33-gauge)
- Soft stop
- External hub
- Luer hub
- Blue cap

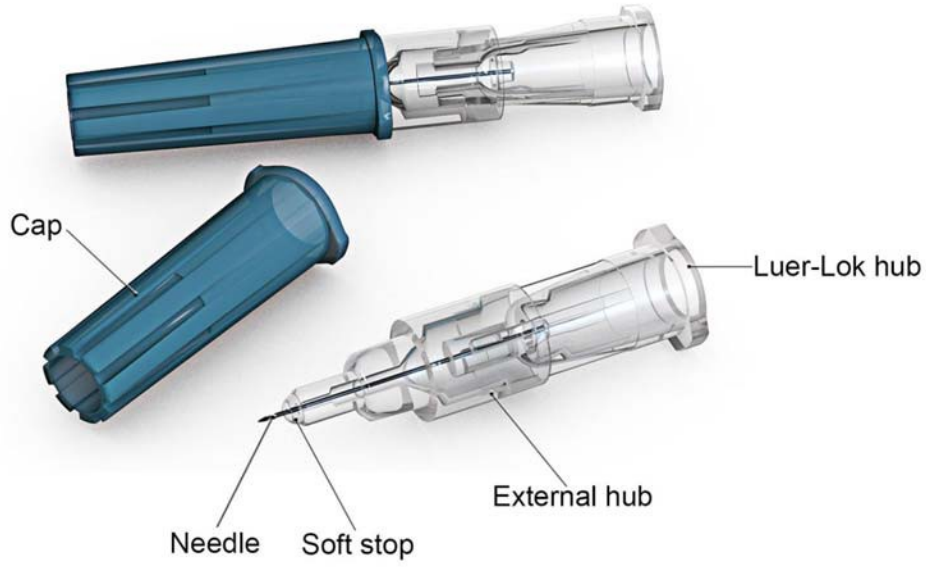
The needle contains a specialized external hub. This hub will be used to guide the syringe along the needle guide channel of the Insertion Tool so that the needle tip will be properly aligned with the Implant septum for Implant filling.

The soft stop surrounds the needle at the junction of the needle and the external hub. The soft stop provides a seal with the septum during Implant filling.

The Initial Fill Needle is packaged in a sterile pouch.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

Figure 3 Initial Fill Needle



2.1.3 Insertion Tool

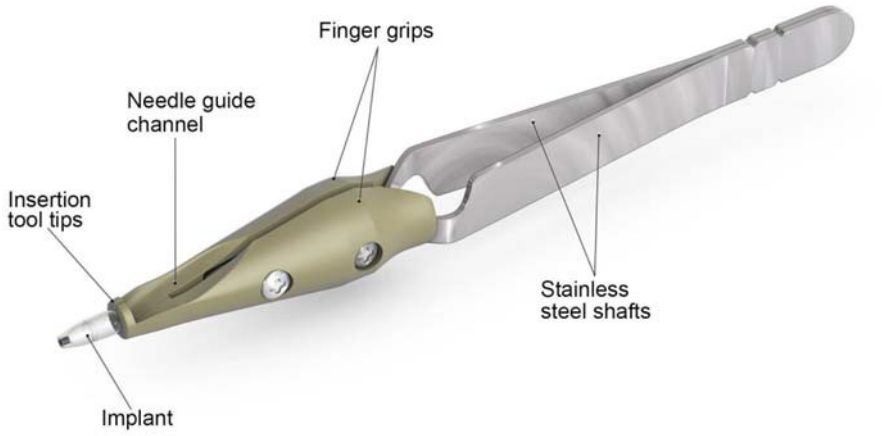
The Insertion Tool is a handheld ophthalmic instrument designed to facilitate handling of the Implant during the initial filling and insertion procedures. The Insertion Tool consists of four primary components (Figure 4):

- Insertion Tool tips
- Finger grips
- Stainless steel shafts
- Needle guide channel

The Insertion Tool arrives preloaded with the Implant in a sterile plastic tray packaged in a sterile pouch.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

Figure 4 Insertion Tool



2.1.4 Refill Needle

The Refill Needle is designed to simultaneously exchange the contents of the Implant reservoir with new ranibizumab in situ. The Refill Needle consists of five primary components (Figure 5):

- Vented needle (34-gauge)
- Soft stop
- Fluid collection reservoir
- Luer hub
- Clear cap

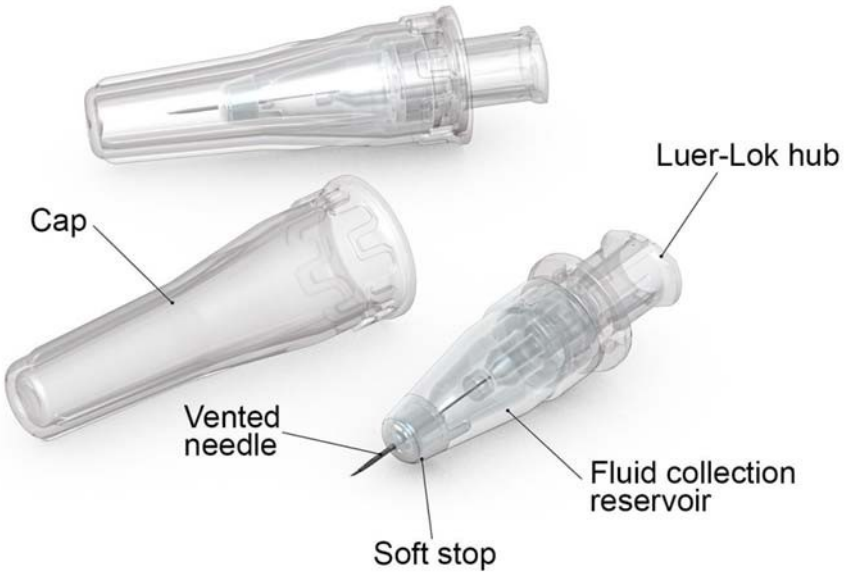
The vented needle and fluid collection reservoir enable exchange of ranibizumab between the Implant and the refill syringe. As fresh drug solution is injected into the Implant through the needle, fluid remaining in the Implant flows through openings in the vented needle and is collected into the fluid collection reservoir.

The soft stop provides a non-traumatic contact surface between the conjunctiva and the Refill Needle during Implant refilling.

The Refill Needle is packaged in a sterile blister.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

Figure 5 Refill Needle



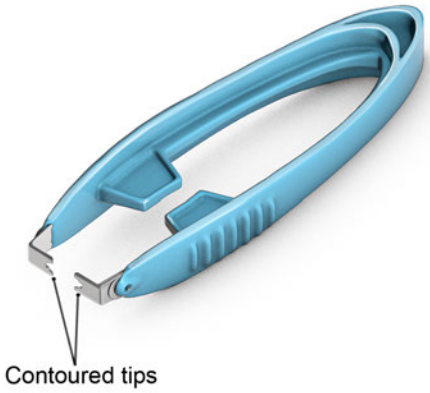
2.1.5 Explant Tool

The Explant Tool consists of a set of forceps with contoured tips. The contoured tips are designed to grasp underneath the Implant flange and securely pull the Implant for explantation (Figure 6).

The Explant Tool is packaged in a sterile blister.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

Figure 6 Explant Tool



2.2 DETAILS CONCERNING THE MANUFACTURER OF THE INVESTIGATIONAL DEVICE

The Sponsor (Genentech) is the manufacturer for the investigational device. The Contract Manufacturing Organizations involved in the manufacture of the RPDS devices are a) [redacted]) or b) [redacted]).

2.3 NAME OR NUMBER OF THE MODEL/TYPE TO PERMIT FULL IDENTIFICATION

Each RPDS device package is labeled with the name of the device as shown below.

- Implant/Insertion Tool
- Initial Fill Needle
- Refill Needle
- Explant Tool

2.4 TRACEABILITY OF THE RPDS COMPONENTS AND INVESTIGATIONAL MEDICINAL PRODUCT

All investigational medicinal product (IMP; ranibizumab) and RPDS required for completion of this study (including all the components of the RPDS) will be provided by the Sponsor. In order to ensure traceability, each RPDS device will be identified by a batch number.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

2.5 INTENDED PURPOSE OF THE INVESTIGATIONAL DEVICE IN THE PROPOSED CLINICAL INVESTIGATION

The following are the intended use of the RPDS devices:

- Implant: The Implant is intended to be inserted through the pars plana of the eye to deliver ranibizumab in a controlled manner into the vitreous humor. The physician will initially fill the reservoir with the drug and refill it in accordance with the instructions for use. The RPDS is contraindicated for use with medications other than ranibizumab.
- Insertion Tool: The Insertion Tool is designed to a) hold the Implant during sterilization and insertion, b) assist with filling of the Implant before insertion, and c) enable insertion of the Implant through a pars plana sclerectomy.
- Initial Fill Needle: The Initial Fill Needle is a 33-gauge Luer-Lock needle designed to perform the initial fill of the Implant while the Implant is held in the Insertion Tool.
- Refill Needles: The Refill Needle is a Luer-Lock needle designed to simultaneously exchange (in situ) any remaining old drug product in the Implant reservoir with new drug product.
- Explant Tool: The Explant Tool is designed to enable the removal of the Implant from the posterior segment of the eye after resection of the conjunctiva and removal of any scar tissue.

For additional RPDS details (e.g., fill, insertion, refill, and explantation of the Implant), consult the RPDS instructions for use (IFU) document and RPDS Investigator's Brochure (IB) Section 3.

2.6 THE POPULATIONS AND INDICATIONS FOR WHICH THE INVESTIGATIONAL DEVICE IS INTENDED

The Implant is intended for intravitreal delivery of ranibizumab for the treatment of neovascular wet AMD.

2.7 DESCRIPTION OF THE INVESTIGATIONAL DEVICE INCLUDING ANY MATERIALS THAT WILL BE IN CONTACT WITH TISSUES OR BODY FLUIDS

Chemical characterization, risk assessment, toxicology, and biocompatibility testing per ISO 10993-1 were performed on RPDS devices. The comprehensive testing demonstrated that the RPDS direct and indirect contacting materials, manufacturing processes, and sterilization process resulted in biocompatible devices.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

2.7.1 Implant

Table 1 Material of Construction of Implant

Component of Implant	Raw Material and/or Trade Name, Vendor	Patient/ User contact
Silicone encasing	Silicone, [redacted]	Patient: eye contact (conjunctiva, vitreous, sclera) User: N/A
Distal/Proximal Body	PSU, [redacted]	Patient: vitreous User: N/A
Septum	Silicone, [redacted]	Patient: eye contact (vitreous) User: N/A
Adhesive bond	Epoxy, [redacted]	Patient: vitreous User: N/A
Release Control Element (RCE)	Titanium, [redacted]	Patient: vitreous User: N/A

N/A = not applicable; PSU = polysulfone.

2.7.2 Initial Fill Needle

The Initial Fill Needle is used to perform the initial fill of the Implant while the Implant is held in the Insertion Tool. The component materials listed in Table 2 below are in indirect contact with the patient's eye. Future material change information on the Initial Fill Needle may be provided to the clinical investigators according to the Sponsor's internal procedure.

Table 2 Material of Construction of Initial Fill Needle

Component of Initial Fill Needle	Raw Material and/or Trade Name, Vendor	Patient/ User contact
Assembly Adhesive, [redacted]	[redacted]	Patient: N/A User: N/A
[redacted] Primer (Manufacturing Material)	Silicone Primer, [redacted]	Patient: N/A User: N/A
[redacted] Silicone	Silicone, [redacted]	Patient: N/A User: N/A
Cannula, 33-1/2G Long, Sterile Needle	Surgical Stainless Steel [redacted]	Patient: indirect contact through the drug User: N/A

Component of Initial Fill Needle	Raw Material and/or Trade Name, Vendor	Patient/ User contact
External hub	Natural Polycarbonate, [redacted]	Patient: indirect contact through the drug User: N/A
Hydrocarbon Solvent (Manufacturing Material)	DCM [redacted]	Patient: indirect contact through the drug User: N/A
Cap	Polypropylene; [redacted]	Patient: N/A User: surgical gloves

DCM = dichloromethane; N/A = not applicable; UV = ultraviolet.

2.7.3 Insertion Tool

The Insertion Tool consists of polyether ether ketone (PEEK) plastic grippers holding the Implant. The grippers are attached with screws to a reverse-action forceps.

If the Implant is repositioned during the insertion, the grippers listed in Table 3 will be in contact with the conjunctiva. Future material change information on the Insertion Tool may be provided to the clinical investigators according to the Sponsor's internal procedure.

Table 3 Materials of Construction of Insertion Tool

Component of Insertion Tool	Raw Material and/or Trade Name, Vendor	Patient/ User contact
Gripper Tips	PEEK, [redacted] PEEK [redacted]	Patient: conjunctiva User: N/A
Tweezers	Stainless steel, [redacted]	Patient: N/A User: surgical gloves
Screws	Stainless steel, [redacted]	Patient: N/A User: surgical gloves

N/A = not applicable; PEEK = polyether ether ketone.

2.7.4 Refill Needle

The component materials listed in Table 4 below are part of the Refill Needle that will have contact (direct contact or indirect contact) with the patient's eye. Future material change information on the Refill Needle may be provided to the clinical investigators according to the Sponsor's internal procedure.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

Table 4 Materials of Construction of Refill Needle

Component of Refill Needle	Raw Material and/or Trade Name, Vendor	Patient/ User contact
Gasket and soft stop	[redacted] thermoplastic elastomer, [redacted] silicone, [redacted]	Patient: eye contact (conjunctiva) Indirect contact (drug contact) User: N/A
Assembly	Adhesive [redacted]	Patient: Indirect contact (drug contact) User: N/A
Body	Polycarbonate, [redacted]	Patient: Indirect contact (drug contact) User: gloves
Outer cannula	Polyimide, [redacted]	Patient: eye contact (conjunctiva) and indirect contact (drug contact) User: N/A
Inner cannula	Stainless steel	Patient: eye contact (conjunctiva) and indirect contact (drug contact) User: N/A
Bushing	Stainless steel	Patient: indirect (drug contact) User: N/A
Needle Cap	[redacted]	Patient: N/A User: surgical gloves

LSR = liquid silicone rubber; N/A = not applicable; UV = ultraviolet.

2.7.5 Explant Tool

The component materials listed in Table 5 below are part of the Explant Tool that will have contact direct contact or indirect contact with the patient's eye. Future material change information on the Explant Tool may be provided to the clinical investigators according to the Sponsor's internal procedure.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

Table 5 Materials of Construction of Explant Tool

Component of Explant Tool	Raw Material and/or Trade Name, Vendor	Patient/ User contact
Contoured Tips	Stainless steel, [redacted]	Patient: eye contact (conjunctiva) User: N/A
Body	Acrylonitrile butadiene styrene polymer, [redacted]	Patient: N/A User: surgical gloves

N/A = not applicable.

2.8 SUMMARY OF THE NECESSARY TRAINING AND EXPERIENCE NEEDED TO USE THE INVESTIGATIONAL DEVICE SYSTEM

The RPDS is intended for use by vitreoretinal surgeons, scrub nurses, other hospital/clinic staff, and patients. Study investigators will be qualified ophthalmologists trained in the management of retinal diseases and ocular surgery, and will be certified by a Sponsor-selected vendor to perform initial Implant fill, insertion, refill, and explantation. The surgical procedures involved in the use of the RPDS are detailed in the RPDS IFU. Scrub nurses will assist the surgeon in selected preparation tasks. Other hospital and clinic staff will perform routine tasks outside of the sterile field, such as receipt or storage of the product. Patients will retain the Implant for an extended period of time.

2.9 DESCRIPTION OF THE SPECIFIC MEDICAL OR SURGICAL PROCEDURES INVOLVED IN THE USE OF THE INVESTIGATIONAL DEVICE

Patients in the Implant treatment arms will have the Implant, prefilled with ranibizumab, surgically inserted into the study eye at the Day 1 visit and subsequently refilled at monthly visits only if the protocol-specified refill criteria are fulfilled. The insertion and explantation procedures must be performed in the surgery room while the refill procedure is permitted in the physician office setting.

The Implant is surgically placed through the pars plana to allow for a sustained delivery of ranibizumab into the vitreous. As the Implant insertion is a surgical procedure that is performed in an operating room, sterile controls must be in place to minimize the risk of ocular infection. The Implant is filled with approximately 20 μL of ranibizumab immediately prior to insertion of the Implant into the patient's study eye.

In addition to standard pre-operative instructions used in practice, patients will be instructed to apply topical antimicrobial ophthalmic drops to the ocular surface 4 times within 24 hours prior to the procedure.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

At each refill, a volume of approximately 100 μL of ranibizumab will be injected in situ into the Implant through the septum to exchange the remaining contents of the Implant with newly introduced ranibizumab. During the refill procedure, the contents of the Implant will be collected in the fluid collection reservoir of the Refill Needle. The volume of newly introduced ranibizumab remaining in the Implant after the refill procedure will be approximately 20 μL

The Implant has undergone design verification confirming Implant performance through the expected use life, including 93 punctures of the Implant septum for Implant refills.

For detailed instructions on the Implant initial fill, insertion, refill, and explantation procedures, refer to the RPDS IFU.

3. JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

The Phase II study is being conducted to determine the dose of ranibizumab that is both efficacious for patients and allows for a dosing schedule that is less frequent than monthly ITV injections. While the design and sample size of this clinical study is aiming at the determination of an appropriate dosing regimen for the drug ranibizumab delivered through the Implant, this study will also appropriately inform the safety and performance of the Implant in human subjects.

This RPDS CIP will document whether the Implant and ancillary devices “work as intended.”

The data extraction and analysis will allow documenting the following aspects:

- Establish that there is no evidence of Implant clogging in more than 10% of patients in the Implant arms at Month 9
- Demonstrate that the AE profile observed when using the Implant is clinically acceptable as compared with ranibizumab dosed using conventional ITV injection. In other words, any complications associated with Implant insertion, refill, or explantation, or associated with the long term presence of the Implant within the posterior chamber of the eye, are manageable and acceptable in an overall benefit-risk assessment versus ITV dosing.

This will include a characterization of the “Prespecified RPDS-associated AEs”, i.e., those adverse device effects (ADEs) that have been pre-specified as being most relevant for the risk assessment of the Implant and the procedures of Implant insertion, refill, and explantation.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

For each AE (including "Prespecified RPDS-associated AEs") observed during the clinical study, the case report form (CRF) will collect a separate assessment of investigator causality for each "study intervention" element (i.e., investigator causality for "drug", investigator causality for "procedures", and investigator causality for Implant or ancillary devices). Investigators will be trained on the requirement to assess each AE for potential causal association to "drug", "procedure", Implant or ancillary devices – so that they may determine whether there is a causal association with one, more than one, or none of the "Study intervention" elements.

- Particular focus will be paid to evaluate the safety of the RPDS, as measured by "Prespecified RPDS-associated AE" (see protocol Section 6.5.1)

The RPDS CIP will evaluate whether the Implant is failing to operate as intended. As a passive diffusion device, the Implant can only operate in four different states as shown in Table 6.

Table 6 Operation States for the Implant

Implant Operational States	Ability to Detect State in Human Study
Failure to Operate State 1: RCE is clogged and no drug diffuses from reservoir	**High detectability** Will be apparent as deterioration in visual function and the development of further disease activity in a patient who had responded to ITV ranibizumab prior to the Implant insertion. The Implant will be assessed for possible clogging if the Implant is explanted. For a full description of the assessments refer to CIP section 5.3
Failure to Operate State 2: RCE rapidly elutes drug from the reservoir	**Low detectability in humans** The proportion of "failure to operate state 2" will be based upon bench testing with the Implant, as this is anticipated to be a very rare event with clinically implanted devices. It would be difficult to reliably observe a typical PK profile for this failure mode in a clinical study due to the potential high variability of the PK measurement. Clinically, the patient would be expected to require frequent refill. From previous high dose ITV studies, no safety signals have been identified that would be indicative of high ITV drug levels. Therefore, this failure mode is best evaluated as part of bench testing after explantation.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

Implant Operational States	Ability to Detect State in Human Study
Failure to Operate State 3: RCE elutes too slowly	**Low detectability in humans** This will be based upon bench testing with the Implant. A target release rate of 4 μg/day and a vitreous concentration no lower than 12 μg/mL is currently established in the specifications.
Implant Operational States	**Ability to Detect State in Human Study**
Successful Operation: Drug diffuses across RCE in a manner consistent with Fick's Law of Diffusion as demonstrated in bench and animal studies.	**No direct detectability in humans of Implant functionality can be shown** Implant functionality is demonstrated best in bench studies. It cannot be demonstrated in humans because there is no ethical method for directly measuring the flow of drug into the vitreous and serum pharmacokinetics is seen as too variable a measurement.

CIP = Clinical Investigational Plan; ITV = intravitreal; PK = pharmacokinetic; RCE = release control element

This RPDS CIP is not designed to determine a therapeutic dosing regimen for ranibizumab. It will determine whether the Implant meets an acceptable rate of failure to Operate State 1.

The Implant is a passive diffusion device, so it cannot act outside of its native physics. It must diffuse the drug in accordance with Fick's Law. Bench studies, in models of the ocular environment, are the most effective ways to document the rate of drug diffusion from the Implant. As a result, it is deemed unnecessary to directly measure the flow of ranibizumab from the Implant in humans. In addition, there is no appropriate method to directly measure the flow of ranibizumab from the Implant in humans. No direct monitoring of drug levels in the reservoir or vitreous would be ethical in humans as there is no benefit to an individual patient that would balance the risk of these repeated invasive collections of vitreous. There is no method for monitoring the drug levels in the Implant reservoir.

Additionally, measurement of serum ranibizumab cannot provide quantitative data for the Implant diffusion. Serum ranibizumab concentration-time data are remote from the site of drug release (Implant → vitreous → serum) and therefore are not a direct quantitative measurement of the drug release rate from the Implant. In addition, serum pharmacokinetics have high intersubject variability when administered by the ITV route; similar variability is expected by the Implant route. This may also confound the use of serum pharmacokinetics as a quantitative reflection of drug release from the Implant.

This high variability was observed in the serum pharmacokinetic (PK) levels following refills in the Phase I human trial. Therefore, PK data will be collected in all patients in the Phase II study, but no clear conclusion on the Implant diffusion rate can be prespecified before results become available.

It can be concluded that human studies will not provide better quantitative information about the diffusion rate of ranibizumab from the Implant than bench studies will.

Adequate data have been generated in bench studies to demonstrate that the Implant will reliably diffuse ranibizumab in a controlled manner into the vitreous humor.

3.1 EVALUATION OF THE RESULTS OF THE RELEVANT PRECLINICAL TESTING/ASSESSMENT CARRIED OUT TO JUSTIFY THE USE OF THE INVESTIGATIONAL DEVICE IN HUMAN SUBJECTS

The RPDS is a drug delivery system intended to release therapeutic levels of ranibizumab into the vitreous humor over an extended period of time. The RPDS includes three primary components: the drug (ranibizumab), the port delivery system permanent implant, and the ancillary devices.

A comprehensive non clinical testing strategy was developed to support the clinical development (Phase II and Phase III) and registration of the Implant. The strategy included the assessment of the in vitro and in vivo functionality and biocompatibility of a prototype implant, Phase II Implant, and the ancillary devices.

In vitro and in vivo biocompatibility studies were chosen based on direct and indirect interaction of the Implant and ancillary devices with ocular tissues and long-term ocular implantation, and are consistent with ISO 10993 (Biological evaluation of medical devices), ISO 11979-5 (Ophthalmic implants-intraocular lenses part 5: biocompatibility); and ANSI Z80.7 (Testing for intraocular lens devices). Biocompatibility testing is conducted with the finished Implant, and extracts from the Implant and ancillary devices.

The nonclinical testing results are summarized in the RPDS IB Section 4.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

3.2 EVALUATION OF CLINICAL DATA THAT ARE RELEVANT TO THE PROPOSED CLINICAL INVESTIGATION

The Implant has been investigated in a prospective, Phase I, open-label study in patients with wet AMD, conducted by FSV4 at a single site in Latvia. The study investigated the safety, tolerability, and duration of ranibizumab exposure delivered with the Implant.

This Phase I Implant was composed of biocompatible materials (polymethyl methacrylate, silicone, 316L stainless steel).

For details of the design of the Phase I study as well as the results, refer to protocol Section 1.3 and to the RPDS IB Section 5.

4. RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

The general approach to identifying, planning, and execution of the risk management activities of the Phase II RPDS is in accordance with ISO 14971:2007/2012: Medical devices – application of risk management to medical devices.

Risk management plans have been created to cover the following:

- Implant, Insertion Tool, Initial Fill Needle, Refill Needle, and Explant Tool
- Labeling
- Packaging manufacturing of the combination product (assembly operations)
- Shipping and storage (e.g., product shipping, handling and storage)
- Clinical trial surveillance (e.g., product monitoring and complaints)
- Components not off-the-shelf (e.g., molding assembly components)

The results of risk/benefit assessment from the overall risk analysis are described in the RPDS IB Section 6.

4.1 ANTICIPATED CLINICAL BENEFITS

As a result of the chronic, progressive nature of wet AMD, frequent ranibizumab ITV injections continue for extended periods for many patients. Pivotal studies of ranibizumab in wet AMD (FV2598g and FVF2587g) demonstrated significant and well-maintained visual acuity (VA) outcomes with monthly ITV injections for 2 years. In these studies it was observed that the treatment effect reaches, on average, a plateau after three consecutive monthly injections. Subsequently, there have been several studies evaluating a PRN treatment regimen, with different re-treatment criteria also showing early response after start of treatment (Busbee et al 2013; CATT Research Group 2011).

In clinical practice, frequent office monitoring visits are required and regular injections are necessary to maintain optimal vision gains. Sustained release of ranibizumab from the Implant is an alternate dosing method that may result in a less frequent need of retreatment than dosing with ITV injections. This decrease in treatment burden could possibly reduce the risk of ITV injection-related AEs, increase compliance, and reduce the burden to patients, their caregivers, and the healthcare system, while maintaining optimum visual outcomes.

4.2 ANTICIPATED ADVERSE DEVICE EFFECTS

The safety of the RPDS, as assessed using the following "Prespecified RPDS-associated AEs" include, but is not limited to an evaluation of:

- Vitreous hemorrhage associated with a >30-letter decrease in best corrected visual acuity (BCVA) on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart compared with the last assessment of BCVA prior to the onset of vitreous hemorrhage lasting >1 month
- Reduced VA (>30-letter loss from previous scheduled visit)
- Traumatic cataract
- Endophthalmitis
- Damage to sclera
- Retinal detachment
- Interference of the Implant with visual field

Refer to protocol Section 6.5.1 and to the RPDS IB Section 6 for additional details.

4.3 RESIDUAL RISKS ASSOCIATED WITH THE INVESTIGATIONAL DEVICE, AS IDENTIFIED IN THE RISK ANALYSIS REPORT

The details of the residual risks identified in the different risk analysis (e.g., failure mode and effects analysis) are described in the RPDS IB Section 6.

4.4 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL INVESTIGATION

The benefit and risks associated with participation in this study are outlined in the Informed Consent Form (ICF) and will be explained to the patient by the investigator. Ranibizumab has a well characterized safety profile, with clearly identified and potential risks associated with its use, which is described in the RPDS IB. The safety and tolerability of ranibizumab exposure delivered through the Implant were investigated in a Phase I prospective, open-label study in a wet AMD patient population by FSV4 at a single site in Latvia. The surgical procedure associated with Implant insertion could

potentially lead to ocular AEs. These include, but are not limited to: ocular tissues inflammation or infection, conjunctival erosion, damage to the sclera, endophthalmitis, hypotony, suprachoroidal hemorrhage, and retinal detachment. The RPDS IFU describes all of the procedures necessary for successful insertion, refilling, and explantation of the Implant. It is imperative that specific surgical procedures are adhered to in order to minimize the risk of ocular AEs related to the procedure.

4.5 POSSIBLE INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

At the discretion of their physician, patients may continue to receive all medications and standard treatments administered for other conditions with certain exceptions as detailed in the protocol Section 4.5.2.

4.6 STEPS THAT WILL BE TAKEN TO CONTROL OR MITIGATE THE RISKS

Patients not considered suited for receiving the RPDS in this clinical investigation are excluded as outlined under exclusion criteria (see the protocol Section 4.1.2).

Study investigators will be qualified ophthalmologists, trained in the management of retinal diseases and ocular surgery, and will be certified by a Sponsor-selected vendor to perform initial Implant fill, insertion, refill, and explantation. The surgical procedures involved in the use of the RPDS are also detailed in the RPDS IFU document.

Patients must adhere to the instructions for prohibited therapy (see Section 4.5) and dose interruptions/study treatment or study discontinuation criteria (protocol Table 6).

Prior to Implant insertion or explantation, patients will be required to verify that they have self-administered their antimicrobial eye drops to the study eye 4 times within the previous 24 hours. As per investigator's discretion, patients may also be required to have self-administered antimicrobial eye drops to the study eye 4 times within the 24 hours prior to Implant refills. It is required that all patients self-administer their antimicrobial drops again 4 times daily for 7 days following Implant insertion or explantation, and 4 times daily for 3 days following refills. Please see the protocol section 5.1 for additional details.

The insertion procedure and, if applicable, the explantation procedure must be performed in the surgery room while the refill procedure is permitted in the physician office setting.

The results of risk/benefit assessment from the overall risk analysis are described in the RPDS IB Section 6.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

4.7 RISK-TO-BENEFIT RATIONALE

The Phase I study provided preliminary evidence of a positive benefit–risk profile for the use of RPDS in patients with wet AMD and supports the evaluation of RPDS in a Phase II study. It is expected that in the Phase II study the drug efficacy of at least one Implant treatment arm will be similar to the control ITV monthly injection treatment arm.

Further details are included in the protocol Section 1.4.

5. OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

The objectives of the Phase II study are described in the protocol section 2. This RPDS CIP provides an overview of the device objectives and focuses on the parameters used for the assessment of RPDS functionality and safety.

5.1 DEVICE OBJECTIVES

- To evaluate the functionality of the Implant by assessing that there is no evidence of Implant clogging in more than 10% of patients in the Implant arms at Month 9
- To explore the serum ranibizumab concentration data with a PK model in an attempt to infer the concentration–time pattern in the vitreous humor and, if possible, derive information on the rate of ranibizumab release from the Implant
- To evaluate the safety of the RPDS, as measured by "Prespecified RPDS-associated AEs" (see protocol Section 6.5.1)

5.2 HYPOTHESES, IMPLANT FUNCTIONALITY TO BE ACCEPTED OR REJECTED BY STATISTICAL DATA FROM THE CLINICAL INVESTIGATION

The hypothesis to be established is that the initial Implant clogging rate does not exceed 10% of Implant arm patients at Month 9. In order to evaluate whether the Implant clogging rate exceeds 10% within the first 9 months, the proportion of clogged Implants will be estimated and the 90% confidence interval will be calculated. All clogging data from patients in the Implant arms will be pooled for this analysis.

In the study, the Implant will be judged as "failed" if it is determined that the RCE is clogged and can no longer deliver the ranibizumab into the ocular space (see Table 6 "Failure to Operate State 1" and description below).

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

5.3 CLAIMS AND INTENDED PERFORMANCE OF THE IMPLANT THAT ARE TO BE VERIFIED

Intended performance of the Implant is demonstrated by successful operation of drug diffusing across the RCE in a manner consistent with Fick's Law of Diffusion as demonstrated in bench and animal studies. Implant functionality is demonstrated best in bench studies since there is no direct detectability in humans of Implant functionality that can be shown. No ethical method exists for directly measuring the flow of drug into the vitreous. Additionally serum pharmacokinetics is seen as too variable a measurement.

The clinical performance of the Implant will be demonstrated by measuring the rate of events related to the occurrence of Implant clogging.

The Implant will be assessed for possible clogging if the Implant is explanted. The following assessments will be performed:

- Serum pharmacokinetics of ranibizumab will be used to judge whether Implant clogging may have occurred. Aqueous and vitreous humor PK samples will also be collected at explantation and may be used to further assess possible Implant clogging. For each individual patient, possible Implant clogging will be documented if at least one of the following conditions is met:
  - For 40-mg/mL or 100-mg/mL dose groups: At Implant insertion and prior to the first refill: serum ranibizumab concentrations are below the lower limit of quantification (BLQ) or below the baseline serum ranibizumab concentration value at all time-points prior to refills, that is, on Day 1 (within 60 min of insertion – only if possible to collect), Day 2, Day 7, Day 14, and all monthly time points after insertion and prior to the first refill or to the last study visit for the patient, if no refill occurs
  - For the 10-mg/mL dose group: At Implant insertion and prior to the first refill: serum ranibizumab concentrations are below the lower limit of quantification (BLQ) value at all time-points prior to refills, that is, on Day 1 (within 60 min of insertion – only if possible to collect), Day 2, Day 7, Day 14, and all monthly timepoints after insertion and prior to the first refill or to the last study visit for the patient, if no refill occurs

    OR
  - After the first refill: serum ranibizumab concentrations are BLQ or below the last pre-refill serum ranibizumab concentration value at all time-points post refills, that is, on Day 7, and all monthly time points prior to the next refill for two consecutive refills, or to the last study visit for the patient, if no further refill occurs

The Implants meeting PK criteria for possible clogging will then undergo further diagnostics if explanted to confirm whether treatment failure was due to clogging. The "implant complete clogging" failure statistics will be summarized across all patients based on the first 9 months of Implant insertion.

5.4 RISKS AND ANTICIPATED ADVERSE DEVICE EFFECTS THAT ARE TO BE ASSESSED

At the end of the study, the incidence of "Prespecified RPDS-associated AEs" will be compared between subjects receiving ranibizumab from the Implant and the control subjects receiving ranibizumab as ITV injections:

- Vitreous hemorrhage associated with a >30-letter decrease in BCVA on the ETDRS chart compared with the last assessment of BCVA prior to the onset of vitreous hemorrhage lasting >1 month
- Reduced VA (>30-letter loss from previous scheduled visit)
- Traumatic cataract
- Endophthalmitis
- Damage to sclera
- Retinal detachment
- Interference of the Implant with visual field

In addition, ocular AEs and serious adverse events (SAEs) attributed by the investigator to: 1) the Implant insertion procedure, 2) the Implant refill procedure, 3) Implant explantation procedure, and 4) the Implant and other RPDS components, will be reported.

Please also refer to the protocol Section 6.5.1.

6. DESIGN OF THE CLINICAL INVESTIGATION

6.1 GENERAL

6.1.1 Type of Clinical Investigation and Rationale

Study GX28228 is a Phase II, multicenter, randomized, active treatment (monthly ITV injection)–controlled study to evaluate ranibizumab delivered through the Implant using three ranibizumab formulation arms (10 mg/mL, 40 mg/mL, and 100 mg/mL) compared with the control arm (0.5-mg monthly ITV injections of 10-mg/mL formulation) in patients with subfoveal neovascular (wet) AMD.

For details of the rationale for the design, refer to the Phase II protocol Section 3.4.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

6.1.2 Measures to Minimize or Avoid Bias

Patients will be randomized through an interactive voice/Web response system to one of four treatment arms.

Study patients and all study site personnel will be masked to the Implant treatment arms' ranibizumab formulation assignment (10 mg/mL vs. 40 mg/mL vs. 100 mg/mL) until the study conclusion.

The Sponsor's personnel directly involved in the study conduct (except the Internal Monitoring Committee [IMC] members) will be masked to the Implant treatment arms' ranibizumab formulation assignment (10 mg/mL vs. 40 mg/mL vs. 100 mg/mL) until the time of primary analyses. The IMC will closely monitor patient safety throughout the study (see protocol Section 3.1.4). The IMC roles and responsibilities will be outlined in the IMC charter.

Clinical pharmacology and PK scientists may be unmasked early for the purposes of interpreting emerging safety and efficacy data; those unmasked staff will not be part of the study team or have any interactions with sites or investigators.

In addition, the VA examiner will only conduct refraction and VA assessments and will be masked to patient study eye assignment and patient treatment assignment. The VA examiner will have no access to patient VA scores from previous visits but will be only aware of the patient's refraction data from previous visits. The VA examiner may perform no other direct patient-care tasks. Patients will be asked not to discuss their study eye assignment (right versus left) with the VA examiner.

Patients and study site personnel will not be masked with regard to patient assignment to the ITV arm or an Implant arm because of the difficulties of maintaining masking following the surgical procedure, the additional safety visits applicable only to the Implant arms, and Implant visualization upon ophthalmic examination.

6.1.3 Device Endpoints, with Rationale for Their Selection and Measurement

The Implant endpoint is the Implant status at the end of trial, which will be reported as either clogged or not clogged. The rationale for selecting Implant clogging as an endpoint is described in Section 3 of this RPDS CIP.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

6.1.4 Methods and Timing for Assessing, Recording, and Analyzing Variables

Details of the assessments to be performed during the study are provided in Appendix 1 of the Phase II protocol. The Implant clogging rate at Month 9 will be determined (see Section 5.3).

6.1.5 Equipment to be Used for Assessing the Clinical Investigation Variables and Arrangements for Monitoring Maintenance and Calibration

Not applicable.

6.1.6 Procedures for the Replacement of Subjects

Patients who discontinue from the study will not be replaced.

6.2 INVESTIGATIONAL DEVICE(S) AND COMPARATOR(S)

6.2.1 Description of the Exposure to the Investigational Device(s) or Comparator(s), If Used

Patients in the Implant Treatment Arms

Patients will have the Implant (prefilled with approximately 20 μL of either the 10-mg/mL [approximately 0.2 mg dose], 40-mg/mL [approximately 0.8 mg dose], or 100-mg/mL formulation [approximately 2 mg dose] of ranibizumab) surgically inserted in the study eye at the Day 1 visit. For further details regarding exposure, refer to protocol Section 4.3.2.2.

Patients in the ITV Injection Treatment (Control) Arm

Patients will receive their first ITV injection of 50 μL of the 10-mg/mL ranibizumab (0.5 mg dose) formulation at the Day 1 visit. For further details regarding exposure, refer to protocol Section 4.3.2.2.

6.2.2 Justification of the Choice of Comparator(s)

Refer to details in protocol Section 3.4.4.

6.2.3 List of Any Other Medical Device or Medication to be Used During the Clinical Investigation

No medical devices other than the RPDS or medication for the treatment of neovascular AMD in the study eye will be used during the clinical investigation.

6.2.4 Number of Investigational Devices to be Used

One Implant per study eye will be used during the clinical investigation in patients randomized to the RPDS treatment arms.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

6.3 SUBJECTS

6.3.1 Inclusion Criteria for Subject Selection

Patients with choroidal neovascularization secondary to AMD will be enrolled in the study. Written informed consent will be obtained before initiation of any study-related procedures.

For the complete list of inclusion criteria, refer to protocol Section 4.1.1.

6.3.2 Exclusion Criteria for Subject Selection

For the complete list of exclusion criteria, refer to protocol Section 4.1.2.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

6.3.3 Criteria and Procedures for Subject Withdrawal or Discontinuation

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. For details, refer to protocol Section 4.7.1.

Discontinued patients will not be allowed to re-enter the study.

6.3.4 Point of Enrollment

The study will include pre-screening (if applicable), “run-in” (if applicable), screening, and randomization visits followed by a treatment period. Subjects will be enrolled into the study at the office of their vitreo-retinal specialist. Patients randomized to the Implant treatment arms will have the Implant (pre-filled with ranibizumab) surgically inserted in the study eye at their Day 1 visit.

For additional details regarding description of study, refer to protocol Section 3.1.

6.3.5 Total Expected Duration of the Clinical Investigation

Approximately 220 patients will be randomized within an approximate 24-month period of time. It is expected that the duration of the clinical investigation (length of study plus enrollment period) will be approximately 38 months.

6.3.6 Expected Duration of Each Subject's Participation

Patients in the ITV injection arm *will be evaluated monthly and will* receive monthly study treatments (Day 1, Month 1 through Month *X* visit, see protocol Appendix 2) *until the Sponsor decides, based on the primary analysis results, to either terminate the*

study and discontinue study treatment, or offer patients entry into the RPDS Extension Study. Their participation (excluding screening period) in the study will last approximately *13–38* months dependent on the date of their randomization to the study.

The patients in the Implant arms will continue to be evaluated monthly for the Implant refill (see protocol Appendix 1)until the Sponsor decides, based on the primary analysis results, to either terminate the study and discontinue study treatment,or offer patients entry into the RPDS *Extension* Study. The Implant arms patients' study participation (excluding screening period) is expected to last approximately 13 to 38 months dependent on the date of their randomization to the study.

6.3.7 Number of Subjects Required to be Included in the Clinical Investigation

Approximately 220 patients up to 60 sites in the United States will be randomized in a 3:3:3:2 ratio to four treatment arms: approximately 60 patients will receive the Implant filled with 10-mg/mL ranibizumab formulation, 60 patients will receive the Implant filled with 40-mg/mL ranibizumab formulation, 60 patients will receive the Implant filled with 100-mg/mL ranibizumab formulation, and 40 patients will receive monthly ITV injections of 10-mg/mL ranibizumab formulation (50 μL for the 0.5-mg dose).

6.3.8 Estimated Time Needed to Select this Number (i.e., Enrolment Period)

The enrolment period is expected to be approximately 24 months.

6.4 PROCEDURES

For details regarding post-trial access to treatment, refer to protocol Section 4.4.2.

6.4.1 Description of All the Clinical-investigation-related Procedures that Subjects Undergo During the Clinical Investigation

Medical history and demographic information will be collected.

Medical history includes clinically significant diseases, surgeries, smoking history, and use of alcohol.

All medications other than protocol-specified procedural medications used by the patient within 7 days prior to the randomization visit until the study completion will be recorded on the electronic case report form (eCRF) concomitant medication log.

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

The Implant insertion and explantation procedures will be captured on video for Investigators' training purposes unless the study center has policies in place that prohibit these procedures being captured by video. The Implant refill procedure video capture is optional.

For a complete list of study assessments, refer to protocol Section 4.6.

Please see the schedule of assessments provided in protocol Appendix 1 and Appendix 2 for the schedule of assessments to be performed at each study visit.

6.4.2 Description of Those Activities Performed by Sponsor Representatives (Excluding Monitoring)

Genentech 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).

For additional details regarding administrative structure, refer to protocol Section 9.4.

6.4.3 Any Known or Foreseeable Factors That May Compromise the Outcome of the Clinical Investigation or the Interpretation of Results

Not applicable.

6.4.4 Monitoring Plan

Study monitors will perform ongoing source data verification 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. Refer to protocol Section 7.4 for additional details regarding source data documentation.

7. STATISTICAL CONSIDERATIONS

7.1 STATISTICAL DESIGN, METHOD AND ANALYTICAL PROCEDURES

One objective in the clinical study is to demonstrate that there is no evidence that the Implant clogging rate exceeds 10% of patients in the Implant arms at Month 9.

Implant clogging data from all patients that receive the Implant will be pooled together for this analysis. If there are 22 or fewer clogged Implants, among 165 evaluable Implants, within 9 months since insertion, we can declare that there is no evidence for the initial Implant clogging rate exceeding 10%. This acceptance criterion will be adjusted based on the actual number of evaluable Implants at end of study. The proportion of Implants

that clog within 9 months and its 90% confidence interval will be estimated based on the binomial distribution.

In addition, the safety data from three Implant arms will be pooled and compared with monthly ITV injection arm. The summary statistics (frequency and percentage) will be provided by Implant arm and monthly ITV arm. The safety assessment will review the following:

- AEs
- SAEs
- "Prespecified RPDS-associated AEs" (see protocol Section 6.5.1)

7.2 SAMPLE SIZE

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

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

7.3 THE LEVEL OF SIGNIFICANCE AND THE POWER OF THE DEVICE CLINICAL INVESTIGATION

The significance level used for Implant clogging data analysis is 0.05 and a one-sided test will be performed. 80% statistical power was used in above sample size section.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

7.4 EXPECTED DROP-OUT RATES

Less than 8% dropout rate is expected based on the previous clinical trials for ranibizumab. Thus, an 8% dropout rate is assumed in the above sample size section for Implant clogging data analysis.

7.5 PASS/FAIL CRITERIA TO BE APPLIED TO THE RESULTS OF THE DEVICE CLINICAL INVESTIGATION

The RPDS clinical investigation will be considered to successfully demonstrate Implant functionality if the following objective is met:

- Establish that there is no evidence that the initial Implant clogging rate within 9 months exceed 10%

The RPDS clinical investigation will be considered to successfully demonstrate RPDS safety if the following objective is met:

- Demonstrate that the AE profile observed when ranibizumab is administered using the Implant is clinically acceptable as compared with ranibizumab dosed using conventional ITV injection. In other words, any complications associated with Implant insertion, refill, or explantation, or associated with the long term presence of the Implant within the posterior chamber of the eye, are manageable and are acceptable in an overall benefit-risk assessment versus ITV dosing.

This will include a characterization of the “Prespecified RPDS-associated AEs”, that is, those ADEs that have been pre-specified as being most relevant for the risk assessment of the Implant and the procedures of insertion, refill, and explantation.

For each AE (including “Prespecified RPDS-associated AEs”) observed during the clinical study, the CRF will collect a separate assessment of investigator causality for each “study intervention” element, that is, investigator causality for “study drug” (i.e., ranibizumab [for both Implant arms and ITV dosing arm]), investigator causality for “procedures” (for both Implant arms and ITV dosing arm), and investigator causality for each of the RPDS components (for Implant arms only – the Implant, the Initial Fill Needle, the Insertion Tool, the Refill Needle, and the Explant Tool). Investigators will be trained on the requirement to assess each AE for potential causal association to “drug”, “procedure” and each of the “RPDS” device components ——so that they may determine whether there is a causal association with one, more than one, or none of the “Study intervention” elements.

If these objectives are not met, further design changes will be mandated.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

7.6 FLEXIBLE INTERIM ANALYSIS

Given the exploratory nature of this study, the Sponsor may choose to conduct up to two interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed by members of the Sponsor's unmasked study team and will be interpreted by the unmasked IMC and appropriate senior management personnel. Access to treatment assignment information will follow the Sponsor's standard procedures. The details of the timing and scope of the interim analysis, if any, will be specified in the IMC Agreement.

7.7 CRITERIA FOR THE TERMINATION OF THE CLINICAL INVESTIGATION

The criteria for stopping the trial or a treatment arm will be outlined in the IMC charter.

7.8 SUBGROUPS

Subgroup analysis will be performed if necessary. The subgroup variables should be pre-defined in the detailed statistical analysis plan before the clinical database lock.

7.9 PROCEDURES THAT TAKE INTO ACCOUNT ALL DATA

All Implant clogging data up to Month 9 visit will be included for analysis.

7.10 MISSING, UNUSED OR SPURIOUS DATA; EXCLUSION OF PARTICULAR INFORMATION

Missing data will not be imputed for Implant clogging assessment; however, all Implant data up to Month 9 visit will be included for Implant clogging data analysis. In case some patients discontinued from study prior to Month 9 visit, all data before last visit will still be used for data analysis.

7.11 NUMBER OF SUBJECTS TO BE INCLUDED FOR EACH CENTER

It is expected that each site will enroll approximately of 3-5 patients.

8. DATA MANAGEMENT

8.1 DATA REVIEW

The Sponsor will be responsible for the data management of this study, including quality checking of the data. For additional details, refer to protocol Section 7.1.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

8.2 VERIFICATION, VALIDATION AND SECURING OF ELECTRONIC CLINICAL DATA SYSTEMS

The Sponsor will perform oversight of the data management of this study. For additional details, refer to protocol Section 7.1.

8.3 DATA RETENTION AND SPECIFIED RETENTION PERIOD

For details, refer to protocol Section 7.6.

8.4 OTHER ASPECTS OF CLINICAL QUALITY ASSURANCE

For details, refer to protocol Section 7.1.

9. AMENDMENTS TO THE RPDS CIP

Any amendments to the RPDS CIP will be prepared by the Sponsor. Protocol and RPDS CIP amendments will be submitted to the Institutional Review Board (IRB)/Ethics Committee (EC) and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (according to local requirements) 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).

10. DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

Investigators must follow instructions and procedures as described in the Phase II protocol. No deviations from the RPDS CIP or protocol are allowed except when necessary to protect the safety, rights, or welfare of patients.

10.1 RECORDING, REPORTING AND ANALYZING RPDS CIP 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.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

10.2 CORRECTIVE AND PREVENTIVE ACTIONS

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 Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline for Good Clinical Practice (GCP)

The Sponsor may also implement additional training for Investigators when warranted.

11. DEVICE ACCOUNTABILITY

All IMP (ranibizumab) and RPDS required for completion of this study (including all the components of the RPDS) will be provided by the Sponsor. For additional details regarding IMP and RPDS accountability, refer to protocol Section 4.3.2.4.2.

12. STATEMENTS OF COMPLIANCE

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. It will also follow ISO 14155 for the Clinical Investigation Plan.

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. Food and Drug Administration regulations and applicable local, state, and federal laws.

This protocol, the ICFs, 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.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

In addition to the requirements for reporting all AEs to the Sponsor, investigators must comply with requirements for reporting SAEs to the local Health Authority (HA) 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 HA requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

The statement for patient's insurance due to injury in the RPDS Phase II clinical trial is available in the RPDS informed consent sample template.

13. INFORMED CONSENT PROCESS

The Sponsor's sample ICF will be provided to each site. For additional details, refer to protocol Section 8.2.

14. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

14.1 DEFINITIONS OF ADVERSE EVENTS AND ADVERSE DEVICE EFFECTS

Refer to protocol Section 5.2.1.

14.2 DEFINITION OF DEVICE DEFICIENCIES

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

14.3 DEFINITIONS OF SERIOUS ADVERSE EVENTS AND SERIOUS ADVERSE DEVICE EFFECTS AND, WHERE APPROPRIATE, UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECTS

Refer to protocol Section 5.2.2.

A serious ADE is an ADE that has resulted in any of the consequences characteristic of an SAE.

14.4 REPORTING OF ADVERSE EVENTS AND DEVICE DEFICIENCIES

The investigator is responsible for ensuring that all AEs are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided. The investigator is also responsible for reporting all complaints associated with any of the components of the RPDS.

For additional details, refer to protocol Section 5.3.1.

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. For details, refer to protocol Section 5.4.

14.5 PROCESS FOR REPORTING ADVERSE EVENTS

After informed consent has been obtained but prior to initiation of study drug (Day 1), only SAEs related to a protocol-mandated intervention will be reported (see protocol Section 5.4.2 for instructions for reporting SAEs).

After initiation of study drug, all AEs, regardless of relationship to study drug, Implant, or ancillary devices, or study procedures, will be reported until the patient's study completion or early termination from the study. All SAEs, (including serious adverse reactions and serious adverse device effects) will be collected and reported to the Sponsor in compliance with GCP guidelines.

Investigators will seek information on AEs at each patient contact. All AEs, 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.

The investigator is responsible for ensuring that all AEs are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided. For each AE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness, severity, and causality.

14.6 PROCESS FOR REPORTING DEVICE DEFICIENCIES

The investigator must report all medical device complaints associated with any of the components of the RPDS to the Sponsor.

For additional details, refer to protocol Section 5.4.4.

14.7 FORESEEABLE ADVERSE EVENTS AND ANTICIPATED ADVERSE DEVICE EFFECTS

The following are "Prespecified RPDS-associated AEs":

- Vitreous hemorrhage associated with a >30-letter decrease in BCVA on the ETDRS chart compared with the last assessment of BCVA prior to the onset of vitreous hemorrhage lasting >1 month
- Reduced VA (>30-letter loss from previous scheduled visit)
- Traumatic cataract
- Endophthalmitis

- Damage to sclera
- Retinal detachment
- Interference of the Implant with visual field

In addition, ocular AEs and SAEs attributed by the investigator to: 1) the Implant insertion procedure, 2) the Implant refill procedure, 3) Implant explantation procedure, and 4) the Implant and other RPDS components, will be reported

14.8 EMERGENCY CONTACT DETAILS FOR REPORTING SERIOUS ADVERSE EVENTS AND SERIOUS ADVERSE DEVICE EFFECTS

The Phase II study is being conducted in the United States only.

Medical Monitor Contact Information for Sponsor's Medical Responsible is provided in protocol Section 5.4.1.

14.9 INFORMATION REGARDING THE SAFETY REVIEW COMMITTEE

Ongoing review of study data (including adverse events of special interest, SAEs, adverse device effects [ADEs], and laboratory abnormalities) will be performed by the IMC. The IMC roles and responsibilities will be outlined in the IMC charter.

15. VULNERABLE POPULATION

15.1 SPECIFIC INFORMED CONSENT PROCESS

This clinical investigation will only enroll patients who are able and willing to provide signed informed consent.

15.2 ETHICS COMMITTEE'S SPECIFIC RESPONSIBILITY

This protocol, the ICFs, 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.

In addition to the requirements for reporting all AEs to the Sponsor, investigators must comply with requirements for reporting SAEs to the local HA 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 HA requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

15.3 MEDICAL CARE PROVIDED FOR SUBJECTS AFTER THE CLINICAL INVESTIGATION HAS BEEN COMPLETED

Currently, the Sponsor doesn't plan to provide ranibizumab via RPDS or via ITV injections or to provide other study interventions to patients after the conclusion of the study or following early patient withdrawal. The Sponsor will evaluate the appropriateness of continuing to provide ranibizumab treatment to RPDS treatment arms patients after evaluating RPDS efficacy, safety, and PK data gathered in the study. The Sponsor may offer study patients entry to a separate RPDS *Extension* Study to continue to provide ranibizumab to RPDS treatment arms patients via Implant in an open-label manner.

For additional information, please refer to the ICF.

16. SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

The Sponsor has the right to terminate this study or close a site at any time. For details, refer to protocol Section 4.7.4.

16.1 REQUIREMENTS FOR SUBJECT FOLLOW-UP

For details refer to protocol Section 4.6.10.3.

17. PUBLICATION POLICY

For details regarding the publication policy, refer to protocol Section 9.5 and the Roche Global Policy on Sharing of Clinical Trials Data.

Appendix 21
Ranibizumab Port Delivery System: Device Clinical Investigation Plan (cont.)

18. BIBLIOGRAPHY

Bressler NM. Submacular surgery. Are randomized trials necessary? Arch Ophthalmol. 1995 Dec;113(12):1557-60.

Busbee BG, Ho AC, Brown DM, et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology; 2013 May;120(5):1046-56.

CATT Research Group et al. Ranibizumab and bevacizumab for age-related macular degeneration (CATT study). N Engl J Med; 2011 May 19;364(20):1897-908.

ISO 14155:2011 Clinical investigation of medical devices for human subjects - Good Clinical Practice.

Klein R, Klein BE, Jensen SC, et al. The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. Ophthalmology. 1997 Jan;104(1):7-21.